Characteristics of included reviews	Inflammatory bowel disease	
Review ID	**Liu 2021**	
Review reference	Liu F, Li D, Wang X, Cui Y, Li X. Polyphenols intervention is an effective strategy to ameliorate inflammatory bowel disease: a systematic review and meta-analysis. Int J Food Sci Nutr. 2021;72(1):14-25. 10.1080/09637486.2020.1760220	
Review objective	To systematically review the published trials investigating the effects of polyphenols supplementation on symptom improvement among IBD patients.	
Author affiliations	Several tertiary institutions in China	
Source of funds	Grants from the National Natural Science Foundation of China, National Key R&D Programme of China, the Grant of Social Development of Suzhou and A Project Funded by the Priority Academic Programme Development of Jiangsu Higher Education Institutions.	
Declared interests of the review authors	The authors declare that they have no competing interests.	
Review method of analysis	Meta-analysis	Data analysis was performed using STATA (SE 11.0 version) using random effects model, chi-square test and the I2 statistic were used to assess the heterogeneity. A p value <0.05 was considered as statistically significant.
Inclusion criteria		
Study design	Randomised controlled trials	
Population	People with IBD	
Intervention	polyphenol extracts in various forms	
Comparator	not specified	
Other	study reports clinical remission rate, clinical reponse rate, or simple colitis activity index score (or similar)	
Exclusion criteria		
Study design	nonRCTs, nonhuman	
Population	--	
Intervention	--	
Comparator	--	
Other	Studies not published in English	
Date of documented search (month/year)	database inception to November 2019	
Databases searched	PubMed, Web of Science, Scopus and Cochrane databases	
Was an non-English database searched?	No	
Were studies in a LOTE included?	No	Only Studies in English included.

Characteristics of included reviews	Inflammatory bowel disease
Review ID	**Liu 2021**
Outcomes considered in the SR (list)	Clinical remission rate, clinical reponse rate, or simple colitis activity index score (or similar)
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: 5-point Jadad scale *Authors summary*: study would be defined as low quality research if the Jadad score was 0–2, and high quality research is the Jadad score was 3–5.
Authors conclusions (key message)	Polyphenols might be an effective adjuvant treatment for ameliorating IBD (to increase odds of clinical remission, endoscopic remission and clinical response in patients with IBD, especially UC). Considering the relatively few studies included in our present study, further clinical trials are required to verify the effects of polyphenols on IBD.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	10 of 12 studies included in the SR met our PICO (UC or Crohn's disease, curcumin, st marys thistle or green tea) Particants were also all on other treatments for IBD (sulfasalazine [SZ], mesalamine [ML] or 5-amino-salicylic acid [5-ASA])

Table 2. Jadad score of included studies.

Author, year	Randomization	Double blind	Withdrawals and dropouts	Score
Hanai et al. (2006)	2	2	0	4
Lang et al. (2015)	1	2	1	4
Kedia et al. (2017)	2	2	1	5
Singla et al. (2014)	2	2	1	5
Masoodi et al. (2018)	2	1	2	4
Banerjee et al. (2017)	1	1	1	3
Kumar et al. (2019)	1	1	0	2
Dryden et al. (2013)	2	2	1	5
Samsami-Kor et al. (2015)	1	2	1	4
Samsamikor et al. (2016)	1	2	1	4
Rastegarpanah et al. (2015)	2	2	1	5
Sugimoto et al. (2019)	1	1	0	2

	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Kumar 2019	High risk	N=53 (28/25) (? yrs) 10 g/day 8 wks.	P: Active UC I: Curcuma longa (adjunct to ML) C: ? O: Clinical response S: India

Characteristics of included reviews	Inflammatory bowel disease			
Review ID	**Liu 2021**			
2	Sugimoto 2019	High risk	N=31 (?/?) (? yrs) 360 mg/day 12 wks.	P: Mild-moderate Crohn's disease I: Theracurmin (adjunct to ?) C: ? O: Clincal & endoscopic remission, inflammatory markers S: ?
3	Masoodi 2018	Low risk	N=56 (28/28) (>18 yrs) 240 mg, 4 wks.	P: Mild-moderate UC I: Curcuminoids nanomicelles (adjunct to ML) C: ? O: Simple clinical colitis activity index S: Iran
4	Banerjee 2017	Low risk	N=47 (22/25) (18-70 yrs) 2x 50 mg, 3 mos.	P: Mild-moderate UC I: Curcumin capsules (adjunct to ML) C: ? O: Endoscopic remission, clinical response S: India
5	Kedia 2017	Low risk	N=62 (29/33) (>18 yrs) 450mg/day 8 wks.	P: Mild-moderate UC I: Curcumin (adjunct to ML) C: ? O: Clinical & endoscopic remission, clinical response S: India
6	Lang 2015	Low risk	N=50 (26/24) (18-70 yrs) 3g/day 1 mos.	P: Mild-moderate UC I: Curcumin (adjunct to 5-ASA) C: ? O: Clinical & endoscopic remission, clinical response S: Hong Kong
7	Singla 2014	Low risk	N=45 (23/22) (>18 yrs) 140 mg enema, 8 wks.	P: Mild-moderate UC I: Curcumin (adjunct to 5-ASA) C: ? O: Clinical & endoscopic remission, clinical response S: India

Characteristics of included reviews	Inflammatory bowel disease			
Review ID	**Liu 2021**			
8	Hanai 2006	Low risk	N=89 (45/44) (13-65 yrs) 2g/day 6 mos.	P: Quiescent UC I: Curcumin (adjunct to SZ or ML) C: ? O: Clinical & endoscopic remission, clinical response S: Japan
9	Rastegarpanah 2015	Low risk	N=80 (42/38) (16-75 yrs) 140 mg/day 6 mos.	P: Mild-moderate UC I: Silymarin (adjunct to standard therapy) C: ? O: haemoglobin, disease activity index, ESR S: Iran
10	Dryden 2013	Low risk	N=20 (16/4) (>18 yrs) 400 or 800 mg/day, 8 wks.	P: Mild-moderate UC I: EGCG, epigallocatechin-3-gallate (adjunct ??) C: ? O: Clinical remission, clinical & endoscopic response, QoL S: USA
11	Two studies below do not meet our PICO criteria (restveratrol not on List A)			
12	Samsamikor 2016	Low risk	N=56 (28/28) (>18 yrs) 500 mg/day 6 wks.	P: Mild-moderate UC I: Resveratrol (adjunct to ?) C: ? O: Simple clinical colitis activity index, IBDQ-9, oxidative stress markers S: Iran
13	Samsami-Kor 2015	Low risk	N=50 (25/25) (>18 yrs) 500 mg/day 6 wks.	P: Mild-moderate UC I: Resveratrol (adjunct to ?) C: ? O: Simple clinical colitis activity index, IBDQ-9, oxidative stress & inflammatory markers S: Iran

= data extracted

= data extracted in more recent SR

= control is an active intervention (data not extracted)

Characteristics of included reviews	Inflammatory bowel disease	
Review ID	**Chandan 2020**	
Review reference	Chandan S, Mohan BP, Chandan OC, Ahmad R, Challa A, Tummala H, et al. Curcumin use in ulcerative colitis: is it ready for prime time? A systematic review and meta-analysis of clinical trials. Ann Gastroenterol. 2020;33(1):53-8. 10.20524/aog.2019.0439	
Review objective	A systematic review and meta-analysis of the current evidence in order to evaluate the role of combination curcumin therapy in patients with UC	
Author affiliations	Several tertiary institutions in the USA (Nebraska, South Ddakota, Utah, Virginia)	
Source of funds	None declared	
Declared interests of the review authors	The authors declare that they have no competing interests.	
Review method of analysis	Meta-analysis	Data analysis was performed using random effects model following the methods suggested by DerSimonian and Laird. Cochran Q and the I2 statistic were used to assess the heterogeneity. Publication bias was ascertained, qualitatively by visual inspection of a funnel plot and quantitatively by the Egger test A p value <0.05 was considered as statistically significant. Predictive factors for the outcomes were assessed by meta-regression methods
Inclusion criteria	.	
Study design	Clinical trials, only RCTs inclued in the meta-analysis	
Population	People with UC	
Intervention	Curcumin	
Comparator	--	
Other	--	
Exclusion criteria		
Study design	Case series, case reports	
Population	--	
Intervention	--	
Comparator	--	
Other	Studies not published in English	
Date of documented search (month/year)	January 2000 to September 2018	
Databases searched	PubMed, EMBASE, Google Scholar, SCOPUS and Web of Science databases	
Was an non-English database searched?	No	
Were studies in a LOTE included?	No	Only Studies in English included.

Characteristics of included reviews	Inflammatory bowel disease
Review ID	**Chandan 2020**
Outcomes considered in the SR (list)	Clinical remission rate, Clincial response, endoscopic reponse/remission, safety Clinical Activity Index (CAI); Simple Clinical Colitis Activity Index (SCCAI); and Disease Activity Index (DAI).
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: 5-point Jadad scale *Authors summary*: All included studies scores 5/5 on Jadad scale.

Supplementary Table 1 Jadad study quality assessment

Study	Hanai	Shivakumar	Singla	Lang	Kedia	Banerjee	Masoodi
Randomization							
Randomization mentioned: +1	1	1	1	1	1	1	1
Randomization appropriate: +1	1	1	1	1	1	1	1
Inappropriate method of randomization: -1	-	-	-	-	-	-	-
Blinding							
Blinding mentioned: +1	1	1	1	1	1	1	1
Method appropriate: +1	1	1	1	1	1	1	1
Method inappropriate: -1	-	-	-	-	-	-	-
Account of all patients							
All pts accounted for: +1	1	1	1	1	1	1	1
Score	5	5	5	5	5	5	5
Quality	High	High	High	High	High	High	High

Authors conclusions (key message)	Combination therapy of curcumin with mesalamine in patients with mild to-moderate UC yields a superior clinical and endoscopic response.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	7 of 7 studies included in the SR met our PICO (UC or Crohn's disease, curcumin) Particants were also all on other treatments for IBD (sulfasalazine [SZ], mesalamine [ML] or 5-amino-salicylic acid [5-ASA])

Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Masoodi 2018	Low risk	N=56 (28/28) (>18 yrs) 240 mg, 4 wks.	P: Mild-moderate UC I: Curcuminoids nanomicelles (adjunct to ML) C: Placebo O: Improvement in score (SCCAI) S: Iran

Characteristics of included reviews	Inflammatory bowel disease			
Review ID	**Chandan 2020**			
2	Banerjee 2017	Low risk	N=47 (19/23)* (18-70 yrs) 2x 50 mg, 12 wks *authors reported PP	P: Mild-moderate UC I: Curcumin (adjunct to 5-ASA) C: Placebo O: Endoscopic remission (score ≤1), clinical response (decrease Mayo score ≥3) S: India
3	Kedia 2017	Low risk	N=62 (29/33) (>18 yrs) 450mg/day 8 wks.	P: Mild-moderate UC I: Curcumin (adjunct to 5-ASA) C: Placebo O: Clinical remission (UCDAI≤2), endoscopic remission (score 0/1), clinical response (decrease UCDAI≥3) S: India
4	Lang 2015	Low risk	N=50 (26/24) (18-70 yrs) 3g/day 4 wks.	P: Mild-moderate UC I: Curcumin (adjunct to 5-ASA) C: Placebo O: Clinical remission (UCDAI<3), endoscopic response (1 point decrease), clinical response (decrease UCDAI≥3) S: Israel
5	Singla 2014	Low risk	N=45 (23/22) (>18 yrs) 140 mg enema, 8 wks.	P: Mild-moderate UC I: Curcumin (adjunct to 5-ASA) C: Placebo O: Clinical remission (UCDAI<3), endoscopic response (1 point decrease), clinical response (decrease UCDAI≥3) S: India
6	Shivakumar 2011	Low risk	N=36 (18/18) (? yrs) 10 g /day, 8 wks.	P: Active UC I: Curcumin (adjunct to ?) C: Placebo O: endoscopic response (1 point decrease in histology), clinical improvement in fecal calpro, S: India
7	--			

Characteristics of included reviews	Inflammatory bowel disease
Review ID	**Chandan 2020**
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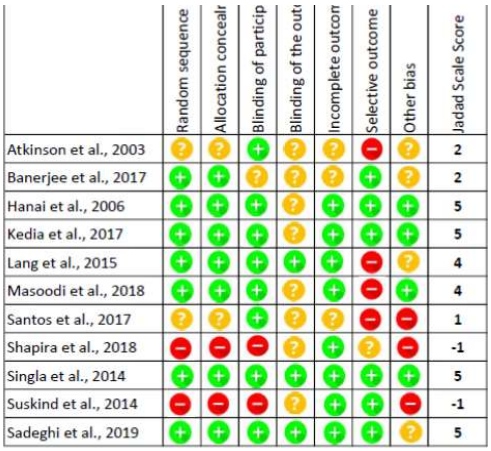
= data extracted

= data extracted in more recent SR

= control is an active intervention (data not extracted)

Characteristics of included reviews	Inflammatory bowel disease
Review ID	**Coelho 2020**
Review reference	Coelho MR, Romi MD, Ferreira DMTP, Zaltman C, Soares-Mota M. The Use of Curcumin as a Complementary Therapy in Ulcerative Colitis: A Systematic Review of Randomized Controlled Clinical Trials. Nutrients. 2020;12(8):2296. 10.3390/nu12082296 PROSPERO: CRD42019104827
Review objective	To analyze the studies published so far, to reviewthe positive or negative effects of the use of curcumin, and to determine whether it is safe and effective as a complementary therapy in the management of IBD, offering fewer side effects than conventional therapies
Author affiliations	Several tertiary institutions in Brazil
Source of funds	This research received no specific grant from any funding agency in the public, commercial, or not for-profit sectors.
Declared interests of the review authors	The authors declare that they have no competing interests.
Review method of analysis	Descriptive
Inclusion criteria	
Study design	Randomised controlled trials
Population	People with IBD (UC or Crohn's)
Intervention	Curcumin supplementation in the form of spice, capsule or enema
Comparator	Placebo or conventional drug therapy
Other	Outcome: Disease activity, clinical or endoscopic activity
Exclusion criteria	
Study design	Review articles, animal studies, editorial letters, in-vitro studies, observational, and descriptive studies, such as case reports and case series
Population	--
Intervention	Studies that did not describe the curcumin dose
Comparator	Studies with a high risk of bias in three or more items were excluded
Other	--
Date of documented search (month/year)	Publsihed up to March 2020
Databases searched	MEDLINE (PubMed), Scopus, Web of Science, Cochrane Library, Lilacs, Food Science and Technology Abstracts, and Science Direct
Was an non-English database searched? Were studies in a LOTE included?	Yes — Lilacs (includes Latin-American and the Caribbean) No — Studies published in any language were accepted, but none found

Characteristics of included reviews	Inflammatory bowel disease
Review ID	**Coelho 2020**
Outcomes considered in the SR (list)	Not specified
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane RoB tool & 5-point Jadad scale *Authors summary*: 
Authors conclusions (key message)	All the RCTs reported that curcumin was well tolerated and was not associated with any serious side effects. Studies show that curcumin may be a safe, effective therapy for maintaining remission in UC when administered with standard treatments. However, the same cannot be stated for Crohn's disease due to the lack of low bias risk studies. Further studies with larger sample sizes are needed before curcumin can be recommended as a complementary therapy for UC.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	6 of 6 studies included in the SR met our PICO (UC or Crohn's disease, curcumin) Particants were also all on other treatments for IBD (sulfasalazine [SZ], mesalamine [ML] or 5-amino-salicylic acid [5-ASA])

	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Hanai 2006	Low risk	N=89 (45/44) (13-65 yrs) 2g/day 24 wks.	P: Quiescent UC I: Curcumin (adjunct to SZ or ML) C: Placebo O: Clinical activty index (CAI), Endoscopic index, relapse S: Japan

Characteristics of included reviews	Inflammatory bowel disease			
Review ID	**Coelho 2020**			
2	Singla 2014	Low risk	N=45 (23/22) (>18 yrs) 140 mg enema, 8 wks.	P: Mild-moderate UC I: Curcumin (adjunct to 5-ASA) C: Placebo O: UCDAI, endoscopic response S: India
3	Lang 2015	Low risk	N=50 (26/24) (18-70 yrs) 3g/day 4 wks.	P: Mild-moderate UC I: Curcumin (adjunct to 5-ASA) C: Placebo O: SCCAI, Mayo endoscopic score S: Israel
4	Masoodi 2018	Low risk	N=56 (28/28) (>18 yrs) 240 mg, 4 wks.	P: Mild-moderate UC I: Curcuminoids nanomicelles (adjunct to ML) C: Placebo O: Improvement in score (SCCAI) S: Iran
5	Kedia 2017	Low risk	N=62 (29/33) (>18 yrs) 450mg/day 8 wks.	P: Mild-moderate UC I: Curcumin (adjunct to 5-ASA) C: Placebo O: UCDAI, endoscopic Baron score S: India
6	Sadeghi 2019	Low risk	N=70 (35/35) (27 to 53 yrs) 1500 mg /day, 8 wks.	P: Mild-moderate proctitis/colitis/pancolitis I: Curcumin (adjunct to routine care) C: Placebo O: SCCAI, IBDQ-9, ESR, CRP, anthropometrics, dietary intakes S: Iran
7	Data from 5 RCTs at high risk of bias not included: Atkinson 2002, Banerjee 2017, Santo 2017 (thesis), Shapira 2018, Suskind 2013			

Characteristics of included reviews	Inflammatory bowel disease
Review ID	**Coelho 2020**
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= data extracted

= data extracted in more recent SR

= control is an active intervention (data not extracted)

Characteristics of included reviews	Inflammatory bowel disease	
Review ID	**Goulart 2020**	
Review reference	Goulart RDA, Barbalho SM, Rubira CJ, Araujo AC, Lima VM, Rogerio Leoni B, et al. Curcumin therapy for ulcerative colitis remission: systematic review and meta-analysis. Expert Review of Gastroenterology and Hepatology. 2020;14(12):1171-9. http://dx.doi.org/10.1080/17474124.2020.1808460	
Review objective	the objective of our study was to perform a systematic review and meta-analysis of trials that investigated the efficacy of orally administered curcumin in UC patients.	
Author affiliations	Several tertiary institutions in Brazil	
Source of funds	This research received no specific grant from any funding agency in the public, commercial, or not for-profit sectors.	
Declared interests of the review authors	The authors declare that they have no competing interests.	
Review method of analysis	Meta-analysis	meta-analysed using RevMan 5.3 software as per Cochrane handbook. Remission was treated as a dichotomous variable with 95% confidence intervals (CI). Data such as the intention-to-treat (ITT) data were extracted.
Inclusion criteria		
Study design	Randomised controlled trials	
Population	People with mild-moderate UC	
Intervention	Oral curcumin	
Comparator	Placebo	
Other	Nil	
Exclusion criteria		
Study design	--	
Population	--	
Intervention	--	
Comparator	--	
Other	Articles not published in full.	
Date of documented search (month/year)	Publsihed up to June 2020	
Databases searched	PubMed/Medline, EMBASE, and Cochrane.	
Was an non-English database searched? Were studies in a LOTE included?	No	
	Yes	Studies published in any language were accepted, but none found

Characteristics of included reviews	Inflammatory bowel disease
Review ID	**Goulart 2020**
Outcomes considered in the SR (list)	Clinical remission, clinical improvement, safety
Risk of bias of the included RCT studies as reported in the SR	*Tool used* GRADE *Authors summary* Consideration for Cochrane RoB domains
Authors conclusions (key message)	Existing meta-analyses are biased because they compare studies using different administration routes and patients in different stages of the disease. Our metaanalysis is the only one that tried to make a comparison with a few of biases as possible and show that curcumin can help in the induction of remission in UC subjects. Another consideration that we cannot overlook is that curcumin can also be used for remission maintenance, perhaps with more critical effects than remission induction. We need to consider rigorous, long-term clinical trials to investigate if curcumin may be better than other drugs in maintaining remission for both nonresponsive and conventional drug-responsive patients.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	4 of 4 studies included in the SR met our PICO (UC, curcumin) 3 RCTs not included: Hanai 2006, Banerjee 2017, Singla 2014 as they did not meet the SR authors PICO criteria.

Study	Ref	Question focus	Appropriate randomization	Allocation blinding	Double-blind	Losses (<20%)	Prognostics or demographic characteristics	Outcomes	Intention to treat analysis	Sample calculation	Adequate follow-up
Lang et al.	[25]	Yes	NR	NR	Yes	Yes	Yes	Yes	Yes	No	Yes
Kedia et al.	[26]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Masoodi et al.	[28]	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sadeghi et al.	[29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

NR: not reported.

	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Lang 2015	Low risk	N=50 (26/24) (18-70 yrs) 3g/day 4 wks.	P: Mild-moderate UC (SCCAI btw 5 & 12) I: Curcumin (adjunct to 5-ASA) C: Placebo O: Remission (SCCAI ≤2, Mayo endoscopic score ≤1), Response (SCCAI decrease ≥ 3), S: Israel, China , Cyprus

Characteristics of included reviews	Inflammatory bowel disease			
Review ID	**Goulart 2020**			
2	Kedia 2017	Low risk	N=62 (29/33) (>18 yrs) 3x 150mg/day 8 wks.	P: Mild-moderate UC (UCDAI btw 3 & 9) I: Curcumin (adjunct to 5-ASA) C: Placebo O: Remission (UCDAI ≤2, endoscopic Baron score 0/1), response (UCDAI decrease ≥3) S: India
3	Masoodi 2018	Low risk	N=56 (28/28) (>18 yrs) 3x 80mg, 4 wks.	P: Mild-moderate UC (SCCAI btw 5 & 11) I: Curcuminoids nanomicelles (adjunct to ML) C: Placebo O: Improvement in score (SCCAI) S: Iran
4	Sadeghi 2019	Low risk	N=70 (35/35) (27 to 53 yrs) 3x 500 mg /day, 8 wks.	P: Mild-moderate proctitis/colitis/pancolitis (SCCAI < 12) I: Curcumin (adjunct to routine care) C: Placebo O: Remission (SCCAI ≤2), Response (SCCAI decrease ≥3), ESR, CRP, anthropometrics, dietary intakes S: Iran
5	--			
6	--			
7	--			

Characteristics of included reviews	Inflammatory bowel disease
Review ID	**Goulart 2020**
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12	--
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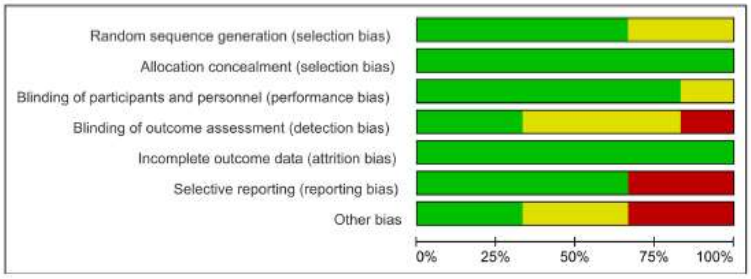
= data extracted

= data extracted in more recent SR

= control is an active intervention (data not extracted)

Characteristics of included reviews	Inflammatory bowel disease	
Review ID	**Zheng 2020**	
Review reference	Zheng T, Wang X, Chen Z, He A, Zheng Z, Liu G. Efficacy of adjuvant curcumin therapy in ulcerative colitis: A meta-analysis of randomized controlled trials. Journal of Gastroenterology & Hepatology. 2020;35(5):722-9. https://dx.doi.org/10.1111/jgh.14911	
Review objective	The aim of this study was to evaluate the efficacy and safety of curcumin in UC and to investigate the effect of curcumin doses, delivery way, form, and intervention time on its efficacy.	
Author affiliations	Department of General Surgery, Tianjin Medical University General Hospital, China	
Source of funds	None declared	
Declared interests of the review authors	The authors declare that they have no competing interests.	
Review method of analysis	Meta-analysis	Meta-analysed using RevMan 5.3 software as per Cochrane handbook. Remission/repsonse treated as a dichotomous variable with 95% confidence intervals (CI). Per-protocol data were extracted. Heterogeneity of included data was assessed by the $\chi 2$ test and the I2 statistic. Publication bias was calculated using a funnel plot
Inclusion criteria		
Study design	Randomised controlled trials	
Population	People with mild-moderate UC (UCDAI 3-9; SCCAI 5-12 or quiscient (CAI ≤4)	
Intervention	Curcumin	
Comparator	Placebo	
Other	Adjunct to standard care (5-ASA or enema), studies reporting clincial or endoscopic remission, or changes in disease activity	
Exclusion criteria		
Study design	--	
Population	People younger than 18 years	
Intervention	--	
Comparator	--	
Other	Studies not providing details on patients selection/allocation, study deisgn, outcomes or measures	
Date of documented search (month/year)	Published up to July 2019	
Databases searched	PubMed, EMBASE, and Cochrane Library	
Was an non-English database searched?	No	
Were studies in a LOTE included?	No	

Characteristics of included reviews	Inflammatory bowel disease
Review ID	**Zheng 2020**
Outcomes considered in the SR (list)	Primary: Clinical & endoscopic remission Secondary: Clinical & endoscopic improvement
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane risk of bias tool *Authors summary*: Only summary risk of bias provided 
Authors conclusions (key message)	Curcumin, as an adjuvant treatment of mesalamine, was proved to be effective and safe in ulcerative colitis. Better efficacy can be achieved with suitable dose, delivery way, formation, and intervention time, which needs further study to verify. We can see the potential advantages in large dosage, topical enema, special drug form, and longer duration from the enrolled studies. There were no severe side effects reported.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	6 of 6 studies included in the SR met our PICO (UC, curcumin) Note: Authors report PP results

	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Kedia 2017	Low risk	N=62 (29/33) (>18 yrs) 3x 150mg/day 8 wks.	P: Mild-moderate UC (UCDAI btw 3 & 9) I: Curcumin (adjunct to 5-ASA) C: Placebo O: Remission (UCDAI ≤2, endoscopic Baron score 0/1), response (UCDAI decrease ≥3) S: India

Characteristics of included reviews	Inflammatory bowel disease			
Review ID	**Zheng 2020**			
2	Lang 2015	Low risk	N=50 (26/24) (18-70 yrs) 3g/day 4 wks.	P: Mild-moderate UC (SCCAI btw 5 & 12) I: Curcumin (adjunct to 5-ASA) C: Placebo O: Remission (SCCAI ≤2, Mayo endoscopic score ≤1), Response (SCCAI decrease ≥ 3), S: Israel, China , Cyprus
3	Singla 2014	Low risk	N=45 (23/22) (>18 yrs) 140 mg enema, 8 wks.	P: Mild-moderate UC I: Curcumin (adjunct to 5-ASA) C: Placebo O: Remission (UCDAI <3), response (UCDAI decrease ≥3), S: India
4	Hanai 2006	Low risk	N=89 (45/44) (13-65 yrs) 2g/day 24 wks.	P: Quiescent UC I: Curcumin (adjunct to SZ or ML) C: Placebo O: Remission (CAI ≤4), Response (CAI & Endoscopic index reduction) S: Japan
5	Banerjee 2017	Low risk	N=47 (19/23)* (18-70 yrs) 2x 50 mg, 12 wks *authors reported PP	P: Mild-moderate UC I: Curcumin (adjunct to 5-ASA) C: Placebo O: Endoscopic remission (score ≤1), clinical response (decrease Mayo score ≥3) S: India
6	Masoodi 2018	Low risk	N=56 (28/28) (>18 yrs) 3x 80mg, 4 wks.	P: Mild-moderate UC (SCCAI btw 5 & 11) I: Curcuminoids nanomicelles (adjunct to ML) C: Placebo O: Improvement in score (SCCAI) S: Iran
7	--			

Characteristics of included reviews	Inflammatory bowel disease
Review ID	**Zheng 2020**
8	--
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12	--
13	--

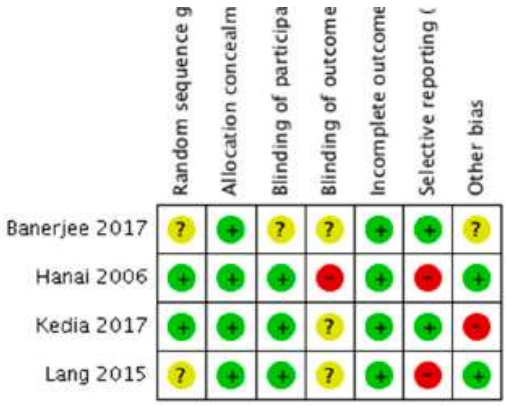
= data extracted

= data extracted in more recent SR

= control is an active intervention (data not extracted)

Characteristics of included reviews	Inflammatory bowel disease	
Review ID	**Grammatikopoulou 2018**	
Review reference	Grammatikopoulou MG, Gkiouras K, Theodoridis X, Asteriou E, Forbes A, Bogdanos DP. Oral Adjuvant Curcumin Therapy for Attaining Clinical Remission in Ulcerative Colitis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 2018;10(11):12. https://dx.doi.org/10.3390/nu10111737 PROSPERO (CRD42018098996)	
Review objective	The purpose of this study was to systematically review the literature for randomized control trials (RCTs) evaluating the efficacy of oral curcumin administration, in patients with ulcerative colitis.	
Author affiliations	Several tertiary institutions in Greece and UK	
Source of funds	No external funding received.	
Declared interests of the review authors	The authors declare that they have no competing interests.	
Review method of analysis	Meta-analysis	Meta-analysed using RevMan 5.3 software as per Cochrane handbook. Remission/repsonse treated as a dichotomous variable with 95% confidence intervals (CI). ITT and Per-protocol data were extracted. Heterogeneity of included data was assessed by the $\chi 2$ test and the I2 statistic. Beta-binomial (B-B) random effects model analysis also carried out on SAS® where non-significant results have the value of 1.0 within their CI range (for studies with 0 events)
Inclusion criteria		
Study design	Randomised controlled trials	
Population	People with endoscopically confirmed mild-moderate UC	
Intervention	Curcumin, oral (as adjuvant to standard therapy)	
Comparator	Placebo (or no intervention)	
Other	Adjunct to standard care (5-ASA or enema), studies reporting clincial or endoscopic remission, or changes in disease activity	
Exclusion criteria		
Study design	--	
Population	People younger than 18 years	
Intervention	Curcmin devleired as enema (not oral)	
Comparator	--	
Other	--	
Date of documented search (month/year)	From inception up to 1 August 2018	
Databases searched	PubMed/Medline, Web of Science, Cochrane CENTRAL, EMBASE, Clinical Trials, WHO International Clinical Trials Registry, Scopus and Google	
Was an non-English database searched? Were studies in a LOTE included?	Yes	Chinese Clincial Trials Registry, Clincial trial registry India, Sri lanka Trial registry, IndMED, PakMediNet, IBECS,
	No	Only studies published in the English language were selected

Characteristics of included reviews	Inflammatory bowel disease
Review ID	**Grammatikopoulou 2018**
Outcomes considered in the SR (list)	Clinical remission, clinical improvement, safety
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane risk of bias tool & 5-point Jadad scale *Authors summary*: Hanai 4/5; Lang 4/5; Kedia 5/5; Banerjee 2/5
Authors conclusions (key message)	The present analyses showed that based on the current available evidence, oral adjuvant curcumin therapy does not appear to contribute to either attaining remission, or ameliorating clinical response among patients with UC. Future RCTs should be planned more cautiously with sufficient size and adhere to the ITT analysis in all outcomes.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	4 of 4 studies included in the SR met our PICO (UC, curcumin) Two ongoing RCTs noted: NCT03122613, NCT02277223



	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Hanai 2006	High risk	N=89 (45/44) (13-65 yrs) 2g/day 24 wks	P: Quiescent UC I: Curcumin (adjunct to SZ or ML) C: Placebo O: Remission (CAI ≤4), Response (CAI & Endoscopic index reduction) S: Japan Funding: Eli and Edythe L. Broad Foundation, but placebo and curcumin tabs supplied by API Co, Ltd. (Japan)

Characteristics of included reviews	Inflammatory bowel disease			
Review ID	**Grammatikopoulou 2018**			
2	Lang 2015	Low risk	N=50 (26/24) (18-70 yrs) 3g/day 4 wks	P: Mild-moderate UC (SCCAI btw 5 & 12) I: Curcumin (adjunct to 5-ASA) C: Placebo O: Remission (SCCAI ≤2, Mayo endoscopic score ≤1), Response (SCCAI decrease ≥ 3), S: Israel, China , Cyprus Funding: Talpiot Medical Leadership grant (Sheba Medical Center, Leona M. and Harry B. Helmsley Charitable Trust)
3	Kedia 2017	Low risk	N=62 (29/33) (>18 yrs) 3x 150mg/day 8 wks	P: Mild-moderate UC (UCDAI btw 3 & 9) I: Curcumin (adjunct to 5-ASA) C: Placebo O: Remission (UCDAI ≤2, endoscopic Baron score 0/1), response (UCDAI decrease ≥3) S: India Funding: NR intervention/placebo supplied by Himalay drug company (India)
4	Banerjee 2017	Some concerns	N=47 (19/23)* (18-70 yrs) 2x 50 mg, 12 wks	P: Mild-moderate UC I: Curcumin (adjunct to 5-ASA) C: Placebo O: Endoscopic remission (score ≤1), clinical response (decrease Mayo score ≥3) S: India Funding: Asian Institute of Gastroenterology
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Characteristics of included reviews	Inflammatory bowel disease
Review ID	**Grammatikopoulou 2018**
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= data extracted

= data extracted in more recent SR

= control is an active intervention (data not extracted)

Characteristics of included reviews	Inflammatory bowel disease	
Review ID	**Iqbal 2018**	
Review reference	Iqbal U, Anwar H, Quadri AA. Use of Curcumin in Achieving Clinical and Endoscopic Remission in Ulcerative Colitis: A Systematic Review and Meta-analysis. American Journal of the Medical Sciences. 2018;356(4):350-6. https://dx.doi.org/10.1016/j.amjms.2018.06.023	
Review objective	To explare the role of curcumin in clinical and endoscopic remission in patients with UC	
Author affiliations	2 tertiary institutions in Pakistan & the US	
Source of funds	No external funding received.	
Declared interests of the review authors	Not specified	
Review method of analysis	Meta-analysis	Data analysis was performed using STATA (MP12.0 version).The 'Metan' command was used to obtain forest plots, OR, pooled OR and 95% confidence interval. Heterogeneity between the studies was calculated by calculating I2. Publication bias was calculated using a funnel plot
Inclusion criteria		
Study design	Randomised controlled trials	
Population	People with mild-moderate UC	
Intervention	Curcumin (as adjuvant to standard therapy)	
Comparator	Not specified	
Other	--	
Exclusion criteria		
Study design	--	
Population	--	
Intervention	--	
Comparator	--	
Other	Studies focused on prevention of relapse excluded. Data available to calculate OR with 95% CI etc.	
Date of documented search (month/year)	From inception up to December 2017	
Databases searched	MEDLINE, Pubmed, and Embase	
Was an non-English database searched?	No	
Were studies in a LOTE included?	No	

Characteristics of included reviews	Inflammatory bowel disease
Review ID	**Iqbal 2018**
Outcomes considered in the SR (list)	Clinical remission, clinical improvement, safety
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: *Authors summary* Not reported. Authors note: all included studies were weel performed wsith an RCT design, and assessed as high quality (Jadad)
Authors conclusions (key message)	This study demonstrates higher clinical remission rates when curcumin was used in combination with mesalamine to achieve remission in patients with UC.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	3 of 3 studies included in the SR met our PICO (UC, curcumin)

	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Lang 2015	Low risk	N=50 (26/24) (18-70 yrs) 3g/day 4 wks	P: Mild-moderate UC (SCCAI btw 5 & 12) I: Curcumin (adjunct to 5-ASA) C: Placebo O: Remission (SCCAI ≤2, Mayo endoscopic score ≤1), Response (SCCAI decrease ≥ 3), S: Israel, China , Cyprus Funding: Talpiot Medical Leadership grant (Sheba Medical Center, Leona M. and Harry B. Helmsley Charitable Trust)

Characteristics of included reviews	Inflammatory bowel disease			
Review ID	**Iqbal 2018**			
2	Singla 2014	Low risk	N=45 (23/22) (>18 yrs) 140 mg enema, 8 wks.	P: Mild-moderate UC I: Curcumin (adjunct to 5-ASA) C: Placebo O: Remission (UCDAI <3), response (UCDAI decrease ≥3), S: India
3	Banerjee 2017	Some concerns	N=47 (19/23)* (18-70 yrs) 2x 50 mg, 12 wks	P: Mild-moderate UC I: Curcumin (adjunct to 5-ASA) C: Placebo O: Endoscopic remission (score ≤1), clinical response (decrease Mayo score ≥3) S: India Funding: Asian Institute of Gastroenterology
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Characteristics of included reviews	Inflammatory bowel disease
Review ID	**Iqbal 2018**
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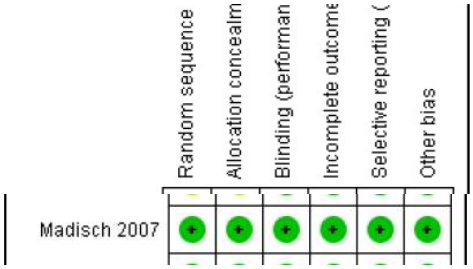
= data extracted

= data extracted in more recent SR

= control is an active intervention (data not extracted)

Characteristics of included reviews	Inflammatory bowel disease	
Review ID	**Kafil 2017**	
Review reference	Kafil TS, Nguyen TM, Patton PH, MacDonald JK, Chande N, McDonald JWD. Interventions for treating collagenous colitis. Cochrane Database of Systematic Reviews. 2017(11). 10.1002/14651858.CD003575.pub6	
Review objective	The primary objective was to assess the benefits and harms of treatments for patients with collagenous colitis.	
Author affiliations	Cochrane Collaboration. Canada	
Source of funds	No external funding received.	
Declared interests of the review authors	One author noted consulting and/or speaker fees from AbbVie, Janssen, Takeda, and Ferring; All of these financial activities are outside the submitted work.	
Review method of analysis	Meta-analysis	Meta-analysed using RevMan 5.3 software as per Cochrane handbook. Remission/repsonse treated as a dichotomous variable with 95% confidence intervals (CI). ITT data were extracted. Heterogeneity of included data was assessed by the χ2 test and the I2 statistic.
Inclusion criteria		
Study design	Randomised controlled trials	
Population	biopsy-proven collagenous colitis that is clinically active at the time of randomization	
Intervention	Any medical therapy	
Comparator	Placebo	
Other	--	
Exclusion criteria		
Study design	--	
Population	--	
Intervention	--	
Comparator	--	
Other	--	
Date of documented search (month/year)	up to 7 November 2016	
Databases searched	MEDLINE (Ovid); 2. EMBASE (Ovid); 3. Cochrane Central Register of Controlled Trials; and 4. The Cochrane IBD Inflammatory Bowel Disease and Functional Bowel Disorders Review Group Specialized Trials Register.	
Was an non-English database searched?	No	
Were studies in a LOTE included?	Not specified	

Characteristics of included reviews	Inflammatory bowel disease
Review ID	**Kafil 2017**
Outcomes considered in the SR (list)	Primary: number of patients with a clinical response expressed as a percentage of patients randomized (ITT). Clinical response was defined as decreased fecal frequency or stool weight or both. Secondary: histological response, effect on quality of life as measured by a validated instrument, and occurrence of adverse events.
Risk of bias of the included RCT studies as reported in the SR	*Tool used* Cochrane risk of bias tool *Authors summary* 
Authors conclusions (key message)	Twelve studies (476 participants) were identified. Four studies were high quality. One study assessing mesalamine and cholestyramine was judged to be low quality and the other studies were judged to be of unclear quality due to poor reporting of methods. Low quality evidence suggests that budesonide may be an effective therapy for active and inactive collagenous colitis. Due to small sample sizes and low study quality we are uncertain about the benefits and harms of therapy with Pepto-Bismol®, Boswellia serrata extract,mesalamine with or without cholestramine, prednisolone and probiotics. These agents and other therapies require further study.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	1 of 12 studies included in the SR met our PICO (Collagenous colitis, Boswellia)

	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Madisch 2007	Low risk	N = 31 (16/15) (18 to 80 years) 3x 400 mg/day; 6 weeks,	P: collagenous colitis (colonoscopy confirmed) I: Boswellia serrata extract C: placebo O: clinical remission (stool frequency < 3 per day); histological improvements, QoL, compliance, safety S: Germany, multicentre

Characteristics of included reviews	Inflammatory bowel disease
Review ID	**Kafil 2017**
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Characteristics of included reviews	Inflammatory bowel disease
Review ID	**Kafil 2017**
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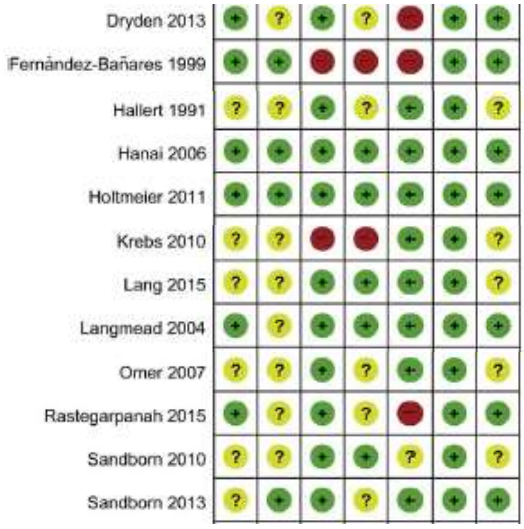
= data extracted

= data extracted in more recent SR

= control is an active intervention (data not extracted)

Characteristics of included reviews	Inflammatory bowel disease	
Review ID	**Kim 2017**	
Review reference	Kim S, Lee BH, Zhang X, Park JW, Lee S, Lee H. Adjunctive herbal medicine therapy for inflammatory bowel disease: A systematic review and meta-analysis. European Journal of Integrative Medicine. 2017;12:12-22. http://dx.doi.org/10.1016/j.eujim.2017.03.009	
Review objective	We have therefore performed a systematic review and meta-analysis to critically evaluate the effectiveness and safety of herbal medicine in both induction and maintenance of remission in UC and CD.	
Author affiliations	Several tertiary institutions in Korea & Australian Research Centre in Complementary and Integrative Medicine	
Source of funds	National Research Foundation of Korea (NRF) Grants funded by the Korean government (Ministry of Science, ICT & Future Planning, grant No. NRF-2014R1A1A2055507) and by the Korea Institute of Oriental Medicine (KIOM, grant No. K16121).	
Declared interests of the review authors	The authors declare that they have no competing interests.	
Review method of analysis	Meta-analysis	Meta-analysed using RevMan 5.1 software as per Cochrane handbook. Remission/repsonse treated as a dichotomous variable with 95% confidence intervals (CI). Random effects moddel. ITT data were extracted. Heterogeneity of included data was assessed by the $\chi 2$ test and the I2 statistic. Sensitivity analysis for bias also conducted.
Inclusion criteria		
Study design	Randomised controlled trials	
Population	IBD in adult patients (aged ≥ 18 years) who were diagnosed with UC or CD	
Intervention	herbal medicine (as adjuvant treatment)	
Comparator	placebo	
Other	trials aiming to induce remission or maintain remission both included	
Exclusion criteria		
Study design	--	
Population	--	
Intervention	--	
Comparator	RCTs comparing herbal medicine alone with conventional medicine or no treatment were excluded	
Other	only studies reporting on clinical outcomes of achieving or maintaining clinical remission were included	
Date of documented search (month/year)	inception to January 2017	
Databases searched	PubMed, EMBASE, CINAHL, AMED, CNKI (China National Knowledge Infrastructure), KMBASE (Korean Medical Database), NDSL (National Digital Science Library), and OASIS (Oriental Medicine Advanced Searching Integrated System).	
Was an non-English database searched? Were studies in a LOTE included?	Yes Yes	

Characteristics of included reviews	Inflammatory bowel disease
Review ID	**Kim 2017**
Outcomes considered in the SR (list)	Primary: percentage of patients who achieved or maintained clinical or comprehensive remission, depending on the disease state (i.e. active or quiescent). Secondary: disease activity index (DAI) and AEs associated with herbal medicine.
Risk of bias of the included RCT studies as reported in the SR	*Tool used* Cochrane risk of bias tool *Authors summary* 
Authors conclusions (key message)	In UC, herbal medicine was superior to placebo for clinical remission and maintaining remission. Traditional Chinese patent medicine with standard therapy reduced the risk of no comprehensive remission by 19% compared to standard therapy alone. In CD, however, the effect of herbal medicine was significant neither for inducing nor maintaining remission. Few serious adverse events were reported. An adjunctive herbal medicine compared to standard therapy appears effective with few adverse events in achieving and maintaining remission in UC, while there is a lack of supporting evidence for CD. Future high quality trials are warranted.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	12 of 29 RCTs (24 UC, 5 CD) included in the SR met our PICO. Kim 2017 reports the proportion of participants who *fail to achieve (or maintain)* remission. The data are inverted in our evidence synthesis to correlate with other reviews that report the proportion of participants who *achieve* or maintain remission.

	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Rastegarpanah 2015	High risk	N = 80 140 mg/day; 6 mos.	P: UC (quiescent) I: St Mary's thistle (adjunct to standard therapy) C: Placebo O: Remission induction S: Iran

Characteristics of included reviews	Inflammatory bowel disease			
Review ID	**Kim 2017**			
2	Lang 2015	Some concerns	N = 50 2x 1500 mg/day; 1 mos	P: UC (active) I: Curcumin (adjunct to mesalazine) C: Placebo O: Remission induction S: Israel, Hong Kong, Cyprus
3	Dryden 2013	High risk	N=20 2x 200 or 2x 400 mg/day, 8 wks.	P: UC (active) I: EGCG, epigallocatechin-3-gallate (adjunct to standard therapy) C: Placebo O: Remission induction S: USA
4	Sandbom 2013	Some concerns	N=224 2x 200 or 2x 400 mg/day, 8 wks.	P: UC (active) I: Andrographis extract (adjunct to mesalazine) C: Placebo O: Remission induction S: US, Canada, Germany, Romania, and Ukraine
5	Hanai 2006	Low risk	N=89 2g/day 24 wks	P: Quiescent UC I: Curcumin (adjunct to SZ or ML) C: Placebo O: Remission induction S: Japan
6	Langmead 2004	Low risk	N=44 2x 100 mL /day, 1 mos.	P: UC (active) I: Aloe vera gel (adjunct to std therapy) C: Placebo O: Remission induction S: UK
7	Hallert 1991	Some concerns	N=36 2x 4 g/day, 2 mos. crossover trial	P: Quiescent UC I: V-Siblin S granules (Psyllium husk) (adjunct to stdd therapy) C: Placebo O: Remission induction S: Sweden

Characteristics of included reviews	Inflammatory bowel disease			
Review ID	**Kim 2017**			
8	Fernández-Bañares 1999	High risk	N=69 2x 10 g/day, 12 mos.	P: Quiescent UC I: Plantago ovata (psyllium seeds) (adjunct to mesalazine) C: No intervention O: Remission maintenance S: Spain
9	Holtmeier 2011	Low risk	N=82 2x 400mg 2x/day, 12 mos.	P: Quiescent Crohn's I: Boswellia serrata resin extract C: Placebo O: Remission induction S: Germany
10	Sandborn 2010	Some concerns	N=101 (51/50) 1200mg/day, 2 mos.	P: Crohn's (active) I: Andrographis extract (adjunct to std therapy) C: Placebo O: Remission induction S: US, Ukraine
11	Omer 2007	Some concerns	N=40 3x 400mg 2x/day, 2.5 mos.	P: Crohn's (active) I: SedaCrohn (Wormwood [Artemisia absinthium] powder) (adjunct to corticosteroids) C: Placebo O: Remission induction S: Germany
12	Krebs 2012	High risk	N=20 3x 400mg 2x/day, 1.5 mos.	P: Crohn's (active) I: SedaCrohn (Wormwood [Artemisia absinthium] powder) (adjunct to corticosteroids) C: No intervention O: Remission induction S: Germany
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= data extracted

= data extracted in more recent SR

= control is an active intervention (data not extracted)

Characteristics of included reviews	Inflammatory bowel disease
Review ID	**Langshorst 2015**
Review reference	Langhorst J, Wulfert H, Lauche R, Klose P, Cramer H, Dobos GJ, et al. Systematic review of complementary and alternative medicine treatments in inflammatory bowel diseases. Journal of Crohn's & colitis. 2015;9(1):86-106. https://dx.doi.org/10.1093/ecco-jcc/jju007
Review objective	a systematic review for Complementary and Alternative Medicine [CAM] as defined by the National Institute of Health in Inflammatory Bowel Disease [IBD], ie Crohn's disease [CD] and ulcerative colitis [UC], with the exception of dietary and nutritional supplements, and manipulative therapies.
Author affiliations	University of Duisburg-Essen, Germany
Source of funds	This review was supported by the Rut- und Klaus-Bahlsen-Foundation
Declared interests of the review authors	The authors declare that they have no competing interests.
Review method of analysis	Descriptive — Authors any provide narrative ddescription of the results but do not provide any
Inclusion criteria	
Study design	Controlled clinical trials, RCTs , randomized controlled cross-over trials, cluster randomized trials.
Population	Patients diagnosed with ulcerative colitis and/or Crohn's disease were eligible, regardless of age
Intervention	CAM therapies according to the NIH definition, including: herbs, botanicals, or helminthes; mind/body intervention, mindfulness-based stress reduction, comprehensive lifestyle modification programs hypnosis, yoga, tai chi or qigong, fasting, traditional Chinese medicine interventions, ayurvedic, anthroposophic or homeopathic therapies, balneotherapy, acupuncture, acupressure and cataplasm
Comparator	Any
Other	Studies reporting induction or maintenance of remission, disease activity or symptom severity, quality of life, or psychological variables & Safety.
Exclusion criteria	
Study design	--
Population	--
Intervention	except psychotherapy, Massages and manipulative therapies, probiotics or omega-3 fatty acids, fish oils, or essential oils as well as vitamins and minerals
Comparator	--
Other	--
Date of documented search (month/year)	Inception through to 12 March 2014
Databases searched	Pubmed/MEDLINE, Scopus, Cochrane central register of controlled trials and PsycInfo
Was an non-English database searched? Were studies in a LOTE included?	No
	Yes — Studies were eligible only if they were published as full papers, and only English or German language publications were considered eligible

Characteristics of included reviews	Inflammatory bowel disease			
Review ID	**Langshorst 2015**			
Outcomes considered in the SR (list)	not specified			
Risk of bias of the included RCT studies as reported in the SR	*Tool used* Cochrane Musculoskeletal group	*Authors summary* Specifc details provided in the review. Scored out of max 12 points (score 6 or more considered low risk)		
Authors conclusions (key message)				
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	12 of 29 RCTs (10 UC, 2 CD) included in the SR met our PICO			
	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Gerhardt 2001	12/12 Low risk	N=102 (50/52) 3x 6 g/day, 8 weeks	P: Active Crohn's I: Boswellia extract C: Mesalazine O: CDAI, Remission induction, AEs S: ?

Characteristics of included reviews	Inflammatory bowel disease			
Review ID	**Langshorst 2015**			
2	Holtmeier 2010	10/12 Low risk	N=82 (42/40) 6x 400mg /day, 12 mos.	P: Quiescent Crohn's I: Boswellia serrata resin extract C: Placebo O: Remission maintenance, time to relapse, CDAI, IBDQ, AEs S: Germany
3	Krebs 2012	6/12 Low risk	N=20 (10/10) 9x 250mg/day, 1.5 mos.	P: Crohn's (active) I: SedaCrohn (Wormwood [Artemisia absinthium] powder) (adjunct to corticosteroids) C: No intervention O: TNF-a, CDAI improvement, IBDQ, HAM-D S: Germany
4	Omer 2007	11/12 Low risk	N=40 (20/20) 2x 250mg/day, 10 weeks	P: Crohn's (active) I: SedaCrohn (Wormwood [Artemisia absinthium] powder) (adjunct to corticosteroids) C: Placebo O: CDDAI, IBDQ, HAM-D, VAS (wellbeing) S: Germany
5	Sandbom 2013	12/12 Low risk	N=224 (75/74/75) 3x 1200 or 3x 1800 mg/day, 8 wks.	P: UC (active) I: Andrographis extract (adjunct to mesalazine) C: Placebo O: Clinical response/remission, mucosal healing, MAYo score, AEs S: US, Canada, Germany, Romania, and Ukraine
6	Tang 2011	10/12 Low risk	N=120 (60/60) 3x 400 mg/day, 8 wks.	P: UC (active) I: Andrographis extract C: mesalazine O: Clinical efficacy, Endoscopic efficacy, Histologic efficacy S: US, Canada, Germany, Romania, and Ukraine
7	Hanai 2006	10/12 Low risk	N=89 (45/44) 2g/day, 24 wks	P: Quiescent UC I: Curcumin (adjunct to SZ or ML) C: Placebo O: CAI, Endoscopic index, Recurrence, AEs S: Japan

Characteristics of included reviews	Inflammatory bowel disease			
Review ID	**Langshorst 2015**			
8	Singla 2014	10/12 Low risk	N=45 (23/22) (>18 yrs) 140 mg enema, 8 wks.	P: Mild-moderate UC I: Curcumin (adjunct to 5-ASA) C: Placebo O: Remission (UCDAI <3), response (UCDAI decrease ≥3), Endoscopic activity, AEs S: India
9	Fernández-Bañares 1999	8/12 Low risk	N=102 (35/30/37) 20 g/day, 12 mos.	P: Quiescent UC I: Plantago ovata (psyllium seeds) (alone OR as adjunct to mesalazine) C: No intervention O: Remission maintenance, fatty acid production, AEs S: Spain
10	Langhorst 2013	12/12 Low risk	N=97 (48/49) 12 mos.	P: UC I: Herbal combination (100 mg myrrh, 70 mg chamomile, 50 mg coffee charcoal) C: mesalazine O: CAI, modified CAI, Enodscopic inedx, Fecal markers, oxidative/inflammatory biomarkers, AEs S: UK
11	Langmead 2004	10/12 Low risk	N=44 (30/14) 2x 100 mL /day, 1 mos.	P: UC (active) I: Aloe vera gel (adjunct to std therapy) C: Placebo O: Remission/improvement (SCCAI), Physical global assessment, IBDQ-9, Histology, biomarkers, AEs S: UK
12	Rastegarpanah 2015	4/12 High risk	N=80 (42/38) 140 mg/day; 6 mos.	P: UC (quiescent) I: St Mary's thistle (adjunct to standard therapy) C: Placebo O: Hb, ESR, symptoms [pain, diarrhoea, fatigue, anorexia, other), DAI, AEs S: Iran
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= data extracted

= data extracted in more recent SR

= control is an active intervention (data not extracted)

Characteristics of included reviews	Irritable bowel syndrome	
Review ID	**Black 2020**	
Review reference	Black CJ, Yuan Y, Selinger CP, Camilleri M, Quigley EMM, Moayyedi P, et al. Efficacy of soluble fibre, antispasmodic drugs, and gut-brain neuromodulators in irritable bowel syndrome: a systematic review and network meta-analysis. Lancet Gastroenterol Hepatol. 2020;5(2):117-31.	
Review objective	To compare and rank the efficacy of traditional therapies in patients with IBS to help inform clinical decisions.	
Author affiliations	Six authors are affiliated with tertiary institutions in UK, Canada and USA, and one author is affiliated with a research centre in USA.	
Source of funds	No funding source for this study	
Declared interests of the review authors	Four authors have declared conflict of interest.	
Review method of analysis	Meta-analysis	Network meta-analysis: We generated comparison-adjusted funnel plots with Stata (version 14.0) to evaluate publication bias and small-study bias for all available treatment comparisons versus placebo. For each treatment, we generated a pooled RR with 95% CIs to summarise the effect of each comparison tested using a random effects model as a conservative estimate
Inclusion criteria		
Study design	RCTs	
Population	>18 with IBS	
Intervention	Ispaghula husk, antispasmodic drugs, peppermint oil, or gut-brain neuromodulator	
Comparator	Placebo or any drugs of interest	
Other	First period of cross over trials were included if they provided efficacy data prior to cross-over. Minimum of 4 weeks and maximum of 12 weeks duration.	
Exclusion criteria		
Study design	Non-RCTs	
Population	Not specified	
Intervention	Not specified	
Comparator	Not specified	
Other		
Date of documented search (month/year)	18 Aug 2019	
Databases searched	Medline, Embase, Cochrane Library, ClinicalTrials.gov, a manual search of conference proceedings (Digestive Disease Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week)	
Was an non-English database searched? Were studies in a LOTE included?	No	
	Yes	No language restrictions were applied, and non-English studies were translated.
Outcomes considered in the SR (list)	Treatment efficacy (% patients who failed to achieve imporvement in global IBS symtpoms) & % who failed to acheve improvement in abdominal pain	

Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Black 2020**
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane risk of bias tool *Authors summary*

Therapy used	Study	Method of Generation of Randomisation Schedule	Method of Concealment of Treatment Allocation	Blinding	Evidence of Incomplete Outcomes Data	Evidence of Selective Reporting of Outcomes
Ispaghula husk	Ritchie 1979 (1)	Low	Unclear	Low	Low	Low
	Longstreth 1981 (3)	Unclear	Unclear	Low	High	Low
	Arthurs 1983 (4)	Unclear	Unclear	Low	High	Low
	Nigam 1984 (2)	Unclear	Unclear	Unclear	Low	Low
	Prior 1987 (5)	Unclear	Unclear	Low	Low	Low
	Jalihal 1990 (6)	Unclear	Unclear	Low	Low	Low
	Bijkerk 2009 (7)	Low	Low	Low	Low	Low
Peppermint oil	Lech 1988 (26)	Unclear	Unclear	Low	Low	Low
	Liu 1997 (27)	Unclear	Unclear	Low	High	Low
	Capanni 2005 (28)	Low	Unclear	Low	Low	Low
	Cappello 2007 (29)	Low	Unclear	Low	High	Low
	Merat 2010 (30)	Low	Low	Low	Low	Low
	Cash 2016 (32)	Low	Low	Low	Low	Low
	Mosaffa-Jahromi 2016 (31)	Low	Unclear	Low	Low	Low
	Weerts 2019 (33)	Low	Low	Low	Low	Low

Authors conclusions (key message)	Peppermint oil was ranked first for efficacy when global symptoms was used as the outcome and when improvements in abdominal pain were used as the endpoint of interest, peppermint oil was significantly more effcacious than placebo after 4-12 weeks. Psyllium was ranked first in terms of total number of adverse events.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	15 of 51 studies included in the SR met our PICO (IBS, peppermint oil, psyllium husk) 1376 N participants in studies that met our PICO

	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Longstreth 1981	High risk (incomplete outcome data)	N=77 6.4g, 3x / day 8 weeks	P: IBS I: Ispaghula husk C: Placebo O: Global improvement S: Secondary care, US
2	Arthurs 1983	High risk (incomplete outcome data)	N=78 6 g / day 4 weeks	P: IBS I: Ispaghula husk C: Placebo O: Global improvement S: Secondary care, Ireland

Characteristics of included reviews	Irritable bowel syndrome			
Review ID	**Black 2020**			
3	Prior 1987	Low risk	N=80 6.4 g 3x / day 12 weeks	P: IBS I: Ispaghula husk C: Placebo O: Global improvement, pain S: Tertiary care, UK
4	Jalihal 1990	Low risk	N=20 30 g / day 4 weeks	P: IBS I: Ispaghula husk C: Placebo O: Global improvement S: Secondary care, India
5	Bijkerk 2009	Low risk	N=178 10 g 2x / day 12 weeks	P: IBS I: Ispaghula husk C: Placebo O: Addequate relief in pain/discomfort, S: Primary care, Netherlands
6	Ritchie 1979	Unclear risk (allocation concealment)	N=36 7 g once daily 12 weeks	P: IBS I: Ispaghula husk OR Hyoscine (10mg 4x daily) C: Placebo O: Global improvement S: Tertiary care, UK
7	Nigam 1984	Unclear risk (randomisation, allocation concealment, blinding)	N=84 7 g once daily 12 weeks	P: IBS I: Ispaghula husk OR Hyoscine (10mg 4x daily) OR Amitriptyline (12.5 mg once daily) C: Placebo O: Global improvement S: Secondary care, India
8	Lech 1988	Unclear risk (randomisation, allocation concealment)	N=47 200mg 3x daily 4 weeks	P: IBS I: Peppermint oil C: Placebo O: Global improvement S: Secondary care, Denmark
9	Liu 1997	High risk (incomplete outcome data)	N=110 187mg 3-4 x daily 4 weeks	P: IBS I: Peppermint oil C: Placebo O: Abdominal pain S: Secondary care, Taiwan
10	Capanni 2005	Unclear risk (allocation concealment)	N=178 2 capsules 3 x daily (dose unknown) 12 weeks	P: IBS I: Peppermint oil C: Placebo O: Global improvement S: Secondary care, Italy

Characteristics of included reviews	Irritable bowel syndrome			
Review ID	**Black 2020**			
11	Capello 2007	High risk (incomplete outcome data)	N=57 450 mg 2 x daily 4 weeks	P: IBS I: Peppermint oil C: Placebo O: Global improvement (>50% from baseline) S: Secondary care, Italy
12	Merat 2010	Low risk	N=90 187 mg 3 x daily 8 weeks	P: IBS I: Peppermint oil C: Placebo O: Absence of pain or discomfort S: Tertiary care, Iran
13	Cash 2016	Low risk	N=72 180 mg 3 x daily 4 weeks	P: IBS I: Peppermint oil C: Placebo O: Global improvement, Abdominal pain/discomfort S: Secondary care, US
14	Mosaffa-Jahromi 2016	Unclear risk (allocation concealment)	N=80 187 mg 3 x daily 4 weeks	P: IBS I: Peppermint oil C: Placebo O: Absence of Symptoms S: Tertiary care, Iran
15	Weerts 2019	Low risk	N=189 182 mg 3 x daily 8 weeks	P: IBS I: Peppermint oil C: Placebo O: Global improvement, Abdominal pain (>30% improvement) S: Secondary & tertiary care, Netherlands
16	--			
17	--			
18	--			

Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Black 2020**
19	--
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Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Black 2020**
27	--
28	--
29	--
30	--
	= data extracted
	= data extracted in more recent SR
	= control is an active intervention (data not extracted)

Characteristics of included reviews	Irritable bowel syndrome	
Review ID	**Hawrelak 2020**	
Review reference	Hawrelak JA, Wohlmuth H, Pattinson M, Myers SP, Goldenberg JZ, Harnett J, et al. Western herbal medicines in the treatment of irritable bowel syndrome: A systematic review and meta-analysis. Complement Ther Med. 2020;48:102233.	
Review objective	To evaluate the efficacy of Western herbal medicines in the treatment of irritable bowel syndrome (IBS).	
Author affiliations	10 authors are affiliated with 12 tertiary institutions in Australia, Canada, USA and South Africa. One authors is affilated with a research institution in USA. One author is affilated with healthcare facility in Australia.	
Source of funds	None declared	
Declared interests of the review authors	One author is an employee of Integria Health care, Australia. Another author received donations from Blackn	
Review method of analysis	Meta-analysis	Meta-analysed using RevMan 5.3 software as per Cochrane handbook. Remission/repsonse treated as a dichotomous variable with 95% confidence intervals (CI). Random effects moddel. ITT data were extracted. Heterogeneity of included data was assessed by the $\chi 2$ test and the I2 statistic. Sensitivity analysis for bias also conducted.
Inclusion criteria		
Study design	Placebo controlled trials	
Population	IBS	
Intervention	Western herbs	
Comparator	Placebo	
Other	Participants were included with diagnosis criteria i.e. Manning, Kruis, Rome I-III or had clinical symptoms of IBS	
Exclusion criteria		
Study design	Restricted to placebo controlled trials	
Population	Not specified	
Intervention	Not specified	
Comparator	Not specified	
Other		
Date of documented search (month/year)	Jul-17	
Databases searched	Medline, CINAHL, AMED, Embase, Cochrane library, GreenFILE, Health source:Nursing/ Academic Edition	
Was an non-English database searched?	Not specified	
Were studies in a LOTE included?	Yes	No language restrictions. For studies written in non-English languages, translations of papers were obtained.
Outcomes considered in the SR (list)	Global imporvement, quality of life, adequate relief of symtpoms, changes in individual symptoms, adverse events	

Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Hawrelak 2020**

Risk of bias of the included RCT studies as reported in the SR

Tool used

Cochrane risk of bias tool

	Random Sequen	Allocation conce	Blinding of partic	Blinding of outco	Incomplete outc	Selective reporti	Other bias	Overall Risk of
Aloe vera								
Davis et al[26]	?	+	+	+	?	?	?	?
Hutchings et al[27]	?	?	+	+	-	+	+	?
Storsrud et al[28]	+	+	+	+	?	+	+	+
Peppermint Essential Oil								
Rees et al[31]	?	?	+	+	+	+	+	+
Evans et al[32]	?	?	?	?	?	+	+	?
Dew et al[33]	?	?	+	+	+	+	+	+
Nash et al[34]	?	?	+	+	-	+	+	?
Lawson et al[35]	?	?	+	+	?	+	+	+
Lech et al[36]	?	?	-	-	?	?	?	?
Weiss & Koelbl[37]	?	?	?	+	-	-	?	?
Wildgrube[38]	?	?	?	?	+	+	+	?
Carling et al[39]	?	?	?	?	+	+	+	?
Schneider & Otten[40]	?	?	?	?	+	+	?	?
Liu et al[41]	-	-	?	-	-	?	-	-
Kline et al[42]	-	-	+	?	-	?	-	-
Capanni et al[43]	+	?	?	?	+	+	?	?
Cappello et al[44]	-	?	+	?	+	?	?	?
Merat et al[45]	?	-	+	+	-	?	?	?
Alam et al[46]	?	-	+	?	-	?	-	?
Cash et al[47]	+	-	+	?	+	?	?	?
Mosaffa-Jahromi et al[48]	+	?	+	+	+	?	-	+

Other Western Herbal Medicines								
Pedersen et al[49]	?	?	?	?	+	+	+	?
Madisch et al[50]	+	+	+	+	+	?	?	+
Brinkhaus et al[51]	+	-	+	?	+	?	?	?
Vejdani et al[52]	-	-	+	-	+	-	-	-
Mangel & Chaturvedi[53]	+	?	+	?	+	?	?	?
Saito et al[54]	+	+	+	+	+	?	?	+
Bortolotti & Porta[55]	-	-	+	?	-	?	-	-
Tilburg et al[56]	+	+	+	-	+	?	-	?
Brown et al[57]	?	+	+	?	+	?	-	?
Mosaffa-Jahromi et al[48]	+	?	+	+	+	?	-	+
Portincasa et al[58]	+	?	?	?	+	?	?	?

