OVERVIEW OF WESTERN HERBAL MEDICINES FOR PREVENTING AND TREATING HEALTH CONDITIONS

Appendices D to H

prepared by
HTANALYSTS

for
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Report information

Authors

Jorgensen MA[1], Ryder I[1], Rutherford L[1], Antony T[1]

[1] **HT**ANALYSTS, Level 8, 46 Kippax Street, Surry Hills NSW 2010 Australia

Dates

This technical report and accompanying evidence evaluation report received approval from the National Health and Medical Research Council (NHMRC) Natural Therapies Working Committee (NTWC) on 20 November 2023.

The protocol for the evidence evaluation received approval from NHMRC's NTWC on 11 March 2021 (PROSPERO: CRD42021243337).

History

NHMRC has been engaged by the Department of Health and Aged Care (the Department) to update the evidence underpinning the *2015 Review of the Australian Government Rebate on Natural Therapies for Private Health Insurance* (2015 Review) (1). The natural therapies to be reviewed are Alexander technique, aromatherapy, Bowen therapy, Buteyko, Feldenkrais, homeopathy, iridology, kinesiology, naturopathy, Pilates, reflexology, Rolfing, shiatsu, tai chi, western herbal medicine and yoga. These therapies are among those excluded from the private health insurance rebate as of 1 April 2019.

To support NHMRC in their evidence review, Health Technology Analysts (**HT**ANALYSTS) was engaged to conduct an overview of the evidence of clinical effectiveness of Western herbal medicines. Eligible studies received from the Department's public call for evidence, the Natural Therapies Review Expert Advisory Panel (NTREAP) and the Natural Therapies Working Committee (NTWC) were included in the evidence evaluation.

This technical report has been developed by **HT**ANALYSTS in conjunction with NHMRC, NTWC, and NTREAP. It provides the appendices and supplementary data related to an evidence valuation of the effect of Western herbal medicines for preventing and treating health conditions. The main body of evidence is presented in the Evidence Evaluation Report. All associated materials have been developed in a robust and transparent manner in accordance with relevant best practice standards (2-5).

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List of abbreviations

BRISA	Regional Base of Health Technology Assessment Reports of the Americas
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COMET	Core Outcome Measures in Effectiveness Trials
DF	degrees of freedom
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ITT	Intent-to-treat
MCID	minimal clinically important differences
MD	mean difference
MID	minimal important difference NHMRC National Health and Medical Research Council
NRSI	Nonrandomised study of an intervention
NSAID	Nonsteroidal anti-inflammatory drug
NTREAP	Natural Therapies Review Expert Advisory Panel
NTWC	Natural Therapies Working Committee
OR	Odds ratios
PAHO	Pan American Health Organization
PICO	Population, Intervention, Comparator, Outcome
PP	Per protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised controlled trial
RoB	Risk of bias
RoM	Ratio of means
RR	Risk ratios
SD	Standard deviation
SMD	standardised mean difference
SR	Systematic review
TIDIER	Template for Intervention Description and Replication

Appendix D Included studies

This appendix documents the studies that met the prespecified inclusion criteria for an overview of systematic reviews examining the effect of Western herbal medicines for preventing and treating any health condition. It provides an overview of the PICO criteria and quality of included systematic reviews, and results of the data synthesis for the main comparisons.

Details relating to eligibility criteria are provided in Appendix A4-A6 and A8 (list of herbs). Additional details concerning the critical appraisal of each systematic review are provided in Appendix E. Characteristics of the included systematic reviews are provided in Appendix F1. Data for outcomes considered to be critical or important for the overview are provided in Appendix F2.

D1 Digestive disorders

D2 Nervous system

D2.1 Anxiety

D2.1.1 List of reviews

A summary of the PICO criteria of the eligible systematic reviews is provided in Table D-25.

A list of herbs examined in the identified primary studies is provided in Table D-26.

There were 9 systematic reviews (76, 77, 174-180) published in 2018 or later that presented results in a meta-analysis and were prioritised for critical appraisal and data extraction (Ghaderi 2020, Shinjyo 2020, Donelli 2019, Hieu 2019, Marx 2019, Moller 2019, Baric 2018, Ooi 2018, Smith 2018). One other review (Janda 2020) (181) did not perform a meta-analysis but reported individual study data therefore was also prioritised for critical appraisal and data extraction. Review details, including all outcome domains and measures reported by the included reviews, are provided in Appendix F1. Outcome data for critical or important outcomes are provided in Appendix F2.

Seven (7) systematic reviews (182-188) published prior to 2018 also presented results in a meta-analysis but were judged to no longer represent the best available evidence (Brondino 2013, Hidalgo 2007, Miyasaka 2007, Miyasaka 2006, Witte 2005, Pittler 2003, Pittler 2000). These reviews were checked for additional studies and results, with one review (Brondino 2013) included for critical appraisal and data extraction as it included one RCT not identified by the other reviews. In the absence of additional data, the 6 other reviews were not considered further.

Two other reviews (189, 190) reported results of a network meta-analysis (NMA) that included RCTs identified across other reviews (Sayed 2020, Yap 2019). The questions of the NMAs were not aligned with that of this overview (e.g., assessing different forms of an herbal preparation); therefore, the data presented in the NMAs were not considered.

Another 17 systematic reviews (149, 160, 191-205) provided a narrative review of study results but did not adequately report data suitable for inclusion in a meta-analysis (Lopresti 2022, Lopresti 2021, Tandon 2020, Kim 2018, Sarris 2018, Pratte 2014, Miroddi 2013, Sarris 2013, Perry 2012, Sarris 2012, Sarris 2011, Lakhan 2010, Provino 2010, Sarris 2009, Sarris 2007, Ernst 2006, Jorm 2004). These reviews were checked for additional studies and results, but in the absence of data were not considered further. Figure D-18 outlines the selection process of the final included systematic reviews.

Figure D-1 Process flow for prioritising systematic reviews: Anxiety

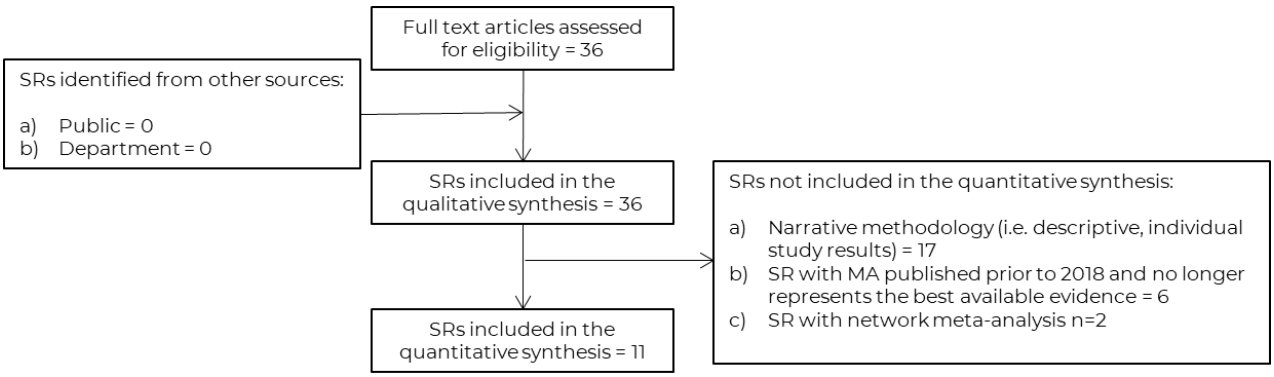


Table D-1 PICO criteria of included systematic reviews: Anxiety

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]	N	Study ID [e]
Ghaderi 2020 (76)	Meta-analysis	Umbrella review (any condition)	Saffron	Placebo OR other intervention	Emotional functioning, C-reactive protein	2 (k=21)	Jafarnia 2017, Mazidi 2016
Janda 2020 (181)	Individual results	Neuropsychiatric disorders	Passionflower	Not specified	Anxiety, sleep quality	1 (k=9)	Akhondzadeh 2001
Shinjyo 2020 (77)	meta-analysis	Umbrella review (any condition)	Valerian root	Placebo OR other intervention	Sleep quality, anxiety and other efficacy measures	60 (k=1)	Andreatini 2002
Donelli 2019 (174)	meta-analysis	Anxiety or symptoms of anxiety #	Lavender (any route of administration) ^	All types of control or comparator	Anxiety	6 (k=65)	Kasper 2016, Kasper 2015, Kasper 2015a, Kasper 2014, Kasper 2010, Woelk 2010
Hieu 2019 (175)	meta-analysis	Anxiety, Insomnia	Chamomile	Placebo	Anxiety, insomnia, sleep quality	2 (k=12)	Mao 2016, Amsterdam 2009
Marx 2019 (176)	meta-analysis	Symptoms of depression and anxiety	Saffron	Placebo OR pharmacotherapy	Anxiety, depression	3 (k=23)	Lopresti 2018, Jafarnia 2017, Mazidi 2016
Moller 2019 (177)	meta-analysis	Subthreshold anxiety (HAM-A ≥ 18 points)	Lavender (oral)	Placebo	Anxiety, Depression, Sleep quality, HRQoL	3 (k=3)	Kasper 2016, Kasper 2015, Kasper 2010
Baric 2018 (178)	meta-analysis	Generalised anxiety disorder or subthreshold anxiety	Complementary and alternative medicines (incl. kava, lavender, chamomile, passionflower, valerian)	Placebo, inactive control (no treatment) OR conventional treatments	Anxiety	11 (k=32)	Mao 2016, Kasper 2014, Sarris 2013, Woelk 2010, Amsterdam 2009, Boerner 2003, Andreatini 2002, Connor 2002, Akhondzadeh 2001, Malsch 2001, Volz 1997
Ooi 2018 (179)	meta-analysis	Generalised anxiety disorder	Kava	Placebo	Anxiety	5 (k=12)	Savage 2015†, Sarris 2013, Connor 2006, Boerner 2003, Connor 2002
Smith 2018 (180)	meta-analysis	Anxiety	Kava	Placebo OR active comparator	Anxiety	7 (k=11)	Sarris 2013, Sarris 2009, Geier 2004, Lehrl 2004, Gastpar 2003, Connor 2002, Malsch 2001
Sayed 2020 (189)	Network meta-analysis**	Anxiety	Lavender (any route of administration) ^	Placebo OR no intervention OR other combinations	Anxiety	6 (k=40)	Kasper 2017, Kasper 2016, Kasper 2015, Kasper 2014, Kasper 2010, Woelk 2010
Yap 2019 (190)	Network meta-analysis**	Anxiety	Lavender (oral)	Placebo OR active comparator	Anxiety	5 (k=5)	Kasper 2016, Kasper 2015, Kasper 2014, Kasper 2010 Woelk 2010

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]	N	Study ID [e]
Brondino 2013 (182)	meta-analysis	Neuropsychiatric disorders*	Ginkgo biloba	Not specified	Specified efficacy measures (anxiety: HAM-A or STAI)	1 (k=11)	Woelk 2007
Hidalgo 2007 (183)	meta-analysis	Generalised anxiety disorder	Any (incl. complementary and alternative medicines)	Placebo	Anxiety (HAM-A)	1 (k=21)	Connor 2002
Miyasaka 2007 (184)	meta-analysis (Cochrane)	Anxiety disorders	Passionflower	Placebo, no intervention, psychotherapy or other	Anxiety, Side effects	1 (k=2)	Akhondzadeh 2001
Miyasaka 2006 (185)	meta-analysis (Cochrane)	Anxiety disorders	Valerian	Placebo, no intervention, psychotherapy	Anxiety, Side effects	1 (k=1)	Andreatini 2002
Witte 2005 (186)	meta-analysis	Non-psychotic anxiety disorders	Kava	Placebo	Anxiety	6 (k=6)	Geier 2004, Lehrl 2004, Malsch 2001, Volz 1997, Kinzler 1991, Warnecke 1991
Pittler 2003 (187)	meta-analysis (Cochrane)	Anxiety	Kava	Placebo	Anxiety	12 (k=12)	Geier 2004, Lehrl 2004, Gastpar 2003, Malsch 2001, Connor 2002, Kinzler 1991, Bhate 1989, Lehmann 1998, Singh 1998, Volz 1997, Warnecke 1991, Warnecke 1990
Pittler 2000 (188)	meta-analysis	Anxiety	Kava	Placebo	Any efficacy or safety outcome	--	--
Lopresti 2022 (191)	descriptive	Umbrella review (any condition)	Any single herb, spice, plant or extract	Not specified	stress response biomarkers	--	--
Lopresti 2021 (192)	descriptive	Umbrella review (any condition)	Withania [ashwagandha]	Not specified	Stress, anxiety, insomnia, athletic performance, cognitive function, and other	4 (k=41)	Lopresti 2019, Kyati 2013, Auddy 2008, Andrade 2000
Tandon 2020 (193)	descriptive	Umbrella review (any condition)	Withania [ashwagandha]	Any	Any efficacy or safety outcome	--	--
Kim 2018 (149)	descriptive	Umbrella review (any condition)	Plant extracts administered orally	Not specified	Anxiety, sleep quality	4 (k=46)	Kasper 2015, Kasper 2010, Jacobs 2005‡, Lehrl 2004

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]	N	Study ID [e]
Sarris 2018 (194) (update of Sarris 2007)	descriptive	Psychiatric disorders	Herbal medicines (oral)	Not specified	Any efficacy or safety outcome	8 (k=NR)	Keefe/Mao 2016, Cropley 2015, Amsterdam 2009, Sarris 2013, Sarris 2009, Woelk 2007, Boerner 2003, Akhondzadeh 2001
Pratte 2014 (195)	descriptive	Anxiety	Withania [ashwagandha]	Not specified	Stress/anxiety	3 (k=5)	Khyati 2014, Auddy 2008, Andrade 2000
Miroddi 2013 (160)	descriptive	Umbrella review (any condition)	Passionflower	Not specified	Any efficacy or safety outcome	--	--
Sarris 2013 (196)	descriptive	Anxiety, OCD, phobias	Plant-based medicine	Not specified	Anxiolytic activity (stress biomarkers)	0 (k=21)	--
Perry 2012 (197)	descriptive	Umbrella review (any condition)	Lavender	Not specified	Stress/anxiety	2 (k=15)	Kasper 2010, Woelk 2010
Sarris 2012 (198)	descriptive	Anxiety disorders	CAM including meditation, diet, exercise and lifestyle modification	Not specified	Anxiety	4 (k=NR)	Amsterdam 2009, Woelk 2007, Akhondzadeh 2001, Volz 1997
Sarris 2011 (199)	descriptive	Generalised anxiety disorder, neurocognition	Kava	Not specified	Any efficacy or safety outcome	--	--
Lakhan 2010 (200)	descriptive	Anxiety related disorders	Nutritional and herbal supplements	Not specified	Anxiety	7 (k=24)	Sarris 2009, Boerner 2003, Gastpar 2003, Connor 2002, Akhondzadeh 2001, Malsch 2001, Volz 1997
Provino 2010 (201)	descriptive	Stress conditions	Adaptogenic herbs	Not specified	Not specified	--	--
Sarris 2009 (202)	descriptive	Mood and anxiety disorders	Kava, St John's wort	Not specified	Any efficacy or safety outcome (anxiety, depression)	--	--
Sarris 2007 (203)	descriptive	Psychiatric disorders	Herbal medicines (oral)	Not specified	Any efficacy and safety outcome	--	--
Ernst 2006 (204)	descriptive	Anxiety	Herbal preparations (oral)	Not specified	Anxiety	--	--
Jorm 2004 (205)	descriptive	Anxiety disorders	Complementary and self-help treatments	Not specified	Anxiety	--	--

Abbreviations: ADHD, attention deficit hyperactivity disorder; CAM, complementary and alternative medicine; GAD, generalised anxiety disorder; HAM-A, NR, not reported

Notes:
N = Number of RCTs meeting our PICO criteria; k = total number of RCTs identified by systematic review.
# Specifically, patients with anxiety, involved in an anxiety-inducing setting or undergoing an anxiety-inducing activity
* including dementia, autism, schizophrenia, depression, anxiety, GAD, ADHD, addiction
^ Studies assessing lavender as aromatherapy not included in this Overview.
† Protocol only.
‡ Mixed population; RCT is included in the assessment for insomnia
a. Systematic review with no population restrictions were eligible for inclusion if they presented data that evaluated participants with anxiety.
b. Systematic reviews were eligible for inclusion if they presented data that examined the effectiveness of eligible WHMs (see Appendix A8).
c. Systematic review with no comparator restrictions were eligible for inclusion if they presented data that compared WHM with control (placebo or no intervention) or another intervention.
d. Outcomes assessed or listed by the systematic review. Grey highlight = nonpriority outcome; Blue highlight = critical or important outcome data extracted
e. Study ID of eligible RCTs that met the PICO criteria of this overview.
-- Systematic review not assessed. The outcome domain was not critical or important for this overview OR a more recent SR nominated as best available is included.

Figure D-2 Critical appraisal summary: review author's judgements about each AMSTAR-2 item for each included systematic review – Anxiety

	Review ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
ANXIETY	Ghaderi 2020	Y	PY	Y	PY	Y	N	N	PY	Y	N	Y	Y	Y	Y	Y	Y
	Janda 2020	Y	PY	Y	PY	Y	Y	N	PY	Y	Y	No meta-analysis	No meta-analysis	Y	N	No meta-analysis	Y
	Shinjyo 2020	Y	PY	Y	PY	N	N	N	Y	PY	N	Y	Y	Y	Y	Y	Y
	Donelli 2019	Y	Y	Y	PY	Y	Y	N	PY	Y	Y	Y	Y	Y	Y	Y	Y
	Hieu 2019	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Marx 2019	Y	Y	Y	PY	Y	Y	N	PY	PY	Y	Y	Y	Y	Y	Y	Y
	Moller 2019	Y	PY	Y	Y	N	N	N	PY	Y	Y	Y	Y	Y	Y	Y	Y
	Baric 2018	Y	PY	Y	Y	Y	Y	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y
	Ooi 2018	Y	PY	Y	PY	Y	N	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y
	Smith 2018	Y	PY	Y	PY	N	N	N	PY	N	Y	Y	N	Y	Y	Y	Y
	Brondino 2013	Y	PY	Y	PY	Y	Y	N	PY	Y	N	Y	Y	Y	Y	Y	Y

N = No; PY = Partial Yes, Y = Yes

Table D-2 List of herbs assessed in the identified primary studies: Anxiety

WHM identified in included studies	Matched to Tier 1 list of WHM: Nervous system disorders [a]
Chamomile (Matricaria recruitica)	X
Ginkgo (Ginkgo biloba)	X
Kava (Piper methysticum)	✓
Lavender (Lavandula officinalis / L. angustifolia)	✓
Passionflower (Passiflora incarnata)	✓
Rhodiola rosea	X
Saffron (Crocus sativus)	X
Valerian (Valeriana officinalis)	✓
Withania somnifera (Ashwagandha)	X

Abbreviations: WHM, Western herbal medicine
✓ = yes; X = no
a. See Appendix A6.3 - Tier 1 herb list was considered in GRADE. Eligibility was based on the herb list in Appendix A8

D2.1.2 Critical appraisal

A summary of the quality of included systematic reviews is provided in Figure D-19 and Table D-27.

The strengths or limitations of the included systematic reviews assessed against each AMSTAR-2 domain is provided in Appendix E1.

Nine (9) of the 11 systematic reviews included in this overview (Ghaderi 2020, Shinjyo 2020, Donelli 2019, Hieu 2019, Marx 2019, Moller 2019, Baric 2018, Ooi 2018, Brondino 2013) were judged to probably provide an accurate and comprehensive summary of the available studies that address the question of interest (i.e. met, or partially met, AMSTAR-2 domains 4, 8, 9 and 11). Two other reviews had one critical flaw as they did not meet domain 9 (Smith 2018, no risk of bias assessment) or domain 11 (Janda 2020, no meta-analysis).

Table D-3 Critical appraisal summary: Anxiety

Review ID	Summary	Notes
Ghaderi 2020	3 non-critical weaknesses in domains 6, 7 & 10	The authors do not perform data extraction in duplicate, do not provide a list of excluded studies read at full text, and they did not report on any funding or support for the RCTs.
Janda 2020	1 critical flaw (domain 11) 2 non-critical weaknesses in domains 7 and 14	No meta-analysis. The authors do not provide a list of excluded studies read at full text, and they did not discuss heterogeneity of the results observed in the review.
Shinjyo 2020	4 non-critical weaknesses in domains 5, 6, 7 & 10	The authors do not perform study selection or data extraction in duplicate, do not provide a list of excluded studies read at full text, and they did not report on any funding or support for the RCTs.
Donelli 2019	1 non-critical weaknesses in domain 7	The authors do not provide a list of excluded studies read at full text,
Hieu 2019	1 non-critical weaknesses in domain 7	The authors do not provide a list of excluded studies read at full text,
Marx 2019	1 non-critical weaknesses in domain 7	The authors do not provide a list of excluded studies read at full text,
Moller 2019	3 non-critical weaknesses in domains 5, 6 & 7	The authors do not perform study selection or data extraction in duplicate, and they did not provide a list of excluded studies read at full text.
Baric 2018	0 non-critical weaknesses	
Ooi 2018	1 non-critical weaknesses in domains	The authors do not perform data extraction in duplicate.
Smith 2018	1 critical flaw (domain 9) 4 non-critical weaknesses in domains 5, 6, 7 & 12	The authors did not assess risk of bias of the included studies. The authors do not perform study selection or data extraction in duplicate, do not provide a list of excluded studies read at full text, and they do not assess the potential impact of RoB in individual studies on the results.

Review ID	Summary	Notes
Brondino 2013	2 non-critical weaknesses in domains 7 & 10	The authors do not provide a list of excluded studies read at full text, and they did not report on any funding or support for the RCTs.

Abbreviations: RCT, randomised controlled trial

D2.1.3 Effects of intervention

Outcomes considered by the NTWC to be critical or important for decision-making in people with anxiety are listed in Table D-28.

Table D-4 Outcomes considered by the NTWC to be critical or important for decision-making: Anxiety

Outcome domain	Measured with	Consensus rating	Data available for comparison 1 or 2	Review ID										
				Ghaderi 2020	Janda 2020	Shinjyo 2020	Donelli 2019	Hieu 2019	Marx 2019	Moller 2019	Baric 2018	Ooi 2018	Smith 2018	Brondino 2013
Anxiety	HAM-A (or other validated measure)	9	Yes	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Depression	HAM-D (or other validated measure)	8	Yes	✓	?	?	?	✓	?	?	?	?	?	?
Global improvement	Clinical Global Impression (or similar)	8	Yes	?	?	?	?	X	?	✓	?	?	?	?
HRQoL	SF-36 (or similar)	7	Yes	?	?	?	?	?	?	✓	?	?	?	?
Physical functioning	SF-36 PCS (or similar)	7	Yes	?	?	?	?	?	?	✓	?	?	?	?
Sleep quality	PSQI	7	Yes		X	X	?	X	?	✓	?	?	?	?
Fatigue	Any validated multi-dimensional measure of fatigue	6	No	?	?	?	?	?	?	?	?	?	?	?

Abbreviations: HAM-A, Hamilton anxiety rating scale; HAM-D, Hamilton depression rating scale; HRQoL, Health-related quality of life; PSQI, Pittsburgh sleep quality index; SF-36, 36-item short form

Notes:

✓ A study result is available for inclusion in the synthesis.

X A study result is NOT available for inclusion because the systematic review does not adequately report the results (data were incomplete). It is unclear if the primary study reported complete data. Due to time and resource constraints, only the information presented in the systematic review is reported.

? The systematic review did not assess this outcome, it is unclear if the outcome was assessed by the primary studies included in the SR. Due to time and resource constraints, only the information presented in the systematic review is reported.

-- The systematic review did not assess this outcome. The outcome was (probably) not assessed by the included primary studies (for reasons unrelated to the *p*-value, magnitude or direction of the results).

Comparison 1 (vs placebo)

Anxiety

There were 25 RCTs (total 2477 participants) that reported symptoms of anxiety, predominantly measured using the Hamilton Anxiety Rating Scale (HAM-A) at the end of treatment (range 3 weeks to 12 weeks).

The HAM-A is a clinician-rated screening tool that consists of 14-items that assess the severity of anxiety symptoms by considering both psychic and somatic anxiety. Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0 to 56. No MCID has been established for the HAM-A, with a score of 7 or less suggesting no/minimal anxiety, a score between 8 and 17 indicating mild anxiety, a score between 18 and 24 being moderate severity, and a score 25 or higher representing severe anxiety (206, 207).

Pooled results from 20 RCTs (total 2087 participants) suggested an effect favouring the WHM group when compared with the placebo group (SMD –0.43; 95% CI –0.59, –0.28; $p < 0.00001$; $I^2 = 61\%$) (*GRADE: Moderate*). (Jafarnia 2017, Kasper 2017, Kasper 2016, Mao 2016, Mazidi 2016, Kasper 2015, Kasper 2014, Sarris 2013, Kasper 2010, Amsterdam 2009, Sarris 2009, Woelk 2007, Geier 2004, Lehrl 2004, Gastpar 2003, Andreatini 2002, Connor 2002, Akhondzadeh 2001, Malsch 2001, Volz 1997). Statistical heterogeneity was unable to be explained by difference in the intervention (see Figure D-20).

Data from 5 RCTs (total 390 participants) were not able to be included in the meta-analysis due to missing information (Lopresti 2019, Lopresti 2018, Khyati 2013, Auddy 2008, Andrade 2000). Of these, 3 RCTs suggested an effect favouring the WHM (Lopresti 2019, Lopresti 2018, Auddy 2008) and 2 RCT suggested there was no difference between the intervention and placebo groups (Khyati 2013, Andrade 2000).

In a sensitivity analysis examining in the impact of 6 RCTs judged to be at high risk of bias (Kasper 2017, Kasper 2016, Kasper 2015, Mao 2016, Amsterdam 2009, Akhondzadeh 2001) the estimate of effect did not materially change (SMD –0.53; 95% CI –0.73, –0.33; $p < 0.00001$; $I^2 = 60\%$).

Similarly, a sensitivity analysis examining the impact of small studies on the estimate of effect (fixed effect, SMD –0.40; 95% CI –0.49, –0.32; < 0.00001; $I^2 = 61\%$) suggest no substantial change. Visual inspection of a funnel plot suggested no asymmetry (see Figure D-21).

Depression

There were 4 RCTs (total 785 participants) reported to assess the impact of WHM on depressive symptoms using the Hamilton Depression Rating Scale or the Beck Depression Inventory (Lopresti 2018, Kasper 2016, Mazidi 2016, Kasper 2014) at the end of treatment (range 8 to 12 weeks). The data for 2 RCTs were not available.

The HAM-D measures the severity of current depressive symptoms and consists of 17 or 21-items relating to symptoms of depression experienced over the past week. Each item on the questionnaire is scored on a 3- or 5-point scale with a total score between 0 and 7 generally accepted to be within the normal range, while a score of 20 or more indicating moderate severity of depression.

Data from 2 RCTs (total 129 participants) suggested an effect favouring WHM (SMD –0.58; 95% CI –0.93, –0.22; $p = 0.001$; I^2=0%) (*GRADE: Low*). None of the RCTs contributing data were judged to be at high risk of bias.

Global improvement

There were 4 RCTs (total 727 participants) that assessed the impact of WHM on overall symptoms of anxiety using the Clinical Global Improvement (CGI) measure (Kasper 2016, Kasper 2015, Kasper 2010, Amsterdam 2009) at the end of treatment (range 8 to 10 weeks). The data for 1 RCT were not available.

The CGI is a clinician-rated summary measure that considers all available information, including a knowledge of the patient's history, psychosocial circumstances, symptoms, behaviour, and the impact of the symptoms on the patient's ability to function. It is comprised of 2 single items (rated on a scale from 1 to 7) that evaluate symptom severity and global improvement observed from the initiation of treatment.

Data from 3 RCTs (total 670 participants) suggested an effect favouring WHM for item 2 (SMD –0.49; 95% CI –0.81, –0.17; $p = 0.003$; I^2=76%) (*GRADE: Low*).

Health-related quality of life

There were 2 RCTs (total 508 participants) that assessed the impact of WHM on health-related quality of life measured using the SF-36 (Kasper 2016, Kasper 2010) at the end of treatment (10 weeks).

The SF-36 is a self-reported multidimensional measure assessing the impact of one's health on everyday life. Eight domains are summarised on a scale from 0 (worse) to 100 (best), which can be summarised into 2 component scores. The physical component summary (PCS) score includes the domains of general health, physical functioning, role physical and body pain. The mental component summary (MCS) score includes the domains of vitality, social functioning, role emotional, and mental health. The PCS and MCS are derived by aggregating individual scores. The MCID for the SF-36 is estimated to be around 2 to 4 points for the general population (i.e. ~0.5 of the SD) (208).

Individual data for the RCTs were not reported by the systematic review authors, with pooled results suggesting an effect favouring the WHM for both SF-36 PCS (MD 7.32; 95% CI 3.88, 10.77; $p < 0.001$; I^2=0%) (*GRADE: Low*) and the SF-36 MCS (MD 10.19; 95% CI 5.78, 14.61; $p < 0.001$; I^2=16%) (*GRADE: Low*).

Sleep quality

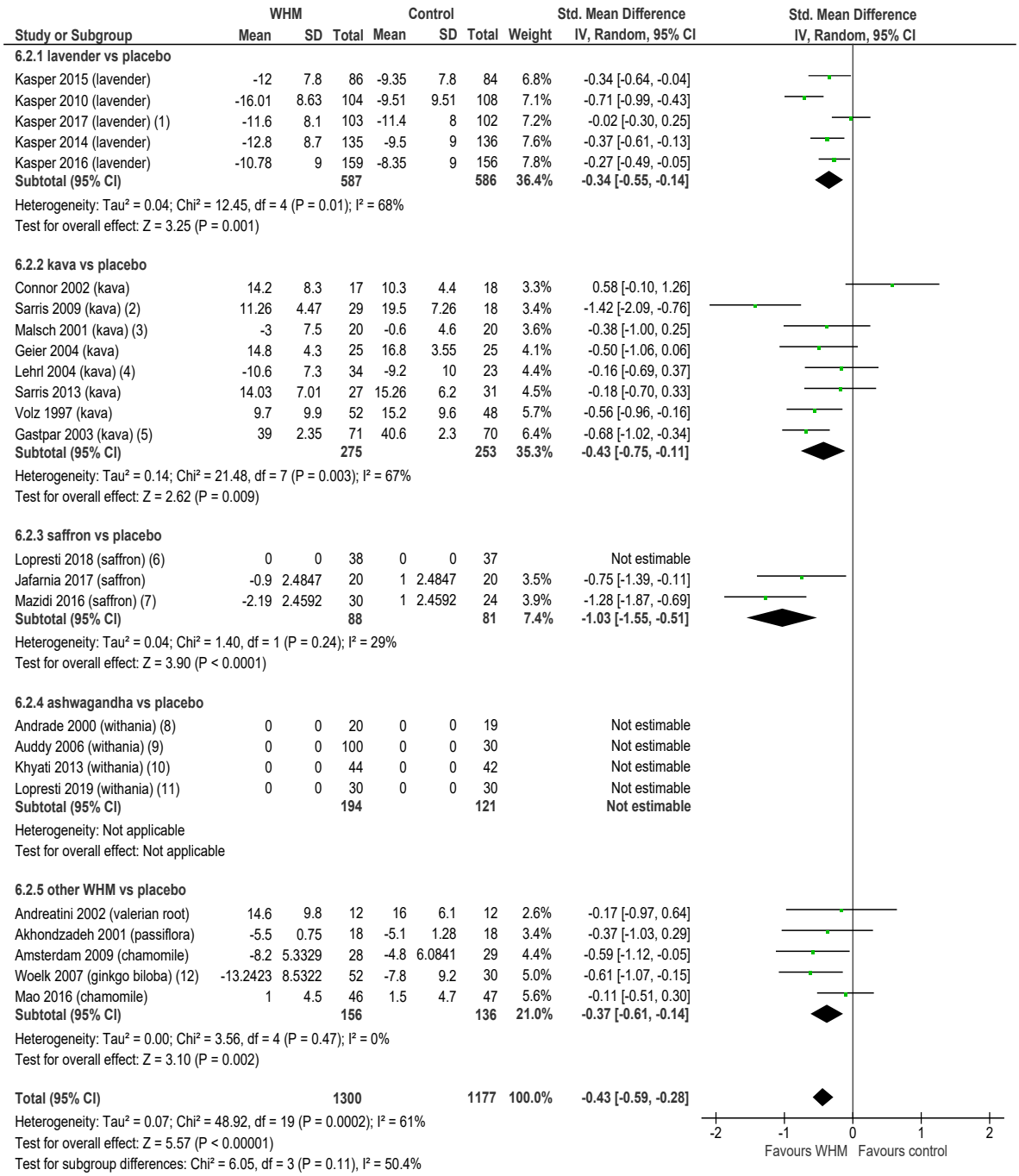
There were 2 RCTs (total 382 participants) that assessed the impact of WHM (lavender) on sleep quality measured using the Pittsburgh Sleep Quality index (PSQI) (Kasper 2015, Kasper 2010) at the end of treatment (10 weeks).

The PSQI is a 19-item questionnaire that assesses the quality of sleep and sleep disturbances of an individual in the previous month. It assesses 7 sleep components including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disorder (sleep disturbance), use of sleeping medication, and daytime dysfunction. Each item is scored (range from 0 to 3) with the total global score ranging from 0 (no problems) to 21 (severe problems). Higher scores represent greater sleep disturbances, with a score of 5 or more considered clinically relevant.

Individual data for the RCTs were not reported by the systematic review authors (Moller 2019), with pooled results reported to suggest an effect favouring the WHM (MD –1.36; 95% CI –2.28, –0.44; $p = 0.004$; I^2 = 26.9%) (*GRADE: Low*). The SR authors also noted that an effect favouring WHM was also observed for 4 subscale components of the PSQI including: sleep quality ($p = 0.051$), sleep latency ($p < 0.001$), sleep disturbances ($p = 0.014$), and daytime dysfunction ($p < 0.001$). The remaining 3 components (sleep duration, habitual sleep efficiency, use of sleeping medication) showed no significant differences between groups the WHM and placebo groups.

The same systematic review authors (Moller 2019) also provided pooled results for the insomnia-subscale of the HAM-A (defined by difficulty in falling asleep, broken sleep, unsatisfying sleep, fatigue on waking, dreams, nightmares, and night terrors) but individual study data were not provided. The authors noted an effect favouring WHM compared with placebo (3 RCTs, N=697; MD –0.38; 95% CI 0.73, –0.03; $p = 0.034$; I^2 = 78.5%).

Figure D-3 Forest plot of comparison: WHM vs placebo: Symptoms of anxiety – anxiety*

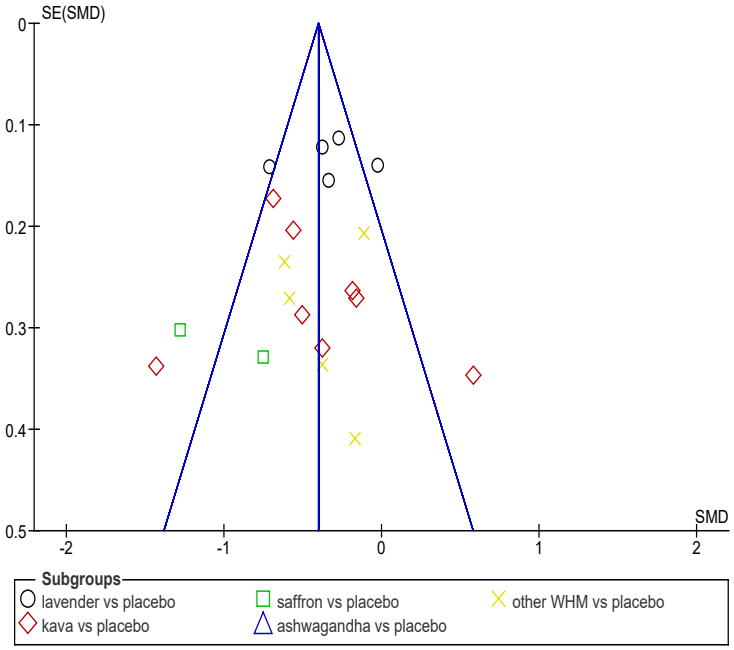


Footnotes

(1) 80 mg/day group
(2) before crossover
(3) reported as median difference (IQR); dichotomised data: responders 12/20 vs 4/20; OR 6.00; 95%CI 1.46 to 24.7; p=0.013
(4) reported as median difference (IQR), p=0.1
(5) Anxiety Status Inventory
(6) RCADS (mean age 14 yrs); SMD -0.739; 95%CI -1.203, -0.276; p=0.002
(7) BAI
(8) response rate: 88% vs 50%, p=NS
(9) data not adequately reported; p=signficant (dose-dependent)
(10) data not adequately reported; p=NS
(11) data not adequately reported; p=significant
(12) high and low dose groups combined

* Measured with Hamilton Anxiety Rating Scale (HAM-A) unless noted.

Figure D-4 Funnel plot of comparison: WHM vs placebo: Symptoms of anxiety – anxiety



Comparison 2 (vs inactive control)

There were no studies found by the included systematic reviews that compared WHM with other inactive interventions in people with symptoms of anxiety.

Comparison 3 (vs other)

There were 6 RCTs found by the included systematic reviews that compared WHM with an active intervention (Mao 2016, Kasper 2014, Woelk 2010, Amsterdam 2009, Boerner 2003, Andreatini 2002). The studies reported data for one outcome (anxiety) (see Appendix F2).

D2.2 Depression and mood disorders

D2.2.1 List of reviews

A summary of the PICO criteria of the eligible systematic reviews is provided in Table D-29.

A list of herbs examined in the identified primary studies is provided in Table D-30.

There were 9 systematic reviews (76, 88, 176, 209-214) published in 2018 or after that presented results in a meta-analysis and were prioritised for critical appraisal and data extraction (Firoozeei 2021, Wang 2021, Dai 2020, Fusar-Poli 2020, Ghaderi 2020, Khaksarian 2019, Marx 2019, Toth 2019, Yang 2018). One other review (215) published prior to 2018 was included for critical appraisal and data extraction as it reported on the efficacy of St John's wort (compared with either placebo or active control), which had not been assessed by the other reviews (Apaydin 2016). Review details, including all outcome domains and measures reported by the included reviews, are provided in Appendix F1. Outcome data for critical or important outcomes are provided in Appendix F2.

Nine (9) systematic reviews (216-224) presented results in a meta-analysis but were published prior to 2018 and were judged to no longer represent the best available evidence (Ng 2017, Ng 2017a, Asher 2017, Al-Karawi 2016, Cui 2016, Linde 2009, Whiskey 2001, Williams 2000, Kim 1999). In the absence of additional data, these 9 reviews were not considered further. Six (6) other reviews (106, 191, 225-228) did not report on outcomes considered critical or important for this overview therefore were not considered further (Lopresti 2022, Karimi 2021, Mousavi 2021, Hallajzadeh 2019, Pourmasoumi 2019, Sahebkar 2016c).

There were 26 narrative reviews (71, 82, 149, 194, 202, 203, 229-248) that provided a descriptive summary or individual study results (Matias 2021, Kim 2018a, McCloskey 2018, Sarris 2018, Yeung 2018, Maher 2016, Hausenblas 2015, Hausenblas 2013, Dhingra 2012, Dwyer 2011, Hung 2011, Sarris 2011a, Ulbricht 2011, Ulbricht 2011a, Sarris 2009, Morgan 2008, Gahlsdorf 2007, Sarris 2007, Clement 2006, Jorm 2006, Frazer 2005, Jorm 2002, Gaster 2000, Stevinson 1999, Volz 1997, Ernst 1995). These reviews were checked for additional studies and results, but in the absence of data were not considered further. Figure D-22 outlines the selection process of the final included systematic reviews.

Figure D-5 Process flow for prioritising systematic reviews: Depression and mood disorders

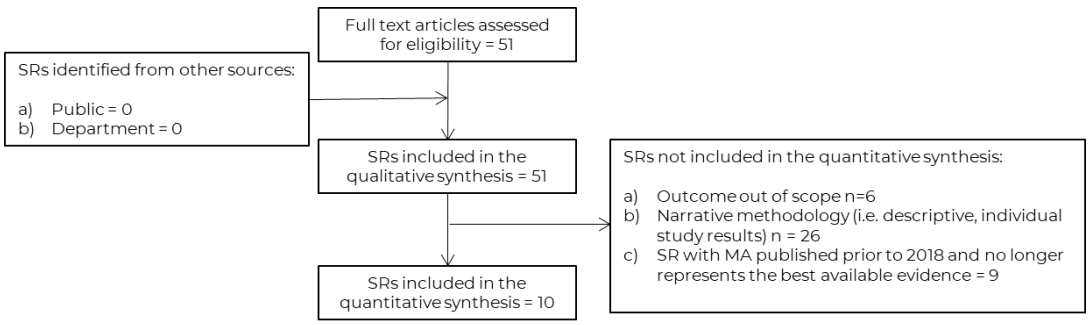


Table D-5 PICO criteria of included systematic reviews: Depression and mood disorders

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]	N	Study ID [e]
Firoozeei 2021 (88)	Meta-analysis	Umbrella review (any condition)	Lavender	Any	Depressive symptoms	1 (k=17)	Araj-Khodaei 2020
Karimi 2021 (228)	Meta-analysis	Umbrella review (any condition)	Saffron	Placebo	Liver function	(k=12)	--
Mousavi 2021 (225)	Meta-analysis	Umbrella review (any condition)	Saffron	Not specified	Liver enzymes	(k=9)	--
Wang 2021 (209)	Meta-analysis	Depression (or symptoms of)	Turmeric	Not specified	Depressive symptoms, response rate, adverse effects	6 (k=10)	Kanchanatawan 2018, Lopresti 2017, Yu 2015, Lopresti 2014, Sanmukhani 2014, Bergman 2013
Dai 2020 (210)	Meta-analysis	Depression (mild-moderate)	Saffron	Placebo or other	Depressive symptoms, response rate, remission rate, adverse effects	6 (k=12)	vs placebo: Tabeshpour 2017, Moshiri 2006, Akhondzadeh 2005 vs antidepressants: Ghajar 2016, Akhondzadeh Basti 2007, Noorbala 2005
Fusar-Poli 2020 (211)	Meta-analysis	Major Depressive disorder (or symptoms of)	Turmeric	Placebo +/- standard care	Depressive symptoms, anxiety, clinical global impression	7 (k=10)	Kanchanatawan 2018, Lopresti 2017, Panahi 2015, Yu 2015, Lopresti 2014, Sanmukhani 2014, Bergman 2013
Ghaderi 2020 (76)	Meta-analysis	Umbrella review (any condition)	Saffron	Placebo OR other intervention	Emotional functioning, C-reactive protein	8 (k=21)	Jelodar 2018, Kell 2017a, Kell 2017b, Tabeshpour 2017, Sahraian 2016, Talaei 2015, Moshiri 2006, Akhondzadeh 2005
Hallajzadeh 2019 (106)	Meta-analysis	Depression	Turmeric	Not specified	Endothelial function	(k=10)	--
Khaksarian 2019 (212)	Meta-analysis	Depression	Saffron	Placebo OR fluoxetine	Depression	6 (k=8)	Akhondzadeh Basti 2008, Akhondzadeh 2005, Moshiri 2006, Noorbala 2005, Akhondzadeh Basti 2007, Kashani 2016
Marx 2019 (176)	Meta-analysis	Symptoms of depression and anxiety	Saffron	Placebo OR pharmacotherapy	Depression, anxiety	15 (k=23)	Jelodar 2018, Lopresti 2018, Kashani 2017, Kell 2017a, Kell 2017b, Tabeshpour 2017, Sahraian 2016, Talaei 2015, Kashani 2013, Modabbernia 2012, Akhondzadeh Basti 2007, Moshiri 2006,

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]	N	Study ID [e]
							Akhondzadeh 2005, Noorbala 2005, Akhondzadeh 2004
Pourmasoumi 2019 (226)	Meta-analysis	Depression	Saffron	Not specified	Cardiovascular risk factors	(k=10)	--
Toth 2019 (213)	Meta-analysis	Depression (mild-moderate)	Saffron	Placebo or active control	Depression	8 (k=11)	Kashani 2017, Tabeshpour 2017, Shahmansouri 2014, Akhondzadeh Basti 2007, Moshiri 2006, Akhondzadeh 2005, Noorbala 2005, Akhondzadeh 2004
Yang 2018 (214)	Meta-analysis	Depression (mild-moderate)	Saffron	Placebo or active control	Depressive symptoms, anxiety, clinical global impression	5 (k=7)	Akhondzadeh Basti 2007, Moshiri 2006, Akhondzadeh 2005, Noorbala 2005, Akhondzadeh 2004
Matias 2021 (229)	Descriptive	Depression	Turmeric	Not specified	symptoms of depression & anxiety	8 (k=10)	Kanchanatawan 2018, Lopresti 2017 Panahi 2015, Yu 2015, Lopresti 2014, Sanmukhani 2014, Bergman 2013, Kashani 2013
Kim 2018a (149)	Descriptive	Umbrella review (any condition)	Plant extracts administered orally (ginkgo biloba)	Not specified	Sleep quality	1 (k=46)	Hemmeter 2001
McCloskey 2018 (230)	Descriptive	Depression (post-partum)	Any complementary health approach: Saffron	Any	Any efficacy or safety outcome	2 (k=10)	Kashani 2017, Tabeshpour 2017
Sarris 2018 (194) (update of Sarris 2007)	Descriptive	Psychiatric disorders	Herbal medicines (oral)^	Not specified	Any efficacy or safety outcome	7 # (k=NR)	Nikfarjam 2017, Jeong 2015, Mao 2015, Nikfarjam 2013, Darbinyan 2007, Akhondzadeh 2003, Lindgaerde 1999
Yeung 2018 (231)	Descriptive	Depression & anxiety	Any single herb, spice, plant or extract: Chamomile, Chaste tree, Ginkgo, Kava, Lavender, Passionflower, Rhodiola, Bacopa	Not specified	Any efficacy or safety outcome	7 (k=100) #	Nikfarjam 2017, Jeong 2015, Mao 2015, Nikfarjam 2013, Darbinyan 2007, Akhondzadeh 2003, Lindgaerde 1999
Ng 2017 (216)	Meta-analysis	Depression	St John's wort	SSRI	Depressive symptoms, anxiety, clinical global	(k=27)	--

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]	N	Study ID [e]
					impression		
Ng 2017a (217)	Meta-analysis	Depression	Turmeric	--	--	--	--
Asher 2017 (218)	Meta-analysis	Major depressive disorder	CAMS: St John's wort	--	--	--	
Al-Karawi 2016 (219)	Meta-analysis	Major depressive disorder	Turmeric	--	--	--	--
Apaydin 2016 (215)	Meta-analysis	Depression	St John's wort	Placebo or SSRI	Depressive symptoms, anxiety, clinical global impression	k=35	Not extracted here.
Cui 2016 (220)	Meta-analysis	Depression	St John's wort	SSRI	Depressive symptoms, anxiety, clinical global impression	k=27	--
Sahebkar 2016b (227)	Meta-analysis	Depression	Turmeric	Not specified	TNF-alpha	--	--
Linde 2009 (221)	Meta-analysis	Depression	St John's wort	--	--	--	--
Whiskey 2001 (222)	Meta-analysis	Depression	St John's wort	--	--	--	--
Williams 2000 (223)	Meta-analysis	Depression	St John's wort	--	--	--	--
Kim 1999 (224)	Meta-analysis	Depression	St John's wort	--	--	--	--
Lopresti 2022 (191)	Descriptive	Umbrella review (any condition)	Any single herb, spice, plant or extract (curcumin, hops)	Not specified	stress response biomarkers	(k=52)	--
Maher 2016 (232)	Descriptive	Major Depressive disorder	St John's wort	Placebo or other	Depressive symptomatology, quality of life, adverse effects	(k=35)	--
Hausenblas 2015 (82)	Descriptive	Umbrella review (any condition)	Saffron	Placebo or other	Psychological and behavioural outcomes	6 (k=12)	--
Hausenblas 2013 (233)	individual study results	Major Depressive disorder	Saffron	Placebo or other	Any efficacy or safety outcome	5 (k=5)	--
Dhingra 2012 (234)	descriptive	Depression	Herbal medicines and nutritional substances: St John's wort, Ginkgo	Not specified	Any efficacy or safety outcome	(k=NR)	--
Dwyer 2011 (235)	individual	Depression (mild-	Saffron, Lavender,	Placebo or other	Any efficacy or safety	(k=9)	--

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]	N	Study ID [e]
	study results	moderate)	Rhodiola		outcome		
Hung 2011 (236)	individual study results	Umbrella review (any condition)	Rhodiola	Placebo or other	Any efficacy or safety outcome	(k=11)	--
Sarris 2011a (237)	Descriptive	Depression, Anxiety, Insomnia	Herbal medicines (Lavender, Saffron, St John's wort)	Any	Any efficacy or safety outcome	--	--
Ulbricht 2011 (71)	Descriptive	Umbrella review (any condition)	Saffron	Placebo or other intervention	--	--	--
Ulbricht 2011a (238)	Descriptive	Umbrella review (any condition)	Rhodiola	Placebo or other	Any efficacy or safety outcome	--	--
Sarris 2009 (202)	Descriptive	Mood and anxiety disorders	Kava, St John's wort	Not specified	Any efficacy or safety outcome (anxiety, depression)	--	--
Morgan 2008 (239)	Descriptive	Depressive disorders	Ginseng, Lavender, Saffron, St John's wort	--	--	--	--
Gahlsdorf 2007 (240)	Descriptive	Depression (mild-moderate)	St John's wort	--	--	--	--
Sarris 2007 (203)	Descriptive	Psychiatric disorders	Herbal medicines (oral)^	Not specified	Any efficacy and safety outcome	--	--
Clement 2006 (241)	Descriptive	Depression (mild-moderate)	St John's wort	--	--	--	--
Jorm 2006 (242)	Descriptive	Depression (children & adults)	Complementary treatments (St John's wort)	--	--	--	--
Frazer 2005 (243)	Descriptive	Depression (older people)	St John's wort	--	--	--	--
Jorm 2002 (244)	Descriptive	Depression	Ginkgo	--	--	--	--
Gaster 2000 (245)	Descriptive	Depression	St John's wort	--	--	--	--
Stevinson 1999 (246)	Descriptive	Depression	St John's wort	--	--	--	--
Volz 1997 (247)	Descriptive	Depression	St John's wort	--	--	--	--
Ernst 1995 (248)	Descriptive	Depression	St John's wort	--	--	--	--

Abbreviations: CAM, complementary and alternative medicine
Notes:
N = Number of RCTs meeting our PICO criteria; k = total number of RCTs identified by systematic review.
a. Systematic review with no population restrictions were eligible for inclusion if they presented data that evaluated participants with depression or mood disorders.
b. Systematic reviews were eligible for inclusion if they presented data that examined the effectiveness of eligible WHMs (see Appendix A8).
c. Systematic review with no comparator restrictions were eligible for inclusion if they presented data that compared WHM with control (placebo or no intervention) or another intervention.
d. Outcomes assessed or listed by the systematic review. Grey highlight = nonpriority outcome
e. Study ID of eligible RCTs that met the PICO criteria of this overview.
-- Systematic review not assessed. The outcome domain was not critical or important for this overview OR a more recent SR nominated as best available is included.
^ Includes saffron, turmeric, St John's wort, ginseng, lavender, rhodiola, chamomile, ginkgo & others.
# RCTs listed are those in WHM other than saffron, turmeric & St John's wort

Figure D-6 Critical appraisal summary: review author's judgements about each AMSTAR-2 item for each included systematic review – Depression and mood disorders

	Review ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
DEPRESSION	Firoozeei 2021	Y	PY	Y	PY	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y
	Wang 2021	Y	PY	Y	PY	Y	Y	N	PY	Y	N	Y	Y	Y	Y	Y	Y
	Dai 2020	Y	PY	Y	PY	Y	Y	N	PY	Y	N	Y	Y	Y	Y	Y	Y
	Fusar-Poli 2020	Y	Y	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y
	Ghaderi 2020	Y	PY	Y	PY	Y	N	N	PY	Y	N	Y	Y	Y	Y	Y	Y
	Khaksarian 2019	Y	PY	Y	PY	Y	N	N	PY	Y	N	Y	Y	Y	Y	Y	Y
	Marx 2019	Y	Y	Y	PY	Y	Y	N	PY	PY	Y	Y	Y	Y	Y	Y	Y
	Toth 2019	Y	PY	Y	PY	N	N	Y	PY	Y	N	Y	Y	Y	Y	Y	Y
	Yang 2018	Y	PY	Y	PY	Y	Y	N	PY	Y	N	Y	Y	Y	Y	Y	Y
	Apaydin 2016	Y	PY	Y	Y	Y	Y	N	PY	Y	N	Y	Y	Y	Y	Y	Y

N = No; PY = Partial Yes, Y = Yes

Table D-6 List of herbs assessed in the identified primary studies: Depression and mood disorders

WHM identified in included studies	Matched to Tier 1 list of WHM: Nervous system disorders [a]
Ginkgo (Ginkgo biloba)	X
Lavender (Lavandula officinalis / L. angustifolia)	✓
Rhodiola (Rhodiola rosea)	X
Saffron (Crocus sativus)	X
St John's wort (Hypericum perforatum)	✓
Turmeric (Curcuma longa)	X

Abbreviations: WHM, Western herbal medicine
✓ = yes; X = no
a. See Appendix A6.3 - Tier 1 herb list was considered in GRADE. Eligibility was based on the herb list in Appendix A8

D2.2.2 Critical appraisal

A summary of the quality of included systematic reviews is provided in Figure D-23 and Table D-31. The strengths or limitations of the included systematic reviews assessed against each AMSTAR-2 domain is provided in Appendix E1.

All included systematic reviews (Firoozeei 2021, Wang 2021, Dai 2020, Fusar-Poli 2020, Ghaderi 2020, Khaksarian 2019, Marx 2019, Toth 2019, Yang 2018, Apaydin 2016) were judged to probably provide an accurate and comprehensive summary of the available studies that address the question of interest (i.e. met, or partially met, AMSTAR-2 domains 4, 8, 9 and 11). The other systematic reviews had at least one critical flaw (did not meet domain 11) and were not further assessed.

Table D-7 Critical appraisal summary: Depression and mood disorders

Review ID	Summary	Notes
Firoozeei 2021	3 non-critical weaknesses in domains 6, 7 & 10	The authors do not perform data extraction in duplicate, do not provide a list of excluded studies read at full text, and they did not report on any funding or support for the RCTs.
Wang 2021	2 non-critical weaknesses in domains 7 & 10	The authors do not provide a list of excluded studies read at full text, and they did not report on any funding or support for the RCTs.
Dai 2020	2 non-critical weaknesses in domains 7 & 10	The authors do not provide a list of excluded studies read at full text, and they did not report on any funding or support for the RCTs.
Fusar-Poli 2020	2 non-critical weaknesses in domains 7 & 10	The authors do not provide a list of excluded studies read at full text, and they did not report on any funding or support for the RCTs.
Ghaderi 2020	3 non-critical weaknesses in domains 6, 7 & 10	The authors do not perform data extraction in duplicate, do not provide a list of excluded studies read at full text, and they did not report on any funding or support for the RCTs.
Khaksarian 2019	3 non-critical weaknesses in domains 6, 7 & 10	The authors do not perform data extraction in duplicate, do not provide a list of excluded studies read at full text, and they did not report on any funding or support for the RCTs.
Marx 2019	1 non-critical weaknesses in domains 7	The authors do not provide a list of excluded studies read at full text.
Toth 2019	3 non-critical weaknesses in domains 5, 6 & 10	The authors do not perform screening or data extraction in duplicate, and they did not report on any funding or support for the RCTs.
Yang 2018	2 non-critical weaknesses in domains 7 & 10	The authors do not provide a list of excluded studies read at full text, and they did not report on any funding or support for the RCTs.
Apaydin 2016	2 non-critical weaknesses in domains 7 & 10	The authors do not provide a list of excluded studies read at full text, and they did not report on any funding or support for the RCTs.

Abbreviations: RCT, randomised controlled trial

D2.2.3 Effects of intervention

Outcomes considered by the NTWC to be critical or important for decision-making in people with depression or mood disorders are listed in Table D-32.

Table D-8 Outcomes considered by the NTWC to be critical or important for decision-making: Depression and mood disorders

Outcome domain	Measured with	Consensus rating	Data available for comparison 1 or 2	Review ID									
				Firoozeei 2021	Wang 2021	Dai 2020	Fusar-Poli 2020	Ghaderi 2020	Khaksarian 2019	Marx 2019	Toth 2019	Yang 2018	Apaydin 2016
Depressive symptoms	BDI, HAM-D, MADS (or similar)	9	Yes	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Anxiety	BAI, HAM-A, STAI (or similar)	8	Yes	?	?	?	?	✓	?	✓	?	?	?
Symptoms of Stress	DASS-21 stress subscale	8	No	?	?	?	?	?	?	X	?	?	?
HRQoL	SF-36 or similar	8	No	?	?	?	?	?	?	?	?	?	?
Emotional functioning	DASS-21, GHQ-28 (or similar)	8	No	?	?	?	?	?	?	?	?	?	?
Global improvement	CGI-severity (or similar)	8	No	?	?	?	?	?	?	?	?	?	?
Physical functioning	SF-36 PCS (or similar)	7	No	?	?	?	?	?	?	?	?	?	?

Abbreviations: BAI, Beck anxiety inventory; BDI, Beck depression inventory; CGI, clinical global impression; DASS-21, 21-item depression anxiety stress scale; GHQ-28, 28-item general health questionnaire; HAM-A, Hamilton anxiety rating scale HAM-D, Hamilton depression rating scale; HRQoL, health-related quality of life; MADS, Montgomery-Asber Depression Scale; PCS, physical component score; SF-36, 36-item short form

Notes:

✓ A study result is available for inclusion in the synthesis.

X A study result is NOT available for inclusion because the systematic review does not adequately report the results (data were incomplete). It is unclear if the primary study reported complete data. Due to time and resource constraints, only the information presented in the systematic review is reported.

? The systematic review did not assess this outcome, it is unclear if the outcome was assessed by the primary studies included in the SR. Due to time and resource constraints, only the information presented in the systematic review is reported.

-- The systematic review did not assess this outcome. The outcome was (probably) not assessed by the included primary studies (for reasons unrelated to the *p*-value, magnitude or direction of the results).

Comparison 1 (vs placebo)

There were 21 RCTs found by the included systematic reviews that compared WHM with placebo in people with depression (or symptoms of depression). Of these, 18 RCTs contributed data relevant to 2 outcomes (depression and anxiety). (Jelodar 2018, Kanchanatawan 2018, Kell 2017, Lopresti 2017, Tabeshpour 2017, Sahraian 2016, Talaei 2015, Panahi 2015, Yu 2015, Lopresti 2014, Sanmukhani 2014, Bergman 2013, Kashani 2013, Modabbernia 2012, Akhondzadeh Basti 2008, Moshiri 2006, Akhondzadeh 2005, Akhondzadeh 2003). A further 16 RCTs comparing St John's wort with placebo provided data relevant to 3 outcomes (depression, emotion functioning and physical functioning).

Three (3) RCTs (Mao 2015, Darbinyan 2007, Lingaerde 1999) did not contribute any data because their results were not adequately reported by the systematic review.

Symptoms of depression

There were 17 RCTs (total 1022 participants) that reported symptoms of depression measured using a variety of measures, including the Hamilton Depression Rating Scale (HAM-D), the Beck Depression Inventory (BDI-II), the Depression, Anxiety, Stress Scale (DASS-21), the Montgomery-Asberg Depression Rating Scale (MADRS), the Self-rated Inventory of Depressive Symptomatology (IDS-SR30), and the Hospital Anxiety and Depression Scale (HADS-D) at the end of treatment (between 6 and 12 weeks).

The HAM-D measures the severity of current depressive symptoms and consists of 17 or 21-items relating to symptoms of depression experienced over the past week. Each item on the questionnaire is scored on a 3- or 5-point scale with a total score between 0 and 7 generally accepted to be within the normal range, while a score of 20 or more indicating moderate severity of depression.

The BDI-II assesses the behavioural and cognitive symptoms of depression and consists of 21 questions, each on a 4-point scale. Scores range from 0 to 63 with a higher score indicating a greater level of depressive symptoms.

The DASS-21 is a quantitative measure of distress along 3 emotional states of depression, anxiety and stress. Each subscale consists of 7 questions, scored on a scale from 0 to 3. The depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest / involvement, anhedonia and inertia. Total scores from the DASS-21 are multiplied by 2 to align with the original DASS-42 scoring (total score range 0 to 42).

The MADRS is a 10-item scale that measures severity of depressive symptoms. Based on clinical interview, each item can be scored from 0 to 6, with the cumulative score ranging between 0 and 60. A higher score indicates a greater level of depressive symptoms.

Pooled results from 17 RCTs (total 1022 participants) suggested an effect favouring the WHM group when compared with placebo (SMD –0.60; 95% CI –0.89, –0.31; $p < 0.0001$; $I^2 = 78\%$) (*GRADE: Moderate*). Statistical heterogeneity was unable to be explained by difference in the intervention (see Figure D-24) or difference in the measure used (data not shown).

In a sensitivity analysis examining in the impact of 7 RCTs judged to be at high risk of bias (Akhondzadeh 2005, Akhondzadeh Basti 2008, Bergman 2013, Panahai 2015, Sanmukhani 2014, Talaei 2015, Yu 2015) the estimate of effect did not materially change (SMD –0.50; 95% CI –0.78, –0.22; $p = 0.0005$; $I^2 = 61\%$).

Similarly, there was no substantial change in the effect estimate when examining the impact of small studies (fixed effect, SMD –0.54; 95% CI –0.67, –0.41; $p < 0.00001$; $I^2 = 78\%$). Visual inspection of a funnel plot suggested no notable asymmetry (see Figure D-25).