Authors summary

Overall, the authors described the risk of bias was varied among the 31 studies. Two peppermint studies had a high risk of bias, 12 studies had and unclear risk of bias and 4 studies were low risk. Aloe had 2 studies with unclear risk of bias and 1 low risk of bias. Two studies investigating other Western herbs were high risk of bias.

Authors conclusions (key message)

Data suggests WHM may provide a relief of IBS symptoms. Peppermint appears effcacious and well tolerated in short term management of IBS with a low number needed to treat (NNT) and good benefit-to-harm ratio. Aloe also shows beneficial effects from pooled data. Combinations of WHM have shown efficacy in well-designed clinical trials for IBS.

Characteristics of eligible RCTs meeting the inclusion criteria for this Overview

30 of 33 studies included in the SR met our PICO

2040 N participants in studies that met our PICO

	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Davis 2006	Unclear risk	N=58 50 mL 4 x daily 4 weeks	P: IBS I: Aloe vera juice C: Placebo O: IBS severity scoring, pain, distention, bowel satifaction, QoL, global improvement S: ?
2	Hutchings 2011	High risk (incomplete outcome data)	N=110 60 mL 2 x daily 20 weeks	P: IBS I: Aloe vera juice C: Placebo O: GI Symptom rating scale, QoL S?

Characteristics of included reviews	Irritable bowel syndrome			
Review ID	**Hawrelak 2020**			
3	Storsrud 2015	Unclear risk (incomplete outcome data)	N=68 250 mg 2 x daily 4 weeks	P: IBS I: Aloe vera juice C: Placebo O: IBS severity scoring, HADS, Addeuqte relief, bowel transit time S: ?
4	Rees 1979	Unclear risk (randomisation, allocation concealment)	N=18 0.2 mL 3-6 x daily 3 weeks	P: IBS I: Peppermint oil C: Placebo O: Changes in abdominal symptoms, stool frequency S: ?
5	Evans 1982	Unclear risk	N=20 0.2 mL 3-6 x daily 2 weeks not included in meta-analysis	P: IBS I: Peppermint oil C: Placebo O: Changes in abdominal symptoms, stool frequency S: ?
6	Dew 1984	Unclear risk (randomisation, allocation)	N=29 0.2 mL 3-6 x daily 2 weeks	P: IBS I: Peppermint oil C: Placebo O: Changes in abdominal symptoms, stool frequency S: ?
7	Nash 1986	High risk (incomplete outcome data)	N=41 400 mg 3 x daily 2 weeks	P: IBS I: Peppermint oil C: Placebo O: Changes in IBS symptoms S: ?
8	Lawson 1988	Unclear risk	N=25 200 mg 3 x daily 4 weeks not included in meta-analysis	P: IBS I: Peppermint oil C: Placebo O: Changes in abdominal symptoms (pain, distension, bloating, diarrhoea, consitpation, incomplete evacuation, gas, mucus), stool frequency S: ?
9	Lech 1988	High risk (blinding)	N=47 200 mg 3 x daily 4 weeks	P: IBS I: Peppermint oil C: Placebo O: Changes in IBS symptoms, global improvement, stool frequency/consistency S: ?
10	Weiss and Koelbl 1988	High risk (incomplete outcome data, selective reporting)	N=60 200 mg 3 x daily 3 weeks	P: IBS I: Peppermint oil C: Placebo O: Changes in IBS symptoms S: ?

Characteristics of included reviews	Irritable bowel syndrome			
Review ID	**Hawrelak 2020**			
11	Wildgrube 1988	Unclear risk	N=40 ? 2 weeks not included in meta-analysis	P: IBS I: Peppermint oil C: Placebo O: Changes in abdominal symptoms (pain, distension, bloating, diarrhoea, consitpation, incomplete evacuation, gas, mucus) S: ?
12	Carling 1989	Unclear risk	N=40 200 mg 3-6 x daily 2 weeks	P: IBS I: Peppermint oil C: Placebo O: Changes in IBS symptoms, stool frequency S: ?
13	Schneider 1990	Unclear risk	N=60 ? 6 weeks not included in meta-analysis	P: IBS I: Peppermint oil C: Placebo O: Changes in abdominal symptoms (pain), global assessment, stool frequency S: ?
14	Liu 1997	High risk	N=110 200 mg 3-6 x daily 2 weeks	P: IBS I: Peppermint oil C: Placebo O: Changes in IBS symptoms (pain, distension, bloating, diarrhoea, consitpation, incomplete evacuation, gas, mucus), stool frequency S: ?
15	Kline 2001	High risk	N=42 100 to 200 mg 3 x daily 4 weeks	P: IBS I: Peppermint oil C: Placebo O: Changes in IBS symptoms S: ?
16	Capanni 2005	Unclear risk	N=178 400 mg 3 x daily 12 weeks	P: IBS I: Peppermint oil C: Placebo O: Changes in IBS symptoms S: ?
17	Cappello 2007	High risk (randomisation)	N=57 450 mg 2 x daily 4 weeks	P: IBS I: Peppermint oil C: Placebo O: Changes in IBS symptoms (pain, distension, bloating, diarrhoea, consitpation, incomplete evacuation, gas, mucus) S: ?
18	Merat 2009	High risk (allocation, incomplete outcome data)	N=90 187 mg 3 x daily 8 weeks not included in meta-analysis	P: IBS I: Peppermint oil C: Placebo O: Changes in abdominal symptoms (pain/discomfort),QoL S: ?

Characteristics of included reviews	Irritable bowel syndrome			
Review ID	**Hawrelak 2020**			
19	Alam 2013	High risk (allocation, incomplete outcome data)	N=74 2 mL 3 x daily 6 weeks not included in meta-analysis	P: IBS I: Peppermint oil C: Placebo O: Changes in abdominal symptoms (pain/discomfort) S: ?
20	Cash 2016	High risk (allocation concealment)	N=72 180 mg 3 x daily 4 weeks not included in meta-analysis	P: IBS I: Peppermint oil C: Placebo O: IBS symtpom score S: ?
21	Mosaffa-Jahromi 2016	High risk (other)	N=80 187 mg 3 x daily 4 weeks	P: IBS I: Peppermint oil OR Curcumin/anise essential oil C: Placebo O: Changes in IBS symptoms (pain, bloating) S: ?
22	Pedersen 1998	Unclear risk	N=59 ? 8 weeks	P: IBS I: Appital (a fixed combination of Capsicum annuum oil, Gentiana lutea root, Carum carvi essential oil, and Curcuma longa rhizome) C: Placebo O: Global symptoms score S: ?
23	Madisch 2004	Unclear risk (selective reporting, other)	N=208 20 drops 3 x daily 4 weeks	P: IBS I: STW-5 OR STW-5-II (a fixed combination of WHM) OR Iberis amara C: Placebo O: Global symptoms score, abdominal pain scale S: ?
24	Brinkhaus 2005	High risk (allocation concealment)	N=106 20 mg 3 x daily 500 mg 3 x daily 18 weeks	P: IBS I: Curcuma OR Fumaria officinalis C: Placebo O: Change in pain/dostention, Global symptoms score, Psychological stress S: ?
25	Vejdani 2006	High risk	N=32 30 drops 3 x daily 8 weeks	P: IBS I: Carmint (fixed combination Melissa officinalis, Mentha spicata, and Coriandrum sativum) C: Placebo O: Change in pain/discomfort, bloating, number of days with pain/bloating S: ?
26	Saito 2010	Unclear risk (selective reporting, other)	N=70 450 mg 2 x daily 12 weeks	P: IBS I: Hypericum perforatum C: Placebo O: Change in symptoms score, adequate relief, QoL S: ?

Characteristics of included reviews	Irritable bowel syndrome			
Review ID	**Hawrelak 2020**			
27	Bortolotti 2011	High risk	N=50 150 mg 4 x daily 6 weeks	P: IBS I: Hypericum perforatum C: Placebo O: Change in abdominal pain, bloating, defecation frequency S: ?
28	Tilburg 2014	High risk (blinding, other)	N=45 1 or 2 g daily 4 weeks	P: IBS I: Zingiber officinale C: Placebo O: Change in IBS severity scale, adequate relief S: ?
29	Brown 2015	High risk (other)	N= 150 mg, 470 mg, 0.2 mL 2 weeks	P: IBS I: A blend of Schinopsis lorentzii (not on ListA), Horse chestnut, and peppermint oil C: Placebo O: Change in bloating, constipation frequency S: ?
30	Portincasa	Unclear risk	N=121	No details provided
	= data extracted			
	= data extracted in more recent SR			
	= control is an active intervention (data not extracted)			

Characteristics of included reviews	Irritable bowel syndrome	
Review ID	**Tan 2020**	
Review reference	Tan N, Gwee KA, Tack J, Zhang M, Li Y, Chen M, et al. Herbal medicine in the treatment of functional gastrointestinal disorders: A systematic review with meta-analysis. J Gastroenterol Hepatol. 2020;35(4):544-56.	
Review objective	To investigate current evidence evaluating the efficacy and safety of herbal medicines in treating functional gastrointestinal disorders (FGID).	
Author affiliations	Five authors affiliated with tertiary institutions in China, one author affiliated with tertiary instititon in Singapore, one author affiliated with tertiary institutions in Belgium.	
Source of funds	Not reported	
Declared interests of the review authors	None declared	
Review method of analysis	Meta-analysis	Meta-analysed using RevMan 5.3 software as per Cochrane handbook. Remission/repsonse treated as a dichotomous variable with 95% confidence intervals (CI). Random effects moddel. ITT data were extracted. Heterogeneity of included data was assessed by the $\chi 2$ test and the I2 statistic.
Inclusion criteria		
Study design	double blinded RCT	
Population	Functional dyspepsia, IBS, Functional Constipation	
Intervention	herbal medicine	
Comparator	placbo, routine western medicine, herbal medicine	
Other		
Exclusion criteria		
Study design	Not specified	
Population	Not specified	
Intervention	Not specified	
Comparator	Not specified	
Other	Limited information about diagnostic criteria, intervention, outcomes (must be defined), duplicated study data, full text cannot be retrieved	
Date of documented search (month/year)	to July 2019	
Databases searched	PubMed, EMbase, Cochrane Library	
Was an non-English database searched?	No	
Were studies in a LOTE included?	No	Language restrictions were applied
Outcomes considered in the SR (list)	Effective rate (Symptom improvement, symtpom-free rate)	

Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Tan 2020**

Risk of bias of the included RCT studies as reported in the SR

Tool used: Cochrane risk of bias tool

Authors summary

	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	other bias	Overall
Cappello G, 2007 (Italy) [36]	U	L	U	U	U	U	U
Davis K, 2006 (UK) [38]	L	L	U	U	U	H	H
Liu J, 1997 (China) [42]	U	L	U	U	U	U	U
Mosaffa-Jahromi M, 2016 (Iran) [45]	L	L	L	L	L	L	L
van Tilburg MAL, 2014 (USA) [51]	L	L	U	L	L	L	U
Portincasa P, 2016 (Italy) [46]	U	L	U	L	L	L	U
Vejdani R, 2006 (Iran) [52]	U	L	U	L	L	U	U
Lauche R, 2016 (Germany) [40]	L	L	L	L	L	L	L
Sallon S, 2002 (Israel) [48]	U	L	U	L	L	L	U
Merat S, 2010 (Iran) [44]	L	L	U	L	L	U	U
Ko S, 2013 (Korea) [39]	U	L	L	U	U	L	U
Storsrud S, 2015 (Sweden) [49]	L	L	U	L	L	L	U
Xiaolan SYTJ, 2013 (China) [55]	U	L	U	L	L	L	U
Tang X, 2018 (China) [50]	L	L	U	L	L	L	U
Wang G, 2006 (China) [53]	L	L	U	L	L	L	U
Wang Y, 2018 (China) [54]	L	L	L	L	L	L	L
Leung WK, 2006 (China) [41]	L	L	U	L	L	L	U
Saito YA, 2010 (USA) [47]	L	L	U	L	L	H	H

Of the nine studies that met our PICO, only one was considered to have a low RoB, six RCTs were assessed as unclear RoB, and two RCTs were judged to be high RoB.

Authors conclusions (key message)

Herbal medicines to treat (FGID) seem well tolerated but requires better quality trials to assess the long-term effectiveness and safety are needed.

Characteristics of eligible RCTs meeting the inclusion criteria for this Overview

9 of 50 RCTs included in the SR met our PICO

739 N participants in studies that met our PICO (enrolled)

	Study ID	*Summary RoB*	*Study design features (PICOS)*
1	Cappello 2007	Unclear risk	N=57 450 mg 2 x daily 4 weeks P: IBS I: Peppermint oil C: Placebo O: Changes in IBS symptoms (pain, distension, bloating, diarrhoea, consitpation, incomplete evacuation, gas, mucus) S: Italy
2	Davis 2006	High risk	N=58 50 mL 4 x daily 4 weeks P: IBS I: Aloe vera juice C: Placebo O: IBS severity scoring, pain, distention, bowel satifaction, QoL, global improvement S: UK

Characteristics of included reviews	Irritable bowel syndrome			
Review ID	**Tan 2020**			
3	Liu 1997	Unclear risk	N=110 200 mg 3-6 x daily 2 weeks	P: IBS I: Peppermint oil C: Placebo O: % responders in IBS symptoms (pain, distension, bloating, diarrhoea, consitpation, incomplete evacuation, gas, mucus), stool frequency S: China
4	Mosaffa-Jahromi 2016	Low risk	N=120 (40/40/40) 187 mg 3 x daily 4 weeks	P: IBS I: Peppermint oil OR Curcumin/anise essential oil C: Placebo O: Changes in IBS symptoms (pain, bloating) S: Iran
5	van Tilburg 2014	Unclear risk (detection)	N=45 1 or 2 g daily 4 weeks	P: IBS I: Zingiber officinale C: Placebo O: Change in IBS severity scale, adequate relief S: USA
6	Portincasa 2016	Unclear risk	N=121 ? 4 weeks	P: IBS I: Curcumin+ fennel oil C: Placebo O: Complete symptom free rate, change in IBS-SSS, symptom improvement (individual items), QOL S: USA
7	Merat 2010	Unclear risk	N=90 187 mg 3 x daily 8 weeks not included in meta-analysis	P: IBS I: Peppermint oil C: Placebo O: Changes in abdominal symptoms (pain/discomfort),QoL S: Iran
8	Storsrud 2015	Unclear risk	N=68 250 mg 2 x daily 4 weeks	P: IBS I: Aloe vera juice C: Placebo O: Response (>50 points), IBS severity scoring, HADS S: Sweden
9	Saito 2010	High risk	N=70 450 mg 2 x daily 12 weeks	P: IBS I: Hypericum perforatum C: Placebo O: Change in symptoms score, adequate relief, QoL S: USA
10	--			

Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Tan 2020**
11	--
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Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Tan 2020**
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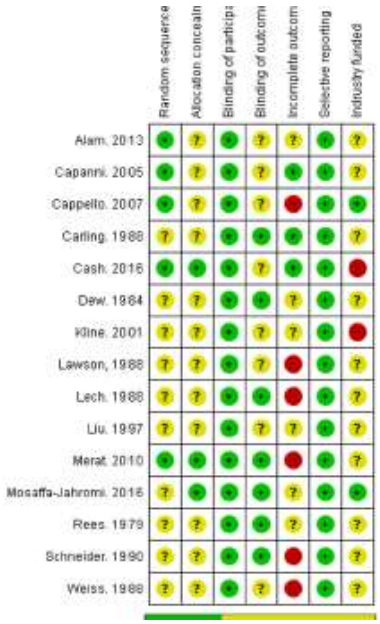
Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Tan 2020**
27	--
28	--
29	--
30	--
	= data extracted
	= data extracted in more recent SR
	= control is an active intervention (data not extracted)

Characteristics of included reviews	Irritable bowel syndrome	
Review ID	**Alammar 2019**	
Review reference	Alammar N, Wang L, Saberi B, Nanavati J, Holtmann G, Shinohara RT, et al. The impact of peppermint oil on the irritable bowel syndrome: a meta-analysis of the pooled clinical data. BMC Complement Altern Med. 2019;19(1):21. PROSPERO: CRD42016050917	
Review objective	To determine the effect of peppermint oil (PO) in reducing the abdominal pain and global symptoms of irritable bowel syndrome and to evaluate the possible side effects of PO as compared to the placebo.	
Author affiliations	Five authors are affliated with tertiary institutions in USA, Saudi Arabia, Australia, one author affiliated with Mount Sinai Hospital, USA.	
Source of funds	None declared	
Declared interests of the review authors	One author is an Associate Editor of BMC Complementary and Alternative Medicine	
Review method of analysis	Meta-analysis	Meta-analysed using RevMan 5.3 software as per Cochrane handbook. Remission/repsonse treated as a dichotomous variable with 95% confidence intervals (CI). Random effects moddel. ITT data were extracted. Heterogeneity of included data was assessed by the $\chi 2$ test and the I2 statistic. We planned to use funnel plots and Egger's test to examine publication bias if the number of studies for an outcome is larger than ten. We conducted sensitivity analyses by removing studies with a high risk of bias.
Inclusion criteria		
Study design	Randomised controlled trials	
Population	Adults (>18 years) with irritable bowel syndrome	
Intervention	enteric-coated peppermint oil	
Comparator	placebo	
Other	no restrictions placed on publication dates.	
Exclusion criteria		
Study design	Non-randomized trials; observational studies such as cohort study, cross-sectional study	
Population	Patients having organic disease or or did not have organic disease excluded	
Intervention	None provided	
Comparator	None provided	
Other	Treatment duration of less than 2 weeks and studies with inadequate data	
Date of documented search (month/year)	from inception to April 11 2018	
Databases searched	PubMed, Web of Science, Embase, and the Cochrane Library	
Was an non-English database searched?	No	No non-english data bases
Were studies in a LOTE included?	No	No language restrictions were reported
Outcomes considered in the SR (list)	global improvement of IBS symptoms, improvement of abdominal pain	

Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Alammar 2019**
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane risk of bias tool *Authors summary*: Six out of the 12 studies were judged by the reviewers as having high risk of attrition bias. Two studies had high risk of bias due to conflict of interest. Many studies had concerns with random sequence generation and allocation concealment weren't reported. 
Authors conclusions (key message)	Author's conclude enteric-coated peppermint oil is a safe and effective therapy for the relief of abdominal pain and global symptoms and in adults with IBS
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	12 of 12 studies included in the SR met our PICO N=835 — N participants in studies that met our PICO (enrolled) 2 studies (Kline, Lawson not included in the meta-analysis by Alammar 2019)

	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Alam 2013	Unclear risk	N=74 2 mL 3 x daily 6 weeks not included in meta-analysis	P: IBS I: Peppermint oil C: Placebo O: Changes in abdominal symptoms (pain/discomfort) S: Bangladesh
2	Cash 2016	High risk (other)	N=72 180 mg 3 x daily 4 weeks	P: IBS I: Peppermint oil C: Placebo O: Global improvement, Abdominal pain/discomfort S: US, multicentre

Characteristics of included reviews	Irritable bowel syndrome			
Review ID	**Alammar 2019**			
3	Capanni 2005	Unclear risk	N=178 400 mg 3 x daily 12 weeks	P: IBS I: Peppermint oil C: Placebo O: Changes in IBS symptoms S: Italy, single centre
4	Cappello 2007	High risk (attrition)	N=57 450 mg 2 x daily 4 weeks	P: IBS I: Peppermint oil C: Placebo O: Changes in IBS symptoms (pain, distension, bloating, diarrhoea, consitpation, incomplete evacuation, gas, mucus)
5	Carling 1989	Unclear risk	N=40 200 mg 3-6 x daily 2 weeks crossover with 1 wk washout	P: IBS I: Peppermint oil C: Placebo O: Changes in IBS symptoms, stool frequency S: Sweden, multi (2) centre
6	Dew 1984	Unclear risk	N=29 0.2 mL 3-6 x daily 2 weeks crossover with washout (NR)	P: IBS I: Peppermint oil C: Placebo O: Changes in abdominal symptoms, stool frequency S: Wales, multicentre
7	Kline 2001	High risk (other)	RCT was not included in analysis by the SR	
8	Lawson 1988	High risk (attrition)	RCT was not included in analysis by the SR	
9	Lech 1988	High risk (attrition)	N=47 200 mg 3 x daily 4 weeks	P: IBS I: Peppermint oil C: Placebo O: Changes in IBS symptoms, global improvement, stool frequency/consistency S: the Netherlands, single centre
10	Liu 1997	Unclear risk	N=110 200 mg 3-6 x daily 4 weeks	P: IBS I: Peppermint oil C: Placebo O: Changes in IBS symptoms (pain, distension, bloating, diarrhoea, consitpation, incomplete evacuation, gas, mucus), stool frequency S: China, single centre

Characteristics of included reviews	Irritable bowel syndrome			
Review ID	**Alammar 2019**			
11	Merat 2009	High risk (attrition)	N=90 187 mg 3 x daily 8 weeks	P: IBS I: Peppermint oil C: Placebo O: Changes in abdominal symptoms (pain/discomfort),QoL S: Iran, single centre
12	Mosaffa-Jahromi 2016	Unclear risk	RCT was not included in analysis by the SR	
13	Rees 1979	Unclear risk	N=18 0.2 mL 3-6 x daily 3 weeks crossover with washout (recurrence of active symptoms)	P: IBS I: Peppermint oil C: Placebo O: Changes in abdominal symptoms, stool frequency S: UK, single centre
14	Schneider 1990	High risk (attrition)	N=60 ? 6 weeks	P: IBS I: Peppermint oil C: Placebo O: Changes in abdominal symptoms (pain), global assessment, stool frequency S: USA, single centre
15	Weiss 1988	High risk (attrition)	N=60 200 mg 3 x daily 3 weeks	P: IBS I: Peppermint oil C: Placebo O: Changes in IBS symptoms S: Germany, single centre
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Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Alammar 2019**
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Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Alammar 2019**
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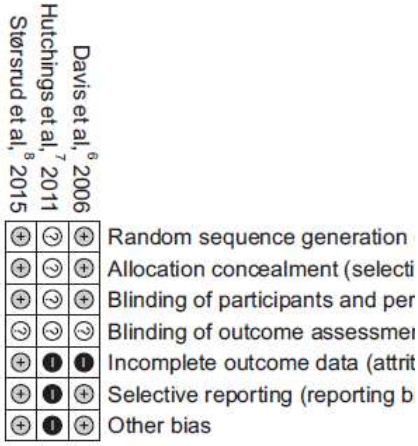
	= data extracted
	= data extracted in more recent SR
	= control is an active intervention (data not extracted)

Characteristics of included reviews	Irritable bowel syndrome	
Review ID	**Hong 2018**	
Review reference	Hong SW, Chun J, Park S, Lee HJ, Im JP, Kim JS. Aloe vera Is Effective and Safe in Short-term Treatment of Irritable Bowel Syndrome: A Systematic Review and Meta-analysis. J Neurogastroenterol Motil. 2018;24(4):528-35.	
Review objective	To evaluate the efficacy and safety of aloe vera in patients with IBS	
Author affiliations	Six authors are affilated with tertiary institutions in Korea.	
Source of funds	None declared	
Declared interests of the review authors	The authors declare no conflict of interest	
Review method of analysis	Meta-analysis	Meta-analysed using RevMan 5.3 software as per Cochrane handbook. Remission/repsonse treated as a dichotomous variable with 95% confidence intervals (CI). Random effects moddel. PP & ITT data were extracted. Heterogeneity of included data was assessed by the χ2 test and the I2 statistic. We planned to use funnel plots and Egger's test to examine publication bias if the number of studies for an outcome is larger than ten. We conducted sensitivity analyses by removing studies with a high risk of bias.
Inclusion criteria		
Study design	Prospective comparative study. All eligible studies compared aloe vera to placebo.	
Population	Adults with IBS	
Intervention	Aloe vera	
Comparator	Placebo	
Other	Followup duration ranged from 1 to 5 months	
Exclusion criteria		
Study design	Non-comparative studies, case reports, review articles, duplicated studies, abstracts and pre-clinical studies	
Population	Not specified	
Intervention	Not specified	
Comparator	Not specified	
Other		
Date of documented search (month/year)	Inception to 1 Dec 2013	
Databases searched	Pubmed, Embase, Cochrane Library	
Was an non-English database searched?	Not specified	
Were studies in a LOTE included?	Not specified	
Outcomes considered in the SR (list)	changes in IBS symptom score before/end of treatment, response rate, adverse events	

Characteristics of included reviews	Irritable bowel syndrome			
Review ID	**Hong 2018**			
Risk of bias of the included RCT studies as reported in the SR	*Tool used* Cochrane risk of bias tool	*Authors summary* Two out of three studies reported clear method of randomisation and allocation concelament. One study reported incomplete outcomes and showed a high drop-out rate.			
Authors conclusions (key message)	Aloe vera was effective for the treatment of IBS compared to placebo in meta-analysis. Short term use of aloe vera may be safe in patients with IBS.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	3 of 3 studies included in the SR met our PICO *236* N participants in studies that met our PICO (enrolled)			
	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Davis 2006	High risk (attrition)	N=58 (31/27) 50 mL 4 x daily 4 & 12 weeks	P: IBS I: Aloe vera juice C: Placebo O: response rate S: UK
2	Hutchings 2011	High risk (attrition, selective reporting, other)	N=110 (55/55) 60 mL 2 x daily 20 weeks crossover	P: IBS I: Aloe vera juice C: Placebo O: GI Symptom rating scale, QoL (EQ-5D) S?

Characteristics of included reviews	Irritable bowel syndrome			
Review ID	**Hong 2018**			
3	Storsrud 2015	Unclear risk (blinding)	N=68 (33/35) 250 mg 2 x daily 4 weeks	P: IBS I: Aloe vera juice C: Placebo O: response rate, IBS severity scoring, HADS, S: Sweden
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Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Hong 2018**
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Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Hong 2018**
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Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Hong 2018**
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	= data extracted
	= data extracted in more recent SR
	= control is an active intervention (data not extracted)

Characteristics of included reviews	Irritable bowel syndrome	
Review ID	**Ng 2018**	
Review reference	Ng QX, Soh AYS, Loke W, Venkatanarayanan N, Lim DY, Yeo WS. A Meta-Analysis of the Clinical Use of Curcumin for Irritable Bowel Syndrome (IBS). J Clin Med. 2018;7(10).	
Review objective	To investigate the hypothesis that curcumin improves IBS symptoms	
Author affiliations	Five authors are affiliated with tertiary institutions in Singapore and the UK. One author is affilated with a holding company for Singapore healthcare institiutions.	
Source of funds	None declared	
Declared interests of the review authors	The authors declare no conflict of interest	
Review method of analysis	Meta-analysis	Meta-analysed using MedCalc Statistical software as per Cochrane handbook. Remission/repsonse treated as a dichotomous variable with 95% confidence intervals (CI). Random effects moddel. PP data were extracted. Heterogeneity of included data was assessed by the I2 statistic and Cochran's Q test. We planned to use funnel plots and Egger's test to examine publication bias if the number of studies for an outcome is larger than ten.
Inclusion criteria		
Study design	Published RCTs	
Population	People with IBS	
Intervention	Curcumin	
Comparator	placebo	
Other		
Exclusion criteria		
Study design	non placebo controlled RCTs	
Population	Not specified	
Intervention	Not specified	
Comparator	Not specified	
Other		
Date of documented search (month/year)	1 Jan 1988 to 1 May 2018	
Databases searched	Pubmed, Medline, Embase, PsychINFO, Web of Science, Google Scholar	
Was an non-English database searched?	No	
Were studies in a LOTE included?	No	Published papers in English were searched
Outcomes considered in the SR (list)	mean change in IBS symptom score before/end of treatment	

Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Ng 2018**
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane risk of bias tool *Authors summary*: Two out of five studies were described to have unsuccessful patient blinding, high patient drop out rates and partial blinding. No studies were considered to be low risk of bias

Table 2: Results of Cochrane collaboration's tool for assessing risk of bias.

Study (Author, Year)	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Outcome Reporting	Other Bias
Alt, 2017 [26]	+	+	+	+	?	?
Bundy, 2004 [24]	+	?	-	+	?	-
Brinkhaus, 2005 [25]	?	+	+	+	?	?
Lauche, 2016 [27]	+	-	-	+	?	?
Portincasa, 2016 [28]	-	+	+	+	?	?

Key: + low risk of bias; - high risk of bias; ? unclear risk of bias.

Authors conclusions (key message)	Curcumin was deemed safe, tolerable and with no serious side effects. Authors conclude there is a positive but not statistcally significant effect of curcumin in comparison to placebo on IBS symptoms.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	2 of 5 RCTs included in the SR met our PICO criteria. The other RCTs had no control group or examined herbs/interventions not on List A (Ayurvedic, neutraceuticals)

227 N participants in studies that met our PICO (enrolled)

	Study ID	*Summary RoB*		
1	Brinkhaus 2005	Unclear risk	N=106 20 mg 3 x daily 500 mg 3 x daily 18 weeks	P: IBS I: Curcuma OR Fumaria officinalis C: Placebo O: Global symptoms score S: Germany
2	Portincasa 2016	High risk (randomisation)	N=121 42 mg/17.5 mg fixed dose 4 weeks	P: IBS (Rome II I: Curcumin+ fennel oil (CU-FEO) C: Placebo O: Change in IBS-SSS, QOL, Adverse events S: Italy

Characteristics of included reviews	Irritable bowel syndrome			
Review ID	**Ng 2018**			
3	~~Bundy 2004~~	~~High risk (blinding)~~	~~N=207 72 & 144 mg tumeric extract (CynaraTM) 1 x daily 8 weeks~~	~~P: IBS (Rome II) I: Curcumin C: NO COMPARATOR GROUP O: IBS symptoms, adverve events S: UK~~
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Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Ng 2018**
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Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Ng 2018**
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Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Ng 2018**
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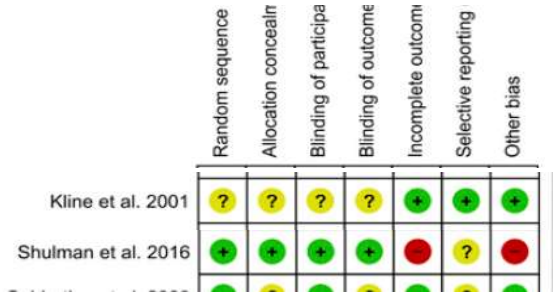
	= data extracted
	= data extracted in more recent SR
	= control is an active intervention (data not extracted)

Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Anheyer 2017**
Review reference	Anheyer, D., et al. (2017). "Herbal Medicines for Gastrointestinal Disorders in Children and Adolescents: A Systematic Review." Pediatrics 139(6).
Review objective	systematically summarize the effectiveness and safety of different herbal treatment options for gastrointestinal disorders in children and adolescents.
Author affiliations	Authors are affilated with tertiary institutions in Germany & Australia
Source of funds	This review was supported by a grant from the Karl and Veronica-Carstens Foundation and the Rut- and Klaus-Bahlsen Foundation
Declared interests of the review authors	Dr Langhorst has received grants from Schwabe Pharma, Steigerwald and Repha; the other authors have indicated they have no conflicts of interest to disclose.
Review method of analysis	Descriptive
Inclusion criteria	
Study design	Randomized controlled trials (RCTs), randomized cross-over trials, and cluster-randomized trials
Population	Children (0-12 yrs) or adolescents (13-18 years) with gastrointenstinal complaints (diarhoea, constipation, IBS, IBD, or other GI disorders)
Intervention	Any herbal medicine
Comparator	treatment as usual or placebo or no treatment
Other	
Exclusion criteria	
Study design	non placebo controlled RCTs
Population	Not specified
Intervention	homeopathic, chinese herbal medicines
Comparator	Not specified
Other	
Date of documented search (month/year)	inception to 15 July 2016
Databases searched	Medline/PubMed, Scopus, and the Cochrane Central Register of Controlled Trials
Was an non-English database searched?	No
Were studies in a LOTE included?	No
Outcomes considered in the SR (list)	mean change in IBS symptom score before/end of treatment

Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Anheyer 2017**
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane risk of bias tool *Authors summary*: 
Authors conclusions (key message)	Few studies on specific indications, single herbs, or herbal preparations could be identified. To underpin evidence outlined in this review, more rigorous clinical trials are needed. For IBS: Two RCTs with a total of 145 participants were conducted to research herbal medicine for the treatment of IBS in children and adolescents. Although capsules of peppermint oil (Colpermin) did not show any significant differences when compared with the placebo, psyllium fiber powder significantly reduced the number of abdominal pain episodes in comparison with the placebo (maltodextrin powder).
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	2 of 14 RCTs included in the SR met our PICO criteria. No usable data were provided
	227 N participants in studies that met our PICO (enrolled)

	Study ID	*Summary RoB*		
1	Kline 2001	Unclear risk	N=42 Age 8-17 yrs (mean 12 yrs) 100 to 200 mg (weight based) 3 x daily 2 weeks	P: IBS I: Peppermint oil capsule C: Placebo (with peanut oil) O: GI symptom rating S: ?
2	Shulman 2016	High risk (attrition, other)	n=1-3 Age 7-18 yrs (median 13 yrs) 6-12 g per day (age-based) 6 weeks	P: IBS I: Psyllium fibre powder C: Placebo (maltodextrin powder) O: Number of pain episodes, severity of pain episodes, % normal stools S: ?

Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Anheyer 2017**
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Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Anheyer 2017**
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Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Anheyer 2017**
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Characteristics of included reviews	Irritable bowel syndrome
Review ID	**Anheyer 2017**
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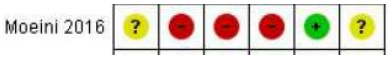
	= data extracted
	= data extracted in more recent SR
	= control is an active intervention (data not extracted)

Characteristics of included reviews	Gastroesophageal reflux disease	
Review ID	**Sadeghi 2020**	
Review reference	Sadeghi, F., Mohammad, S., Sepehri, B., Khodaie, L., Monirifar, H., & Mirghafourvand, M. (2020). Effects of herbal medicine in gastroesophageal reflux disease symptoms: a systematic review and meta-analysis. Traditional Medicine Research, 5, 425–506. https://doi.org/https://doi.org/10.53388/TMR20200929200	
Review objective	Investigate the effects of medicinal herbs on gastgastroesophageal reflux disease and adverse events.	
Author affiliations	All six authors were affiliated with tertiary instituions in Iran.	
Source of funds	None declared	
Declared interests of the review authors	The authors declared there were no competing interests	
Review method of analysis	Meta-analysis	The Review Manager Software version 5.3 (Cochrane Collaboration, Europe) was used to pool effect sizes. The mean difference (MD) or standardized mean difference (SMD), odds ratio, and 95% confidence interval (95% CI)
Inclusion criteria		
Study design	RCTs	
Population	Gastroesophageal reflux disease	
Intervention	Medicinal herbs	
Comparator	Placebo or conventional Western drugs	
Other		
Exclusion criteria		
Study design	Not specified	
Population	Patients ≤18, infants, pregnant and nursing women and patients with severe disease.	
Intervention	Not specified	
Comparator	Not specified	
Other	Not specified	
Date of documented search (month/year)	Not specified	
Databases searched	Medline, Scopus Science Direct, Cochrane Central Register of controlled trials, Web of Science and Persian Data bases (Magiran, Scientific information Database).	
Was an non-English database searched? Were studies in a LOTE included?	Yes	Magiran, Scientific information Database
	Yes	Persian
Outcomes considered in the SR (list)	The improvement of GERD symptoms was the primary outcome (scores, reflux, heartburn, non-cardiac chest pain, effective rate, etc.), and adverse event was the secondary outcome.	
Risk of bias of the included RCT studies as reported in the SR	*Tool used*	*Authors summary*
	Cochrane risk of bias tool	The study that met our PICO was described as having unclear random sequence generation, high-risk allocation concealment and performance bias. Detection bias was described as low. The randomisation techniques were not described in the study.
		
Authors conclusions (key message)	The authors concluded that the results of the meta-analysis showed that herbal medicines were effective in treating GORD.	

Characteristics of included reviews	Gastroesophageal reflux disease				
Review ID	**Sadeghi 2020**				
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	Thirteen RCTs identified, one RCT met our PICO 80 participants in studies that met our PICO (enrolled)				
	Study ID	*Summary RoB*	*Study design features (PICOS)*		
1	Moeini 2016	High risk	N=80 (41/39) 4 weeks	P: GORD I: Hawthorn C: Placebo	O: Symptom severity (not described) S: Not specified
	= data extracted				
	= data extracted in more recent SR				
	= control is an active intervention (data not extracted)				

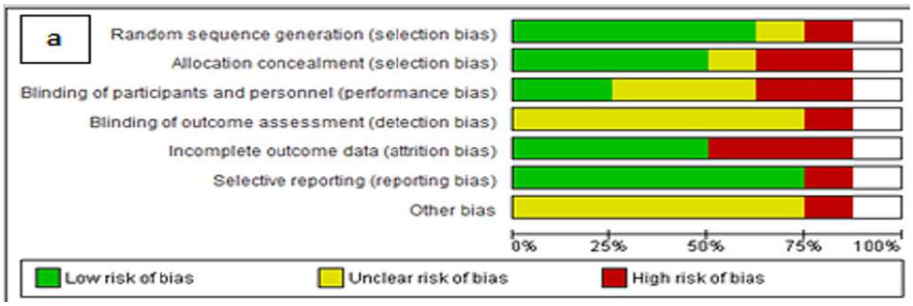
Characteristics of included reviews	Menstrual conditions (dysmenorrhoea)	
Review ID	**Negi 2021**	
Review reference	Negi R, Sharma SK, Gaur R, Bahadur A, Jelly P. Efficacy of ginger in the treatment of primary dysmenorrhoea: a systematic review and meta-analysis. Cureus 13(3):e13743	
Review objective	Efficacy of ginger in the treatment of primary dysmenorrhea: a systematic review and meta-analysis	
Author affiliations	Nursing, obstetrics and gynecology departments of Medical Science Institutes in India	
Source of funds	None reported	
Declared interests of the review authors	Authors report no competing interests	
Review method of analysis	Meta-analysis	Random effects model; continuous variables expressed as MD (95% CI) using RevMan 5.
Inclusion criteria		
Study design	RCTs	
Population	Women with primary dysmenorrhoea	
Intervention	Oral ginger	
Comparator	Placebo or NSAID	
Other	Evaluated by patient-reported outcome measure	
Exclusion criteria		
Study design	Non-RCTs, case control, cohort, letters, reviews	
Population	Non-human or in vitro studies	
Intervention	Ginger combined with other substances	
Comparator	None reported	
Other	Not in English	
Date of documented search (month/year)	2008-2020 publication dates considered for inclusion	
Databases searched	PubMed, Embase, Ovid, ClinicalKey, Medline, electronic database	
Was an non-English database searched?	No	No non-English databases reported
Were studies in a LOTE included?	No	
Outcomes considered in the SR (list)	Pain severity, pain duration, changes in bleeding, side effects of the drug, rate of satisfaction	

Characteristics of included reviews	Menstrual conditions (dysmenorrhoea)

Review ID **Negi 2021**

Risk of bias measurement as reported in the SR

Tool used	*Authors summary*
Cochrane tool	The majority of studies expressed a low to unclear level of risk of bias



Authors conclusions (key message)

The finding in this study has verified the possibility of ginger efficacy in the treatment of primary dysmenorrhea, though no/small side effects have been identified and its use is associated with health benefits.

Characteristics of eligible RCTs meeting the inclusion criteria for this Overview

8 RCTs identified. 5 RCTs meet our PICO criteria.

Total N=688 in eligible RCTs

	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Jenabi 2013	Some concerns (missing information)	N=69 (35/34) Ginger 500 mg TID x 3 days (first 3 days of a period)	P: moderate to severe dysmenorrhoea I: Ginger C: Placebo O: Pain (VAS) S: College students, Iran
2	Rahnama 2012	Some concerns (incomplete outcome data)	N=105 (59/46) Ginger powder 50 mg TID for 5 days (protocol 1) or 3 days (protocol 2) [first 3 days of a period]	P: moderate to severe dysmenorrhoea I: Ginger C: Placebo O: Pain (VAS) and pain duration (hours) S: College students, Iran
3	Kashefi 2014	Some concerns (blinding of outcome assessment)	N=146 (47/45 placebo/54 zinc) Ginger 250 mg TID x 4 days for 2 cycles	P: moderate to severe dysmenorrhoea I: Ginger C: Placebo or Zinc O: Pain (VAS) S: Secondary students, Iran

Characteristics of included reviews	Menstrual conditions (dysmenorrhoea)			
Review ID	**Negi 2021**			
4	Ozgoli 2009	Some concerns (allocation, randomisation)	N=150 (50/50 ibuprofen/50 mefenamic acid) Ginger 250 mg QID x 3 days	P: moderate to severe dysmenorrhoea I: Ginger C: Ibuprofen or mefenamic acid O: Pain (VMS) S: College students, Iran
5	Shirvani 2015	Unclear risk (due to no information)	N=122 (61/61) Ginger 250 mg QID	P: moderate to severe dysmenorrhoea I: Ginger C: Mefenamic acid O: Worst pain (VAS) and pain duration (days) S: College students, Iran
6	Abadi 2020	Some concerns (blinding, incomplete data)	N=210 (70 ginger/70 control/70 placebo) Ginger 250 mg TID x 4 days	P: Dysmenorrhoea I: Ginger C: Placebo or control O: Pain duration S: not specified
7	Pakniat 2019	Some concerns (allocation, blinding, incomplete data)	N=200 (50 ginger/100 control/50 placebo) Ginger capsule 250 mg BD x 3 days	P: moderate to severe dysmenorrhoea I: Ginger C: mefenamic acid or placebo O: Pain (measure not specified) S: Not specified
8	Rad 2018	Some concerns (selective reporting)	N=168 (78/90) Ginger 200 QID x 2 days	P: grade 2-3 dysmenorrhoea I: Ginger C: Novafen (NSAID) 200 mg QID O: Pain (measure not specified) S: Not specified
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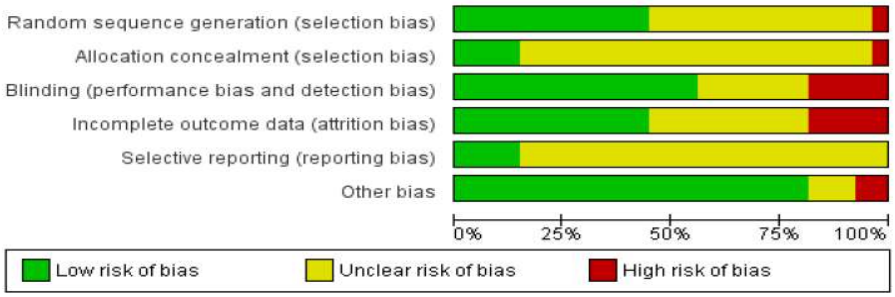
= data extracted
= data extracted in more recent SR
= control is an active intervention (data not extracted)

Characteristics of included reviews	Menstrual conditions (dysmenorrhoea)	
Review ID	**Xu 2020**	
Review reference	Xu Y, Yang Q, Wang X. Efficacy of herbal medicines (cinnamon/fennel/ginger) for primary dysmenorrhoea: a systematic review and meta-analysis of randmised controlled trials. Journal of International Medical Research 2020; 48(6): 1-12	
Review objective	To assess the efficacy of herbal medicine (cinnamon/fennel/ginger) for treating primary dysmenorrhea	
Author affiliations	Tertiary Colleges in China	
Source of funds	This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.	
Declared interests of the review authors	Authors report no competing interests	
Review method of analysis	Meta-analysis	STATA 15.1 software was used to analyse the data. WMD 95% CI was used as effect estimator
Inclusion criteria		
Study design	RCTs	
Population	Women diagnosed with primary dysmenorrhea	
Intervention	Herbal medicine (cinnamon/fennel/ginger)	
Comparator	Placebo	
Other	Published in english; outcome was pain intensity and/or duration	
Exclusion criteria		
Study design	Observational studies, reviews, metaanalyses, letters, editorial articles, animal experiments	
Population	None reported	
Intervention	None reported	
Comparator	None reported	
Other	Duplicated studies; published in nonEnglish language	
Date of documented search (month/year)	Databse inception to 19 Dec 2019	
Databases searched	PubMed, Embase, Cochrane Library, Web of Science	
Was an non-English database searched?	No	
Were studies in a LOTE included?	No	Non English publications were excluded
Outcomes considered in the SR (list)	Pain intensity, pain duration	

Characteristics of included reviews	Menstrual conditions (dysmenorrhoea)
Review ID	**Xu 2020**
Risk of bias measurement as reported in the SR	*Tool used*: Modified Jadad scale *Authors summary*: The quality of the included studies was relatively high, and only two studies were considered low quality.