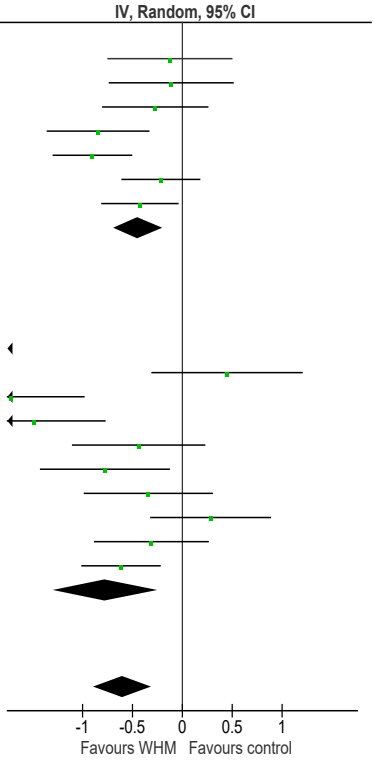
For St John's wort (SJW), the review by Apaydin 2016 (215) reported that participants receiving SJW had significantly lower mean depression scores than participants receiving a placebo (16 RCTs; N = 2888; SMD –0.49; 95% CI –0.74, –0.23; $I^2 = 89\%$). The authors noted that substantial heterogeneity lowered the quality of evidence (*GRADE: Moderate*) and sensitivity analyses showed very similar results when excluding poor quality studies.

Symptoms of anxiety

There were 6 RCTs (total 462 participants) that reported symptoms of anxiety measured using a variety of measures, including the Hamilton Anxiety Rating Scale (HAM-A), the Beck Anxiety Inventory (BAI), the Depression, Anxiety, Stress Scale (DASS-21), and the Hospital Anxiety and Depression Scale (HADS-A) at the end of treatment (between 6 and 12 weeks).

Pooled results from 5 RCTs (total 397 participants) suggested an effect favouring the WHM group when compared with placebo (SMD –1.49; 95% CI –2.39, –0.59; $p = 0.001$; $I^2 = 93\%$) (*GRADE: Low*). Statistical heterogeneity was high. In a sensitivity analysis examining in the impact of one RCT judged to be at high risk of bias (Talaei 2015) the estimate of effect did not materially change (SMD –0.97; 95% CI –1.69, –0.25; $p = 0.009$; $I^2 = 90\%$).

Figure D-7 Forest plot of comparison: WHM vs placebo: Depression – depressive symptoms

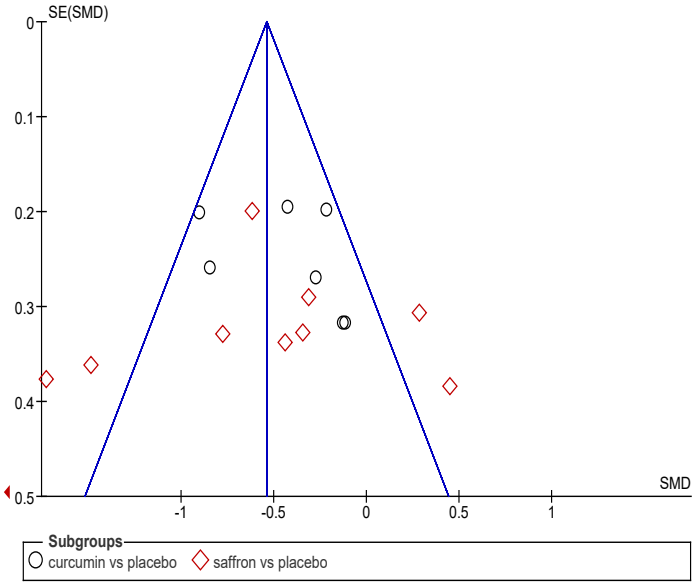


Study or Subgroup	WHM Mean	WHM SD	WHM Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
7.2.1 curcumin vs placebo								
Bergman 2013 (curcumin)	-17.9	6.39	20	-16.2	17.8	20	5.8%	-0.12 [-0.75, 0.50]
Sanmukhani 2014 (curcumin)	-14.8	5.63	20	-14	8.17	20	5.8%	-0.11 [-0.73, 0.51]
Lopresti 2014 (curcumin) (1)	-10.33	9.39	28	-7.25	12.73	28	6.2%	-0.27 [-0.80, 0.25]
Kanchanatawan 2018 (curcumin) (2)	-20.86	5.03	33	-16.98	3.97	32	6.3%	-0.84 [-1.35, -0.34]
Panahai 2015 (curcumin) (3)	0.049	1.0484	61	1	1.0484	50	6.8%	-0.90 [-1.29, -0.51]
Lopresti 2017 (curcumin) (4)	-11.46	11.1	87	-8.91	13.32	36	6.9%	-0.22 [-0.60, 0.17]
Yu 2015 (curcumin)	-4.52	3.17	54	-3.3	2.48	54	6.9%	-0.43 [-0.81, -0.04]
Subtotal (95% CI)			**303**			**240**	**44.6%**	**-0.44 [-0.69, -0.20]**
Heterogeneity: Tau² = 0.05; Chi² = 11.41, df = 6 (P = 0.08); I² = 47%								
Test for overall effect: Z = 3.51 (P = 0.0005)								
7.2.2 saffron vs placebo								
Talaei 2015 (saffron) (5)	-17.65	3.11	20	-6.15	3.82	20	4.2%	-3.24 [-4.21, -2.27]
Sahraian 2016 (saffron) (6)	2.03	2.2355	11	1	2.2355	19	5.1%	0.45 [-0.30, 1.20]
Moshiri 2006 (saffron)	-14.01	5.53	20	-5.05	4.63	20	5.2%	-1.72 [-2.46, -0.99]
Akhondzadeh 2005 (saffron)	-12.2	4.67	20	-5.1	4.71	20	5.3%	-1.48 [-2.19, -0.78]
Modabbernia 2012 (saffron)	0.515	1.083	18	1	1.083	18	5.6%	-0.44 [-1.10, 0.22]
Jelodar 2018 (saffron) (7)	-7.72	4.356	20	-4.27	4.356	20	5.6%	-0.78 [-1.42, -0.13]
Kashani 2013 (saffron)	0.637	1.0418	19	1	1.0418	19	5.7%	-0.34 [-0.98, 0.30]
Akhondzadeh basti 2008 (saffron)	-12.18	3.72	19	-13.45	4.84	25	5.9%	0.28 [-0.32, 0.88]
Tabeshpour 2017 (saffron) (8)	8.4	20.2657	30	15.3	24.1495	20	6.0%	-0.31 [-0.88, 0.26]
Kell 2017 a&b (saffron) (9)	0.316	1.1058	83	1	1.1058	38	6.8%	-0.61 [-1.01, -0.22]
Subtotal (95% CI)			**260**			**219**	**55.4%**	**-0.77 [-1.30, -0.25]**
Heterogeneity: Tau² = 0.59; Chi² = 61.05, df = 9 (P < 0.00001); I² = 85%								
Test for overall effect: Z = 2.90 (P = 0.004)								
Total (95% CI)			**563**			**459**	**100.0%**	**-0.60 [-0.89, -0.31]**
Heterogeneity: Tau² = 0.28; Chi² = 74.17, df = 16 (P < 0.00001); I² = 78%								
Test for overall effect: Z = 4.07 (P < 0.0001)								
Test for subgroup differences: Chi² = 1.25, df = 1 (P = 0.26), I² = 20.2%								

Footnotes

(1) IDS-SR30
(2) MADRS
(3) HADS-D
(4) IDS-SR30
(5) BDI
(6) BDI
(7) BDI
(8) BDI
(9) DASS-21

Figure D-8 Funnel plot of comparison: WHM vs placebo: Depression – depressive symptoms



Emotional functioning

There were no RCTs found by the included systematic reviews that assessed WHM (other than St Jonn's wort) compared with placebo and reported on emotional functioning.

For St John's wort (SJW), the review by Apaydin 2016 (215) reported that participants receiving SJW had higher SF-36 mental component scores than participants receiving a placebo (2 RCTs; N = 358; SMD 0.48; 95% CI 0.24, 0.73; I^2 = not reported). The authors noted that the effect was not present when excluding poor quality studies and the studies not designed or not powered to assess the outcome (*GRADE: Low*).

Physical functioning

There were no RCTs found by the included systematic reviews that assessed WHM (other than St Jonn's wort) compared with placebo and reported on physical functioning.

For St John's wort (SJW), the review by Apaydin 2016 (215) reported that SF-36 physical component scores were not significantly different for participants receiving SJW compared with participants receiving a placebo (2 RCTs; N = 358; SMD 0.28; 95% CI –1.03, 0.47; I^2 = not reported). The authors noted there was inconsistency and that the effect was not present when excluding poor quality studies and the studies not designed or not powered to assess the outcome (*GRADE: Very low*).

Comparison 2 (vs inactive control)

There were no RCTs found by the included systematic reviews that compared WHM with other inactive interventions in people with depression or mood disorders.

Comparison 3 (vs other)

There were 6 RCTs found by the included systematic reviews that compared WHM (other than St John's Wort) with an active intervention (Araj-Khodaei 2020, Ghajar 2017, Kashani 2017, Akhondzadeh Basti 2007, Noorbala 2005, Akhondzadeh 2004). The studies compared WHM (saffron or lavender) with selective serotonin reuptake inhibitors (fluoxetine, citalopram) or tricyclic antidepressant (imipramine) and provided data for one critical or important outcome.

A further 14 RCTs comparing St John's wort with SSRIs or tricyclic antidepressants and provided data relevant to 3 outcomes.

Symptoms of depression

Six (6) RCTs comparing WHM (other than St John's wort) with an active intervention reported symptoms of depression measured using the Hamilton Depression Rating Scale (HAM-D) at the end of treatment (between 6 and 8 weeks). One RCT (Araj-Khodaei 2020) was not able to be include in the analysis because the number of participants analysed in each group were not provided. The review author had noted there were no important difference between treatment groups (SMD 0.57; 95% CI –0.12 to 1.26; *p* = 0.877).

The HAM-D measures the severity of current depressive symptoms and consists of 17 or 21-items relating to symptoms of depression experienced over the past week. Each item on the questionnaire is scored on a 3- or 5-point scale with a total score between 0 and 7 generally accepted to be within the normal range, while a score of 20 or more indicating moderate severity of depression.

Pooled data from 5 RCTs (total 224 participants) comparing WHM (other than St John's wort) with antidepressants suggested no important difference between treatment groups (SMD 0.15, 95% CI –0.15, 0.46; *p* = 0.32; I^2 = 24%) *(GRADE: Low)*. None of the included studies were judged to be at high risk of bias (see Appendix F1)

For St John's wort (SJW), the review by Apaydin 2016 (215) reported that depression scores in participants receiving SJW were not different from those receiving antidepressants (14 RCTs; N = 2248; SMD –0.03, 95% CI –0.21, 0.15; I^2 = 74%) *(GRADE: Moderate)*.

Emotional functioning

There were no RCTs found by the included systematic reviews that assessed WHM other than St Jonn's wort compared with active interventions and reported on emotional functioning.

For St John's wort (SJW), the review by Apaydin 2016 (215) reported that SF-36 mental component scores in participants receiving SJW were not different from those receiving antidepressants (1 RCT; N = 216; SMD –0.11; 95% CI –0.15, 0.38). The authors noted there was inconsistency and that the effect was not present when excluding poor quality studies and the studies not designed or not powered to assess the outcome (*GRADE: Very Low*).

Physical functioning

There were no RCTs found by the included systematic reviews that assessed WHM other than St Jonn's wort compared with active interventions and reported on physical functioning.

For St John's wort (SJW), the review by Apaydin 2016 (215) reported that participants receiving SJW had higher SF-36 physical component scores than participants receiving an antidepressant (1 RCT; N = 153; SMD 0.35; 95% CI 0.01, 0.70). The authors noted there was inconsistency and that the effect was not present when excluding poor quality studies and the studies not designed or not powered to assess the outcome (*GRADE: Very Low*).

D2.3 Insomnia

D2.3.1 List of reviews

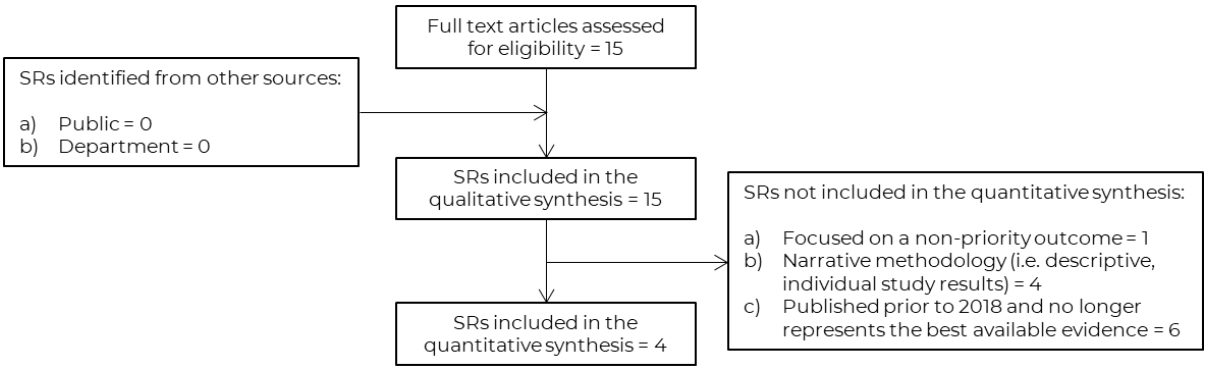
A summary the PICO criteria of the eligible systematic reviews is provided in Table D-33.

A list of herbs included in the identified studies is provided in Table D-34.

There were 4 systematic reviews (Shinjyo 2020, Hieu 2019, Leach 2015, Fernandez-San-Martin 2010) that presented results in a meta-analysis and were prioritised for critical appraisal and data extraction. The other 11 reviews provided a descriptive or narrative review of individual study results. Of these, 6 reviews (Taslaman 2014, Ulbricht 2012, Sarris 2011a, Sarris 2011b, Taibi 2007, Stevinson 2000) were published prior to 2018 and were judged to no longer represent the best available evidence. The other 5 reviews published in 2018 or after (Lopresti 2021, Sys 2020, Tandon 2020, Feizi 2019, Kim 2018a) were checked for additional studies and results, but in the absence of usable data were not considered further. Figure D-26 outlines the selection process of the final included systematic reviews.

Review details, including all outcome domains and measures reported by the included reviews, are provided in Appendix F1. Outcome data for critical or important outcomes are provided in Appendix F2.

Figure D-9 Process flow for prioritising systematic reviews: Insomnia



Abbreviations: SR, systematic review

Table D-9 PICO criteria of included systematic reviews: Insomnia

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]	N	Study IDs [e]
Lopresti 2021 (192)	Descriptive	No population restrictions	Oral use of herbs, spices, plants, fruits, vegetables, or their extracts used as a mono preparation	Placebo or control	Stress biomarkers	--	Langade 2019
Shinjyo 2020 (63)	Meta-analysis	Insomnia	Valerian	Placebo, active comparator (oxazepam)	Sleep quality, anxiety	12 (k=60)	Maroo 2013, Taavoni 2011, Taibi 2009, Koetter 2007#, Oxman 2007, Jacobs 2005, Morin 2005, Coxeter 2003, Farag 2003, Ziegler 2002, Donath 2000, *Leathwood 1985*#
Sys 2020 (249)	Descriptive	Insomnia	Alternative sedative medications (valerian)	Any	Any efficacy outcome	1 (k=24)	Taibi 2009
Tandon 2020 (193)	Descriptive	No population restrictions	Withania	Any	Efficacy and safety	1 (k=39)	Langade 2019
Feizi 2019 (250)	Descriptive	Insomnia	WHM (chamomile, kava, lavender, valerian)	Any	Any efficacy outcome	4 (k=12)	Zick 2011, Oxman 2007, Coxeter 2003, Donath 2000
Hieu 2019 (175)	Meta-analysis	Symptoms of anxiety, GAD, Insomnia, Sleep problems	Chamomile	Placebo	Anxiety, Insomnia, Sleep quality	1 (k=12)	Zick 2011
Kim 2018a (149)	Descriptive	Insomnia or sleep problems	Singel plant-derived extracts (valerian, chamomile, hops, kava)	Any	Clinical efficacy	7 (k=24)	Zick 2011, *Cornu 2010^,* Taibi 2009, Oxman 2007, Coxeter 2003, Ziegler 2002, Donath 2000
Leach 2015 (251)	Meta-analysis	Insomnia	Herbal medicines (valerian, chamomile)	Any	Clinical efficacy	7 (k=14)	Zick 2011, Taibi 2009, Oxman 2007, Jacobs 2005, Coxeter 2003, Ziegler 2002, Donath 2000
Taslaman 2014 (252)	Descriptive	Insomnia	WHM (valerian, hops)	Any	Clinical efficacy	5 (k=9)	Zick 2011, Taibi 2009, Oxman 2007, Jacobs 2005, Coxeter 2003
Ulbricht 2012 (162)	Descriptive	Any	Hops, Combination	Any	Clinical efficacy, safety	--	--
Sarris 2011a (237)	Descriptive	Depression, Anxiety, Insomnia	Herbal medicines (passionflower, valerian)	Any	Clinical efficacy, safety	--	--
Sarris 2011b (253)	Descriptive	Insomnia	Complementary medicines (valerian, kava, combination)	Any	Clinical efficacy	--	--

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]	N	Study IDs [e]
Fernandez-San-Martin 2010 (254)	Meta-analysis	Insomnia	Valerian preparations	Placebo	Clinical efficacy	9 (k=18)	Taibi 2009, *Koetter 2007#*, Oxman 2007, Jacobs 2005, Coxeter 2003, Donath 2000, *Kuhlmann 1999#*, *Vorbach 1996#*, *Leathwood 1985#*
Taibi 2007 (255)	Descriptive	Insomnia or sleep problems	Valerian preparations	Any	Clinical efficacy, safety	--	--
Stevinson 2000 (256)	Descriptive	Insomnia	Valerian	Any	Clinical efficacy	--	--

Abbreviations: GAD, generalised anxiety disorder; WHM, Western herbal medicines

Notes:

N = Number of RCTs meeting our PICO criteria; k = total number of RCTs identified by systematic review.

a. Systematic review with no population restrictions were eligible for inclusion if they presented data that evaluated participants with insomnia or sleep problems.

b. Systematic reviews were eligible for inclusion if they presented data that examined the effectiveness of eligible WHMs (see Appendix A8).

c. Systematic review with no comparator restrictions were eligible for inclusion if they presented data that compared WHM with control (placebo or no intervention) or another intervention.

d. Outcomes assessed or listed by the systematic review. Grey highlight = nonpriority outcome; Blue highlight = critical or important outcome

e. Study ID of eligible RCTs that met the PICO criteria of this overview.

-- Systematic review not assessed. The outcome domain was not critical or important for this overview OR a more recent SR nominated as best available is included.

Not clear if the populations in the RCT meets our PICO. Participants are diagnosed with insomnia according to ICD-10 criteria or were described as having a nonorganic sleep disorder, or sleep problems.

^ Intervention does not meets our PICO. Fixed combination 260mg of Soya oil [Glycine max], 173 mg of Cade oil [Cannabis sativa], 50 mg of Houblon [Humulus lupulus], and 6mg [Soya lecithin])

Figure D-10 Critical appraisal summary: review author's judgements about each AMSTAR-2 item for each included systematic review – Insomnia

	Review ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
INSOMNIA	Shinjyo 2020	Y	Y	Y	PY	N	Y	N	PY	PY	N	Y	Y	Y	Y	Y	Y
	Hieu 2019	Y	Y	N	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y
	Leach 2015	Y	PY	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N	Y
	Fernandez-San-Martin 2010	Y	PY	N	PY	Y	Y	N	PY	Y	N	Y	Y	Y	Y	Y	N

N = No; PY = Partial Yes, Y = Yes

Table D-10 List of herbs included in the identified studies: Insomnia

WHM identified in included studies	Matched to Tier 1 list of WHM: Nervous system disorders [a]
Herbal combination*	X
Chamomile (Matricaria recruitica)	X
Hops (Humulus lupulus)	✓
Kava (Piper methysticum)	✓
Passionflower (Passiflora incarnata)	✓
Valerian (Valeriana officinalis)	✓
Withania somnifera (Ashwagandha)	X

Abbreviations: WHM, Western herbal medicine
✓ = yes; X = no
* Including Indian valerian + cabbage rose + Spikenard + Heart-leaved moonseed + Withania + ginger + black pepper + liquorice + Shankha Pushpi
a. See Appendix A6.3 - Tier 1 herb list was considered in GRADE. Eligibility was based on the herb list in Appendix A8

D2.3.2 Critical appraisal

A summary of the quality of included systematic reviews is provided in Figure D-27 and Table D-35. The strengths or limitations of the included systematic reviews assessed against each AMSTAR-2 domain is provided in Appendix E1.

All systematic reviews that included a meta-analysis (Shinjyo 2020, Hieu 2019, Leach 2015, Fernandez-San-Martin 2010) were judged to probably provide an accurate and comprehensive summary of the available studies that address the question of interest (i.e. met, or partially met, AMSTAR-2 domains 4, 8, 9 and 11).

The other 11 systematic reviews (Lopresti 2021, Sys 2020, Tandon 2020, Feizi 2019, Kim 2018a, Taslaman 2014, Ulbricht 2012, Sarris 2011a, Sarris 2011b, Taibi 2007, Stevinson 2000) had at least one critical flaw (did not meet domain 11) and were not further assessed.

Table D-11 Critical appraisal summary: Insomnia

Review ID	Summary	Notes
Shinjyo 2020	3 non-critical weaknesses in domain 5, 7 and 10.	The authors did not perform a comprehensive literature search strategy, they did not describe the study setting in detail, or perform data extraction in duplicate. The authors also did not discuss risk of bias assessing truly random allocation sequence, or report on the sources of funding for the studies included in the review.
Hieu 2019	3 non-critical weaknesses in domains 3, 7 and 15.	The authors did not specifically justify only including RCTs, they did not provide a list of excluded studies read at full text, and did not provide an adequate investigation or discussion of small study bias and discuss its likely impact on the results of the review
Leach 2015	3 non-critical weaknesses in domains 7, 10 and 15.	The authors did not provide a list of excluded studies read at full text, they did not report on the sources of funding for the studies included in the review, and they did not provide an adequate investigation or discussion of small study bias and discuss its likely impact on the results of the review
Fernandez-San-Martin 2010	3 non-critical weaknesses in domains 3, 7, 10 and 16.	The authors did not specifically justify only including RCTs, they did not provide a list of excluded studies read at full text, they did not report on the sources of funding for the studies included in the review, and they did not describe potential sources of conflict of interest, including any funding they received for conducting the review.

D2.3.3 Effects of intervention

Outcomes considered by the NTWC to be critical or important for decision-making in people with insomnia are listed in Table D-36.

Table D-12 Outcomes considered by the NTWC to be critical or important for decision-making: Insomnia

Outcome domain	Measured with	Consensus rating	Data available for comparison 1 or 2	Review ID			
				Shinjyo 2020	Hieu 2019	Leach 2015	Fernandez-San-Martin 2010
Sleep quality	Multidimensional measure (PQSI or ISI) [a]	8	Yes	✓	✓	✓	✓
Patient reported improvement	Global assessment	7	No	--	--	--	--
HRQoL	SF-36 (or similar)	7	No	X	?	?	?
Symptoms of depression	BDI (or similar)	7	No	--	X	--	--
Symptoms of anxiety	STAI (or similar)	7	Yes	✓	✓	?	?
Physical functioning	SF-36 physical component score (or similar)	7	No	--	--	--	--
Fatigue	FSS (or similar)	7	No	X	X	?	?

Abbreviations BDI, Beck Depression Inventory; FSS, Fatigue severity scale; HRQoL, health-related quality of life; ISI, Insomnia Severity Index; PSQI, Pittsburgh Sleep Quality Index; SF-36, 36-item short form

Notes:

a. In the absence of multi-dimensional measures of sleep quality, data were included from studies that used a single item-measure.

✓ A study result is available for inclusion in the synthesis.

X A study result is NOT available for inclusion because the systematic review does not adequately report the results (data were incomplete). It is unclear if the primary study reported complete data. Due to time and resource constraints, only the information presented in the systematic review is reported.

? The systematic review did not assess this outcome, it is unclear if the outcome was assessed by the primary studies included in the SR. Due to time and resource constraints, only the information presented in the systematic review is reported.

-- The systematic review did not assess this outcome. The outcome was (probably) not assessed by the included primary studies (for reasons unrelated to the *p*-value, magnitude or direction of the results).

Comparison 1 (vs placebo)

There were 11 RCTs (found by the included systematic reviews that compared WHM[a] with placebo in people with insomnia. Of these, 5 RCTs (Taavoni 2011, Zick 2011, Oxman 2007, Taibi 2009, Jacobs 2005) contributed data to at least one critical or important outcome. Four (4) RCTs (Langade 2019, Morin 2005, Coxeter 2003, Donath 2000) could have contributed data but the results were not adequately reported in the reviews. The other 2 RCTs (Koetter 2007, Farag 2003) did not measure or report an outcome considered to be critical or important for this review.

There was one systematic review awaiting classification (Bostanova 2018) that could have contributed data to these outcomes, but there was not information to make an assessment.

Sleep quality

There were 5 RCTs (Taavoni 2011, Zick 2011, Oxman 2007, Taibi 2009, Jacobs 2005) (total 946 participants) that reported sleep quality measured using the Pittsburgh sleep quality index (PSQI), the insomnia severity index (ISI) or a self-rated visual analogue scale[b] at the end of treatment (range 2 to 24 weeks). Data were missing from 4 other RCTs (total 284 participants), of which 3 (Morin 2005, Coxeter 2003, Donath 2000) had suggested that was no important differences between the treatment groups, and one RCT (Langade 2019) had suggested an effect favouring WHM.

[a] Valerian or combinations of the following: valerian and hops; Indian valerian, cabbage rose, spikenard, Heart-leaved moonseed, Withania, ginger, black pepper, liquorice, Convolvulus pluricalis

[b] Not adequately described by the reviews. Assumed to be a simple visual analogue scale (scale range unknown) (higher is better).

Both the PSQI and the ISI are used to measure sleep quality and disturbances. The PSQI is a self-reported questionnaire that assesses sleep quality over the past month. It measures 7 components of sleep quality: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction (257). Each item is scored on a range from 0 to 3, with the total global score ranging from 0 (no problems) to 21 (severe problems). A score of five or more is associated with poor sleep quality.

The ISI is also a self-reported questionnaire that assesses subjective feelings about insomnia symptoms such as difficulty falling asleep, difficulty staying asleep, early morning awakenings, and daytime impairment over the previous two weeks. Each question is summed to give a total score that ranges from 0 to 28. Scores are categorised as follows: 0-7, no clinical insomnia; 8-14, subclinical insomnia; 15-21, clinical insomnia (moderate); 22-28, clinical insomnia (severe). A cut-off score of 10 has been found to maximise sensitivity and specificity in a community sample (258). In a clinical sample of people seeking treatment for insomnia, an improvement of 8.4 points corresponded to a moderate improvement in insomnia (258).

Pooled results (total 946 participants) suggested there was little to no improvement in overall sleep quality comparing WHM with placebo (SMD –0.12; 95% CI –0.44, 0.21; $p = 0.48$; $I^2 = 78\%$) (*GRADE: Moderate*). The results were not substantially different when only the multidimensional measures of sleep quality (PSQI and ISI) were included in the analysis (SMD –0.20; 95% CI –0.70, 0.30; $p = 0.43$; $I^2 = 85\%$).

Health-related quality of life

One RCT (total 184 participants) measured health-related quality of life using an unspecified measure at the end of treatment (4 weeks) (Morin 2005). The systematic review authors did not provide any data; therefore, the results were not able to be included in the evidence synthesis. An effect favouring WHM was noted.

Symptoms of depression

One RCT (total 34 participants) measured symptoms of depression using the Beck Depression Inventory (BDI) at the end of treatment (4 weeks) (Zick 2011). The systematic review authors did not provide any further information; therefore, the results were not able to be included in the evidence synthesis.

Symptoms of anxiety

There were 2 RCTs (total 425 participants) that measured anxiety using the State-Trait Anxiety Inventory (STAI) at the end of treatment (4 weeks) (Zick 2011, Jacobs 2005). Data were missing from one RCT (Langade 2019) (total 60 participants) that measured anxiety using the Hamilton anxiety rating scale (HAM-A) and was reported as showing an effect favouring WHM.

The STAI is a self-assessment tool that consists of 20 questions evaluating obvious (state) anxiety and 20 questions evaluating hidden (trait) anxiety. The range of scores for each subscale is 20 to 80 (higher is worse). State anxiety, evaluates the individuals feeling in the moment and trait anxiety, measures the individuals usual and general feelings. Determining meaningful difference can be difficult for the trait anxiety subscale as it is intended to identify susceptibility and is less responsive to change compared to state anxiety. For the state anxiety subscale, a cut point of 39-40 is suggested to detect clinically significant symptoms (259).

The HAM-A is a clinician-rated scale that measures the severity of anxiety symptoms (psychological and somatic). The scale consists of 14 items each scored on a scale from 0 (not present) to 4 (severe) to yield a total score from 0 to 56. A higher score indicates more severe anxiety.

Pooled results (total 425 participants) suggested there is little to no effect of WHM on anxiety when compared with placebo (MD 1.71; 95% CI –1.39, 4.80; $p = 0.28$; $I^2 = 25\%$) (*GRADE: Low*).

Fatigue

One RCT (total 34 participants) measured fatigue using the fatigue severity scale (FSS) at the end of treatment (4 weeks) (Zick 2011). The systematic review authors did not provide any further information; therefore, the results were not able to be included in the evidence synthesis.

Comparison 2 (vs inactive control)

There were no studies identified by the included systematic reviews that compared WHM with inactive control (no intervention, waitlist or usual care) in people with insomnia.

Comparison 3 (vs other)

There were 3 RCTs (Maroo 2013, Morin 2005, Ziegler 2002) found by the included systematic reviews that compared WHM with an active intervention[c] in people with insomnia (total 464 participants).

Data from these studies are presented in Appendix F2 Supplementary outcome data.

[c] zolpidem, oxazepam or diphenhydramine

D2.4 Inflammatory bowel disease

D2.4.1 List of reviews

A summary of the PICO criteria of the eligible systematic reviews is provided in Table D-1.

A list of herbs examined in the identified primary studies is provided in Table D-2.