Authors conclusions (key message)	For primary dysmenorrhea, cinnamon/fennel/ginger can effectively relieve the intensity of pain, and cinnamon can shorten the duration of pain. However, these findings must be further confirmed in a large number of studies with large sample sizes.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	9 RCTs identified. 6 studies meet our PICO criteria. Total N=654 in eligible RCTs

	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Jenabi 2013	High quality (Jadad score 5)	N=69 (35/34) Ginger 500 mg TID x 3 days	P: moderate to severe dysmenorrhoea I: Ginger C: Placebo O: Pain (VAS) S: College students, Iran
2	Rahnama 2012	High quality (Jadad score 6)	N=105 (59/46) Ginger 50 mg TID x 3 or 5 days (unclear which protocol was reported)	P: moderate to severe dysmenorrhoea I: Ginger C: Placebo O: Pain (VAS) and pain duration (hours) S: College students, Iran
3	Kashefi 2014	High quality (Jadad score 5)	N=146 (47/45 placebo/54 zinc) Ginger 250 mg TID x 4 days for 2 cycles	P: moderate to severe dysmenorrhoea I: Ginger C: Placebo or Zinc O: Pain (VAS) S: Secondary students, Iran

Characteristics of included reviews	Menstrual conditions (dysmenorrhoea)			
Review ID	**Xu 2020**			
4	Pakniat 2019	(High quality (Jadad score 4)	N=200 (50 ginger/100 control/50 placebo) Ginger 250 mg BD x 3 days	P: moderate to severe dysmenorrhoea I: Ginger C: mefenamic acid or placebo O: Pain (measure not specified) S: Not specified
5	Jaafarpour 2015	High quality (Jadad score 4)	N=76 (38/38) Cinnamon 420 mg capsule 3 times/day x 3 days	P: Primary dysmenorrhoea I: Cinnamon C: Placebo (Starch capsules, 3 times/day for 3 days) O: Pain intensity (VAS), pain duration S: Students, Iran
6	Jahangirifar 2018	High quality (Jadad score 4)	N=58 (30/28) Cinnamon 1000 mg 3 times/day x 3 days	P: Primary dysmenorrhoea I: Cinnamon C: Placebo (1000 mg starch, 3 times/day for 3 days) O: Pain (VAS) S: Students, Iran
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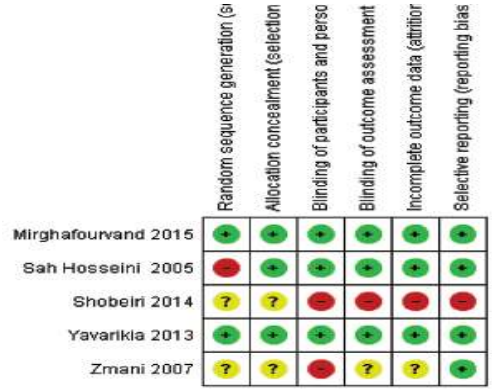
= data extracted
= data extracted in more recent SR
= control is an active intervention (data not extracted)

Characteristics of included reviews	Menstrual conditions (menstrual bleeding)	
Review ID	**Mollazadeh 2019**	
Review reference	Mollazadeh S, Mirghafourvand M, Abdollahi NG. The effects of vitax agnus-castus on menstrual bleeding: a systematic review and meta-analysis. Journal of Complementary and Integrative Medicine 2019; 20180053/	
Review objective	To examine the effects of vitex on menstrual bleeding and its side effects among trials in the field	
Author affiliations	Midwifery and Health Research Centres in Iran	
Source of funds	None declared	
Declared interests of the review authors	The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication	
Review method of analysis	Meta-analysis	RevMan 5.3 for meta-analysis and risk of bias charts. Meta-analysis reported as MD 95% CI; heterogeneity examined by I2
Inclusion criteria		
Study design	RCTs, quasi experimental and crossover studies	
Population	Women of reproductive age with no gynecologic disorders; ovarian cysts, adenomyosis, endometriosis, uterine fibroids, pelvic inflammatory disease, heavy menstrual bleeding, age of 15–45, no bleeding between menstruation periods, regular menstrual cycles of 22–35 days, no genital tract infection, and willingness to participate in the study	
Intervention	Vitex in tablet, capsule or oral drop form	
Comparator	Placebo or mefenamic acid	
Other	Outcome was determining the amount of menstrual bleeding, calculated using the Higham tool.	
Exclusion criteria		
Study design	None reported	
Population	None reported	
Intervention	None reported	
Comparator	None reported	
Other	None reported	
Date of documented search (month/year)	December 2017, no time limits	
Databases searched	Medline (through PubMed), Scopus, Embase (through Ovid), Cochrane Library, Web of Sciences, Google Scholar, SID, Magiran, Irandoc, and Iranmedex	
Was an non-English database searched?	Yes	
Were studies in a LOTE included?	Yes	All studies including English and Persian were searched
Outcomes considered in the SR (list)	Menstrual blood loss, side effects	

Characteristics of included reviews	Menstrual conditions (menstrual bleeding)
Review ID	**Mollazadeh 2019**
Risk of bias measurement as reported in the SR	*Tool used*: Cochrane tool *Authors summary*: No overall comment on RoB



Authors conclusions (key message)	The results of this study showed that the consumption of Vitex in the intervention group did not have a significant effect on menstrual bleeding in comparison with the placebo group. However, due to the relatively low quality of the papers, it is essential to perform clinical trials with an appropriate design to determine the effect of Vitex on menstrual bleeding.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	5 RCTs identified. 2 studies meet our PICO criteria. Total N=180 in eligible RCTs

	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Sah Hosseini 2005	High risk (selection, allocation by odd and even numbers)	N=60 (30/30) Vitex 40 drops fasting every morning on menstruation days	P: Primary dysmenorrhoea I: Vitex C: Placebo drops O: Menstrual bleeding severity (Higham score) S: Students, Iran
2	Shobheiri 2014	High risk (blinding, attitrition, reporting)	N=120 (30 vitex/30 placebo/30 mefanamic acid) Vitex 40 drops fasting from day -1 to 3	P: Heavy menstrual bleeding I: Vitex C: Placebo drops OR Mefenamic acid O: Menstrual bleeding severity (Higham score) S: Students, Iran
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Characteristics of included reviews	Menstrual conditions (menstrual bleeding)
Review ID	**Mollazadeh 2019**
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= data extracted
= data extracted in more recent SR
= control is an active intervention (data not extracted)

Characteristics of included reviews	Menstrual conditions (dysmenorrhoea)
Review ID	**Pellow 2018**
Review reference	Pellow J and Nienuis C. Medicinal plants for primary dysmenorrhoea: a systematic review. Complementary Therapies in Medicines 2018;37:13-26
Review objective	The aim of this systematic review was to synthesise the most recent evidence relating to the treatment of primary dysmenorrhoea with medicinal plants.
Author affiliations	University in South Africa
Source of funds	Not mentioned
Declared interests of the review authors	None declared
Review method of analysis	Descriptive NA
Inclusion criteria	
Study design	RCTs
Population	Women with primary dysmenorrhoea
Intervention	Single medicinal plant applications
Comparator	Placebo or standard pharmaceutical treatment
Other	Primary or secondary outcomes included evaluating menstrual pain and associated symptoms (nausea, vomiting, back pain etc)
Exclusion criteria	
Study design	None reported
Population	None reported
Intervention	None reported
Comparator	None reported
Other	Studies scoring below 3 on the JADAD scale were excluded; published before 2008; not in English
Date of documented search (month/year)	Published between 2008-2016; search updated on 30 Aug 2016
Databases searched	The UJ Health Sciences Databases were initially searched in combination and included: AMED (The Allied and Complementary Medicine Database), Health Source: Nursing/Academic Edition, Health Source – Consumer Edition, MEDLINE, CINAHL, and SPORTDiscus.
Was an non-English database searched?	Not specified
Were studies in a LOTE included?	No Search applied language filters for English publications
Outcomes considered in the SR (list)	Menstrual pain, associated symptoms (nausea, vomiting, back pain etc)

Characteristics of included reviews	Menstrual conditions (dysmenorrhoea)
Review ID	**Pellow 2018**
Risk of bias measurement as reported in the SR	*Tool used*: Cochrane tool & Jadad *Authors summary*: Four studies were found to have a high risk of bias and are therefore not considered reliable evidence. Only one study, on the use of Rosa damascena, had a low risk of bias, and therefore can be considered supportive evidence for the potential efficacy of this medicinal plant, warranting further investigation. All other studies however, received an unclear risk of bias, largely due to insufficient reporting in the published articles. Their results should therefore be interpreted with caution.
Authors conclusions (key message)	Promising evidence was found for the efficacy of certain medicinal plants, however the results from these studies needs to be interpreted with caution, due to the high or unclear risk of bias, small number of included RCTs and poor methodological quality of some of the trials.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	22 RCTs identified. 6 studies meet our PICO criteria Total N=623 in eligible RCTs

	Study ID	*Summary RoB*	*Study design features (PICO)*	*Setting*
1	Jenabi 2013	Unclear risk (blinding); JADAD score 3	N=69 (35/34) Ginger 500 mg TID x 3 days	P: moderate to severe dysmenorrhoea I: Ginger C: Placebo O: Pain (VAS) S: College students, Iran
2	Rahnama 2012	Unclear risk (incomplete data, selective reporting); JADAD score 5	N=105 (59/46) Ginger 50 mg TID x 3 or 5 days (unclear which protocol was reported)	P: moderate to severe dysmenorrhoea I: Ginger C: Placebo O: Pain (VAS) and pain duration (hours) S: College students, Iran
3	Kashefi 2014	Unclear risk (allocation, incomplete data); JADAD score 5	N=146 (47/45 placebo/54 zinc) Ginger 250 mg TID x 4 days for 2 cycles	P: moderate to severe dysmenorrhoea I: Ginger C: Placebo or Zinc O: Pain (VAS) S: Secondary students, Iran

Characteristics of included reviews	Menstrual conditions (dysmenorrhoea)			
Review ID	**Pellow 2018**			
4	Younesy 2014	Unclear risk (allocation, incomplete data); JADAD score 5	N=101 (51/50) Fenugreek 900 mg, 2-3 capsules TID x 3 days	P: moderate to severe dysmenorrhoea I: Fenugreek C: Placebo (starch) O: Pain severity (VAS), multidimensional verbal scoring system, use of analgesics S: Students, Iran
5	Heshmati 2016	Unclear risk (allocation, selective reporting); JADAD score 5	N=102 (46/44) Peppermint 990 mg daily on days 1-3	P: moderate to severe dysmenorrhoea I: Fenugreek C: Placebo O: Pain severity (SF-MPQ) S: Students, Iran
6	Mirabi 2011	Unclear risk (allocation, selective reporting); JADAD score 5	N=100 (51/49) Valerian 675 mg daily in days 1-3	P: moderate to severe dysmenorrhoea I: Valerian C: Placebo O: Pain severity (VAS), multidimensional verbal scoring system (associated symptoms) S: Students, Iran
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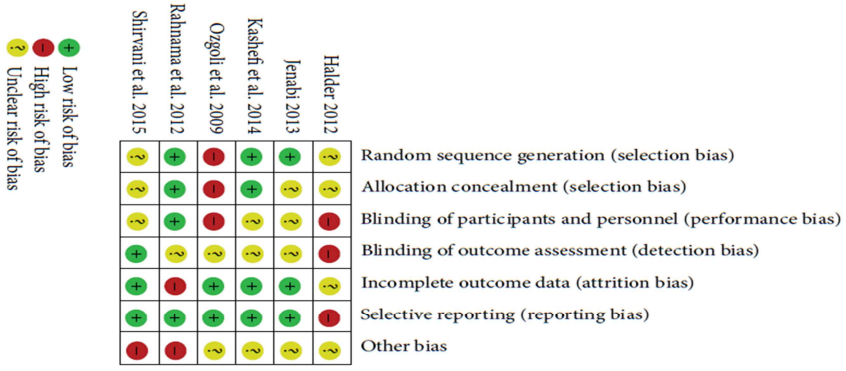
= data extracted
= data extracted in more recent SR
= control is an active intervention (data not extracted)

Characteristics of included reviews	Menstrual conditions (dysmenorrhoea)	
Review ID	**Chen 2016**	
Review reference	Chen CX, Barrett B & Kwekkeboom KL. Efficacy of Oral Ginger (Zingiber officinale) for Dysmenorrhea: A Systematic Review and Meta-Analysis. Evidence-Based Complementary and Alternative Medicine 2016;6295737.	
Review objective	To determine whether oral ginger as compared to placebo control or other interventions is efficacious in reducing menstrual pain in women with dysmenorrhoea	
Author affiliations	Universities and Nursing Institutions in the US	
Source of funds	National Institute of Nursing Research (Grant number 5T32 NR007066) National Center for Complementary and Integrative Health from the National Institutes of Health (K24 Midcareer Investigator Aware K24AT006543)	
Declared interests of the review authors	Authors report no competing interests	
Review method of analysis	Meta-analysis	RevMan 5.3 and R software were used for the meta-analysis
Inclusion criteria		
Study design	RCTs	
Population	Women with dysmenorrhoea	
Intervention	Ginger (oral administration)	
Comparator	Placebo or active treatment	
Other	None reported	
Exclusion criteria		
Study design	Observational studies	
Population	Non-human or in vitro studies	
Intervention	Ginger combined with other potentially active substances; non-oral ginger use	
Comparator	None reported	
Other	None reported	
Date of documented search (month/year)	Inception to May 2015	
Databases searched	PubMed, EMBASE, Cochrane Library, CINAHL, Web of Science Core Collection, PsycINFO, AMED, LILACS, International Pharmaceutical Abstracts, and Biological Abstracts, Clinical trial registries	
Was an non-English database searched? Were studies in a LOTE included?	No	No non-English databases reported
	Yes	Bilingual colleagues were sought to assist with translating non-English publications
Outcomes considered in the SR (list)	Menstrual pain severity assessed by a patient-reported outcome measure	

Characteristics of included reviews	Menstrual conditions (dysmenorrhoea)
Review ID	**Chen 2016**
Risk of bias measurement as reported in the SR	*Tool used*: Cochrane tool *Authors summary*: Some studies had high or unclear risk of selectoin bias for inadequate random sequence generation; allocation concealment judged as high risk in one study; only one study was double-blinded (insufficient evidence to assess blinding in 3 studies); one study had high risk of bias related to incomplete outcome data due to attrition rates; selective reporting bias judged low in most studies. 
Authors conclusions (key message)	Available data suggest that oral ginger could be an effective treatment for menstrual pain in dysmenorrhoea. Findings however need to be interpreted with caution because of the small number of studies, poor methodological quality of the studies and high heterogeneity across trials.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	6 RCTs identified. 6 RCTs meet our PICO criteria Total N=667 in eligible RCTs

	Study ID	*Summary RoB*	*Study design features (PICO)*	*Setting*
1	Jenabi 2013	Unclear risk	N=69 (35/34) Ginger 500 mg TID x 3 days	P: moderate to severe dysmenorrhoea I: Ginger C: Placebo O: Pain (VAS) S: College students, Iran
2	Rahnama 2012	High risk (attrition, other)	N=105 (59/46) Ginger 50 mg TID x 3 or 5 days (unclear which protocol was reported)	P: moderate to severe dysmenorrhoea I: Ginger C: Placebo O: Pain (VAS) and pain duration (hours) S: College students, Iran
3	Kashefi 2014	Unclear risk	N=146 (47/45 placebo/54 zinc) Capsule of ginger powder 250mg TID x 4 days 2 menstrual cycles	P: moderate to severe dysmenorrhoea I: Ginger C: Placebo or Zinc (220 mg 3 times/day for 4 days) O: Pain (VAS) S: Secondary students, Iran

Characteristics of included reviews	Menstrual conditions (dysmenorrhoea)			
Review ID	**Chen 2016**			
4	Ozgoli 2009	High risk (randomisation, allocation, blinding)	N=150 (50/50 ibuprofen/50 mefenamic acid) Capsule of ginger powder 250 mg QID x 3 days	P: moderate to severe dysmenorrhoea I: Ginger C: Ibuprofen (400 mg QID) or mefenamic acid (250 mg QID) for 3 days O: Pain (VMS) S: College students, Iran
5	Shirvani 2015	High risk (other)	N=122 (61/61) Capsule of ginger powder 250 mg QID until pain relieved	P: moderate to severe dysmenorrhoea I: Ginger C: Mefenamic acid (250 mg TID until pain was relieved) O: Worst pain (VAS) and pain duration (days) S: College students, Iran
6	Halder 2012	High risk (blinding, sleective reporting)	N=75 (25/25 PMR/25 control) Capsule of ginger powder 1000 mg BID x 3 days	P: primary or secondary dysmenorrhoea I: Ginger C: Progressive muscle relaxation (once daily for 3 days) or control (no information) O: Dysmenorrhoea severity (5-point scale) S: College students, India
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	Additional study notes			
8	Ozgoli 2009	An alternate assignment approach was used; ginger and the NSAIDS were produced by different companies which made it possible to identify pills		
9	Shirvani 2015	There was differential use of extra analgesics between the ginger group and the NSAID group, with higher usage in the ginger group		
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= data extracted
= data extracted in more recent SR
= control is an active intervention (data not extracted)

Characteristics of included reviews	Menstrual conditions (dysmenorrhoea)	
Review ID	**Pattanittum 2016**	
Review reference	Pattanittum P, Kunyanone N, Brown J, Sangkomkamhang US, Barnes J, Seyfoddin V, Majoribanks J. Dietary supplements for dysmenorrhoea. Cochrane Database of Systematic Reviews 2016; Issue 3; DOI: 10.1002/14651858.CD002124.pub2.	
Review objective	To determine the efficacy and safety of dietary supplements for treating dysmenorrhoea	
Author affiliations	University affiliated research departments in New Zealand and Thailand	
Source of funds	Cochrane Thailand and Thailand Research Fund as honorarium to one review author	
Declared interests of the review authors	Authors report no competing interests	
Review method of analysis	Meta-analysis	We combined the data using a fixed-effect model provided there was no moderate or substantial statistical heterogeneity (IT statistic value of less than 50%). If there was moderate heterogeneity (IT statistic value of 50% to 75%), we applied a random-eCects model. If we detected substantial heterogeneity (I2 statistic value greater than 75%), we did not pool the data across studies.
Inclusion criteria		
Study design	Parallel group or crossover RCTs	
Population	Women with moderate to severe primary dysmenorrhoea or secondary dysmenorrhoea of identifiable pathology	
Intervention	Dietary supplements	
Comparator	Placebo, no treatment, against each other or any other conventional treatment	
Other	None reported	
Exclusion criteria		
Study design	None reported	
Population	Women with mild dysmenorrhoea, irregular or infrequent menstrual cycles or those using IUD or OCP	
Intervention	Chinese medicinal herbs (the subject of another Cochrane review)	
Comparator	None reported	
Other	None reported	
Date of documented search (month/year)	Database inception to 23 March 2015	
Databases searched	CGF Specialised Register, CENTRAL, OvidMEDLINE, EMBASE, PsycINFO, AMED, clinicaltrials.gov, apps.who.int/trialsearch	
Was an non-English database searched? Were studies in a LOTE included?	No	No non-English databases reported
	Yes	No language barriers imposed, full text translations undertaken
Outcomes considered in the SR (list)	Pain, adverse effects from treatments, requirements for additional medication, restriction of ADL, absence from work or school	

Characteristics of included reviews	Menstrual conditions (dysmenorrhoea)
Review ID	**Pattanittum 2016**
Risk of bias measurement as reported in the SR	*Tool used*: Cochrane Tool *Authors summary*: The evidence was low or very low quality; main limitations were imprecision due to very small sample sizes, failure to report study methods and inconsistency.
Authors conclusions (key message)	There is no high quality evidence to support the effectiveness of any dietary supplement for dysmenorrhoea, and evidence of safety is lacking. However for several supplements there was some low quality evidence of effectiveness. Participants in the included studies may be unrepresentative of all populations of women with dysmenorrhoea. The results of this review should be treated with caution.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	27 RCTs identified. 10 studies meet our PICO criteria. Other studies were in herbs not on List A (e.g. dill seed, fennel, guava extract) or included other interventions (e.g. (Vitamin E) Total N=1007 in eligible RCTs

	Study ID	*Summary RoB*	*Study design features (PICO)*	*Setting*
1	Jenabi 2013	Unclear risk (allocation, blinding and selective reporting)	N=69 (35/34) Ginger 500 mg TID x 3 days	P: moderate to severe dysmenorrhoea I: Ginger C: Placebo O: Pain (VAS) S: College students, Iran
2	Rahnama 2012	High risk (randomisation, incomplete data)	N=105 (59/46) Ginger 50 mg TID x 3 or 5 days (unclear which protocol was reported)	P: moderate to severe dysmenorrhoea I: Ginger C: Placebo O: Pain (VAS) and pain duration (hours) S: College students, Iran
3	Kashefi 2014	Unclear risk (incomplete data, allocation)	N=146 (47/45 placebo/54 zinc) Ginger 250 mg TID x 4 days for 2 cycles	P: moderate to severe dysmenorrhoea I: Ginger C: Placebo or Zinc O: Pain (VAS) S: Secondary students, Iran

Characteristics of included reviews	Menstrual conditions (dysmenorrhoea)			
Review ID	**Pattanittum 2016**			
4	Akbari 2012	Low risk	N=106 (53/53) Fenugreek 900 mg, 2-3 capsules 3 times/days x 3 days	P: Moderate to severe dysmenorrhoea I: Fenugreek C: Placebo O: Pain (VAS), pain duration, systematic signs, sedative drugs taken S: Students, Iran
5	Akhavan Amjadi 2009	Insufficient details to assess	N=47 (unclear how many randomised) 420 mg, 5 capsules/day up to 3 days after pain started	P: Moderate to severe dysmenorrhoea I: Cinnamon C: Placebo O: Pain (0-3 scale) S: Students, Iran
6	Dolation 2010	Insufficient details to assess	N=106 (51/49) Valerian 255 mg 3 times daily x 3 days	P: moderate to severe dysmenorrhoea I: Valerian root C: Placebo O: Sedative drugs taken for dysmenorrhoea, pain severity (VAS), systemic symptoms associated with menstruation S: Students, Iran
7	Jenabi 2010	High risk (not blinded)	N=82 (40/40) Chamomile tea, 2 cups/day x 5 days	P: primary dysmenorrhoea I: Chamomile C: Control (no intervention) O: Pain (SF-MPQ) S: Students, Iran
8	Jenabi 2012	Insufficient details to assess	N=108 (54/54) Valerian root 250 mg every 8 hours x 3 days	P: primary dysmenorrhoea I: Valerian C: Mefenamic acid O: Pain (VAS) S: Students, Iran
9	Modaress 2011	Insufficient details to assess	N=160 (80/80) German chamomile capsules (400 mg, 4 capsules daily maximum)	P: moderate to severe dysmenorrhoea I: German chamomile + mefenamic acid C: Mefenamic acid O: Pain (VAS) S: Students, Iran
10	Rahnama 2010	Insufficient details to assess	N=78 (37/41) Ginger 500 mg tds x 3 days	P: primary dysmenorrhoea I: Ginger C: Placebo O: Pain (VAS), pain duration, number of days of bleeding S: Students, Iran

= data extracted

= data extracted in more recent SR

= control is an active intervention (data not extracted)

Characteristics of included reviews	Menstrual conditions (dysmenorrhoea)
Review ID	**Daily 2015**
Review reference	Daily JW, Zhang X, Kim DS & Park S. Efficacy of Ginger for Alleviating the Symptoms of Primary Dysmenorrhea: A Systematic Review and Meta-analysis of Randomized Clinical Trials. Pain Med 2015;16:2243-2255.
Review objective	To systematically evaluate all RCTs of ginger for treating primary dysmenorrhoea and to elucidate the efficacy of ginger for alleviating the symptoms of primary dysmenorrhoea
Author affiliations	Daily Manufacturing (USA) and a University in South Korea
Source of funds	Ministry of Trade, Industry and Energy, Korea
Declared interests of the review authors	James Daily is President of Daily Manufacturing, a manufacturer of dietary supplements; no other authors have any conflicts of interest
Review method of analysis	Meta-analysis SMD (95% CI) calculated for VAS using RevMan 5.0
Inclusion criteria	
Study design	RCTs
Population	Women (young?) with primary dysmenorrhoea
Intervention	Ginger
Comparator	Placebo
Other	None reported
Exclusion criteria	
Study design	In vitro studies, non clinical trial studies, Studies with only an abstract available,
Population	None reported
Intervention	Complex herbal remedies that included ginger as an ingredient
Comparator	None reported
Other	studies in which primary dysmenorrhoea was not the primary outcome
Date of documented search (month/year)	Not reported
Databases searched	12 databases including PubMed, EMBASE, Cochrane Library, Korean databases such as Dbpia, RISS, KISS, CNKI, the Chinese Scientific Journals Database, the Indian Medical Journals and the Indian Journals. Dissertations included.
Was an non-English database searched?	Yes Search conducted in databases with the proper languages of English, Korean and Chinese
Were studies in a LOTE included?	Yes No language barriers were imposed, but all included studies were in English
Outcomes considered in the SR (list)	SR included studies with primary dysmenorrhoea as the outcome

Characteristics of included reviews	Menstrual conditions (dysmenorrhoea)
Review ID	**Daily 2015**
Risk of bias measurement as reported in the SR	*Tool used*: Cochrane Tool *Authors summary*: The seven RCTs included in the SR had low to moderate risk of bias.

	Random Sequence Generation	Allocation Concealment	Patient and Practitioner Blinding	Assessor Blinding	Reporting Drop-out or Withdrawal	Intention-to Treat Analysis	Selective Outcome Reporting	Other Potential Bias	No. of Reference
Shirvani et al. (2014)	U	U	U	U	L	L	L	U	[28]
Kashefi et al. (2014)	U	U	L	L	L	L	L	U	[24]
Gupta et al. (2013)	U	U	H	H	L	U	U	U	[30]
Jenabi (2013)	L	U	U	U	L	L	L	U	[25]
Rahnama et al. (2012)	L	U	L	U	L	L	L	U	[27]
Halder (2011)	U	U	U	U	L	L	L	U	[26]
Ozgoli et al. (2009)	U	U	L	L	L	U	U	U	[29]

Authors conclusions (key message)	These RCTs provide suggestive evidence for the effectiveness of 750-2000mg ginger powder during the first 3-4 days of menstrual cycle for primary dysmenorrhoea.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	7 RCTs identified. 7 RCTs meet our PICO criteria. Total N=384 in eligible RCTs

	Study ID	*Summary RoB*	*Study design features (PICO)*	*Setting*
1	Jenabi 2013	Some concerns (blinding)	N=69 (35/34) Ginger 500 mg TID x 3 days	P: moderate to severe dysmenorrhoea I: Ginger C: Placebo O: Pain (VAS) S: College students, Iran
2	Rahnama 2012	Overall low risk	N=105 (59/46) Ginger 50 mg TID x 3 or 5 days (unclear which protocol was reported)	P: moderate to severe dysmenorrhoea I: Ginger C: Placebo O: Pain (VAS) and pain duration (hours) S: College students, Iran
3	Kashefi 2014	Some concerns (method of randomisation)	N=146 (47/45 placebo/54 zinc) Ginger 250 mg TID x 4 days for 2 cycles	P: moderate to severe dysmenorrhoea I: Ginger C: Placebo or Zinc O: Pain (VAS) S: Secondary students, Iran

Characteristics of included reviews	Menstrual conditions (dysmenorrhoea)			
Review ID	**Daily 2015**			
4	Ozgoli 2009	Some concerns (method of randomisation)	N=150 (50/50 ibuprofen/50 mefenamic acid) Ginger 250 mg QID x 3 days	P: moderate to severe dysmenorrhoea I: Ginger C: Ibuprofen or mefenamic acid O: Pain (VMS) S: College students, Iran
5	Shirvani 2014	Some concerns (method of randomisation, blinding)	N=122 (61/61) Ginger 250 mg QID	P: moderate to severe dysmenorrhoea I: Ginger C: Mefenamic acid O: Worst pain (VAS) and pain duration (days) S: College students, Iran
6	Halder 2012	Some concerns (method of randomisation, blinding)	N=75 (25/25 PMR/25 control) Ginger 1000 mg BID x 3 days	P: primary or secondary dysmenorrhoea I: Ginger C: Progressive muscle relaxation or control (no information) O: Dysmenorrhoea severity (5-point scale) S: College students, India
7	Gupta 2013	Some concerns (method of randomisation, blinding)	N=64 (34/30) Ginger 500 mg twice daily x 3 days	P: primary dysmenorrhoea I: Ginger + exercise C: Exercise (specified muscle strengthening and stretching exercises, 2 x 20 mins first 3 days of menstruation) O: Pain (NRS) and menstrual distress questionnaire (MDQ) S: Not specified
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= data extracted
= data extracted in more recent SR
= control is an active intervention (data not extracted)

Characteristics of included reviews	Premenstrual syndrome
Review ID	**Ghaderi 2020**
Review reference	Ghaderi, A., Asbaghi, O., Reiner, Ž., Kolahdooz, F., Amirani, E., Mirzaei, H., Banafshe, H. R., Maleki Dana, P., & Asemi, Z. (2020). The effects of saffron (Crocus sativus L.) on mental health parameters and C-reactive protein: A meta-analysis of randomized clinical trials. Complement Ther Med, 48, 102250. https://doi.org/10.1016/j.ctim.2019.102250
Review objective	to summarize all the existing RCTs evidence and to evaluate the effects of saffron intake on parameters of mental health and CRP.
Author affiliations	The authors were affiliated with tertiary institutions in Iran, Croatia and Canada
Source of funds	None declared
Declared interests of the review authors	The authors declare no conflict of interest
Review method of analysis	Meta-analysis: Weighted mean difference (WMD) with 95 % CI was used for pooling data to determine the effect sizes. The change score approach was used to calculate the effect size of saffron intake on the analyzed parameter. The random-effect model was used to report the pooled effect sizes using 95 % CI. Publication bias was evaluated using the funnel plots.
Inclusion criteria	
Study design	RCTs
Population	Not specified, only that mental health and c-reactive protein (CRP) were going to be measured.
Intervention	saffron
Comparator	Placebo
Other	Not specified
Exclusion criteria	Animal experiments, in vitro studies, case reports, observational studies, trials without a control group, and studies that did not achieve the least quality score were excluded from this meta-analysis
Study design	in vitro studies, case reports, observational studies, trials without a control group, and studies that did not achieve the least quality score were excluded.
Population	Animal experiments
Intervention	Not specified
Comparator	without control group
Other	Not specified
Date of documented search (month/year)	Jul-19
Databases searched	PubMed, Scopus, ISI, (Web of Science), Cochrane Central Register of Controlled Trials, EMBASE, Google Scholar
Was an non-English database searched?	No
Were studies in a LOTE included?	No

Characteristics of included reviews	Premenstrual syndrome			
Review ID	**Ghaderi 2020**			
Outcomes considered in the SR (list)	Effects of saffron on parameters of mental health and CRP with standard deviation (SD) and related 95 % confidence interval (CI) for the both intervention and placebo groups: 1) BDI, 2) BAI, 3) HAMD and 4) CRP.			
	Tool used	*Authors summary*		
Risk of bias of the included RCT studies as reported in the SR	Cochrane risk of bias tool	The authors report assessing Risk of bias, but do not provided any other information - other than noting the "*quality of all included studies was high*" . Individual RoB not reported.		
Authors conclusions (key message)	This meta-analysis demonstrated that saffron intake significantly reduced BDI, BAI and PSQI scores, but did not affect HDRS-D, HARS-A scores and CRP levels.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	Of the 21 RCTS that were included, one study met our PICO			
	total N =	47	participants that met our PICO	
	Study ID	*Summary RoB*	*Study design features (PICO)*	
1	Agha-Hosseini 2008	Individual RoB not reported.	N = 23/24 (47) Saffron 30mg/day, 8 weeks	P: Premenstrual syndrome I: Saffron C: Placebo O: HDRS-D S: Iran
2	--	Publication bias was evaluated by Egger's test. The results indicated no evidence of publication bias in the meta-analysis for the effects of saffron intake on HARS-A (P = 0.660), BAI (P = 0.857) and CRP (P =0.825). However, **there was publication bias for HDRS-D (P =0.013),** BDI (P<0.001) and PSQI (P = 0.015).		
3	--			

Characteristics of included reviews	Premenstrual syndrome			
Review ID	**Ghaderi 2020**			
4	--			
5	**Additional primary studies mentioned in other reviews for which there is insufficient information**			
6	*Study ID*	*Summary RoB*	*Study design features (PICO)*	
7	Najafi 2018	NR	N=118	P: PMS I: Chamomile 250mg capsule C: placebo O: PMS symptoms (NR)
8	Sharifi 2014	NR	N=90	P: PMS I: Chamomile 100mg capsule C: Mefenamic Acid (250mg, tid) O: PMS symptoms (emotional)
9	Karimian 2013	NR	N=90	P: PMS I: Chamomile 250mg capsule C: Mefenamic Acid (250mg, tid) O: PMS symptoms (physical)
10	Modaress 2011	NR	N=80	P: PMS I: Chamomile 250mg capsule C: Mefenamic Acid (250mg, tid) O: PMS symptoms (NR)
11	Canning 2010	NR	N=17	P: PMS I: St John's wort C: Placebo O: PMS symptoms (DSR)
12	Masumeh 2010	NR	N=85	P: PMS I: St John's wort C: Cellulose tablets O: PMS symptoms (DSR, anxiety, depression, carvings, hydration)

Characteristics of included reviews	Premenstrual syndrome			
Review ID	**Ghaderi 2020**			
13	Ozgoli 2009	NR	N=45	P: PMS I: Ginkgo biloba 40mg C: Placebo O: PMS symptoms, Severity of psychological symptoms
14	Hicks 2004	NR	N=64	P: PMS I: St John's wort C: Placebo O: PMS symptoms (diary)
15	Tamborini 1993	NR	N=165	P: PMS I: Ginkgo biloba 160mg C: Placebo O: PMS symptoms (DSR)
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= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Premenstrual syndrome	
Review ID	**Shinjo 2020**	
Review reference	Shinjyo, N., Waddell, G., & Green, J. (2020). Valerian Root in Treating Sleep Problems and Associated Disorders-A Systematic Review and Meta-Analysis. J Evid Based Integr Med, 25, 2515690x20967323. https://doi.org/10.1177/2515690x20967323	
Review objective	to evaluate the effectiveness of valerian as a treatment of sleep problems and associated disorders, and to discuss possible reasons behind the inconsistent research outcomes, by particularly focusing on the herbal preparations used in the studies	
Author affiliations	Authors were affiliated with tertiary institutions in Japan and the UK	
Source of funds	None declared	
Declared interests of the review authors	None declared	
Review method of analysis	Meta-analysis	Meta-analyses were performed using Meta-Essentials. Adjusted effect sizes (Hedges' g) were calculated from summary measures such as means and standard deviations or confidence intervals, odds ratio (for binary outcomes), and sample sizes, using reported formula. I2 statistic was used to estimate heterogeneity. Publication bias was evaluated using the funnel plots.
Inclusion criteria		
Study design	Clinical studies	
Population	sleep or related health problems	
Intervention	Valerian alone or in combination	
Comparator	Not specified	
Other		
Exclusion criteria	Articles published in any non-English language, studies using unknown substances, and studies on non-human subjects	
Study design	Reviews, unrelated studies, and works without available full text were excluded	
Population	Studies on non-human subjects.	
Intervention	Studies using unknown substance.	
Comparator	Not specified	
Other	Articles published in any non-English language	
Date of documented search (month/year)	Dec-19	
Databases searched	Pubmed, ScienceDirect and Cochrane Library	
Was an non-English database searched?	No	
Were studies in a LOTE included?	No	

Characteristics of included reviews	Premenstrual syndrome			
Review ID	**Shinjo 2020**			
Outcomes considered in the SR (list)	Any sleep measure (e.g., PSQI, ISI, sleepy diary), Anxiety, Safety and other rpeorted outcomes including symtpoms improvement (OCD), hot flashes, & pain severity (dysmenorohea)			
	Tool used	*Authors summary*		
Risk of bias of the included RCT studies as reported in the SR	Jadad	Jadad scores for all studies ranged between Jadad 1 and 5		
Authors conclusions (key message)	Valerian could be a safe and effective herb to promote sleep and prevent associated disorders However, Results suggested that inconsistent outcomes were possibly due to the variable quality of herbal extracts and that more reliable effects could be expected from the whole root/rhizome. In addition, therapeutic benefits could be optimized when it was combined with appropriate herbal partners. There were no severe adverse events associated with valerian intake in subjects aged between 7 and 80 years.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	Of the 60 identified studies, one study met our PICO			
	total N =	100	participants that met our PICO	
	Study ID	*Summary RoB*	*Study design features (PICO)*	
1	Behboodi Moghadam 2016	High quality (Jadad score 5)	N = 100, valerian 630 mg twice daily in the last 7 days of menstrual period for 3 cycles	P: Female students having premenstrual syndrome I: valerian C: Placebo O: severity or emotional, behavioural and physical premenstrual symptoms S: Not reported
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Characteristics of included reviews	Premenstrual syndrome
Review ID	**Shinjo 2020**
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Characteristics of included reviews	Premenstrual syndrome
Review ID	**Shinjo 2020**
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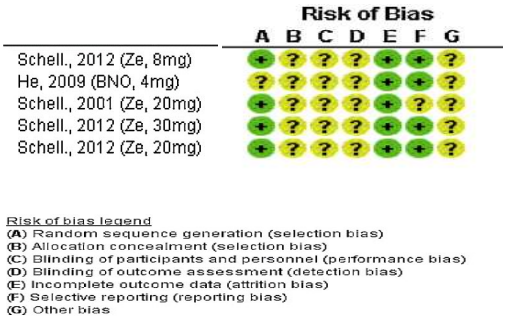
= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Premenstrual syndrome
Review ID	**Csupor 2019**
Review reference	Csupor, D., Lantos, T., Hegyi, P., Benkő, R., Viola, R., Gyöngyi, Z., Csécsei, P., Tóth, B., Vasas, A., Márta, K., Rostás, I., Szentesi, A., & Matuz, M. (2019). Vitex agnus-castus in premenstrual syndrome: A meta-analysis of double-blind randomised controlled trials. Complement Ther Med, 47, 102190. https://doi.org/10.1016/j.ctim.2019.08.024
Review objective	To perform a meta-analysis of double-blinded placebo RCTs using products with sufficiently characterised composition to provide reliable conclusions on the clinical efficacy of VAC for PMS
Author affiliations	All authors were affiliated with tertiary institutions in Hungary
Source of funds	The study was supported by an Economic Development and Innovation Operative Programme Grant [GINOP 2.3.2-15-2016-00048], the European Social Fund [EFOP-3.6.1-16-2016-00008], New National Excellence Program of the Ministry of Human Capacities [PTE/46539/2017], and a research grant [115796] from the National Research Development and Innovation Office.
Declared interests of the review authors	The authors declare no conflict of interest
Review method of analysis	Meta-analysis: All the statistical analyses were conducted using RevMan. The random effects model was used to calculate pooled relative risk (RR) and 95% confidence interval (CI). Summarised RRs were estimated using the average of the natural logarithm of the RRs of each study weighted by the inverse of its variance and then unweighted by a variance component that corresponded to the amount of heterogeneity in the analysis. A two-tailed $p < 0.05$ was considered statistically significant. I2 statistic was used to estimate heterogeneity. Publication bias was evaluated using the funnel plots.
Inclusion criteria	
Study design	Randomised placebo-controlled trials
Population	Premenstrual syndrome
Intervention	Chasteberry
Comparator	Placebo
Other	
Exclusion criteria	Trials that studied homeopathic preparations of VAC or VAC in combination with other treatments were excluded.
Study design	Non-placebo-controlled RCTs
Population	Not specified
Intervention	Homeopathic preparations of chasteberry or chasteberry combinations with other treatments
Comparator	Not specified
Other	Not specified
Date of documented search (month/year)	Feb-19
Databases searched	Pubmed, Embase, the Cochrane Central Register of Controlled trials, and Web of Science
Was an non-English database searched?	No
Were studies in a LOTE included?	No

Characteristics of included reviews	Premenstrual syndrome
Review ID	**Csupor 2019**
Outcomes considered in the SR (list)	Efficacy (Responder rate)
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Jadad scale & Cochrane ROB *Authors summary*: 
Authors conclusions (key message)	VAC preparations were confirmed to be effective in the reduction of PMS symptoms: women taking VAC were 2.57 (95% CI 1.52–4.35) times more likely to experience a remission in their symptoms compared to those taking the placebo.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	All three studies were included total N = 520 participants that met our PICO

	Study ID	*Summary RoB*	*Study design features (PICO)*	
1	Schellenberg 2012	High quality (Jadad score 4)	N= 35/35 chaste tree ZE440 8, 20 & 30mg	P: premenstrual syndrome (18 to 45 yrs) I: chaste berry C: Placebo O: total symptom score (VAS), responders (decrease in TSS of ≥50%) S: Germany
2	He 2009	High quality (Jadad score 4)	N= 208 chaste tree BNO1095 4mg	P: premenstrual syndrome I: chaste berry C: Placebo O: PMS self rating scale (VAS), PMSD (symptom diary), responders (improvement in PMSD of ≥60%) S: China
3	Schellenberg 2001	High quality (Jadad score 4)	N= 140 chaste tree ZE440, 20mg	P: premenstrual syndrome I: chaste berry C: Placebo O: clinical global impression (VAS), responders (decrease in TSS of ≥50%) S: Germany

Characteristics of included reviews	Premenstrual syndrome
Review ID	**Csupor 2019**
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Characteristics of included reviews	Premenstrual syndrome
Review ID	**Csupor 2019**
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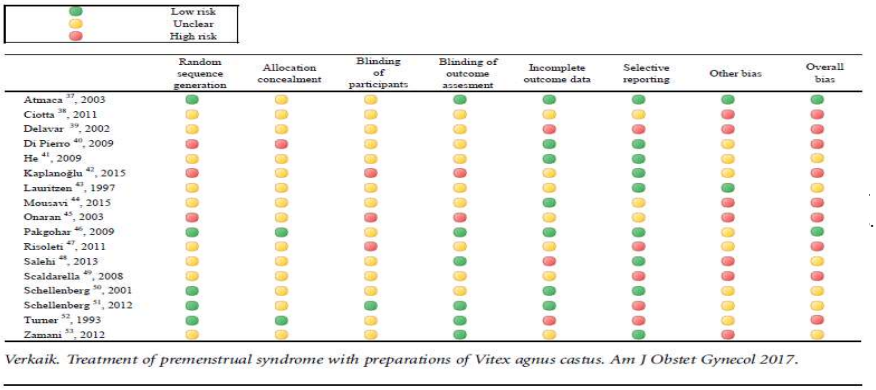
= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Premenstrual syndrome	
Review ID	**Verkaik 2017**	
Review reference	Verkaik, S., Kamperman, A. M., van Westrhenen, R., & Schulte, P. F. J. (2017). The treatment of premenstrual syndrome with preparations of Vitex agnus castus: a systematic review and meta-analysis. Am J Obstet Gynecol, 217(2), 150-166. https://doi.org/10.1016/j.ajog.2017.02.028	
Review objective	to determine the efficacy, tolerability, and acceptability of Vitex agnus castus preparations for treatment of premenstrual syndrome.	
Author affiliations	Authors were affiliated with tertiary institutions in the Netherlands	
Source of funds	None declared	
Declared interests of the review authors	Three authors declare no conflict of interest. One author	
Review method of analysis	Meta-analysis	we calculated pooled estimates using biascorrected standardized mean estimates, ie, Hedges g, with 95% CI between the intervention group and the control group at the end of the trial. Cochran Q test, I2, and T-squared (T2) statistics were used to quantify heterogeneity across trials. Heterogeneity was further explored by conducting sensitivity analyses within the subset of placebo controlled trials with overall PMS symptoms as outcome.
Inclusion criteria		
Study design	RCT	
Population	Trials among women of reproductive age diagnosed with PMDD or PMS	
Intervention	Chaste tree	
Comparator	placebo or pharmacotherapy	
Other		
Exclusion criteria	Trials that studied homeopathic preparations of VAC and combinations of VAC with other treatments were excluded.	
Study design	Conference abstracts, case series, and case reports	
Population	Not specified	
Intervention	Combination of chaste tree with homeopathic preparations	
Comparator	Not specified	
Other	Not specified	
Date of documented search (month/year)	Dec-14	
Databases searched	Embase, Medline, Web of Science, Scopus, PsycINFO, Cochrane, Pubmed, Google scholar	
Was an non-English database searched? Were studies in a LOTE included?	No	
	Yes	Four studies written in Farsi, three were in Italian and two in Turkish.

Characteristics of included reviews	Premenstrual syndrome
Review ID	**Verkaik 2017**
Outcomes considered in the SR (list)	Efficacy and safety Analysis were stratified for overall PMS symptoms and specific psychiatric PMS symptoms within the subset of placebo controlled studies
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane Risk of Bias Tool *Authors summary*: Th Si:
Authors conclusions (key message)	Although meta-analysis shows a large pooled effect of Vitex agnus castus in placebo-controlled trials, the high risk of bias, high heterogeneity, and risk of publication bias of the included studies preclude a definitive conclusion.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	All seventeen studies were included. There are only 2 studies for which the reviewers rate the risk of bias within the studies as low. Six studies have a moderate risk of bias, while 9 studies are rated as having a high risk of bias. 2401 All seventeen studies



Verkaik. Treatment of premenstrual syndrome with preparations of Vitex agnus castus. Am J Obstet Gynecol 2017.

	Study ID	*Summary RoB*	*Study design features (PICO)*	
1	Atmaca 2003	Low risk	N = 41 chaste tree 20-40mg vs fluoxetine 40mg for 8 weeks	P: PMDD I: chaste tree C: fluoxetine O: Daily symptom rating; HAM-D, CGI-SI;CGI-I)
2	Cioatta 2011	High risk	N = 31/26 chaste tree 20 mg vs fluoxetine 20-40mg for 2 months	P: PMDD I: chaste tree C: fluoxetine O: 4 Item HAM-D (depressed mood, work interest, psychic anxiety, general somatic symptoms)
3	Delavar 2002	High risk	N = 82 chaste tree 40 mg or magnesium oxide 300 mg/d for 3 menstrual cycles	P: PMDD I: chaste tree C: magnesium O: VAS on 8 symptoms

Characteristics of included reviews	Premenstrual syndrome			
Review ID	**Verkaik 2017**			
4	Di Pierro 2009	High risk	N = 42/40, chaste tree 40 mg tablet once daily/ 300 mg oxidize once daily	P: PMS I: chaste tree C: magnesium O: severity or emotional, behavioural and physical premenstrual symptoms
5	He 2009	Unclear risk	N = 217/202, chaste tree 40 mg daily for 3 cycles	P: PMS I: Chaste tree C: placebo O: PMSD and PMTS
6	Kaplanoglu 2015	*High risk*	N = 120 chaste tree 20 mg or placebo 10 drops of water for 3 menstrual cycles	P: PMS I: chaste tree C: placebo OR oral contraceptive pill O: VAS on 15 symptoms
7	Lauritzen 1997	Unclear risk	N = 127/127/105 chaste tree (3.5-4.2 mg per day) vs placebo OR pyridoxine-HCL (100mg of pyridoxine-HCL twice daily)	P: PMS I: chaste tree C: pyridoxine-HCL O: PMTS, CGI
8	Mousavi 2015	High risk	N = 72 chaste tree or placebo, 40 drops for 3 cycles	P: PMS I: chaste tree C: placebo O: VAS
9	Onaran 2003	High risk	N = 124 chaste tree 40 mg or 100 ug vs 20ug oral contraceptive for 3 menstrual cycles)	P: PMS I: chaste tree C: contraceptive O: COPE, HADS (depression/ anxiety)
10	Pakgohar 2009	Low risk	N = 116/99 chaste tree 4.3-4.8 mg extract vs placebo for 2 cycles	P: PMS I: chaste tree C: placebo O: Daily symptom rating scale
11	Risoleti 2011	High risk	N = 72 chaste tree 1 tablet daily vs placebo vs contraceptive for 3	P: PMS I: chaste tree C: placebo OR contraceptive O: PMSD
12	Salehi 2013	Unclear risk	N = 225 chaste tree 1 tablet daily vs St John's wort vs vitamin E for 2 cycles	P: PMS I: chaste tree and St John's wort C: St John's wort OR Vitamin E O: PMTS

Characteristics of included reviews	Premenstrual syndrome			
Review ID	**Verkaik 2017**			
13	Scaldarella 2008	High risk	N = 60 chaste tree 1 tablet daily vs pyridoxine for 3 cycles	P: PMS I: chaste tree C: pyridoxine O: VAS
14	Schellenberg 2001	Unclear risk	N = 178/170 chaste tree 20mg daily vs placebo for 3 cycles	P: PMS I: chaste tree C: placebo O: Daily symptom rating scale
15	Schellenberg 2012	Unclear risk	N = 162 chaste tree 8/20/30mg vs placebo for 3 menstrual cycles	P: PMS I: chaste tree C: placebo O: VAS
16	Turner 1993	High risk	N = 600 ITT /217 PP chaste tree 1800 mg a day vs soy based placebo for 3 months	P: PMS I: chaste tree C: placebo O: Moos Menstrual Distress Questionnaire
17	Zamani 2012	Unclear risk	N = 134/128 chaste tree vs placebo 40 drops for 6 days before menses for 6 cycles	P: PMS I: chaste tree C: placebo O: Moos Menstrual Distress Questionnaire

= data extracted

= data extracted from more recent SR (or better SR)

= control is an active intervention

Characteristics of included reviews	Premenstrual syndrome	
Review ID	**van Die 2013**	
Review reference	van Die, M. D., Burger, H. G., Teede, H. J., & Bone, K. M. (2013). Vitex agnus-castus extracts for female reproductive disorders: a systematic review of clinical trials. Planta Med, 79(7), 562-575. https://doi.org/10.1055/s-0032-1327831	
Review objective	to identify and systematically review all the data generated from randomised, controlled trials (RCTs) on the efficacy of Vitex agnus-castus in these conditions.	
Author affiliations	All authors were affiliated with tertiary institutions in Australia	
Source of funds	Not speficied	
Declared interests of the review authors	One author is a founder and director of research and development of MediHerb Australia Pty. Ltd. and is rela	
Review method of analysis	Meta-analysis	Meta-analysis was performed using Revman
Inclusion criteria		
Study design	RCTs	
Population	Female reproductive conditions	
Intervention	Chaste tree	
Comparator	placebo or comparator treatment	
Other		
Exclusion criteria	Studies investigating multicomponent herbal formulations and homoeopathic preparations were excluded	
Study design		
Population	Not specified	
Intervention	Not specified	
Comparator	Studies investigating multicomponent herbal formulations and homoeopathic preparations	
Other	Not specified	
Date of documented search (month/year)	2012'	
Databases searched	Medline, PubMed, EMBASE, The Cochrane Library, CINAHL, Ovid, Google scholar, and Web of Science	
Was an non-English database searched? Were studies in a LOTE included?	No	
	Yes	No language restrictions were imposed.

Characteristics of included reviews	Premenstrual syndrome			
Review ID	**van Die 2013**			
Outcomes considered in the SR (list)	Not specified			
	Tool used	*Authors summary*		
Risk of bias of the included RCT studies as reported in the SR	Jadad scale & Cochrane	High risk of bias was only detected in two of the studies, on one, two, and three of the criteria, respectively. Overall, low risk of bias was most commonly identified for reporting bias (all studies), selection and attrition bias.		
Authors conclusions (key message)	The results from randomised, controlled trials to date suggest benefits for Vitex extracts in the treatment of premenstrual syndrome, premenstrual dysphoric disorder and latent hyperprolactinaemia. Further research is recommended, and greater transparency in reporting for future trials.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	12 RCTs, eight met our PICO			
	total N =	2681	participants that met our PICO	
	Study ID	*Summary RoB*	*Study design features (PICO)*	
1	Di Pierro 2009	Unclear risk	N = 42/40, chaste tree 40 mg once daily / 300 mg oxidize once daily	P: PMS I: chaste tree C: Magnesium O: severity or emotional, behavioural and physical premenstrual symptoms
2	He 2009	Unclear risk	N = 217/ 202, chaste tree 40 mg daily for 3 cycles	P: PMS I: Chaste tree C: placebo O: PMSD and PMTS
3	Lauritzen 1997	High risk	N = 127/127/105 chaste tree 3.5-4.2 mg per day/ placebo / 100mg of pyridoxine-HCL twice daily	P: PMS I: chaste tree C: placebo OR pyridoxine-HCL O: PMTS, CGI

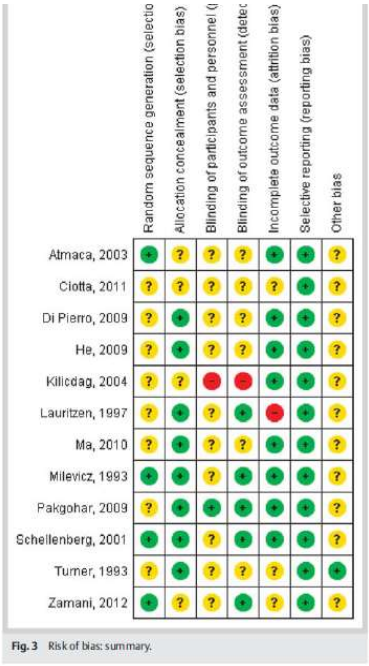


Fig. 3 Risk of bias: summary.

Characteristics of included reviews	Premenstrual syndrome			
Review ID	**van Die 2013**			
4	Ma 2010	Unclear risk	N = 67/33 (chaste tree 40 mg once daily vs placebo for 3 cycles)	P: PMS I: chaste tree C: placebo O: PMSD and PMTS
5	Pakgohar 2009	Unclear risk	N = 116/99 (chaste tree 4.3-4.8 mg extract vs placebo for 2 cycles)	P: PMS I: chaste tree C: placebo O: Daily symptom rating scale
6	Schellenberg 2001	Unclear risk	N = 178/170 (chaste tree 20mg daily vs placebo for 3 cycles)	P: PMS I: chaste tree C: placebo O: Daily symptom rating scale
7	Turner 1993	Unclear risk	N = 600/217 (chaste tree 1800 mg a day/ soy based placebo for 3 months)	P: PMS I: chaste tree C: placebo O: Moos Menstrual Distress Questionnaire
8	Zamani 2012	Unclear risk	N = 134/128 (chaste tree 40 drops for 6 days before menses vs placebo)	P: PMS I: chaste tree C: placebo O: Moos Menstrual Distress Questionnaire
9	Ciotta 2011	Unclear risk	N = 31/26 (chaste tree 20 mg vs fluoxetine 20-40mg for 2 months)	P: PMDD I: chaste tree C: fluoxetine O: 4 Item HAM-D (depressed mood, work interest, psychic anxiety, general somatic symptoms)
10	Atmaca 2003	Unclear risk	N = 41 (chaste tree 20-40mg vs fluoxetine 40mg for 8 weeks)	P: PMDD I: chaste tree C: fluoxetine O: Daily symptom rating; HAM-D, CGI-SI;CGI-I
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Characteristics of included reviews	Premenstrual syndrome
Review ID	**van Die 2013**
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= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Symptoms of menopause
Review ID	**Castelo-Branco 2021**
Review reference	Castelo-Branco C, Gambacciani M, Cano A, Minkin MJ, Rachoń D, Ruan X, et al. Review & meta-analysis: isopropanolic black cohosh extract iCR for menopausal symptoms – an update on the evidence. Climacteric. 2021;24(2):109-19. 10.1080/13697137.2020.1820477
Review objective	This review's purpose is to give a current update and overview of all placebo-controlled clinical data (irrespective of publication date) and additional data from clinical studies with iCR during a broader time span ranging from the establishment of the EU Guideline on Good Clinical Practice E6 in 1997 until January 2020
Author affiliations	Clinic Institute of Gnyecology, Obstetrics and Neonatology, Faculty of Medicine, University of Barcelona, Hospital Clinic-Institut d'Investigacions Biomediques
Source of funds	Nil.
Declared interests of the review authors	1 author received fees from Schaper & Brummer (manufacturer of iCR) outside the submitted work in 2019. 2 authors are employees of Schaper & Brummer (manufacturer).
Review method of analysis	Meta-analysis The meta-analysis was performed using SAS version 9.4 under the fixed-effect size model. For studies that did not directly report the standardized group difference and the corresponding confidence interval, these parameters were deduced either from the published means, standard deviations, and sample size N or from the published means, sample size N, and p-values
Inclusion criteria	
Study design	Any
Population	Menopausal symptoms
Intervention	medical use of iCR (Cimicifuga racemosa syn. Actaea racemosa [black cohosh])
Comparator	Any
Other	No restrictions regarding patients' ages, menopausal status, and treatment duration were made
Exclusion criteria	
Study design	No restrictions
Population	No restrictions
Intervention	iCR as herbal medicine (not food)

Characteristics of included reviews	Symptoms of menopause
Review ID	**Castelo-Branco 2021**
Comparator	No restrictions
Other	
Date of documented search (month/year)	1997 to Jan 2020
Databases searched	MEDLINE, EMBASE, EMBASE Alert, BIOSIS, and PubMed
Was an non-English database searched? Were studies in a LOTE included?	No Not specified
Outcomes considered in the SR (list)	Outcomes: neurovegetative and psychological climacteric symptoms additional clinical benefits, occurrence and frequency of adverse events, and influence on liver, hormones, and estrogen-sensitive organs
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: revised Cochrane RoB v2.0 *Authors summary*

RCT (Author, Year)	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
Jiang, 2015	+	+	+	+	?	?
Li Yilin, 2011	?	−	−	+	?	−
Osmers, 2005	+	+	+	+	+	+
Stoll, 1987	+	+	+	+	+	+
Jacobson, 2001	?	+	+	+	?	?
Uebelhack, 2006	+	+	+	+	+	+

+ Low risk ? Some concerns − High risk

Figure 1. Risk of bias assessment of the placebo-controlled randomized controlled trials (RCTs).

Characteristics of included reviews	Symptoms of menopause			
Review ID	**Castelo-Branco 2021**			
Authors conclusions (key message)	the clinical data and our meta-analysis consistently demonstrate that iCR/iCRþHP is an effective and safe, evidence-based treatment option for natural neurovegetative and psychological climacteric symptoms, meeting increasing patients' demands for non-hormonal, herbal therapies. As benefits clearly outweigh risks, iCR/iCRþHP should be recommended to these women. With its good safety profile in general and at estrogen-sensitive organs, iCR can also be used in patients with hormone-dependent tumors suffering from iatrogenic menopausal symptoms.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	1 MA, 16 RCTs and 19 open controlled studies found. The 6 placebo-controlled trials were reported and discussed in detail. Others were narratively described. Total N not reported			
	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Jiang 2015	Overall unclear risk of bias	N=48 (24/24) iCR 40 mg 6 months	P: Symptoms of menopause (45-60yrs) I: Black cahoosh C: Placebo O: Sleep quality, wake-onset, MenQoL S: Asian
2	Li 2011	Overall high risk of bias	N=77 (45/32) iCR 40 mg 3 months	P: Symptoms of menopause (45-55 yrs) I: Black cahoosh C: Placebo O: KMI, hot flushes S: Asian
3	Osmers 2005	Overall low risk of bias	N=304 (153/151) iCR 40 mg 3 months	P: Symptoms of menopause (>45 yrs) I: Black cahoosh C: Placebo O: MRS total, vasomotor symptoms S: NR, caucasian
4	Stoll 1987	Overall low risk of bias	N=50 (30/20) iCR 8mg 3 months	P: Symptoms of menopause (46-58 yrs) I: Black cahoosh C: Placebo O: KMI, HAM-A S: NR, caucasian
5	Jacobson 2001	Overall unclear risk of bias	N=77 (42/43) iCR 40 mg 2 months	P: Menopause due to breast cancer I: Black cahoosh C: Placebo O: hot flushes S: NR, causasian, Asian, African-American
6	Uelelhack 2006	Overall low risk of bias	N=301 (151/150) iCR + St John's 128 mg 4 months	P: Symptoms of menopause (45-60 yrs) I: Black cahoosh+ St John's wort C: Placebo O: MRS, HAM-D S: NR, caucasian
7	The review authors also identify 10 RCTs (study ID listed below) comparing iCR with another intervention (such as hormone therapy, vitamins/minerals, or antidepressants). Data for these studies were not reported.			
8	Liske 2002, Sun 2012, Chen 2014, Chen 2013, Bai 2007, Wang 2019, Zhang 2015, Huang 2013, Nappi 2005, Xi 2014			

Characteristics of included reviews	Symptoms of menopause
Review ID	**Castelo-Branco 2021**
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16	HAMA, Hamilton Rating Scale for Anxiety; HAMD, Hamilton Rating Scale for Depression; HT; KMI, Kupperman Menopause Index; Men-QoL, Menopause-specific Quality of Life Questionnaire; MRS, Menopause Rating Scale
	= data extracted
	= data extracted from more recent SR (or better SR)
	= control is an active intervention

Characteristics of included reviews	Symptoms of menopause
Review ID	**Firoozeei 2021**
Review reference	Firoozeei TS, Feizi A, Rezaeizadeh H, Zargaran A, Roohafza HR, Karimi M. The Antidepressant Effects of Lavender (Lavandula angustifolia Mill.): A Systematic Review and Meta-Analysis of Randomized Controlled Clinical Trials. Complementary Therapies in Medicine. 2021:102679. https://dx.doi.org/10.1016/j.ctim.2021.102679
Review objective	the aim of this study was to determine the efficacy of lavender on depression severity
Author affiliations	Department of Traditional Medicine, School of Persian Medicine, Tehran University of Medical Sciences
Source of funds	In a collaborative study between Tehran University of Medical Sciences and Isfahan University of Medical Sciences, the research has been supported in part by Isfahan University of Medical Sciences. (Research Project NO:199280)
Declared interests of the review authors	The authors declared there were no conflicts of interest
Review method of analysis	Meta-analysis Meta-analysis was conducted using STATA software version 11.2 The standardized mean difference (SMD) was used to assess the effects of treatment on main outcome i.e. depression score. Heterogeneity was evaluated by using Cochran Q test and I-squared statistics and visual inspection of forest plot. effect size of lavender on depression score and corresponding 95 % CIs was calculated by random-effect model in cases of medium and high heterogeneity. Possible sources of heterogeneity were explored and adopted by sensitivity analysis, meta-regression, and subgroup analyses if possible. Publication bias assessed with funnelplot and Egger linear regression
Inclusion criteria	
Study design	RCTs
Population	Any disease of medical condition
Intervention	Lavender, all routes of administration
Comparator	Any (pacebo or active control)
Other	Antidepressant effects
Exclusion criteria	
Study design	RCTs only
Population	No age or sex restrictions
Intervention	No restrictions

Characteristics of included reviews	Symptoms of menopause
Review ID	**Firoozeei 2021**
Comparator	No restrictions
Other	
Date of documented search (month/year)	Jan 200 to Dec 2020
Databases searched	PubMed, Scopus, Embase, Cochrane library and Web of science
Was an non-English database searched? Were studies in a LOTE included?	No Not specified
Outcomes considered in the SR (list)	Depression as the main outcome measure or as a subscale of any valid assessment tool.
Risk of bias of the included RCT studies as reported in the SR	*Tool used* *Authors summary* Cochrane & Jadad

Table 3
Cochrane risk of bias assessment (a) and Jadad score (b).

1 st Author (year)	Cochrane risk of bias	Jadad scores (Total score)	Reference number
Araj Khodai (2020),	H, L, L, L, L, L, L	1, 1,1, 0, 1 (4)	42
Bagheri Nesami (2017) Iran	L, U, U, U, U, U, L	1, 0, 0, 1, 0 (2)	38
Bahrami(2017)Iran	U, L, H, L, L, L, L	1, 0, 1, 0, 0 (2)	31
Bazrafshan(2020)Iran	U, U, U, L, L, L, L	1, 0, 0, 1, 0 (2)	30
Chen(2015)Taiwan	U, U, U, U, H, L, L	1, 0, 1, 0, 0 (2)	35
Effati-daryani (2017) Iran	L, L, H, L, L, L, L	1, 0, 1, 1, 0 (3)	32
Effati-Daryani(2015) Iran	L, L, H, L, L, L, L	1, 1, 1, 1, 0 (4)	33
Jafari(2019)Iran	L, L, U, U, L, L, L	1, 0, 1, 1, 0 (3)	28
Jokar (2018) Iran	L. L, H, L, L, L, L	1, 0, 1, 1, 0 (3)	30
Kianpour(2016)Iran	U, U, H, U, U, L, L	1, 0, 1, 1, 0 (3)	26
Kamalifard(2017)Iran	L, L, L, L, L, L, L	1, 1, 1, 1, 1 (5)	34
Kasper(2016) Germany	L, L, L, L, L, L, L	1, 1, 1, 1, 1 (5)	36
Lari(2020)Iran	L, L, H, L, H, L, L	1, 0, 1, 1, 0 (3)	27
Matsumoto(2013) Japan	U, U, H, U, U, U, L	1, 0, 0, 0, 0 (1)	25
Nategh (2020) Iran	U, U, H, U, L, L, L	1, 0, 1, 0, 0 (2)	40
Nikjou (2017), Iran	L, L, H, U, U, H, L	1, 1, 0, 1, 1 (4)	41
Uzuncakmak(2018) Turkey	U, U, U, U, L, L, L	1, 0, 1, 1, 0 (3)	37
Soden(2004)UK	U, L, U, L, L, H, L	1, 0, 0, 0, 0 (1)	24
Tayebi(2015)Iran	U, U, H, U, L, L, L	1, 0, 1, 1, 0 (3)	29

a: High risk (H), unclear risk (U) or low risk (L) of bias in random sequence generation.
allocation concealment, blinding of participants, blinding of outcome assessors. incomplete outcome data, selective outcome reporting, and other sources of. bias.
b: Yes (1) or No (0). The study is described as randomized, the study is double blind, the study has described the numbers and reasons of withdrawals and dropouts, the study has described an appropriate randomization method, the study has described an appropriate blinding method.

Characteristics of included reviews	Symptoms of menopause			
Review ID	**Firoozeei 2021**			
Authors conclusions (key message)	The current meta-analysis concludes that lavender has significant antidepressant effects. However, due to aforementioned limitations such as diversity of population under study and small sample sizes, further large clinical trials are recommended with more homogeneous populations and rigorous designs.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	19 eligible studies, 17 studies included in the synthesis (2 missing data) 1 RCT met out PICO			
	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Kamalifard 2017	Overall low risk of bias	N=48 (24/24) Lavender 500 mg bid 8 weeks	P: Menopausal depression I: Oral lavender OR Oral bitter orange C: Placebo (starch capsules) O: Beck Depression Inventory S: Iran
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8	--			

Characteristics of included reviews	Symptoms of menopause
Review ID	**Firoozeei 2021**
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= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Symptoms of menopause	
Review ID	**Kanadys 2021**	
Review reference	Kanadys W, Baranska A, Drop B, Malm M, Blaszczuk A, Polz-Dacewicz M, et al. Evaluation of clinical meaningfulness of red clover (Trifolium pratense l.) extract to relieve hot flushes and menopausal symptoms in peri-and post-menopausal women: A systematic review and meta-analysis of randomized controlled trials. Nutrients. 2021;13(4):1258. http://dx.doi.org/10.3390/nu13041258	
Review objective	To examine the efficacy of red clover isoflavones in relieving hot flushes and menopausal symptoms in perimenopausal and postmenopausal women.	
Author affiliations	1. Department of Informatics and Medical Statistics, Medical University of Lublin, 20-090 Lublin, Poland; 2. Department of Virology with SARS Laboratory, Medical University of Lublin, 20-093 Lublin, Poland; 3. Department of Social Medicine and Public Health, Warsaw Medical University, 02-007 Warsaw, Poland;	
Source of funds	Nil.	
Declared interests of the review authors	The authors declared there were no conflicts of interest	
Review method of analysis	Meta-analysis	The random effects model was used to calculate the weighted mean difference (WMD) and 95% CI, and p < 0.05 considered significant. Cochrane Q and I2 statistic were used to assess the heterogeneity. The percentage of total variation indicated the degree of heterogeneity; I2 values of ≤25% were considered low, >25% as moderate, and ≥75% as high
Inclusion criteria		
Study design	parallel-group controlled trials (crossovers eligible)	
Population	perimenopausal and menopausal women experiencing moderate to severe hot flashes at tleast 3 x per day in a 2-week period	
Intervention	red clover isoflavone extract (RCIE)	
Comparator	placebo	
Other	primary outcome of change in freq. of hot flashes, symptom ratings	
Exclusion criteria		
Study design		
Population		
Intervention	RCIE was combined with other plant medicines,	

Characteristics of included reviews	Symptoms of menopause
Review ID	**Kanadys 2021**
Comparator	
Other	Studies were excluded if they were duplicated reports, the duration of the study was less than 12 weeks, lacked sufficien information, and if results were presented as graphics or percentage changes
Date of documented search (month/year)	1999 to Jan 2020
Databases searched	MEDLINE (PubMed), Embase, and the Cochrane Library
Was an non-English database searched? Were studies in a LOTE included?	No Not specified
Outcomes considered in the SR (list)	primary outcome of change in freq. of hot flashes, symptom ratings scales
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane risk of bias tool *Authors summary*: Several trials were characterized as "unclear risk", relating to the lack of sufficient information in the categories random sequence generation (selection bias) and allocation concealment (selection bias). In the category of incomplete outcome data (attrition bias), "unclear bias" was demonstrated in 25% of studies; it was not clear whether dropouts were likely to influence results. With respect to the selective reporting category, five studies presented a "high risk of bias" associated with the lack of reports of adverse effects.