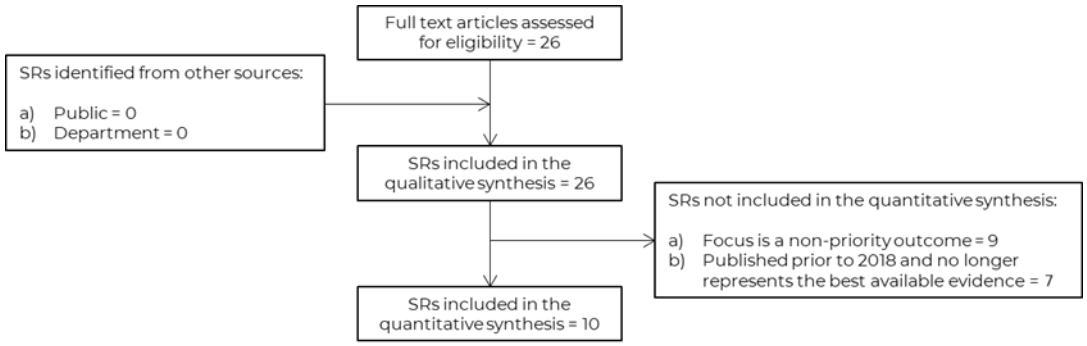
There were 26 reviews assessed for eligibility. Seven (7) reviews (Liu 2021, Chandan 2020, Coelho 2020, Goulart 2020, Zheng 2020, Grammatikopoulou 2018, Iqbal 2018) published in 2018 or after presented results in a meta-analysis and were prioritised for critical appraisal and data extraction.

Nine (9) reviews published after 2018 (Ghassab-Abdollahi 2021, Montazeri 2021, Morvaridzadeh 2021, Ardiana 2020, Goulart 2020a, Hallajzadeh 2020, Jalali 2020, Mohit 2020, Tavakoly 2019) were not considered further as they did not report on outcomes considered critical or important for this review.

The other 10 reviews (Kafil 2017, Kim 2017, Restellini 2017, Schnieder 2017, Simadibrata 2017, Langhorst 2015, Ng 2013, Rahimi 2013, Kumar 2012, Ernst 2008) were published prior to 2018 and were judged to no longer represent the best available evidence. Most of these reviews provided a descriptive or narrative review or individual study results, noting that results were too heterogeneous to conduct a meaningful meta-analysis. These reviews were checked for additional studies and results, with 3 reviews (Kafil 2017, Kim 2017, Langhorst 2015) providing additional data to be considered in the evidence synthesis. In the absence of data, the other 7 reviews (Restellini 2017, Schnieder 2017, Simadibrata 2017, Ng 2013, Rahimi 2013, Kumar 2012, Ernst 2008) were not considered for critical appraisal or data extraction. Figure D-1 outlines the selection process of the included systematic reviews.

Review details, including all outcome domains and measures reported by the included reviews, are provided in Appendix F1. Outcome data for critical or important outcomes are provided in Appendix F2.

Figure D-11 Process flow for prioritising systematic reviews: Inflammatory bowel disease



Abbreviations: SR, systematic review

Table D-13 PICO criteria of eligible systematic reviews: Inflammatory bowel disease

Review ID	Method of analysis	Population [a]	Intervention (relevant herbs) [b]	Comparator [c]	Outcome domains [d]	N	Study ID [e]
Ghassab-Abdollahi 2021 (6)	Meta-analysis	Any	Nigella sativa	Placebo or no intervention	oxidative stress and inflammatory biomarkers	1 (k=11)	Nikkhah-Bodaghi 2019
Montazeri 2021 (7)	Meta-analysis	Any	Nigella sativa	Placebo or no intervention	oxidative stress and inflammatory biomarkers	1 (k=10)	Nikkhah-Bodaghi 2019
Liu 2021 (8)	Meta-analysis	IBD	Polyphenols (curcumin, EGCG, silymarin)	Any	Endoscopic remission, clinical response	10 (k=12)	Hanai 2006, Dryden 2013, Singla 2014, Lang 2015, Rastegarpanah 2015, Banerjee 2017, Kedia 2017, Masoodi 2018, Kumar 2019, Sugimoto 2019
Morvaridzadeh 2021 (9)	Meta-analysis	Any	Ginger	Placebo or no intervention	oxidative stress biomarkers	1 (k=12)	Nikkhah-Bodaghi 2019
Ardiana 2020 (10)	Meta-analysis	Any	Nigella sativa	Placebo or no intervention	oxidative stress and inflammatory biomarkers	1 (k=5)	Nikkhah-Bodaghi 2019
Chandan 2020 (11)	Meta-analysis	UC	Curcumin	Any	Endoscopic remission, clinical response	7 (k=7)	Hanai 2006, Shivakumar 2011, Singla 2014, Lang 2015, Kedia 2017, Banerjee 2017, Masoodi 2018
Coelho 2020 (12)	Individual study results	IBD	Curcumin	Any	Endoscopic remission, clinical response	6 (k=11)	Hanai 2006, Singla 2014, Lang 2015, Kedia 2017, Masoodi 2018, Sadeghi 2019
Goulart 2020 (13)	Meta-analysis	Mild to moderate UC	Curcumin	Any	Endoscopic remission, clinical response	4 (k=4)	Sadeghi 2019, Masoodi 2018, Kedia 2017, Lang 2015
Goulart 2020a (14)	Descriptive	UC & Crohn's disease	Curcumin	Any	oxidative stress and inflammatory biomarkers	8 (k=7)	Sugimoto 2019, Sadeghi 2019, Masoodi 2018, Kedia 2017, Banerjee 2017, Lang 2015, Singla 2014, Hanai 2006
Hallajzadeh 2020 (15)	Meta-analysis	Any	Nigella sativa	Any	glycaemic control, lipid profiles, oxidative stress and inflammatory biomarkers	1 (k=50)	Nikkhah-Bodaghi 2019
Jalali 2020 (16)	Meta-analysis	Any	Ginger	Any	oxidative stress and inflammatory biomarkers	1 (k=20)	Nikkhah-Bodaghi 2019

Review ID	Method of analysis	Population [a]	Intervention (relevant herbs) [b]	Comparator [c]	Outcome domains [d]	N	Study ID [e]
Mohit 2020 (17)	Meta-analysis	Any	Nigella sativa	Any	oxidative stress and inflammatory biomarkers	1 (k=12)	Nikkhah-Bodaghi 2019
Zheng 2020 (18)	Meta-analysis	UC	Curcumin	Any	Clinical / endoscopic remission or improvement	6 (k=6)	Masoodi 2018, Banerjee 2017, Kedia 2017, Lang 2015, Singla 2014, Hanai 2006
Tavakoly 2019 (19)	Meta-analysis	Any	Nigella sativa	Any	C-reactive protein	1 (k=5)	Nikkhah-Bodaghi2019
Grammatikopoulou 2018 (20)	Meta-analysis	UC	Curcumin	Any	Endoscopic remission, clinical response	(k=4)	Banerjee 2017, Kedia 2017, Lang 2015, Hanai 2006
Iqbal 2018 (21)	Meta-analysis	UC	Curcumin	Placebo	Endoscopic remission, clinical response	(k=3)	Banerjee 2017, Lang 2015, Singla 2014
Restellini 2017 (22)	Meta-analysis	IBD (prior to colonoscopy)	Colon-cleansing products (Senna)	Any (castor oil)	Bowel cleansing, adverse effects	1 (k=4)	Gould 1982
Kafil 2017 (23)	Meta-analysis	Collagenous colitis	Any (Boswellia)	Any (placebo)	Clinical response, histological response, QoL, adverse effects	1 (k=12)	Madisch 2007
Kim 2017 (24)	Meta-analysis	UC & Crohn's disease	Herbal medicine (Aloe vera, Andrographis, Artemisia, Boswellia, curcumin, green tea extract, milk thistle, psyllium, wormwood)	Any	Clinical remission/ maintenance, adverse events	12 (k=29)	Lang 2015, Rastegarpanah 2015, Dryden 2013, Sandbom 2013, Holtmeier 2011, Krebs 2012, Sandborn 2010, Omer 2007, Hanai 2006, Langmead 2004, Fernández-Bañares 1999, Hallert 1991
Schneider 2017 (25)	Descriptive	Crohn's disease	Curcumin	Any	Inflammatory biomarkers, disease activity index	0 (k=16)	no RCTs found
Simadibrata 2017 (26)	Descriptive	UC	Curcumin	Placebo	Clinical remission/ maintenance	3 (k=3)	Lang 2015, Singla 2014, Hanai 2006
Langhorst 2015 (27)	Descriptive	UC & Crohn's disease	Any CAM (Aloe vera, Andrographis, Artemisia, Boswellia, chamomile, curcumin, green tea extract, milk thistle, myrrh, psyllium, wormwood)	Any	None specified	12 (k=29)	Rastegarpanah 2015, Singla 2014, Langhorst 2013, Sandborn 2013, Holtmeier 2011, Tang 2011, Krebs 2012, Omer 2007, Hanai 2006, Langmead 2004, Gerhardt 2001, Fernández-Bañares 1999
Ng 2013 (28)	Descriptive	UC & Crohn's	Herbal medicine	Any	Clinical remission /	8	Sandborn 2013, Krebs 2012,

Review ID	Method of analysis	Population [a]	Intervention (relevant herbs) [b]	Comparator [c]	Outcome domains [d]	N	Study ID [e]
		disease			maintenance	(k=21)	Holtmeier 2011, Omer 2007, Hanai 2006, Langmead 2004, Gerhardt 2001, Fernández-Bañares 1999
Rahimi 2013 (29)	Meta-analysis	IBD	Herbal medicine (Andrographis, psyllium)	5-aminosalicylates	Endoscopic remission, clinical response, relapse, adverse events	2 (k=8)	Tang 2011, Fernández-Bañares 1999
Kumar 2012 (30)	Individual study results	IBD	Curcumin	Any	Clinical remission / maintenance	1 (k=1)	Hanai 2006
Ernst 2008 (31)	Descriptive	Any	Boswellia serrata	Any	Any	1 (k=7)	Gerhardt 2001

Abbreviations: CAM, complementary and alternative medicine; EGCG, epigallocatechin-3-gallate (green tea extract); IBD, inflammatory bowel disease; UC, ulcerative colitis
Notes:
N = Number of RCTs meeting our PICO criteria; k = total number of RCTs identified by systematic review.
a. Systematic review with no population restrictions were eligible for inclusion if they presented data that evaluated participants with IBD.
b. Systematic reviews were eligible for inclusion if they presented data that examined the effectiveness of eligible WHMs (see Appendix A8).
c. Systematic review with no comparator restrictions were eligible for inclusion if they presented data that compared WHM with control (placebo or no intervention) or another intervention.
d. Outcomes assessed or listed by the systematic review. Grey highlight = nonpriority outcome; Blue highlight = critical or important outcome
e. Study ID of eligible RCTs that met the PICO criteria of this overview.

Figure D-12 Critical appraisal summary: overview author's judgements about each AMSTAR-2 item for each included systematic review – Inflammatory bowel disease

	Review ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Inflammatory bowel disease	Liu 2021	Y	PY	N	PY	Y	Y	Y	N	PY	N	Y	N	N	Y	N	Y
	Chadan 2020	N	PY	Y	PY	Y	Y	N	PY	PY	N	Y	Y	Y	Y	N	Y
	Coelho 2020	Y	PY	N	PY	Y	Y	Y	PY	Y	N	No meta-analysis	Y	Y	N	No meta-analysis	Y
	Goulart 2020	Y	PY	N	PY	Y	Y	Y	PY	Y	N	Y	Y	Y	N	N	Y
	Zheng 2020	Y	PY	N	PY	Y	Y	N	PY	Y	Y	Y	N	N	Y	N	Y
	Grammatikopoulou 2018	Y	Y	N	Y	Y	Y	N	Y	PY	Y	Y	N	N	Y	Y	Y
	Iqbal 2018	N	N	N	PY	Y	Y	N	Y	N	Y	Y	N	N	N	Y	N
	Kafil 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	No meta-analysis	No meta-analysis	Y	Y	No meta-analysis	Y
	Kim 2017	Y	PY	N	Y	Y	Y	N	PY	Y	N	Y	Y	Y	Y	N	Y
	Langhorst 2015	Y	PY	N	PY	Y	Y	Y	PY	Y	Y	No meta-analysis	No meta-analysis	Y	N	No meta-analysis	Y

N = No; PY = Partial Yes, Y = Yes

Table D-14 List of herbs assessed in the identified primary studies: Inflammatory bowel disease

WHM assessed in identified primary studies	Matched to Tier 1 list of WHM: Digestive system [a]
Aloe (Aloe spp.)	✓
Andrographis (Andrographis paniculate)	✓
Black cumin (Nigella sativa)	!
Boswellia (Boswellia serrata)	✓
Ginger (Zingiber officinale)	!
Liquorice (Glycyrrhiza glabra)	X
Plantain (Ribwort)	X
Psyllium (Plantago ovata)	✓
Senna (Cassia angustifolia)	!
St Mary's thistle (Silybum marianum)	✓
Turmeric (Curcuma longa)	✓
Wormwood (Artemisia absinthium)	✓

Abbreviations: WHM, Western herbal medicine
✓ = yes; X = no;
! = herb identified but the reported outcomes were considered not critical or important for decision-making
a. See Appendix A6.3 - Tier 1 herb list was considered in GRADE. Eligibility was based on the herb list in Appendix A8.

D2.4.2 Critical appraisal

A summary of the quality of included systematic reviews is provided in Figure D-2 and Table D-3. The strengths or limitations of the included systematic reviews assessed against each AMSTAR-2 item is provided in Appendix E1.

There were 5 systematic reviews (Chandan 2020, Goulart 2020, Zheng 2020, Grammatikopoulou 2018, Kim 2017) that included a meta-analysis and were judged to probably provide an accurate and comprehensive summary of the available studies that address the question of interest (i.e. met, or partially met, AMSTAR-2 domains 4, 8, 9 and 11). The 5 other systematic reviews that provided data for this review had at least one critical flaw, as they did not meet domain 8 (Liu 2021) or did not conduct a meta-analysis (domain 11) (Coelho 2020, Iqbal 2018, Kafil 2017, Langhorst 2015).

Table D-15 Critical appraisal summary: Inflammatory bowel disease

Review ID	Summary	Notes
Liu 2021	1 critical flaw (domain 8) and 5 non-critical weaknesses in domains 3, 10, 12, 13 & 15	The authors did not explain their selection of the study designs for inclusion in the review, they did not report on the sources of funding of included studies, they did not investigate the possible impact of risk of bias or account for risk of bias in summary effect estimates, and they did not investigate or discuss the likelihood or impact of publication bias.
Chandan 2020	4 non-critical weaknesses in domains 1, 7, 10 & 15	The authors did not provide comparator details of included studies, they did not provide a list of excluded studies read at full text, they did not report on the sources of funding of included studies, and they did not investigate or discuss the likelihood or impact of publication bias.
Coelho 2020	1 critical flaw (domain 11) and 3 non-critical weaknesses in domains 3, 10 & 14	No meta-analysis. The authors did not explain their selection of the study designs for inclusion in the review, they did not report on the sources of funding of included studies, they did not discuss or explain heterogeneity observed in the results
Goulart 2020	4 non-critical weaknesses in domains 3, 10, 14 & 1 5	The authors did not provide comparator details of included studies, they did not report on the sources of funding of included studies, they did not discuss or explain heterogeneity observed in the results, and they did not investigate or discuss the likelihood or impact of publication bias.

Review ID	Summary	Notes
Zheng 2020	5 non-critical weaknesses in domains 3, 7, 12, 13 & 15	The authors did not provide comparator details of included studies, they did not provide a list of excluded studies read at full text., they did not investigate the possible impact of risk of bias or account for risk of bias in summary effect estimates, and they did not investigate or discuss the likelihood or impact of publication bias.
Grammatikopoulou 2018	4 non-critical weaknesses in domains 3, 7, 12 & 13	The authors did not provide comparator details of included studies, they did not provide a list of excluded studies read at full text, they did not investigate the possible impact of risk of bias or account for risk of bias in summary effect estimates,
Iqbal 2018	1 critical flaw (domain 11) and 8 non-critical weaknesses in domains 1, 2, 7, 9, 12, 13, 14 & 16	No meta-analysis. The authors did not provide comparator details of included studies, they did not assess the risk of bias of included studies, they did not provide a list of excluded studies read at full text, they did not investigate the possible impact of risk of bias or account for risk of bias in summary effect estimates, they did not discuss or explain heterogeneity observed in the results, and they did not report on any potential sources of conflict of interest.
Kafil 2017	1 critical flaw (domain 11) and 0 non-critical weaknesses	No meta-analysis.
Kim 2017	4 non-critical weaknesses in domains 3, 7, 10 & 15	The authors did not provide comparator details of included studies, they did not provide a list of excluded studies read at full text, they did not report on the sources of funding of included studies, and they did not investigate or discuss the likelihood or impact of publication bias.
Langhorst 2015	1 critical flaw (domain 11) and 2 non-critical weaknesses in domains 3 & 14	No meta-analysis. The authors did not provide comparator details of included studies and they did not discuss or explain heterogeneity observed in the results.

D2.4.3 Effects of intervention

Outcomes considered by the NTWC to be critical or important for decision-making in people with inflammatory bowel disease are listed in Table D-4.

Table D-16 Outcomes considered by the NTWC to be critical or important for decision-making: Inflammatory bowel disease

Outcome domain	Measured with (or similar validated scale)	Consensus rating	Data available for comparison 1 or 2	Review ID									
				Liu 2021	Chandan 2020	Coelho 2020	Goulart 2020	Zheng 2020	Grammatikopoulou 2018	Iqbal 2018	Kafil 2017	Kim 2017	Langhorst 2015
Improvement/ remission	CDAI, SCAI, UCDAI	8	Yes	✓	✓	✓	✓	X	✓	X	✓	✓	X
Pain	VAS	8	No	--	--	--	--	--	--	--	--	--	--
HRQoL	IBDQ-9	7	No	X	?	X	?	?	?	?	?	?	X
Emotional functioning	HAM-D / HAM-A	7	No	?	?	?	?	?	?	?	?	?	X
Physical functioning	SF-36 physical component score	7	No	--	--	--	--	--	--	--	--	--	--
Stool quality/ frequency	Any validated measure	6	No	?	?	X	?	?	?	?	?	?	?

Abbreviations: CDAI, Crohn's disease activity index; HAM-A, Hamilton anxiety rating scale; HAM-D, Hamilton depression rating scale; HRQoL, Health-related quality of life; IBDQ-9, inflammatory bowel disease questionnaire; SCCAI, simple clinical colitis activity index; SF-36, 36-item short form; UCDAI, ulcerative colitis disease activity index

Notes:

✓ A study result is available for inclusion in the synthesis.

X A study result is NOT available for inclusion because the systematic review does not adequately report the results (data were incomplete). It is unclear if the primary study reported complete data. Due to time and resource constraints, only the information presented in the systematic review is reported.

? The systematic review did not assess this outcome, it is unclear if the outcome was assessed by the primary studies included in the SR. Due to time and resource constraints, only the information presented in the systematic review is reported.

-- The systematic review did not assess this outcome. The outcome was (probably) not assessed by the included primary studies (for reasons unrelated to the *p*-value, magnitude or direction of the results).

Comparison 1 (vs placebo)

There were 22 RCTs found by the included systematic reviews that compared WHM with placebo in people with IBD (usually as an adjunct to standard therapy). Of these, 17 RCTs (Kumar 2019, Sadeghi 2019, Masoodi 2018, Banerjee 2017, Kedia 2017, Lang 2015, Rastegarpanah 2015, Singla 2014, Dryden 2013, Sandbom 2013, Holtmeier 2011, Shivakumar 2011, Sandbom 2010, Madisch 2007, Omer 2007, Hanai 2006, Langmead 2004) contributed data relevant to at least one critical or important outcome. Four (4) RCTs (Sugimoto 2019, Shapira 2018, Suskind 2013, Atkinson 2002) did not contribute any data because the review authors had judged the studies to be at high risk of bias and one RCT (Hallert 1991) did not report results prior to crossover, therefore were not able to be used in the synthesis.

Clinical improvement and/or remission

The included RCTs reported clinical improvement and/or remission in people with UC or Crohn's disease based on one of the commonly used tools to measure disease activity (e.g. CDAI, UCDAI, SCCAI) at the end of treatment (range 4 to 24 weeks).

The Ulcerative Colitis Disease Activity Index (UCDAI), Simple Clinical Colitis Activity Index (SCCAI) and the Clinical Activity Index (CAI) each incorporate scoring of objective measures (e.g., stool frequency per week, rectal bleeding appearance on endoscopy, temperature) with subjective measures (e.g. physician's assessment, general well-being, abdominal pain and/or cramps) to generate a score for each parameter. The total score ranges from 0 to 12 for the UCDAI, 0 to 20 for the SCCAI, and 0 to 25 for the CAI. Higher scores indicate more severe disease, with various cutoff used to denote disease severity (32-34). The minimal clinically important differences (MCID) for the UCDAI, CAI, or SCCAI have not been established (35).

Similarly, the Crohn's Disease Activity Index (CDAI) incorporates symptoms (e.g. number of loose stools/day), signs (e.g. palpable abdominal mass) and laboratory test results (e.g., haematocrit) to generate a score that ranges from 0 to 600. Scores less than 150 corresponds to remission (or disease quiescence), whereas scores greater than 450 indicate severe disease. A decrease in more than 100 points for the CDAI indicates a clinical response.

Mean end of treatment scores for each group were reported in 2 RCTs (total 151 participants), with pooled results suggesting little to no improvement in disease activity in the WHM group (curcumin) compared with the placebo group (SMD –0.37; 95% CI –0.77, 0.04; $p = 0.08$; $I^2 = 36\%$) (*GRADE: Low*). Data were missing from 20 RCTs (total 1115 participants). It is not clear if DAI scores were reported in the RCTs or were not considered by the included systematic reviews.

For disease improvement, all reviews reported dichotomised data, denoting the proportion of participants in each group who had a prespecified minimal change in the disease activity measure (typically 3 or more points on UCDAI, but varied according to the measure). Pooled results from 8 RCTs (total 403 participants) suggested an improvement in disease activity in the WHM group (curcumin or green tea extract) compared with the placebo group (RR 1.66; 95% CI 1.15, 2.41; $p = 0.007$, $I^2 = 54\%$) (*GRADE: Low*). Data were missing from 14 RCTs (more than 763 participants). In a sensitivity analysis examining the impact of studies at high risk of bias (Dryden 2013, Kumar 2019), the observed result did not substantially change (RR 1.76; 95% CI 1.14, 2.72; $p = 0.01$; $I^2 = 59\%$).

For disease remission, the reviews reported dichotomised data, denoting the proportion of participants in each group who had reached, maintained (or failed to maintain) a prespecified cut-off that indicates inactive disease (remission or quiescence). Pooled results from 14 RCTs (total 974 participants) suggested disease remission in the WHM group compared with the placebo group (RR 1.54; 95% CI 1.24, 1.90; $p < 0.0001$, $I^2 = 41\%$) (*GRADE: Moderate*). Data were missing from 8 RCTs (more than 192 participants). In a sensitivity analysis examining the impact of studies at high risk of bias (Dryden 2013, Rastegarpanah 2015) the observed result did not substantially change (RR 1.56; 95% CI 1.21, 2.01; $p = 0.007$; $I^2 = 49\%$).

Quality of life

There were 4 RCTs (Sadeghi 2019, Holtmeier 2011, Omer 2007, Langmead 2004) (total 236 participants) that reported quality of life measured using the Inflammatory Bowel Disease Questionnaire (IBDQ) or the IBDQ-9 at the end of treatment (range 8 to 52 weeks). The review authors did not provide sufficient information to include in the evidence synthesis, noting 2 RCTs suggested an effect favouring WHM, 1 RCT suggested no difference between groups, and one RCT suggested an effect favouring placebo.

The IBDQ is a 32-item physician-administered questionnaire that assesses HRQoL in the preceding 2 weeks. It can be divided into four domains relating to bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items) and social function (5 items) (36). Higher scores represent better quality of life, with each item having a graded response from 1 (worst situation) to 7 (best situation) (score range from 32 to 244). The IBDQ-9 is a shortened version of the IBDQ and measure 9-items relating to nausea, delay social engagement, passing wind, bowel movements, abdominal cramps, unwellness, fatigue, feeling happy and energy level in people with IBD (score range from 9 to 63).

Emotional functioning

One RCT (Omer 2007) (total 40 participants) reported emotional wellbeing measured using the Hamilton depression score (HAM-D) at the end of treatment (10 weeks). The review authors did not provide sufficient information to include in the evidence synthesis, noting the results suggested there was no difference between treatment groups.

Comparison 2 (vs inactive control)

There were 2 RCTs found by the included systematic reviews that compared WHM with no intervention in people with Crohn's disease (Krebs 2012[d]) or ulcerative colitis (Fernández-Bañares 1999[e]) that contributed data relevant to at least one critical or important outcome.

Clinical improvement and/or remission

Two RCTs reported clinical remission in people with UC or Crohn's disease based on one of the commonly used tools to measure disease activity (e.g. CDAI, UCDAI) at the end of treatment (range 6 to 52 weeks). For disease remission, the reviews reported dichotomised data, denoting the proportion of participants in each group who had reached or maintained a prespecified cut-off that indicates inactive disease (remission or quiescence).

Pooled results (total 87 participants) showed little or no disease remission in the WHM group compared with the inactive control (RR 1.82; 95% CI 0.47, 7.02; $p < 0.0001$, $I^2 = 41\%$) (*GRADE: Very low*).

Quality of life

One RCT (Krebs 2012) (total 20 participants) reported quality of life measured using the IBDQ at the end of treatment (6 weeks). The review authors did not provide sufficient information to include in the evidence synthesis, noting the results suggested an effect favouring WHM.

[d] delivered as an adjunct to corticosteroids

[e] delivered alone or as an adjunct to mesalazine

Emotional functioning

One RCT (Krebs 2012) (total 20 participants) reported emotional wellbeing measured using the Hamilton depression score (HAM-D) at the end of treatment (6 weeks). The review authors did not provide sufficient information to include in the evidence synthesis, noting the results suggested an effect favouring WHM.

Comparison 3 (vs other)

There were 3 RCTs found by the included systematic reviews that compared WHM with an active intervention (mesalazine) in people with Crohn's disease (Gerhardt 2001) or ulcerative colitis (Langhorst 2013, Tang 2011) that contributed data relevant to at least one critical or important outcome.

Data from these studies are presented in Appendix F2 Supplementary outcome data.

D2.5 Irritable bowel syndrome

D2.5.1 List of reviews

A summary of the PICO criteria of the eligible systematic reviews is provided in Table D-5.

A list of herbs examined in the identified primary studies is provided in Table D-6.

There were 19 reviews assessed for eligibility. Six (6) systematic reviews published in 2018 or after (Black 2020, Hawrelak 2020, Tan 2020, Alammar 2019, Hong 2018, Ng 2018) presented results in a meta-analysis and were prioritised for critical appraisal and data extraction.

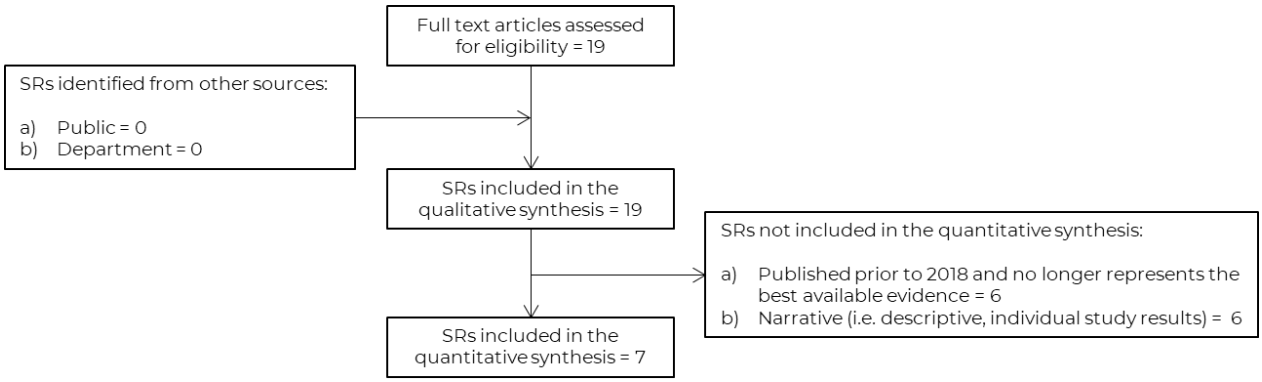
Six (6) other systematic reviews published prior to 2018 presented results in a meta-analysis (Lakhan 2015, Khanna 2014, Ford 2008, Huertas-Ceballos 2008, Liu 2006, Pittler 1998) but were not further assessed as the reviews were judged to no longer represent the best available evidence.

A further 7 reviews provided a descriptive or narrative summary of individual study results (Anh 2020, Anheyer 2017a, Korterink 2015, Ruepert 2011, Shen 2009, Grigoleit 2005, Jailwala 2000), noting that results were too heterogeneous to conduct a meaningful meta-analysis. These reviews were checked for additional studies and results, but in the absence of usable data were not considered further. One of these reviews (Anheyer 2017a) identified an additional RCT and was included in the quantitative synthesis.

Figure D-3 outlines the selection process of the final systematic reviews included in the quantitative synthesis.

Review details, including all outcome domains and measures reported by the included reviews, are provided in Appendix F1. Outcome data for critical or important outcomes are provided in Appendix F2.