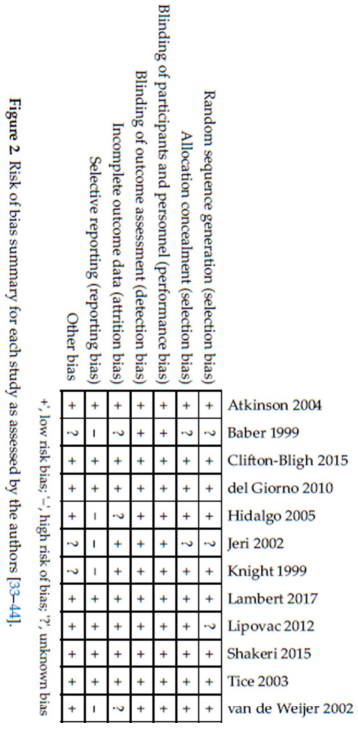

Figure 2. Risk of bias summary for each study as assessed by the authors [33–44].

Characteristics of included reviews	Symptoms of menopause			
Review ID	**Kanadys 2021**			
Authors conclusions (key message)	This meta-analysis of randomized controlled trials assessing the effect of a specific standardized extract of red clover isoflavones on menopausal symptoms showed a statistically moderate relationship with the reduction in the daily frequency of hot flushes. However, further well-designed studies are required to confirm the present findings and to finally determine the effects of red clover on the relief of flushing episodes, to provide more comprehensive information about well-defined preparations, and the optimal dose and duration of taking red clover aglycones to achieve their highest effectiveness.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	Overall, 1179 women experiencing menopause participated in the 12 studies, and sample size ranged from 37 to 252 (1043 participants were included in the final analysis). The average red clover isoflavone dose was 65.1 mg/day.			
	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Knight 1999	Overall high risk of bias	N=37 Red clover 160 mg/ 40 mg 12 weeks	P: Menopausal symptoms (40-65 yrs) I: Red clover C: Placebo O: hot flashes, GCS S: Australia
2	Baber 1999	Overall high risk of bias	N=51 Red clover 40 mg 90 days	P: Menopausal symptoms (45-65 yrs) I: Red clover C: Placebo O: hot flashes, GCS S: Australia
3	Jeri 2002	Overall high risk of bias	N=30 Red clover 40 mg 16 weeks	P: Menopausal symptoms (<60 yrs) I: Red clover C: Placebo O: hot flashes, S: Peru
4	van de Weijer 2002	Overall high risk of bias	N=30 (ITT) 26 (PP) Red clover 80 mg 12 weeks	P: Menopausal symptoms (49-65 yrs) I: Red clover C: Placebo O: hot flashes, GCS S: Netherlands
5	Tice 2003	Overall low risk of bias	N=252 Red clover 80 / 57 mg 12 weeks	P: Menopausal symptoms (45-60 yrs) I: Red clover C: Placebo O: hot flashes, S: USA
6	Atkinson 2004	Overall low risk of bias	N=205 (ITT) 99 (PP) Red clover 40 mg 12 months	P: Menopausal symptoms (49-65 yrs) I: Red clover C: Placebo O: hot flashes, GCS S: UK
7	Hidalgo 2005	Overall high risk of bias	N=60 (ITT) 53 (PP) Red clover 80 mg 90 days	P: Menopausal symptoms (>40 yrs) I: Red clover C: Placebo O: hot flashes, KMI S: Ecuador
8	del Giorno 2010	Overall low risk of bias	N=120 (ITT) 100 (PP) Red clover 40 mg 12 months	P: Menopausal symptoms (45-65 yrs) I: Red clover C: Placebo O: hot flashes, KMI S: Brazil

Characteristics of included reviews	Symptoms of menopause			
Review ID	**Kanadys 2021**			
9	Lipovac 2012	Overall unclear risk of bias	N=113 (ITT) 109 (PP) Red clover 80 mg 12 months	P: Menopausal symptoms (>40 yrs) I: Red clover C: Placebo O: hot flashes, KMI S: Austria
10	Clifton-Bligh 2015	Overall low risk of bias	N=147 (ITT) 103 (PP) Red clover 57 mg 2 years	P: Menopausal symptoms (45-65 yrs) I: Red clover C: Placebo O: hot flashes, GCS S: Australia
11	Shakeri 2015	Overall low risk of bias	N=72 (ITT) 71 (PP) Red clover 80 mg 12 weeks	P: Menopausal symptoms (50-59 yrs) I: Red clover C: Placebo O: hot flashes, MRS S: Iran
12	Lambert 2017	Overall low risk of bias	N=62 (ITT) 59 (PP) Red clover 37.1 mg 12 weeks	P: Menopausal symptoms (40-65 yrs) I: Red clover C: Placebo O: hot flashes, GCS S: Denmark
13	--			
14	--			
15	--			
16	GCS, Greene Climacteric Scale; KMI, Kupperman Menopausal Index; MRS, Menopause Rating Scale			

= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Symptoms of menopause	
Review ID	**Ghaderi 2020**	
Review reference	Ghaderi, A., Asbaghi, O., Reiner, Ž., Kolahdooz, F., Amirani, E., Mirzaei, H., Banafshe, H. R., Maleki Dana, P., & Asemi, Z. (2020). The effects of saffron (Crocus sativus L.) on mental health parameters and C-reactive protein: A meta-analysis of randomized clinical trials. Complement Ther Med, 48, 102250. https://doi.org/10.1016/j.ctim.2019.102250	
Review objective	to summarize all the existing RCTs evidence and to evaluate the effects of saffron intake on parameters of mental health and CRP.	
Author affiliations	The authors were affiliated with tertiary institutions in Iran, Croatia and Canada	
Source of funds	Nil.	
Declared interests of the review authors	The authors declared there were no conflicts of interest	
Review method of analysis	Meta-analysis	Weighted mean difference (WMD) with 95 % CI was used for pooling data to determine the effect sizes. The change score approach was used to calculate the effect size of saffron intake on the analyzed parameter. The random-effect model was used to report the pooled effect sizes using 95 % CI. Publication bias was evaluated using the funnel plots.
Inclusion criteria		
Study design	RCTs	
Population	Not specified, only that mental health and c-reactive protein (CRP) were going to be measured.	
Intervention	saffron	
Comparator	Placebo	
Other	Not specified	
Exclusion criteria		
Study design	Animal experiments, in vitro studies, case reports, observational studies, trials without a control group, and studies that did not achieve the least quality score were excluded from this meta-analysis	
Population	Animal experiments	
Intervention	Not specified	

Characteristics of included reviews	Symptoms of menopause
Review ID	**Ghaderi 2020**
Comparator	without control group
Other	Not specified
Date of documented search (month/year)	Inception to July 2019
Databases searched	PubMed, Scopus, ISI, (Web of Science), Cochrane Central Register of Controlled Trials, EMBASE, Google Scholar
Was an non-English database searched?	No
Were studies in a LOTE included?	No
Outcomes considered in the SR (list)	Effects of saffron on parameters of mental health and CRP with standard deviation (SD) and related 95 % confidence interval (CI) for the both intervention and placebo groups: 1) BDI, 2) BAI, 3) HAMD and 4) CRP.
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane risk of bias tool *Authors summary*: The authors report assessing Risk of bias, but do not provided any other information - other than noting the "*quality of all included studies was high*" . Individual RoB not reported.

Characteristics of included reviews	Symptoms of menopause			
Review ID	**Ghaderi 2020**			
Authors conclusions (key message)	This meta-analysis demonstrated that saffron intake significantly reduced BDI, BAI and PSQI scores, but did not affect HDRS-D, HARS-A scores and CRP levels.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	Of the 21 RCTS that were included, one study met our PICO			
	total N =	56	participants that met our PICO	
	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Kashani 2018	NR	N=56 (28/28) Saffron 30 mg/day 6 weeks	P: Menopausal symptoms (mean 55 yrs) I: Saffron C: Placebo O: HAM-D S: Iran
2	--	Publication bias was evaluated by Egger's test. The results indicated no evidence of publication bias in the meta-analysis for the effects of saffron intake on HARS-A (P = 0.660), BAI (P = 0.857) and CRP (P =0.825). However, there was publication bias for HDRS-D (P =0.013), BDI (P<0.001) and PSQI (P = 0.015).		
3	--	Saffron intake did not affect HDRS-D (6 studies) (WMD: -1.61; 95 % CI: -5.81, 2.58)		
4	--			
5	--			
6	--			
7	--			
8	--			

Characteristics of included reviews	Symptoms of menopause
Review ID	Ghaderi 2020
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16	--

= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Symptoms of menopause
Review ID	**Shinjyo 2020**
Review reference	Shinjyo, N., Waddell, G., & Green, J. (2020). Valerian Root in Treating Sleep Problems and Associated Disorders-A Systematic Review and Meta-Analysis. J Evid Based Integr Med, 25, 2515690x20967323. https://doi.org/10.1177/2515690x20967323
Review objective	to evaluate the effectiveness of valerian as a treatment of sleep problems and associated disorders, and to discuss possible reasons behind the inconsistent research outcomes, by particularly focusing on the herbal preparations used in the studies
Author affiliations	Authors were affiliated with tertiary institutions in Japan and the UK
Source of funds	Nil.
Declared interests of the review authors	The authors declared there were no conflicts of interest
Review method of analysis	Meta-analysis: Meta-analyses were performed using Meta-Essentials. Adjusted effect sizes (Hedges' g) were calculated from summary measures such as means and standard deviations or confidence intervals, odds ratio (for binary outcomes), and sample sizes, using reported formula. I2 statistic was used to estimate heterogeneity. Publication bias was evaluated using the funnel plots.
Inclusion criteria	
Study design	Clinical studies
Population	sleep or related health problems
Intervention	Valerian alone or in combination
Comparator	Not specified
Other	
Exclusion criteria	
Study design	Reviews, unrelated studies, and works without available full text were excluded
Population	Studies on non-human subjects.
Intervention	Studies using unknown substance.

Characteristics of included reviews	Symptoms of menopause
Review ID	**Shinjyo 2020**
Comparator	Not specified
Other	Articles published in any non-English language
Date of documented search (month/year)	inception to Dec 2019
Databases searched	Pubmed, ScienceDirect and Cochrane Library
Was an non-English database searched?	No
Were studies in a LOTE included?	No
Outcomes considered in the SR (list)	Any sleep measure (e.g., PSQI, ISI, sleepy diary), Anxiety, Safety and other reported outcomes including symtpoms improvement (OCD), hot flashes, & pain severity (dysmenorohea)
Risk of bias of the included RCT studies as reported in the SR	*Tool used* / *Authors summary*
	Jadad / Jadad scores for all studies ranged between Jadad 1 and 5

Characteristics of included reviews	Symptoms of menopause			
Review ID	**Shinjyo 2020**			
Authors conclusions (key message)	Valerian could be a safe and effective herb to promote sleep and prevent associated disorders However, Results suggested that inconsistent outcomes were possibly due to the variable quality of herbal extracts and that more reliable effects could be expected from the whole root/rhizome. In addition, therapeutic benefits could be optimized when it was combined with appropriate herbal partners. There were no severe adverse events associated with valerian intake in subjects aged between 7 and 80 years.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	Of the 60 identified studies, 3 study met our PICO			
	total N =	100	participants that met our PICO	
	Study ID	*Summary RoB*	*Study design features (PICO)*	
1	Jenabi 2017	Jadad score 4	N=60 (NR) Valerian root 225 mg tid 8 weeks	P: Menopausal symptoms with hot flashes I: Valerian root C: Placebo O: Severity and frequency of hot flashes S: NR
2	Mirabi 2013	Jadad score 4	N=68 (NR) Valerian root 675 mg / day 8 weeks	P: Menopausal symptoms with hot flashes I: Valerian root C: Placebo O: Severity and frequency of hot flashes S: NR
3	Taavoni 2011	Jadad score 4	N=100 (NR) Valerian root 530 mg bid 4 weeks	P: Menopausal symptoms with insomnia (self-reported) I: Valerian root C: Placebo O: PSQI S: NR
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8	--			

Characteristics of included reviews	Symptoms of menopause
Review ID	Shinjyo 2020
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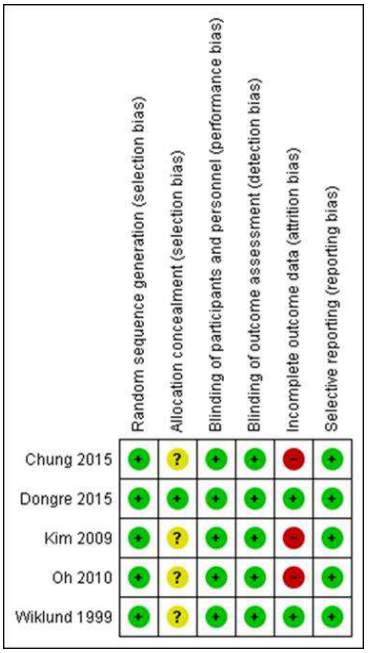
16	--

= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Symptoms of menopause
Review ID	**Ghorbani 2019**
Review reference	Ghorbani Z, Mirghafourvand M. A meta-analysis of the efficacy of panax ginseng on menopausal women's sexual function. International Journal of Women's Health and Reproduction Sciences. 2019;7(1):124-33. http://dx.doi.org/10.15296/ijwhr.2019.20
Review objective	This study was designed to evaluate the efficacy and adverse events of ginseng that could be used as a herbal medicine in women with sexual dysfunction.
Author affiliations	Midwifery Department, Tabriz University of Medical Sciences, Iran.
Source of funds	Nil.
Declared interests of the review authors	The authors declared there were no conflicts of interest
Review method of analysis	Meta-analysis: RevMan software, version 5.3 was employed for data analysis. standardized mean difference (SMD) was reported using Random effect model. I2 statistic was used to estimate heterogeneity.
Inclusion criteria	
Study design	Randomized clinical trials (RCTs)
Population	Women who were married, had a fixed heterosexual partner or at least one sexual intercourse per month, were affected by sexual dysfunction based on various sexual function questionnaires, and were in pre- and post-menopausal period.
Intervention	Panax ginseng. Studies in Ashwaganda also included.
Comparator	Placebo
Other	Published in English, assessed sexual function as a primary or secondary outcome and also trials evaluating the quality of life and health status were systematically investigated.
Exclusion criteria	
Study design	
Population	Uncontrolled chronic diseases such as hypertension, diabetes, and other diseases were among the exclusion
Intervention	RCTs that made ginseng as a part of the herbal compound were excluded from this study

Characteristics of included reviews	Symptoms of menopause
Review ID	**Ghorbani 2019**
Comparator	
Other	
Date of documented search (month/year)	inception to May 2018
Databases searched	Cochrane Library, MEDLINE, Web of Science, Embase, Scopus, ProQuest, Google Scholar, and Persian databases (e.g., Magiran, SID, & Barakat), Clinical trial registries
Was an non-English database searched? Were studies in a LOTE included?	Yes — Persian databases (e.g., Magiran, SID, & Barakat) No
Outcomes considered in the SR (list)	Yes — Sexual function; Quality of life
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: The Cochrane Collaboration tool *Authors summary*



Characteristics of included reviews	Symptoms of menopause
Review ID	**Ghorbani 2019**
Authors conclusions (key message)	The meta-analysis of the five included studies (with 531 participants) did not approve a significant effect of ginseng on menopausal women's sexual function compared to the placebo group [SMD = 0.26; 95% CI: -0.26 to 0.76]. However, there was a considerable heterogeneity among the studies (I2 = 81%; P < 0.0001).
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	5 RCT were identified by the reivew

	Study ID	*Summary RoB*	*Study design features (PICO)*	
1	Oh 2010	Overall high risk of bias	N= 32 (NR) Korean red ginseng 3000 mg/ day 8 weeks	P: Menopausal symptoms (1 yr amenorrhea) I: Ginseng (dried powder) C: Placebo O: FSFI, GAQ S: Korea
2	Chung 2015	Overall high risk of bias	N= 41 (NR) Korean red ginseng 3000 mg/day 8 weeks	P: Menopausal symptoms (31-51 yrs) I: Ginseng (dried powder) C: Placebo O: FSFI S: Korea
3	Kim 2009	Overall high risk of bias	N= 24 (NR) Red ginseng 6000 mg/day 6 weeks	P: Menopausal symptoms (30-45 yrs) I: Ginseng (dried powder) C: Placebo O: FSFI, SF-36 S: Korea
4	Dongre 2015	Overall low risk of bias	N= 50 (NR) Indian ginseng 300 mg bid 8 weeks	P: Menopausal symptoms (30-45 yrs) I: Ginseng C: Placebo O: FSFI, FSDS S: India
5	Wiklund 1999	Overall unclear risk of bias	N= 384 (NR) Ginseng 200 mg/day 16 weeks	P: Menopausal symptoms with hot flashes (6mths amennorohea) I: Ginseng C: Placebo O: WHQ, PGWBI S: Sweden
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Characteristics of included reviews	Symptoms of menopause
Review ID	**Ghorbani 2019**
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16	FSFI: Female Sexual Function Index; KRG: Korean red Ginseng; GAQ: Global assessment questionnaire; SF-36: 36-item short form health survey; WHQ: Women's health questionnaire; FSDS: Female sexual distress scale; PGWBI: Psychological general well-being index.
	= data extracted
	= data extracted from more recent SR (or better SR)
	= control is an active intervention

Characteristics of included reviews	Symptoms of menopause
Review ID	**Shahmohammadi 2019**
Review reference	Shahmohammadi A, Ramezanpour N, Mahdavi Siuki M, Dizavandi F, Ghazanfarpour M, Rahmani Y, et al. The efficacy of herbal medicines on anxiety and depression in peri- and postmenopausal women: A systematic review and meta-analysis. Post Reproductive Health. 2019;25(3):131-41. 10.1177/2053369119841166
Review objective	To analyse herbal medicine interventions for anxiety and depression to detect possible benefits of herbal medicines in peri- and postmenopausal women.
Author affiliations	Department of Nursing and Midwifery, Razi School of Nursing and Midwifery, Kerman University of Medical Sciences, Kerman, Iran
Source of funds	Nil.
Declared interests of the review authors	The authors declared there were no conflicts of interest
Review method of analysis	Meta-analysis: The main effect size was measured using standardized mean difference (SMD). Results were reported based on a random effects model (DerSimonian and Laird method) due to high heterogeneity among studies. Cochrane Q test ($p<0.05$ as statistically significant) and I2 index were employed to evaluate the heterogeneity. The I2 index assessed whether the variance across studies was real or not due to sampling errors. All statistical analyses were performed using Comprehensive Meta-Analysis Version 2 (Biostat, Englewood, NJ, USA).
Inclusion criteria	
Study design	Randomized clinical trials (RCTs)
Population	perimenopause and postmenopausal women
Intervention	monopreparation of herbal medicines
Comparator	not specified
Other	assessing at least one of the depression or anxiety symptoms
Exclusion criteria	
Study design	not specified
Population	not specified
Intervention	not specified

Characteristics of included reviews	Symptoms of menopause					
Review ID	**Shahmohammadi 2019**					
Comparator	not specified					
Other	not specified					
Date of documented search (month/year)	Inception to Aug 2017					
Databases searched	MEDLINE, ISI Web of Science, Scopus and Cochran central register of controlled trials					
Was an non-English database searched? Were studies in a LOTE included?	No Not specified					
Outcomes considered in the SR (list)	Yes	Anxiety	Depression			
Risk of bias of the included RCT studies as reported in the SR	*Tool used*	*Authors summary*				
	Oxford Centre for Evidence-Based Medicine Checklist for RCTs quality	Randomisation	Blinding	ITT	Baseline comparability	Dropouts

Characteristics of included reviews	Symptoms of menopause			
Review ID	**Shahmohammadi 2019**			
Authors conclusions (key message)	The anxiety score was lower in the phytoestrogen group compared to the placebo (SMD= -1.19, 95% CI: -232 to -0.053; p=0.04; six trials). The depression score was decreased in the phytoestrogen group than in the placebo group (SMD= -0.952; 95% CI= -1.77 to -0.132; p=0.023; five trials). Heterogeneity was notably high for both outcomes.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	21 RCT included in the review: 5 (depression analysis); 6 (anxiety analysis)			
	Study ID	*Summary RoB*	*Study design features (PICO)*	
1	Geller 2009	Overall unclear risk of bias	N= 14/20/17 Red clover OR black cahoosh 12 weeks	P: Menopausal symptoms I: Red clover OR black cahoosh C: placebo O: anxiety S: NR
2	Charandabi 2013	Overall unclear risk of bias	N= (42/42) Black cahoosh 6.5mg 8 weeks	P: Menopausal symptoms I: Black cahoosh C: placebo O: Psychological symptoms S: NR
3	Aghamiri 2016	Overall unclear risk of bias	N= (60/60) Hops 12 weeks	P: Menopausal symptoms (post) I: Hops C: placebo O: Depression, anxiety S: NR
4	Rahimi Kian 2017	Overall unclear risk of bias	N= (45/45) Fennel ? Weeks	P: Menopausal symptoms (post) I: Fennel C: placebo O: MenQoL-psychosocial S: NR
5	Ghazanfarpour 2018	Overall unclear risk of bias	N= (25/24) Fennel 100 mg 12 weeks	P: Menopausal symptoms (post) I: Fennel C: placebo O: Depression, anxiety S: NR
6	Steels 2017	Overall low risk of bias	N= (59/56) Fenugreek dehusked 600 mg/day 12 weeks	P: Menopausal symptoms (peri) I: Fenugreek dehusked C: placebo O: Psychosocial S: NR
7	Shamshad Begum 2016	Overall low risk of bias	N= (44/44) Fenugreek husk 1000 mg/day 13 weeks	P: Menopausal symptoms I: Fenugreek husk C: placebo O: Depression, anxiety S: NR
8	Lambert 2017	Overall unclear risk of bias	N= (29/30) Red clover 34 mg/day 12 weeks	P: Menopausal symptoms (40-65 yrs) I: Red clover C: Placebo O: GCS-psychosocial S: Demnark

Characteristics of included reviews	Symptoms of menopause			
Review ID	**Shahmohammadi 2019**			
9	Hidalgo 2005	Overall high risk of bias	N= (53/53) Red clover 80 mg 12 weeks crossover	P: Menopausal symptoms (>40 yrs) I: Red clover C: Placebo O: KMI-depression S: Ecuador
10	Tice 2003	Overall low risk of bias	N=252 (82/83/84) Red clover 80 / 57 mg 12 weeks	P: Menopausal symptoms (45-60 yrs) I: Red clover C: Placebo O: anxiety, depression and psycosocial S: USA
11	Ehsanpour 2012	Overall unclear risk of bias	N=55 (28/27) Red clover 45 mg/day 8 weeks	P: Menopausal symptoms (post) I: Red clover C: Placebo O: Psychosocial S: NR
12	Lipovac 2012	Overall unclear risk of bias	N= (50/59) Red clover 80 mg 12 months	P: Menopausal symptoms (>40 yrs) I: Red clover C: Placebo O: KMI-anxiety, KMI-depression S: Austria
13	Shakeri 2015	Overall low risk of bias	N=72 (35/36) Red clover 80 mg 12 weeks	P: Menopausal symptoms (post) I: Red clover C: Placebo O: psychosocial S: Iran
14	--			
15	--			
16	--			

= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Symptoms of menopause	
Review ID	**Najafi 2018a**	
Review reference	Najaf Najafi M, Ghazanfarpour M. Effect of phytoestrogens on sexual function in menopausal women: a systematic review and meta-analysis. Climacteric. 2018;21(5):437-45. 10.1080/13697137.2018.1472566	
Review objective	To explore the impact of phytoestrogens on sexual dysfunction symptoms in perimenopausal and postmenopausal women	
Author affiliations	Department of Nursing and Midwifery, Razi School of Nursing and Midwifery, Kerman University of Medical Sciences, Kerman, Iran	
Source of funds	Nil.	
Declared interests of the review authors	The authors declared there were no conflicts of interest	
Review method of analysis	Meta-analysis	The mean difference (MD) of data was calculated as the main effect size in our meta-analysis. The random-effect and fixed-effect models were used for pooling across studies. For heterogeneity evaluation, Cochrane Q and the I2 index were used. All analyses were conducted by Comprehensive Metaanalysis Version 2 (Biostat, Englewood, NJ, USA).
Inclusion criteria		
Study design	Randomized clinical trials (RCTs)	
Population	Premenopausal and postmenopausal women	
Intervention	Phytoestrogen was orally administrated as monotherapy or in combination with other herbal medicines at any dose for treatment of sexual dysfunction	
Comparator	No limits.	
Other		
Exclusion criteria		
Study design	None specified	
Population	None specified	
Intervention	None specified	

Characteristics of included reviews	Symptoms of menopause
Review ID	**Najafi 2018a**
Comparator	Studies that used hormone therapy as a comparator
Other	Papers that measured the effect of phytoestrogens on vaginal atrophy or dryness were excluded
Date of documented search (month/year)	Inception to 29 Sept 2017
Databases searched	PubMed, Cochrane Library, ISI Web of Science, and Scopus
Was an non-English database searched? Were studies in a LOTE included?	No Not specified
Outcomes considered in the SR (list)	Yes — total score of sexual function and subgroups such as orgasm, dyspareunia, libido, arousal function, sexual satisfaction, and sexual domain of the Greene Climacteric Scale, Menopause Rating Scale, Menopause-Specific Quality of Life (MENQOL), Golombok Rust Inventory of Sexual Satisfaction, Female Sexual Function Index, Women's Health Questionnaire, and Kupperman Index.
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Jadad scale *Authors summary*

Table 1. Assessment of the quality of studies included in the systematic review and meta-analysis.

	Randomization			Blinding					
Reference	Mention randomization	Appropriate method	Inappropriate method	Mention blinding	Appropriate method	Inappropriate method	Report of dropping out	Intention to treat	Baseline comparability
Davinelli *et al.*[8]	*	*	–	*	*	–	*	–	*
Steels *et al.*[22]	*	*	–	*	*	–	*	*	*
Rahimi Kian *et al.*[23]	*	*	–	*	*	–	*	–	*
Shamshad Begum *et al.*[9]	*	*	–	*	*	–	*	*	*
Nourozi *et al.*[24]	*	–	–	–	–	–	*	–	*
Shakeri *et al.*[11]	*	*	–	*	*	–	*	–	*
Ehsanpour *et al.*[25]	*	–	–	*	*	–	*	–	*
Del Giorno *et al.*[12]	*	*	–	*	*	–	*	–	*
Oh *et al.*[1]	*	*	–	*	*	–	*	–	*
Basaria *et al.*[26]	*	*	–	*	*	–	*	–	*
Brooks *et al.*[27]	*	–	*	*	*	–	*	–	*
Welty *et al.*[29]	*	–	–	–	–	–	*	–	*
Hanachi and Golkho[28]	*	–	–	–	–	–	?	–	–
Yang *et al.*[30]	*	–	*	*	*	–	*	–	*
Lewis *et al.*[31]	*	*	–	*	*	–	*	*	*
Tice *et al.*[32]	*	*	–	*	*	–	*	*	*

"*" indicates that the specific criteria/aspect was noted in the study while "–" denotes the absence of the criteria/aspect. "?" shows that it was not possible to evaluate the specific criteria/aspect.

Characteristics of included reviews	Symptoms of menopause			
Review ID	**Najafi 2018a**			
Authors conclusions (key message)	Phytoestrogens have various effects on sexual function. Published reports show that maritime pine bark, T. foenum-graecum L., and F. vulgare could be considered as agents to overcome sexual dysfunctions while soy, red clover, genistein, and flaxseed had no promising effects on these conditions.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	16 trials included in the review.			
	Study ID	*Summary RoB*		
1	Steels 2017	Overall low risk of bias	N= (59/56) Fenugreek dehusked 600 mg/day 12 weeks	P: Menopausal symptoms (peri) I: Fenugreek dehusked C: placebo O: MenQoL S: NR
2	Rahimi Kian 2017	Overall unclear risk of bias	N= (45/45) Fennel ? Weeks	P: Menopausal symptoms (post) I: Fennel C: placebo O: MenQoL S: NR
3	Shamshad Begum 2016	Overall low risk of bias	N= (44/44) Fenugreek husk 1000 mg/day 13 weeks	P: Menopausal symptoms (45-58 yrs) I: Fenugreek husk C: placebo O: GCS S: NR
4	Shakeri 2015	Overall low risk of bias	N=72 (36/36) Red clover 80 mg 12 weeks	P: Menopausal symptoms (50-59 yrs) I: Red clover C: Placebo O: MRS S: Iran
5	Ehsanpour 2012	Overall unclear risk of bias (>20% dropouts)	N=72 (36/36) Red clover 45 mg/day 8 weeks	P: Menopausal symptoms (>45 yrs) I: Red clover C: Placebo O: MenQoL S: NR
6	del Giorno 2010	Overall low risk of bias	N=120 (ITT) 100 (PP) Red clover 40 mg 12 months	P: Menopausal symptoms (45-65 yrs) I: Red clover C: Placebo O: Sexual satisfaction S: Brazil
7	Oh 2010	Overall high risk of bias (>30% dropouts)	N= 32 (16/16) Korean red ginseng 3000 mg/ day 8 weeks	P: Menopausal symptoms (1 yr amenorrhea) I: Ginseng (dried powder) C: Placebo O: FSFI S: Korea
8	Tice 2003	Overall low risk of bias	N=252 (84/83/85) Red clover 41 mg/ 28.6 mg mg 12 weeks	P: Menopausal symptoms (45-60 yrs) I: Red clover C: Placebo O: GCS S: USA

Characteristics of included reviews	Symptoms of menopause
Review ID	**Najafi 2018a**
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16	--

= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Symptoms of menopause
Review ID	**Franco 2016**
Review reference	Franco OH, Chowdhury R, Troup J, Voortman T, Kunutsor S, Kavousi M, et al. Use of Plant-Based Therapies and Menopausal Symptoms: A Systematic Review and Meta-analysis. JAMA. 2016;315(23):2554-63. https://dx.doi.org/10.1001/jama.2016.8012
Review objective	To determine the association of plant-based therapies with menopausal symptoms, including hot flashes, night sweats, and vaginal dryness.
Author affiliations	Department of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom Department of Nutrition, Harvard T. H. Chan School of Public Health, Boston, Massachusetts
Source of funds	This study was sponsored by Metagenics Inc.
Declared interests of the review authors	Drs Muka, Voortman, and Franco and Ms Troup reported that they work in ErasmusAGE, a center for aging research across the life course funded by Nestlé Nutrition (Nestec Ltd),Metagenics Inc, and AXA. Dr Franco reported receiving grants or research support fromMetagenics Inc. Dr Kavousi reported receiving support from the AXA Research Fund. No other authors reported disclosures.
Review method of analysis	Meta-analysis Treatment effects were defined as the differences in outcomes between the treatment and placebo at the end of the trial. For continuous outcomes, summary measures were presented asmean differences. For data reported as medians, ranges, or 95% confidence intervals, we calculated means and standard deviations. Most crossover trials in this review did not report adequate crossover analysis; therefore, we used data from the first period only. The inverse variance weighted method was used to combine summary measures using random-effects models. We evaluated publication bias using funnel plots and Egger regression symmetry tests. Sensitivity analyses were performed to assess the influence of each individual study
Inclusion criteria	
Study design	Randomized clinical trials (RCTs)
Population	perimenopausal, menopausal, or postmenopausal women
Intervention	any plant-based therapy: dietary soy isoflavones and soy extracts; herbal remedies such as red clover and black cohosh; and Chinese and other medicinal herbs
Comparator	compared with a placebo or no treatment
Other	collected end points for menopausal symptoms, including hot flashes, night sweats, and vaginal dryness
Exclusion criteria	
Study design	None specified
Population	None specified
Intervention	None specified

Characteristics of included reviews	Symptoms of menopause
Review ID	**Franco 2016**
Comparator	head-to-head trials without a placebo group that compared nonhormonal therapies with estrogen or with other medications were excluded
Other	No restriction on length of follow-up was applied
Date of documented search (month/year)	Inception to Mar 27 2016
Databases searched	Ovid MEDLINE, EMBASE, and Cochrane Central
Was an non-English database searched? Were studies in a LOTE included?	No Not specified
Outcomes considered in the SR (list)	Yes hot flashes, night sweats, and vaginal dryness.
Risk of bias of the included RCT studies as reported in the SR	*Tool used* *Authors summary* The Cochrane Collaboration's tool

eTable 8. Risk-of-Bias Assessments for the Included Clinical Trials

Lead author, publication date	Random sequence generation	Allocation concealment	Blinding of participants & personnel	Blinding of outcome assessments	Incomplete outcome data	Selective reporting	Other bias
Phytoestrogens							
Albertazzi, 2005[30]	Low	Low	Low	Unclear	Low	Low	Unclear
Albertazzi, 1998[1]	Low	Low	Low	Unclear	Low	Low	Unclear
Aso, 2012[9]	High	Unclear	Low	High	High	Low	High
Atkinson, 2004[23]	Low	Unclear	Low	Low	Low	Low	Low
Baber, 1999[24]	Low	Unclear	Low	Unclear	Low	Low	Unclear
Han, 2002[*]	Low	Unclear	Low	Low	Low	Low	Unclear
Jeri, 2002[25]	Low	Unclear	Low	Unclear	High	Low	Unclear
Knight, 1999[26]	Low	Unclear	Low	Unclear	Low	Unclear	Unclear
Komesaroff,	Low	Unclear	Low	Unclear	Low	Low	Unclear
Lipovac, 2012[27]	Unclear	High	High	High	Low	Low	High
Liu, 2014[6]	Low	Low	Low	Unclear	Low	Low	Low
MacGregor, Scambia, 2000[21]	Unclear Unclear	Unclear Unclear	Unclear Unclear	Unclear Unclear	High High	Low Low	High High
Shakeri, 2015[37]	Low	Low	Low	Low	High	High	Unclear
Tice, 2003[28]	Low	Low	Low	Unclear	Low	Low	Low
Upmalis, 2000[22]	Unclear	Unclear	Unclear	Unclear	High	Low	Low
van de Weijer, 2002[29]	Low	Unclear	Low	High	Low	Low	Unclear
Van Patten, 2002[8]	Low	Unclear	Low	High	Low	Low	Unclear
Black Cohosh							
Charandabi, 2013[62]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Chung, 2007[36]	Unclear	Unclear	Low	High	Low	Low	Unclear
Frei-Kleiner, 2005[39]	Unclear	Unclear	Low	High	Unclear	Low	Unclear
Jiang, 2015[59]	Low	Low	Low	Low	Low	High	Unclear
Newton, 2006[40]	Low	Low	Low	Low	Low	Low	Low
Pockaj, 2006[41]	Unclear	Unclear	Low	High	Low	Low	Unclear
Rotem, 2007[42]	Unclear	High	Low	High	Low	Low	Unclear
Shahnazi, 2013[43]	Low	Low	Low	Unclear	Low	Low	Unclear
Other Biologically-based therapies							
Abdali, 2010[55]	High	Unclear	Low	High	Low	Low	Unclear
Colli, 2012[57]	Unclear	Unclear	Low	Unclear	High	Low	Unclear
Dodin, 2005[61]	Low	Low	Low	Low	Low	Low	Low
Farzaneh, 2013[58]	Low	Unclear	Low	Unclear	high	low	Unclear
Simbalista, 2010[44]	Low	Low	Low	Unclear	Low	Low	Unclear
van Die, 2009[45]	Low	Unclear	Low	High	Low	Low	Unclear
Verhoeven, 2005[46]	Low	Unclear	Low	Unclear	Low	Low	Unclear
Medicinal Herbs							

Characteristics of included reviews	Symptoms of menopause			
Review ID	**Franco 2016**			
Authors conclusions (key message)	Composite phytoestrogen supplementation and individual phytoestrogen interventions, such as dietary and supplemental soy isoflavones, were associated with improvement in some menopausal symptoms, including modest reductions in hot flashes and vaginal dryness but no significant reduction in night sweats. However, because of general suboptimal quality and the heterogeneous nature of the current evidence, further rigorous studies are needed to determine the association of plant-based and natural therapies with menopausal health.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview				
	Study ID	*Summary RoB*		
1	Knight 1999	Overall unclear risk of bias	N=37 Red clover 160 mg/ 40 mg 12 weeks	P: Menopausal symptoms (40-65 yrs) I: Red clover C: Placebo O: hot flashes, GCS S: Australia
2	Baber 1999	Overall unclear risk of bias	N=51 Red clover 40 mg 90 days	P: Menopausal symptoms (45-65 yrs) I: Red clover C: Placebo O: hot flashes, GCS S: Australia
3	Jeri 2002	Overall high risk of bias	N=30 Red clover 40 mg 16 weeks	P: Menopausal symptoms (<60 yrs) I: Red clover C: Placebo O: hot flashes, S: Peru
4	Atkinson 2004	Overall low risk of bias	N=205 (ITT) 99 (PP) Red clover 40 mg 12 months	P: Menopausal symptoms (49-65 yrs) I: Red clover C: Placebo O: hot flashes, GCS S: UK
5	Lipovac 2012	Overall high risk of bias	N=113 (ITT) 109 (PP) Red clover 80 mg 12 months	P: Menopausal symptoms (>40 yrs) I: Red clover C: Placebo O: hot flashes, KMI S: Austria
6	van de Weijer 2002	Overall high risk of bias	N=30 (ITT) 26 (PP) Red clover 80 mg 12 weeks	P: Menopausal symptoms (49-65 yrs) I: Red clover C: Placebo O: hot flashes, GCS S: Netherlands
7	Tice 2003	Overall low risk of bias	N=252 Red clover 80 / 57 mg 12 weeks	P: Menopausal symptoms (45-60 yrs) I: Red clover C: Placebo O: hot flashes, S: USA
8	Charandabi 2013	Overall unclear risk of bias	N= (42/42) Black cahoosh 6.5mg 8 weeks	P: Menopausal symptoms I: Black cahoosh C: placebo O: Vasomotor symptoms S: Iran

Characteristics of included reviews	Symptoms of menopause			
Review ID	**Franco 2016**			
9	Chung 2007	Overall high risk of bias	N=89 (NR) Black cohosh, St John's wort 12 weeks	P: Menopausal symptoms I: Combination STW, black cohosh C: placebo O: Hot flash score S: Korea
10	Frei-Kleiner 2005	Overall high risk of bias	N=122 (NR) Black cohosh 42 mg 12 weeks	P: Menopausal symptoms I: Black cahoosh C: placebo O: Daily hot flashes S: Switzerland
11	Newton 2006	Overall low risk of bias	N=351 (NR) Black cohosh 160 mg 48 weeks	P: Menopausal symptoms I: Black cahoosh C: placebo O: Daily hot flashes S: USA
12	Pockaj 2006	Overall high risk of bias	N=84 (NR) Black cohosh 40 mg 8 weeks	P: Menopausal symptoms I: Black cahoosh C: placebo O: Daily hot flashes S: USA
13	Shahnazi 2013	Overall unclear risk of bias	N=84 (NR) Black cohosh 6.5 mg 8 weeks	P: Menopausal symptoms I: Black cahoosh C: placebo O: Daily hot flashes S: Iran
14	Jiang 2015	Overall unclear risk of bias	N=89 (NR) Black cohosh 2.5 mg 24 weeks	P: Menopausal symptoms I: Combination STW, black cohosh C: placebo O: MenQoL vasomotor score S: China
15	Abdali 2010	Overall high risk of bias	N=100 (NR) St John's wort 20 drops tid 8 weeks	P: Menopausal symptoms I: St John's wort C: distilled water O: Daily hot flashes & severity S: Iran
16	van Die 2009	Overall high risk of bias	N=100 (NR) St John's wort 900mg + Chaste tree berry 1000mg 17 weeks	P: Menopausal symptoms I: Combination STW, Chaste tree C: placebo O: Daily hot flashes, GCS vasomotor S: Australia

= data extracted

= data extracted from more recent SR (or better SR)

= control is an active intervention

Characteristics of included reviews	Anxiety
Review ID	**Ghaderi 2020**
Review reference	Ghaderi, A., Asbaghi, O., Reiner, Ž., Kolahdooz, F., Amirani, E., Mirzaei, H., Banafshe, H. R., Maleki Dana, P., & Asemi, Z. (2020). The effects of saffron (Crocus sativus L.) on mental health parameters and C-reactive protein: A meta-analysis of randomized clinical trials. Complement Ther Med, 48, 102250. https://doi.org/10.1016/j.ctim.2019.102250
Review objective	to summarize all the existing RCTs evidence and to evaluate the effects of saffron intake on parameters of mental health and CRP.
Author affiliations	The authors were affiliated with tertiary institutions in Iran, Croatia and Canada
Source of funds	Nil.
Declared interests of the review authors	The authors declared there were no conflicts of interest
Review method of analysis	Meta-analysis: Weighted mean difference (WMD) with 95 % CI was used for pooling data to determine the effect sizes. The change score approach was used to calculate the effect size of saffron intake on the analyzed parameter. The random-effect model was used to report the pooled effect sizes using 95 % CI. Publication bias was evaluated using the funnel plots.
Inclusion criteria	
Study design	RCTs
Population	Not specified, only that mental health and c-reactive protein (CRP) were going to be measured.
Intervention	saffron
Comparator	Placebo
Other	Not specified
Exclusion criteria	
Study design	Animal experiments, in vitro studies, case reports, observational studies, trials without a control group, and studies that did not achieve the least quality score were excluded from this meta-analysis
Population	Animal experiments
Intervention	Not specified
Comparator	without control group
Other	Not specified
Date of documented search (month/year)	Inception to July 2019

Characteristics of included reviews	Anxiety
Review ID	**Ghaderi 2020**
Databases searched	PubMed, Scopus, ISI, (Web of Science), Cochrane Central Register of Controlled Trials, EMBASE, Google Scholar
Was an non-English database searched?	No
Were studies in a LOTE included?	No
Outcomes considered in the SR (list)	Effects of saffron on parameters of mental health and CRP with standard deviation (SD) and related 95 % confidence interval (CI) for the both intervention and placebo groups: 1) BDI, 2) BAI, 3) HAMD and 4) CRP.
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane risk of bias tool *Authors summary*: The authors report assessing Risk of bias, but do not provided any other information - other than noting the "*quality of all included studies was high*". Individual RoB not reported.
Authors conclusions (key message)	This meta-analysis demonstrated that saffron intake significantly reduced BDI, BAI and PSQI scores, but did not affect HDRS-D, HARS-A scores and CRP levels.

Characteristics of included reviews	Anxiety			
Review ID	**Ghaderi 2020**			
	Of the 21 RCTS that were included, 2 studies met our PICO			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	total N =	94	participants that met our PICO	
	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Jafarnia 2017	NR	N=40 (20/20) Saffron 450mg/day + sertraline 50 mg 4 weeks	P: GAD I: Saffron C: Placebo + sertraline 50 mg O: HAM-A S: Iran
2	Mazidi 2016	NR	N=54 (30/24) Saffron 100 mg/day 12 weeks	P: Anxiety & Depression I: Saffron C: Placebo O: BDI, BAI S: Iran
3	--	Publication bias was evaluated by Egger's test. The results indicated no evidence of publication bias in the meta-analysis for the effects of saffron intake on HARS-A (P = 0.660), BAI (P = 0.857) and CRP (P =0.825). However, there was publication bias for HDRS-D (P =0.013), BDI (P<0.001) and PSQI (P = 0.015).		
4	--	Saffron intake did not affect HDRS-D (6 studies) (WMD: -1.61; 95 % CI: -5.81, 2.58)		
5	--			
6	--			

Characteristics of included reviews	Anxiety
Review ID	**Ghaderi 2020**
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= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Anxiety
Review ID	**Janda 2020**
Review reference	Janda K, Wojtkowska K, Jakubczyk K, Antoniewicz J, Skonieczna-Żydecka K. Passiflora incarnata in Neuropsychiatric Disorders—A Systematic Review. Nutrients. 2020;12(12):3894. 10.3390/nu12123894
Review objective	The objective of this systematic review was to evaluate the efficacy of Passiflora incarnata preparations in the treatment of neuropsychiatric disorders. The systematic review included randomized controlled trials (RCT) which investigated the relationship between the use of Passiflora incarnata and a range of disorders of the nervous system.
Author affiliations	Pomeranian Medical University in Szczecin, Poland
Source of funds	The project was financed from the program of the Minister of Science and Higher Education, under the name "Regional Initiative of Excellence", in 2019–2022, project number 002/RID/2018/19, amount of financing 12 000 000 PLN.
Declared interests of the review authors	The authors declared there were no conflicts of interest
Review method of analysis	Meta-analysis
Inclusion criteria	
Study design	RCTs
Population	(v) studies carried out in humans
Intervention	(iii) studies in which the treatment included any products (supplements, tinctures, extracts, infusions, raw materials, etc.) containing Passiflora incarnata,
Comparator	Not specified
Other	(i) original studies, (ii) studies with access to full text, (iv) presence of meta-analytical data (change score/endpoint) on psychiatric symptoms in the process of each neuropsychiatric disease,
Exclusion criteria	
Study design	(ii) meta-analyses, systematic reviews, and review works.
Population	Not specified
Intervention	(i) intervention with products containing other psychoactive substances;
Comparator	Not specified
Other	Not specified
Date of documented search (month/year)	database inception until 22 October 2019

Characteristics of included reviews	Anxiety
Review ID	**Janda 2020**
Databases searched	PubMed/MEDLINE/Embase
Was an non-English database searched? Were studies in a LOTE included?	No Not specified
Outcomes considered in the SR (list)	The results that were compared in the systematic review involved various scales and tests, such as the Hamilton Rating Scale for Depression (HRSD), Visual Analogue Scale (VAS), Numerical Rating Scale (NRS), Observers Assessment of Alertness and Sedation Scale (OAA/S), Corah's Dental Anxiety Scale, Revised (DAS-R), Ramsey Scale, Digit symbol substitution test (DSST), Concentration Endurance Test, (The d2 test), Memory test, Continuous Performance Task/Test (CPT), Trieger Dot Test (TDT), Perceptive Accuracy Test (PAT), Finger Tapping Test (FTT), and State-Trait Anxiety Inventory (STAI-S, STAI-T).
Risk of bias of the included RCT studies as reported in the SR	*Tool used* Cochrane risk of bias tool *Authors summary*

Reference/Country	Publication Year	Random Generation of The Error Sequence (Selection Error)	Hiding the Allocation (Selection Variation)	Blinding of Participants and Staff (Biased Evaluation)	Performance Evaluation Blindness (Detection Error)	Incomplete Result Data	Selective Reporting (Reporting Error)	Other Biases
Akhondzadeh et al. (Iran) [12]	2001	L	?	L	?	L	L	L

Authors conclusions (key message)	In each of the papers, the effects of passionflower were measured by using a number of different tests and scales. The majority of studies reported reduced anxiety levels following the administration of Passiflora incarnata preparations, with the effect less evident in people with mild anxiety symptoms. No adverse effects, including memory loss or collapse of psychometric functions, were observed.

Characteristics of included reviews	Anxiety			
Review ID	**Janda 2020**			
	The systematic review included nine clinical trials. Of these, 1 met our PICO criteria			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	total N =	56	participants that met our PICO	
	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Akhondzadeh 2001	Overall unclear risk of bias	N=36 (NR) Passiflora 45 drops/day + oxazepam (30 mg/day) 4 weeks	P: GAD I: Passiflora C: Placebo + oxazepam (30 mg/day) O: HAM-A S: Iran
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Characteristics of included reviews	Anxiety
Review ID	**Janda 2020**
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= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Anxiety
Review ID	**Sayad 2020**
Review reference	Sayed AM, Morsy S, Tawfik GM, Naveed S, Minh-Duc NT, Hieu TH, et al. The best route of administration of lavender for anxiety: a systematic review and network meta-analysis. General Hospital Psychiatry. 2020;64:33-40. https://doi.org/10.1016/j.genhosppsych.2020.02.001
Review objective	Our goal is to elucidate the best route of administration for lavender as a treatment for anxiety.
Author affiliations	Authors were affiliated with tertiary institutions in Japan, Egypt. Vietnam, Bangladesh and the USA. Main: Evidence Based Medicine Research Group & Faculty of Applied Sciences, Ton Duc Thang University, Ho Chi Minh City, Viet Nam.
Source of funds	None
Declared interests of the review authors	The authors report there are no conflicts of interest.
Review method of analysis	Meta-analysis: Frequentist network meta-analysis was conducted to compare the efficacy of different treatment arms. Treatment efficacy was evaluated based on the decrease in scores measuring anxiety on different scales. Fixed model network meta-analysis was conducted if there was no significant heterogeneity as assessed using Q-statistics (P > 0.1), otherwise, the random effect model was used. Bayesian random effect model network meta-regression with unrelated coefficients based on Markov chain Monte Carlo simulation (MCMC) was employed to detect the effect of treatment duration on the efficacy of each treatment arm.
Inclusion criteria	
Study design	RCTs
Population	Anxiety
Intervention	All RCTs reporting lavender as treatment for anxiety were considered for inclusion.
Comparator	Not specified
Other	Not specified
Exclusion criteria	
Study design	i) abstract-only articles, case reports and case series; ii) overlapping data set; iii) in-vitro or animal studies; iv) studies with unreliable data which included non-peer-reviewed publications and studies with unclear assessments.
Population	
Intervention	Not specified
Comparator	Not specified
Other	Not specified
Date of documented search (month/year)	July 2017

Characteristics of included reviews	Anxiety
Review ID	**Sayad 2020**
Databases searched	13 electronic databases were searched including PubMed, Scopus, ISI Web of Science, Clinical trials, WHO Global Health Library (WHO GHL), the WHO International Clinical Trials Registry Platform (ICTRP),Virtual Health Library (VHL), Google Scholar, POPLINE, New York Academy of Medicine Grey Literature Report (NYAM), System for Information on Grey Literature Report in Europe (SIGLE) and PsycINFO via PsycNET
Was an non-English database searched? Were studies in a LOTE included?	Not specified Not specified No restrictions on language
Outcomes considered in the SR (list)	Treatment efficacy was evaluated based on the decrease in scores measuring anxiety on different scales.
Risk of bias of the included RCT studies as reported in the SR	*Tool used* *Authors summary* Cochrane risk of bias tool Authors provided overview % acorss studies. Indiviudal study data not provided.
Authors conclusions (key message)	Bayesian meta-regression results suggested that oral Silexan 80 mg was a more effective long term anxiety treatment, compared to other lavender administration routes.

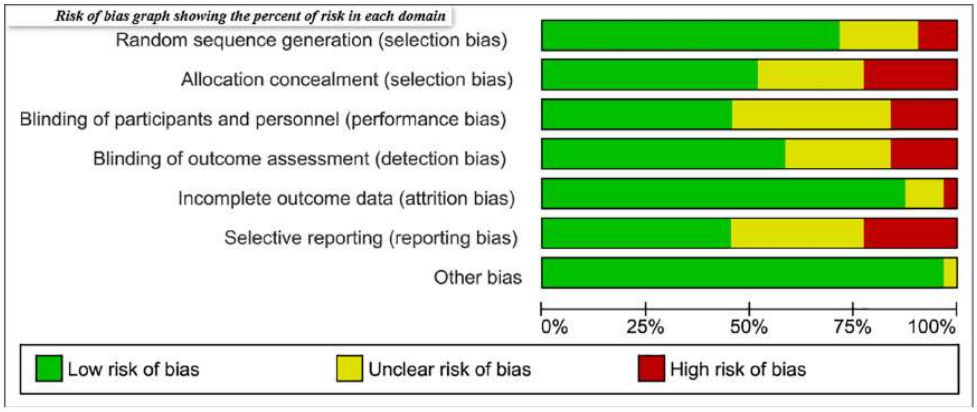

Fig. 2. Risk of bias graph showing the percent of risk in each domain.

Characteristics of included reviews	Anxiety			
Review ID	**Sayad 2020** 6 studies in people with anxiety disorder.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	total N =	NR	participants that met our PICO	
	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1		**All studies included in Donelli 2019**		
2	Kasper 2016	NR	Silexan (oral lavender)	Study characterisitics provided in a supplementary file - not accessible via the journal website
3	Woelk 2010	NR	Silexan (oral lavender)	Study characterisitics provided in a supplementary file - not accessible via the journal website
4	Kasper 2010	NR	Silexan (oral lavender)	Study characterisitics provided in a supplementary file - not accessible via the journal website
5	Kasper 2014	NR	Silexan (oral lavender)	Study characterisitics provided in a supplementary file - not accessible via the journal website
6	Kasper 2015	NR	Silexan (oral lavender)	Study characterisitics provided in a supplementary file - not accessible via the journal website

Characteristics of included reviews	Anxiety			
Review ID	**Sayad 2020**			
7	Kasper 2017	NR	Silexan (oral lavender)	Study characterisitics provided in a supplementary file - not accessible via the journal website
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= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Anxiety
Review ID	**Shinjyo 2020**
Review reference	Shinjyo, N., Waddell, G., & Green, J. (2020). Valerian Root in Treating Sleep Problems and Associated Disorders-A Systematic Review and Meta-Analysis. J Evid Based Integr Med, 25, 2515690x20967323. https://doi.org/10.1177/2515690x20967323
Review objective	to evaluate the effectiveness of valerian as a treatment of sleep problems and associated disorders, and to discuss possible reasons behind the inconsistent research outcomes, by particularly focusing on the herbal preparations used in the studies
Author affiliations	Authors were affiliated with tertiary institutions in Japan and the UK
Source of funds	Nil.
Declared interests of the review authors	The authors declared there were no conflicts of interest
Review method of analysis	Meta-analysis: Meta-analyses were performed using Meta-Essentials. Adjusted effect sizes (Hedges' g) were calculated from summary measures such as means and standard deviations or confidence intervals, odds ratio (for binary outcomes), and sample sizes, using reported formula. I2 statistic was used to estimate heterogeneity. Publication bias was evaluated using the funnel plots.
Inclusion criteria	
Study design	Clinical studies
Population	sleep or related health problems
Intervention	Valerian alone or in combination
Comparator	Not specified
Other	Not specified
Exclusion criteria	
Study design	Reviews, unrelated studies, and works without available full text were excluded
Population	Studies on non-human subjects.
Intervention	Studies using unknown substance.
Comparator	Not specified
Other	Articles published in any non-English language
Date of documented search (month/year)	inception to Dec 2019

Characteristics of included reviews	Anxiety
Review ID	**Shinjyo 2020**
Databases searched	Pubmed, ScienceDirect and Cochrane Library
Was an non-English database searched?	No
Were studies in a LOTE included?	Not specified
Outcomes considered in the SR (list)	Any sleep measure (e.g., PSQI, ISI, sleepy diary), Anxiety, Safety and other reported outcomes including symtpoms improvement (OCD), hot flashes, & pain severity (dysmenorohea)
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Jadad *Authors summary*: Jadad scores for all studies ranged between Jadad 1 and 5
Authors conclusions (key message)	Valerian could be a safe and effective herb to promote sleep and prevent associated disorders However, Results suggested that inconsistent outcomes were possibly due to the variable quality of herbal extracts and that more reliable effects could be expected from the whole root/rhizome. In addition, therapeutic benefits could be optimized when it was combined with appropriate herbal partners. There were no severe adverse events associated with valerian intake in subjects aged between 7 and 80 years.

Characteristics of included reviews	Anxiety			
Review ID	**Shinjyo 2020**			
	Of the 60 identified studies, one study met our PICO			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	total N =	36	participants that met our PICO	
	Study ID	*Summary RoB*	*Study design features (PICO)*	
1	Andreatini 2002	Jadad score 5	N=36 (12/12/12) valerian extract 4 weeks	P: GAD I: Valerian extract C: Placebo OR diazepam O: HAM-A S: Brazil
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Characteristics of included reviews	Anxiety
Review ID	**Shinjyo 2020**
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= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Anxiety
Review ID	**Donelli 2019**
Review reference	Donelli D, Antonelli M, Bellinazzi C, Gensini GF, Firenzuoli F. Effects of lavender on anxiety: A systematic review and meta-analysis. Phytomedicine. 2019;65:N.PAG-N.PAG. https://doi.org/10.1016/j.phymed.2019.153099
Review objective	The objective of this review is to assess the efficacy of lavender, in any form and way of administration, on anxiety and anxiety-related conditions.
Author affiliations	Authors were affiliated with tertiary institutions and hospitals in Italy
Source of funds	This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Declared interests of the review authors	none specified
Review method of analysis	Meta-analysis: A quantitative synthesis was performed using RevMan, version 5.3. An analysis was also conducted in "R" using RStudio ver. 1.2.1335 and the packages "meta" (Schwarzer et al., 2015) and "metafor" (Viechtbauer, 2010). Pre-post effect size meta-analysis (namely the use of post-test data as intervention values and pre-test data as control values) was excluded due to possibly biased outcomes. strictest criteria when selecting trials for inclusion in the meta-analysis, in order to achieve the best possible homogeneity without impeding from performing a quantitative assessment.
Inclusion criteria	Below are criteria for studies included in the meta-analysis
Study design	RCTs
Population	patients with anxiety, involved in an anxiety-inducing setting or undergoing an anxiety-inducing activity.
Intervention	oral administration of a standardized lavender product (Silexan®), inhalation or massage with lavender essential oil.
Comparator	usual care, no intervention, sham intervention or placebo, massage without lavender essential oil.
Other	anxiety measured with validated scales only. Systolic Blood Pressure (SBP) was also considered as a physiological measure which indirectly estimates anxiety levels.
Exclusion criteria	
Study design	Not specified
Population	Not specified
Intervention	Not specified
Comparator	Not specified
Other	Not specified
Date of documented search (month/year)	Inception to Nov 2018

Characteristics of included reviews	Anxiety
Review ID	**Donelli 2019**
Databases searched	Medline via PubMed, Scopus, Web of Science, Cochrane Library, EMBASE, and Google Scholar
Was an non-English database searched? Were studies in a LOTE included?	No Not specified
Outcomes considered in the SR (list)	all possible scales to evaluate anxiety levels and all physiological parameters which indirectly estimate anxiety levels.
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane risk of bias tool *Authors summary*: When considering performance bias as a key domain, the overall risk of bias was rated as low in 3 RCTs (Bikmoradi et al., 2015; Kasper et al., 2010; Shahnazi et al., 2012), unclear in 4 RCTs (Farshbaf- Khalili et al., 2018; Hashemi and Faghih, 2018; Hozumi et al., 2017; Kasper et al., 2014), and high in the other 58 RCTs. Overall risk summarised in table, details in the supplementary not included here.
Authors conclusions (key message)	The most important limitation of this review is the low average quality of available studies on the topic. The majority of included RCTs were characterized by a high overall risk of bias. Another limitation regards the heterogeneity of study designs, especially with regard to non-oral ways of administration. Overall, oral administration of lavender essential oil proves to be effective in the treatment of anxiety, whereas for inhalation there is only an indication of an effect of reasonable size, due to the heterogeneity of available studies.

First Author (Date)	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Overall risk of bias
Kasper et al (2010)	L	L	L	L	L	L	L	L
Kasper et al (2014)	L	L	L	L	L	L	U	U
Kasper et al (2015)	L	L	L	L	L	L	H	H
Kasper et al (2016)	L	L	L	L	L	H	H	H
Kasper et al (2017) - Trial “A”	L	L	L	L	U	L	U	H
Woelk and Schläfke (2010)	L	U	L	L	L	L	H	H

Characteristics of included reviews	Anxiety			
Review ID	**Donelli 2019**			
	65 RCTs (7993 participants) and 25 NRSs (1200 participants) were included in the qualitative synthesis and 37 RCTs (3964 participants) were included in the quantitative synthesis.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	A significant effect in diminishing anxiety levels was also found in favor of the use of oral Silexan® 80 mg/die for at least 6 weeks (Hamilton Anxiety Scale mean difference=−2.90 [95% CI −4.86 to −0.95], p= 0.004, 1173 participants; Zung Self-rating Anxiety Scale mean difference=−2.62 [95% CI −4.84 to −0.39], p< 0.05, 451 participants			
	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Kasper 2016	Overall high risk of bias	N= 318 (159/156) Silexan (80 mg od) NR	P: Anxiety & depression (symptoms) I: Lavender oil C: Placebo O: HAM-A S: NR
2	Kasper 2017	Overall high risk of bias	N= 461 (103/100/97/102) Silexan (10, 40 & 80 mg od) NR	P: Anxiety (symptoms) I: Lavender oil C: Placebo O: HAM-A S: NR
3	Kasper 2010	Overall low risk of bias	N= 216 (87/90) Silexan (80 mg od) NR	P: Anxiety (subsyndromal) I: Lavender oil C: Placebo O: HAM-A, SAS S: NR
4	Kasper 2014	Overall unclear risk of bias	N= 539 (103/119/114) Silexan (160 or 80 mg) NR	P: GAD I: Lavender oil C: Placebo O: HAM-A, HAM-D, CAS S: NR
5	Kasper 2015	Overall high risk of bias	N= 170 (86/84) Silexan (80 mg od) NR	P: Anxiety (symptoms) I: Lavender oil C: Placebo O: HAM-A, SAS S: NR
6	Woelk 2010	Overall high risk of bias	N= 77 (36/33) Silexan (80 mg od) 6 weeks	P: Anxiety (symptoms) I: Lavender oil C: Lorazepam O: HAM-A S: NR

Characteristics of included reviews	Anxiety
Review ID	**Donelli 2019**
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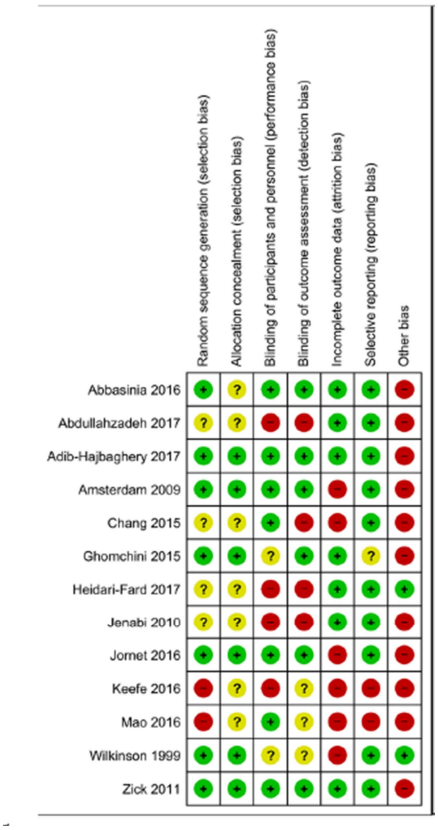
= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Anxiety
Review ID	**Hieu 2019**
Review reference	Hieu TH, Dibas M, Surya Dila KA, Sherif NA, Hashmi MU, Mahmoud M, et al. Therapeutic efficacy and safety of chamomile for state anxiety, generalized anxiety disorder, insomnia, and sleep quality: A systematic review and meta-analysis of randomized trials and quasi-randomized trials. Phytother Res. 2019;33(6):1604-15. https://doi.org/10.1002/ptr.6349
Review objective	This systematic review and meta-analysis aimed to study the efficacy and safety of chamomile for the treatment of state anxiety, generalized anxiety disorders (GADs), sleep quality, and insomnia in human.
Author affiliations	Authors were affiliated with tertiary institutions and hospitals in Vietnam, Japan, Saudi Arabia, Indonesia, Pakistan, & Syria
Source of funds	Joint Usage/Research Center on Tropical Disease, Institute of Tropical Medicine, Nagasaki University, Japan; Institute of Allied Health Sciences, National Cheng Kung University
Declared interests of the review authors	The authors declared there were no conflicts of interest
Review method of analysis	Meta-analysis: Random effect meta-analysis was performed by meta package of R statistical software version 3.4.3 and RevMan version 5.3.
Inclusion criteria	
Study design	RCTs and quasi RCTs
Population	Humans studies (any)
Intervention	Chamomile
Comparator	placebo
Other	Outcomes: anxiety, GAD, insomnia, sleep quality
Exclusion criteria	
Study design	Not specified
Population	Not specified
Intervention	Not specified
Comparator	Not specified
Other	There was no restriction applied to language, publication date, age, or place.
Date of documented search (month/year)	

Characteristics of included reviews	Anxiety
Review ID	**Hieu 2019**
Databases searched	PubMed, Science Direct, Cochrane Central, Scopus, Google Scholar, WHO Global Health Library (GHL), ISI Web of Science, Virtual Health Library, Controlled Trials (mRCT), EMBASE, and Clinical trials.gov
Was an non-English database searched?	Yes
Were studies in a LOTE included?	Yes
Outcomes considered in the SR (list)	Insomnia, Anxiety, Sleep quality, Safety
Risk of bias of the included RCT studies as reported in the SR	*Tool used* Cochrane risk of bias tool *Authors summary* 
Authors conclusions (key message)	Three publications (two RCTs) reported the efficacy of chamomile in treating GAD (Amsterdam et al., 2009; Keefe et al., 2016; Mao et al., 2016). HAMA scoring was significantly reduced, indicating an improvement in GAD patients after 2 and 4 weeks of treatment (MD = −1.43, 95% CI [−2.47, −0.39], P = 0.007) and (MD = −1.79, 95% CI [−3.14, −0.43], P = 0.0097), respectively. However, there was no significant reduction after 8 weeks (MD = −1.71, 95% CI [−4.52, 1.09], P = 0.23).

Characteristics of included reviews	Anxiety
Review ID	**Hieu 2019** 12 RCTs were included
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	A total of 965 patients (479 in chamomile group and 486 placebo group) were included in this study, of which five RCTs studied the effect of chamomile on anxiety, two RCTs on GAD, six RCTs on sleep quality, and only one RCT for its effect on insomnia. The mean age ranged from 25.6 to 74.3 years old in the chamomile group, and the placebo group had an age range from 26.9 to 74.3. There were more females (N = 765) reported than males (N = 200). The route of administration of chamomile differed between the studies with nine RCTs reporting having it administered orally, and three studies through inhalation, topical gel, and massage. The time of outcome assessment after intervention differed between the studies ranging from minutes to 26 weeks.

	Study ID	*Summary RoB*	*Study design features (PICO)*	
1	Amsterdam 2009 (Keefe 2016)	Overall high risk of bias	N= (28/29) German chamomile 220mg bid 8 weeks	P: GAD (mild to moderate) I: German chamomile C: Placebo OR diazepam O: HAM-A, BAI, PGWB, CGI-S S: USA
2	Mao 2016	Overall high risk of bias	N= (46/47) German chamomile 500mg tid 12 weeks	P: GAD I: German chamomile C: Placebo OR diazepam O: GAD-7, HAM-D, BAI, PGWB-anxiety S: USA
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Characteristics of included reviews	Anxiety
Review ID	**Hieu 2019**
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= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Anxiety
Review ID	**Marx 2019**
Review reference	Marx W, Lane M, Rocks T, Ruusunen A, Loughman A, Lopresti A, et al. Effect of saffron supplementation on symptoms of depression and anxiety: a systematic review and meta-analysis. Nutrition Reviews. 2019;77(8):557-71. https://doi.org/10.1093/nutrit/nuz023
Review objective	This systematic review and meta-analysis aims to examine the transdiagnostic effects of saffron supplementation (as a stand-alone or adjunctive intervention) on symptoms of mental illness in both clinical and general populations compared with pharmacotherapy or placebo.
Author affiliations	Authors were affiliated with tertiary institutions in Australia (Deakin University, Murdoch Research Institute, U Melbourne, Murdoch University), Finland, and the Black Dog Institute
Source of funds	No funding was provided for the development of this manuscript. Researchers were funded by various fello\
Declared interests of the review authors	Most authors declared there were no conflicts of interest. Others were declared for various grants/research support from NHMRC, Rotary Health, Ian Potter, Meat and Livestock, Lilly, Pfizer and numerous other companies.
Review method of analysis	Meta-analysis: The meta-analyses were conducted in Comprehensive Meta-Analysis 3.020 using a DerSimonian-Laird random- effects model21 to account for heterogeneity between studies. Mean change scores in symptoms for saffron and control conditions were compared using randomeffects meta-analyses to compute effect size of saffron compared with control condition as Hedges' g (with 95%CI). To examine the possibility of publication bias affecting results, Egger's t test was conducted. subgroup analyses were also conducted
Inclusion criteria	
Study design	RCT (incl. crossover trials)
Population	Human participants, both clinically diagnosed with a mental illness and otherwise
Intervention	Saffron supplementation (incl. whole or as extract)
Comparator	Placebo or standard antidepressants
Other	Outcomes: symtpoms of mental illness, adverse events
Exclusion criteria	
Study design	Not specified
Population	No limit on age or population was included.
Intervention	combined interventions with other novel ingredients were excluded.
Comparator	Not specified
Other	Outcomes not related to mental health were not extracted for this review.
Date of documented search (month/year)	

Characteristics of included reviews	Anxiety
Review ID	**Marx 2019**
Databases searched	Medline (Pubmed), PsychInfo, Embase, the Cochrane Library, and CINAHL.
Was an non-English database searched? Were studies in a LOTE included?	No Not specified
Outcomes considered in the SR (list)	Measure of Depression, Anxiety, Mood & Adverse events.
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Jadad score *Authors summary*: Risk of bias across most studies was low, with 20 studies receiving a score of 4 or 5 (out of 5) on the Jadad Scale. Thirteen studies were conducted by the same research group.
Authors conclusions (key message)	Saffron had a large positive effect size when compared with placebo for depressive symptoms (g = 0.99, P < 0.001) and anxiety symptoms (g = 0.95, P < 0.006). Saffron also had a large positive effect size when used as an adjunct to antidepressants for depressive symptoms (g = 1.23, P = 0.028). Egger's regression test found evidence of publication bias. Saffron could be an effective intervention for symptoms of depression and anxiety; however, due to evidence of publication bias and lack of regional diversity, further trials are required.

Reference	Was the study described as random?	Was the study described as double-blind?	Was there a description of dropouts and withdrawals?	**Total Jadad Score**
1. Abedimanesh N et al. 2017[S1]	2	2	1	**5**
2. Agha-Hosseini M et al. 2008 [S2]	2	1	1	**4**
3. Akhondzadeh S et al. 2005 [S3]	2	1	1	**4**
4. Akhondzadeh Basti A et al. 2007 [S4]	2	2	1	**5**
5. Akhondzadeh S et al. 2004 [S5]	2	2	1	**5**
6. Ghajar A et al. 2016 [S6]	2	2	1	**5**
7. Jafarnia N et al. 2017 [S7]	1	1	1	**3**
8. Jam IN et al. 2017 [S8]	1	2	1	**4**
9. Jelodar G et al. 2018 [S9]	2	2	1	**5**
10. Kashani L et al. 2018 [S10]	2	2	1	**5**
11. Kashani L et al. 2013 [S11]	2	1	1	**4**
12. Kashani L et al. 2017 [S12]	2	2	1	**5**
13. Kell G et al. 2017 [S13]	2	2	1	**5**
14. Lopresti AL et al. 2018 [S14]	2	2	1	**5**
15. Mazidi M et al. 2016 [S15]	2	2	1	**5**
16. Moazen-Zadeh E et al. 2017 [S16]	2	2	1	**5**
17. Modabbernia A et al. 2012 [S17]	2	2	1	**5**
18. Moshiri E et al. 2006 [S18]	2	1	0	**3**
19. Noorbala AA et al. 2005 [S19]	2	1	0	**3**
20. Sahraian A et al. 2015 [S20]	2	2	1	**5**
21. Shahmansouri N et al. 2013 [S21]	2	2	1	**5**
22. Tabeshpour J et al. 2017 [S22]	2	2	1	**5**
23. Talaei A et al. 2015 [S23]	2	2	0	**4**

Characteristics of included reviews	Anxiety			
Review ID	**Marx 2019**			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	Twentythree studies were included. A total of 1237 participants were enrolled in the included studies, with 30–128 participants in each study. Trials ran 4–12 weeks with 6 weeks being the most common trial length (n ¼ 9/23). Seventeen studies investigated saffron monotherapy (n ¼ 11 studies) or saffron as an adjunctive pharmacotherapy compared with placebo (n ¼ 6 studies). Six studies compared saffron monotherapy with an antidepressant medication (including fluoxetine,23,32,40,42 imipramine,25 and citalopram 27) No study investigated saffron as an adjunct to psychotherapy. Nineteen studies included participants with either clinical diagnosis of mental illness or clinical symptoms of mental illness using a validated tool. The average age of participants was 39 years, with a range of 14–57 years.			
	Study ID	*Summary RoB*	*Study design features (PICO)*	
1	Jafarnia 2017	NR	N=40 (20/20) Saffron 450mg/day + sertraline 50 mg 6 weeks	P: GAD I: Saffron C: Placebo + sertraline 50 mg O: HAM-A S: Iran
2	Mazidi 2016	NR	N=60 (30/24) Saffron 100 mg/day 12 weeks	P: Anxiety & Depression I: Saffron C: Placebo O: BDI, BAI S: Iran
3	Lopresti 2018	NR	N=80 (NR) Saffron 14 mg 8 weeks	P: Anxiety & Depression (mean 14 years) I: Saffron C: Placebo O: Child Anxiety & Depression Scale-revised (RCADS) S: Australia
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Characteristics of included reviews	Anxiety
Review ID	**Marx 2019**
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= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Anxiety
Review ID	**Moller 2019**
Review reference	Moller HJ, Volz HP, Dienel A, Schlafke S, Kasper S. Efficacy of Silexan in subthreshold anxiety: Meta-analysis of randomised, placebo-controlled trials. European Archives of Psychiatry and Clinical Neuroscience. 2019;269(2):183-93. https://doi.org/10.1007/s00406-017-0852-4
Review objective	To investigate the anxiolytic effect of Silexan, an active substance from lavender oil for oral administration, in patients with subthreshold anxiety
Author affiliations	Authors were affiliated with tertiary institutions in Germany
Source of funds	funded by Dr. Willmar Schwabe GmbH & Co. KG, manufacturer of Silexan, who was also the sponsor of the trials included in the meta-analysis.
Declared interests of the review authors	Conflicts of interest declared - and include the manufacturere of Silexan.
Review method of analysis	Meta-analysis: The meta-analysis of treatment efficacy was based on the original (raw) data of the included trials and was performed for the primary efficacy analysis data sets. missing data for efficacy outcomes were imputed by carrying forward the last valid observation. Patient age, sex, and premature withdrawal rate were analysed using descriptive statistics. Within each trial continuous outcomes were analysed using analysis of covariance (ANCOVA) with treatment as a factor, the intraindividual difference between treatment end and baseline for the outcome of interest as the dependent variable, and the baseline value of the outcome as a covariate. Meta-analyses were computed with the R software package meta (version 4.3.2) and in SAS statistical software version 9.3.
Inclusion criteria	
Study design	RCT
Population	patients with subthreshold anxiety (baseline HAM-A 18 or above)
Intervention	Silexan
Comparator	Placebo
Other	Outcomes: HAM-A
Exclusion criteria	
Study design	Not specified
Population	Not specified
Intervention	Not specified
Comparator	Not specified
Other	Not specified
Date of documented search (month/year)	

Characteristics of included reviews	Anxiety
Review ID	**Moller 2019**
Databases searched	MEDLINE database as well as of the ClinicalTrials.gov registry, the EMA Clinical Trials Register, and the ISRCTN registry
Was an non-English database searched? Were studies in a LOTE included?	No Not specified
Outcomes considered in the SR (list)	Measure of Anxiety, Sleep quality, Clinical gobal impression, Quality of life
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane Risk of Bias tool *Authors summary*

Table 2 Risk of bias assessments according to Higgins et al. [28]

Trial	A [14]	B [16]	C [15]
Random sequence generation	Low	Low	Low
Allocation concealment	Low	Low	Low
Blinding of participants and personnel	Low	Low	Low
Blinding of outcome assessment	Low	Low	Low
Incomplete outcome data	Low	High[a]	Low
Selective reporting	Low	Low	Low
Other sources of bias	Low	Low	Low

[a]Probably favouring placebo

Authors conclusions (key message)	Silexan was superior to placebo in reducing the HAMA total score during 10 weeks' treatment [MD: 3.83 (1.28; 6.37) points]. Superiority was comparably pronounced for psychic and somatic anxiety as well as for observer- and self-rated anxiety. Silexan had a beneficial effect on sleep (secondary to the anxiolytic effect) without causing sedation and improved the patients' health-related quality of life. Adverse event incidence in both treatment groups was comparable [risk ratio: 1.06 (0.85; 1.33)]. Silexan has a significant and clinically meaningful anxiolytic effect in subthreshold anxiety. The results cannot be generalised to other lavender oil products.

Characteristics of included reviews	Anxiety
Review ID	**Moller 2019**
	3 RCTs were included
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	Across all trials included into our analyses 709 patients (Silexan 356; placebo 353) were randomised, 704 (353 and 351) were assessed for safety, and 697 (349 and 348) were analysed for efficacy. More than two-thirds of the participants of all studies were female. Across all trials, the patients in both treatment groups were on average about 47 years old.

	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Kasper 2010	Overall low risk of bias	N= 216 (87/90) Silexan (80 mg od) 10 weeks	P: Anxiety (NOS) I: Lavender oil C: Placebo O: HAM-A, SAS, PSQI, SF-36, CGI S: NR
2	Kasper 2015	Overall high risk of bias	N= 170 (86/84) Silexan (80 mg od) 10 weeks	P: Anxiety (symptoms) I: Lavender oil C: Placebo O: HAM-A, SAS, PSQI, CGI S: NR
3	Kasper 2016	Overall low risk of bias	N= 318 (159/156) Silexan (80 mg od) 10 weeks	P: Anxiety & depression (symptoms) I: Lavender oil C: Placebo O: HAM-A, HADS, SF-36, CGI S: NR
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Characteristics of included reviews	Anxiety
Review ID	**Moller 2019**
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= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Anxiety
Review ID	**Baric 2018**
Review reference	Barić H, Đorđević V, Cerovečki I, Trkulja V. Complementary and Alternative Medicine Treatments for Generalized Anxiety Disorder: Systematic Review and Meta-analysis of Randomized Controlled Trials. Advances in Therapy. 2018;35(3):261-88. https://doi.org/10.1007/s12325-018-0680-6
Review objective	to evaluate efficacy/safety of complementary and alternative medicine (CAM) methods for generalized anxiety disorder (GAD) based on randomized controlled trials in adults.
Author affiliations	Authors were affiliated with tertiary institutions in Croatia
Source of funds	No funding or sponsorship was received for this study or publication of this article.
Declared interests of the review authors	Authors had nothing to disclose
Review method of analysis	Meta-analysis: random-effects meta-analysis to generate pooled estimates of efficacy outcomes: weighted (or standardized) mean difference; and Mantel–Haenszel odds ratio and inverse variance method for (log) hazard ratios. Hartung–Knapp–Sidik–Jonkman correction for the standard error of the estimate. prediction intervals used as the best illustration of the heterogeneity of effects
Inclusion criteria	
Study design	RCTs
Population	adults (18 years or older) with GAD diagnosed
Intervention	Any CAM treatment
Comparator	Not specified
Other	Not specified
Exclusion criteria	
Study design	Not specified
Population	Participants had to be free of psychiatric comorbidities such as bipolar disorder, schizophrenia, major depressive disorder, posttraumatic stress disorder, organic brain syndrome or substance abuse, and condition severity had to be assessed using one of the established validated anxiety rating scales.
Intervention	Not specified
Comparator	Not specified
Other	Not specified
Date of documented search (month/year)	To March 2017

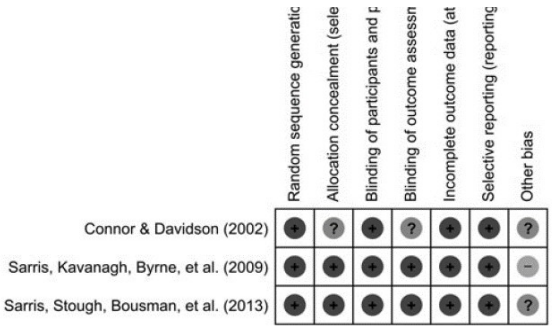
Characteristics of included reviews	Anxiety
Review ID	**Baric 2018**
Databases searched	six electronic databases [Medline, Web of Science, EBSCO (Academic Search Complete, CINHAL and ERIC), Scopus—Health Sciences, Google Scholar and all Cochrane Library
Was an non-English database searched? Were studies in a LOTE included?	No Yes — Studies had to be published in full-text in the English or German languages.
Outcomes considered in the SR (list)	primary outcome was reduction of anxiety (vs. baseline) or alternatively severity of anxiety at the end of treatment
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane *Authors summary*: The main quality issues were related to performance bias (open-label trials), lack of explicit statement of blinded outcome assessment (detection bias) particularly in open-label trials and attrition bias; four trials [37, 38, 46, 48] had a high risk of attrition bias and the level of risk was unclear in a further six [31, 39, 45, 49, 57, 58]. Detailed quality assessment is available in the supplementary material  **Supplementary eFigure 1.** Risk of bias in the included trials Low risk Unclear risk High risk a. Random sequence generation (selection bias) b. Allocation concealment (selection bias) c. Blinding of participants and personnel (performance bias) d. Blinding of outcome assessment (detection bias) e. Incomplete outcome data (attrition bias) f. Selective reporting (reporting bias) Trials of biologically-based treatments Akhondzadeh 2001 Amsterdam 2009 Andreatini 2002 Boerner 2003 Bonne 2003 Connor 2002 Dubois 2010 Eich 2000 Gupta 2014 Hanus 2004 Herrera-Arellano 2007 Herrera-Arellano 2012 Herring 2012 Jonsson 2016 Kasper 2014 Koszycki 2010 Koszycki 2014 Ma 2013 Malsch 2001 Mao 2016 Merom 2008 Park 2014 Rappaport 2016 Sarris 2013 Sayyah 2011 Sherman 2010 Tubaki 2012 Volz 1997 Wang 2012 Wheatley 2001 Woelk 2010 Zhang 2002
Authors conclusions (key message)	Evidence about efficacy/safety of most CAM methods in GAD is limited. Apparent efficacy of certain herbal preparations and body-based therapies requires further confirmation. Considering the circumstances (available standard treatments, required quality of evidence), it does not seem likely that any of the reviewed treatments would be investigated to the extent that would provide evidence to justify their alternative use (i.e., instead of the standard treatments), ; however, it appears feasible and justified to evaluate their complementary use (alongside standard treatments).

Characteristics of included reviews	Anxiety			
Review ID	**Baric 2018**			
	11 RCTs met our PICO. one cross-over trial assessing two dosing schedules not included here.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	2x chamomile (Mao 2016, Amsterdam 2009), 2 lavender oil (Kasper 2014, Woelk 2010); 1 valerian (Andreatini 2002) 1x Passiflora (Akhondzadeh 2001), 5 Kava (Sarris 2013, Boerner 2003,Connor 2002, Malsch 2001, Volz 1997)			
	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Mao 2016	Overall unclear risk of bias	N= (46/47) German chamomile 500mg tid 12 weeks	P: GAD I: German chamomile C: Placebo OR diazepam O: GAD-7, HAM-D, BAI, PGWB-anxiety S: USA
2	Amsterdam 2009 (Keefe 2016)	Overall high risk of bias	N= (28/29) German chamomile 220mg bid 8 weeks	P: GAD (mild to moderate) I: German chamomile C: Placebo OR diazepam O: HAM-A, BAI, PGWB, CGI-S S: USA
3	Kasper 2014	Overall unclear risk of bias	N= 539 (103/119/114) Silexan (160 or 80 mg) NR	P: GAD I: Lavender oil C: Placebo O: HAM-A, HAM-D, CAS S: Germany
4	Woelk 2010	Overall unclear risk of bias	N= 77 (40/37) Silexan (80 mg od) 6 weeks	P: Anxiety (symptoms) I: Lavender oil C: Lorazepam O: HAM-A, CGI, SAS, PSWQ, SF-36, Sleep diary S: NR
5	Andreatini 2002	Overall unclear risk of bias	N=36 (12/12/12) valerian extract 4 weeks	P: GAD I: Valerian extract C: Placebo OR diazepam O: HAM-A, STAI S: Brazil
6	Akhondzadeh 2001	Overall high risk of bias	N=36 (NR) Passiflora 45 drops/day + oxazepam (30 mg/day) 4 weeks	P: GAD I: Passiflora C: Placebo + oxazepam (30 mg/day) O: HAM-A S: Iran

Characteristics of included reviews	Anxiety			
Review ID	**Baric 2018**			
7	Sarris 2013	Overall low risk of bias	N=(27/31) Kava 60-120mg bid 6 weeks	P: GAD I: Kava Kava extract C: Placebo O: HAM-A, BAI, MADRS S: NR
8	Boerner 2003	Overall low risk of bias	N=(43/43) Kava 120mg bid 8 weeks	P: GAD I: Kava Kava extract C: buspirone OR opipramol O: HAM-A, CGI, Bf-S. BOEA, SAS, SF-B, AL S: NR
9	Connor 2002	Overall unclear risk of bias	N=(19/18) Kava 70-140mg bid 3 weeks	P: GAD I: Kava Kava extract C: Placebo O: HAM-A, HADS, SARA S: NR
10	Malsch 2001	Overall unclear risk of bias	N=(20/20) Kava 35-70mg bid 5 weeks	P: GAD I: Kava Kava extract C: Placebo O: HAM-A, CGI, Bf-S, EAAS S: NR
11	Volz 1997	Overall unclear risk of bias	N=(52/49) Kava 70mg tid 24 weeks	P: GAD I: Kava Kava extract C: Placebo O: HAM-A, CGI, SCL-90-R, Bf-S S: NR
15	Bf-S subjective well-being scale; PGWB Psychological General Well-being index; PSWQ Penn State Worry Questionnaire; SAS Self-rating Anxiety Scale, SCL-90-R Symptom Checklist 90-revised; Sf-B sleep questionnaire; Sf-36 Health Survey Questionnaire, STAI State-trait Anxiety Inventory			

= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Anxiety
Review ID	**Ooi 2018**
Review reference	Ooi SL, Henderson P, Pak SC. Kava for Generalized Anxiety Disorder: A Review of Current Evidence. Journal of Alternative & Complementary Medicine. 2018;24(8):770-80. https://doi.org/10.1089/acm.2018.0001
Review objective	To perform a systematic review and meta-analysis of the available evidence on Kava as a treatment for GAD.
Author affiliations	Authors were affiliated with tertiary institutions in Singapore and Australia (Charles Sturt)
Source of funds	None specified
Declared interests of the review authors	The authors declared that there is no conflict of interest.
Review method of analysis	Meta-analysis: For meta-analysis, the authors calculated the standardized mean difference (SMD) between Kava and placebo groups using a random effect model. The authors examined the heterogeneity between studies using I2 statistics, with values of 25%, 50%, and 75% reflecting low, moderate, and high heterogeneity, respectively.
Inclusion criteria	
Study design	Clinical trial (only RCTs include in the meta-analysis)
Population	Majority of participants diagnosed with GAD (ICD or DSM criteria)
Intervention	Kava extract a monotherapy
Comparator	Not specified
Other	Not specified
Exclusion criteria	
Study design	Not specified
Population	Not specified
Intervention	Not specified
Comparator	Not specified
Other	Not specified
Date of documented search (month/year)	To June 2017

Characteristics of included reviews	Anxiety
Review ID	**Ooi 2018**
Databases searched	PubMed, Cochrane Library (Issue 5 of 12, May 2017), CINAHL, Embase, and PsycINFO (1967 to June week 1 2017)
Was an non-English database searched?	No
Were studies in a LOTE included?	No — English studies only.
Outcomes considered in the SR (list)	primary outcome was reduction of anxiety measured using HAM-A
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane RoB v1.0 *Authors summary*: 
Authors conclusions (key message)	Twelve articles were included in this review. Evidence supporting Kava as an effective treatment for GAD was found in two placebo-controlled trials and a reference-controlled trial. One negative trial demonstrated that Kava was not more effective than placebo. Current evidence, although promising, is insufficient to confirm the effect of Kava for GAD treatment beyond placebo.

Characteristics of included reviews	Anxiety			
Review ID	**Ooi 2018**			
	11 RCTs met our PICO. one cross-over trial assessing two dosing schedules not included here.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	2x chamomile (Mao 2016, Amsterdam 2009), 2 lavender oil (Kasper 2014, Woelk 2010); 1 valerian (Andreatini 2002) 1x Passiflora (Akhondzadeh 2001), 5 Kava (Sarris 2013, Boerner 2003,Connor 2002, Malsch 2001, Volz 1997)			
	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Connor 2006	Study discontinued	N=(6/7) Kava 140 to 280mg /day 4 weeks	P: GAD I: Kava Kava extract C: Placebo O: HAM-A, HADS, SARA S: NR
2	Savage 2015	Protocol only. Study not published NCT02219880	N=210 (105/105) Kava 140mg od 12 weeks	P: GAD I: Kava Kava extract C: Placebo O: HAM-A, HADS, SARA S: NR
3	--	**No additional data provided by the SR. Studies below already ID'd**		
4	Sarris 2013	Overall low risk of bias	N=(27/31) Kava 60-120mg bid 6 weeks	P: GAD I: Kava Kava extract C: Placebo O: HAM-A, BAI, MADRS S: NR
5	Boerner 2003	Not reported	N=(43/43) Kava 120mg bid 8 weeks	P: GAD I: Kava Kava extract C: buspirone OR opipramol O: HAM-A, CGI, Bf-S. BOEA, SAS, SF-B, AL S: NR
6	Connor 2002	Overall unclear risk of bias	N=(19/18) Kava 70-140mg bid 3 weeks	P: GAD I: Kava Kava extract C: Placebo O: HAM-A, HADS, SARA S: NR

Characteristics of included reviews	Anxiety
Review ID	**Ooi 2018**
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= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Anxiety
Review ID	**Smith 2018**
Review reference	Smith K, Leiras C. The effectiveness and safety of Kava Kava for treating anxiety symptoms: A systematic review and analysis of randomized clinical trials. Complementary Therapies in Clinical Practice. 2018;33:107-17. https://doi.org/10.1016/j.ctcp.2018.09.003
Review objective	To determine if Kava Kava is an effective treatment for combating symptoms of anxiety despite warnings of hepatotoxicity from the Centers for Disease Control and Prevention (CDC).
Author affiliations	Authors were affiliated with tertiary institutions in USA (Michigan)
Source of funds	This review did not receive any grant funding from agencies in the public, commercial, or not-for-profit sect
Declared interests of the review authors	The authors do not have any conflicts of interest to disclose.
Review method of analysis	Meta-analysis: Analysis of results focused on differences in means or medians, responder rates, and percentage/number of adverse events. Demographics pooled included sample size, age, gender, and baseline HAMA score from the intent-to-treat population. Responder rates were used to create a funnel plot to measure publication bias. A test for overall effect and heterogeneity was performed to help assess sampling error and/or bias using the heterogeneity coefficient (I2) statistic.
Inclusion criteria	
Study design	RCTs
Population	adult participants with anxiety (18 yrs or older)
Intervention	Kava Kava products
Comparator	Not specified
Other	Not specified
Exclusion criteria	
Study design	non-peer reviewed articles
Population	other interfering mental disorders, illnesses, or drug abuse/addictions, not related to anxiety; or utilized healthy volunteers
Intervention	used additional concurrent interventions with Kava Kava;
Comparator	
Other	published prior to 2000
Date of documented search (month/year)	studies published between January 1, 2000, and December 31, 2017

Characteristics of included reviews	Anxiety
Review ID	**Smith 2018**
Databases searched	PubMed, CINAHL, and PsycINFO
Was an non-English database searched?	No
Were studies in a LOTE included?	No English langauge only
Outcomes considered in the SR (list)	Analysis of results focused on differences in means or medians, responder rates, and percentage/number of adverse events. Changes in scores of Hamilton Anxiety Scale (HAMA), "Befindlichkeits-Skala" subjective well-being scale (Bf-S), Anxiety Status Inventory (ASI), and/ or State–Trait Anxiety Inventory-State (STAI-S) were contrasted with one another.
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Not assessed *Authors summary*
Authors conclusions (key message)	Kava Kava appears to be a short-term treatment for anxiety, but not a replacement for prolonged anti-anxiety use. Although not witnessed in this review, liver toxicity is especially possible if taken longer than 8 weeks.

Characteristics of included reviews	Anxiety			
Review ID	**Smith 2018**			
	The 11 articles meeting inclusion/exclusion criteria included 9 studies that were randomized, double-blinded studies with at least two parallel groups and 2 that detailed adverse events			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	Sarris 2013, Sarris 2012, Sarris 2009, Geier 2004, Lehrl 2004, Gastpar 2003, Connor 2002, Malsch 2001			
	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Sarris 2009	Not reported	N= 60 Kava 250mg /day 3 wks (1 wk run in) crossover	P: anxiety (>10 in BAI) I: Kava Kava extract C: Placebo O: HAM-A, BAI, Montgomery–Asberg Depression Scale S: NR
2	Geier 2004	Not reported	N= 50 Kava 50mg tid 7 wks (1 wk run in)	P: Mixed - GAD, phobias, adjustment disorder I: Kava Kava extract C: Placebo O: HAM-A S: NR
3	Lehrl 2004	Not reported	N= 57 Kava 100mg bid 7 wks (1 wk run in)	P: anxiety (>15 in HAM-A) I: Kava Kava extract C: Placebo O: HAM-A, Bf-S (mood) S: NR
4	Gastpar 2003	Not reported	N= 141 Kava 50mg tid 7 wks (1 wk run in)	P: GAD I: Kava Kava extract C: Placebo O: Anxiety Status Inventory, Bf-S (mood) S: NR
5		**No additional data provided by the SR.** **Studies below already ID'd**		
6	Sarris 2013	Overall high risk of bias	N= 58 (27/31) Kava 120mg bid 8 weeks (1 wk run in, 1 wk followup)	P: GAD I: Kava Kava extract C: Placebo O: HAM-A, BAI, MADRS S: NR

Characteristics of included reviews	Anxiety			
Review ID	**Smith 2018**			
7	Connor 2002	Overall unclear risk of bias	N= 35 (19/18) Kava 70mg bid 4 wks	P: GAD I: Kava Kava extract C: Placebo O: HAM-A, HADS, SARA S: NR
8	Malsch 2001	Overall unclear risk of bias	N=(20/20) Kava 35-70mg bid 5 wks + 3 wks followup	P: GAD I: Kava Kava extract C: Placebo O: HAM-A, CGI, Bf-S (mood), EAAS S: NR
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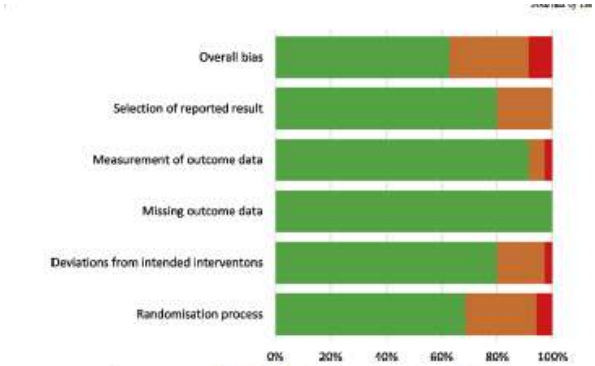
= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Anxiety
Review ID	**Lopresti 2021**
Review reference	Lopresti AL, Smith SJ. Ashwagandha (Withania somnifera) for the treatment and enhancement of mental and physical conditions: A systematic review of human trials. Journal of Herbal Medicine. 2021;28:100434. 10.1016/j.hermed.2021.100434
Review objective	to summarise and critically appraise results from human trials on ashwagandha that have been conducted to date.
Author affiliations	Australia, Murdoch University
Source of funds	No financial support from any organisation has been obtained for the submitted manuscript.
Declared interests of the review authors	AL and SJS have received funding in the past to conduct clinical trials on ashwagandha and other herbal and nutraceutical ingredients.
Review method of analysis	Descriptive — Narrative summary only.
Inclusion criteria	
Study design	human interventional trial (randomised controlled, nonrandomised, open-label, and observational)
Population	Adults: mental conditions/wellbeing, physical and medical conditions/wellbeing, cognitive performance, sexual function and fertility, or athletic/exercise performance
Intervention	Ashwaganda alone or as adjunct
Comparator	None specified
Other	completed pre- and post-intervention outcome measures;
Exclusion criteria	
Study design	in virto trials
Population	--
Intervention	Ashwagandha as component of multi-ingredient formulation
Comparator	--
Other	--
Date of documented search (month/year)	Data base inception to April 2020

Characteristics of included reviews	Anxiety
Review ID	**Lopresti 2021**
Databases searched	Medline (Pubmed), Cochrane Library, Scopus, Web of Science, and CINAHL databases
Was an non-English database searched?	No
Were studies in a LOTE included?	No — English langauge only
Outcomes considered in the SR (list)	Efficacy outcomes
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane Collaboration's risk of bias tool (RoB 2) *Authors summary*: summary risk of bias provided. Individual results in supplementary data (not able to access)  Fig. 3. Summary of Risk of Bias analyses for randomised controlled trials.
Authors conclusions (key message)	All doses were associated with improvements in the total HAM-A anxiety scores compared to the placebo with trends to suggest greater efficacy with the higher dose. Compared to the placebo, there were also greater reductions in several (but not all) symptom scores such as fatigue, feelings of impending doom, sleeplessness, forgetfulness, irritability, and an inability to concentrate in the ashwagandha-treated groups.

Characteristics of included reviews	Anxiety
Review ID	**Lopresti 2021**
	Of the 41 trials identified in this review, the effects of ashwagandha were investigated on stress and anxiety (7 studies).
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	Seven randomised, double-blind, placebo-controlled studies comprising a total of 491 recruited participants were identified examining the effects of ashwagandha on stress and anxiety symptoms. 4 RCTs met our PICO criteria (anxiety) (Lopresti 2019, Kyati 2013, Auddy 2008, Andrade 2000) the other 3 RCTs were in people with stress/burnout (Chandrasekhar 2012, Choudhary 2017, Salve 2019)

	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Lopresti 2019	Overall low risk of bias	N= 60 (20/20/20) Ashwagandha 125 & 300 mg bid 8 weeks	P: Moderate anxiety (HAM-A 6-17) I: Ashwagandha C: Placebo O: HAM-A, PSS, cortisol, sleep quality S: India
2	Kyati 2013	Overall low risk of bias	N= NR (44/42) Ashwagandha 4g qd 8 weeks	P: GAD I: Ashwagandha C: Placebo O: HAM-A S: India
3	Auddy 2008	Overall low risk of bias	N= 130 (30/35/35/30) Ashwagandha 125, 250 & 500 mg per day 8 weeks	P: Anxiety (HAM-A 24-42) I: Ashwagandha C: Placebo O: HAM-A, biomarkers S: India
4	Andrade 2000	Overall low risk of bias	N= 39 (20/19) Ashwagandha 250 mg bid 6 weeks	P: Anxiety (HAM-A 24-42) I: Ashwagandha C: Placebo O: HAM-A, CGI S: India
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Characteristics of included reviews	Anxiety
Review ID	**Lopresti 2021**
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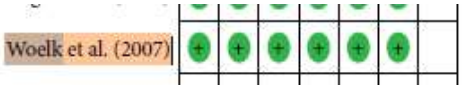
= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Anxiety
Review ID	**Brondino 2013**
Review reference	Brondino N, De Silvestri A, Re S, Lanati N, Thiemann P, Verna A, et al. A Systematic Review and Meta-Analysis of Ginkgo biloba in Neuropsychiatric Disorders: From Ancient Tradition to Modern-Day Medicine. Evidence-based Complementary & Alternative Medicine (eCAM). 2013;2013:1-11. https://doi.org/10.1155/2013/915691
Review objective	To perform a systematic review on the effects of Ginkgo biloboa in different psychiatric conditions.
Author affiliations	Authors were affiliated with tertiary institutions in Italy and Germany
Source of funds	This research received no specific grant from any funding agency in the public, commercial, or noprofit sectors.
Declared interests of the review authors	Anna Verna is an employee of nVH Italia Srl. All the other authors have no conflicts of interests.
Review method of analysis	Meta-analysis: When it was possible, datawere pooled by means ofmetaanalysis. Effect measures on rating scales were expressed as standardized mean differences (SMDs) with the 95% CIs. A random-effects model (DerSimonian-Laird) was used to calculate a pooled effect estimate, because of heterogeneity. A p value <0.05 was regarded as statistically significant. Heterogeneity of effect sizes was evaluated by the I^2 statistic
Inclusion criteria	
Study design	RCTs
Population	Neuropsychiatric patients
Intervention	gingko biloba
Comparator	None specified
Other	a minimum number of participants of ten per group, a treatment period of at least 6 weeks, and the availability of a full-text publication.
Exclusion criteria	
Study design	None specified
Population	None specified
Intervention	None specified
Comparator	None specified
Other	None specified
Date of documented search (month/year)	up to April 2012

Characteristics of included reviews	Anxiety
Review ID	**Brondino 2013**
Databases searched	MEDLINE, EMBASE, PsycINFO, and the Cochrane Database of Systematic Reviews.
Was an non-English database searched? Were studies in a LOTE included?	No Not specified
Outcomes considered in the SR (list)	The following rating scales were accepted for clinical outcomes realting to anxiety: Hamilton Rating Scale for Anxiety (HAMA) & State-Trait Anxiety Inventory (STAI)
Risk of bias of the included RCT studies as reported in the SR	*Tool used* Cochrane RoB v1.0 *Authors summary* 
Authors conclusions (key message)	Gb treatment reduced positive symptoms in patients with schizophrenia and improved cognitive function and activities of daily living in patients with dementia. No effect of Gb on negative symptoms in schizophrenic patients was found.The general lack of evidence prevents drawing conclusions regarding Gb effectiveness in other neuropsychiatric conditions (i.e., autism, depression, anxiety, attentiondeficit hyperactivity disorder, and addiction). Our data support the use of Gb in patients with dementia and as an adjunctive therapy in schizophrenic patients.

Characteristics of included reviews	Anxiety			
Review ID	**Brondino 2013**			
	systematic review and a meta-analysis of 3 RCTs in patients with schizophrenia and 8 RCTs in patients with dementia			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	Woelk 2007			
	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Woelk 2007	Overall low risk of bias	N= 82 (25/27/30) Ginkgo 240 & 480 mg /day 4 weeks	P: GAD I: Ginkgo C: Placebo O: HAM-A S: NR
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Characteristics of included reviews	Anxiety
Review ID	**Brondino 2013**
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= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Depression
Review ID	**Firoozeei 2021**
Review reference	Firoozeei TS, Feizi A, Rezaeizadeh H, Zargaran A, Roohafza HR, Karimi M. The Antidepressant Effects of Lavender (Lavandula angustifolia Mill.): A Systematic Review and Meta-Analysis of Randomized Controlled Clinical Trials. Complementary Therapies in Medicine. 2021:102679. https://dx.doi.org/10.1016/j.ctim.2021.102679
Review objective	the aim of this study was to determine the efficacy of lavender on depression severity
Author affiliations	Department of Traditional Medicine, School of Persian Medicine, Tehran University of Medical Sciences
Source of funds	In a collaborative study between Tehran University of Medical Sciences and Isfahan University of Medical Sciences, the research has been supported in part by Isfahan University of Medical Sciences. (Research Project NO:199280)
Declared interests of the review authors	The authors declared there were no conflicts of interest
Review method of analysis	Meta-analysis: Meta-analysis was conducted using STATA software version 11.2 The standardized mean difference (SMD) was used to assess the effects of treatment on main outcome i.e. depression score. Heterogeneity was evaluated by using Cochran Q test and I-squared statistics and visual inspection of forest plot. effect size of lavender on depression score and corresponding 95 % CIs was calculated by random-effect model in cases of medium and high heterogeneity. Possible sources of heterogeneity were explored and adopted by sensitivity analysis, meta-regression, and subgroup analyses if possible. Publication bias assessed with funnelplot and Egger linear regression
Inclusion criteria	
Study design	RCTs
Population	Any disease of medical condition
Intervention	Lavender, all routes of administration
Comparator	Any (placebo or active control)
Other	Antidepressant effects
Exclusion criteria	
Study design	RCTs only
Population	No age or sex restrictions

Characteristics of included reviews	Depression
Review ID	**Firoozeei 2021**
Intervention	No restrictions
Comparator	No restrictions
Other	
Date of documented search (month/year)	Jan 2000 to Dec 2020
Databases searched	PubMed, Scopus, Embase, Cochrane library and Web of science
Was an non-English database searched? Were studies in a LOTE included?	No Not specified
Outcomes considered in the SR (list)	Depression as the main outcome measure or as a subscale of any valid assessment tool.
Risk of bias of the included RCT studies as reported in the SR	*Tool used* Cochrane risk of bias tool *Authors summary* **Table 3** **Cochrane risk of bias assessment (a) and Jadad score (b).** 1 st Author (year) / Cochrane risk of bias / Jadad scores (Total score) Araj Khodai (2020), / H, L, L, L, L, L, L / 1, 1,1, 0, 1 (4)

Characteristics of included reviews	Depression			
Review ID	**Firoozeei 2021**			
Authors conclusions (key message)	there was a significant reduction in depression scores in the group receiving oral lavender capsules comparable with the group consuming fluoxetine.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	*Study ID*	*Summary RoB*	*Study design features (PICOS)*	
1	Araj-Khodaei 2020	Overall high risk of bias	N= 50 (NR/NR/NR) Lavender 500 mg bid, Lemon balm 500 mg bid 8 weeks	P: Depression (mild-to-moderate; HAM-D 8 to 24) I: Lavender (oral) OR Lemon balm C: Fluoxetine 5 mg bid O: HAM-D S: Iran
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Characteristics of included reviews	Depression
Review ID	**Firoozeei 2021**
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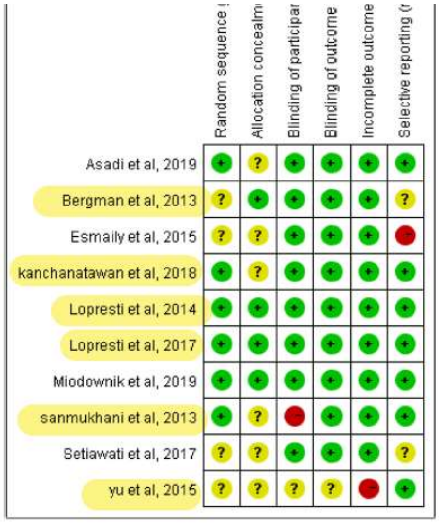
= data extracted

= data extracted from more recent SR (or better SR)

= control is an active intervention

Characteristics of included reviews	Depression
Review ID	**Wang 2021**
Review reference	Wang Z, Zhang Q, Huang H, Liu Z. The efficacy and acceptability of curcumin for the treatment of depression or depressive symptoms: A systematic review and meta-analysis. Journal of Affective Disorders. 2021;282:242-51. https://doi.org/10.1016/j.jad.2020.12.158
Review objective	Curcumin, a potential natural substance is a promising complementary and alternative therapeutic intervention for depression or depressive symptoms. We undertook a systematic review and meta-analysis to evaluate the efficacy and acceptability.
Author affiliations	The first hospital of China Medical University
Source of funds	This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors
Declared interests of the review authors	The authors declared there were no conflicts of interest
Review method of analysis	Meta-analysis — We analyzed data using Stata and Review Manager and pooled data for meta-analysis. For continuous outcomes, the standardized mean difference (SMD) was calculated; for dichotomous results, the odds ratios (ORs) were calculated. SMD was used because we expected that different scales to be used in different studies.
Inclusion criteria	
Study design	RCTs including both parral and cross-over design.
Population	Patients could be diagnosed with depression or have depressive symptoms.
Intervention	Curcumin was performed at any dosage in the intervention group
Comparator	placebo plus standard care or standard care alone
Other	Not specified
Exclusion criteria	
Study design	Not specified
Population	Not specified

Characteristics of included reviews	Depression
Review ID	**Wang 2021**
Intervention	Not specified
Comparator	Not specified
Other	Not specified
Date of documented search (month/year)	Inception up until March 4, 2020.
Databases searched	EMBASE, PubMed, PsycINFO, Web of Science, Cochrane Library and ClinicalTrials.gov
Was an non-English database searched? Were studies in a LOTE included?	No Yes There were no restrictions on language or year of publication
Outcomes considered in the SR (list)	Our primary outcome was the standardized mean difference (SMD) of the scores in the standard scales before and after treatments. Other secondary outcomes were response rates, drop-out rates, and adverse effects. The response was defined as ≥50% reduction from baseline on the scale at the study end.
Risk of bias of the included RCT studies as reported in the SR	*Tool used* Cochrane risk of bias tool *Authors summary*  Fig. 2. Risk of bias assessment of the included studies.

Characteristics of included reviews	Depression
Review ID	**Wang 2021**
Authors conclusions (key message)	Data relating to the primary outcome (post-treatment depression scores) were available from all the RCTs (three were at high risk of bias, four at unclear risk of bias and three at low risk of bias). Curcumin was better than the placebo with an SMD of -0.32 (95% CI: -0.50 to -0.13) with ten studies and 594 patients. There was no significant heterogeneity in effect size (I 15%, p=0.30) (Fig. 3). No significant publication = bias was found in the funnel plots or the Egger test (p= 0.09). Considering the limited number of studies, the potential heterogeneity and the low level of evidence, there is great uncertainty about the efficacy and acceptability of curcumin for the treatment of depression or depressive symptoms. But curcumin is a safe and simple intervention that could potentially be beneficial for patients with depression or depressive symptoms, large sample sizes randomized controlled trials should be done to explore the effects of curcumin for future studies
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	10 RCTs of which 6 met our PICO. The other RCTs were in people with diabetes, obesity, schizophrenia and systeamtic lupus erythmatosus.

	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Kanchanatawan 2018	Overall low risk of bias	N= (33/32) Curcumin 500 mg increasing to 1500mg per day 12 weeks	P: MDD (mini 6.0) C: Placebo O: MADRS S: ?
2	Lopresti 2017	Overall low risk of bias	N= (28/28) Curcumin 1000mg per day 8 weeks	P: MDD (DSM-IV) C: Placebo O: IDS-SR30 S: ?
3	Yu 2015	Overall high risk of bias	N= (54/54) Curcumin 1000 mg per day 6 weeks	P: MDD (DSM-IV) C: Placebo O: HAM-D S: ?
4	Lopresti 2014	Overall low risk of bias	N= (33/28/26/36) Curcumin 500mg/250 mg/ 250 mg + saffron per day 12 weeks	P: MDD (DSM-IV) C: Placebo O: IDS-SR30 S: ?
5	Sanmukhani 2014	Overall high risk of bias	N= (20/20) Curcumin 1000 mg per day 6 weeks	P: MDD (DSM-IV) C: Placebo O: HAM-D S: ?
6	Bergman 2013	Overall unclear risk of bias	N= (20/20) Curcumin 500 mg per day 6 weeks	P: MDD (DSM-IV) C: Placebo O: HAM-D S: ?

Characteristics of included reviews	Depression
Review ID	**Wang 2021**
7	BDI: Beck Depression Inventory; CDSS: Calgary Depression Scale for Schizophrenia; DASS-21-items: Depression, Anxiety, Stress Scale; DSM: Diagnostic and statistical manual of mental disorders; HAM-D: Hamilton Depression Rating Scale; IDS-SR30: Self-rated Inventory of Depressive Symptomatology; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; Mini: the MINI-International Neuropsychiatric Interview
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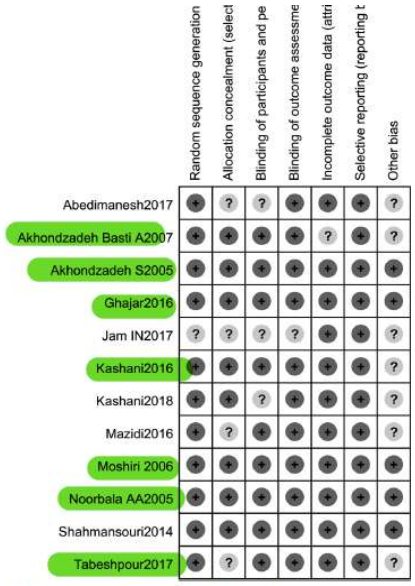
	= data extracted
	= data extracted from more recent SR (or better SR)
	= control is an active intervention

Characteristics of included reviews	Depression
Review ID	**Dai 2020**
Review reference	Dai L, Chen L, Wang W. Safety and Efficacy of Saffron (Crocus sativus L.) for Treating Mild to Moderate Depression: A Systematic Review and Meta-analysis. Journal of Nervous & Mental Disease. 2020;208(4):269-76. https://doi.org/10.1097/NMD.0000000000001118
Review objective	Herbal remedies are becoming increasingly popular for the treatment of depression. Recently, accumulating evidences reveal a positive effect of saffron (Crocus sativus L.) in relieving depressive symptoms. The objective of this meta-analysis was to assess the safety and efficacy of saffron in treating mild to moderate depression by synthesizing all available data.
Author affiliations	The authors were affiliated with tertiary institutions in China
Source of funds	This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors
Declared interests of the review authors	The authors declared there were no conflicts of interest
Review method of analysis	Meta-analysis: Stata software version 15.0 (Stata Corporation, College Station, TX) was used to perform this meta-analysis. Comparisons between saffron and placebo or between saffron and antidepressants were analyzed, respectively. The overall effect for continuous parameters, regarding changes of depression scale score (HAM-D or BDI scores), was summarized using weighted mean differences (WMDs) with 95% confidence intervals (CIs). For dichotomous variables such as the number of patients under remission or response, risk ratios (RRs) with its 95% CIs were estimated. Possible heterogeneity among the included studies was assessed by chi-square Q-test and I2 statistics
Inclusion criteria	
Study design	Double-blind randomized controlled trials (RCTs)
Population	1) patients, adult with symptoms of mild to moderate depression;
Intervention	2) treatment, both saffron and control group only received monotherapy without other intervention;
Comparator	3) comparator, control group patients received placebo or antidepressant treatment; a
Other	nd 4) outcome, included proper outcome for the comparison of efficacy and safety between groups, such as changes in depression scale score, response rate, remission rate, and adverse effects.
Exclusion criteria	
Study design	Studies that did not met the aforementioned criteria, review articles, case reports, abstracts, and ongoing trials were excluded.
Population	Not specified

Characteristics of included reviews	Depression
Review ID	**Dai 2020**
Intervention	Not specified
Comparator	Not specified
Other	Not specified
Date of documented search (month/year)	Literature search was completed before February 28, 2019.
Databases searched	Records were retrieved from electronic databases PubMed, Embase, and ScienceDirect
Was an non-English database searched? Were studies in a LOTE included?	No Yes There were no restrictions on language or year of publication
Outcomes considered in the SR (list)	outcome measures (timing of evaluation, measurement tools), and overall results (changes in Hamilton Rating Scale for Depression, 17 items [HAM-D] or Beck Depression Inventory [BDI] scores from baseline to follow-up, response rate, remission rate, and adverse effects) were extracted
Risk of bias of the included RCT studies as reported in the SR	*Tool used* Cochrane risk of bias tool *Authors summary*  **FIGURE 2.** Risk for bias summary of 12 included studies in the meta-analysis.

Characteristics of included reviews	Depression			
Review ID	**Dai 2020**			
Authors conclusions (key message)	Twelve studies were included in the meta-analysis. Overall results showed that saffron possessed better efficacy in the improvement of depressive symptoms when compared with placebo, whereas saffron was as effective as synthetic antidepressants. No significant differencewas detected in the incidence of adverse effects between saffron and placebo or between saffron and antidepressants. Conclusions: Saffron could be considered as an alternative to synthetic antidepressants in the treatment of mild to moderate depression. However, multicenter trials with larger sample size, longer treatment duration, and different ethnic groups are required to verify our results.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	Of the 12 RCTs included in the review, 7 met our PICO critera. The other RCTs were in people with menopause, metabolic syndrome, coronary artery disease, post PCI, or anxiety			
	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Ghajar 2017	Overall low risk of bias	N= (30/20) Saffron 30mg per day 6 weeks	P: Major depression (moderate HAM-D <19) I: Saffron C: Citalopram O: HAM-D S: ?
2	Kashani 2016	Overall unclear risk of bias	N= (32/17) Saffron 30mg per day 6 weeks	P: Postpartum depression (mild-mod HAM-D >9 to <19) I: Saffron C: Fluoxetine O: HAM-D S: ?
3	Tabeshpour 2017	Overall unclear risk of bias	N= (30/20) Saffron 40mg per day 8 weeks	P: Postpartum depression (BDI </=30) I: Saffron C: Placebo O: BDI S: ?
4	Akhondzadeh Basti 2007	Overall unclear risk of bias	N= (20/19) Saffron 30mg per day 8 weeks	P: Depression (mild-to-moderate HAM-D >17 to <26) I: Saffron C: Fluoxetine O: HAM-D S: ?
5	Moshiri 2006	Overall low risk of bias	N= (20/30) Saffron 30mg per day 6 weeks	P: Depression (mild-to-moderate HAM-D >17) I: Saffron C: Placebo O: HAM-D S: ?
6	Akhondzadeh 2005	Overall low risk of bias	N= (20/20) Saffron 30mg per day 6 weeks	P: Depression (mild-to-moderate HAM-D >17) I: Saffron C: Placebo O: HAM-D S: ?

Characteristics of included reviews	Depression			
Review ID	**Dai 2020**			
7	Noorbala 2005	Overall low risk of bias	N= (20/20) Saffron 30mg per day 6 weeks	P: Depression (mild-to-moderate HAM-D >17) I: Saffron C: Fluoxetine O: HAM-D S: ?
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= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Depression
Review ID	**Fusar-Poli 2020**
Review reference	Fusar-Poli L, Vozza L, Gabbiadini A, Vanella A, Concas I, Tinacci S, et al. Curcumin for depression: a meta-analysis. Critical Reviews in Food Science & Nutrition. 2020;60(15):2643-53. https://doi.org/10.1080/10408398.2019.1653260 The protocol has been published on Figshare, an online repository for research data sharing (doi:10.6084/m9.figshare.9114422).
Review objective	Given its anti-inflammatory and antioxidant properties, it has been hypothesized that curcumin might be effective in treating symptoms of a variety of neuropsychiatric disorders, such as depression.
Author affiliations	Department of Clinical and Experimental Medicine, Psychiatry Unit, University of Catania, Catania, Italy
Source of funds	This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors
Declared interests of the review authors	The authors declared there were no conflicts of interest
Review method of analysis	Meta-analysis: A random-effects model was used for calculation of the effect size. For continuous outcomes, we pooled the Hedge's g to correct the effect size for small sample sizes. According to Rosenthal and Rosnow (1991), we adopted a conservative pre-post correlation coefficient of 0.7, if not reported in the original article.
Inclusion criteria	
Study design	Study design: randomized or controlled clinical trials, both parallel and crossover.
Population	individuals with a diagnosis of major depressive disorder (MDD), according to international valid diagnostic criteria or measured by a validated scale. We have also included individuals with depressive symptoms unrelated to a specific depressive syndrome, but secondary to other psychiatric or medical conditions.
Intervention	Intervention: curcumin, administered at any dosage and in any form.
Comparator	Comparison: placebo plus standard care or standard care alone.
Other	There were no restrictions on language or year of publication
Exclusion criteria	
Study design	Not specified
Population	We excluded studies in which participants did not have clinically significant levels of depression at baseline.