Figure D-13 Process flow for prioritising systematic reviews: Irritable bowel syndrome



Abbreviations: SR, systematic review

Table D-17 PICO criteria of eligible systematic reviews: Irritable bowel syndrome

Review ID	Method of analysis	Population [a]	Intervention (relevant herbs) [b]	Comparator [c]	Outcomes [d]	N	Study IDs [e]
Anh 2020 (37)	Descriptive	Any	Ginger	No comparator restrictions	Any (IBSSS, ARRS)	1 (k=109)	Tilburg 2014
Black 2020 (38)	Network meta-analysis	IBS	Soluble fibre (ispaghula husk), peppermint oil, antispasmodic drugs, gut-brain neuromodulators	Control (placebo or each other)	Global symptom improvement, Pain, Adverse events	15 (k = 51)	Arthurs 1983, Bijkerk 2009, Capanni 2005, Cappello 2007, Cash 2016, Jalihal 1990, Lech 1988, Liu 1997, Longstreth 1981, Merat 2009, Mosaffa-Jahromi 2016, Nigam 1984, Prior 1987, Ritchie 1979, Weerts 2019
Hawrelak 2020 (39)	Meta-analysis	IBS	WHM (peppermint oil, aloe, St John's wort, ginger, turmeric, STW-5 combination, capsicum, aniseed	Control (placebo)	Global symptom improvement, Pain, QoL, adequate relief of symptoms, bloating distension, cramping, stool frequency, emotional functioning	30 (k = 33)	Alam 2013, Bortolotti 2011, Brinkhaus 2005, Brown 2015, Capanni 2005, Cappello 2007, Carling 1989, Cash 2016, Davis 2006, Dew 1984, Evans 1982, Hutchings 2011, Kline 2001, Lawson 1988, Lech 1988, Liu 1997, Madisch 2004, Merat 2009, Mosaffa-Jahromi 2016, Nash 1986, Pedersen 1998, Portincasa 2016, Rees 1979, Saito 2010, Schneider 1990, Storsrud 2015, Tilburg 2014, Vejdani 2006, Weiss 1988, Wildgrube 1988
Tan 2020 (40)	Meta-analysis	Functional gastrointestinal disorders	WHM (peppermint oil, aloe, ginger, St John's wort, anise oil, curcumin, spearmint, lemon balm	Control (placebo or other)	Global symptom improvement	9 (k = 50)	Cappello 2007, Davis 2006, Liu 1997, Merat 2009, Mosaffa-Jahromi 2016, Portincasa 2016, Storsrud 2015, Saito 2010, Tilburg 2014
Alammar 2019 (41)	Meta-analysis	IBS	Peppermint oil	Control (placebo)	Global symptom improvement, Pain, Adverse effects	12 (k =12)	Alam 2013, Capanni 2005, Cappello 2007, Carling 1989, Cash 2016, Dew 1984, Lech 1988, Liu 1997, Merat 2009, Rees 1979, Schneider 1990, Weiss 1988
Hong 2018 (42)	Meta-analysis	IBS	Aloe vera	Control (placebo)	Global symptom improvement, HRQoL, Anxiety, Adverse events	3 (k = 3)	Davis 2006, Hutchings 2011, Storsrud 2015
Ng 2018 (43)	Meta-analysis	IBS	Curcumin	Control (placebo)	Global symptom improvement, HRQoL	2 (k = 5)	Brinkhaus 2005, Portincasa 2016
Anheyer 2017a (44)	Descriptive	Gastrointestinal disorders in children	WHM (Peppermint oil, Psyllium fibre)	Control (placebo or other)	Symptom rating, Pain	2 (k=14)	Kline 2001, Shulman 2016
Korterink 2015 (45)	Descriptive	Functional abdominal pain in children	Any (Peppermint)	Any	Pain, HRQoL, functional disability, adverse events	1 (k=6)	Kline 2001

Review ID	Method of analysis	Population [a]	Intervention (relevant herbs) [b]	Comparator [c]	Outcomes [d]	N	Study IDs [e]
Lakhan 2015 (46)	Meta-analysis	Pain (includes IBS)	Zingiberaceae (Curcumin)	Any	Pain	0 (k=8)	--
Khanna 2014 (47)	Meta-analysis	IBS	Peppermint	Control (placebo)	Global symptom improvement, Pain Adverse events	(k=5)	--
Ruepert 2011 (48)	individual study results	IBS	Bulking agents, antispasmodics, antidepressants (Psyllium)	Control (placebo)	Global symptom improvement, Pain	--	--
Shen 2009 (49)	Descriptive	IBS	Peppermint, psyllium	--	--	--	--
Ford 2008 (50)	Meta-analysis	IBS	Peppermint	--	--	--	--
Huertas-Ceballos 2008 (51)	Meta-analysis	IBS and recurrent abdominal pain	Peppermint	--	--	--	--
Liu 2006 (52)	Meta-analysis	IBS	Iberogast	--	--	--	--
Grigoleit 2005 (53)	Descriptive	IBS	Peppermint	--	--	--	--
Jailwala 2000 (54)	Descriptive	IBS	Peppermint	--	--	--	--
Pittler 1998 (55)	Meta-analysis	IBS	Peppermint	--	--	--	--

Abbreviations: ARRS, adequate relief rating scale; HRQoL, health-related quality of life; IBS, irritable bowel syndrome; IBSSS, IBS severity scale; WHM, Western herbal medicine

Notes:

N = Number of RCTs meeting our PICO criteria; k = total number of RCTs identified by systematic review.

a. Systematic review with no population restrictions were eligible for inclusion if they presented data that evaluated participants with IBS.

b. Systematic reviews were eligible for inclusion if they presented data that examined the effectiveness of eligible WHMs (see Appendix A8).

c. Systematic review with no comparator restrictions were eligible for inclusion if they presented data that compared WHM with control (placebo or no intervention) or another intervention.

d. Outcomes assessed or listed by the systematic review. Grey highlight = nonpriority outcome; Blue highlight = critical or important outcome

e. Study ID of eligible RCTs that met the PICO criteria of this overview.

-- Systematic review not assessed. The outcome domain was not critical or important for this overview OR a more recent SR nominated as best available is included.

Figure D-14 Critical appraisal summary: review author's judgements about each AMSTAR-2 item for each included systematic review – Irritable bowel syndrome

	Review ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Inflammatory bowel disease	Anh 2020	Y	PY	Y	PY	Y	Y	N	Y	Y	Y	No meta-analysis	No meta-analysis	Y	Y	No meta-analysis	Y
	Black 2020	Y	PY	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Hawrelak 2020	Y	Y	N	PY	Y	Y	N	PY	Y	Y	Y	Y	Y	Y	Y	Y
	Tan 2020	Y	PY	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y
	Alammar 2019	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Hong 2018	Y	PY	N	Y	Y	Y	N	PY	Y	Y	Y	Y	Y	Y	Y	Y
	Ng 2018	Y	PY	N	PY	Y	Y	Y	PY	Y	N	Y	Y	Y	Y	Y	Y
	Anheyer 2017a	Y	PY	Y	PY	Y	Y	N	PY	Y	N	No meta-analysis	No meta-analysis	N	N	No meta-analysis	Y

N = No; PY = Partial Yes, Y = Yes

Table D-18 List of herbs assessed in the identified primary studies: Irritable bowel syndrome

WHM identified in included studies	Matched to Tier 1 list of WHM: Digestive system [a]
Herbal combination (Iberogast)	X
Herbal combination (Turmeric [Curcuma longa]) (+ fennel essential oil*)	✓
Aloe (Aloe spp.)	X
Aniseed (Pimpinella anisum)	X
Artichoke (Cynara scolymus)	✓
Capsicum (Capsicum minimum)	X
Celandine (Chelidonium majus)	✓
Ginger (Zingiber officinale)	X
Lemon balm (Melissa officinalis), Spearmint (Mentha spicata) (+ Coriandrum sativum*) combination	✓
Peppermint (Mentha x piperita)	✓
Psyllium (Plantago ovata)	X
Senna (Cassia angustifolia)	X
St John's wort (Hypericum perforatum)	X

Abbreviations: WHM, Western herbal medicine
✓ = yes; X = no;
* not on List A
a. See Appendix A6.3 - Tier 1 herb list was considered in GRADE. Eligibility was based on the herb list in Appendix A8

D2.5.2 Critical appraisal

A summary of the quality of included systematic reviews is provided in Figure D-4 and Table D-7. The strengths or limitations of the included systematic reviews assessed against each AMSTAR-2 domain is provided in Appendix E1.

The 6 systematic reviews that included a meta-analysis and were published in 2018 or after (Black 2020, Hawrelak 2020, Tan 2020, Alammar 2019, Hong 2018, Ng 2018) were judged to probably provide an accurate and comprehensive summary of the available studies that address the question of interest (i.e. met, or partially met, AMSTAR-2 domains 4, 8, 9 and 11). The other systematic reviews that provided data for this review (Anh 2020, Anheyer 2017a) had at least one critical flaw, as they did not conduct a meta-analysis (domain 11).

Table D-19 Critical appraisal summary: Irritable bowel syndrome

Review ID	Summary	Notes
Anh 2020	1 critical flaw (domain 11) 1 non-critical weaknesses in domain 7	No meta-analysis The authors do not provide a list of excluded studies read at full text.
Black 2020	1 non-critical weaknesses in domain 7	The authors do not provide a list of excluded studies read at full text.
Hawrelak 2020	2 non-critical weaknesses in domains 3 and 7	The authors do not comment on choosing RCTs and did not provide a list of excluded studies read in full text.
Tan 2020	2 non-critical weaknesses in domains 7 and 10	The authors do not provide a list of studies read at full text but excluded and they did not report on any funding or support for the RCTs.
Alammar 2019	No non-critical weaknesses detected	
Hong 2018	2 non-critical weaknesses in domains 3 and 7	The authors do not comment on choosing RCTs and did not provide a list of excluded studies read in full text.
Ng 2018	2 non-critical weaknesses in domains 3 and 10	The authors do not comment on choosing RCTs and they did not report on any funding or support for the RCTs.
Anheyer 2017a	1 critical flaw (domain 11)	No meta-analysis

Review ID	Summary	Notes
	4 non-critical weaknesses in domains 7, 10, 13 & 14	The authors do not provide a list of studies read at full text but excluded, they did not report on any funding or support for the RCTs, they did not account for risk of bias when discussing results, and they did not discuss heterogeneity observed in the review

Abbreviations: IBS, irritable bowel syndrome; PICO, population, intervention, comparison, outcome; RCT, randomised control trial; systematic review, systematic review

D2.5.3 Effects of intervention

Outcomes considered by the NTWC to be critical or important for decision-making in people with irritable bowel syndrome are listed in Table D-8.

Table D-20 Outcomes considered by the NTWC to be critical or important for decision-making: Irritable bowel syndrome

Outcome domain	Measured with (or similar)	Consensus rating	Data available for comparison 1 or 2	Review ID							
				Anh 2020	Black 2020	Hawrelak 2020	Tan 2020	Alammar 2019	Hong 2018	Ng 2018	Anheyer 2017a
Clinical improvement	IBS-SSS, GSRS or ARRS	8	Yes	--	X	✓	✓	✓	✓	X	X
Pain	VAS	8	Yes	X	X	✓	✓	✓	--	X	X
HRQoL	SF-36	7	No	--	--	X	--	?	--	X	--
Emotional functioning	HADS	7	No	--	--	X	--	--	--	--	--
Bloating, distension, cramping	GISRS (items)	7	No	--	--	X	--	?	X	--	--
Stool quality, frequency	Bowel transit time, changes in stool frequency	6	No	--	--	X	--	?	X	--	X

Abbreviations: ARRS, adequate relief rating scale; GSRS, Gastrointestinal symptoms rating scale; HADS, Hamilton anxiety and depression score; HRQoL, Health-related quality of life; IBS, irritable bowel syndrome; IBSSS, IBS symptom severity score; SF-36, 36-item short form; VAS, visual analogue scale

Notes:

✓ A study result is available for inclusion in the synthesis.

X A study result is NOT available for inclusion because the systematic review does not adequately report the results (data were incomplete). It is unclear if the primary study reported complete data. Due to time and resource constraints, only the information presented in the systematic review is reported.

? The systematic review did not assess this outcome, it is unclear if the outcome was assessed by the primary studies included in the SR. Due to time and resource constraints, only the information presented in the systematic review is reported.

-- The systematic review did not assess this outcome. The outcome was (probably) not assessed by the included primary studies (for reasons unrelated to the *p*-value, magnitude or direction of the results).

Comparison 1 (vs placebo)

There were 40 RCTs identified in the included systematic reviews that compared WHM[f] with placebo in people with IBS. Of these, 21 RCTs (Cash 2016, Mosaffa-Jahromi 2016, Portincasa 2016, Storsrud 2015, Tilburg 2014, Hutchings 2011, Saito 2010, Merat 2009, Cappello 2007, Davis 2006, Vejdani 2006, Capanni 2005, Kline 2001, Liu 1997, Schneider 1990, Carling 1989, Lech 1988, Weiss 1988, Nash 1986, Dew 1984, Rees 1979) contributed data relevant to at least one critical or important outcome.

[f] Including peppermint oil, aloe vera, turmeric, psyllium, St John's wort, capsicum, ginger, anise oil, senna or fixed dose herbal combinations

The other 19 RCTs (Weerts 2019, Shulman 2016, Brown 2015, Alam 2013, Bortolotti 2011, Bijkerk 2009, Brinkhaus 2005, Bundy 2004, Madisch 2004, Jalihal 1990, Nigam 1990, Lawson 1988, Pedersen 1998, Prior 1987, Wildgrube 1988, Arthurs 1983, Evans 1982, Longstreth 1981, Ritchie 1979) did not contribute data because study results were not adequately reported, either by the primary study or the included systematic reviews.

Clinical improvement

The included RCTs reported improvement (or relief) in IBS symptoms (patient or clinician reported) measured using the IBS-Symptoms Severity Scale (IBS-SSS), the gastrointestinal symptoms rating scale (GSRS), or a non-specified bowel symptom scale at the end of treatment (between 2 weeks and 20 weeks). The measure used in the RCTs was often not clearly described by the systematic reviews.

The IBS-SSS is a widely used questionnaire to assess the severity of IBS symptoms during the preceding week, and measures abdominal pain intensity, abdominal pain frequency, abdominal distension, dissatisfaction with bowel habits, and influence of IBS on life on a 0-100 scale (56). The total IBS-SSS score ranges between 0 and 500, with a higher score indicating more severe symptoms.

The GSRS is a 15-item tool that assesses gastrointestinal symptoms[g] in the preceding week in people with peptic ulcer disease and IBS. Items are rated on a 3 point scale from 0 (no discomfort) to 3 (severe discomfort) with the total maximum score of 45 (high is worse) (57).

Mean change scores were reported in 3 RCTs (total 236 participants), with pooled results suggesting an effect that favours the WHM group (aloe vera juice) compared with placebo (SMD –0.44; 95% CI –0.70, –0.18; $p = 0.0008$; $I^2 = 0\%$) (*GRADE: Low*). Data were missing from 22 RCTs (total 1606 participants). Mean scores were generally not considered by the included systematic reviews, but it is not clear if they were also not reported by the primary studies.

In a sensitivity analysis examining the impact of one RCT at high risk of bias (Hutchings 2011) the size of the effect estimate decreased but did not substantially change the overall direction of effect (SMD –0.39; 95% CI –0.75, –0.04; $p = 0.03$; $I^2 = 0\%$).

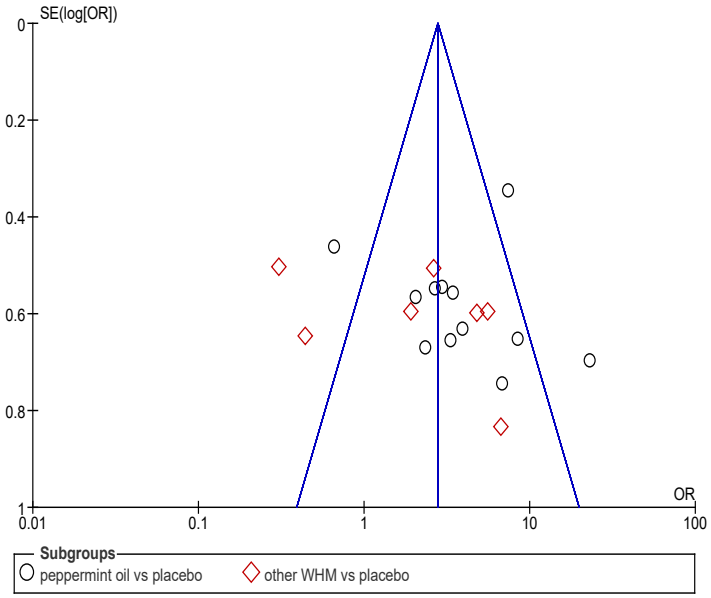
Most systematic reviews reported response rates, indicating the proportion of participants who achieved a global improvement in IBS symptoms, but the specific criteria used to a convey a response was often not described. There were 19 RCTs (total 1279 participants) with available data that reported response rates. Pooled results suggested an effect that favours WHM compared with placebo (RR 1.78; 95% CI 1.37, 2.33; $p < 0.0001$; $I^2 = 67\%$) (*GRADE: Moderate*). Data were incomplete for 6 RCTs (total 563 participants), with 3 RCTs noting an effect favouring WHM ($p < 0.05$), and 3 RCTs noting no difference between groups ($p > 0.05$).

Statistical heterogeneity was reduced when the RCTs examining the effect of peppermint oil (RR 1.98; 95% CI 1.53, 2.56; $p < 0.0001$; $I^2 = 46\%$) were examined separate to those examining the effect of other WHMs (RR 1.48; 95% CI 0.84, 2.61; $p = 0.17$; $I^2 = 77\%$). Visual inspection of the funnel plot (see Figure D-5) suggests the likelihood of statistical heterogeneity relating to clinical differences between studies (e.g. differences in the intervention, participants, setting).

In a sensitivity analysis examining the impact of 8 RCTs at high risk of bias (Portincasa 2016, Merat 2010, Cappello 2007, Davis 2006, Vejdani 2006, Cappani 2005, Kline 2001, Weiss 1988) the overall direction was unchanged, but the size of the effect estimate decreased (RR 1.50; 95% CI 1.01, 2.24; $p = 0.04$; $I^2 = 74\%$). Statistical heterogeneity remained high (see Figure D-6).

[g] including pain or discomfort, diarrhoea, constipation, bloating, burping, rumbling, hunger pains, heartburn, nausea, acid reflux, gas, loose stools, hard stools, urgency, and incomplete emptying

Figure D-15 Funnel plot of comparison: WHM vs placebo: irritable bowel syndrome – Global improvement in IBS symptoms



Abdominal pain

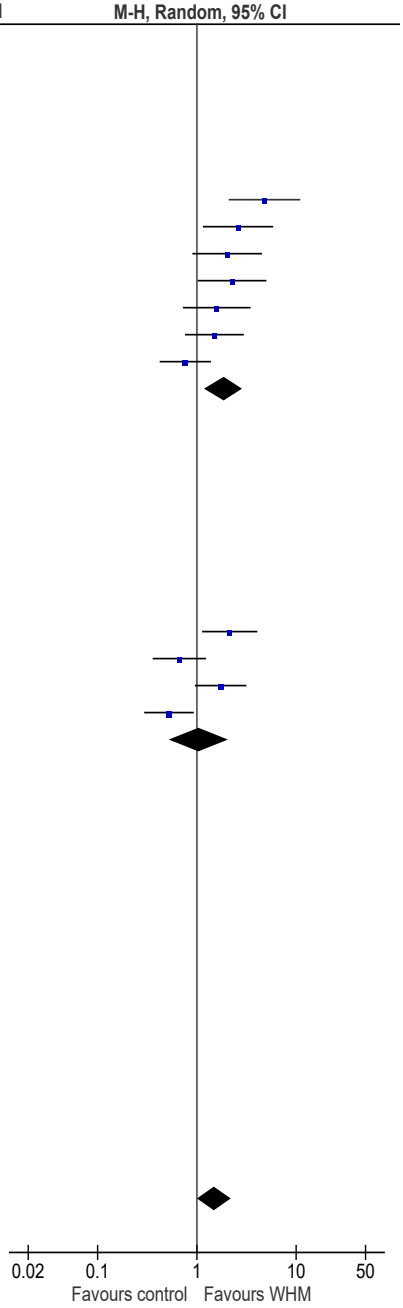
There were 7 RCTs (total 606 participants) with available data that reported improvement in abdominal pain at the end of treatment (range 2 to 18 weeks). The measure used in the RCTs was often not clearly described by the systematic review authors, but dichotomised data were reported and assumed to be the proportion of participants with change from baseline in abdominal symptoms-subscales of the GRSR or IBS-SSS (or visual analogue scale or other). The criteria used to indicate a response was not specified.

Pooled results suggested an effect that favours WHM compared with placebo (RR 1.85; 95% CI 1.50, 2.28; $p < 0.0001$; $I^2 = 0\%$) (*GRADE: Low*). Data were incomplete for 13 RCTs (total 983 participants), with 9 RCTs noting an effect favouring WHM ($p < 0.05$), and 4 RCTs noting no difference between groups ($p > 0.05$).

A sensitivity analysis examined the impact of RCTs at high risk of bias was not conducted, as all but one RCT (Cash 2016) were judged to be at high risk of bias.

Figure D-16 Forest plot of comparison: WHM vs placebo: irritable bowel syndrome – Global improvement in IBS symptoms (sensitivity analysis)

Study or Subgroup	WHM Events	WHM Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 peppermint oil vs placebo						
Weiss 1988 (peppermint oil)	17	30	4	30	0.0%	4.25 [1.62, 11.15]
Cappello 2007 (peppermint oil)	18	28	10	29	0.0%	1.86 [1.05, 3.31]
Kline 2001 (peppermint oil)	15	21	9	21	0.0%	1.67 [0.95, 2.93]
Capanni 2005 (peppermint oil)	73	91	31	87	0.0%	2.25 [1.67, 3.04]
Merat 2010 (peppermint oil)	14	45	6	45	0.0%	2.33 [0.98, 5.53]
Dew 1984 (peppermint oil)	24	29	5	29	8.2%	4.80 [2.13, 10.84]
Rees 1979 (peppermint oil)	13	18	5	18	8.3%	2.60 [1.17, 5.78]
Cash 2016 (peppermint oil)	13	34	7	37	8.3%	2.02 [0.92, 4.46]
Lech 1988 (peppermint oil)	13	23	6	24	8.4%	2.26 [1.04, 4.93]
Carling 1989 (peppermint oil)	17	30	5	14	8.5%	1.59 [0.74, 3.42]
Mosaffa-Jahromi 2016 (peppermint oil)	21	40	7	20	9.2%	1.50 [0.77, 2.92]
Nash 1986 (peppermint oil)	13	41	17	41	9.9%	0.76 [0.43, 1.36]
Subtotal (95% CI)		**215**		**183**	**60.9%**	**1.87 [1.19, 2.92]**
Total events	114		52			
Heterogeneity: Tau² = 0.22; Chi² = 15.68, df = 6 (P = 0.02); I² = 62%						
Test for overall effect: Z = 2.72 (P = 0.006)						
2.2.2 other WHM vs placebo						
Portincasa 2016 (curcumin+fennel)	15	60	4	61	0.0%	3.81 [1.34, 10.83]
Vejdani 2006 (Carmint+Psyllium)	8	14	3	18	0.0%	3.43 [1.11, 10.59]
Davis 2006 (aloe vera juice)	11	31	6	27	0.0%	1.60 [0.68, 3.74]
Mosaffa-Jahromi 2016 (anise oil)	30	40	7	20	9.5%	2.14 [1.15, 4.00]
Tilburg 2014 (ginger)	12	30	9	15	9.7%	0.67 [0.37, 1.22]
Storsrud 2015 (aloe vera juice)	18	33	11	35	9.9%	1.74 [0.97, 3.10]
Saito 2010 (St John's wort)	11	35	21	35	10.0%	0.52 [0.30, 0.92]
Subtotal (95% CI)		**138**		**105**	**39.1%**	**1.06 [0.54, 2.11]**
Total events	71		48			
Heterogeneity: Tau² = 0.40; Chi² = 16.12, df = 3 (P = 0.001); I² = 81%						
Test for overall effect: Z = 0.17 (P = 0.86)						
2.2.3 Not reported (missing data)						
Brinkhaus 2005 (curcumin) (1)	0	53	0	53		Not estimable
Evans 1982 (peppermint oil) (2)	0	10	0	10		Not estimable
Hutchings 2011 (aloe vera juice) (3)	0	55	0	55		Not estimable
Madisch 2004 (Iberogast) (4)	0	104	0	104		Not estimable
Pedersen 1998 (Appital) (5)	0	29	0	30		Not estimable
Schneider 1990 (peppermint oil) (6)	0	30	0	30		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**353**		**288**	**100.0%**	**1.50 [1.01, 2.24]**
Total events	185		100			
Heterogeneity: Tau² = 0.33; Chi² = 38.17, df = 10 (P < 0.0001); I² = 74%						
Test for overall effect: Z = 2.02 (P = 0.04)						
Test for subgroup differences: Chi² = 1.82, df = 1 (P = 0.18), I² = 45.1%						



Footnotes
(1) p>0.05
(2) p<0.005
(3) p>0.05
(4) p=0.001
(5) p=0.081
(6) p=0.002

Health-related quality of life

Four RCTs (total 411 participants) measured HRQoL using the IBS quality of life instrument (Portincasa 2016, Hutchings 2011, Saito 2010) or the SF-36 (Merat 2010) at the end of treatment (range 4 to 20 weeks). The systematic reviews did not report complete data, but noted 2 RCTs reported an effect favouring WHM (peppermint, curcumin plus fennel) and 2 RCTs reported there was no difference between the WHM (aloe vera juice, St John's wort) and placebo groups. Due to time and resource constraints, retrieval of primary studies was not pursued.

Emotional functioning

Two RCTs (total 144 participants) measured emotional functioning using the hospital anxiety and depression scale (HADS) (Storsrud 2015) or an unspecified measure for psychological distress (Brinkhaus 2005) at the end of treatment (range 4 to 18 weeks). The systematic reviews did not report complete data but noted there was no difference between the WHM (aloe vera juice, curcumin) and placebo groups. Due to time and resource constraints, retrieval of primary studies was not pursued.

Bloating, distension or cramping

There were 6 RCTs (total 243 participants) that measured bloating, distension or cramping at the end of treatment (range 2 to 8 weeks) (Mosaffa-Jahromi 2016, Brown 2015, Bortolotti 2011, Vejdani 2006, Lawson 1988, Wildgrube 1988). The systematic reviews did not report complete data and the measure used in the RCTs were not clearly described but assumed to be the proportion of participants with improvement in symptom-subscales of the GRSR or IBS-SSS, or changes in severity scores (7-point Likert scale or similar). An effect favouring WHM[h] was noted in 4 RCTs and 2 RCTs suggested there was no difference between the WHM (peppermint oil, cayenne) and placebo groups. Due to time and resource constraints, retrieval of primary studies was not pursued.

Stool frequency or quality

There were 9 RCTs (total 518 participants) that measured stool frequency or quality at the end of treatment (range 2 to 6 weeks) (Storsrud 2015, Bortolotti 2011, Liu 1997, Schneider 1990, Lawson 1988, Lech 1988, Nash 1986, Dew 1984, Rees 1979). The systematic reviews did not report complete data and the measure used in the RCTs were not clearly described but assumed to be the proportion of participants with improvement in symptom-subscales of the GRSR or IBS-SSS, or changes in severity scores (7-point Likert scale or similar). An effect favouring WHM (peppermint oil) was noted in 2 RCTs, 5 RCTs suggested there was no difference between the WHM (peppermint oil, cayenne) and placebo groups, and 2 RCTs did not provide results. Due to time and resource constraints, retrieval of primary studies was not pursued.

Comparison 2 (vs inactive control)

There were no studies found by the included systematic reviews that compared WHM with other interventions in people with IBS.

Comparison 3 (vs other)

Two RCTs (Ritchie 1979, Nigam 1984) were identified in the included systematic reviews comparing WHM with another intervention (amitriptyline or hyoscine butyl bromide) in people with IBS. No individual study results were available, and retrieval of primary study results were not pursued.

[h] Peppermint oil, fixed dose of lemon balm, peppermint oil & Coriandrum sativum, or fixed dose of horse chestnut, peppermint oil & Schinopsis lorentzii

D2.6 Gastro-oesophageal reflux disease

D2.6.1 List of reviews

A summary of the PICO criteria of the eligible systematic reviews is provided in Table D-9.

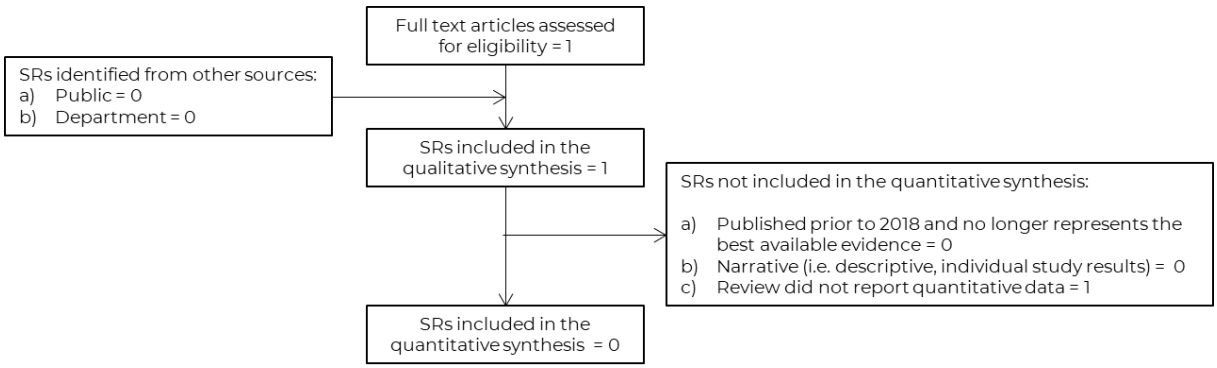
A list of herbs examined in the identified primary studies is provided in Table D-10.

One systematic review (Sadeghi 2020) identified one RCT (Moeini 2016) that met our PICO criteria but did not present a study result available for inclusion in the synthesis. Due to time and resource constraints retrieval of primary studies was not pursued.

Figure D-7 outlines the selection process of the final systematic reviews included in the quantitative synthesis.

Review details, including all outcome domains and measures reported by the included reviews, are provided in Appendix F1. Outcome data for critical or important outcomes are provided in Appendix F2.

Figure D-17 Process flow for prioritising systematic reviews: Gastro-oesophageal reflux disease



Abbreviations: SR, systematic review

Table D-21 PICO criteria of included systematic reviews: Gastro-oesophageal reflux disease

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]	N	Study ID [e]
Sadeghi 2020 (58)	Meta-analysis	GORD	Hawthorn	Control (placebo)	Improvement of GORD symptoms	1 (k=13)	Moeini 2016

Abbreviations: GORD, gastro-oesophageal reflux disease
Notes:
N = Number of RCTs meeting our PICO criteria; k = total number of RCTs identified by systematic review.
a. Systematic review with no population restrictions were eligible for inclusion if they presented data that evaluated participants with GORD.
b. Systematic reviews were eligible for inclusion if they presented data that examined the effectiveness of eligible WHMs (see Appendix A8).
c. Systematic review with no comparator restrictions were eligible for inclusion if they presented data that compared WHM with control (placebo or no intervention) or another intervention.
d. Outcomes assessed or listed by the systematic review. Grey highlight = nonpriority outcome; Blue highlight = critical or important outcome
e. Study ID of eligible RCTs that met the PICO criteria of this overview.

Table D-22 List of herbs assessed in the identified primary studies: Gastro-oesophageal reflux disease

WHM identified in included studies	Matched to Tier 1 list of WHM: Digestive system [a]
Hawthorn (Crataegus oxyacantha / C. monogyna)	X

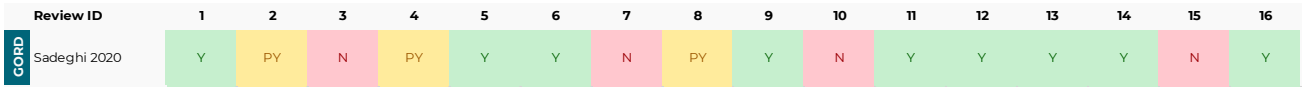
Abbreviations: WHM, Western herbal medicine
✓ = yes; X = no
a. See Appendix A6.3 - Tier 1 herb list was considered in GRADE. Eligibility was based on the herb list in Appendix A8

D2.6.2 Critical appraisal

A summary of the quality of the included systematic review is provided in Figure D-8 and Table D-11. The strengths or limitations of the included systematic reviews assessed against each AMSTAR-2 domain is provided in Appendix E1.

Sadeghi 2020 was judged to probably provide an accurate and comprehensive summary of the available studies that address the question of interest (i.e. met, or partially met, AMSTAR-2 domains 4, 8, 9 and 11).

Figure D-18 Critical appraisal summary: review author's judgements about each AMSTAR-2 item for each included systematic review – Gastro-oesophageal reflux disease



N = No; PY = Partial Yes, Y = Yes

Table D-23 Critical appraisal summary: Gastro-oesophageal reflux disease

Review ID	Summary	Notes
Sadeghi 2020	4 non-critical weaknesses in domains 3, 7, 10 and 15.	The authors did not justify selecting study designs to be included and they do not provide a list of excluded studies read at full text. The source of funding of included studies was not described and no graphical or statistical interpretation for publication bias was considered or conducted.