Characteristics of included reviews	Depression
Review ID	**Fusar-Poli 2020**
Intervention	Not specified
Comparator	Not specified
Other	Not specified
Date of documented search (month/year)	from inception to 1st August 2019:
Databases searched	MEDLINEVR , KCI – Korean Journal Database, Russian Science Citation Index and SciELO Citation Index), CIN.
Was an non-English database searched?	Yes
Were studies in a LOTE included?	Yes There were no restrictions on language or year of publication
Outcomes considered in the SR (list)	Outcomes: Our primary outcome was represented by depressive symptoms, evaluated with standard measures. Secondary outcomes were represented by anxiety symptoms and clinical global impression.
Risk of bias of the included RCT studies as reported in the SR	*Tool used* Cochrane risk of bias tool *Authors summary* 

Characteristics of included reviews	Depression			
Review ID	**Fusar-Poli 2020**			
Authors conclusions (key message)	Curcumin was generally well-tolerated by patients. Our findings suggest that curcumin, if added to standard care, might improve depressive and anxiety symptoms in people with depression. However, given the small sample size, our results should be cautiously interpreted. Further trials should be implemented, particularly in Western countries, where curcumin does not represent a usual component of dietary regimens.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	Of the 10 RCTs included in the SR, 7 met our PICO criteria.			
	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Kanchanatawan 2018	Overall unclear risk of bias	N= (33/32) Curcumin 500 mg increasing to 1500mg per day 12 weeks	P: MDD (mini 6.0) C: Placebo (adjunct to antidepressants) O: MADRS, HAM-A S: Thailand
2	Lopresti 2017	Overall low risk of bias	N= (28/28) Curcumin 1000mg per day 8 weeks	P: MDD (DSM-IV) C: Placebo (adjunct to antidepressants) O: IDS-SR30, STAI S: Australia
3	Yu 2015	Overall unclear risk of bias	N= (54/54) Curcumin 1000 mg per day 6 weeks	P: MDD (DSM-IV) C: Placebo (adjunct to escitalopram) O: HAM-D, MADRS S: China
4	Lopresti 2014	Overall low risk of bias	N= (33/28/26/36) Curcumin 500mg/250 mg/ 250 mg + saffron per day 12 weeks	P: MDD (DSM-IV) C: Placebo (adjunct to antidepressants) O: IDS-SR30, STAI S: Australia
5	Sanmukhani 2014	Overall high risk of bias	N= (20/20) Curcumin 1000 mg per day 6 weeks	P: MDD (DSM-IV) C: Placebo (adjunct to antidepressants) O: HAM-D, CGI S: India
6	Bergman 2013	Overall high risk of bias	N= (20/20) Curcumin 500 mg per day 6 weeks	P: MDD (DSM-IV) C: Placebo (adjunct to antidepressants) O: HAM-D, MADRS, CGI S: Israel

Characteristics of included reviews	Depression			
Review ID	**Fusar-Poli 2020**			
7	Panahi 2015	Overall high risk of bias (open label)	N= (61/50) Curcumin 1000 mg per day 6 weeks	P: MDD (DSM-IV) C: Placebo (adjunct to antidepressants) O: BDI, HADS-A, HADS-D S: Israel
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= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Depression	
Review ID	**Ghaderi 2020**	
Review reference	Ghaderi, A., Asbaghi, O., Reiner, Ž., Kolahdooz, F., Amirani, E., Mirzaei, H., Banafshe, H. R., Maleki Dana, P., & Asemi, Z. (2020). The effects of saffron (Crocus sativus L.) on mental health parameters and C-reactive protein: A meta-analysis of randomized clinical trials. Complement Ther Med, 48, 102250. https://doi.org/10.1016/j.ctim.2019.102250	
Review objective	to summarize all the existing RCTs evidence and to evaluate the effects of saffron intake on parameters of mental health and CRP.	
Author affiliations	The authors were affiliated with tertiary institutions in Iran, Croatia and Canada	
Source of funds	This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors	
Declared interests of the review authors	The authors declared there were no conflicts of interest	
Review method of analysis	Meta-analysis	Weighted mean difference (WMD) with 95 % CI was used for pooling data to determine the effect sizes. The change score approach was used to calculate the effect size of saffron intake on the analyzed parameter. The random-effect model was used to report the pooled effect sizes using 95 % CI. Publication bias was evaluated using the funnel plots.
Inclusion criteria		
Study design	RCTs	
Population	Not specified, only that mental health and c-reactive protein (CRP) were going to be measured.	
Intervention	saffron	
Comparator	Placebo	
Other	Not specified	
Exclusion criteria		
Study design	Animal experiments, in vitro studies, case reports, observational studies, trials without a control group, and studies that did not achieve the least quality score were excluded from this meta-analysis	
Population	Animal experiments	

Characteristics of included reviews	Depression
Review ID	**Ghaderi 2020**
Intervention	Not specified
Comparator	without control group
Other	Not specified
Date of documented search (month/year)	Inception to July 2019
Databases searched	PubMed, Scopus, ISI, (Web of Science), Cochrane Central Register of Controlled Trials, EMBASE, Google Scholar
Was an non-English database searched?	No
Were studies in a LOTE included?	No
Outcomes considered in the SR (list)	Effects of saffron on parameters of mental health and CRP with standard deviation (SD) and related 95 % confidence interval (CI) for the both intervention and placebo groups: 1) BDI, 2) BAI, 3) HAMD and 4) CRP.
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane risk of bias tool *Authors summary*: The authors report assessing Risk of bias, but do not provided any other information - other than noting the "*quality of all included studies was high*" . Individual RoB not reported.

Characteristics of included reviews	Depression			
Review ID	**Ghaderi 2020**			
Authors conclusions (key message)	This meta-analysis demonstrated that saffron intake significantly reduced BDI, BAI and PSQI scores, but did not affect HDRS-D, HARS-A scores and CRP levels.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	Of the 21 RCTS that were included, 7 met our PICO			
	total N =			
	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Talaei 2015	Not reported	N= (20/20) Saffron 30mg crocin per day 4 weeks	P: MDD I: Saffron C: Placebo (adjuct to SSRI) O: BDI, BAI S: Iran
2	Sahraian 2016	Not reported	N= (11/19) Saffron 30mg per day 4 weeks	P: MDD I: Saffron C: Placebo O: BDI S: Iran
3	Kell 2017a & b	Not reported	N= (16/37 & 17/39) Saffron 19 & 28 mg per day 4 weeks	P: Low mood I: Saffron C: Placebo O: PSQI S: Australia
4	Jelodar 2018	Not reported	N= (20/20) Saffron 30mg per day 4 weeks	P: MDD I: Saffron C: Placebo (adjunct to 20 mg/day fluoxetine) O: BDI S: Iran
5	**RCTs listed below already identified**			
6	Akhondzadeh 2005	Overall low risk of bias	N= (20/20) Saffron 30mg per day 6 weeks	P: Depression (mild-to-moderate HAM-D >17) I: Saffron C: Placebo O: HAM-D S: Iran

Characteristics of included reviews	Depression			
Review ID	**Ghaderi 2020**			
7	Moshiri 2006	Overall low risk of bias	N= (20/30) Saffron 30mg per day 6 weeks	P: Depression (mild-to-moderate HAM-D >17) I: Saffron C: Placebo O: HAM-D S: Iran
8	Tabeshpour 2017	Overall unclear risk of bias	N= (30/20) Saffron 40mg per day 8 weeks	P: Postpartum depression (BDI </=30) I: Saffron C: Placebo O: BDI S: ?
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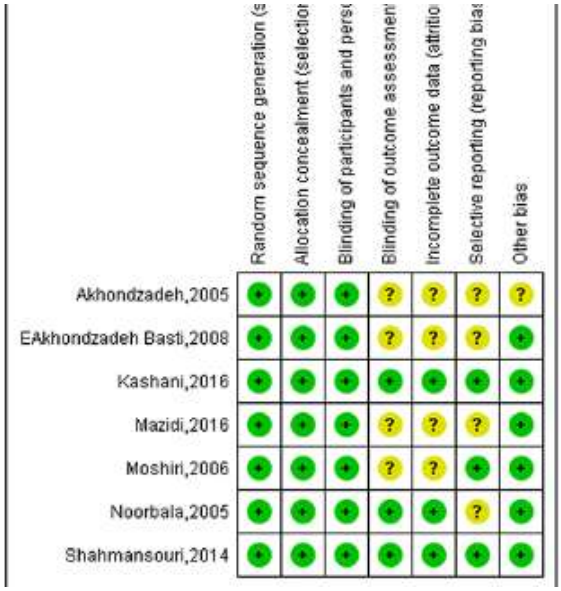
	= data extracted			
	= data extracted from more recent SR (or better SR)			
	= control is an active intervention			

Characteristics of included reviews	Depression
Review ID	**Khaksarian 2019**
Review reference	Khaksarian M, Behzadifar M, Behzadifar M, Alipour M, Jahanpanah F, Re TS, et al. The efficacy of Crocus sativus (Saffron) versus placebo and Fluoxetine in treating depression: A systematic review and meta-analysis. Psychology Research and Behavior Management. 2019;12:297-305. https://doi.org/10.2147/PRBM.S199343
Review objective	Crocus sativus (Saffron) is a herbal remedy that has anti-cancer, anti-oxidant, anti-inflammatory and anti-platelet properties. However, the exact mechanisms of Saffron in treating depression are not yet clear. This study was conducted to evaluate the effectiveness of Saffron versus placebo and Fluoxetine in the treatment of depressed patients.
Author affiliations	Department of Health Sciences (DISSAL), Postgraduate School of Public Health, University of Genoa, Italy
Source of funds	This study was supported by the Razi Herbal Medicines Research Center, Lorestan University of Medical Sciences (No: A-10-1289-1).
Declared interests of the review authors	The authors declared there were no conflicts of interest
Review method of analysis	Meta-analysis: Effect sizes were computed as Standardized Mean Differences (SMD) using a random-effects model with their 95% confidence interval (CI).20 The sensitivity analysis was performed to check the stability and reliability of results. To evaluate the heterogeneity of the studies, I2 test was carried out.21 P-values less than 0.05 were considered as significant values. Due to the fact that the number of studies entered was less than 10, there was no possibility to check the publication bias. R environment (version 3.4.0) was used to analyze the data
Inclusion criteria	
Study design	Sstudies designed as randomized clinical trial or RCTs.
Population	Studies performed in humans and recruiting patients with an official diagnosis of depression, established according to the Diagnostic and Statistical Manual of Mental Disorders – DSM – criteria; any type of depression was considered, without any restriction with regards to the severity – mild or severe depression – or the kind of patient affected – youth or post-partum depression;
Intervention	Studies in which Saffron was utilized in one arm and placebo or Fluoxetine were used in the other arm;
Comparator	Saffron versus placebo or Fluoxetine;
Other	
Exclusion criteria	
Study design	Studies were excluded if: studies designed as review papers, letters to the editor, case-report and case-series; and,
Population	performed in animals or in nondepressed patients;

Characteristics of included reviews	Depression
Review ID	**Khaksarian 2019**
Intervention	using saffron in combinationwith another drug or compound;
Comparator	--
Other	studies results of which were not clear or not sufficiently detailed.
Date of documented search (month/year)	to May 2018
Databases searched	Cochrane Library, Scopus, PubMed/ MEDLINE, Centre for Reviews and Dissemination (CRD), EMBASE, and ISI/Web of Science (WOS). The Clinical Trial, the Trial Register, as well as international congresses on depression such as the International Depressive Disorder and Anxiety Disorders and Depression were also searched.
Was an non-English database searched? Were studies in a LOTE included?	No
	Not specified
Outcomes considered in the SR (list)	Any measure of depression
Risk of bias of the included RCT studies as reported in the SR	*Tool used* Cochrane risk of bias tool *Authors summary* 

Characteristics of included reviews	Depression			
Review ID	**Khaksarian 2019**			
Authors conclusions (key message)	The findings of the present systematic review and metaanalysis showed that the use of saffron improved the symptoms of depressed patients. However, on the basis of the abovementioned shortcomings, to ensure the effectiveness of this compound in treating depression, further high-quality studies are needed to provide more solid and valuable evidence.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	*Study ID*	*Summary RoB*	*Study design features (PICOS)*	
1	Akhondzadeh Basti 2008	Overall unclear risk of bias	N= 44 (NR) Saffron XXmg per day 6 weeks	P: Depression (mild-to-moderate HAM-D >17 to <26) I: Saffron C: Placebo O: HAM-D S: Iran
2	**RCTs listed below already identified**			
3	Akhondzadeh 2005	Overall low risk of bias	N= (20/20) Saffron 30mg per day 6 weeks	P: Depression (mild-to-moderate HAM-D >17) I: Saffron C: Placebo O: HAM-D S: Iran
4	Moshiri 2006	Overall low risk of bias	N= (20/20) Saffron 30mg per day 6 weeks	P: Depression (mild-to-moderate HAM-D >17) I: Saffron C: Placebo O: HAM-D S: Iran
5	Noorbala 2005	Overall low risk of bias	N= (20/20) Saffron 30mg per day 6 weeks	P: Depression (mild-to-moderate HAM-D >17) I: Saffron C: Fluoxetine 40 mg/day O: HAM-D S: Iran
6	Akhondzadeh Basti 2007	Overall unclear risk of bias	N= (20/19) Saffron 30mg per day 8 weeks	P: Depression (mild-to-moderate HAM-D >17 to <26) I: Saffron C: Fluoxetine 20 mg/day O: HAM-D S: Iran

Characteristics of included reviews	Depression			
Review ID	**Khaksarian 2019**			
7	Kashani 2016	Overall unclear risk of bias high dropout in C group	N= (32/32) Saffron 30mg per day 6 weeks	P: Postpartum depression (mild-mod HAM-D >9 to <19) I: Saffron C: Fluoxetine 40 mg/day O: HAM-D S: Iran
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	= data extracted			
	= data extracted from more recent SR (or better SR)			
	= control is an active intervention			

Characteristics of included reviews	Depression
Review ID	**Marx 2019**
Review reference	Marx W, Lane M, Rocks T, Ruusunen A, Loughman A, Lopresti A, et al. Effect of saffron supplementation on symptoms of depression and anxiety: a systematic review and meta-analysis. Nutrition Reviews. 2019;77(8):557-71. https://doi.org/10.1093/nutrit/nuz023
Review objective	This systematic review and meta-analysis aims to examine the transdiagnostic effects of saffron supplementation (as a stand-alone or adjunctive intervention) on symptoms of mental illness in both clinical and general populations compared with pharmacotherapy or placebo.
Author affiliations	Authors were affiliated with tertiary institutions in Australia (Deakin University, Murdoch Research Institute, U Melbourne, Murdoch University), Finland, and the Black Dog Institute
Source of funds	No funding was provided for the development of this manuscript. Researchers were funded by various fellowships.
Declared interests of the review authors	Most authors declared there were no conflicts of interest. Others were declared for various grants/research support from NHMRC, Rotary Health, Ian Potter, Meat and Livestock, Lilly, Pfizer and numerous other
Review method of analysis	Meta-analysis: The meta-analyses were conducted in Comprehensive Meta-Analysis 3.020 using a DerSimonian-Laird random- effects model21 to account for heterogeneity between studies. Mean change scores in symptoms for saffron and control conditions were compared using randomeffects meta-analyses to compute effect size of saffron compared with control condition as Hedges' g (with 95%CI). To examine the possibility of publication bias affecting results, Egger's t test was conducted. subgroup analyses were also conducted
Inclusion criteria	
Study design	RCT (incl. crossover trials)
Population	Human participants, both clinically diagnosed with a mental illness and otherwise
Intervention	Saffron supplementation (incl. whole or as extract)
Comparator	Placebo or standard antidepressants
Other	Outcomes: symtpoms of mental illness, adverse events
Exclusion criteria	
Study design	Not specified
Population	No limit on age or population was included.

Characteristics of included reviews	Depression
Review ID	**Marx 2019**
Intervention	combined interventions with other novel ingredients were excluded.
Comparator	Not specified
Other	Outcomes not related to mental health were not extracted for this review.
Date of documented search (month/year)	
Databases searched	Medline (Pubmed), PsychInfo, Embase, the Cochrane Library, and CINAHL.
Was an non-English database searched? Were studies in a LOTE included?	No Not specified
Outcomes considered in the SR (list)	Measure of Depression, Anxiety, Mood & Adverse events.
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Jadad score *Authors summary*: Risk of bias across most studies was low, with 20 studies receiving a score of 4 or 5 (out of 5) on the Jadad Scale

Reference	Was the study described as random?	Was the study described as double-blind?	Was there a description of dropouts and withdrawals?	Total Jadad Score
1. Abedimanesh N et al. 2017[S1]	2	2	1	**5**
2. Agha-Hosseini M et al. 2008 [S2]	2	1	1	**4**
3. Akhondzadeh S et al. 2005 [S3]	2	1	1	**4**
4. Akhondzadeh Basti A et al. 2007 [S4]	2	2	1	**5**
5. Akhondzadeh S et al. 2004 [S5]	2	2	1	**5**
6. Ghajar A et al. 2016 [S6]	2	2	1	**5**
7. Jafarnia N et al. 2017 [S7]	1	1	1	**3**
8. Jam IN et al. 2017 [S8]	1	2	1	**4**
9. Jelodar G et al. 2018 [S9]	2	2	1	**5**
10. Kashani L et al. 2018 [S10]	2	2	1	**5**
11. Kashani L et al. 2013 [S11]	2	1	1	**4**
12. Kashani L et al. 2017 [S12]	2	2	1	**5**
13. Kell G et al. 2017 [S13]	2	2	1	**5**
14. Lopresti AL et al. 2018 [S14]	2	2	1	**5**
15. Mazidi M et al. 2016 [S15]	2	2	1	**5**
16. Moazen-Zadeh E et al. 2017 [S16]	2	2	1	**5**
17. Modabbernia A et al. 2012 [S17]	2	2	1	**5**
18. Moshiri E et al. 2006 [S18]	2	1	0	**3**
19. Noorbala AA et al. 2005 [S19]	2	1	0	**3**
20. Sahraian A et al. 2015 [S20]	2	2	1	**5**
21. Shahmansouri N et al. 2013 [S21]	2	2	1	**5**
22. Tabeshpour J et al. 2017 [S22]	2	2	1	**5**
23. Talaei A et al. 2015 [S23]	2	2	0	**4**

Characteristics of included reviews	Depression			
Review ID	**Marx 2019**			
Authors conclusions (key message)	Saffron had a large positive effect size when compared with placebo for depressive symptoms (g = 0.99, P < 0.001) and anxiety symptoms (g = 0.95, P < 0.006). Saffron also had a large positive effect size when used as an adjunct to antidepressants for depressive symptoms (g = 1.23, P = 0.028). Egger's regression test found evidence of publication bias. Saffron could be an effective intervention for symptoms of depression and anxiety; however, due to evidence of publication bias and lack of regional diversity, further trials are required.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	23 RCTs included in the review: 3 in people with anxiety (Jafarnia 2017, Mazidi 2016, Lopresti 2018)			
	Study ID	*Summary RoB*	*Study design features (PICO)*	
1	Akhondzadeh 2004	Jadad score 5	N= 30 (NR) Saffron 30mg per day 6 weeks	P: Depression (DSM-IV) I: Saffron C: Imipramine 100mg O: HAM-D S: Iran
2	Kashani 2013	Jadad score 4	N= 38 (NR) Saffron 30mg per day 4 weeks	P: Major depression (DSM-IV) I: Saffron (adjunct to Fluoxetine 40 mg/day) C: Placebo O: HAM-D S: Iran
3	Modabbernia 2012	Jadad score 5	N= 36 (NR) Saffron 30mg per day 4 weeks	P: Major depressive disorder I: Saffron (adjunct to Fluoxetine 40 mg/day) C: Placebo O: HAM-D S: Iran
4	**RCTs listed below already identified**			
5	Akhondzadeh Basti 2007	Jadad score 5	N= (20/19) Saffron 30mg per day 8 weeks	P: Depression (mild-to-moderate HAM-D >17 to <26) I: Saffron C: Fluoxetine 20 mg/day O: HAM-D S: Iran
6	Akhondzadeh 2005	Jadad score 4	N= (20/20) Saffron 30mg per day 6 weeks	P: Depression (mild-to-moderate HAM-D >17) I: Saffron C: Placebo O: HAM-D S: Iran

Characteristics of included reviews	Depression			
Review ID	**Marx 2019**			
7	Ghajar 2017	Jadad score 5	N= 66 (NR) Saffron 30mg per day 6 weeks	P: Major depression (moderate HAM-D <19) I: Saffron C: Citalopram 40 mg O: HAM-D, HAM-A S: ?
8	Jelodar 2018	Jadad score 5	N= (20/20) Saffron 30mg per day 4 weeks	P: MDD I: Saffron C: Placebo (adjunct to 20 mg/day fluoxetine) O: BDI S: Iran
9	Kashani 2016	Jadad score 5	N= 68 (32/32) Saffron 30mg per day 6 weeks	P: Postpartum depression (mild-mod HAM-D >9 to <19) I: Saffron C: Fluoxetine 20 mg/day O: HAM-D S: Iran
10	Kell 2017a & b	Jadad score 5	N= 128 (16/37 & 17/39) Saffron 19 & 28 mg per day 4 weeks	P: Low mood I: Saffron C: Placebo O: PSQI, POMS, PANAS, DASS-21 S: Australia
11	Moshiri 2006	Jadad score 3	N= (20/20) Saffron 30mg per day 6 weeks	P: Depression (mild-to-moderate HAM-D >17) I: Saffron C: Placebo O: HAM-D S: Iran
12	Noorbala 2005	Jadad score 3	N= (20/20) Saffron 30mg per day 6 weeks	P: Depression (mild-to-moderate HAM-D >17) I: Saffron C: Fluoxetine 20 mg/day O: HAM-D S: Iran
13	Sahraian 2016	Jadad score 5	N= 40 (11/19) Saffron 30mg per day 4 weeks	P: MDD (DSM-IV) I: Saffron (adjunct to fluoxetine 20mg/day) C: Placebo O: BDI S: Iran
14	Tabeshpour 2017	Jadad score 5	N= 78 (30/30) Saffron 30mg per day 8 weeks	P: Postpartum depression (BDI </=30) I: Saffron C: Placebo O: BDI S: Iran
15	Talaei 2015	Jadad score 4	N= 46 (20/20) Saffron 30mg [crocin] per day 4 weeks	P: MDD I: Saffron (adjuct to SSRI) C: Placebo O: BDI, BAI, MDQ S: Iran

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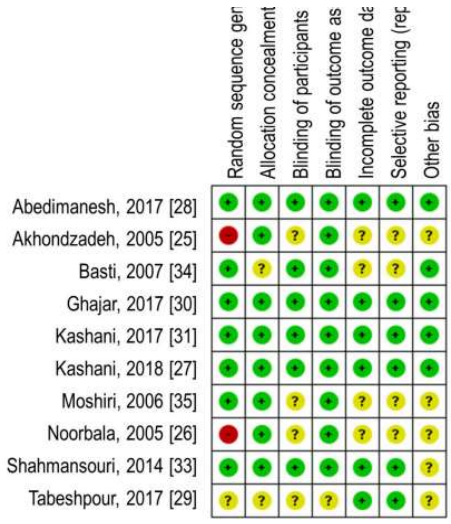
= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Depression
Review ID	**Toth 2019**
Review reference	Tóth B, Hegyi P, Lantos T, Szakács Z, Kerémi B, Varga G, et al. The Efficacy of Saffron in the Treatment of Mild to Moderate Depression: A Meta-analysis. Planta Medica. 2019;85(1):24-31. https://doi.org/10.1055/a-0660-9565
Review objective	We have carried out a literature review of currently available published randomized, controlled clinical trials to give an up-to-date evaluation of the efficacy of saffron in mild to moderate depression, compared to placebo or routinely used antidepressants.
Author affiliations	Department of Pharmacognosy, Faculty of Pharmacy, University of Szeged Hungary
Source of funds	This study was supported by an Economic Development and Innovation Operative Programme Grant and an Institutional Developments for Enhancing Intelligent Specialization Grant awarded by the National Research, Development and Innovation Office, a János Bolyai Research Scholarship awarded by the Hungarian Academy of Sciences (to D.C.), and a research grant (115796) awarded by the National Research, Development and Innovation Office (to D.C.).
Declared interests of the review authors	The authors declare no conflict of interest.
Review method of analysis	Meta-analysis: The meta-analysis is reported according to PRISMA guidelines and was conducted using the statistical programs Comprehensive Meta-analysis and RevMan. Hedges' g was used to calculate effect sizes. Risk of bias was assessed using the Cochrane Collaboration tool, and heterogeneity was tested by both performing the Cochran's Q test and calculating Higgins' I2 indicator.
Inclusion criteria	
Study design	randomized clinical studies
Population	patients suffering from mild to moderate depression
Intervention	pharmacological doses of saffron per os
Comparator	placebo or active controlled,
Other	O = changes in the severity of the depression.
Exclusion criteria	
Study design	Not specified
Population	Not specified

Characteristics of included reviews	Depression
Review ID	**Toth 2019**
Intervention	Not specified
Comparator	Not specified
Other	Not specified
Date of documented search (month/year)	Not specified
Databases searched	PubMed, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science databases were searched for relevant studies.
Was an non-English database searched? Were studies in a LOTE included?	No Not specified
Outcomes considered in the SR (list)	O = changes in the severity of the depression.
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane risk of bias tool *Authors summary* 

Characteristics of included reviews	Depression			
Review ID	**Toth 2019**			
Authors conclusions (key message)	According to the present meta-analysis, saffron has a significant effect on the severity of depression. Available data from randomized, controlled clinical trials support that saffron is significantly more effective than placebo (g = 0.891; 95% CI: 0.369–1.412, p = 0.001), and non-inferior to tested antidepressant drugs (g = − 0.246; 95% CI: − 0.495– 0.004, p = 0.053).			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	Eleven randomized trials were included in the qualitative analysis, and nine were pooled for statistical analysis.			
	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	**RCTs listed below already identified**			
2	Tabeshpour 2017	Overall unclear risk of bias	N= 78 (30/30) Saffron 30mg per day 8 weeks	P: Postpartum depression (BDI </=30) I: Saffron C: Placebo O: BDI S: Iran
3	Kashani 2017	Overall low risk of bias	N= 68 (32/32) Saffron 30mg per day 6 weeks	P: Postpartum depression (mild-mod HAM-D >9 to <19) I: Saffron C: Fluoxetine 20 mg/day O: HAM-D S: Iran
4	Ghajar 2017	Overall low risk of bias	N= 66 (NR) Saffron 30mg per day 6 weeks	P: Major depression (moderate HAM-D <19) I: Saffron C: Citalopram 40 mg O: HAM-D, HAM-A S: Iran
5	Akhondzadeh Basti 2007	Overall unclear risk of bias	N= (20/19) Saffron 30mg per day 8 weeks	P: Depression (mild-to-moderate HAM-D >17 to <26) I: Saffron C: Fluoxetine 20 mg/day O: HAM-D S: Iran
6	Moshiri 2006	Overall unclear risk of bias	N= (20/20) Saffron 30mg per day 6 weeks	P: Depression (mild-to-moderate HAM-D >17) I: Saffron C: Placebo O: HAM-D S: Iran

Characteristics of included reviews	Depression			
Review ID	**Toth 2019**			
7	Noorbala 2005	Overall high risk of bias	N= (20/20) Saffron 30mg per day 6 weeks	P: Depression (mild-to-moderate HAM-D >17) I: Saffron C: Fluoxetine 20 mg/day O: HAM-D S: Iran
8	Akhondzadeh 2005	Overall high risk of bias	N= (20/20) Saffron 30mg per day 6 weeks	P: Depression (mild-to-moderate HAM-D >17) I: Saffron C: Placebo O: HAM-D S: Iran
9	Akhondzadeh 2004	Overall high risk of bias	N= 30 (NR) Saffron 30mg per day 6 weeks	P: Depression (DSM-IV) I: Saffron C: Imipramine 100mg O: HAM-D S: Iran
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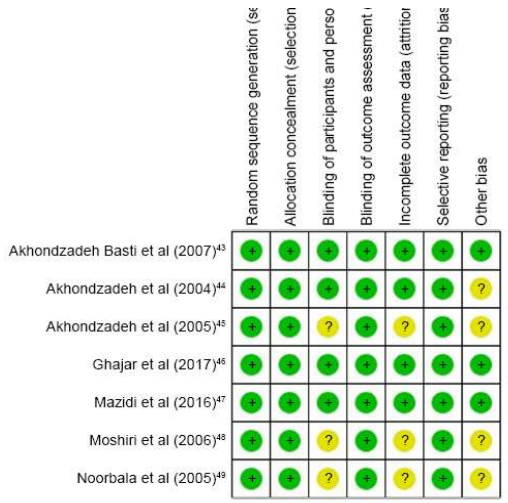
= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Depression
Review ID	**Yang 2019**
Review reference	Yang X, Chen X, Fu Y, Luo Q, Du L, Qiu H, et al. Comparative efficacy and safety of Crocus sativus L. for treating mild to moderate major depressive disorder in adults: a meta-analysis of randomized controlled trials. Neuropsychiatr Dis Treat. 2018;14:1297-305. https://doi.org/10.2147/ndt.S157550
Review objective	To investigate the efficacy and safety of saffron in the treatment of major depressive disorder (MDD) in comparison to placebo and synthetic antidepressants.
Author affiliations	The First Affiliated Hospital of Chongqing Medical University, Chongqing,
Source of funds	None specified
Declared interests of the review authors	The authors report no conflicts of interest in this work.
Review method of analysis	Meta-analysis: RevMan5 software (Cochrane Information Management System) was used to perform this meta-analysis. When standard deviation (SD) was not provided in an article and the authors could not be contacted, an estimated SD would be calculated from the reported P-values, confidence intervals (CIs), or standard errors (SEs) in that article.39 We chose a random-effects model in order to obtain more conservative results. Standardized mean differences (SMDs) with 95% CIs were estimated as the overall effect index for continuous measures (the change scores on HAMD or BDI), and the odds ratios (ORs) with 95% CIs for dichotomous measures (the number of patients under remission and response, and the number of dropouts for all reasons) by inverse variance models. Possible heterogeneity across the included studies was evaluated by the test of inconsistency (I2).
Inclusion criteria	
Study design	We included double-blind randomized controlled trials (RCTs)
Population	MDD should be diagnosed based on standardized diagnostic criteria, such as Diagnostic and Statistical Manual of Mental Disorders (DSM)28–32 or International Classification of Diseases.
Intervention	Saffron - Only as oral monotherapy
Comparator	comparing to either placebo or synthetic antidepressants.
Other	Not specified
Exclusion criteria	
Study design	Trials without adequate data, trials with quasi-random, or trials with small sample size (less than 10) were also excluded
Population	In this analysis, we excluded trials on depression secondary to physical diseases and trials on child and adole

Characteristics of included reviews	Depression
Review ID	**Yang 2019**
Intervention	Not specified
Comparator	Not specified
Other	Not specified
Date of documented search (month/year)	up to September 20, 2017.
Databases searched	PubMed, Embase, Cochrane Library, Web of Science, and websites of ClinicalTrials.gov from their inception
Was an non-English database searched? Were studies in a LOTE included?	No Not specified
Outcomes considered in the SR (list)	the primary outcome was defined as the mean overall change of depressive symptoms from baseline to end point.
Risk of bias of the included RCT studies as reported in the SR	*Tool used* Cochrane risk of bias tool *Authors summary*  **Figure 2** Quality assessments for each included study. **Notes:** "+" means "low bias", "–" means "high bias", and "?" means "unclear bias".

Characteristics of included reviews	Depression			
Review ID	**Yang 2019**			
Authors conclusions (key message)	Saffron was effective in the treatment of MDD and had comparable efficacy to synthetic antidepressants. Saffron was also a safe drug without serious adverse events reported. As for the primary outcome, saffron showed more improvements in depression symptoms when compared with placebo, with an SMD of -1.22 (95% CI -1.94, -0.49, P=0.001). Meanwhile, saffron was as effective as synthetic antidepressants, with an SMD of 0.16 (95% CI -0.25, 0.57, P=0.44). Moderate heterogeneity existed in our analysis.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	Seven studies were included in this meta-analysis. Overall quality of these included studies was moderate.			
	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	**RCTs listed below already identified**			
2	Akhondzadeh Basti 2007	Overall low risk of bias	N= (20/19) Saffron 30mg per day 8 weeks	P: Depression (mild-to-moderate HAM-D >17 to <26) I: Saffron C: Fluoxetine 20 mg/day O: HAM-D S: Iran
3	Akhondzadeh 2004	Overall unclear risk of bias	N= 30 (NR) Saffron 30mg per day 6 weeks	P: Depression (DSM-IV) I: Saffron C: Imipramine 100mg O: HAM-D S: Iran
4	Akhondzadeh 2005	Overall unclear risk of bias	N= (20/20) Saffron 30mg per day 6 weeks	P: Depression (mild-to-moderate HAM-D >17) I: Saffron C: Placebo O: HAM-D S: Iran
5	Ghajar 2017	Overall low risk of bias	N= 66 (NR) Saffron 30mg per day 6 weeks	P: Major depression (moderate HAM-D <19) I: Saffron C: Citalopram 40 mg O: HAM-D, HAM-A S: ?
6	Moshiri 2006	Overall unclear risk of bias	N= (20/20) Saffron 30mg per day 6 weeks	P: Depression (mild-to-moderate HAM-D >17) I: Saffron C: Placebo O: HAM-D S: Iran

Characteristics of included reviews	Depression			
Review ID	**Yang 2019**			
7	Noorbala 2005	Overall unclear risk of bias	N= (20/20) Saffron 30mg per day 6 weeks	P: Depression (mild-to-moderate HAM-D >17) I: Saffron C: Fluoxetine 20 mg/day O: HAM-D S: Iran
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	= data extracted			
	= data extracted from more recent SR (or better SR)			
	= control is an active intervention			

Characteristics of included reviews	Depression
Review ID	**Sarris 2018**
Review reference	Sarris J. Herbal medicines in the treatment of psychiatric disorders: 10-year updated review. Phytotherapy Research. 2018;32(7):1147-62. https://doi.org/10.1002/ptr.6055
Review objective	This paper provides a 10-year update of the 2007 systematic review of herbal medicines studied in a broad range of psychiatric disorders, including depression, anxiety, obsessive–compulsive, seasonal affective, bipolar, psychotic, phobic, somatoform, and attention-deficit hyperactivity disorders
Author affiliations	NICM Health Research Institute, School of Science and Health, Western Sydney University, Westmead
Source of funds	J. S. has received either presentation honoraria, travel support, clinical trial grants, book royalties, or independent consultancy payments from a variety of pharnaceutical and non-pahranceutical companies.
Declared interests of the review authors	
Review method of analysis	Descriptive
Inclusion criteria	
Study design	Any (RCTs, Nonrandomized- or nonplacebo-controlled human trials were reviewed)
Population	Not specified (major psychiatric disorders or mental health symptoms)
Intervention	Not specified
Comparator	Not specified
Other	The major change in this updated review is that traditional Chinese or Kampo formulas found in the original search
Exclusion criteria	
Study design	Not specified
Population	Not specified

Characteristics of included reviews	Depression
Review ID	**Sarris 2018**
Intervention	Not specified
Comparator	Not specified
Other	Not specified
Date of documented search (month/year)	originally accessed in early 2007; with an updated search occurring during September to October 2017.
Databases searched	Ovid Medline, PubMed, and The Cochrane Library
Was an non-English database searched?	No
Were studies in a LOTE included?	Not specified
Outcomes considered in the SR (list)	Not specified
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane risk of bias tool; *Authors summary*: Not provided

Characteristics of included reviews	Depression	
Review ID	**Sarris 2018**	
Authors conclusions (key message)	This updated review now covers clinical trial evidence for 24 herbal medicines in 11 psychiatric disorders. High-quality evidence was found to exist for the use of Piper methysticum (Kava), Passiflora spp. (passionflower) and Galphimia glauca (galphimia) for anxiety disorders; and Hypericum perforatum (St John's wort) and Crocus sativus (saffron) for major depressive disorder. Other encouraging herbal medicines with preliminary evidence include Curcuma longa (turmeric) in depression, Withania somnifera (ashwagandha) in affective disorders, and Ginkgo biloba (ginkgo) as an adjunctive treatment in Schizophrenia.	
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview		
1	Nikfarjam 2017	Narrative review - no information provided
2	Nikfarjam 2013	Narrative review - no information provided
3	Akhondzadeh 2003	Narrative review - no information provided
4	Mao 2015	Narrative review - no information provided
5	Darbinyan 2007	Narrative review - no information provided
6	--	

Characteristics of included reviews	Depression
Review ID	**Sarris 2018**
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= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Depression	
Review ID	**Apaydin 2016**	
Review reference	Apaydin EA, Maher AR, Shanman R, Booth MS, Miles JNV, Sorbero ME, et al. A systematic review of St. John's wort for major depressive disorder. Systematic Reviews. 2016;5(1):148. https://doi.org/10.1186/s13643-016-0325-2 PROSPERO CRD42015016406	
Review objective	This systematic review evaluated St. John's wort (SJW) for the treatment of Major Depressive Disorder (MDD). The objectives of this review are to (1) evaluate the efficacy and safety of SJW in adults with MDD compared to placebo and active comparator and (2) evaluate whether the effects vary by severity of MDD.	
Author affiliations	RAND Corporation,	
Source of funds	None declared	
Declared interests of the review authors	None declared	
Review method of analysis	Meta-analysis	Comparative effectiveness results and equivalence assessments of the efficacy and safety took the consistency of effects across individual studies and the statistical power to detect a statistically significant difference between treatment groups into account. For all efficacy outcomes and the number of patients with adverse events, we used the Hartung-Knapp-Sidik-Jonkman method for a random effects meta-analysis
Inclusion criteria		
Study design	RCTs	
Population	Studies in adults, male and female, 18 years of age and over, with a diagnosis of MDD were eligible for inclusion in the review	
Intervention	RCTs testing the efficacy and safety of SJW—used adjunctively or as monotherapy— Studies that administered a supplement that contained a known amount of SJW, and the amount and type of active compounds contained in the SJW supplement that was specified (i.e., naphthodianthrones, hypericin, pseudohypericin, flavonoids, phloroglucinols, hyperforin, and adhyperforin), were eligible. SJW could be evaluated alone or in conjunction with pharmacologic and/or psychotherapy.	
Comparator	Studies comparing SJW with placebo or with active comparators, or against another amount or extract of SJW, were eligible.	
Other	Studies that reported Hamilton clinical rating scale for depression (HAMD) scores or other validated depression scale scores were eligible for inclusion as well as studies that reported other changes in depressive symptoms (e.g., suicidal ideation) or the rate of treatment responders.	
Exclusion criteria		
Study design	Only studies with a treatment duration of 4 weeks or longer were eligible.	
Population	Not specified	

Characteristics of included reviews	Depression
Review ID	**Apaydin 2016**
Intervention	Not specified
Comparator	Not specified
Other	Studies were not limited by setting (e.g., country, physical location of treatment).
Date of documented search (month/year)	from January 2007 to November 2014
Databases searched	PubMed, CINAHL (Cumulative Index to Nursing and Allied Health Literature), PsycINFO, CENTRAL (Cochrane Central Register of Controlled Trials), Embase, AMED (Allied and Complementary Health Database), MANTIS (Manual, Alternative, and Natural Therapy Index System), Web of Science, and ICTRP (International Clinical Trials Registry Platform)
Was an non-English database searched? Were studies in a LOTE included?	No
	Not specified without language restriction
Outcomes considered in the SR (list)	
Risk of bias of the included RCT studies as reported in the SR	*Tool used* Cochrane risk of bias tool *Authors summary* **Table 1** Study quality/risk of bias for individual included studies

Study ID	Recruitment method (random sequence generation)	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting of outcome data	Other: all receive TAU, only treatment group receives SJW (no placebo for controls)	Other: appropriate washout period or exclusion of individuals taking personal supplements	Other: baseline assessment, appropriate statistical analysis, COI)	USPSTF quality rating (good, fair, poor)
Behnke, 2002 [17]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	NA	Low risk	Poor
Bernhardt, 1993 [16]	Unclear risk	Unclear risk	High risk	High risk	Unclear risk	Unclear risk	Low risk	NA	Unclear risk	Poor
Bjerkenstedt, 2005 [18]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	NA	Low risk	Fair
Brenner, 2000 [19]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	NA	Low risk	Fair
Fava, 2005 [20]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	NA	Low risk	Poor
Gastpar, 2005 [21]	Low risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	NA	Low risk	Poor
Gastpar, 2006 [22]	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	NA	Low risk	Good
HDTSG, 2002 [23]	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	NA	Low risk	Fair
Hangsen, 1994 [48]	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	NA	Low risk	Poor
Harrer, 1993 [24]	Low risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	NA	Low risk	Poor
Harrer, 1999 [25]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	NA	Low risk	Fair
Kalb, 2001 [26]	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	NA	Low risk	Good
Kasper, 2006 [27]	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	NA	Low risk	Fair
Kasper, 2008 [28]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Fair
Laakmann, 1998 [29]	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	NA	Low risk	Good
Lecrubier, 2002 [30]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	NA	Low risk	Fair
Lenoir, 1999 [31]	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	NA	Low risk	Poor
Liu, 2010 [32]	High risk	Unclear risk	High risk	Unclear risk	Low risk	Unclear risk	Low risk	NA	Low risk	Poor

Characteristics of included reviews	Depression	
Review ID	**Apaydin 2016**	
Authors conclusions (key message)	SJW monotherapy for mild and moderate depression is superior to placebo in improving depression symptoms and not significantly different from antidepressant medication. However, evidence of heterogeneity and a lack of research on severe depression reduce the quality of the evidence. Adverse events reported in RCTs were comparable to placebo and fewer compared with antidepressants. However, assessments were limited due to poor reporting of adverse events and studies were not designed to assess rare events. Consequently, the findings should be interpreted with caution.	
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview		
1	--	35 RCTs identified by the SR. Details not extracted here.
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Table 1 Study quality/risk of bias for individual included studies *(Continued)*

Mannel, 2010 [33]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	NA	Low risk	Good
Montgomery, 2000 [34]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	NA	Unclear risk	Poor
Morenq, 2005 [35]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	NA	Low risk	Fair
Pakseresht, 2012 [36]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	NA	Low risk	Fair
Philipp, 1999 [37]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	NA	Low risk	Fair
Rahman, 2008 [38]	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	NA	Low risk	Poor
Schrader, 1998 [40]	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	NA	Low risk	Good
Schrader, 2000 [39]	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	NA	Low risk	Fair
Shelton, 2001 [41]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	NA	Low risk	Good
Szegedi, 2005 [42]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	NA	Low risk	Fair
Uebelhack, 2004 [43]	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	NA	Low risk	Good
Volz, 2000 [50]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	NA	Low risk	Good
Vorbach, 1997 [44]	Low risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	NA	Low risk	Poor
Wheatley, 1997 [45]	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	NA	Low risk	Good
Witte, 1995 [49]	Unclear risk	Low risk	Low risk	High risk	Low risk	Unclear risk	Low risk	NA	Low risk	Good
Woelk, 2000 [46]	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	NA	Low risk	Fair
van Gurp, 2002 [47]	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	NA	Low risk	Fair

SJW St. John's wort, *ITT* intention-to-treat analysis, *TAU* treatment as usual

Characteristics of included reviews	Depression
Review ID	**Apaydin 2016**
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	= data extracted
	= data extracted from more recent SR (or better SR)
	= control is an active intervention

Characteristics of included reviews	Insomnia
Review ID	**Lopresti 2021**
Review reference	Lopresti AL, Smith SJ. Ashwagandha (Withania somnifera) for the treatment and enhancement of mental and physical conditions: A systematic review of human trials. Journal of Herbal Medicine. 2021;28:100434. 10.1016/j.hermed.2021.100434
Review objective	to summarise and critically appraise results from human trials on ashwagandha that have been conducted to date.
Author affiliations	Australia, Murdoch University
Source of funds	No financial support from any organisation has been obtained for the submitted manuscript.
Declared interests of the review authors	AL and SJS have received funding in the past to conduct clinical trials on ashwagandha and other herbal and nutraceutical ingredients.
Review method of analysis	Descriptive Narrative summary only.
Inclusion criteria	
Study design	human interventional trial (randomised controlled, nonrandomised, open-label, and observational)
Population	Adults: mental conditions/wellbeing, physical and medical conditions/wellbeing, cognitive performance, sexual function and fertility, or athletic/exercise performance
Intervention	Ashwaganda alone or as adjunct
Comparator	None specified
Other	completed pre- and post-intervention outcome measures;
Exclusion criteria	
Study design	in virto trials
Population	--
Intervention	Ashwagandha as component of multi-ingredient formulation
Comparator	--
Other	--
Date of documented search (month/year)	Data base inception to April 2020
Databases searched	Medline (Pubmed), Cochrane Library, Scopus, Web of Science, and CINAHL databases
Was an non-English database searched?	No
Were studies in a LOTE included?	No English langauge only

Characteristics of included reviews	Insomnia		
Review ID	**Lopresti 2021**		
Outcomes considered in the SR (list)	Efficacy outcomes		
Risk of bias of the included RCT studies as reported in the SR	Cochrane Collaboration's risk of bias tool (RoB 2)	independently assessed by the two authors (A.L. and S.J.S)	
Authors conclusions (key message)	The 10-week intake of an ashwagandha root extract (KSM-66®) at 600 mg daily was associated with significantly greater improvements in latency of sleep onset and sleep efficiency as measured by a sleep actigraphy. Sleep quality measured with the Pittsburgh Sleep Quality Index, a validated sleep questionnaire, also improved significantly in the ashwagandha group compared to the placebo group. Moreover, there was a significantly greater reduction in anxiety as measured by the HAM-A.		
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	1 RCT met our PICO criteria (out of 41)		
	60		
	Study ID	*Summary RoB*	*Study design features (PICOS)*
1	Langade 2019	Low risk	N=60 (40/20) P: Insomnia (mean 39 yrs) I: Ashwagandha 300 mg root extract 2x daily for 10 weeks C: Placebo O: Sleep actigraphy, sleep diary, PSQI, HAM-A, Sleep quality & mental alterness on waking S: India
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3	--		

Characteristics of included reviews	Insomnia
Review ID	**Lopresti 2021**
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Characteristics of included reviews	Insomnia
Review ID	**Lopresti 2021**
11	--

= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Insomnia	
Review ID	**Shinjyo 2020**	
Review reference	Shinjyo N, Waddell G, Green J. Valerian Root in Treating Sleep Problems and Associated Disorders-A Systematic Review and Meta-Analysis. J Evid Based Integr Med. 2020;25:2515690x20967323.	
Review objective	To evaluate the effectiveness of valerian as a treatment of sleep problems and associated disorders	
Author affiliations	Four authors are affiliated with tertiary institutions in Japan and the UK.	
Source of funds	None declared	
Declared interests of the review authors	The authors declare no conflict of interest	
Review method of analysis	Meta-analysis	Adjusted effect sizes (Hedges' g) were calculated from summary measures such as means and standard deviations or confidence intervals, odds ratio (for binary outcomes), and sample sizes, using reported formula. Meta-analyses were performed using Meta-Essentials. I2 statistic was used to estimate heterogeneity. Publication bias was evaluated using the funnel plots.
Inclusion criteria		
Study design	RCTs, clinical trials	
Population	Individuals with sleep problems	
Intervention	Valerian monotherapy or in combination	
Comparator	Placebo	
Other	--	
Exclusion criteria		
Study design	--	
Population	Non human subjects	
Intervention	Studies with unknown substances	
Comparator	Not defined	
Other	--	
Date of documented search (month/year)	Dec-19	
Databases searched	Pubmed, Science direct, Cochrane Library	
Was an non-English database searched?	No	
Were studies in a LOTE included?	No	Articles published in languages other than English were excluded

Characteristics of included reviews	Insomnia		
Review ID	**Shinjyo 2020**		
Outcomes considered in the SR (list)	Sleep quality, anxiety		
Risk of bias of the included RCT studies as reported in the SR	*Tool used* Jadad	*Authors summary* Of the RCTs meeting our PICO, four studies had a Jadad score of 5, two studies had a Jadad score of 4, two studies had a Jadad score of 3, and one study had a Jadad score of 2. (Identified studies only)	
Authors conclusions (key message)	Valerian could be a safe and effective treatment to promote sleep, however, given the differences in herbal preparation, standardisation of the formulation may be necessary		
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	Out of 60 studies identified, 10 met our PICO criteria 1188 Total N from eligible RCTs		
	Study ID	*Summary RoB*	*Study design features (PICOS)*
1	Coxeter 2003	Jadad score 5/5 High quality	N= 24 P: chronic insomnia I: valerian extract 450 mg, 30 min before bed for 3 weeks C: placebo O: Sleep diary S: ?
2	Donath 2000	Jadad score 2/5 Low quality	N= 16 P: psychopsycological insomnia I: valerian extract 600 mg, 60 min before bed for 14 days C: placebo O: sleep efficiency, sleep onset latency, polysomnogrpahy, sleep quality (VAS) S: ?
3	Farag 2003	Jadad score 4/5 High quality	N= 25, crossover (10 days washout) P: sleep onset insomnia I: herbal combination*, 4 days C: placebo O: sleep onset latency S: ? * V. wallichi 320 mg, Rosa centifolia, Nardostachys jatamansi, Tinospora cordifolia, Withania somnifera, Piper negrum, Zingiber officinalis, Convolvulus pluricalis, and Glycyrrhiza glabra.

Characteristics of included reviews	Insomnia		
Review ID	**Shinjyo 2020**		
4	Jacobs 2005	Jadad score 5/5 High quality	N= 391 (135/121/135) P: anxiety and insomnia I: valerian 6.4 mg OR kava 100 mg extract for 28 days C: placebo O: anxiety (STAI), insomnia severity (ISI) S: ?
5	Morin 2005	Jadad score 3/5 Good quality	N= 184 P: mild insomnia I: combination valerian 187 mg and hops 41.9 mg for 28 days C: placebo OR diphenhydramine 25mg for the first 14 days, followed by placebo for another 14 days O: Sleep diary, polysomnography, QoL S: ?
6	Oxman 2007	Jadad score 5/5 High quality	N= 405 P: untreated insomnia I: valerian 600 mg for 14 days C: placebo O: sleep dairy (onset, latency, night wakenings, duration, quality, energy level), global assessment (VAS) S: ?
7	Taavoni 2011	Jadad score 4/5 High quality	N= 100 P: post-menopausal participants with self-reported insomnia I: valerian 520 mg for 4 weeks C: placebo O: PSQI S: ?
8	Taibi 2009	Jadad score 5/5 High quality	N= 16 P: women with insomnia I: valerian extract, 300 mg 30 mins before bed for 2 weeks C: placebo O: polysomnography, sleep diary (onset, latency, night wakenings, duration, quality) S: ?
9	Ziegler 2002	Jadad score 2/5 Low quality	N= 202 P: nonorganic insomnia I: valerian extract, 300 mg 60 mins before bed for 6 weeks C: Oxazepan 5mg O: Insomnia severity index S: ?
10	Koetter 2007	Jadad score 3/5 Good quality	N= 27 P: nonorganic sleep disorders I: valerian extract, 500 mg for 4 weeks C: placebo O: sleep latency, night wakenings, sleep eficiency, sleep stages, REM latency S: ?

Characteristics of included reviews	Insomnia		
Review ID	**Shinjyo 2020**		
11	Maroo 2013	Jadad score 4/5 High quality	N= 78 P: primary insomnia I: combination valerian extract 300 mg, passionflower 80 mg and hops 30 mg for 2 weeks C: Zolpidem 10mg O : Insomnia severity index, Epsworth sleepiness scale S: ?

= data extracted

= data extracted from more recent SR (or better SR)

= control is an active intervention

Characteristics of included reviews	Insomnia	
Review ID	**Hieu 2019**	
Review reference	Hieu TH, Dibas M, Surya Dila KA, Sherif NA, Hashmi MU, Mahmoud M, et al. Therapeutic efficacy and safety of chamomile for state anxiety, generalized anxiety disorder, insomnia, and sleep quality: A systematic review and meta-analysis of randomized trials and quasi-randomized trials. Phytother Res. 2019;33(6):1604-15.	
Review objective	To determine efficacy and safety of chamomile for the treatment of generalised anxiety disorder (GAD), state anxiety, sleep quality and insomnia	
Author affiliations	Twelve authors are affiliated with tertiary institutions in Vietnam, Japan Saudi Arabia, Egypt, Pakistan, Syria. Two authors are affiliated with research groups based in Japan and Vietnam.	
Source of funds	Funding declared- Joint usage/ Research Centre on Tropical Disease, Institute Tropical Medicine, Nagasaki University, Japan; Institute of Allied Health Sciences, National Cheng Kung University	
Declared interests of the review authors	The authors declare no conflict of interest	
Review method of analysis	Meta-analysis	Statistical analysis was performed by using the meta package of R statistical software version 3.4.3 and RevMan version 5.3. The random effect model was adopted in all analyzed outcomes. For continuous outcome variables, mean difference and 95% confidence interval were adopted if the scales were identically presented across the studies; otherwise, the standardized mean difference (SMD) was used. Risk ratio (RR) will be used to calculate the effect size of dichotomous variables. We used sensitivity analysis to test the strength of the evidence by excluding one study each time from the analysis
Inclusion criteria		
Study design	RCTs and quasi-RCTs in humans	
Population	Anxiety, GAD, sleep quality, insomnia	
Intervention	Chamomile	
Comparator	Placebo	
Other	No language, publications restrictions,	
Exclusion criteria		
Study design	Conference papers, posters, letters, chapters, books, commentaries, editorials, theses, review	
Population	--	
Intervention	--	
Comparator	--	
Other	"Unreliable" data	
Date of documented search (month/year)	Nov-15	
Databases searched	PubMed, Science Direct, Cochrane Central, Scopus, Google Scholar, WHO Global Health Library (GHL), ISI Web of Science, Virtual Health Library, Controlled Trials (mRCT), EMBASE, and Clinical trials.gov	
Was an non-English database searched?	No	
Were studies in a LOTE included?	No	Non English studies were excluded

Characteristics of included reviews	Insomnia
Review ID	**Hieu 2019**
Outcomes considered in the SR (list)	Anxiety, Insomnia, Sleep quality
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane Risk of Bias tool *Authors summary*: Most of the identified studies were considered unclear to high risk of bias. Attrition bias and other bias were considered the most common high risk domain. No sudies had low risk of bias in every domain. Few studies were of low quality. 
Authors conclusions (key message)	Chamomile seems safe for anxiety and sleep qualty however there is limited high quality evidence to suggest chamomile is effective for anxiety and insomnia.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	Twelve RCTs identified, one relevant to PICO 34 Total N from eligible RCTs

	Study ID	*Summary RoB*	*Study design features (PICOS)*
1	Zick 2011	Low risk (High risk for other)	N= 34 P: adults with primary insomnia > 6months I: chamomile extract 270 mg BID for 28 days C: placebo O: Insomnia severity index, depression (BDI), anxiety (STAI), sleep quality (PSQI) S: USA, single-centre
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3	--		

Characteristics of included reviews	Insomnia
Review ID	**Hieu 2019**
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Characteristics of included reviews	Insomnia
Review ID	**Hieu 2019**
11	--

= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Insomnia	
Review ID	**Leach 2015**	
Review reference	Leach MJ, Page AT. Herbal medicine for insomnia: A systematic review and meta-analysis. Sleep Med Rev. 2015;24:1-12.	
Review objective	To evaluate the safety and efficaccy of herbal medicine for the management of insomnia	
Author affiliations	Both authors are affiliated with teritiary institutions in Australia	
Source of funds	None declared	
Declared interests of the review authors	The authors declare no conflict of interest	
Review method of analysis	Meta-analysis	The authors combined risk ratios for dichotomous data, and mean differences for continuous data, using random-effects models and Review Manager (RevMan) 5.1 software, provided there were more than three studies in the meta-analysis. Funnel plots were planned in an exploratory data analysis to assess for the potential existence of small study/publication bias. Heterogeneity was identified by visual inspection of the forest plots, by using a standard X2 test and a significance level of 0.1. Sensitivity analyses were performed to explore the influence of the following factors on effect size: risk of bias & study duration (>52 weeks) or study size (>200 subjects)
Inclusion criteria		
Study design	RCTs (published and unpublished)	
Population	insomnia	
Intervention	herbal medicine	
Comparator	no intervention, placebo, pharmaceutical agents, herbal, homeopathic or nutritional preparations	
Other		
Exclusion criteria		
Study design	non RCTs	
Population	Participants with comorbidities or secondary insomnia	
Intervention	combination herbs	
Comparator	none	
Other	published in English	
Date of documented search (month/year)	Mar-14	
Databases searched	EbscoHost, AMED (OVID), Pubmed, CINAHL (EbscoHost), EMBASE (OVID), Medline (OVID), Natural medicines comprehensive database, ProQuest, PsycINFO, Cochrane Library, Web of Science, The Meta Register of Controlled Trials, The National Institutes of Health Trials Register, The Australian New Zealand Clinical Trials Registry, The European Union Clinical Trials Register, handsearching was also conducted and reference list of included studies was searched.	
Was an non-English database searched?	No	
Were studies in a LOTE included?	No	full text publications had to be published in the English language

Characteristics of included reviews	Insomnia		
Review ID	**Leach 2015**		
Outcomes considered in the SR (list)	Clinical efficacy outcomes		
Risk of bias of the included RCT studies as reported in the SR	*Tool used* Cochrane Risk of Bias tool	*Authors summary* Overall, most of the studies were considered unclear risk of bias since the RCTs did not describe the methodology in great detail, and were considered high risk of bias in areas pertaining to sponsership, sampling bias and ascertainment bias. No figure provided.	
Authors conclusions (key message)	In all studies, and for all interventions, herbal medicine was found to be no more effective than placebo or active controls. Overall, there is insufficient evidence to conclude herbal medicines (valerian, chamomile and kava) benefit adults with incsomnia		
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	Fourteen studies identified, six studies met PICO		
	918	Total N from eligible RCTs	
	Study ID	*Summary RoB*	*Study design features (PICOS)*
1	Coxeter 2003	High risk (selective reporting, other)	N= 24 P: chronic insomnia I: valerian extract 450 mg, 30 min before bed for 3 weeks C: placebo O: Sleep diary (onset, latency, night wakenings, duration, quality, energy level), S: Australia
2	Donath 2000	High risk (other)	N= 16 P: psychopsycological insomnia I: valerian extract 600 mg, 60 min before bed for 14 days C: placebo O: sleep onset latency, sleep duration, daytime functioning S: Germany
3	Jacobs 2005	Unclear risk (selective reporting) High risk (other)	N= 391 P: anxiety and insomnia I: valerian 6.4 mg OR kava 100 mg extract 60 mins before bed for 28 days C: placebo O: insomnia severity (ISI) sleep onset latency, night awakenings S: USA

Characteristics of included reviews	Insomnia		
Review ID	**Leach 2015**		
4	Koetter 2007	Unclear risk (high risk for other)	N= 30 P: nonorganic sleep disorders I: valerian extract, 500 mg for 4 weeks C: placebo O: sleep latency, wake after onset, sleep duration S: Germany
5	Oxman 2007	Low risk (High risk for other)	N= 405 P: untreated insomnia I: valerian 600 mg for 14 days C: placebo O: sleep dairy (onset, latency, night wakenings, duration, quality, energy level), global assessment (VAS) S: Norway
6	Zick 2011	High risk (selective reporting)	N= 34 P: adults with primary insomnia > 6months I: chamomile extract 270 mg BID for 28 days C: placebo O: Insomnia severity index, depression (BDI), anxiety (STAI), sleep quality (PSQI) S: USA, single-centre
7	Ziegler 2002	Unclear risk (high risk for other)	N= 202 P: nonorganic insomnia I: valerian extract, 300 mg 60 mins before bed for 6 weeks C: Oxazepan 5mg O: Insomnia severity index S: Germany
8	Taibi 2009	Jadad score 5/5 High quality	N= 16 P: women with PSQI >5, ISI < 22 I: valerian extract, 300 mg 30 mins before bed for 2 weeks C: placebo O: sleep diary (onset, latency, wake after onset, efficiency, quality) S: USA
9	--		
10	--		

Characteristics of included reviews	Insomnia
Review ID	**Leach 2015**
11	--

= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Insomnia	
Review ID	**Fernández-San-Martín 2010**	
Review reference	Fernández-San-Martín MI, Masa-Font R, Palacios-Soler L, Sancho-Gómez P, Calbó-Caldentey C, Flores-Mateo G. Effectiveness of Valerian on insomnia: a meta-analysis of randomized placebo-controlled trials. Sleep Med. 2010;11(6):505-11.	
Review objective	To evaluate the effectiveness of valerian relative to insomnia	
Author affiliations	Two authors are affiliated with tertiary institutions in Spain and three authors are affiliated with a public medical centre in Spain.	
Source of funds	Not reported	
Declared interests of the review authors	Not reported	
Review method of analysis	Meta-analysis	Statistical analyses were conducted with Stata version 9.3. We used an inverse-variance weighted random effects model. The effect size was calculated using the Hedge adjustment. Relative risks and their 95% CIs were extracted or derived by using data reported in the publications. Heterogeneity was quantified with the I2 statistic. We used meta-regression to evaluate whether results were different between two groups formed based on the Jadad scale score [27] (greater or equal to 4, or less than 4). We conducted an analysis of the sensitivity by omitting each study from the estimated pool at every step. Finally, publication bias was evaluated using the funnel plots
Inclusion criteria		
Study design	RCTs	
Population	insomnia	
Intervention	valerian	
Comparator	placebo	
Other		
Exclusion criteria		
Study design	No original research (reviews, editorials, non-research letters)	
Population	Non humans	
Intervention	Combination valerian	
Comparator	Comparators not placebo	
Other		
Date of documented search (month/year)	Sep-08	
Databases searched	Medline, Cochrane Library, Embase and Biosis	
Was an non-English database searched?	No	
Were studies in a LOTE included?	Yes	No language limitations

Characteristics of included reviews	Insomnia		
Review ID	**Fernández-San-Martín 2010**		
Outcomes considered in the SR (list)	Clinical efficacy outcomes		
Risk of bias of the included RCT studies as reported in the SR	*Tool used* Jadad scale	*Authors summary* For studies that meet our PICO - Five RCTs had a maximum score of 5 on JADAD (highest quality). Three studies had a score of three, and one study had a score of two.	
Authors conclusions (key message)	Valerian seems to subjectively improve insomnia, however its effectiveness has not been demnstrated with quanitative or obejective measurements.		
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	Eighteen studies identified, eight met our PICO		
	765	Total N from eligible RCTs	
	Study ID	*Summary RoB*	*Study design features (PICOS)*
1	Leathwood 1985	Jadad score 5/5 High quality	N= 6 P: light insomnia (ICD-10) I: valerian extract 450 mg OR 900 mg for 18 days C: placebo O: Sleep quality (VAS), polysomnography S: ?
2	Vorbach 1996	Jadad score 5/5 High quality	N= 121 P: Insomnia (ICD-10) I: valerian extract 600 mg for 28 days C: placebo O: Sleep quality (Görtelmeyer Schlaffragebogen B), S: ?
3	Kuhlmann 1999	Jadad score 3/5 Good quality	N= 102 P: Insomnia (ICD-10) I: valerian extract 600 mg for 28 days C: placebo O: Sleep quality (VAS) S: ?

Characteristics of included reviews	Insomnia		
Review ID	**Fernández-San-Martín 2010**		
4	Donath 2000	Jadad score 2/5 Low quality	N= 16 P: psychopsycological insomnia I: valerian extract 600 mg, 60 min before bed for 14 days C: placebo O: sleep onset latency, sleep duration, daytime functioning S: Germany
5	Coxeter 2003	Jadad score 5/5 High quality	N= 24 P: chronic insomnia I: valerian extract 450 mg, 30 min before bed for 3 weeks C: placebo O: Sleep diary (onset, latency, night wakenings, duration, quality, energy level), S: Australia
6	Oxman 2007	Jadad score 5/5 High quality	N= 405 P: untreated insomnia I: valerian 600 mg for 14 days C: placebo O: sleep dairy (onset, latency, night wakenings, duration, quality, energy level), global assessment (VAS) S: Norway
7	Koetter 2007	Jadad score 3/5 Good quality	N= 30 P: nonorganic sleep disorders I: valerian extract, 500 mg for 4 weeks C: placebo O: sleep latency, wake after onset, sleep duration S: Germany
8	Taibi 2009	Jadad score 5/5 High quality	N= 16 P: women with PSQI >5, ISI < 22 I: valerian extract, 300 mg 30 mins before bed for 2 weeks C: placebo O: sleep diary (onset, latency, wake after onset, efficiency, quality) S: USA
9	--		
10	--		

Characteristics of included reviews	Insomnia
Review ID	**Fernández-San-Martín 2010**
11	--

= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Diabetes
Review ID	**Altobelli 2021**
Review reference	Altobelli E, Angeletti PM, Marziliano C, Mastrodomenico M, Giuliani AR, Petrocelli R. Potential Therapeutic Effects of Curcumin on Glycemic and Lipid Profile in Uncomplicated Type 2 Diabetes-A Meta-Analysis of Randomized Controlled Trial. Nutrients. 2021 Jan 27;13(2):404. doi: 10.3390/nu13020404. Anna Rita Giuliani and Reimondo Petrocelli (2021).
Review objective	To evaluate the effect of curcumin on glycemic and lipid profile in subjects with uncomplicated T2DM
Author affiliations	Tertiary institutions and local and regional health authorities in Italy
Source of funds	This research received no external funding
Declared interests of the review authors	The authors declare no conflicts of interest
Review method of analysis	Meta-analysis: Random effects model; Cohen's d, with 95% confidence interval (CI) to measure effect size; Q statistics, I2, Tau, and Tau2 to assess heterogeneity; ANOVA-Q test to value differences among groups. PROMETA 3 software.
Inclusion criteria	
Study design	RCT
Population	Human subjects with uncomplicated type 2 diabetes
Intervention	Curcumin
Comparator	Placebo
Other	Not specified
Exclusion criteria	
Study design	Not specified
Population	Prediabetes; complicated diabetes (i.e. organ damage)
Intervention	Other drug plus curcumin
Comparator	Other comparators than placebo
Other	Not specified
Date of documented search (month/year)	Published from 2000 to 2020 as of October 2020
Databases searched	MEDLINE, EMBASE, Scopus, Clinicaltrials.gov, Web of Science, and Cochrane Library
Was an non-English database searched?	No

Characteristics of included reviews	Diabetes
Review ID	**Altobelli 2021**
Were studies in a LOTE included?	No — Only studies published in English were considered
Outcomes considered in the SR (list)	Body mass index (BMI), homeostasis model assessment-insulin resistance index (HOMA-IR), glycosylated hemoglobin (Hb1Ac), Triglycerides (TG), Total Cholesterol (TC), High-density lipoprotein (HDL), and LDL
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane Collaboration tool *Authors summary*: The papers included in this meta-analysis showed a low risk of bias.

Table S2. Risk of Bias Assesment

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	Selective reporting (reporting bias)
Hodei	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Adibian	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Adab	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Rahimi	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Chuengsamarn	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Na	**Unclear**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Ushrarani	**Unclear**	**Low**	**High**	**Low**	**Low**	**Low**	**Low**

Authors conclusions (key message)	The daily supplement of curcumin could improve some metabolic aspects of uncomplicated T2DM patients.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	7 out of 7 studies included in the SR met our PICO Total N=590 in eligible studies *Study ID* — *Summary RoB* — *Study design features (PICOS)*

Characteristics of included reviews	Diabetes			
Review ID	**Altobelli 2021**			
1	Hodaei 2019	Low risk	N=44 (21/23)	P: Uncomplicated T2DM I: Curcumin 1500 mg C: Placebo O: BMI, HOMA-IR, Hb1Ac S: Iran
2	Adibian 2019	Low risk	N=44 (21/23)	P: Uncomplicated T2DM I: Curcumin 1500 mg C: Placebo O: TG, TC, HDL, LDL S: Iran
3	Adab 2018	Low risk	N=75 (39/36)	P: Uncomplicated T2DM I: Curcumin 2100 mg C: Placebo O: BMI, HOMA-IR, Hb1Ac, TG, TC, HDL, LDL S: Iran
4	Rahimi 2015	Low risk	N=70 (35/35)	P: Uncomplicated T2DM I: Curcumin 80 mg C: Placebo O: BMI, Hb1Ac, TG, TC, HDL, LDL S: Iran
5	Chuengsamarn 2014	Low risk	N=213 (107/106)	P: Uncomplicated T2DM I: Curcumin C: Placebo O: HOMA-IR, TG S: Thailand
6	Na 2013	Low risk	N=100 (50/50)	P: Uncomplicated T2DM I: Curcumin 300 mg C: Placebo O: HOMA-IR, Hb1Ac, TG, TC, HDL, LDL S: China

Characteristics of included reviews	Diabetes			
Review ID	**Altobelli 2021**			
7	Usharani 2008	Low risk	N=44 (23/21)	P: Uncomplicated T2DM I: Curcumin 300 mg C: Placebo O: Hb1Ac, TG, TC, HDL, LDL S: India
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Characteristics of included reviews	Diabetes
Review ID	**Altobelli 2021**
16	--
17	--
18	--

= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Diabetes
Review ID	**Asbaghi 2021**
Review reference	Asbaghi O, Fouladvand F, Gonzalez MJ, Ashtary-Larky D, Choghakhori R, Abbasnezhad A. Effect of green tea on glycemic control in patients with type 2 diabetes mellitus: A systematic review and meta-analysis. Diabetes Metab Syndr. 2021 Jan-Feb;15(1):23-31. doi: 10.1016/j.dsx.2020.11.004.
Review objective	To pool data from RCTs that assessed the effect of supplementary intake of green tea on fasting plasma glucose (FPG), fasting insulin, hemoglobin A1c (HbA1c) and homeostatic model assessment for insulin resistance (HOMA-IR) in patients with T2DM
Author affiliations	All authors were affiliated with tertiary institutions in Iran or Puerto Rico
Source of funds	There are no financial or other competing interests for principal investigators, patients included or any member of the trial
Declared interests of the review authors	The authors declare no conflicts of interest
Review method of analysis	Meta-analysis: Random and fixed effects model; effect sizes expressed as weighted mean differences (WMDs) and 95% CI. Cochrane's Q test to evaluate heterogeneity. STATA software version 14.
Inclusion criteria	
Study design	RCT
Population	Patients aged 18 years and older with T2DM
Intervention	Green tea
Comparator	Control (unspecified)
Other	RCTs that provided sufficient data on baseline and final measures of fasting plasma glucose (FPG) levels, insulin levels, hemoglobin A1C and HOMA-IR in both green tea and control groups
Exclusion criteria	
Study design	Non-RCT
Population	Children, animals and subjects without T2DM
Intervention	Not specified
Comparator	Not specified
Other	Did not provide sufficient information for the outcomes in the green tea or control groups
Date of documented search (month/year)	To June 2019, no date restriction
Databases searched	Scopus, PubMed, and ISI Web of science. In addition, reference lists of included articles and related reviews were manually checked.
Was an non-English database searched?	No

Characteristics of included reviews	Diabetes
Review ID	**Asbaghi 2021**
Were studies in a LOTE included?	Not specified — No language restriction in search
Outcomes considered in the SR (list)	FPG levels, insulin levels, hemoglobin A1C and HOMA-IR
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane scoring system *Authors summary*: 8 studies provided comprehensive explanations of random sequence generation. 6 studies had low-risk of bias regarding allocation concealment. 9 articles had low-risk of bias regarding the blinding of participant's/personnel, and the majority of studies had low-risk of bias regarding the blinding of outcome assessors. 10 articles were low-risk of bias in relation to incomplete outcome data. All studies had low risk of bias regarding selective outcome reporting.

Supplemental table 1. Quality Assessment (Method: Cochrane Collaboration's Tool for Assessing Risk of Bias)

Study	Random Sequence Generation	Allocation concealment	Blinding of participants personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Fukino et al. 2005	U	U	H	L	L	L	U
Fukino et al. 2008	U	U	H	L	L	L	U
Mirzaei et al. 2009	U	U	U	L	H	L	U
Nagao et al. 2010	U	U	L	L	L	L	U
Mohammadi et al. 2010	L	U	L	L	H	L	U
Hsu et al. 2011	L	L	L	L	L	L	U
Mousavi et al. 2013	U	U	U	L	L	L	U
Lasaite et al. 2014	U	U	L	L	H	L	U
Liu et al. 2014	L	L	L	L	L	L	U
Borges et al. 2016	L	L	L	L	L	L	L
Zandi Dareh Gharibi et al. 2018	L	U	H	H	H	L	U
Sobhani et al. 2019	L	L	L	U	L	L	U
Quezada-Fernández et al. 2019	L	L	L	L	L	L	L
Hosseini et al. 2018	L	L	L	U	L	L	U

L, low-risk of bias; U, unclear-risk of bias; H, high-risk of bias.

Authors conclusions (key message)	The supplementary intake of green tea had no significant effect on FPG, fasting insulin, HbA1c and HOMA-IR in patients with T2DM.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	14 out of 14 studies included in the SR met our PICO Total N=800 in eligible studies *Study ID* — *Summary RoB* — *Study design features (PICOS)*

Characteristics of included reviews	Diabetes			
Review ID	**Asbaghi 2021**			
1	Fukino 2005	High risk (blinding)	N=66 (33/33)	P: T2DM I: Green tea extract 544 mg/day C: Control (unspecified) O: FPG, HbA1c, HOMA-IR, insulin S: Japan
2	Fukino 2008	High risk (blinding)	N=120 (60/60)	P: T2DM I: Green tea extract 544 mg/day C: Control (unspecified) O: FPG, HbA1c, HOMA-IR, insulin S: Japan
3	Mirzaei 2009	High risk (incomplete outcome data)	N=72 (26/46)	P: T2DM I: Green tea extract 1500 mg/day C: Control (unspecified) O: FPG, HbA1c, insulin S: Iran
4	Nagao 2010	Unclear risk (randomisation, other)	N=43 (23/20) 4, 8 and 12 weeks	P: T2DM I: Green tea extract 582.8 mg/day C: Control (unspecified) O: FPG, HbA1c, insulin S: Japan
5	Mohammadi 2010	High risk (incomplete outcome data)	N=58 (29/29)	P: T2DM I: Green tea extract 1500 mg/day C: Control (unspecified) O: FPG, HbA1c, HOMA-IR, insulin S: Iran
6	Hsu 2011	Overall low risk	N=68 (35/33)	P: T2DM I: Green tea extract 1500 mg/day C: Control (unspecified) O: FPG, HbA1c, HOMA-IR, insulin S: Taiwan

Characteristics of included reviews	Diabetes			
Review ID	**Asbaghi 2021**			
7	Mousavi 2013	Unclear risk (randomisation, allocation, blinding, other)	N=65 (26/25/14)	P: T2DM I: Green tea 10000 mg/day and 5000 mg/day C: Control (unspecified) O: FPG S: Iran
8	Lasaite 2014	High risk (incomplete outcome data)	N=92 (46/46)	P: T2DM I: Green tea extract 500 mg/day C: Control (unspecified) O: HbA1c S: Taiwan
9	Liu 2014	Overall low risk	N=45 (20/25)	P: T2DM I: Green tea extract 400 mg/day and 600 mg/day C: Control (unspecified) O: FPG, HbA1c, HOMA-IR, insulin S: Lithuania
10	Borges 2016	Low risk	N=47 (23/24)	P: T2DM I: Green tea extract 800 mg/day C: Control (unspecified) O: HbA1c S: Brazil
11	Zandi Dareh Gharibi 2018	High risk (blinding, incomplete outcome data)	N=22 (12/10)	P: T2DM. I: Green tea extract 1500 mg/day C: Control (unspecified) O: FPG, HOMA-IR, insulin S: Iran
12	Sobhani 2019	Unclear risk (blinding, other)	N=22 (11/11)	P: T2DM I: Green tea extract 1500 mg/day C: Control (unspecified) O: FPG, HOMA-IR, insulin S: Iran
13	Quezada-Fernandez 2019	Low risk	N=20 (10/10)	P: T2DM I: Green tea extract 400 mg/day C: Control (unspecified) O: FPG, HbA1c S: Mexico
14	Hosseini 2018	Unclear risk (blinding, other)	N=60 (20/20/20)	P: T2DM I: Green tea (epigallocatechin-gallate) 300 mg/day C: Control (unspecified) O: FPG, HOMA-IR, insulin S: Iran
15	--			

Characteristics of included reviews	Diabetes
Review ID	**Asbaghi 2021**
16	--
17	--
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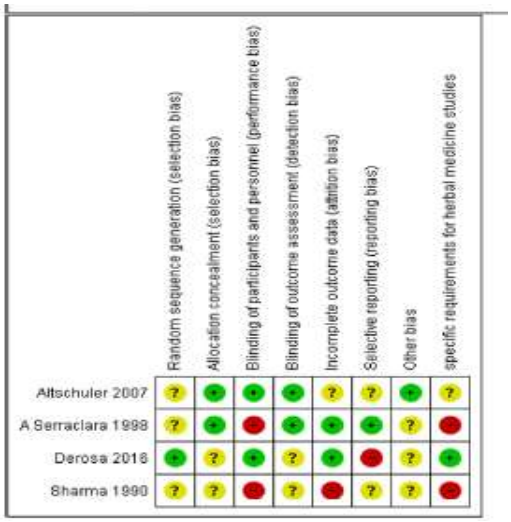
= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Diabetes
Review ID	**Barzkar 2020**
Review reference	Barzkar F, Baradaran HR, Khamseh ME, Vesal Azad R, Koohpayehzadeh J, Moradi Y. Medicinal plants in the adjunctive treatment of patients with type-1 diabetes: a systematic review of randomized clinical trials. J Diabetes Metab Disord. 2020 Sep 22;19(2):1917-1929. doi: 10.1007/s40200-020-00633-x.
Review objective	To systematically review the randomized controlled trials that address the effectiveness and safety of herbal medicine in patients with type 1 diabetes
Author affiliations	All authors were affiliated with tertiary institutions in Iran
Source of funds	This work was supported by the Iran University of Medical Sciences (IUMS). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript
Declared interests of the review authors	The authors declare no conflicts of interest
Review method of analysis	Individual study results: Mean differences used to analyse effect sizes of continuous outcomes. Effect sizes for dichotomous data expressed in terms of relative risks or odds ratio. No meta-analysis was applicable as only one study was found for each intervention.
Inclusion criteria	
Study design	RCT
Population	Children and adults with type 1 diabetes
Intervention	Any type of herbal medicines including extract from herbs, single herb or a compound of herbs alone or along with Insulin. No limitation was applied for the mode of administration or the method of preparation of the herbal medicine.
Comparator	Placebo that should have been a drug without an effect on blood glucose levels
Other	Not specified
Exclusion criteria	
Study design	Non-RCT
Population	Type 2 diabetes
Intervention	Studies on medicinal herbs plus other therapies such as a holistic treatment, for example, herbs plus cupping or acupuncture
Comparator	Not specified
Other	Not specified
Date of documented search (month/year)	Not specified (until recent)
Databases searched	Cochrane Library; MEDLINE; EMBASE; AMED (Allied and Complementary Medicine Database); Google Scholar and CINHAL. Authors of relevant identified studies and other experts (authors of reviews) were contacted in order to obtain additional references, unpublished trials, or ongoing trials. Reference lists of included trials searched to identify additional studies.
Was an non-English database searched?	No

Characteristics of included reviews	Diabetes
Review ID *Were studies in a LOTE included?*	**Barzkar 2020** Not specified
Outcomes considered in the SR (list)	Primary outcomes: glycemic control (as measured by glycated hemoglobin levels (HbA1c) and fasting blood glucose levels); adverse events (for example liver toxicity, kidney damage). Secondary outcomes: diabetes complications (for example, neuropathy, retinopathy, nephropathy, sexual dysfunction); health-related quality-of-life; all-cause mortality; costs.
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane Risk of Bias tool *Authors summary*: The risk of bias varied significantly from unclear, and low to high. The quality of reporting was suboptimal. This was especially a concern since they did not have sufficient description of their methods including their methods of randomization and sequence generation, as well as blinding which made it difficult for the researchers to draw clear judgements about risk of bias.
Authors conclusions (key message)	There is insufficient evidence to draw conclusions about the efficacy of fenugreek, Berberine/Silymarine compound capsule, oral fig leaf decoction and cinnamon for glycemic control in type 1 diabetes. In addition, the evidence is inconclusive regarding the optimal doses and methods of preparations of these herbs and their safety in these patients. There is insufficient evidence to support the use of medicinal plants in patients with type 1 diabetes.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	2 out of 4 studies included in the SR met our PICO. One study (Seraclara 1998) was excluded as ficus carica (fig) leaf was not on the list of core herbs; the other study (Derosa 2016) studied combination product Berberis aristata/Silybum marianum (B. aristata not on core list). Total N=177 in eligible studies *Study ID* *Summary RoB* *Study design features (PICOS)*



Characteristics of included reviews	Diabetes			
Review ID	**Barzkar 2020**			
1	Altschuler 1990	Unclear risk	N=72	P: Type 1 diabetes mellitus I: Cinnamomum zeylanicum(cinnamon) pills C: Placebo (lactose) pills O: A1C, total daily insulin intake, adverse events S: ?
2	Sharma 1990	High risk	N=10	P: Type 1 diabetes mellitus I: Trigonella foenum-graecum(fenugreek) powder added to local bread C: No Fenugreek powder O: Oral glucose tolerance test, 24-h urinary glucose, areas under the glucose and insulin concentration curves S: ?
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Characteristics of included reviews	Diabetes
Review ID	Barzkar 2020
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Characteristics of included reviews	Diabetes
Review ID	**Barzkar 2020**
16	--
17	--
18	--

= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Diabetes
Review ID	**Durg 2020**
Review reference	Durg S, Bavage S, Shivaram SB. Withania somnifera (Indian ginseng) in diabetes mellitus: A systematic review and meta-analysis of scientific evidence from experimental research to clinical application. Phytother Res. 2020 May;34(5):1041-1059. doi: 10.1002/ptr.6589.
Review objective	Systematic evaluation and meta-analysis of W. somnifera effects in managing diabetes mellitus
Author affiliations	All authors were independent researchers in India
Source of funds	None specified; authors were independent researchers
Declared interests of the review authors	The authors declare no conflicts of interest
Review method of analysis	Meta-analysis: Meta-analysis performed using RevMan 5.3. Continuous outcomes pooled using mean difference with 95% CIs; however, SMD was used if studies reported the same continuous outcome in different units. I2 statistic to assess heterogeneity. Random effects model used to address vatiation across studies.
Inclusion criteria	
Study design	Experimental (in-vitro/pre-clinical) and clinical studies
Population	Experimental studies - diabetes; Clinical trials - Type 1/2 diabetes
Intervention	W. somnifera
Comparator	Not specified
Other	Experimental in-vitro studies assessing the role of W. somnifera in diabetes. Pre-clinical studies reporting W. somnifera (any part or isolated marker) activity in diabetes, regardless of different diabetes inducing agents (alloxan monohydrate [AM] and streptozotocin [STZ]).
Exclusion criteria	
Study design	Not specified
Population	Not specified
Intervention	Not specified
Comparator	Not specified
Other	Non-English studies; commentaries and conference proceedings
Date of documented search (month/year)	Inception to April 2019
Databases searched	PubMed/MEDLINE, EMBASE, Scopus and CENTRAL. Unpublished studies were searched in Clinicaltrials.gov and the WHO Clinical Trials Search Portal
Was an non-English database searched?	No

Characteristics of included reviews	Diabetes
Review ID	**Durg 2020**
Were studies in a LOTE included?	No Non-English studies excluded
Outcomes considered in the SR (list)	Body weight, blood glucose, glycosylated haemoglobin (HbAlc), insulin level/sensitivity and HOMA-IR (homeostasis model assessment of insulin resistance), lipid profile (total cholesterol [TC], triglyceride [TG], low density lipoprotein [LDL], very low density lipoprotein [VLDL], high density lipoprotein [HDL]), serum markers including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), acid phosphatase (ACP), total protein, albumin, albumin:globulin (A:G), and liver glycogen, as well oxidative stress markers such as superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), glutathione peroxidase (GPx), glutathione S-transferase (GST), glutathione reductase (GR), and lipid peroxidation (LPO)
Risk of bias of the included RCT studies as reported in the SR	*Tool used* SYRCLE's tool for pre-clinical studies; Cochrane's collaboration tool for RCTs; Newcastle-Ottawa scale for observational studies *Authors summary* Table S2: Sources of Risk of Bias of selected clinical studies **The Cochrane Collaboration tool** (Higgins et al., 2011)

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Agnihotri et al., 2013	Low Risk Patients were randomly allocated by SAS systems of Windows to *withania somnifera* extract (WSE) or placebo	Low Risk Patients were randomly allocated to two groups (WSE and placebo) of 15 each, to receive either WSE capsule or matching placebo	Low Risk Double-blind; the two groups received either WSE (400 mg per capsule) or matching placebo given as one capsule thrice daily for a month	Low Risk Double-blind	Unclear Risk Of 30 included patients, 3 from WSE and 2 from placebo were lost to follow-up; reasons for drop-out were not mentioned in the study	Low Risk The published article reported all pre-specified outcomes from methodology
Nayak et al., 2015	Unclear Risk Randomly allocated with no further details	Unclear Risk Randomly allocated with no further details	High Risk No details are available	High Risk No details are available	Unclear Risk 60 ambulatory type-2 DM patients were selected; however, only patients with a considerable stress level (DDS17 Score $\geq$ 3) were registered for the study. During the trial, 2 patients from test group and 3 from placebo were dropped-out before study completion due to some reason or the other	Unclear Risk Study protocol was not available; however, all pre-specified outcomes from methodology are reported in the published article except urine – RE and ME
Usharani et al., 2014a	Unclear Risk Reported as randomized with no further details on randomization method	Low Risk Identical matching placebo capsules were used in case of control	Low Risk Double-blind	Low Risk Double-blind	Low Risk Of 66 screened subjects, 60 completed the study; four patients were excluded because of abnormal lab investigation, two patients relocated, hence unable to continue the study	Unclear Risk Study protocol was not available, but the published article reported all pre-specified outcomes from methodology
Usharani et al., 2014b	Unclear Risk Reported as randomized with no further details on randomization method	Unclear Risk No details on identical appearance of *phyllanthus emblica* (CAPROS®), *withania somnifera* (SENSORIL®), or a combination of CAPSORIL® (CAPROS®+SENSORIL®) twice daily	Low Risk Double-blind	Low Risk Double-blind	Low Risk All 30 eligible subjects completed the study	Low Risk Study protocol was not available, but the published article reported all pre-specified outcomes from methodology

The Newcastle-Ottawa scale (Wells et al., 2013)

Study	Selection	Comparability	Exposure
Andallu and Radhika, 2000	**	*	*

Authors conclusions (key message)	The collective experimental data in this study look modest. However, clinical data of five studies are too limited to provide novel and sufficiently robust evidence of the benefits of W. somnifera to recommend in managing DM.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	3 out of 24 studies included in the SR met our PICO. Of the excluded studies: one was an observational study vs oral hypoglycaemic drug (Andallu 2000), one was a study comparing against combination Phyllanthus emblica/W. somnifera (Usharani, Kishan et al. 2014) and the remaining 19 were in vitro or pre-clinical studies. Total N= in eligible studies *Study ID* *Summary RoB* *Study design features (PICOS)*

Characteristics of included reviews	Diabetes			
Review ID	**Durg 2020**			
1	Agnihotri 2013	Unclear risk (incomplete outcome data)	N=25 (12/13) W. somnifera extract 400 mg per capsule, one capsule TID for 1 month	P: Schizophrenia patients, suffering from metabolic syndrome, on second-generation antipsychotics for 6 months or more, with FBG level >100 mg/dl, serum TGs >150 mg/dl, HDL-C <40 mg/dl in men and <50 mg/dl in women I: *Withania* C: Matching placebo, one capsule TID for 1 month O: Body weight, FBG and lipid profile (TG and HDL-C), blood pressure S: ?
2	Nayak 2015	High risk (blinding)	N=55 (28/27) W. somnifera capsule of 300 mg root extract in ground nut oil base, one capsule BID with a cup of Luke warm milk for 6 weeks	P: T2DM patients treated with fixed OHAs (metformin, 500 mg + glimepride, 1 mg), FBS ≥126 and ≤180 mg/dl, PPBS ≤240 mg/dl, HbA1C ≥7%, and mean total DDS scoring ≥3 I: Withania C: Soft gelatine capsule of only ground nut oil, one capsule BID with a cup of Luke warm milk for 6 weeks O: DDS17 score (emotional burden, physician related distress, regimen related distress, and interpersonal distress), FBS, PPBS, HbA1c, lipid profile (TC) and adverse events S: ?
3	Usharani, Fatima et al. 2014	Unclear risk (randomisation, selective reporting)	N = 60 (20/20/20)	P: T2DM patients with FBG between 110–126 mg/dl, HbA1c between 6.5 and 8.0%, on oral hypoglycemic agents for last 8 weeks (metformin, 1,500-2,000 mg/day) prior to screening visit, endothelial dysfunction defined as ≤6% change in reflection index (RI) on post salbutamol challenge test I: *W. somnifera* capsule of 250 mg root extract BID for 12 weeks or 500 mg BID for 12 weeks C: Identical matching capsule BID for 12 weeks O: Endothelial dysfunction (RI), oxidative stress biomarkers (NO, MDA, GSH and hs-CRP), lipid profile (TC, TG, HDL-C, LDL-C and VLDL-C), safety and tolerability S: ?
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Characteristics of included reviews	Diabetes
Review ID	Durg 2020
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Characteristics of included reviews	Diabetes
Review ID	**Durg 2020**
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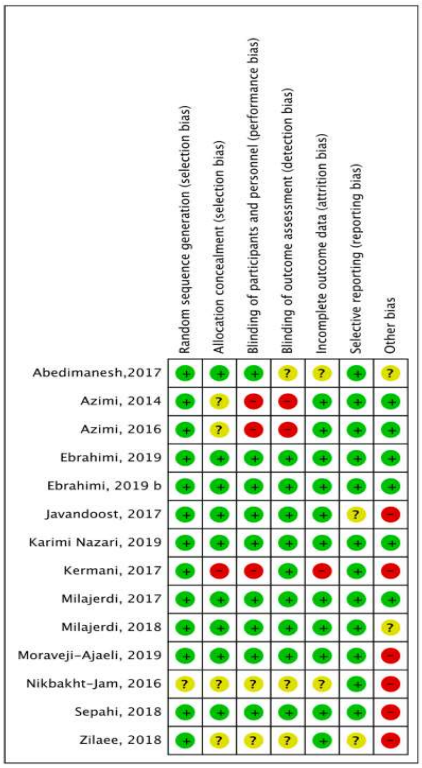
= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Diabetes
Review ID	**Giannoulaki 2020**
Review reference	Giannoulaki P, Kotzakioulafi E, Chourdakis M, Hatzitolios A, Didangelos T. Impact of Crocus Sativus L. on Metabolic Profile in Patients with Diabetes Mellitus or Metabolic Syndrome: A Systematic Review. Nutrients. 2020 May 14;12(5):1424. doi: 10.3390/nu12051424.
Review objective	To present and assess the results of relevant studies, regarding the impact of saffron and its bioactive components on the metabolic profile of patients with diabetes mellitus and metabolic syndrome
Author affiliations	All authors were affiliated with tertiary institutions in Greece
Source of funds	This research received no external funding
Declared interests of the review authors	The authors declare no conflicts of interest
Review method of analysis	Individual study results: Narrative synthesis and analysis of the data of each study was made. No meta-analysis was performed due to the high heterogeneity regarding study design and reported outcomes between included studies. Wherever there were two intervention groups in a study, the statistics of these two groups were combined in one, using the handbook Cochrane formula for combining two groups.
Inclusion criteria	
Study design	RCT
Population	Human subjects with DM and MS
Intervention	Saffron and its bioactive components (“crocus sativus” or “crocin” or “picrocrocin” or “saffron” or “safranal”)
Comparator	Not specified
Other	Had biochemical metabolic markers, such as t-chol, HDL-c, LDL-c, TGlevels, FBG, HbA1c, waist circumference (WC), systolic and diastolic blood pressure (SBP and DBP) as an outcome
Exclusion criteria	
Study design	Reviews, meta-analyses, experimental studies in vitro
Population	Studies examining other diseases
Intervention	Studies examining other herbal compounds
Comparator	Not specified
Other	Studies that examined different outcomes other than the metabolic profile; in vivo and clinical trials that were ongoing or had not published results yet; full text not retrieved or not available in English
Date of documented search (month/year)	July 2019 to September 2019; final search in January 2020 to identify new publications
Databases searched	MEDLINE (via PubMed), Scopus (Science Direct), Cochrane Library Database of Systematic Reviews, Google Scholar and Clinicaltrials.gov
Was an non-English database searched?	No

Characteristics of included reviews	Diabetes
Review ID	**Giannoulaki 2020**
Were studies in a LOTE included?	No — Full text not available in English excluded
Outcomes considered in the SR (list)	FBG, HbA1c, t-chol, LDL-c, HDL-c, TG, WC, SBP, and DBP
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane Collaboration's tool *Authors summary*:  **Figure 3.** Risk of bias assessment summary for each included study.
Authors conclusions (key message)	Findings from this review are implausible due to the low-quality clinical trials assessed. It may be a favorable effect of saffron in FBG, but further research needs to be carried out in populations with greater homogeneity, different ethnic groups, more particular doses, and duration of supplementation. Also, it is necessary for the titration of the supplement used to provide more consistent results.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	14 out of 14 studies included in the SR met our PICO Total N= in eligible studies *Study ID* — *Summary RoB* — *Study design features (PICOS)*

Characteristics of included reviews	Diabetes			
Review ID	**Giannoulaki 2020**			
1	Abedimanesh 2017	Unclear risk (blinding, other)	N=75	P: Coronary artery disease (17% DM) I: Saffron aqueous extract 30mg, Crocin 30 mg C: Placebo O: FBG, t-chol, HDL-c, LDL-C, TG, WC S: ?
2	Azimi 2014	High risk (blinding)	N=208	P: DM-2 I: Black tea 3 gl + cardamom 3 g; black tea 3 gl + cinnamon 3 g; black tea 3 gl + ginger 3 g; black tea 3 gl + saffron 1 g C: Black tea 3 gl O: FBG, t-chol, TG, LDL-c, HDL-C, HbA1c S: ?
3	Azimi 2016	High risk (blinding)	N=208	P: DM-2 I: Black tea 3 gl + cardamom 3 g; black tea 3 gl + cinnamon 3 g; black tea 3 gl + ginger 3 g; black tea 3 gl + saffron 1 g C: Black tea 3 gl O: WC, SBP, DBP S: ?
4	Ebrahimi 2019	Low risk	N=90	P: DM-2 I: Saffron 100 mg C: Placebo O: SBP, DBP S: ?
5	Ebrahimi 2019b	Low risk	N=90	P: DM-2 I: Saffron 100 mg C: Placebo O: FBG, HbA1c, TG, t-chol, HDL-C, LDL-C, WC S: ?
6	Javandoost 2017	High risk (other)	N=44	P: MS I: Crocin 30 mg C: Placebo O: FBG, TG, HDL-C, LDL-C, t-chol S: ?

Characteristics of included reviews	Diabetes			
Review ID	**Giannoulaki 2020**			
7	Karimi Nazari 2019	Low risk	N=80	P: Prediabetes I: Saffron 15 mg C: Placebo O: FBG, TG, HDL-C, LDL-C, t-chol S: ?
8	Kermani 2017	High risk (allocation, blinding, incomplete outcome data, other)	N=48	P: MS I: Crocin 100 mg C: Placebo O: FBG, TG, HDL-C, LDL-c, t-chol, SBP, DBP, WC S: ?
9	Milajerdi 2017	Low risk	N=54	P: DM-2 I: Saffron 30 mg C: Placebo O: WC, SBP, DBP (does not report full data) S: ?
10	Milajerdi 2018	Unclear risk (other)	N=54	P: DM-2 I: Saffron 30 mg C: Placebo O: FBG, t-chol, TG, HDL-C, LDL-C, HbA1c S: ?
11	Moravej Aleali 2019	High risk (other)	N=64	P: DM-2 I: Saffron 30 mg C: Placebo O: FBG, t-chol, TG, HDL-C, LDL-C, HbA1c S: ?
12	Nikbakht-Jam 2016	High risk (other)	N=60	P: MS (DM 16%) I: Crocin 30mg C: Placebo O: FBG, t-chol, TG, HDL-C, LDL S: ?
13	Zilaee 2018	High risk (other)	N=76	P: MS I: Saffron 100mg C: Placebo O: LDL-C, HDL-C, TG, t-chol, WC S: ?
14	Sepahi 2018	High risk (other)	N=60	P: DM-1 (10), DM-2 (50) I: Crocin 5mg, crocin 15mg C: Placebo O: FBG, HbA1c, HDL-C, LDL-C, TG, t-Chol S: ?
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Characteristics of included reviews	Diabetes
Review ID	**Giannoulaki 2020**
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= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Diabetes
Review ID	**Jamali 2020**
Review reference	Jamali N, Jalali M, Saffari-Chaleshtori J, Samare-Najaf M, Samareh A. Effect of cinnamon supplementation on blood pressure and anthropometric parameters in patients with type 2 diabetes: A systematic review and meta-analysis of clinical trials, Diabetes Metab Syndr. 2020; 14(2):119-125. doi:10.1016/j.dsx.2020.01.009.
Review objective	To assess the effect of cinnamon supplementation on the SBP and DBP and anthropometric parameters as critical risk factors of hypertension
Author affiliations	All authors were affiliated with tertiary institutions in Iran
Source of funds	The study was performed without any specific funding
Declared interests of the review authors	The authors declare no conflicts of interest
Review method of analysis	Meta-analysis: Meta-analysis performed using STATA 13 software. SMD and 95% CI used to evaluate effects. Fixed or random effect models used in the case of significant heterogeneity. Heterogeneity assessed using I2 index and P value.
Inclusion criteria	
Study design	Clinical trials
Population	Human subjects with type 2 diabetes
Intervention	Cinnamon consumed in the form of supplement
Comparator	Not specified
Other	High-quality clinical trials (scoring equal to or greater than 3 of the 5 points on the Jadad scale); trials reporting at least one of the primary outcomes such as SBP or DBP and secondary ones, including body weight (BW), body mass index (BMI) and waist circumference (WC)
Exclusion criteria	
Study design	Not specified
Population	Healthy subjects or participants with other types of disorders
Intervention	Not specified
Comparator	Not specified
Other	Not specified
Date of documented search (month/year)	Up to August 22, 2019
Databases searched	PubMed, Embase, Scopus, Web of Science and Cochrane trials; manual search of reference lists and Google Scholar
Was an non-English database searched?	No

Characteristics of included reviews	Diabetes
Review ID *Were studies in a LOTE included?*	**Jamali 2020** Not specified
Outcomes considered in the SR (list)	Primary outcomes: SBP or DBP Secondary outcomes: body weight (BW), body mass index (BMI) and waist circumference (WC)
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Jadad scale *Authors summary*: Results of assessment not described however authors stated that only high-quality clinical trials were included in the meta-analysis, with studies scoring at least 3 of the 5 points considered high-quality studies.
Authors conclusions (key message)	Cinnamon supplementation significantly decreased the SBP and DBP; however, it did not affect the BW, WC, and BMI. Overall, cinnamon can be useful as an herbal medicine to reduce blood pressure in patients with type 2 diabetes. However, more well-designed clinical trials are suggested to confirm the results of the present study.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	9 out of 9 studies included in the SR met our PICO Total N= in eligible studies *Study ID* *Summary RoB* *Study design features (PICOS)*

Characteristics of included reviews	Diabetes			
Review ID	**Jamali 2020**			
1	Suppapitiporn 2006	High quality (Jadad score 3 or higher)	N=60 (20/40)	P: Type 2 Diabetes I: Cinnamon capsule 4.5 g/day for 3 months C: Control O: BW S: Thailand
2	Akilen 2010	High quality (Jadad score 3 or higher)	N=58 (30/28)	P: Type 2 Diabetes I: Cinnamon capsule 2 g/day for 3 months C: Control O: SBP, DBP, BW, BMI, WC S: United Kingdom
3	Wainstein 2011	High quality (Jadad score 3 or higher)	N=59 (29/30)	P: Type 2 Diabetes I: Cinnamon capsule 1.2 g/day for 3 months C: Control O: SBP, DBP, BW, BMI, WC S: Israel
4	Haghighian 2011	High quality (Jadad score 3 or higher)	N=60 (30/30)	P: Type 2 Diabetes I: Cinnamon capsule 1.5 g/day for 2 months C: Control O: BW, BMI S: Iran
5	Vafa 2012	High quality (Jadad score 3 or higher)	N=37 (19/18)	P: Type 2 Diabetes I: Cinnamon capsule 3 g/day for 2 months C: Control O: SBP, DBP, BW, BMI, WC S: Iran
6	Mirfeizi 2015	High quality (Jadad score 3 or higher)	N=33 (30/3)	P: Type 2 Diabetes I: Cinnamon capsule 1 g/day for 3 months C: Control O: BMI S: Iran

Characteristics of included reviews	Diabetes			
Review ID	**Jamali 2020**			
7	Azimi 2016	High quality (Jadad score 3 or higher)	N=79 (40/39)	P: Type 2 Diabetes I: Cinnamon powder 3 g/day for 2 months C: Control O: SBP, DBP, BW, BMI, WC S: Iran
8	Sengsuk 2016	High quality (Jadad score 3 or higher)	N=99 (49/50)	P: Type 2 Diabetes I: Cinnamon capsule 1.5 g/day for 2 months C: Control O: SBP, DBP S: Thailand
9	Zare 2019	High quality (Jadad score 3 or higher)	N=138 (69/69)	P: Type 2 Diabetes I: Cinnamon capsule 1 g/day for 3 months C: Control O: BW, BMI S: Iran
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Characteristics of included reviews	Diabetes
Review ID	**Jamali 2020**
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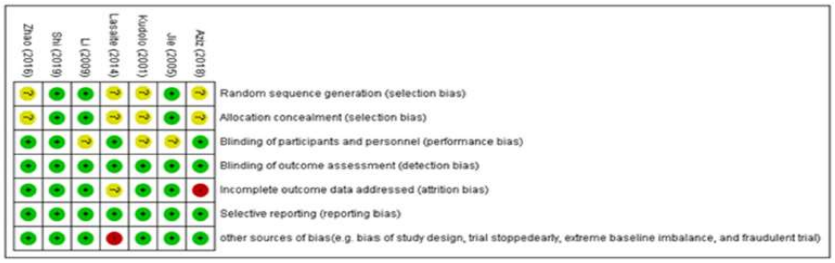
	= data extracted
	= data extracted from more recent SR (or better SR)
	= control is an active intervention

Characteristics of included reviews	Diabetes
Review ID	**Tabrizi 2020**
Review reference	Tabrizi R, Nowrouzi-Sohrabi P, Hessami K, et al. Effects of Ginkgo biloba intake on cardiometabolic parameters in patients with type 2 diabetes mellitus: A systematic review and meta-analysis of clinical trials. Phytotherapy Research. 2020;1–10. https://doi.org/10.1002/ptr.6822
Review objective	To conduct a systematic review and metaanalysis of the effects of GKB intake on cardiometabolic parameters such as glycemic control, lipid profile, systolic and diastolic blood pressure in patients with T2DM.
Author affiliations	All authors were affiliated with tertiary or research institutions in Iran
Source of funds	Social Determinants of Health Research Center of Shahid Beheshti University of Medical Sciences, Tehran, Iran
Declared interests of the review authors	The authors declare no competing interests
Review method of analysis	Meta-analysis: All statistical analyses using Stata 13. Heterogeneity assessed using I2 and p value. In case of existence heterogeneity, fixed or random-effects model were performed to pool WMDs and 95% Cis.
Inclusion criteria	
Study design	Parallel design clinical trials
Population	Type 2 diabetes patients
Intervention	Gingko biloba (GKB)
Comparator	Not specified
Other	Published in Engligh; reported sufficient data of the effects of GKB on at least one of the parameters of lipid profile factors (triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol), glycemic indices (FBS, HbA1c) and blood pressure (SBP, DBP) in the diagnosed type 2 diabetic patients for more than 1 month
Exclusion criteria	
Study design	Animal design studies
Population	Complicated participants
Intervention	Combined supplement
Comparator	Papers without suitable control group
Other	Trials with lack of any essential data, reported insufficient data about change of outcomes at the end of the study from baseline; conference abstract, book chapter, editorials, patents, dissertations and/or brief reports
Date of documented search (month/year)	Inception to September 2, 2019
Databases searched	PubMed, Embase, Scopus, Web of Sciences, Google Scholar and Cochrane Library. Manual search of reference lists
Was an non-English database searched?	No

Characteristics of included reviews	Diabetes
Review ID	**Tabrizi 2020**
Were studies in a LOTE included?	No — Only trials published in English included in search
Outcomes considered in the SR (list)	Serum/plasma levels of triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol, FBS, HbA1c and also SBP and DBP
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane Collaboration risk of bias tool *Authors summary*: 
Authors conclusions (key message)	GKB supplementation significantly improves HDL-cholesterol, but also increases HbA1c levels. However, the authors were not able to show any significant change in other lipidemic, glycemic and blood pressure variables. Due to uncertainties related to the limited number of studies, it is too early to conclude whether GKB has any potential effects on the cardiometabolic factors in patients with T2DM or not.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	7 out of 7 studies included in the SR met our PICO Total N=768 in eligible studies *Study ID* — *Summary RoB* — *Study design features (PICOS)*

Characteristics of included reviews	Diabetes			
Review ID	**Tabrizi 2020**			
1	Kudolo 2001	Unclear risk (randomisation, allocation, blinding)	N=12 (6/6)	P: NIDDM I: GKB capsule, ingestion C: Control (unspecified) O: FBS, HbA1c, SBP, DBP, TG, TC, LDL-C, HDL-C S: USA
2	Jie 2005	Uncler risk (blinding)	N=60 (30/30)	P: Early stage diabetic nephropathy (T2DM) I: GKB ampoule, injection C: Control (unspecified) O: FBS, HbA1c, SBP, DBP, TG, TC, LDL-C, HDL-C S: China
3	Li 2009	Unclear risk (blinding)	N=64 (32/32)	P: Early stage diabetic nephropathy (T2DM) I: GKB tablet, oral C: Control (unspecified) O: FBS S: China
4	Lasaite 2014	High risk (other)	N=39 (25/14)	P: T2DM I: GKB capsule, ingestion C: Control (unspecified) O: HbA1c S: Lithuania
5	Zhao 2016	Unclear risk (randomisation, allocation)	N=115 (59/56)	P: T2DM I: GKB tablet, oral C: Control (unspecified) O: FBS, HbA1c, SBP, DBP, TG, TC, LDL-C, HDL-C S: China
6	Aziz 2018	High risk (incomplete outcome data)	N=47 (27/20)	P: Uncontrolled T2DM I: GKB capsule, oral C: Control (unspecified) O: FBS, HbA1c S: Iraq

Characteristics of included reviews	Diabetes			
Review ID	**Tabrizi 2020**			
7	Shi 2019	Low risk	N=431 (225/206)	P: T2DM I: GKB tablet, oral C: Control (unspecified) O: FBS, HbA1c, SBP, DBP, TG, TC, LDL-C, HDL-C S: China
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Characteristics of included reviews	Diabetes
Review ID	**Tabrizi 2020**
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= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Diabetes
Review ID	**Xu 2020**
Review reference	Xu R, Bai Y, Yang K, Chen G. Effects of green tea consumption on glycemic control: a systematic review and meta-analysis of randomized controlled trials. Nutr Metab (Lond). 2020 Jul 10;17:56. doi: 10.1186/s12986-020-00469-5.
Review objective	To update the evidence which quantitatively assess the effect of green tea supplementation on measures of glucose control and insulin sensitivity.
Author affiliations	All authors were affiliated with Huazhong University of Science and Technology in China
Source of funds	National Natural Science Foundation of China
Declared interests of the review authors	The authors declare no competing interests
Review method of analysis	Meta-analysis: Meta-analysis performed with STATA 11. For parallel trials, treatment effects were calculated as WMD and SD in the change from baseline to follow-up in the green tea group versus control group. For crossover trials, treatment effects were calculated as WMD and SD at follow-up in the green tea intervention versus control periods. Variances were imputed if SD were not reported directly and missing SD values for paired differences were imputed. Cochran's Q test and I2 index to assess heterogeneity. Random effects models.
Inclusion criteria	
Study design	RCTs with both parallel and crossover interventions
Population	Adult subjects
Intervention	Green tea consumed for equal or greater than 2 weeks
Comparator	Concurrent control group with the only difference between the treatment and control groups being the consumption of either green tea or green tea extract.
Other	Blood glucose was evaluated by estimating the concentrations of FBG, fasting blood insulin (FBI) and HbA1c; English-language articles
Exclusion criteria	
Study design	Not specified
Population	Not specified
Intervention	Green tea extract was given as part of a multicomponent supplement
Comparator	Not specified
Other	Subjects in each group ≤10; RCTs that did not report mean (SD) changes in fasting glucose, fasting insulin, or HbA1c in each treatment group and could not be calculated from the data available
Date of documented search (month/year)	Index date of each database through February 2020.
Databases searched	PubMed, Embase, Cochrane Library. Additional studies identified by manually screening references of originally identified reviews and research reports or the clinical trials.
Was an non-English database searched?	No

Characteristics of included reviews	Diabetes
Review ID	**Xu 2020**
Were studies in a LOTE included?	No — English-language articles included in search
Outcomes considered in the SR (list)	Primary outcome measures: WMD in FBG, FBI, and HbA1c after green tea supplementation Secondary outcome measures: WMD in HOMA-IR concentration
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Jadad scoring criteria *Authors summary*: The study quality of the 27 included RCTs varied. Fourteen studies were classified as high-quality (Jadad score ≥ 4), and the remaining 13 studies were classified as low-quality (Jadad score < 4).

Table 2 Validity of included studies

References	Randomization	Allocation concealment	Masking of participants	Masking of researches	Generation of random numbers reported	Reporting of withdraws	Jadad score
Basu 2011 [22]	Yes	Adequate	Yes	No	Yes	Yes	4
Bogdanski 2012 [23]	Yes	Adequate	Yes	Yes	No	Yes	4
Brown 2009 [24]	Yes	Adequate	Yes	Yes	Yes	Yes	5
Brown 2011 [25]	Yes	Adequate	Yes	Yes	Yes	Yes	5
Chan 2006 [26]	Yes	Unclear	Yes	Yes	Yes	Yes	4
Chen 2016	Yes	Adequate	Yes	Yes	Yes	Yes	5
Diepvens 2006 [28]	Yes	Unclear	Yes	Yes	No	No	2
Dostal 2016	Yes	Adequate	Yes	Yes	Yes	Yes	5
Frank 2009 [30]	Yes	Unclear	Yes	Yes	No	Yes	3
Fukino 2005 [31]	Yes	Unclear	No	No	No	Yes	2
Fukino 2008 [32]	Yes	Unclear	No	No	No	Yes	2
Hill 2007 [33]	Yes	Adequate	No	No	No	Yes	3
Hsu 2008 [34]	Yes	Adequate	Yes	Yes	Yes	Yes	5
Hsu 2011 [35]	Yes	Adequate	Yes	Yes	Yes	Yes	5
Kovacs 2004 [36]	Yes	Unclear	Yes	Yes	No	Yes	3
Liu 2014 [37]	Yes	Unclear	Yes	Yes	No	Yes	3
Lu 2016 [38]	Yes	Adequate	Yes	Yes	Yes	Yes	5
Mielgo-Ayuso 2014 [39]	Yes	Adequate	Yes	Yes	Yes	Yes	5
Mirzaei 2009 [40]	Yes	Unclear	Yes	Yes	No	No	2
Miyazaki 2013 [41]	Yes	Unclear	Yes	Yes	No	Yes	3
Nagao 2007 [42]	Yes	Unclear	Yes	Yes	No	Yes	3
Nagao 2009 [43]	Yes	Unclear	Yes	Yes	No	Yes	3
Ryu 2006 [44]	Yes	Unclear	No	No	No	No	1
Sone 2011 [45]	Yes	Adequate	Yes	Yes	No	Yes	4
Suliburska 2012 [46]	Yes	Unclear	Yes	Yes	Yes	Yes	4
Tadayon 2018	Yes	Adequate	Yes	Yes	Yes	Yes	5
Wu 2012 [48]	Yes	Unclear	Yes	Yes	No	Yes	3

Authors conclusions (key message)	Green tea intake had a favorable effect on fasting blood glucose concentration. However, green tea intake did not significantly affect fasting blood insulin or HbA1c.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	27 studies were included in the SR. None met our PICO as it was not possible to determine which studies were conducted in patients with diabetes (eligible studies included those conducted in healthy subjects). Total N=0 in eligible studies

Study ID	*Summary RoB*	*Study design features (PICOS)*

Characteristics of included reviews	Diabetes
Review ID	**Xu 2020**
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Characteristics of included reviews	Diabetes
Review ID	Xu 2020
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Characteristics of included reviews	Diabetes
Review ID	**Xu 2020**
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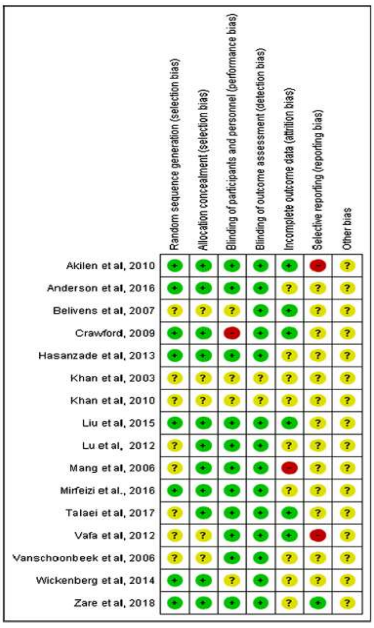
= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Diabetes
Review ID	**Denyo 2019**
Review reference	Deyno S, Eneyew K, Seyfe S, Tuyiringire N, Peter EL, Muluye RA, Tolo CU, Ogwang PE. Efficacy and safety of cinnamon in type 2 diabetes mellitus and pre-diabetes patients: A meta-analysis and meta-regression. Diabetes Res Clin Pract. 2019 Oct;156:107815. doi: 10.1016/j.diabres.2019.107815.
Review objective	To systematically review and synthesize evidence on the efficacy of cinnamon for the treatment of patients with T2DM and pre-diabetes patients.
Author affiliations	All authors were affiliated with tertiary, research or public health institutions in East Africa
Source of funds	Support from World Bank project, PHARMBIOTRAC. No specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Declared interests of the review authors	The authors have no competing interests
Review method of analysis	Meta-analysis: Meta-analysis conducted using RevMan 5.3 and Stata 13. All of the variables in this study were continuous, and the inverse of the variance-weighted method was used for pooling WMD and 95% CI. Heterogeneity assessed using Chi-square test and I2 tests. Random-effects model (REM) was used to estimate the pooled MD and 95% CIs due to significant heterogeneity.
Inclusion criteria	
Study design	RCT
Population	T2DM or pre-diabetes patients aged 18 years and older of either sex
Intervention	Cinnamon
Comparator	Not specified
Other	Follow up duration of at least four weeks for both primary and secondary outcomes
Exclusion criteria	
Study design	Non-randomized clinical trials, cross-sectional studies, case series and case reports studies
Population	Patients younger than 18 years, type 1 DM
Intervention	Not specified
Comparator	Not specified
Other	Not specified
Date of documented search (month/year)	Not specified
Databases searched	PubMed, Web of Sciences, SCOPUS, CINAHL, and the Cochrane library. Reference list of all identified studies searched for additional studies. Unpublished studies searched in Google and Google Scholar. Ongoing clinical trials searched through clinicaltrials.gov.
Was an non-English database searched?	No

Characteristics of included reviews	Diabetes
Review ID *Were studies in a LOTE included?*	**Denyo 2019** Not specified
Outcomes considered in the SR (list)	FBG, HbA1c, insulin level, LDL, HDL, TC, BMI, HOMA-IR, Alanine aminotransferase (ALT), and Aspartate aminotransferase (AST)
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane risk of bias tool *Authors summary*: The risk of bias was particularly high in the domain of detection, selection and performance bias due to failure of the included studies to adequately blind participants, personnel and outcome assessment as well as to sufficiently conceal allocation sequence. 
Authors conclusions (key message)	Cinnamon significantly reduced elevated FBG and HOMA-IR compared to placebo. However, there is no significant reduction in HbA1c and lipid profiles levels between cinnamon treated and placebo-treated T2DM patients or pre-diabetes patients. Meta-regression did not provide evidence for high level of heterogeneity.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	16 out of 16 studies included in the SR met our PICO Total N=977 in eligible studies *Study ID* *Summary RoB* *Study design features (PICOS)*

Characteristics of included reviews	Diabetes			
Review ID	**Denyo 2019**			
1	Akilen 2010 [39]	High risk (selective reporting)	N=58	P: Type II Diabetes I: C. cassia 2 g/d, 12 week follow up duration C: Placebo (starch) O: FBG, HbA1c level, LDL, HDL, TC, TG, BMI S: ?
2	Anderson 2015 [40]	Unclear risk (incomplete outcome data, selective reporting, other)	N=137	P: Pre-diabetes I: Commercial spray-dried extract of cinnamon 1 g/d, 3 month follow up duration C: Placebo (wheat flour) O: FBG, HOMA-IR, insulin level, LDL, HDL, TC, TG, BMI S: ?
3	Blevins 2007 [47]	Unclear risk (randomisation, allocation, blinding, selective reporting, other)	N=43	P: Type II diabetes I: C. cassia capsules 1 g/d, 3 month follow up duration C: Placebo (wheat flour) O: FBG, insulin level, HbA1c level, LDL, HDL, TG, BMI S: ?
4	Crawford 2009 [41]	High risk (blinding)	N=89	P: Type II diabetes I: C. cassia capsules 1 g/d, 3 month follow up duration C: Placebo (usual care) O: HbA1c level S: ?
5	Hasanzade 2013 [42]	Unclear risk (incomplete outcome data, selective reporting, other)	N=35	P: Type II diabetes I: C. cassia capsules 1 g/d, 60 days follow up duration C: Placebo (not specified) O: FBG, HbA1c level S: ?
6	Khan 2010 [52]	Overall unclear risk	N=14	P: Type II diabetes I: Cinnamon capsules (botanical source not given) 1.5 g/d, 30 days follow up duration C: Placebo (maize flour) O: FBG, LDL, HDL TC, TG S: ?