Abbreviations: GORD, gastroesophageal reflux disease

D2.6.3 Effects of intervention

Outcomes considered by the NTWC to be critical or important for decision-making in people with inflammatory bowel disease conditions are listed in Table D-12.

Table D-24 Outcomes considered by the NTWC to be critical or important for decision-making: Gastro-oesophageal reflux disease

Outcome domain	Measured with	Consensus rating	Data available for comparison 1 or 2	Review ID
				Sadeghi 2020
GORD symptoms [a]	Symptom severity (scale not specified)	8	No	X
Pain	Symptom severity (scale not specified)	8	No	X
HRQoL	SF-36 or similar	7	No	?
Emotional functioning	SF-36 mental component score (or similar)	7	No	?
Physical functioning	SF-36 physical component score (or similar)	7	No	?
Patient reported improvement	Symptom severity (scale not specified)	7	No	X
Regurgitation	Symptom severity (scale not specified)	7	No	X

Abbreviations: HRQoL, Health-related quality of life; SF-36 36-item short form

Notes:

a. Including heartburn, oesophagitis, (silent) acid reflux, dysphagia and belching.

✓ A study result is available for inclusion in the synthesis.

X A study result is NOT available for inclusion because the systematic review does not adequately report the results (data were incomplete). It is unclear if the primary study reported complete data. Due to time and resource constraints, only the information presented in the systematic review is reported.

? The systematic review did not assess this outcome, it is unclear if the outcome was assessed by the primary studies included in the SR. Due to time and resource constraints, only the information presented in the systematic review is reported.

-- The systematic review did not assess this outcome. The outcome was (probably) not assessed by the included primary studies (for reasons unrelated to the *p*-value, magnitude or direction of the results).

Comparison 1 (vs placebo)

One RCT (Moeini 2016) was found by the included systematic review that compared hawthorn with placebo in people with GORD. The RCT could have contributed data relevant to at least one of the prioritised outcomes, however there was insufficient information reported in the review to make an assessment.

There was one review awaiting classification (59) that aims to examine the use of aloe vera in the management of people with GORD that could contribute data to this comparison.

Regurgitation

One RCT (Moeini 2016) (total 80 participants) was reported to measure GORD symptoms (heartburn and regurgitation) at the end of treatment (4 weeks). The systematic review authors (Sadeghi 2020) stated the RCT used a validated scale to detect the severity of symptoms, and noted the RCT reported an improvement ($p = 0.02$) in acid regurgitation in those who received hawthorn compared with the placebo group, but no other data were provided.

Comparison 2 (v inactive control)

There were no studies identified by the included systematic reviews that compared WHM with inactive control (no intervention, waitlist or usual care) in people with GORD.

Comparison 3 (other)

There were no studies identified by the included systematic reviews that compared WHM with other interventions in people with GORD.

D3 Gynaecological/Reproductive

D3.1 Menstrual conditions (endometriosis, amenorrhea, dysmenorrhoea etc.)

D3.1.1 List of reviews

A summary of the PICO criteria of the eligible systematic reviews is provided in Table D-13.

A list of herbs examined in the identified primary studies is provided in Table D-14.

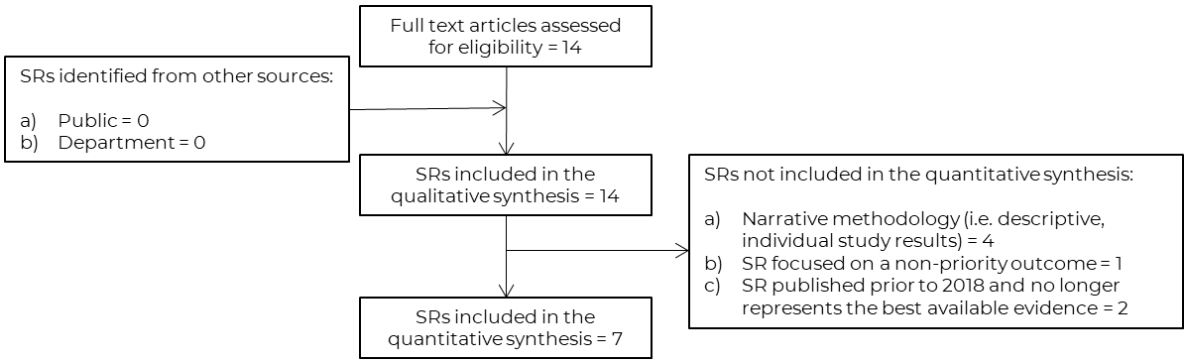
There were 6 reviews (Negi 2021, Mollazadeh 2020, Xu 2020, Pattanittum 2016, Chen 2016, Daily 2015) that presented results in a meta-analysis and were prioritised for critical appraisal and data extraction. Three reviews (Shinjyo 2020, Ursoniu 2016, Lakhan 2015) that presented results in a meta-analysis were not prioritised as they did not identify any RCTs meeting our PICO criteria, or they were judged to no longer represent the best available evidence as the identified RCTs were already identified in other (more recent) reviews.

There were 5 descriptive reviews (Anh 2020, Pellow 2018, Javan 2016, Terry 2011, Ulbricht 2011) that provided a narrative summary of results or presented individual study results, noting that results were too heterogeneous to conduct a meaningful meta-analysis. These reviews were checked for additional studies and results, with one review (Pellow 2018) included for critical appraisal and data extraction as it identified additional relevant RCTs not identified by the other reviews. In the absence of additional data, the 4 other reviews were not considered further.

Figure D-9 outlines the selection process of the final included systematic reviews.

Review details, including all outcome domains and measures reported by the included reviews, are provided in Appendix F1. Outcome data for critical or important outcomes are provided in Appendix F2.

Figure D-19 Process flow for prioritising systematic reviews: menstrual conditions



Abbreviations: SR, systematic review

Table D-25 PICO criteria of included systematic reviews: Menstrual conditions

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcome [d]	N	Study ID [e]
Negi 2021 (60)	Meta-analysis	Dysmenorrhoea	Ginger	Placebo or NSAIDs	Pain	8 (k=8)	Abadi 2020, Jenabi 2013, Kashefi 2014, Ozgoli 2009, Pakniat 2019, Rad 2018, Rahnama 2012, Shirvani 2014
Xu 2020 (61)	Meta-analysis	Dysmenorrhoea	Cinnamon, ginger, fennel	Placebo	Pain	6 (k=9)	Kashefi 2014, Rahnama 2012, Jenabi 2013, Pakniat 2019, Jaafarpour 2015, Jahangirifar 2018
Mollazadeh 2020 (62)	Meta-analysis	Ovarian cysts, adenomyosis, endometriosis, uterine fibroids, pelvic inflammatory disease, heavy menstrual bleeding; dysmenorrhoea	Vitex/ Chaste tree	Placebo or mefenamic acid	Menstrual bleeding	2 (k=5)	Shahhosseini 2005, Shobeiri 2014
Anh 2020 (37)	Descriptive	No restriction	Ginger	Not specified	Blood loss	1 (k=109)	Kashefi 2015
Shinjyo 2020 (63)	Meta-analysis	Sleep or related health problems	Valerian	Not specified	Not specified	1 (k=60)	Mirabi 2011
Pellow 2018 (64)	Descriptive	Dysmenorrhoea	Single medicinal plant applications	Placebo or conventional analgesia	Pain	6 (k=22)	Jenabi 2013, Rahnama 2012, Kashefi 2014, Younesy 2014, Heshmati 2016, Mirabi 2011
Pattanittum 2016 (65)	Meta-analysis	Dysmenorrhoea	Dietary supplements	Placebo, dietary supplements, no treatment, or conventional analgesia	Pain	10 (k=27)	Abkari 2012, Akhavan Amjadi 2009, Dolation 2010, Jenabi 2010, Jenabi 2012, Jenabi 2013, Kashefi 2014, Modaress 2011, Rahnama 2010, Rahnama 2012
Chen 2016 (66)	Meta-analysis	Dysmenorrhoea	Ginger	Placebo, control or active treatment (conventional analgesia or exercise)	Pain	6 (k=6)	Jenabi 2013, Rahnama 2012, Kashefi 2014, Ozgoli 2009, Shirvani 2015, Halder 2012
Javan 2016 (67)	Descriptive	Heavy menstrual bleeding	Medicinal plant preparations	Placebo	Blood loss	1 (k=3)	Kashefi 2015

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcome [d]	N	Study ID [e]
Ursoniu 2016 (68)	Meta-analysis	No restrictions	Flaxseed	Not clear	--	--	--
Daily 2015 (69)	Meta-analysis	Dysmenorrhoea	Ginger	Placebo or active treatment (conventional analgesia or exercise)	Pain	7 (k=7)	Shirvani 2015, Kashefi 2014, Gupta 2013, Jenabi 2013, Rahnama 2012, Halder 2011, Ozgoli 2009
Lakhan 2015 (46)	Meta-analysis	Any pain condition	Zingiberaceae family extracts	Placebo	Pain	1 (k=8)	Rahnama 2012
Terry 2011 (70)	Descriptive	Any pain condition	Ginger	Placebo or other intervention	--	--	--
Ulbricht 2011 (71)	Descriptive	Any*	Saffron	Placebo or other intervention	--	--	--

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; RCT, randomised controlled trial

Notes:

N = Number of RCTs meeting our PICO criteria; k = total number of RCTs identified by systematic review.

a. Systematic review with no population restrictions were eligible for inclusion if they presented data that evaluated participants with menstrual conditions.

b. Systematic reviews were eligible for inclusion if they presented data that examined the effectiveness of eligible WHMs (see Appendix A8).

c. Systematic review with no comparator restrictions were eligible for inclusion if they presented data that compared WHM with control (placebo or no intervention) or another intervention.

d. Outcomes assessed or listed by the systematic review.

e. Study ID of eligible RCTs that met the PICO criteria of this overview.

* The authors discussed studies relating to the following 4 conditions: depression, Alzheimer's disease, asthma, dysmenorrhea, erectile dysfunction, exercise performance enhancement, infertility (male), premenstrual syndrome, psoriasis

-- Systematic review not assessed. The outcome domain was not critical or important for this overview OR a more recent SR nominated as best available is included.

Figure D-20 Critical appraisal summary: review author's judgements about each AMSTAR-2 item for each included systematic review – menstrual conditions

	Review ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Menstrual conditions	Negi 2021	Y	PY	Y	PY	Y	Y	N	PY	Y	Y	Y	Y	Y	Y	Y	Y
	Xu 2020	Y	PY	Y	PY	Y	Y	N	PY	Y	Y	Y	Y	Y	Y	Y	Y
	Mollazadeh 2019	Y	PY	Y	PY	Y	Y	Y	PY	Y	Y	Y	N	Y	Y	N	Y
	Pellow 2018	Y	PY	Y	N	Y	Y	N	PY	Y	Y	No meta-analysis	No meta-analysis	Y	Y	No meta-analysis	Y
	Chen 2016	Y	Y	Y	PY	Y	Y	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y
	Pattanittum 2016	Y	Y	Y	PY	Y	Y	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y
	Daily 2015	Y	PY	Y	PY	Y	N	N	PY	Y	N	Y	N	Y	Y	Y	N

N = No; PY = Partial Yes, Y = Yes

Table D-26 List of herbs assessed in the identified primary studies: Menstrual conditions

WHM identified in included studies	Matched to Tier 1 list of WHM: Gynaecological / reproductive disorders [a]
Chamomile (Matricaria recruitica)	X
Cinnamon (Cinnamomum zeylanicum / C. cassia)	X
Fenugreek (Trigonella foenum-graecum)	X
Ginger (Zingiber officinale)	X
Peppermint (Mentha piperita)	X
Valerian (Valeriana officinalis)	X
Vitex/ chaste tree (Vitex agnus-castus)	✓

Abbreviations: WHM, Western herbal medicine
✓ = yes; X = no
a. See Appendix A6.3 - Tier 1 herb list was considered in GRADE. Eligibility was based on the herb list in Appendix A8

D3.1.2 Critical appraisal

A summary of the quality of included systematic reviews is provided in Figure D-10 and Table D-15. The strengths or limitations of the included systematic reviews assessed against each AMSTAR-2 domain is provided in Appendix E1.

The 6 systematic reviews that included a meta-analysis (Chen 2016, Daily 2015, Negi 2021, Pattanittum 2016, Pellow 2018, Xu 2020) were judged to probably provide an accurate and comprehensive summary of the available studies that address the question of interest (i.e. met, or partially met, AMSTAR-2 domains 4, 8, 9 and 11). One review (Pellow 2018) had two critical flaws (i.e. did not meet, or partially meet, one of the prespecified critical AMSTAR-2 domains) as it did not conduct a comprehensive literature search and did not include a meta-analysis (domains 4 & 11).

Table D-27 Critical appraisal summary: Menstrual conditions

Review ID	Summary	Notes
Negi 2021	1 non-critical weakness in domain 7	The authors did not provide a list of studies excluded at full-text review.
Mollazadeh 2020	2 non-critical weakness in domains 12 and 15	The authors did not investigate the possible impact of risk of bias on summary estimates of effect or discuss the likelihood of publication bias.
Xu 2020	1 non-critical weakness in domain 7	The authors did not provide a list of studies excluded at full-text review.
Pellow 2018	2 critical flaws (domain 4 & 11) and 1 non-critical weakness in domain 7	No meta-analysis. The authors did not justify language and date restrictions applied to the literature search or provide a list of studies excluded at full-text review.
Chen 2016	0 critical flaws and 0 non-critical weaknesses	
Pattanittum 2016	0 critical flaws and 0 non-critical weaknesses	
Daily 2015	5 non-critical weaknesses in domains 6, 7, 10, 12, 16	The authors did not report that data extraction was performed in duplicate, justify the exclusion of studies at full text or provide a list of full-text studies excluded, report on funding sources for RCTs, investigate the impact of risk of bias on summary estimates of effect, and did report a potential conflict of interest without explaining how this was managed.

D3.1.3 Effects of intervention

Outcomes considered by the NTWC to be critical or important for decision-making in people with menstrual conditions are listed in Table D-16.

Table D-28 Outcomes considered by the NTWC to be critical or important for decision-making: Menstrual conditions

Outcome domain	Measured with	Consensus rating	Data available for comparison 1 or 2	Review ID						
				Chen 2016	Daily 2015	Mollazadeh 2019	Negi 2021	Pattanittum 2016	Pellow 2018	Xu 2020
Pain	VAS (or any validated measure)	8	Yes	✓	✓	?	✓	✓	✓	✓
Patient reported improvement	No eligible reviews reported this outcome	8	No	?	?	?	?	?	?	?
Health-related quality of life	No eligible reviews reported this outcome	7	No	?	?	?	?	?	?	?
Emotional functioning	No eligible reviews reported this outcome	7	No	?	?	?	?	?	?	?
Physical functioning	No eligible reviews reported this outcome	7	No	?	?	?	?	?	?	?
Menstrual regularity	No eligible reviews reported this outcome	7	No	?	?	?	?	?	?	?
Patient-reported blood loss	Higham score	6	Yes	--	--	✓	--	--	--	--

Abbreviations: NTWC, Natural Therapies Working Committee; VAS, visual analogue scale.
Notes:
✓ A study result is available for inclusion in the synthesis.
X A study result is NOT available for inclusion because the systematic review does not adequately report the results (data were incomplete). It is unclear if the primary study reported complete data. Due to time and resource constraints, only the information presented in the systematic review is reported.
? The systematic review did not assess this outcome, it is unclear if the outcome was assessed by the primary studies included in the SR. Due to time and resource constraints, only the information presented in the systematic review is reported.
-- The systematic review did not assess this outcome. The outcome was (probably) not assessed by the included primary studies (for reasons unrelated to the *p*-value, magnitude or direction of the results).

Comparison 1 (vs placebo)

There were 13 RCTs found by the included systematic reviews that compared WHM with placebo in people with dysmenorrhea or heavy menstrual bleeding. Of these, 8 RCTs (Jahangirifar 2018, Jaafarpour 2015, Shobeiri 2014, Kashefi 2014, Jenabi 2013, Abkari 2012, Rahnama 2012, Dolation 2010) contributed data relevant to 2 critical or important outcomes (pain intensity and patient-reported blood loss). The result for 5 other RCTs were not adequately reported by the systematic reviews and data from those studies do not contribute to the pooled results described below.

Pain intensity

Seven (7) RCTs (total 601 participants) reported pain intensity measured using a visual analogue scale (VAS) at the end of treatment (range one to 3 menstrual cycles) (Jahangirifar 2018, Jaafarpour 2015, Abkari 2012, Dolation 2010, Jenabi 2013, Kashefi 2014, Rahnama 2012).

The VAS is subjective tool that can be used to measure a variety of outcomes. It is measured on a continuous scale (mm) from 0 (no pain) to 100 (worst imaginable pain)[i], with higher scores indicating a higher intensity of pain. The MCID for pain not been established in people with primary dysmenorrhoea, with the MCID reported to be 10 mm (or 1 on a 10–point scale) in people with endometriosis (72). The median absolute MCID on a VAS scale in people with chronic pain is reported to be 20 mm (IQR 15–30) (73).

Pooled results suggest an effect favouring WHM when compared with placebo for the reduction of pain, although there is substantial statistical heterogeneity (MD –2.34, 95% CI –2.92, –1.76, $p < 0.00001$; $I^2 = 90\%$) (*GRADE: Moderate*). Data were missing from 4 RCTs (total 396 participants), all of which were reported by the review authors to suggest an effect favouring the WHM ($p < 0.05$).

In a sensitivity analysis examining the impact of one RCT (Rahnama 2012) judged to be at high risk of bias (contributing <10% of data), the pooled effect estimate did not materially change (MD –2.46, 95% CI –3.06, –1.83, $p < 0.00001$; $I^2 = 92\%$). Similar results were observed when 2 RCTs (Jahangirifar 2018, Jaafarpour 2015) for which we had imputed data were not included in the analysis (MD –2.58, 95% CI –3.30, –1.87, $p < 0.00001$; $I^2 = 81\%$).

Patient-reported blood loss

One RCT (total 60 participants) reported menstrual blood loss using the Higham score at the end of treatment (one menstrual cycle) (Shobeiri 2014).

The Higham score is a tool that considers different components to assess menstrual blood loss: 1) pictorial blood loss assessment chart; 2) duration of menstrual bleeding; 3) number of tampons or pads used; and 4) presence of clots. Each component is assigned a score, and the total is used to classify menstrual blood loss. There have been many different iterations of the Higham scoring tool (74) and the specific version used was not specified in the systematic review. In one iteration, a score of 0 to 5 represents normal blood loss, 6 to 10 mildly increased blood loss, 11 to 20 moderately increased blood loss and a score of 21 or more representing severely increased blood loss. It was assumed that this iteration of the Higham score was used by the included RCT (Shobeiri 2014).

The results suggested there was no important difference on patient-reported blood loss comparing WHM with placebo in people with heavy menstrual bleeding (MD 1.00; 95% CI –5.32, 7.32; $p = 0.76$) (*GRADE: Very low*).

Comparison 2 (vs inactive control)

Three (3) RCTs (Modaress 2011, Jenabi 2010, Gupta 2013) were identified by the included systematic reviews that examined the effect of WHM compared with an inactive control in people with dysmenorrhoea. Two RCTs (Jenabi 2010, Modaress 2011) compared the effect of chamomile with no treatment, with participants in one RCT (Modaress 2011) also receiving an NSAID (mefenamic acid). One RCT (Gupta 2013) studied the effect of ginger versus no treatment, with participants in both groups also instructed to follow a daily muscle strengthening and stretching regimen. No other studies were identified that compared WHM versus inactive control (no intervention, waitlist or usual care) and measured the prioritised outcomes of interest.

Pain intensity

Three (3) RCTs (total 304 participants) reported pain intensity measured using a VAS (Modaress 2011), a numeric rating scale (NRS) (Gupta 2013), or the short form McGill pain questionnaire (SF-MPQ) (Jenabi 2010) at the end of treatment (range 2 to 3 menstrual cycles).

[i] or from 0 (no pain) to 10 (worst pain) on a 10-cm scale

The NRS is a segmented version of a VAS that is administered verbally or graphically. The 11-point scale ranges from 0 (representing no pain) to 10 (representing pain as bad as you can imagine). The SF-MPQ is a self-reported measure of pain that assesses both the quality and the intensity of subjective pain. It consists of 15 words (11 sensory, 4 affective), of which respondents choose those that best describe their experience of pain. Three pain scores are derived from the sum of the intensity rank values for sensory, affective, and total pain score which ranges from 0 to 45 (75). The measure also includes a present pain intensity index measured using a VAS for pain (0-10)[j]. A higher score is indicative of more severe pain. An MCID of at least 5 points has been proposed in a sample of people with musculoskeletal and rheumatic pain (75). No MCID in people with menstrual conditions was identified.

Pooled results from the 3 RCTs suggest an effect that favours WHM compared with no intervention (MD –2.29, 95% CI –4.49, –0.09; $p = 0.04$; $I^2 = 89\%$) (*GRADE: Very low*), however all studies contributing data were judged to have a high risk of bias and there was a high level of heterogeneity.

Comparison 3 (vs other)

There were 7 RCTs that compared the effect of WHM against an active comparator; being either progressive muscle relaxation (Halder 2012), nutritional supplements[k] (Kashefi 2014) or non-steroidal anti-inflammatory drugs[l] (Pakniat 2019, Rad 2018, Shirvani 2015, Jenabi 2012, Ozgoli 2009) that contributed data to at least one critical or important outcome (pain intensity).

Data from these studies are presented in Appendix F2 Supplementary outcome data.

[j] Note the 0-10 score is reported by the RCT.

[k] zinc sulphate

[l] mefenamic acid, Ibuprofen or a fixed-combination NSAID (containing paracetamol, ibuprofen and caffeine)..

D3.2 Premenstrual disturbances

D3.2.1 List of reviews

A summary of the PICO criteria of the eligible systematic reviews is provided in Table D-18.

A list of herbs examined in the identified primary studies is provided in Table D-17.

There were 5 reviews (Ghaderi 2020, Shinjyo 2020, Csupor 2019, Verkaik 2017, van Die 2013) that presented results in a meta-analysis and were prioritised for critical appraisal and data extraction. The other 7 reviews (Khalesi 2019, Cerqueira 2017, Hausenblas 2015, Su Hee 2014, Dante 2011, Ulbricht 2011, Whelan 2009) provided a descriptive or narrative review of individual study results but did not provide any meaningful data for inclusion in a meta-analysis (with many simply noting the benefits or harms of the intervention). These reviews were checked for additional studies and results, but in the absence of data were not considered for critical appraisal or data extraction.

Figure D-11 outlines the selection process of the final included systematic reviews.

Review details, including all outcome domains and measures reported by the included reviews, are provided in Appendix F1. Outcome data for critical or important outcomes are provided in Appendix F2.

Table D-29 List of herbs assessed in the identified primary studies: Premenstrual disturbances

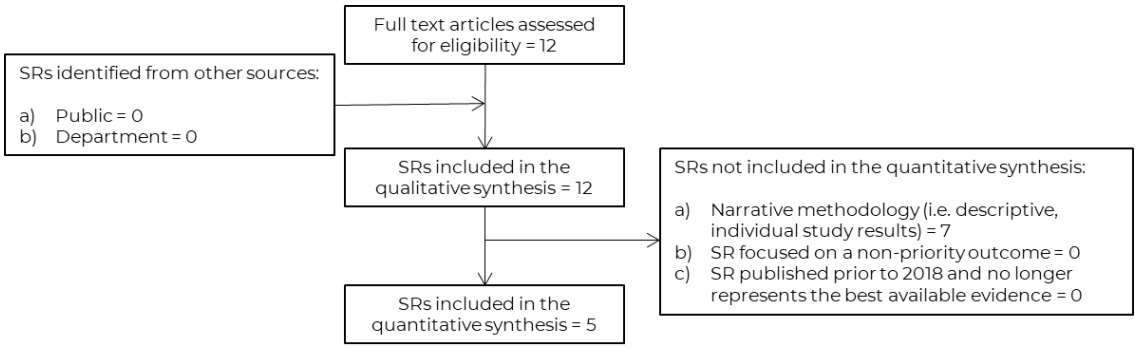
WHM identified in included studies	Matched to Tier 1 list of WHM: Gynaecological / reproductive disorders [a]
Chamomile (Matricaria recruitica)	X
Chaste tree (Vitex agnus castus)	✓
Ginkgo (Ginkgo biloba)	X
Saffron (Crocus sativus)	X
St John's wort (Hypericum perforatum)	X
Valerian (Valeriana officinalis)	X

Abbreviations: WHM, Western herbal medicine

✓ = yes; X = no

a. See Appendix A6.3 - Tier 1 herb list was considered in GRADE. Eligibility was based on the herb list in Appendix A8

Figure D-21 Process flow for prioritising systematic reviews: Premenstrual disturbances



Abbreviations: SR, systematic review

Table D-30 PICO criteria of included systematic reviews: Premenstrual disturbances

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]	N	Study ID [e]
Ghaderi 2020 (76)	Meta-analysis	Umbrella review (any condition)	Saffron	Placebo OR other intervention	Emotional functioning, C-reactive protein	1 (k=21)	Agha-Hosseini 2008
Shinjyo 2020 (77)	Meta-analysis	Sleep problems and associated disorders	Valerian	Placebo	Sleep problems, Anxiety	1 (k=60)	Behboodi Moghadam Z 2016
Csupor 2019 (78)	Meta-analysis	Premenstrual syndrome	Chaste tree berry*	Placebo	Patient reported improvement, Pain	3 (k=3)	Schellenberg 2012, He 2009, Schellenberg 2001
Khalesi 2019 (79)	Descriptive	Premenstrual syndrome	Chamomile	Placebo OR other intervention	PMS symptoms, Anxiety, Bloating/retention, Physical symptoms, Pain	4 (k=8)	Najafi 2018, Sharifi 2014, Karimian 2013, Modaress 2011
Cerqueira 2017 (80)	Descriptive	Premenstrual syndrome and PMDD	Chaste tree berry	Placebo OR other intervention	PMS symptoms	8 (k=8)	Schellenberg 2012, Zamani 2012, Ciotta 2011, Ma 2010, He 2009, Atmaca 2003, Schellenberg 2001, Lauritzen 1997
Verkaik 2017 (81)	Meta-analysis	Premenstrual syndrome and PMDD	Chaste tree berry	Placebo	Emotional functioning, Pain, Patient-reported improvement	17 (k=17)	Kaplanoglu 2015, Mousavi 2015, Salehi 2013, Schellenberg 2012, Zamani 2012, Ciotta 2011, Risoleti 2011, Di Pierro 2009, He 2009, Pakgohar 2009, Scaldarella 2008, Atmaca 2003, Onaran 2003, Delavar 2002, Schellenberg 2001, Lauritzen 1997, Turner 1993
Hausenblas 2015 (82)	Descriptive	Any**	Saffron	Placebo OR other intervention	PMS symptoms, depression	1 (k=12)	Agha-Hosseini 2008
Su Hee 2014 (83)	Descriptive	Premenstrual syndrome	Acupuncture OR any herbal medicine ***	Placebo OR other intervention	PMS symptoms, anxiety, depression	9 (k=19)	Zamani 2012, Canning 2010, Ma 2010, Masumeh 2010, He 2009, Ozgoli 2009, Agha-Hosseini 2008, Hicks 2004, Atmaca 2003
van Die 2013 (84)	Meta-analysis	Female reproductive disorders	Chaste tree berry	Placebo	Patient reported improvement, PMS symptoms, Clinical global impression	10 (k=12)	Zamani 2012., Ciotta 2011, Ma 2010, Di Pierro 2009, He 2009, Pakgohar 2009, Atmaca 2003, Schellenberg 2001, Lauritzen 1997, Turner 1993

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]	N	Study ID [e]
Dante 2011 (85)	Descriptive	Premenstrual syndrome	Any herbal medicine***	Placebo OR other intervention	PMS symptoms	11 (k=17)	Canning 2010, Ma 2010, He 2009, Ozgoli 2009, Agha-Hosseini 2008, Hicks 2004, Atmaca 2003, Schellenberg 2001, Lauritzen 1997, Tamborini 1993, Turner 1993
Ulbricht 2011 (71)	Descriptive	Any	Saffron	Placebo OR other intervention	Any effectiveness OR safety outcomes	--	--
Whelan 2009 (86)	Individual data	Premenstrual syndrome and PMDD	Herbs, vitamins and minerals ***	Placebo OR other intervention	Any effectiveness OR safety outcomes	7 (k=11)	Agha-Hosseini 2008, Hicks 2004, Atmaca 2003, Schellenberg 2001, Lauritzen 1997, Tamborini 1993, Turner 1993

Abbreviations: PMDD, premenstrual dysphoric disorder; RCT, randomised controlled trial; SR, systematic review

Notes:

N = Number of RCTs meeting our PICO criteria; k = total number of RCTs identified by systematic review.

a. Systematic review with no population restrictions were eligible for inclusion if they presented data that evaluated participants with premenstrual disturbances.

b. Systematic reviews were eligible for inclusion if they presented data that examined the effectiveness of eligible WHMs (see Appendix A8).

c. Systematic review with no comparator restrictions were eligible for inclusion if they presented data that compared WHM with control (placebo or no intervention) or another intervention.

d. Outcomes assessed or listed by the systematic review. Grey highlight = nonpriority outcome; Blue highlight = critical or important outcome

e. Study ID of eligible RCTs that met the PICO criteria of this overview.

* The authors assessed RCTs with 'properly characterised chasteberry products' only.

** The authors discussed studies relating to the following 4 conditions: Depression, Sexual dysfunction, PMS, Weight management

*** The authors found evidence for the following herbs: chaste tree berry, St John's wort, saffron, & ginkgo biloba

**** The authors discussed studies relating to the following 4 conditions: depression, Alzheimer's disease, asthma, dysmenorrhea, erectile dysfunction, exercise performance enhancement, infertility (male), premenstrual syndrome, psoriasis

-- Systematic review not assessed. The outcome domain was not critical or important for this overview OR a more recent SR nominated as best available is included.

Figure D-22 Critical appraisal summary: review author's judgements about each AMSTAR-2 item for each included systematic review – Premenstrual disturbances

	Review ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
PREMENTRUAL DISTURBANCES	Ghaderi 2020	Y	PY	Y	PY	Y	N	N	PY	Y	N	Y	Y	Y	Y	Y	Y
	Shinjyo 2020	Y	PY	Y	PY	N	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y
	Csupor 2019	Y	PY	Y	PY	Y	Y	Y	PY	Y	N	Y	Y	Y	N	N	Y
	Verkaik 2017	Y	PY	Y	PY	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
	van Die 2013	Y	PY	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y

N = No; PY = Partial Yes, Y = Yes

D3.2.2 Critical appraisal

A summary of the quality of included systematic reviews is provided in Figure D-12 and Table D-19. The strengths or limitations of the included systematic reviews assessed against each AMSTAR-2 domain is provided in Appendix E1.