Characteristics of included reviews	Diabetes			
Review ID	**Denyo 2019**			
7	Khan 2003 [51]	Overall unclear risk	N=60	P: Type II diabetes I: C. cassia 6 g/d,, 60 days follow up duration C: Placebo (wheat flour) O: FBG, LDL, TC, TG S: ?
8	Liu 2015 [43]	Unclear risk (selective reporting, other)	N=52	P: Pre-diabetic I: C. cassia capsules 1.2 g/d, 4 month follow up duration C: Placebo (not specified) O: FBG, HOMA-IR, insulin level, HbA1c level, LDL, HDL, TC, TG, BMI S: ?
9	Lu 2012 [53]	Unclear risk (randomisation, incomplete outcome data, selective reporting, other)	N=66	P: Type II diabetes I: C. aromaticum 14.4 g/d, 3 month follow up duration C: Placebo (not specified) O: FBG, HbA1c level, LDL, HDL, TC, TG S: ?
10	Mang 2006 [48]	High risk (incomplete outcome data)	N=65	P: Type II diabetes I: C. cassia 3 g/d, 4 month follow up duration C: Placebo (cellulose) O: FBG, HbA1c level, LDL, HDL, TC, TG S: ?
11	Mirfeizi 2015 [44]	Unclear risk (incomplete outcome data, selective reporting, other)	N=102	P: Type 2 Diabetes I: Cinnamon (botanical source and formulation not specified) 1 g/day, 3 months follow-up duration C: Placebo (starch) O: FBG, HOMA-IR, insulin level, HbA1c level, LDL, HDL, TC, TG, BMI
12	Talaei 2017 [54]	Unclear risk (randomisation, selective reporting, other)	N=39	P: Type II diabetes I: C. zeylanicum 3 g/d, 8 weeks follow up duration C: Placebo (cellulose) O: FBG, HbA1c level S: ?
13	Vafa 2012 [49]	High risk (selective reporting)	N=37	P: Type 2 Diabetes I: C. zeylanicum 3 g/day, 8 weeks follow up duration C: Placebo (wheat flour) O: FBG, insulin level, HbA1c level, LDL, HDL, TC, TG, BMI S: ?
14	Vanschoonbeek 2006 [50]	Unclear risk (randomisation, allocation, incomplete outcome data, selective reporting, other)	N=25	P: Type II diabetes I: C. cassia 1.5 g/d, 6 week follow up duration C: Placebo (wheat flour) O: FBG, insulin level, HbA1c level, LDL, HDL, TC, TG S: ?
15	Wickenberg 2014 [45]	Unclear risk (blinding, incomplete outcome data, selective reporting, other)	N=17	P: Pre-diabetes I: C. cassia capsule 12 g/d, 12 week follow up duration C: Placebo (cellulose) O: FBG, insulin level, HbA1c level, LDL, HDL, TC, TG S: ?

Characteristics of included reviews	Diabetes			
Review ID	**Denyo 2019**			
16	Zare 2018 [46]	Unclear risk (incomplete outcome data, other)	N=138	P: Type 2 Diabetes I: C. verum capsule 1 g/day, 3 month follow up duration C: Placebo (starch) O: FBG, HOMA-IR, insulin level, HbA1c level, LDL, HDL, TC, TG, BMI S: ?
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= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Diabetes
Review ID	**Huang 2019**
Review reference	Huang FY, Deng T, Meng LX, Ma XL. Dietary ginger as a traditional therapy for blood sugar control in patients with type 2 diabetes mellitus: A systematic review and meta-analysis. Medicine (Baltimore). 2019 Mar;98(13):e15054. doi: 10.1097/MD.0000000000015054.
Review objective	To systematically compare fasting blood sugar (FBS) and glycated hemoglobin (HbA1c) at baseline versus at follow-up in T2DM patients who consumed and who did not consume ginger
Author affiliations	Youjiang Medical University for Nationalities, Baise, Guangxi, PR China
Source of funds	No funding or sponsorship was received for the publication of this article. The article processing charges were funded by the authors.
Declared interests of the review authors	The authors have no conflicts of interest to disclose
Review method of analysis	Meta-analysis: Meta-analysis conducted using RevMan 5.3. Effects expressed as WMD with 95% CI. Heterogeneity assessed by Q statistic test and I2 test. Fixed effect model or random effect model.
Inclusion criteria	
Study design	RCT
Population	T2DM patients
Intervention	Ginger supplement
Comparator	Control group (unspecified)
Other	Comparing FBS and HbA1c in participants who were assigned to a ginger and a control group; reporting FBS and HbA1c at baseline and at follow-up
Exclusion criteria	
Study design	Nonrandomized trials, systematic reviews, meta-analyses, and case studies
Population	Healthy volunteers; did not involve patients with T2DM
Intervention	Not based on patients who were assigned to ginger supplements
Comparator	Not specified
Other	Did not report FBS and HbA1c; included data which could not be used
Date of documented search (month/year)	To July 2018
Databases searched	MEDLINE (PubMed), Embase, the Cochrane Central database, and www.ClinicalTrials.gov
Was an non-English database searched?	No

Characteristics of included reviews	Diabetes
Review ID	**Huang 2019**
Were studies in a LOTE included?	No — English-published trials included in search
Outcomes considered in the SR (list)	Fasting blood sugar (FBS) and glycated hemoglobin (HbA1c)
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane Collaboration *Authors summary*: Following the methodological assessment, a grade B was allotted to all the trials based on the criteria suggested by the Cochrane Collaboration.

General features of the studies.

Trials	Total no of DM patients assigned to ginger group (n)	Total no of DM patients assigned to control group (n)	Type of study	Bias risk grade
Arablou 2014	33	30	Randomized trial	B
Arzati 2017	25	25	Randomized trial	B
Azimi 2015	41	39	Randomized trial	B
Bordia 1997	30	—	Randomized trial	B
Khandouzi 2015	22	19	Randomized trial	B
Khosravi 2014	40	41	Randomized trial	B
Mahluji 2013	32	32	Randomized trial	B
Shidfar 2015	22	23	Randomized trial	B
Total no. of DM patients (n)	245	209		

DM = diabetes mellitus.

Authors conclusions (key message)	This analysis involving patients with T2DM showed no significant difference in FBS with ginger consumption. However, dietary ginger significantly improved HbA1c from baseline to follow-up showing that this natural medicine might have an impact on glucose control over a longer period of time in patients with T2DM.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	8 out of 8 studies included in the SR met our PICO. One study (Bordia 1997) was excluded as no subjects were assigned to the control group. Total N=454 in eligible studies *Study ID* — *Summary RoB* — *Study design features (PICOS)*

Characteristics of included reviews	Diabetes			
Review ID	**Huang 2019**			
1	Arablou 2014	Bias risk grade B (unspecified)	N=60 (33/30)	P: T2DM I: Ginger 1600 mg, 12 weeks follow-up period C: Control (unspecified) O: Fasting blood sugar, HbA1c S: ?
2	Arzati 2017	Bias risk grade B (unspecified)	N=50 (25/25)	P: T2DM I: Ginger 2000 mg, 10 weeks follow-up period C: Control (unspecified) O: Fasting blood sugar, HbA1c S: ?
3	Azimi 2015	Bias risk grade B (unspecified)	N=80 (41/39)	P: T2DM I: Ginger 3000 mg, 8 weeks follow-up period C: Control (unspecified) O: Fasting blood sugar, HbA1c S: ?
4	Bordia 1997	Bias risk grade B (unspecified)	N=30 (30/0)	P: T2DM I: Ginger 4000 mg, 12 weeks follow-up period C: Control (unspecified) O: Fasting blood sugar S: ?
5	Khandouzi 2015	Bias risk grade B (unspecified)	N=41 (22/19)	P: T2DM I: Ginger 2000 mg, 12 weeks follow-up period C: Control (unspecified) O: Fasting blood sugar, HbA1c S: ?
6	Khosravi 2014	Bias risk grade B (unspecified)	N=81 (40/41)	P: T2DM I: Ginger 3000 mg, 8 weeks follow-up period C: Control (unspecified) O: Fasting blood sugar, HbA1c S: ?

Characteristics of included reviews	Diabetes			
Review ID	**Huang 2019**			
7	Mahluji 2013	Bias risk grade B (unspecified)	N=64 (32/32)	P: T2DM I: Ginger 2000 mg, 8 weeks follow-up period C: Control (unspecified) O: Fasting blood sugar, HbA1c S: ?
8	Shidfar 2015	Bias risk grade B (unspecified)	N=454 (245/209)	P: T2DM I: Ginger 3000 mg, 12 weeks follow-up period C: Control (unspecified) O: Fasting blood sugar, HbA1c S: ?
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Characteristics of included reviews	Diabetes
Review ID	**Huang 2019**
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= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Diabetes
Review ID	**Namazi 2019**
Review reference	Namazi N, Khodamoradi K, Khamechi SP, Heshmati J, Ayati MH, Larijani B. The impact of cinnamon on anthropometric indices and glycemic status in patients with type 2 diabetes: A systematic review and meta-analysis of clinical trials. Complement Ther Med. 2019 Apr;43:92-101. doi: 10.1016/j.ctim.2019.01.002.
Review objective	To systematically review the effects of cinnamon on glycemic status and anthropometric indices in patients with T2DM
Author affiliations	All authors were affiliated with tertiary institutions in Iran
Source of funds	Not specified
Declared interests of the review authors	Authors declared no conflict of interest
Review method of analysis	Meta-analysis: Effect estimates reported as WMDs and 95% CI and pooled using a random effects model. Heterogeneity assessed by Cochran's Q test and the I2 test. All statistical analysis performed using STATA 11.
Inclusion criteria	
Study design	RCT (parallel or cross-over design)
Population	Adult subjects with T2DM
Intervention	Any form of cinnamon (whole herb not effective components)
Comparator	Placebo
Other	Examined the effects of cinnamon on at least FBS at baseline and at the end of the trial in both intervention and placebo groups; reported sufficient information including mean or mean differences with standard deviation (SD), standard error (SE) or 95% confidence intervals (95% CI)
Exclusion criteria	
Study design	Any study design other than clinical trials such as animal or in vitro/In vivo studies; before-after studies
Population	Other types of diabetes, diseases or healthy subjects; children/adolescent (younger than 18 years old); athletes
Intervention	Effective components of cinnamon or food/beverages with added cinnamon; combination with other herbal or non-herbal ingredients
Comparator	Not specified
Other	Did not report FBS concentrations (even if it reported other glycemic status and anthropometric indices); grey literature including theses, abstract in conferences, interviews, books
Date of documented search (month/year)	Published between January 2000 and 31 February 2018
Databases searched	PubMed/Medline, SCOPUS, Web of Sciences, EMBASE, and the Cochrane library. Reference lists of the relevant original articles, narrative reviews, systematic reviews and meta-analyses were hand searched.
Was an non-English database searched?	No

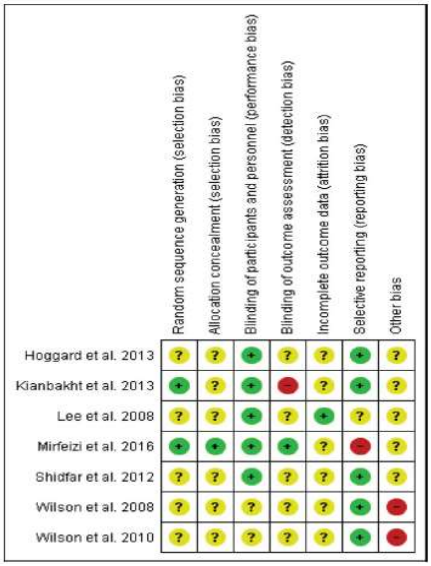
Characteristics of included reviews	Diabetes
Review ID	**Namazi 2019**
Were studies in a LOTE included?	Not specified — No language limitations in search
Outcomes considered in the SR (list)	Primary outcome: FBS (mg/dL) Secondary outcomes: HbA1c (%); insulin levels (pmol/L); HOMA-IR; and QUIKI; weight (kg); BMI (kg/m2); waist circumference (cm)
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Jadad checklist *Authors summary*: According to Jadad scale, 10 studies had high quality (score ≥ 3; 14,19,22–25,30,32,34,35) and the remaining (n=8; 16–18,20,31,33,36,37) posed low quality (score<3).
Authors conclusions (key message)	Supplementation with cinnamon can reduce serum levels of glucose with no changes in other glycemic parameters and anthropometric indices. Mechanisms other than losing weight, increasing serum levels of insulin, and reduction in insulin resistance following cinnamon intake might be involved in its anti-diabetic effects. However due to high heterogeneity, findings should be interpreted with great caution.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	18 out of 18 studies included in the SR met our PICO Total N=1100 in eligible studies *Study ID* — *Summary RoB* — *Study design features (PICOS)*

Characteristics of included reviews	Diabetes			
Review ID	**Namazi 2019**			
1	Zare 2018	High quality	N=138	P: T2DM I: Cinnamon (type not clear) powder 1 g/day C: Placebo O: FBS S: Iran
2	Zahedifar 2018	Low quality	N=55	P: T2DM I: Cinnamon (type not clear) powder 2 g/day C: Placebo O: FBS, HbA1c S: Iran
3	Talaei 2017	High quality	N=39	P: T2DM I: C. cassia powder 3 g/day C: Placebo O: FBS, HbA1c S: Iran
4	Sengsuk 2016	High quality	N=99	P: T2DM I: Cinnamon (type not clear) powder 1.5 g/day C: Placebo O: FBS, HbA1c S: Thailand
5	Tangvarasittichai 2015	High quality	N=106	P: T2DM I: C. cassia powder 1.5 g/day C: Placebo O: FBS S: Thailand
6	Azimi 2014	High quality	N=79	P: T2DM I: Cinnamon (type not clear) powder 3 g/day C: Placebo O: FBS, HbA1c, body weight, BMI, WC S: Iran

Characteristics of included reviews	Diabetes			
Review ID	**Namazi 2019**			
7	Mirfeizi 2014	High quality	N=72	P: T2DM I: Cinnamon (type not clear) powder 1 g/day C: Placebo O: FBS, HbA1c, BMI S: Iran
8	Hasanzadeh 2013	High quality	N=70	P: T2DM I: C. cassia powder 1 g/day C: Placebo O: FBS, HbA1c S: Iran
9	Vafa 2012	Low quality	N=37	P: T2DM I: Cinnamon (type not clear) powder 3 g/day C: Placebo O: FBS, HbA1c, body weight, BMI S: Iran
10	Lu 2012	Low quality	N=43	P: T2DM I: Cinnamon (type not clear) extract 0.12 g/day C: Placebo O: FBS, HbA1c S: China
11	Zahmatkesh 2012	High quality	N=55	P: T2DM I: Cinnamon (type not clear) powder 2 g/day C: Placebo O: FBS, HbA1c S: Iran
12	Haghighian 2011	Low quality	N=60	P: T2DM I: Cinnamon (type not clear) powder 1.5 g/day C: Placebo O: FBS, body weight, BMI S: Iran
13	Akilen 2010	High quality	N=58	P: T2DM I: C. cassia powder 2 g/day C: Placebo O: FBS, HbA1c, body weight, BMI, WC S: England
14	Otto 2010	Low quality	N=22	P: T2DM I: Cinnamon (type not clear) aqueous extract 0.5 g/day C: Placebo O: S: USA
15	Blevins 2007	Low quality	N=57	P: T2DM I: C. cassia powder 1 g/day C: Placebo O: FBS, HbA1c S: USA

Characteristics of included reviews	Diabetes			
Review ID	**Namazi 2019**			
16	Mang 2006	Low quality	N=65	P: T2DM I: Cinnamon (type not clear) powder 3 g/day C: Placebo O: FBS, HbA1c S: Germany
17	Vanschoonbeek 2006	High quality	N=25	P: T2DM, female only I: C. cassia (form unspecified) 1.5 g/day C: Placebo O: FBS, HbA1c S: Netherlands
18	Khan 2003	Low quality	N=20	P: T2DM I: C. cassia powder 1, 3 and 6 g/day C: Placebo O: FBS S: Pakistan
	= data extracted			
	= data extracted from more recent SR (or better SR)			
	= control is an active intervention			

Characteristics of included reviews	Diabetes
Review ID	**Rocha 2019**
Review reference	Rocha DMUP, Caldas APS, da Silva BP, Hermsdorff HHM, Alfenas RCG. Effects of blueberry and cranberry consumption on type 2 diabetes glycemic control: A systematic review. Crit Rev Food Sci Nutr. 2019;59(11):1816-1828. doi: 10.1080/10408398.2018.1430019.
Review objective	To assess the effect of berries (blueberry and cranberry) consumption on T2DM glucose control. Some evidences were also discussed on anti-diabetic mechanisms exerted by berries polyphenols.
Author affiliations	All authors were affiliated with a tertiary institutions in Brazil
Source of funds	CAPES, FAPEMIG, CNPq
Declared interests of the review authors	The authors state that they have no conflict of interest
Review method of analysis	Descriptive NA
Inclusion criteria	
Study design	RCT
Population	Subjects aged 18 years old or above with T2DM
Intervention	Any dose and form of berries (cranberry or blueberry) in oral administration. Studies in which the simultaneous administration of either one of these berries with insulin, oral hypoglycemic agents or both were included when there is already a constant use of these drugs.
Comparator	Non-exposed control group; placebo; no treatment
Other	Not specified
Exclusion criteria	
Study design	Not specified
Population	Children and adolescents
Intervention	Studies assessing the effect of treatments containing either both berries or combinations with other berries at the same time
Comparator	Not specified
Other	Not specified
Date of documented search (month/year)	June 11, 2017; no date restrictions
Databases searched	LILACS (Latin American and Caribbean Center on Health Sciences Information), PubMed/MEDLINE, Scopus, The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials [CENTRAL]) and Web of Science (Science and Social Science Citation Index)
Was an non-English database searched?	Yes LILACS (Latin American and Caribbean Center on Health Sciences Information)

Characteristics of included reviews	Diabetes
Review ID	**Rocha 2019**
Were studies in a LOTE included?	No — All the seven selected studies were published in English
Outcomes considered in the SR (list)	Primary outcome: blood glucose concentrations Secondary outcomes: blood insulin concentrations, insulin sensitivity evaluated using homeostasis model assessment of insulin resistance (HOMA-IR), glycosylated hemoglobin A1c (HbA1c), and other metabolic markers related to glucose homeostasis.
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane collaboration tool *Authors summary*: The 7 RCTs could be classified by their quality into one with moderate risk of bias and six with high risk of bias. 
Authors conclusions (key message)	A beneficial effect on glucose control was observed in response to the consumption of blueberry extract or powder supplementation (9.1 to 9.8 mg of anthocyanins, respectively) for 8 to 12 weeks as well as to daily consumption of cranberry juice (240 mL) for 12 weeks. Altogether, outcomes indicate a promising use of these berries in T2DMmanagement; although more studies are required to better understand the mechanisms involved.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	7 out of 7 studies included in the SR met our PICO Total N=195 in eligible studies *Study ID* — *Summary RoB* — *Study design features (PICOS)*

Characteristics of included reviews	Diabetes			
Review ID	**Rocha 2019**			
1	Wilson 2008	High risk (other)	N=12	P: T2DM, taking hypoglycemic agents but not insulin I: Cranberry (specie N/A) 45.7 mg of phenolics - normal calorie cranberry juice (240 mL), low calorie cranberry juice (240 mL) C: Normal calorie control (240 mL), low calorie control (240 mL) O: Postprandial glucose, postprandial insulin S: ?
2	Wilson 2010	High risk (other)	N=13	P: T2DM, taking hypoglycemic agents but not insulin I: Cranberry (specie N/A) - raw cranberry (55 g), sweetened dried cranberry (40 g, 131 mg of phenolics), sweetened dried with less sugar cranberry (40 g, 163 mg of phenolics) C: White bread (57 g) O: Glucose AUC, insulin AUC S: ?
3	Hoggard 2013	Unclear risk (randomisation, allocation, blinding, incomplete outcome data, other)	N=8	P: T2DM, taking hypoglycemic agents but not insulin, males only I: Blueberry (Vaccinium myrtillus L) - hydro alcoholic extract of blueberry; 0.47 mg/capsule; 1 capsule/day (169 mg of anthocyanins) C: Placebo (capsule - microcrystalline cellulose) O: Glucose AUC, insulin AUC S: ?
4	Lee 2008	Unclear risk (randomisation, allocation, blinding, selective reporting, other)	N=30	P: T2DM, taking hypoglycemic agents but not insulin I: Cranberry (specie N/A) - Cranberry extract powder; 500 mg/ capsule; 3 capsules/day C: Placebo O: Fasting glucose, HbA1c, Insulin, HOMA-IR S: ?
5	Shidfar 2012	Unclear risk (randomisation, allocation, blinding, incomplete outcome data,	N=58	P: T2DM, taking hypoglycemic agents but not insulin, males only I: Cranberry (specie N/A) - cranberry juice (240 mL) C: Placebo (mineral water with strawberry flavour) 240 mL O: Fasting glucose
6	Kianbakht 2013	High risk (blinding)	N=74	P: T2DM, taking hypoglycemic agents but not insulin I: Blueberry (Vacinium arctostaphylos L) - hydro alcoholic extract of blueberry; 350 mg/ capsule; 3 capsules/day (9.1 mg of anthocyanins) C: Placebo (capsule - toast powder) O: Fasting glucose

Characteristics of included reviews	Diabetes			
Review ID	**Rocha 2019**			
7	Mirfeizi 2016	High risk (selective reporting)	N=102	P: T2DM, taking hypoglycemic agents but not insulin I: Blueberry (Vacinium arctostaphylos L) - blueberry powder 500 mg/capsule, 2 capsules/day (9.8 mg of anthocyanins); Cinnamon 500 mg/capsule, 2 capsules/day C: Placebo (starch), 500mg capsule, 2 capsules/day
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Characteristics of included reviews	Diabetes
Review ID	**Rocha 2019**
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= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Diabetes	
Review ID	**Shabani 2019**	
Review reference	Shabani E, Sayemiri K, Mohammadpour M. The effect of garlic on lipid profile and glucose parameters in diabetic patients: A systematic review and meta-analysis. Prim Care Diabetes. 2019 Feb;13(1):28-42. doi: 10.1016/j.pcd.2018.07.007.	
Review objective	To investigate the effect of garlic on lipid parameters and serum glucose levels in diabetic patients	
Author affiliations	All authors were affiliated with tertiary institutions in Iran	
Source of funds	Not specified	
Declared interests of the review authors	The authors state that they have no conflict of interest	
Review method of analysis	Meta-analysis	The studies' distribution was conducted on the basis of the weighted average. Random-effects model meta-analysis to combine results. I2 index, Cochran test for estimating heterogeneity. STATA software.
Inclusion criteria		
Study design	Not specified	
Population	Patients with dyslipidemia with TC > 200 mg/dl; LDL > 130 mg/dl; HDL < 40 mg/dl and TG > 150 mg/dl and diabetic patients with fasting blood glucose >126 mg/dl; 2 h post prandial glucose (2HPP) > 200 mg/dl; not being in special groups	
Intervention	Garlic	
Comparator	Placebo	
Other	Availability the full text article in English and Persian; sufficient sample size; and the result of studies based on mean ± standard deviation (SD)	
Exclusion criteria		
Study design	Non-clinical trials	
Population	Healthy people; smokers; pregnancies at risk of eclampsia and pre-eclampsia; people with gastrointestinal disorders	
Intervention	Compound products (garlic + drug)	
Comparator	Not specified	
Other	Not specified	
Date of documented search (month/year)	Published from 1988 to end of 2016	
Databases searched	SID medical information databases, Mag Iran, Iran doc, Med lib, Iran Med ex, Science Direct, Scopus, Google and Pub Med. References used in all the articles that were found during the search were evaluated for additional sources.	
Was an non-English database searched?	Yes	Mag Iran, Iran doc, Med lib, Iran Med ex

Characteristics of included reviews	Diabetes
Review ID	**Shabani 2019**
Were studies in a LOTE included?	Not specified — Persian and English-language articles included in search
Outcomes considered in the SR (list)	TC, HDL, TG, LDL, HBA1C, FBS serum
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: None reported — *Authors summary*: No information on RoB assessment was provided in the report.
Authors conclusions (key message)	Garlic reduces lipid profile and blood glucose. Although, there are certain benefits in the use of standard medications for diabetes and increasing serum lipids, the side effects of these drugs are their limitation usage in some diabetic patients. Therefore, garlic consumption may be a safe and effective method for patients with mild increases in serum lipid profile and glucose and cannot tolerate chemical drugs.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	33 studies were included in the SR. None met our PICO as the studies included patients with dyslipidaemia or diabetes but these were not differentiated in the description of included studies. Total N=0 in eligible studies *Study ID* — *Summary RoB* — *Study design features (PICOS)*

Characteristics of included reviews	Diabetes
Review ID	**Shabani 2019**
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Characteristics of included reviews	Diabetes
Review ID	Shabani 2019
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Characteristics of included reviews	Diabetes
Review ID	**Shabani 2019**
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= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Diabetes
Review ID	**Ziaei 2019**
Review reference	Ziaei R, Foshati S, Hadi A, Kermani MAH, Ghavami A, Clark CCT, Tarrahi MJ. The effect of nettle (Urtica dioica) supplementation on the glycemic control of patients with type 2 diabetes mellitus: A systematic review and meta-analysis. Phytother Res. 2020 Feb;34(2):282-294. doi: 10.1002/ptr.6535.
Review objective	To evaluate the efficacy of nettle supplementation on markers of glycemic status in adults with T2DM
Author affiliations	Six authors affiliated with tertiary institutions (five with Isfahan University of Medical Sciences in Iran and one with Coventry University UK); one author affiliated with a research institute in Iran
Source of funds	This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Declared interests of the review authors	The authors declare no conflict of interest
Review method of analysis	Meta-analysis — All meta-analyses performed in STATA 12 using random effects model. Effect size expressed as WMD and SD. Heterogeneity examined by I2 index.
Inclusion criteria	
Study design	RCT (parallel or cross-over design)
Population	Adults aged 18 years and older with T2DM
Intervention	Nettle supplementation
Comparator	Placebo
Other	Fasting blood sugar (FBS) concentrations, insulin levels, homeostasis model assessmentestimated insulin resistance index (HOMA-IR), and glycosylated hemoglobin percentage
Exclusion criteria	
Study design	Not specified
Population	Not specified
Intervention	Supplemented nettle in combination with any other drugs, minerals, or botanicals (unless a separate arm controlled the effect of the mixed substance);
Comparator	Not specified
Other	Trials with follow-up duration less than 4 weeks; studies without sufficient data
Date of documented search (month/year)	Inception to June 2019, no publication date restrictions
Databases searched	PubMed, Scopus, ISI Web of Science, and Cochrane library. Complemented by hand searches of reference lists of eligible articles.
Was an non-English database searched?	No

Characteristics of included reviews	Diabetes
Review ID	**Ziaei 2019**
Were studies in a LOTE included?	Not specified — No language restrictions in search
Outcomes considered in the SR (list)	FBS, glycosylated hemoglobin, insulin level, HOMA-IR index
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane risk of bias tool *Authors summary*: Among eight studies included in the systematic review, five were categorized as good quality, one was fair quality, and two were low quality
Authors conclusions (key message)	The findings tentatively support the use of nettle as an antidiabetic plant and suggest that nettle supplementation can be effective in controlling FBS in T2DM patients. Nevertheless, its holistic efficacy remains questionable, and further, larger, and longer duration trials are needed for clarification.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	8 out of 8 studies included in the SR met our PICO Total N=401 in eligible studies *Study ID* — *Summary RoB* — *Study design features (PICOS)*

First author (publication year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Kianbakht (2013)	L	L	L	L	L	U	U
Korani (2016)	L	L	L	L	L	U	U
Dabagh (2015)	L	L	H	H	U	U	U
Ghalavand (2017)	U	U	H	H	H	U	U
Dadvar (2017)	L	L	H	H	L	L	U
Tarighat (2011)	L	L	L	L	L	U	U
Mehrizi (2015)	L	L	L	L	L	U	U
Hassani (2015)	U	U	H	H	H	U	U

Abbreviations: H, high risk of bias; L, low risk of bias; U, unclear risk of bias.

Characteristics of included reviews	Diabetes			
Review ID	**Ziaei 2019**			
1	Ghalavand (a) 2017	Unclear risk (selective reporting, other)	N=20 (10/10)	P: T2DM, males I: Nettle 10 g/day C: Placebo O: FBS S: Iran
2	Ghalavand (b) 2017	Unclear risk (selective reporting, other)	N=20 (10/10)	P: T2DM, males I: Nettle 10 g/day C: Placebo O: FBS S: Iran
3	Dadvar (a) 2017	High risk (blinding)	N=20 (10/10)	P: T2DM, females I: Nettle 10 g/day C: Placebo O: FBS S: Iran
4	Dadvar (b) 2017	High risk (blinding)	N=20 (10/10)	P: T2DM, females I: Nettle 10 g/day C: Placebo O: FBS S: Iran
5	Korani 2016	Unclear risk (selective reporting, other)	N=44 (22/22)	P: T2DM I: Nettle 20 mg/kg/day C: Placebo O: FBS, HbA1c, insulin S: Iran
6	Dabagh (a) 2015	High risk (blinding)	N=20 (10/10)	P: T2DM, males I: Nettle 10 g/day C: Placebo O: FBS S: Iran

Characteristics of included reviews	Diabetes			
Review ID	**Ziaei 2019**			
7	Dabagh (b) 2015	High risk (blinding)	N=20 (10/10)	P: T2DM, males I: Nettle 10 g/day C: Placebo O: FBS S: Iran
8	Hassani (a) 2015	High risk (blinding, incomplete outcome data)	N=20 (13/7)	P: T2DM, females I: Nettle 6 mL/kg/day C: Placebo O: HOMA-IR S: Iran
9	Hassani (b) 2015	High risk (blinding, incomplete outcome data)	N=26 (13/13)	P: T2DM, females I: Nettle 6 mL/kg/day C: Placebo O: HOMA-IR S: Iran
10	Mehrizi 2015	Unclear risk (selective reporting, other)	N=49 (25/24)	P: T2DM I: Nettle 100 mg/kg/day C: Placebo O: HOMA-IR, insulin S: Iran
11	Kianbakht 2013	Unclear risk (selective reporting, other)	N=92 (46/46)	P: T2DM I: Nettle 1.5 g/day C: Placebo O: FBS, HbA1c S: Iran
12	Tarighat 2011	Unclear risk (selective reporting, other)	N=50 (25/25)	P: T2DM I: Nettle 100 mg/kg/day C: Placebo O: FBS, HbA1c, HOMA-IR, insulin S: Iran
13	--			
14	--			
15	--			

Characteristics of included reviews	Diabetes
Review ID	**Ziaei 2019**
16	--
17	--
18	--

= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Diabetes
Review ID	**Zhu 2018**
Review reference	Zhu J, Chen H, Song Z, Wang X, Sun Z. Effects of Ginger (Zingiber officinale Roscoe) on Type 2 Diabetes Mellitus and Components of the Metabolic Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Evid Based Complement Alternat Med. 2018 Jan 9;2018:5692962. doi: 10.1155/2018/5692962.
Review objective	To summarise the convincing evidence of current studies to clarify the efficacy of ginger on T2DM and components of MetS.
Author affiliations	Four authors affiliated with Nanjing University of Chinese Medicine and one author with Henan Provincial People's Hospital in China
Source of funds	Not specified
Declared interests of the review authors	The authors declare that they have no conflicts of interest
Review method of analysis	Meta-analysis: RevMan 5.3.5 used. Fixed-effect model was used when there was no statistical heterogeneity; otherwise, a random-effect model was applied. Heterogeneity assessed using degree of freedom P value and I2 test statistic. Meta-analysis was performed when data of outcomes of interest were available from at least two studies. WMD and CI calculated for continuous variables.
Inclusion criteria	
Study design	RCT
Population	Subjects with T2DM and/or at least one of components of MetS according to the International Diabetes Federation standards
Intervention	Ginger alone
Comparator	Placebo
Other	Not specified
Exclusion criteria	
Study design	Not specified
Population	Non-standardized diagnosis
Intervention	Not specified
Comparator	Control group being treated with other methods besides the placebo
Other	Editorials, case reports, and correspondences
Date of documented search (month/year)	Inception to May 19, 2017
Databases searched	PubMed, Embase, the Cochrane Library, Chinese Biomedical Database (CBM), ChinaNational Knowledge Infrastructure (CNKI), and Wanfang Database. Supplemented with potentially eligible articles by browsing the literature in the reference lists and manual search was conducted through relevant journals in the field of diabetes and MetS
Was an non-English database searched?	Yes: Chinese Biomedical Database (CBM), ChinaNational Knowledge Infrastructure (CNKI), and Wanfang Database

Characteristics of included reviews	Diabetes
Review ID *Were studies in a LOTE included?*	**Zhu 2018** Not specified
Outcomes considered in the SR (list)	Serum triglyceride (TG), serum total cholesterol (TC), high density lipoprotein-cholesterol (HDL-c), low density lipoprotein-cholesterol (LDL-c), fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), homeostasis model assessment-insulin resistance index (HOMA-IR), and body mass index (BMI)
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane Collaboration RoB tool *Authors summary*: Although the included studies were carried out with RCTs, the method of randomization was declared only in four studies, and allocation concealment in five studies. In addition, seven articles were at high risk in terms of selective reporting because of multiple reports from the same study with different outcomes of interest and incomplete data of outcomes.
Authors conclusions (key message)	The systematic review and meta-analysis provide convincing evidence for the effects of ginger on glucose control, insulin sensitivity, and improvement of blood lipid profile. Based on the positive effects and negligible side effects, ginger may be a promising adjuvant therapy for T2DM and MetS.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	5 out of 10 studies included in the SR met our PICO. The remaining 5 studies were conducted in patients with hyperlipidaemia, obesity or CAPD. Total N= in eligible studies *Study ID* *Summary RoB* *Study design features (PICOS)*

eTable 2 - Cochrane risk of bias assessment of the studies included in the systematic review.

First author (y)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Alizadeh-Navaei 2008	Unclear	Unclear	Low	Low	Unclear	Unclear	Unclear
Andallu 2003	High	High	High	High	Unclear	High	Unclear
Arablou 2014	Unclear	Unclear	Low	Low	Low	Unclear	Unclear
Mahluji 2013	Unclear	Low	Low	Low	Low	Unclear	Low
Mozaffari-Khosravi 2014	Low	Low	Low	Low	Low	Low	Unclear
Shidfar 2015	Low	Low	Low	Low	Unclear	Unclear	Unclear
Atashak 2011	Unclear	Unclear	Low	Low	Unclear	High	Unclear
Attari 2015	Low	Low	Low	Low	Low	High	Unclear
Attari 2016	Low	Low	Low	Low	Low	High	Unclear
Karimi 2015	Unclear	High	High	High	Unclear	High	Unclear
Imani 2015	Unclear	Unclear	Unclear	Unclear	Low	High	Unclear
Tabibi 2016	Unclear	Unclear	Unclear	Unclear	Low	High	Unclear

Characteristics of included reviews	Diabetes			
Review ID	**Zhu 2018**			
1	Andallu 2003	High risk (randomisation, allocation, blinding, selective reporting)	N=16 (8/8)	P: T2DM I: Ginger capsule (3 g/d) C: Not reported O: FBG, TG, TC, LDL-C, HCL-C S: India
2	Arablou 2014	Unclear risk (randomisation, allocation, selective reporting, other)	N=63 (33/30)	P: T2DM I: Ginger capsule (1.6 g/d) C: Wheat flour capsule (1.6 g/d) O: FBG, TG, TC, LDL-C, HDL-C S: Iran
3	Mahluji 2013	Unclear risk (randomisation, , selective reporting)	N=58 (28/30)	P: T2DM I: Ginger tablet (2 g/d) C: Corn starch tablet (2 g/d) O: FBG, HbA1c, Insulin, HOMA-IR, TG, TC, LDL-C, HDL-C, BMI S: Iran
4	Mozaffari-Khosravi 2014	Unclear risk (other)	N=81 (40/41)	P: T2DM I: Ginger capsule (3 g/d) C: Cellulose microcrystalline capsule (3 g/d) O: FBG, HbA1c, Insulin, HOMA-IR, TG, TC, LDL-C, HDL-C, BMI S: Iran
5	Shidfar 2015	Unclear risk (incomplete outcome data, selective reporting)	N=45 (22/23)	P: T2DM I: Ginger capsule (3 g/d) C: Lactose capsule (3 g/d) O: FBG, HbA1c, Insulin, HOMA-IR S: Iran
6	--			

Characteristics of included reviews	Diabetes
Review ID	Zhu 2018
7	--
8	--
9	--
10	--
11	--
12	--
13	--
14	--
15	--

Characteristics of included reviews	Diabetes
Review ID	**Zhu 2018**
16	--
17	--
18	--

= data extracted
= data extracted from more recent SR (or better SR)
= control is an active intervention

Characteristics of included reviews	Fatigue	
Review ID	**Bach 2016**	
Review reference	Bach HV, Kim J, Myung S-K, Cho YA. Efficacy of Ginseng Supplements on Fatigue and Physical Performance: a Meta-analysis. J Korean Med Sci. 2016;31(12):1879-86.	
Review objective	To investigate the efficacy of ginseng supplements on fatigue relief and physical performance enhancement by using a meta-analysis of RCTs.	
Author affiliations	Research centres in Korea.	
Source of funds	National Cancer Centre of Korea (1510040)	
Declared interests of the review authors	Authors report no conflict of interest	
Review method of analysis	Meta-analysis	Analysis was conducted with Stata SE software as per Cochrane guidance. The standardized mean difference (SMD) for the fatigue symptom scale scores was used for the summary effect estimates. When substantial heterogeneity was observed, the SMD based on the random-effects model was reported
Inclusion criteria		
Study design	RCTs	
Population	Individuals with fatigue	
Intervention	Ginseng	
Comparator	Placebo	
Other	None provided	
Exclusion criteria		
Study design	None provided	
Population	None provided	
Intervention	None provided	
Comparator	None provided	
Other	None provided	
Date of documented search (month/year)	Oct-15	
Databases searched	PubMed, EMBASE, and Cochrane Library	
Was an non-English database searched?	No	No non-english data bases
Were studies in a LOTE included?	No	No language restrictions were implemented
Outcomes considered in the SR (list)	Fatigue & physical performance	
Risk of bias measurement as reported in the SR	*Tool used*	*Authors summary*

Characteristics of included reviews	Fatigue			
Review ID	**Bach 2016**			
	Jadad scale	Overall, all 12 studies scored between 3-5 on the Jadad Scale implying low risk of bias, (one study score 3, six studies scored 4, five studies scored 5)		
Authors conclusions (key message)	Author's conclude there is insufficient clinical evidence to support the use of ginseng supplements for reducing fatigue and enhancing physical perfomance, due to the small sample sizes and limited RCTs			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	12 RCTs involving 630 participants included in the analysis. 2 of these RCTs met out PICO. Other RCTs were in healthy participants. Total N=140 in eligible RCTs			
	Study ID	*Summary RoB*	*Study design features (PICOS)*	
1	Kim 2013	Jadad 4/5 - Low risk Concerns regarding "*using identical placebo* ". Not clear what this means?	N=88	P: Chronic fatigue I: Panax ginseng 1000-2000 mg/day C: Placebo O: Fatigue S: Community, Korea
2	Etemadifar 2013	Jadad 5/5 - Low risk	N=52 females	P: multiple sclerosis I: Panax ginseng 500 mg/day C: Placebo O: Fatigue S: Community, Iran
3	--			
4	--			
5	--			

= data extracted
= data extracted in more recent SR
= control is an active intervention (data not extracted)

Characteristics of included reviews	Fatigue	
Review ID	**Jin 2020**	
Review reference	Jin TY, Rong PQ, Liang HY, Zhang PP, Zheng GQ, Lin Y. Clinical and Preclinical Systematic Review of Panax ginseng C. A. Mey and Its Compounds for Fatigue. Front Pharmacol. 2020;11:1031. 10.3389/fphar.2020.01031	
Review objective	To investigate the efficacy and safety of panax ginseng for fatigue in both RCTs and preclinical animal studies	
Author affiliations	Yuying Children's Hospital of Wenzhou Medical University	
Source of funds	grant from the National Natural Science Foundation of China (81973657/H2902);	
Declared interests of the review authors	None declared	
Review method of analysis	meta-analysis	Analysis was conducted with RevMan 5.3 and Stata SE software as per Cochrane guidance.
Inclusion criteria		
Study design	RCTs	
Population	Chronic fatigue or healthy addults after exercise	
Intervention	Panax ginseng as monotherapy	
Comparator	Placebo	
Other	Animal studies also eligible (not described or considered in this review)	
Exclusion criteria		
Study design	Nonrandomised studies	
Population	fatigue caused by amedical condition, or withdrawal frommedicines or substance	
Intervention	None described	
Comparator	None described	
Other	Studies with no available data	
Date of documented search (month/year)	inception to August 2019	
Databases searched	EMBASE, PubMed, Cochrane Library, China National Knowledge Infrastructure (CNKI), VIP database (VIP), China Biology Medicine Database (CBM) and Wangfang database	
Was an non-English database searched?	Yes	
Were studies in a LOTE included?	Yes	Chinese
Outcomes considered in the SR (list)	scales of fatigue and/or objective evaluation criteria (e.g. physical performance, biochemical parameters). The secondary outcome measures were clinical effect according to fatigue scales and adverse events.	
Risk of bias measurement as reported in the SR	*Tool used*	*Authors summary*

Characteristics of included reviews	Fatigue
Review ID	**Jin 2020**
	Cochrane tool: All included studies reported the method of random sequences generation, the criteria of a double-blind study design, and taking the complete outcome data into account. Some studies at unclear risk for allocation concealment, blinding during outcome assessment, and protocol not avialable to assessment reporting bias.
Authors conclusions (key message)	The present findings supported, to a certain degree, that Panax ginseng can be recommended for routine use in fatigue.
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	8 RCTs identified. 5 met our PICO criteria. 3 studies (Engels 1996, 2001, 2003) are not eligible for inclusion is they were conducted in healthy participants (fatigue after exercise) Total N=635 in eligible RCTs

TABLE 5 | The methodological quality of included randomized control trials.

included studies	A	B	C	D	E	F	G	Total score
Engels et al., 1996	+	?	+	?	+	?	+	4+
Engels et al., 2001	+	?	+	?	+	?	+	4+
Engels et al., 2003	+	?	+	?	+	?	+	4+
Hartz et al., 2004	+	+	+	+	+	?	+	6+
Hyeong-Geug et al., 2013	+	+	+	?	+	+	+	6+
Kim et al., 2016	+	?	+	?	+	+	+	5+
Lee et al., 2016	+	+	+	+	+	+	+	7+
Gal et al., 1996	+	?	+	?	+	?	+	4+

A, random sequence generation; B, allocation concealment; C, blinding of participants and personnel; D, blinding of outcome assessment; E, incomplete outcome data; F, selective reporting; G, other sources of bias.

	Study ID	*Summary RoB*	*Study design features (PICOS)*
1	Kim 2016	Unclear risk	N=149 (72/77) 50 mg 2x daily, 4 weeks P: Chronic fatigue I: Panax ginseng C: Placebo O: Checklist individual strength, liver enzymes, oxidative stress biomarkers S: not reported
2	Lee 2016	Low risk	N=52 (26/26) 500 mg 2x daily, 4 weeks P: Chronic fatigue I: Panax ginseng C: Placebo O: Fatigue (VAS, Piper), SF-36 S: not reported
3	Hyeong-Geug 2013	Unclear risk	N=120 (90/30) 1 or 2g 4x daily, 4 weeks P: Chronic fatigue I: Panax ginseng C: Placebo O: Fatigue, oxidative stress biomarkers S: not specified
4	Hartz 2004	Unclear risk	N=96 (36/40) 800 mg 2x daily, 2 months P: Chronic fatigue I: Panax ginseng C: Placebo O: Fatigue, Vitality, MASQ, Fatigue duration, AEs S: not specified
5	Le Gal 1996	Unclear risk	N= 218 (109/109) Phamaton 1 capsule 2x daily. 6 weeks P: Chronic fatigue I: Panax ginseng C: Placebo O: Fatigue, Adverse event S: Not specified

= data extracted
= data extracted in more recent SR
= control is an active intervention (data not extracted)

Characteristics of included reviews	Fatigue	
Review ID	**Kim 2020**	
Review reference	Kim T-H, Kim D-H, Kang JW. Medicinal herbs for managing fatigue symptoms in patients with idiopathic chronic fatigue: A PRISMA compliant updated systematic review and meta-analysis of randomized controlled trials based on the GRADE approach. European Journal of Integrative Medicine. 2020;35:101069.	
Review objective	Review evidence for the efficacy of herbal medicines in patients with idiopathic chronic fatigue	
Author affiliations	Research centres and universities in South Korea	
Source of funds	None reported	
Declared interests of the review authors	One author is an associate editor for the European Journal of Integrative Medicine	
Review method of analysis	Meta-analysis	Pairwise direct comparisons were made between each herbal medicine and its active, placebo, or wait-list control. The standardized mean difference (SMD) for the fatigue symptom scale scores was used for the summary effect estimates.
Inclusion criteria		
Study design	RCT	
Population	Individuals with idiopathic chronic fatigue	
Intervention	Herbal medicines	
Comparator	Placebo, waitlist, or active conventional drug treatment group	
Other	Studies which included fatigue symptoms or adverse events	
Exclusion criteria		
Study design	Herbal medicine v herbal medicine, not clinical trial, inapproporate control intervention, survey, review article, accupuncture vs herbal medicine	
Population	Known rheumatic disorder, such as rheumatoid arthritis or systemic lupus erythematosus, a cardiovascular disorder such as coronary artery disease or valvular heart disease, a metabolic disease such as a thyroid disorder and pituitary tumor, any type of cancer, infectious disease, a neurologic disorder such as Parkinson's disease, a hematologic condition such as anemia, or psychiatric condition such as depression	
Intervention	None provided	
Comparator	None provided	
Other	Inappropraite outcome, insufficient data available, duplicate citation	
Date of documented search (month/year)	May-19	
Databases searched	PubMed, EMBASE, the Cochrane Library, CNKI, OASIS, and J-STAGE	
Was an non-English database searched?	Yes	CNKI (for Chinese literature), OASIS (for Korean literature), and J-STAGE (for Japanese literature)
Were studies in a LOTE included?	Not specified	
Outcomes considered in the SR (list)	We evaluated fatigue symptoms as the primary outcome that had been assessed using various tools, adverse events	
Risk of bias measurement as reported in the SR	*Tool used*	*Authors summary*

Characteristics of included reviews	Fatigue			
Review ID	**Kim 2020**			
	Cochrane tool	The assessment of overall risk of bias showed that most studies did not have adequate methodological quality. Except for two placebo controlled trials, the studies were at high risk of bias with regard to blinding of participants.		
Authors conclusions (key message)	Herbal medicine might be effective in reducing fatigue symptoms of CFS with a low risk of minor adverse events. However, its efficacy cannot be confirmed because of the methodological limitations of the included studies.			
Characteristics of eligible RCTs meeting the inclusion criteria for this Overview	*Study ID*	*Summary RoB*	*Study design features (PICOS)*	
1	Hartz 2004	Not reported.	N=46	P: Chronic fatigue I: Siberian ginseng (2000 mg) C: Placebo O: Fatigue S: Community, US
2	--			
3	--			
4	--			
5	--			

= data extracted
= data extracted in more recent SR
= control is an active intervention (data not extracted)

Characteristics of included reviews	Acne
Review ID	**Kim 2021**
Review reference	Kim, S., Park, T. H., Kim, W. I., Park, S., Kim, J. H., & Cho, M. K. (2021). The effects of green tea on acne vulgaris: A systematic review and meta-analysis of randomized clinical trials. Phytother Res, 35(1), 374-383. https://doi.org/10.1002/ptr.6809
Review objective	To examine the effects of green tea extract on acne.
Author affiliations	All authors were affiliated with tertiary institutions in South Korea.
Source of funds	The research was funded by Soonchunhyang University Research Fund.
Declared interests of the review authors	The authors declare no conflict of interest
Review method of analysis	Meta-analysis
Inclusion criteria	
Study design	Human clinical studies
Population	Acne
Intervention	Products containing green tea
Comparator	--
Other	--
Exclusion criteria	
Study design	were not original articles (e.g., review, case report, or comments); in vitro & non-human trials
Population	--
Intervention	--
Comparator	--
Other	duplicate publications; were articles without the necessary information; or were not published in English.
Date of documented search (month/year)	1 Aug 2019
Databases searched	PubMed, Embase, and Cochrane Library
Was an non-English database searched?	No
Were studies in a LOTE included?	No
Outcomes considered in the SR (list)	Main outcomes (type of lesion, acne lesion count, adverse events)
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: Cochrane RoB *Authors summary*: All five included studies used randomly generated sequences. Two studies were double-blinded and the other three studies were single-blinded. Two studies (Sharquie et al., 2006; Sharquie et al., 2008) were considered as having low quality, and the remaining three studies have high quality.

TABLE 3 Assessment of risk of bias of five included studies using a revised Cochrane risk of the bias assessment tool

Study	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other bias
Sharquie et al. (2006)	L	U	L	H	U	U
Sharquie et al. (2008)	L	U	L	L	U	U
Yoon et al. (2013)	L	U	L	L	L	L
Lu and Hsu ()	L	L	L	L	L	L
Waranuch et al. (2019)	L	L	L	L	L	L

Note: H, high risk of bias; L, low risk of bias; U, unclear or unrevealed risk of bias.

Authors conclusions (key message)	This meta-analysis demonstrated that GTE, particularly topical GTE application, was effective in reducing total acne lesion counts in both inflammatory and non-inflammatory lesions without causing any serious adverse events than oral intake.
Characteristics of eligible RCTs meeting the inclusion	Of the nine studies included in the SR, 5 RCTs met our PICO N=247

Characteristics of included reviews	Acne		
Review ID	**Kim 2021**		
RCTs meeting the inclusion criteria for this Overview	*Study ID*	*Summary RoB*	*Study design features (PICOS)*
1	Lu 2016	Low risk	N=60 4 weeks, 500 mg, once daily P: moderate-severe acne I: Oral decaffeinated green tea extract C: Placebo (cellulose) O: Non- & Inflammatory lesion count S: Taiwan
2	Sharquie 2008	High risk	N=47 8 weeks P: mild-moderate acne I: 2% tea lotion C: 5% Zinc sulfate solution O: Inflammatory lesion count, treatment response S: Iraq
3	Sharquie 2006	Unclear risk	N=60 2 months, P: mild-moderate acne I: 2% tea lotion C: Placebo O: Inflammatory lesion count, treatment response, patient satisfaction S: Iraq
4	Waranuch 2019	Low risk	N=60 4 weeks, twice daily P: Mild-moderate acne I: Hydrogel (Aloe barbadensis, Garcinia peel, Camellia leaf extract) C: 1% Clindamycin gel O: Leed's score, Non- and Inflammatory lesion count, VAS score S: Thailand
5	Yoon 2013	Low risk	N=37 8 weeks, twice daily P: Acne (not specified) I: 1% & 5% green tea extract solution (Epigallocatechin-3-Gallate) C: Placebo (3% ethanol) O: Leed's score, Non- and Inflammatory lesion count, VAS score S: Sth Korea
	= data extracted		
	= data extracted in more recent SR		
	= control is an active intervention (data not extracted)		

Characteristics of included reviews	Acne
Review ID	**Vaughn 2016**
Review reference	Vaughn, A. R., Branum, A., & Sivamani, R. K. (2016). Effects of Turmeric (Curcuma longa) on Skin Health: A Systematic Review of the Clinical Evidence. Phytother Res, 30(8), 1243-1264. https://doi.org/10.1002/ptr.5640
Review objective	To identify the clinical studies examining the effects of topical and ingested turmeric and curcumin on the skin.
Author affiliations	All authors were affiliated with tertiary institutions in the US (California, Philadelphia)
Source of funds	None specified
Declared interests of the review authors	The authors declare no conflict of interest
Review method of analysis	Descriptive
Inclusion criteria	
Study design	RCT, Clinical or cohort study
Population	Subjects diagnosed with skin condition
Intervention	Turmeric or curcumin
Comparator	--
Other	Published in English
Exclusion criteria	
Study design	in vitro & non-human trials
Population	--
Intervention	--
Comparator	--
Other	--
Date of documented search (month/year)	18 August 2015
Databases searched	PubMed, Embase
Was an non-English database searched?	No
Were studies in a LOTE included?	No
Outcomes considered in the SR (list)	None specified
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: 5-Point Jadad scale *Authors summary*: Summary assessment for individual studies reported. No further details provided.
Authors conclusions (key message)	There is early evidence curcumin products and supplements, both oral and topical, may provie therapeutic benefits in skin conditions. Current studies are limited and furtehr evidence is needed.
Characteristics of eligible RCTs meeting the inclusion	1 RCT met our PICO criteria.

Characteristics of included reviews	Acne		
Review ID	**Vaughn 2016**		
RCTs meeting the inclusion criteria for this Overview	*Study ID*	*Summary RoB*	*Study design features (PICOS)*
1	Lalla 2001	5/5 - Low risk	N=33 4 weeks, dose unknown P: Acne vulgaris I: Oral combination tablet (Curcumin + other*) & Topical gel or cream (Curcumin + other**) C: Placebo O: Improvement in acne lesions (Leed's) 4-point scale S: Not specified
2	--		
3	--		
4	--		
5	--		

*Curcuma longa, Aloe, Azardirachta indica, Hemidesmus indicus, Linn, Terminalia chebula, Terminalia arjuna, Withania somnifera, and Piper longum

**Curcuma longa, Aloe, Azardirachta indica, Hemidesmus indicus, Linn, Terminalia chebula, Terminalia arjuna, Withania somnifera

= data extracted

= data extracted in more recent SR

= control is an active intervention (data not extracted)

Characteristics of included reviews	Acne
Review ID	**Tuong 2015**
Review reference	Tuong W, Walker L, Sivamani RK. Polyphenols as novel treatment options for dermatological diseases: A systematic review of clinical trials. J Dermatolog Treat. 2015;26(4):381-8. 10.3109/09546634.2014.991675
Review objective	To evaluate polyphenol-based therapeutics in treating dermatological diseases
Author affiliations	All authors were affiliated with tertiary institutions in the US (California)
Source of funds	None specified
Declared interests of the review authors	The authors declare no conflict of interest
Review method of analysis	Descriptive
Inclusion criteria	
Study design	Human clinical studies
Population	Subjects diagnosed with skin condition
Intervention	Polyphenol containing products
Comparator	--
Other	Published in English
Exclusion criteria	
Study design	--
Population	--
Intervention	Product contained other phytochemicals
Comparator	--
Other	Inadequately described product type/concentration, less than 10 subjects
Date of documented search (month/year)	4 July 2014
Databases searched	PubMed, Embase
Was an non-English database searched?	No
Were studies in a LOTE included?	No
Outcomes considered in the SR (list)	None specified
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: 5-Point Jadad scale *Authors summary*: Summary assessment for individual studies reported. No further details provided.
Authors conclusions (key message)	Polyphenols may be effective in cerain dermatological conditions. Additional rigorously conducted trials are needed.
Characteristics of eligible RCTs meeting the inclusion	1 RCT met our PICO criteria.

Characteristics of included reviews	Acne		
Review ID	**Tuong 2015**		
RCTs meeting the inclusion criteria for this Overview	*Study ID*	*Summary RoB*	*Study design features (PICOS)*
1	Jung 2012	0/5 - High risk	N=30 8 weeks P: Acne vulgaris I: Green tea extract (20mg/ml, topical, bid) C: None O: Acne lesion count S: Not specified
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5	--		

= data extracted

= data extracted in more recent SR

= control is an active intervention (data not extracted)

Characteristics of included reviews	Acne
Review ID	**Ernst 2002**
Review reference	Ernst E, Pittler MH, Stevinson C. Complementary/alternative medicine in dermatology: evidence-assessed efficacy of two diseases and two treatments. Am J Clin Dermatol. 2002;3(5):341-8. 10.2165/00128071-200203050-00006
Review objective	To evaluate CAM therapies in treating dermatological diseases: focus on two diseases (atopic dermatitis, chronic venous insufficiency)
Author affiliations	All authors were affiliated with tertiary institution in the UK (Exeter)
Source of funds	None specified
Declared interests of the review authors	None specified
Review method of analysis	Descriptive
Inclusion criteria	
Study design	Human clinical studies
Population	Subjects diagnosed with skin condition
Intervention	Any alternative therapy including: herbal medicine, acupuncture, homeopathy, chiropractic, osteopathy, reflexology, aromatherapy
Comparator	--
Other	--
Exclusion criteria	
Study design	--
Population	--
Intervention	--
Comparator	--
Other	--
Date of documented search (month/year)	October 2000
Databases searched	Medline, Embase, Cochrane Library, CISCOM, AMED
Was an non-English database searched?	No
Were studies in a LOTE included?	No
Outcomes considered in the SR (list)	None specified
Risk of bias of the included RCT studies as reported in the SR	*Tool used* *Authors summary* Not assessed
Authors conclusions (key message)	Compelling evidence for CAM therapies is lacking. Some promising data for some therapies, including horse chestnut seed for CVI. Data for aloe vera and tea tree oil is lacking.
Characteristics of eligible RCTs meeting the inclusion	

Characteristics of included reviews	Acne		
Review ID	**Ernst 2002**		
RCTs meeting the inclusion criteria for this Overview	*Study ID*	*Summary RoB*	*Study design features (PICOS)*
1	Fulton 1990	Not assessed	N=17 time to wound healing post dermabrasion P: Acne vulgaris I: Aloe vera (half face) C: Std polyethylene oxide gel (half face) O: Time to re-epithelialization S: Not specified
2	Basset 1990	Not assessed	N=124 3 months, once daily P: moderate acne I: Tea tree oil (5%) C: Benzoyl peroxide lotion (5%) O: Improvement in inflammed lesions S: Not specified
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= data extracted

= data extracted in more recent SR

= control is an active intervention (data not extracted)

Characteristics of included reviews	Acne
Review ID	**Vogler 1999**
Review reference	Vogler BK, Ernst E. Aloe vera: a systematic review of its clinical effectiveness. Br J Gen Pract. 1999;49(447):823-8.
Review objective	To evaluate aloe vera in treating any condition
Author affiliations	Author was affiliated with tertiary institution in the UK (Exeter)
Source of funds	None specified
Declared interests of the review authors	None specified
Review method of analysis	Descriptive
Inclusion criteria	
Study design	Controlled clinical trials
Population	Any clinical condition
Intervention	Any Aloe monotherapy
Comparator	--
Other	--
Exclusion criteria	
Study design	--
Population	--
Intervention	Aloe vera preparations not as monotherapy
Comparator	--
Other	--
Date of documented search (month/year)	May 1998
Databases searched	Medline, Embase, Biosis, Cochrane Library
Was an non-English database searched?	No
Were studies in a LOTE included?	No
Outcomes considered in the SR (list)	None specified
Risk of bias of the included RCT studies as reported in the SR	*Tool used*: 7-Point Jadad scale; *Authors summary*: Summary assessment for individual studies reported. No further details provided.
Authors conclusions (key message)	Data on the dlinical effectiveness of aloe vera is not sufficient at present.
Characteristics of eligible RCTs meeting the inclusion	

Characteristics of included reviews	Acne		
Review ID	**Vogler 1999**		
RCTs meeting the inclusion criteria for this Overview	*Study ID*	*Summary RoB*	*Study design features (PICOS)*
1	Fulton 1990	Not assessed	N=17 time to wound healing post dermabrasion P: Acne vulgaris I: Aloe vera (half face) C: Std polyethylene oxide gel (half face) O: Time to re-epithelialization S: Not specified
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4	--		
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	= data extracted		
	= data extracted in more recent SR		
	= control is an active intervention (data not extracted)		