All 5 systematic reviews that included a meta-analysis (Ghaderi 2020, Shinjyo 2020, Csupor 2019, Verkaik 2017, van Die 2013) were judged to probably provide an accurate and comprehensive summary of the available studies that address the question of interest (i.e. met, or partially met, AMSTAR-2 domains 4, 8, 9 and 11). However, reporting of results within the systematic reviews were often limited. The other 7 systematic reviews (Cerqueira 2017, Khalesi 2019, Hausenblas 2015, Su Hee 2014, Dante 2011, Ulbricht 2011, Whelan 2009) had at least one critical flaw (did not meet domain 11) and were not further assessed.

Table D-31 Critical appraisal summary: Premenstrual disturbances

Review ID	Summary	Notes
Ghaderi 2020	3 non-critical weaknesses in domains 6, 7 & 10	The authors do not perform data extraction in duplicate, do not provide a list of excluded studies read at full text, and they did not report on any funding or support for the RCTs.
Shinjyo 2020	4 non-critical weaknesses in domains 5, 6, 7 & 10	The authors do not perform study selection or data extraction in duplicate, do not provide a list of excluded studies read at full text, and they did not report on any funding or support for the RCTs.
Csupor 2019	3 non-critical weaknesses in domains 10, 14 & 15	The authors do not report on any funding or support for the RCT, they do not discuss heterogeneity observed in the review, and they do not investigate publication bias.
Verkaik 2017	1 non-critical weaknesses in domain 10	The authors do not report on any funding or support for the RCT.
van Die 2013	2 non-critical weaknesses in domain 7 & 15	The authors do not provide a list of excluded studies read at full text and they do not investigate publication bias.

Abbreviations: RCT, randomised controlled trial

D3.2.3 Effects of intervention

Outcomes considered by the NTWC to be critical or important for decision-making in people with premenstrual disturbances are listed in Table D-20.

Table D-32 Outcomes considered by the NTWC to be critical or important for decision-making: Premenstrual disturbances

Outcome domain	Measured with	Consensus rating	Data available for comparison 1 or 2	Review ID				
				Ghaderi 2020	Shinjyo 2020	Csupor 2019	Verkaik 2017	van Die 2013
PMS symptoms	PMSD, MMDQ (or other)	9	Yes	--	--	✓	✓	✓
Patient reported improvement	VAS, CGI (or other)	9	Yes	--	--	X	✓	✓
Depression	BDI, HAM-D (or other)	7	Yes	X	X	X	✓	X
Anxiety	STAI (or other)	7	Yes	X	X	X	✓	X
Emotional functioning	SF-36 MCS (or similar)	7	No	?	X	X	?	?
Physical functioning	SF-36 PCS (or similar)	7	No	--	--	X	?	?
HRQoL	SF-36 or similar	7	No	--	--	--	--	--

Abbreviations: BDI, Beck depression inventory; HAM-D, Hamilton depression rating scale; HRQoL, health-related quality of life; MCS, mental component score; MMDQ, Moos menstrual distress questionnaire; PCS, physical component score; PMSD, premenstrual tension syndrome self-rating scale; STAI, state-trait anxiety inventory; VAS, visual analogue scale

Notes:

✓ A study result is available for inclusion in the synthesis.
X A study result is NOT available for inclusion because the systematic review does not adequately report the results (data were incomplete). It is unclear if the primary study reported complete data. Due to time and resource constraints, only the information presented in the systematic review is reported.
? The systematic review did not assess this outcome, it is unclear if the outcome was assessed by the primary studies included in the SR. Due to time and resource constraints, only the information presented in the systematic review is reported.
-- The systematic review did not assess this outcome. The outcome was (probably) not assessed by the included primary studies (for reasons unrelated to the *p*-value, magnitude or direction of the results).

Comparison 1 (vs placebo)

There were 18 RCTs identified in the included systematic reviews that compared WHM with placebo in people with premenstrual disturbances. Of these, 13 RCTs contributed data relevant to at least one critical or important outcome (Agha-Hosseini 2008, Behboodi Moghadam 2016, Kaplanoglu 2015[m], Mousavi 2015, Schellenberg 2012, Zamani 2012, Risoleti 2011[m], Ma 2010, He 2009, Pakgohar 2009, Delavar 2002, Schellenberg 2001, Turner 1993).

Five (5) other RCTs (Najafi 2018, Canning 2010, Ozgoli 2009, Hicks 2004, Tamborini 1993) did not contribute data because study results were not adequately reported, either by the primary study or the included systematic reviews.

PMS symptom severity

Nine (9) RCTs (total 1200 participants) reported PMS symptoms measured using a premenstrual symptom diary (PMSD), Moos Menstrual Distress Questionnaire (MMDQ), a daily symptoms rating scale (DSR), or a combined score of visual analogue scales (VAS) at the end of treatment (range 2 to 6 menstrual cycles). Data were missing from 6 other RCTs (Najafi 2018, Canning 2010, Ozgoli 2009, Hicks 2004, Tamborini 1993, Turner 1993) as they were not adequately reported by the reviews.

Specific details about the measures used (e.g. symptoms assessed, scale range or maximum score, timing of assessment) were also often not provided, with the systematic review authors noting difficulties in combining results for analysis due to the reporting of results being different across RCTs (and often incomplete). For example, many studies did not report end of treatment scores, some reported a total symptom score (sum of VAS scores across a range of symptoms) while others reported mean scores for individual symptoms (without standard deviations or standard errors). Some provided dichotomised data indicating the proportion of participants who had 'improvement', but the definition of improvement was often not provided (e.g. ideally occurring between ovulation and the first days of menstrual bleeding).

Given these limitations, the pooled results from one systematic review (Verkaik 2017[n]) are reported here, with no further data synthesis applied. Data from one RCT (Ma 2010) is missing from this analysis (SMD –0.80; 95% CI –1.30, –0.30), and we did not perform a sensitivity analysis on the results to examine the impact of studies judged to be at high risk of bias.

The pooled results from 8 RCTs (total 1133 participants) suggested an effect favouring WHM (chaste tree berry) when compared with placebo for overall improvement in PMS symptoms, although there is substantial statistical heterogeneity (SMD –1.31; 95% CI –1.82, –0.80; I^2=92.6%) (*GRADE: Low*).

The systematic review authors noted that a large, pooled effect was observed, however, the high risk of bias, high heterogeneity, and risk of publication bias of the included studies precluded a definitive conclusion (see Appendix F2). Regarding the overall risk of bias, the review authors found no significant impact on treatment effect (df=1; Q=2.88; p = 0.089; $I^2_{\text{high risk}}$, 86%; $I^2_{\text{moderate risk}}$, 95%) but noted studies with selective reporting were more likely to report a larger effect size. In a funnel plot analysis, the review authors reported that Egger tests suggest the presence of publication bias (8 studies; 10 effect sizes) (intercept, –8.65; 95% CI, –14.93 to –2.37; p = 0.013), with a large number of RCTs located outside the 95% CI of their funnel plot. This suggests there is an over-representation of smaller studies with larger effect sizes.

[m] Study included three treatment groups: WHM, placebo and active control.

[n] Pooled estimated were corrected for bias (i.e. Hedge's g) and were results according to per protocol analysis.

Patient-reported improvement

There were 6 RCTs (total 839 participants) with available data that reported the proportion of participants who achieved a global improvement in PMS symptoms at the end of treatment (between 2 and 6 menstrual cycles), but the specific criteria used to a convey a response was often not described. In one RCT, it was recorded as being a minimum 60% improvement in PMS symptoms diary scores, and in 2 RCTs it was a minimum 50% decrease in total symptoms scores. Data were missing for 9 RCTs (total 736 participants).

Pooled results suggested an effect that favours WHM compared with placebo (RR 1.98; 95% CI 1.52, 2.58; $p < 0.0000l$; $I^2 = 57\%$) (*GRADE: Moderate*).

In a sensitivity analysis examining the impact of one RCT (Turner 1993) judged to be at high risk of bias, the size of the effect estimate did not materially change (RR 2.04; 95% CI 1.48, 2.80; $p < 0.0001$; $I^2 = 66\%$).

Depression

Six (6) RCTs (total 660 participants) were found that reported depressive symptoms measured using a visual analogue scale (VAS), the Beck Depression Inventory (BDI) or the MDQ-negative affect subscale at the end of treatment (range 2 to 6 menstrual cycles) (Kaplanoglu 2015, Mousavi 2015, Zamani 2012, Pakgohar 2009, Agha-Hosseini 2008, Turner 1993).

Data were missing from 12 other RCTs (Najafi 2018, Behboodi Moghadam 2016, Schellenberg 2012, Risoleti 2011, Canning 2010, Ma 2010, He 2009, Ozgoli 2009, Hicks 2004, Delavar 2002, Schellenberg 2001, Tamborini 1993) because study results were not adequately reported, either by the primary study[o] or the included systematic reviews.

The pooled results from one systematic review (Verkaik 2017[n]) are reported here, with no further data synthesis applied. The results suggested an effect favouring WHM (chaste tree berry) when compared with placebo for improvement depressive symptoms (5 RCTs, total 613 participants), although there is substantial statistical heterogeneity (SMD –1.02; 95% CI –1.67, –0.38; $I^2 = 92.4\%$) (*GRADE: Low*).

Data from one RCT (Agha-Hosseini 2008; saffron) is missing from this analysis (SMD 6.23; 95% CI 5.21, 7.25) [not able to be added due to missing information], and we could not perform a sensitivity analysis on the results to examine the impact of studies judged to be at high risk of bias.

Anxiety

Three (3) RCTs (total 308 participants) were found that reported anxiety measured using a visual analogue scale (VAS) at the end of treatment (range 3 to 6 menstrual cycles) (Kaplanoglu 2015, Behboodi Moghadam 2016, Zamani 2012).

Data were missing from 15 other RCTs (Najafi 2018, Mousavi 2015, Schellenberg 2012, Risoleti 2011, Canning 2010, Ma 2010, He 2009, Ozgoli 2009, Pakgohar 2009, Agha-Hosseini 2008, Hicks 2004, Delavar 2002, Schellenberg 2001, Tamborini 1993, Turner 1993) because study results were not adequately reported, either by the primary study or the included systematic reviews[p].

The pooled results from one systematic review (Verkaik 2017[n]) are reported here, with no further data synthesis applied. The results suggested an effect favouring WHM (chaste tree berry) when compared with placebo for improvement depressive symptoms (2 RCTs, total 208 participants) (SMD –1.44; 95% CI –1.91, –0.97; I^2=54.9%) (*GRADE: Low*).

Data from one RCT (Behboodi Moghadam 2016; valerian) is missing from this analysis (SMD 1.9; 95% CI 1.44, 2.39) [not able to be added due to missing information], and we could not perform a sensitivity analysis on the results to examine the impact of studies judged to be at high risk of bias.

[o] It is assumed depression was included as part of a PMS symptoms diary (or VAS) and hence results should be available.

[p] It is assumed anxiety was included as part of a PMS symptoms diary (or VAS) and hence results should be available.

Comparison 2 (vs inactive control)

There were no studies found by the included systematic reviews that compared WHM with other inactive interventions in people with premenstrual disturbances.

Comparison 3 (vs other)

There were 9 RCTs identified in the included systematic reviews that compared WHM with an active comparator in people with premenstrual disturbances that contributed data relevant to a critical or important outcome (Atmaca 2003, Ciotta 2011, Di Pierro 2009, Kaplanoglu 2015, Lauritzen 1997, Onaran 2003, Risoleti 2011, Salehi 2013, Scaldarella 2008).

Data from these studies are presented in Appendix F2 Supplementary outcome data.

Four other RCTs (Sharifi 2014, Karimian 2013, Modaress 2011, Masumeh 2010) did not contribute data because study results were not adequately reported, either by the primary study or the included systematic reviews.

D3.3 Symptoms of menopause

D3.3.1 List of reviews

A summary of the PICO criteria of the eligible systematic reviews is provided in Table D-21.

A list of herbs examined in the identified primary studies is provided in Table D-22.

There were 8 systematic reviews (76, 77, 87-92) published in 2018 or after that presented results in a meta-analysis and were prioritised for critical appraisal and data extraction (Castelo-Branco 2021, Firoozeei 2021, Kanadys 2021, Ghaderi 2020, Shinjyo 2020, Ghorbani 2019, Shahmohammadi 2019, Najafi 2018a). One other review published prior to 2018 (93) was also included (Franco 2016). Review details, including all outcome domains and measures reported by the included reviews, are provided in Appendix F1. Outcome data for critical or important outcomes are provided in Appendix F2.

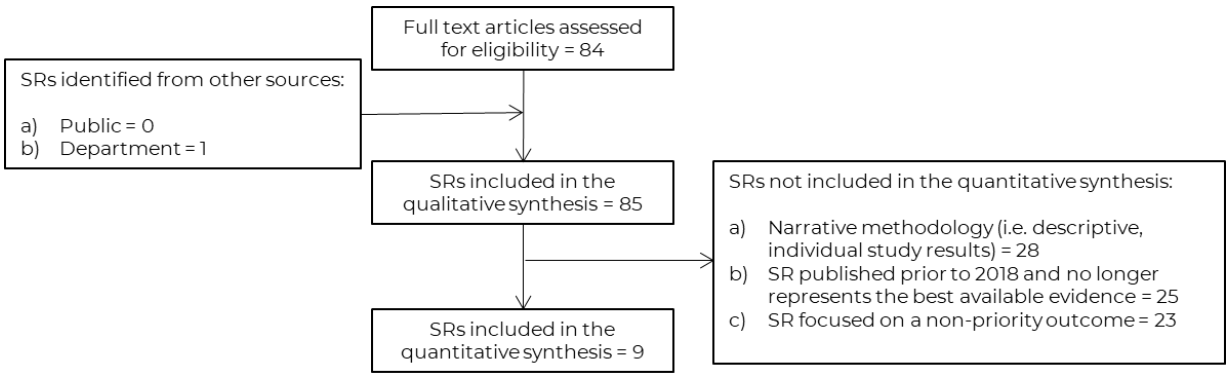
A further 23 systematic reviews (15, 94-115) that were published in 2018 or after were not considered further as they did not report on outcomes considered critical or important for this review (Askari 2021, Azizi 2021, Koushki 2021, Ghavami 2020, Hallajzadeh 2020, Kanadys 2020, Mirzavandi 2020, Moosavian 2020, Razmpoosh 2020, Xu 2020, Ziaei 2020, Askari 2019, Hadi 2019, Hallajzadeh 2019, Hernandez-Garcia 2019, Mohammadi 2019, Saboori 2019, Jovanovski 2018, Khadivzadeh 2018, Liu 2018, Luis 2018, Mousavi 2018, Rahmani 2018).

Twenty-five (25) systematic reviews (68, 116-140) presented results in a meta-analysis but were published prior to 2018 and were judged to no longer represent the best available evidence (Haghighatdoost 2017, Kapoor 2017, Mohammadi-Sartang 2017, Myers 2017, Sarri 2017, Ghazanfarpour 2016, Sahebkar 2016, Sahebkar 2016b, Ursoniu 2016, Chen 2015a, Ghazanfarpour 2015, Khalesi 2015, Yarmolinsky 2015, Gartoulla 2014, Liu 2014a, Onakpoya 2014, Lethaby 2013, Shergis 2013, Leach 2012, Hooper 2010, Shams 2010, Jacobs 2009, Coon 2007, Tempfer 2007, Nelson 2006).

Another 28 reviews provided a descriptive or narrative review or individual study results (141-168), but did not provide suitable data for inclusion in the synthesis, noting that results were often too heterogeneous to conduct a meaningful meta-analysis (Koliji 2021, Lopresti 2021, Ebrahimi 2020, Rashidi Fakari 2020, Darand 2019, Dizavandi 2019, Niazi 2019, Roozbeh 2019, Kim 2018a, Fattah 2017, Thaung Zaw 2017, Abdi 2016, Ghazanfarpour 2016, Mohtashami 2016, Ismail 2015, Ulbricht 2015, Thomas 2014, Dew 2013, Kim 2013, Miroddi 2013, Laakmann 2012, Ulbricht 2012, Clement 2011, Borrelli 2008, Booth 2006, Krebs 2004, Huntley 2003, Borelli 2002). These reviews were checked for additional studies and results, but in the absence of data were not considered further.

Figure D-13 outlines the selection process of the final included systematic reviews.

Figure D-23 Process flow for prioritising systematic reviews: Symptoms of menopause



Abbreviations: SR, systematic review

Table D-33 PICO criteria of included systematic reviews: Symptoms of menopause

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]	N	Study ID [e]
Askari 2021 (94)	meta-analysis	Umbrella review (any condition)	Garlic	Placebo OR other intervention	Oxidative stress (antioxidant biomarkers)	0 (k=12)	--
Azizi 2021 (95)	meta-analysis	Umbrella review (any condition)	Black cumin	Placebo OR other intervention	Liver enzyme levels	0 (k=8)	--
Castelo-Branco 2021 (87)	meta-analysis	Symptoms of menopause	Black cohosh (isopropanolic extract)	Placebo OR other intervention	Any efficacy measure including Climacteric symptoms and AEs	6 (k=16)	Jang 2015, Li 2011, Uebelhack 2006, Osmers 2005, Jacobson 2001 (BC), Stoll 1987
Firoozeei 2021 (88)	meta-analysis	Umbrella review (any condition)	Lavender	Placebo OR other intervention	Depression	1 (k=17)	Kamalifard 2017
Kanadys 2021 (89)	meta-analysis	Symptoms of menopause	Red clover	Placebo	Symptoms (hot flushes)	12 (k=12)	Lambert 2017, Clifton-Bligh 2015, Shakeri 2015, Lipovac 2012, del Giorno 2010, Hidalgo 2005, Atkinsoon 2004, Tice 2003, Jeri 2002, van de Weijer 2002, Baber 1999, Knight 1999
Koushki 2021 (96)	meta-analysis	Umbrella review (any condition)	Garlic	Placebo OR other intervention	Inflammatory mediators	0 (k=10)	--
Ghaderi 2020 (76)	Meta-analysis	Umbrella review (any condition)	Saffron	Placebo OR other intervention	Emotional functioning, C-reactive protein	1 (k=21)	Kashani 2018
Ghavami 2020 (97)	meta-analysis	Umbrella review (any condition)	Ginseng	Placebo OR other intervention	Liver enzymes	0 k=14)	--
Hallajzadeh 2020 (15)	meta-analysis	Umbrella review (any condition)	Black cumin	Placebo OR other intervention	Glycaemic control, lipid profiles, inflammatory biomarkers, oxidative stress biomarkers	0 (k=50)	--
Kanadys 2020 (98)	meta-analysis	Symptoms of menopause	Red clover	Placebo OR other intervention	Lipid profiles	0 (k=10)	--
Mirzavandi 2020 (99)	meta-analysis	Umbrella review (any condition)	Garlic	Placebo OR other intervention	Inflammatory markers	0 (k=17)	--
Moosavian 2020 (100)	meta-analysis	Umbrella review (any condition)	Garlic	Placebo OR other intervention	Oxidative stress markers	0 (k=7)	--

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]	N	Study ID [e]
Razmpoosh 2020 (101)	meta-analysis	Umbrella review (any condition)	Black cumin	Placebo OR other intervention	Liver and kidney parameters	0 (k=19)	--
Shinjyo 2020 (77)	meta-analysis	Umbrella review (any condition)	Valerian root	Placebo OR other intervention	Sleep quality, anxiety, hot flushes	2 (k=60)	Jenabi 2017, Mirabi 2013
Xu 2020 (102)	meta-analysis	Umbrella review (any condition)	Green tea	Placebo OR other intervention	Lipid profile	0 (k=27)	--
Ziaei 2020 (103)	meta-analysis	Menopause	Ginseng	Placebo OR other intervention	Lipid profile	0 (k=27)	--
Askari 2019 (104)	meta-analysis	Umbrella review (any condition)	Black cumin	Placebo OR other intervention	Glycaemic control	0 (k=17)	--
Ghorbani 2019 (90)	meta-analysis	Symptoms of menopause	Panax ginseng	Placebo	Sexual function	5 (k=5)	Chung 2015, Dongre 2015, Oh 2010, Kim 2009, Wiklund 1999
Hadi 2019 (105)	meta-analysis	Umbrella review (any condition)	Turmeric	Placebo OR other intervention	Blood pressure modulation (SBP, DBP)	0 (k=11)	--
Hallajzadeh 2019 (106)	meta-analysis	Umbrella review (any condition)	Turmeric	Placebo OR other intervention	Endothelial function	0 (k=10)	--
Hernandez-Garcia 2019 (107)	meta-analysis	Umbrella review (any condition)	Ginseng	Placebo OR other intervention	Lipid profile	0 (k=18)	--
Mohammadi 2019 (108)	meta-analysis	Umbrella review (any condition)	Ginseng	Placebo OR other intervention	Inflammatory markers	0 (k=8)	--
Saboori 2019 (109)	meta-analysis	Umbrella review (any condition)	Ginseng	Placebo OR other intervention	C-reactive protein	0 (k=9)	--
Shahmohammadi 2019 (91)	meta-analysis	Symptoms of menopause	Black cohosh, Linseed, Hops, Red clover, Fenugreek	Placebo OR other intervention	Anxiety and depression	12 (k=21)	Kashani 2018, Lambert 2017, Rahimi Kian 2017, Steels 2017, Aghamiri 2016, Shamshad 2016, Shakeri 2015, Charandabi 2013, Ehsanpour 2012, Geller 2009, Hidalgo 2005, Tice 2003
Jovanovski 2018 (110)	meta-analysis	Umbrella review (any condition)	Psyllium	Placebo OR other intervention	Lipid profile	0 (k=28)	--
Khadivzadeh 2018 (111)	meta-analysis	Symptoms of menopause	Red clover , Fenugreek, Schisandra, Combination	Placebo OR other intervention	Sleep dysfunction	0 (k=12)	--

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]	N	Study ID [e]
Liu 2018 (112)	meta-analysis	Burning mouth syndrome	Any (incl. St John's wort, Olive oil)	Placebo OR other intervention	Pain or burning symptoms	0 (k=22)	--
Luis 2018 (113)	meta-analysis	Symptoms of menopause	Red clover	Placebo OR other intervention	Lipid profile	0 (k=12)	--
Mousavi 2018 (114)	meta-analysis	Umbrella review (any condition)	Black cumin	Placebo OR other intervention	Obesity indices (BMI, WC, weight)	0 (k=13)	--
Najafi 2018 (92)	meta-analysis	Symptoms of menopause	Red clover, Fenugreek, Flaxseed, Ginseng	Placebo OR other intervention	Sexual function	6 (k=16)	Steels 2017, Rahimi 2017, Shamshad 2016, Shakeri 2015, Ehsanpour 2012, Oh 2010
Rahmani 2018 (115)	meta-analysis	Symptoms of menopause	Flaxseed, Red clover	Placebo OR other intervention	Maturation of vaginal epithelial cells	0 (k=13)	--
Haghighatdoost 2017 (116)	meta-analysis	Umbrella review (any condition)	Green tea	--	Plasma adiponectin levels	--	--
Kapoor 2017 (117)	meta-analysis	Umbrella review (any condition)	Green tea	--	Fat oxidation	--	--
Mohammadi-Sartang 2017 (118)	meta-analysis	Umbrella review (any condition)	Linseed	--	Body weight, composition	--	--
Myers 2017 (119)	meta-analysis	Symptoms of menopause	Red clover	--	Hot flushes	--	--
Sarri 2017 (120)	Network meta-analysis	Symptoms of menopause	Black cohosh, Red clover, Valerian	--	Vasomotor symptoms	--	--
Franco 2016 (93)	meta-analysis	Symptoms of menopause	Red clover, Black cohosh, St John's wort, Combination	Placebo OR other intervention	Hot flushes, night sweats, vaginal dryness	14 (k=62)	Shahnazi 2013, Lipovac 2012, Abdali 2010, van Die 2009, Chung 2007, Frei-Kleiner 2005, Pockaj 2006, Newton 2006, Atkinson 2004, Tice 2003, Jeri 2002, van de Weijer 2002, Knight 1999, Baber 1999
Ghazanfarpour 2016 (121)	meta-analysis	Symptoms of menopause	Red clover	--	Hot flushes, hormone levels	--	--
Li 2016 (122)	meta-analysis	Women with breast cancer	Black cohosh	--	Hot flushes	--	--
Sahebkar 2016 (123)	meta-analysis	Umbrella review (any condition)	Black cumin	--	Lipid profiles	--	--

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]	N	Study ID [e]
Sahebkar 2016b (124)	meta-analysis	Umbrella review (any condition)	Black cumin	--	Blood pressure	--	--
Ursoniu 2016 (68)	meta-analysis	Umbrella review (any condition)	Linseed	--	Blood pressure	--	--
Chen 2015a (125)	meta-analysis	Symptoms of menopause	Oral phytoestrogens (incl. Red clover)	--	Symptoms, Hot flushes	--	--
Ghazanfarpour 2015 (126)	meta-analysis	Symptoms of menopause	Red clover	--	Hot flushes, hormone levels	--	--
Khalesi 2015 (127)	meta-analysis	Umbrella review (any condition)	Linseed	--	Blood pressure	--	--
Yarmolinsky 2015 (128)	meta-analysis	Umbrella review (any condition)	Green tea	--	Blood pressure	--	--
Gartoulla 2014 (129)	meta-analysis	Symptoms of menopause	Red clover	--	Hot flushes	--	--
Liu 2014 (130)	meta-analysis	Symptoms of menopause	St John's wort, Combination	--	Symptom	--	--
Onakpoya 2014 (131)	meta-analysis	Umbrella review (any condition)	Green tea	--	Blood pressure, lipid profile	--	--
Lethaby 2013 (132)	meta-analysis (Cochrane)	Symptoms of menopause	Red clover	--	Vasomotor symptoms	--	--
Shergis 2013 (133)	meta-analysis	Umbrella review (any condition)	Panax ginseng	--	Any efficacy measure	--	--
Leach 2012 (134)	meta-analysis (Cochrane)	Symptoms of menopause	Black cohosh	--	Symptoms	--	--
Hooper 2010 (135)	meta-analysis	Symptoms of menopause	Red clover	--	Breast density	--	--
Shams 2010 (136)	meta-analysis	Symptoms of menopause	Black cohosh, Combination	--	Symptoms	--	--
Jacobs 2009 (137)	meta-analysis	Symptoms of menopause	Red clover	--	Symptoms	--	--
Coon 2007 (138)	meta-analysis	Symptoms of menopause	Red clover	--	Hot flushes	--	--
Tempfer 2007 (139)	meta-analysis	Symptoms of menopause	Red clover	--	Symptoms	--	--

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]	N	Study ID [e]
Nelson 2006 (140)	meta-analysis	Symptoms of menopause	Red clover	--	Hot flushes	--	--
Koliji 2021 (141)	descriptive	Symptoms of menopause	Ginseng, Fenugreek, Red clover, Black cohosh, Schisandra, Black cumin, Combination	--	Sexual function	--	--
Lopresti 2021 (142)	descriptive	Umbrella review (any)	Black cohosh, Ginseng,	--	--	--	--
Ebrahimi 2020 (143)	descriptive	Symptoms of menopause	Chaste tree, Passionflower, St John's wort, Linseed, Valerian, Lemon balm, liquorice, Aniseed, multiple other herbs listed	--	Symptoms	--	--
Rashidi Fakari 2020 (144)	descriptive	Symptoms of menopause	Liquorice, Chamomile	--	Vaginal atrophy	--	--
Darand 2019 (145)	descriptive	Infertility	Black cumin	--	Sexual function, hormone levels	--	--
Dizavandi 2019 (146)	descriptive	Symptoms of menopause	Linseed, Fenugreek, Red clover	--	Vaginal atrophy, dyspareunia	--	--
Niazi 2019 (147)	descriptive	Symptoms of menopause	Fenugreek, Liquorice, Red clover, Ginseng, Ginkgo, Red clover	--	Sexual function	--	--
Roozbeh 2019 (148)	descriptive	Menopause	Lavender	--	Sleep, sexual function, vasomotor, psychological, physical symptoms	--	--
Kim 2018a (149)	descriptive	Umbrella review (any)	Valerian, St John's wort	--	Sleep quality, anxiety	--	--
Fattah 2017 (150)	descriptive	Symptoms of menopause	Hops, Kava, Red clover	--	Depression, anxiety	--	--
Thaung Zaw 2017 (151)	descriptive	Umbrella review (any)	Red clover, Black cohosh	--	Cognition, executive function, memory	--	--

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]	N	Study ID [e]
Abdi 2016 (152)	descriptive	Symptoms of menopause	Red clover	--	Bone mineral density	--	--
Ghazanfarpour 2016 (153)	descriptive	Symptoms of menopause	Black cohosh, Aniseed, Red clover, Valerian , St John's wort, Sage, Linseed, Fenugreek	--	Hot flushes	--	--
Mohtashami 2016 (154)	descriptive	Umbrella review (any)	Black cumin	--	Blood parameters, antropometrics	--	--
Ismail 2015 (155)	descriptive	Symptoms of menopause	Black cohosh, St John's wort, Red clover	--	Symptoms	--	--
Ulbricht 2015 (156)	descriptive	Umbrella review (any)	Black cohosh	--	Clinical efficacy	--	--
Thomas 2014 (157)	descriptive	Symptoms of menopause	Red clover	--	Symptoms, hot flushes	--	--
Dew 2013 (158)	descriptive	Symptoms of menopause	Linseed	--	Symptoms, bone health	--	--
Kim 2013 (159)	descriptive	Symptoms of menopause	Ginseng	--	Symptoms	--	--
Miroddi 2013 (160)	descriptive	Umbrella review (any)	Passionflower	--	Clinical efficacy	--	--
Laakmann 2012 (161)	descriptive	Symptoms of menopause	Black cohosh	--	Symptoms	--	--
Ulbricht 2012 (162)	descriptive	Umbrella review (any)	Hops	--	Clinical efficacy	--	--
Clement 2011 (163)	descriptive	Symptoms of menopause	Red clover, Combination	--	Cognition	--	--
Borrelli 2008 (164)	individual study results	Symptoms of menopause	Black cohosh	--	Symptoms	--	--
Booth 2006 (165)	descriptive	Symptoms of menopause	Red clover	--	Symptoms	--	--
Krebs 2004 (166)	individual study results	Symptoms of menopause	Red clover	--	Symptoms	--	--
Huntley 2003 (167)	descriptive	Symptoms of menopause	Black cohosh, Red clover, Ginseng	--	Symptoms	--	--
Borrelli 2002 (168)	descriptive	Umbrella review (any)	Black cohosh	--	Clinical efficacy	--	--

Abbreviations: CAM, complementary and alternative medicine
Notes:
N = Number of RCTs meeting our PICO criteria; k = total number of RCTs identified by systematic review.
a. Systematic review with no population restrictions were eligible for inclusion if they presented data that evaluated participants with symptoms of menopause.
b. Systematic reviews were eligible for inclusion if they presented data that examined the effectiveness of eligible WHMs (see Appendix A8).
c. Systematic review with no comparator restrictions were eligible for inclusion if they presented data that compared WHM with control (placebo or no intervention) or another intervention.
d. Outcomes assessed or listed by the systematic review. Grey highlight = nonpriority outcome; Blue highlight = critical or important outcome
e. Study ID of eligible RCTs that met the PICO criteria of this overview.
-- Systematic review not assessed. The outcome domain was not critical or important for this overview OR a more recent SR nominated as best available is included.

Figure D-24 Critical appraisal summary: review author's judgements about each AMSTAR-2 item for each included systematic review – Symptoms of menopause

	Review ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
SYMPTOMS OF MENOPAUSE	Castelo-Branco 2021	Y	N	Y	PY	N	N	N	PY	Y	N	Y	Y	Y	Y	N	Y
	Firoozeei 2021	Y	PY	Y	PY	Y	Y	Y	PY	Y	N	Y	Y	Y	Y	Y	Y
	Kanadys 2021	Y	PY	Y	PY	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
	Ghaderi 2020	Y	PY	Y	PY	Y	N	N	PY	Y	N	Y	Y	Y	Y	Y	Y
	Shinjyo 2020	Y	PY	Y	PY	N	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y
	Ghorbani 2019	Y	PY	Y	PY	N	N	N	PY	Y	N	Y	N	Y	Y	Y	Y
	Shahmohammadi 2019	Y	PY	Y	PY	N	Y	N	PY	N	N	Y	Y	N	Y	Y	Y
	Najafi 2018a	Y	PY	Y	PY	Y	Y	Y	PY	PY	N	Y	Y	Y	Y	Y	Y
	Franco 2016	Y	PY	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y

N = No; PY = Partial Yes, Y = Yes

Table D-34 List of herbs assessed in the identified primary studies: Symptoms of menopause

WHM identified in included studies	Matched to Tier 1 list of WHM: Gynaecological / reproductive disorders [a]
Herbal combination	X
Black cohosh (Actaea racemosa)	✓
Black cumin (Nigella sativa)	X
Fenugreek (Trigonella foenum-graecum)	X
Ginseng (Panax ginseng)	X
Hops (Humulus lupulus)	X
Piper methysticum (Kava kava)	X
Red clover (Trifolium pratense)	X
Saffron (Crocus sativus)	X
St John's wort (Hypericum perforatum)	X
Valerian (Valeriana officinalis)	X
Vitex agnus-castus (chaste tree)	✓
Withania somnifera (Ashwagandha)	X

Abbreviations: WHM, Western herbal medicine
✓ = yes; X = no
a. See Appendix A6.3 - Tier 1 herb list was considered in GRADE. Eligibility was based on the herb list in Appendix A8

D3.3.2 Critical appraisal

A summary of the quality of included systematic reviews is provided in Figure D-14 and Table D-23. The strengths or limitations of the included systematic reviews assessed against each AMSTAR-2 domain is provided in Appendix E1.

Eight (8) systematic reviews that included a meta-analysis (Castelo-Branco 2021, Firoozeei 2021, Kanadys 2021, Ghaderi 2020, Shinjyo 2020, Ghorbani 2019, Najafi 2018a, Franco 2016) were judged to probably provide an accurate and comprehensive summary of the available studies that address the question of interest (i.e. met, or partially met, AMSTAR-2 domains 4, 8, 9 and 11). One review (Shahmohammadi 2019) did not meet AMSTAR domain 8, as the risk of bias of RCTs included in the review was not adequately reported.

Table D-35 Critical appraisal summary: Symptoms of menopause

Review ID	Summary	Notes
Castelo-Branco 2021	5 non-critical weaknesses in domains 2, 5, 6, 7 & 10	The authors do not provide the search strategy, they do not perform study selection or data extraction in duplicate, they do not provide a list of excluded studies read at full text, and they did not report on any funding or support for the RCTs.
Firoozeei 2021	1 non-critical weakness in domain 10	The authors do not report on the sources of funding for the studies included in the review.
Kanadys 2021	1 non-critical weakness in domain 10	The authors do not report on the sources of funding for the studies included in the review.
Ghaderi 2020	3 non-critical weaknesses in domains 6, 7 & 10	The authors do not perform data extraction in duplicate, do not provide a list of excluded studies read at full text, and they did not report on any funding or support for the RCTs.
Shinjyo 2020	4 non-critical weaknesses in domains 5, 6, 7 & 10	The authors do not perform study selection or data extraction in duplicate, do not provide a list of excluded studies read at full text, and they did not report on any funding or support for the RCTs.
Ghorbani 2019	5 non-critical weaknesses in domains 5, 6, 7, 10 & 12	The authors do not perform study selection or data extraction in duplicate, do not provide a list of excluded studies read at full text, they did not report on any funding or support for the RCTs, and they did not investigate the impact of studies at risk of bias.
Shahmohammadi 2019	1 critical flaw	Risk of bias of RCTs included in the review not reported.

Review ID	Summary	Notes
	4 non-critical weaknesses in domains 5, 7, 10 & 13	The authors do not perform study selection in duplicate, they do not provide a list of excluded studies read at full text, they did not report on any funding or support for the RCTs, and they did not discuss the impact of studies at risk of bias.
Najafi 2018a	1 non-critical weakness in domain 10	The authors do not report on the sources of funding for the studies included in the review.
Franco 2016	1 non-critical weakness in domains 7 & 10	The authors do not provide a list of excluded studies read at full text and they did not report on the funding or support for the RCTs.

Abbreviations: RCT, randomised controlled trial

D3.3.3 Effects of intervention

Outcomes considered by the NTWC to be critical or important for decision-making in people with symptoms of menopause are listed in Table D-24.

Table D-36 Outcomes considered by the NTWC to be critical or important for decision-making: Symptoms of menopause

Outcome domain	Measured with	Consensus rating	Data available for comparison 1 or 2	Review ID								
				Castelo-Branco 2021	Firoozeei 2021	Kanadys 2021	Ghaderi 2020	Shinjyo 2020	Ghorbani 2019	Shahmohammadi 2019	Najafi 2018a	Franco 2016
Symptom severity	KMI, GCS, MRS (or other validated measure)	8	Yes	✓	?	✓	X	?	?	?	?	--
Hot flushes	Frequency or intensity	8	Yes	X	?	✓	X	X	?	?	?	✓
Sexual Function	Female Sexual Function Index	8	Yes	?	?	?	?	?	✓	?	✓	--
HRQoL	MenQoL	7	No	X	?	X	?	?	?	?	?	--
Emotional functioning	SF-36 MCS (or other)	7	Yes	X	?	X	X	?	?	✓	?	--
Depression	BDI, HAM-D (or other)	7	Yes	X	X	X	✓	?	?	✓	?	--
Anxiety	HAM-A (or other)	6	Yes	X	?	X	?	?	?	✓	?	--

Abbreviations: BDI, Beck depression inventory; GCS, Greene Climacteric Scale; HAM-A, Hamilton anxiety rating scale; HAM-D, Hamilton depression rating scale; HRQoL, Health-related quality of life; KMI, Kupperman menopause index; MenQoL, Menopause-Specific Quality of Life; MRS, Menopause Rating Scale; SF-36 36-item short form

Notes:

✓ A study result is available for inclusion in the synthesis.

X A study result is NOT available for inclusion because the systematic review does not adequately report the results (data were incomplete). It is unclear if the primary study reported complete data. Due to time and resource constraints, only the information presented in the systematic review is reported.

? The systematic review did not assess this outcome, it is unclear if the outcome was assessed by the primary studies included in the SR. Due to time and resource constraints, only the information presented in the systematic review is reported.

-- The systematic review did not assess this outcome. The outcome was (probably) not assessed by the included primary studies (for reasons unrelated to the *p*-value, magnitude or direction of the results).

Comparison 1 (vs placebo)

There were 42 RCTs found by the included systematic reviews that compared WHM with placebo in people with symptoms of menopause. Of these, 34 RCTs contributed data relevant to 6 outcomes (symptoms severity, hot flushes, sexual function, emotional functioning, depression anxiety) (Ghazanfarpour 2018, Kashani 2018, Lambert 2017, Aghamiri 2016, Clifton-Bligh 2015, Chung 2015, Dongre 2015, Jiang 2015, Shakeri 2015, Shahnazi 2013, Ehsanpour 2012, Lipovac 2012, Li 2011, Abdali 2010, del Giorno 2010, Oh 2010, Geller 2009, Kim 2009, van Die 2009, Newton 2006, Pockaj 2006, Uebelhack 2006, Frei-Kleiner 2005, Hidalgo 2005, Osmers 2005, Atkinson 2004, Tice 2003, Jeri 2002, van de Weijer 2002, Jacobson 2001, Baber 1999, Knight 1999, Wiklund 1999, Stoll 1987).

Another 8 RCTs (Jenabi 2017, Kamalifard 2017, Rahimi Kian 2017, Steels 2017, Shamshad 2016, Charandabi 2013, Mirabi 2013, Chung 2007) did not contribute any data because their results were not adequately reported by the primary study or the included systematic reviews.

Symptom severity

There were 16 RCTs that reported improvement in overall symptoms severity in people with symptoms of menopause measured using either the Greene Climacteric Scale (GCS), the Kupperman Menopausal Index (KMI), or the Menopause Rating Scale (MRS) at the end of treatment (range 8 weeks to 2 years) (Lambert 2017, Clifton-Bligh 2015, Jiang 2015, Shakeri 2015, Lipovac 2012, Li 2011, del Giorno 2010, Uebelhack 2006, Hidalgo 2005, Osmers 2005, Atkinson 2004, van de Weijer 2002, Jacobson 2001, Knight 1999, Baber 1999, Stoll 1987). The data were often incomplete and were mixed with regards to reporting mean change from baseline scores or end of treatment scores, with systematic review authors often having imputed mean scores from available data or obtained data from the primary study authors that was previously not published.

The GCS is used to assess changes in 21 different menopause symptoms, before and after menopause treatment (169). Four main areas are measured: psychological (items 1 to 11), physical (items 12 to 18), vasomotor (items 19 and 20) and sexual interest (item 21). Symptoms are rated on a 4-point Likert scale from 0 (not at all) to 3 (extremely). An MCID for the GCS is not established (170).

The KMI is used to assess different menopause symptoms, including sweating/hot flushes, palpitation, vertigo, headache, paraesthesia, formication, arthralgia, and myalgia (categorized as somatic symptoms), and fatigue, nervousness, and melancholia (categorized as psychological symptoms) (171). Symptoms are rated on a Likert scale from 0 (not at all) to 3 (extremely), with the total score ranging from 0 to 63. An MCID for the KMI is a final score <15 (170).

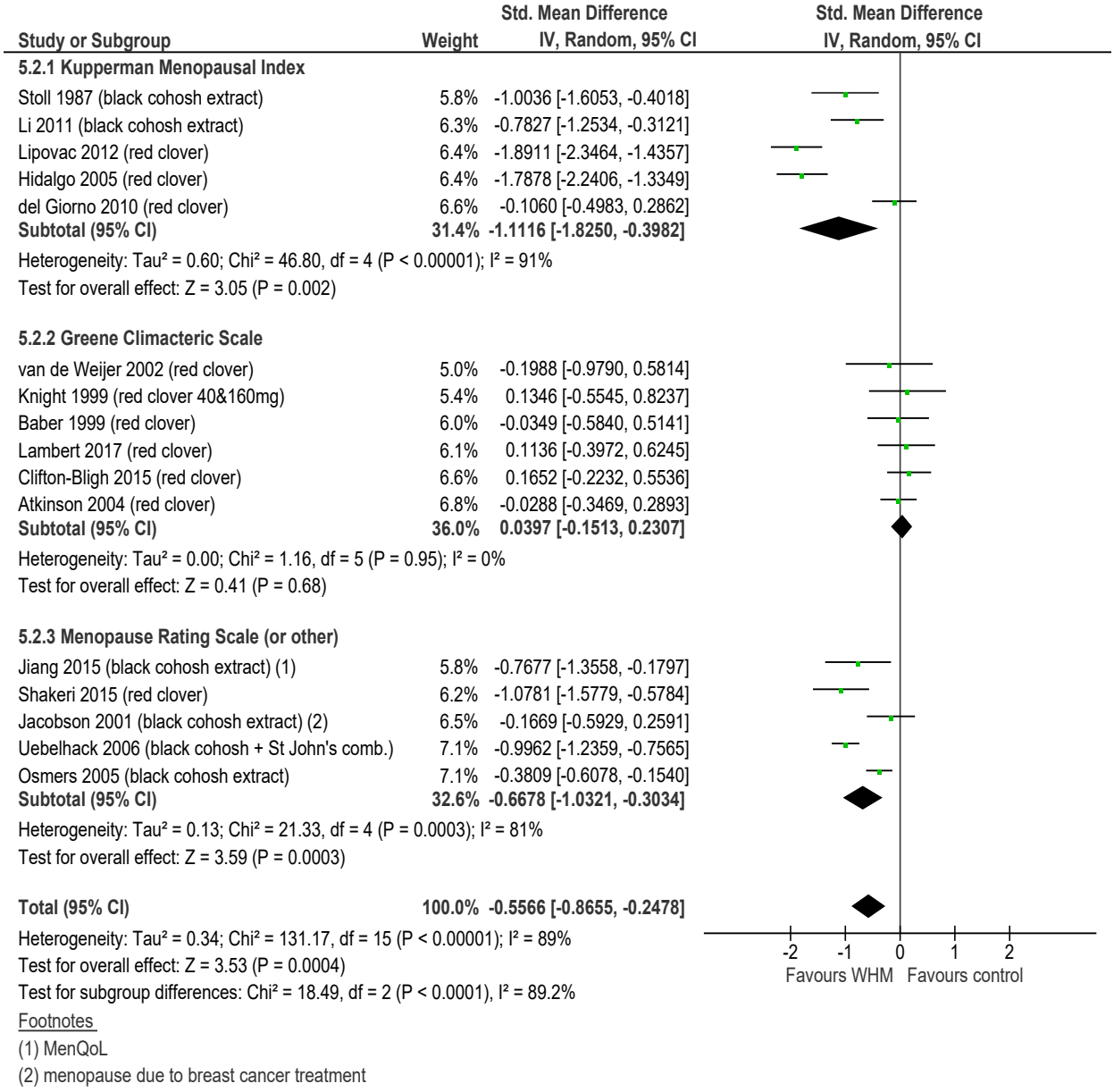
The MRS consists of 11-items categorised into 3 subscale measuring somatovegetative symptoms (sweating/hot flushes, heart discomfort, sleep problems, joint and muscle problems), psychological symptoms (depressive mood, irritability, anxiety, and physical/mental exhaustion), and urogenital symptoms (sexual problems, bladder problems, and vaginal dryness) (172). Symptoms are rated on a Likert scale from 0 (not at all) to 4 (very severe), with the total score ranging from 0 to 44. An MCID for the MRS was not found.

Pooled results from 16 RCTs (total 1680 participants) suggested a moderate improvement in overall symptoms in the WHM (black cohosh, red clover) group when compared with the placebo group (SMD –0.56; 95% CI –0.87, –0.25; $p = 0.0004$; $I^2 = 89\%$) (*GRADE: Moderate*). Statistical heterogeneity was high; therefore, the studies were stratified by the WHM received, which showed some improvement for studies examined the effect of black cohosh (SMD –0.67; 95% CI –0.97, –0.36; $p < 0.0001$; $I^2 = 75\%$) compared with those for red clover (SMD –0.48; 95% CI –0.99, –0.03; $p = 0.07$; $I^2 = 92\%$). Statistical heterogeneity was better explained when the studies were stratified according to the outcome measure used (see Figure D-15).

In a sensitivity analysis that examined the impact of 5 RCTs judged to be at high risk of bias (Li 2011, Hidalgo 2005, van de Weijer 2002, Knight 1999, Baber 1999) the overall direction or estimate of the effect did not materially change (SMD –0.55; 95% CI –0.90, –0.20; $p = 0.002$; $I^2 = 89\%$).

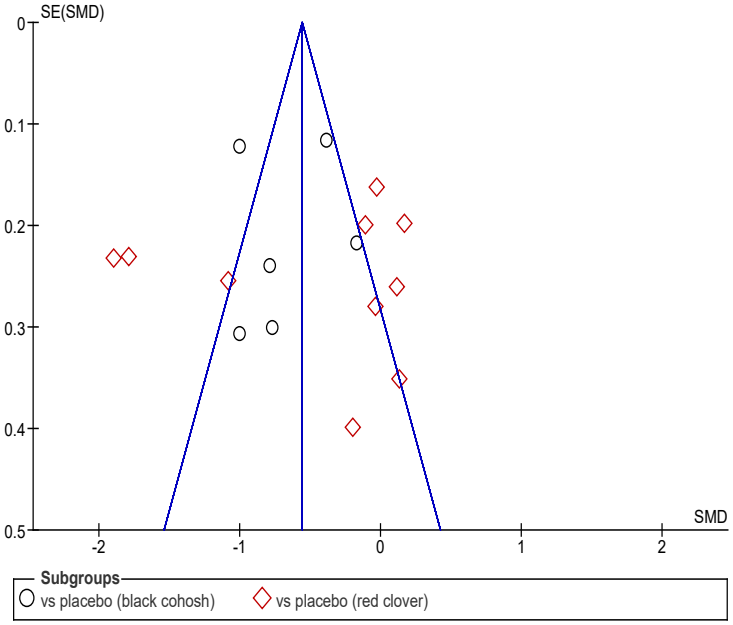
In a sensitivity analysis examining the impact of small studies, the estimate of the effect did not materially change (fixed effect, SMD –0.56; 95% CI –0.66, –0.46; p = 0.002; I^2 = 89%). Visual inspection of a funnel plot suggests there is some asymmetry (see Figure D-16), likely associated with small studies of lower methodological quality producing larger intervention effect estimates.

Figure D-25 Forest plot of comparison: WHM vs placebo: Symptoms of menopause - improvement in KMI, MRS or GCS total symptoms scores



Note: Raw data (mean, N) not shown as data were not provided by the SR authors.

Figure D-26 Funnel plot of comparison: WHM vs placebo: Symptoms of menopause – improvement in KMI, MRS or GCS total symptoms scores



Hot flushes

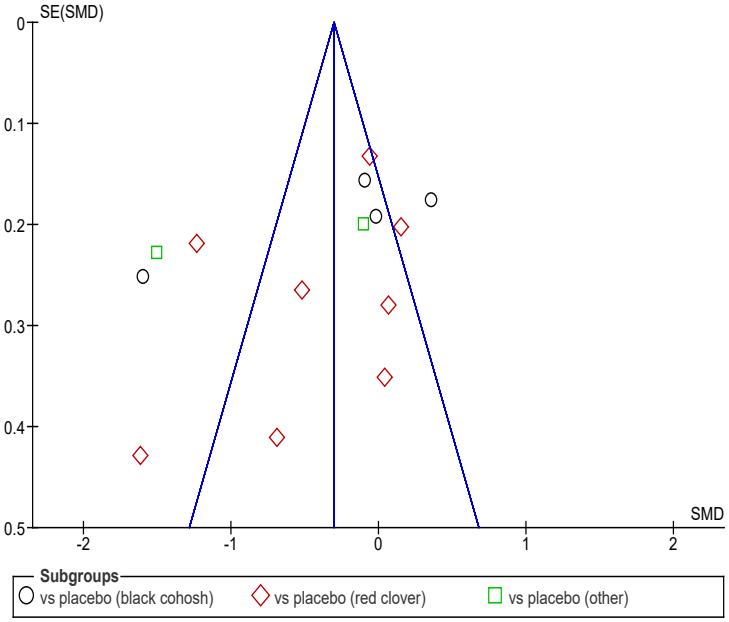
There were 16 RCTs that reported the daily frequency of hot flushes in people with symptoms of menopause at the end of treatment (range 8 weeks to 2 years) (Jenabi 2017, Lambert 2017, Lipovac 2012, Shahnazi 2013, Mirabi 2011, Abdali 2010, van Die 2009, Newton 2006, Pockaj 2006, Frei-Kleiner 2005, Atkinson 2004, Tice 2003, Jeri 2002, van de Weijer 2002, Baber 1999, Knight 1999). The measure used was often not reported, although was sometimes obtained from domains or items reported within the GCS, KMI, or the MRS. Data were missing from 2 RCTs (Jenabi 2017, Mirabi 2011).

Pooled results from 14 RCTs (total 1355 participants) suggested a slight improvement in overall symptoms in the WHM group when compared with the placebo group (SMD –0.46; 95% CI –0.80, –0.12; $p = 0.009$; $I^2 = 89\%$) (*GRADE: Low*). Statistical heterogeneity was high; therefore, the studies were stratified by the WHM received, which showed little improvement re: heterogeneity for studies that examined the effect of red clover (SMD –0.44; 95% CI –0.86, –0.02; $p = 0.04$; $I^2 = 82\%$) compared with those for black cohosh (SMD –0.32; 95% CI –1.01, 0.38; $p = 0.37$; $I^2 = 93\%$).

A sensitivity analysis examining the impact of 8 RCTs (Lipovac 2012, Abdali 2010, van Die 2009, Frei-Kleiner 2005, Jeri 2002, van de Weijer 2002, Baber 1999, Knight 1999) at high risk of bias the estimate of effect was smaller and overlapped with no important difference (SMD –0.27; 95% CI –0.72, 0.18; $p = 0.025$; $I^2 = 89\%$). Heterogeneity remained high.

In a sensitivity analysis examining the impact of small studies, the estimate of the effect was smaller (fixed effect, SMD –0.30; 95% CI –0.42, –0.19; $p < 0.00001$; $I^2 = 89\%$). Visual inspection of a funnel plot suggests there is some asymmetry (see Figure D-17), likely associated with small studies of lower methodological quality producing larger intervention effect estimates.

Figure D-27 Funnel plot of comparison: WHM vs placebo: Symptoms of menopause – hot flush daily frequency



Sexual functioning

There were 11 RCTs that reported sexual function measured using the Female Sexual Function Index (FSFI) or the sexual domain/item from the Greene Climacteric Scale, Menopause Rating Scale, the Kupperman Menopause Index, Women's Health Questionnaire, or the Menopause-Specific Quality of Life at the end of treatment (range 6 weeks to 16 weeks) (Rahimi Kian 2017, Steels 2017, Shamshad Begum 2016, Chung 2015, Dongre 2015, Shakeri 2015, Ehsanpour 2012, Oh 2010, Kiim 2009, Tice 2003, Wiklund 1999).

The FSFI is a multidimensional measure that quantifies female sexual dysfunction across six domains: desire (items 1 to 2), arousal (items 3 to 6), lubrication (items 7 to 10), orgasm (items 11 to 13), satisfaction (items 14 to 16) and pain (items 17 to 19) (173). The total score ranges from 2 to 36, with the higher scores indicating better sexual function.

Pooled results from 7 RCTs (total 887 participants) suggested little to no improvement in overall sexual function in the WHM group when compared with the placebo group (SMD –0.25; 95% CI –0.58, 0.08; p = 0.14; I^2 = 78%) (*GRADE: Moderate*). Statistical heterogeneity was high, but likely explained by differences in the WHM received among participants. Removal of one study from the analysis (Dongre 2015 [withania]), statistical heterogeneity was removed (I^2 = 2% [data not shown]). Data were missing from 4 RCTs (Rahimi Kian 2017, Steels 2017, Shamshad Begum 2016, Shakeri 2015), of which 2 RCTs suggested no difference between groups and 2 RCTs suggested an effect favouring the WHM.

In a sensitivity analysis examining the impact of 3 RCTs (Chung 2015, Kim 2009, Oh 2010) judged to be at high risk of bias, the estimate of effect did not materially change, and statistical heterogeneity remained high (SMD –0.42; 95% CI –0.90, 0.06; p = 0.09; I^2 = 87%).

Emotional functioning

There were 6 RCTs that reported emotional functioning measured using the psychosocial domain from the Greene Climacteric Scale, Menopause Rating Scale, or the Kupperman Menopause Index at the end of treatment (range 8 weeks to 12 weeks) (Lambert 2017, Rahimi Kian 2017, Steels 2017, Shakeri 2015, Charandabi 2013, Ehsanpour 2012).

Pooled results from 2 RCTs (total 114 participants) suggested little to no improvement in overall emotional functioning in the WHM group when compared with the placebo group (SMD –0.47; 95% CI –1.33, 0.39; $p = 0.28$; $I^2 = 81\%$) (*GRADE: Very low*). Statistical heterogeneity was high, and unable to be explained. Data from 4 RCTs were incomplete (Rahimi Kian 2017, Steels 2017, Shakeri 2015, Charandabi 2013), with the review authors only noting the direction of effect (all 4 RCTs suggested an effect favouring the WHM).

A sensitivity analysis examining in the impact of RCTs at high risk of bias was not conducted (no RCTs at high risk of bias).

Depression

There were 8 RCTs that reported symptoms of depression measured using the Hamilton Depression Rating Scale or the depression domain from the Kupperman Menopause Index or the Menopause Rating Scale at the end of treatment (range 8 weeks to 12 months) (Ghazanfarpour 2018, Kashani 2018, Kamalifard 2017, Aghamiri 2016, Shamshad Begum 2016, Lipovac 2012, Hidalgo 2005, Tice 2003).

Pooled results from 5 RCTs (total 585 participants) suggested little to no improvement in symptoms of depression in the WHM group when compared with the placebo group (SMD –0.26; 95% CI –1.00, 0.48; $p = 0.49$; $I^2 = 94\%$) (*GRADE: Very low*). Statistical heterogeneity was high, and unable to be explained by difference in the intervention. Removal of one study (Kashani 2018 [saffron]) from the analysis suggested an effect favouring WHM, indicating differences in the intervention may influence the results (SMD –0.63; 95% CI –1.23, –0.04; $p = 0.04$; $I^2 = 89\%$). Data from 3 RCTs were incomplete (Kamalifard 2017, Shamshad Begum 2016, Hidalgo 2005) and not able to be included in the synthesis, with all 3 RCTs suggesting an effect favouring the WHM.

In a sensitivity analysis examining in the impact of 2 RCTs (Aghamiri 2016, Lipovac 2012) judged to be at high risk of bias, the direction of the effect estimate changed (SMD 0.34; 95% CI –0.52, 1.19; $p = 0.44$; $I^2 = 90\%$).

Anxiety

There were 7 RCTs that reported symptoms of anxiety measured using the Hamilton Anxiety Rating Scale or the anxiety domain from the Kupperman Menopause Index or the Menopause Rating Scale at the end of treatment (range 8 weeks to 12 months) (Ghazanfarour 2018, Aghamiri 2016, Shamshad Begum 2016, Lipovac 2012, Geller 2009, Hidalgo 2005, Tice 2003)

Pooled results from 5 RCTs (total 560 participants) suggested an effect favouring the WHM group when compared with the placebo group (SMD –0.90; 95% CI –1.79, –0.01; $p = 0.05$; $I^2 = 95\%$) (*GRADE: Very low*). Statistical heterogeneity was high, and unable to be explained by difference in the intervention. Data from 3 RCTs were incomplete and not able to be included in the synthesis, with 2 RCTs reported to show an effect favouring the WHM (Shamshad Begum 2016, Hidalgo 2005) and one RCT (Geller 2009) suggesting there was no difference between the groups.

In a sensitivity analysis examining in the impact of 2 RCTs (Aghamiri 2016, Lipovac 2012) judged to be at high risk of bias, the estimate of effect was notably smaller (SMD –0.19; 95% CI –0.49, 0.10; $p = 0.20$; $I^2 = 22\%$).

Comparison 2 (vs inactive control)

There were no RCTs found by the included systematic reviews that compared WHM with inactive control (no intervention, waitlist or usual care) in people with symptoms of menopause.

Comparison 3 (vs other)

None of the included systematic reviews included data from RCTs comparing WHM with other interventions in people with symptoms of menopause. There were 11 RCTs comparing black cohosh extract with other interventions (such as hormone therapy, vitamins/minerals, or antidepressants) and one other RCT comparing lavender with bitter orange, but details about these studies were not provided (see Appendix F2).

D4 Endocrine and metabolic

D4.1 Diabetes and impaired glucose tolerance

D4.1.1 List of reviews

A summary of the PICO criteria of the eligible systematic reviews is provided in Table D-38.

A list of herbs included in the identified studies is provided in Table D-37.

There were 89 reviews that were published in 2018 or after that presented results in a meta-analysis and were prioritised for critical appraisal and data extraction. Of these, 23 reviews (260-282) focused on people with diabetes or metabolic disorders, with the other 66 being umbrella reviews that included primary studies in people with diabetes or pre-diabetes (6, 7, 9, 10, 15-17, 76, 94-97, 99, 101-106, 108-110, 114, 225, 226, 228, 283-322).

A further 42 reviews (68, 116, 118, 123, 127, 128, 131, 133, 227, 323-355) presented results in a meta-analysis but were published prior to 2018 and were judged to no longer represent the best available evidence. The other 35 reviews (37, 154, 192, 193, 229, 352, 356-384) provided a descriptive or narrative review of individual study results, but in the absence of data were not considered further.

Given the time and resource constraints further assessment of these reviews was not able to be performed. NTWC was not involved in selection of which prioritised conditions were completed versus not completed (see NHMRC process report for additional information).

Table D-37 List of herbs assessed in the identified primary studies: Diabetes and impaired glucose tolerance

WHM identified in included studies	Matched to Tier 1 list of WHM: Endocrine and metabolic [a]
Aloe (Aloe spp.)	X
Artichoke (Cynara scolymus)	X
Astragalus (Astragalus membranaceous, Euphorbia)	X
Barberry (Berberis vulgaris)	X
Bilberry (Vaccinium myrtillus)	X
Black cumin (Nigella sativa)	X
Capsicum/ Cayenne (Capsicum minimum)	X
Chamomile (Matricaria recruitica)	X
Cinnamon (Cinnamomum zeylanicum / C. cassia)	X
Cranberry (Vaccinium macrocarpon)	X
Fenugreek (Trigonella foenum-graecum, Euphrasia officinalis)	✓
Garlic (Allium sativum)	X
Ginger (Zingiber officinale)	X
Ginkgo (Ginkgo biloba)	X
Ginseng (Panax ginseng)	✓
Green tea (Centella asiatica, Camillia sinensis)	X
Gymnema (Gymnema sylvestre)	✓
Hops (Humulus lupulus)	X
Lemon balm (Melissa officinalis)	X
Linseed (Tilia spp.)	X
Nettle (Urtica dioica)	X
Oats (Avena sativa)	X
Psyllium (Plantago ovata)	X
Saffron (Crocus sativus)	X
St Mary's thistle (Ulmus rubra)	X
Turmeric (Curcuma longa)	X

Withania (Withania somnifera)	✓

Abbreviations: WHM, Western herbal medicine
✓ = yes; X = no
a. See Appendix A6.3 - Tier 1 herb list was considered in GRADE. Eligibility was based on the herb list in Appendix A8

Table D-38 PICO criteria of included systematic reviews: Diabetes and impaired glucose tolerance

Review ID	Method of analysis	Population [a]	Intervention [b]	Outcomes [d]
Asbaghi 2020 (260)	meta-analysis	Diabetes	Green tea	Lipid profiles
Asbaghi 2020a (261)	meta-analysis	Diabetes	Green tea	Adiponectin
Durg 2020 (262)	meta-analysis	Diabetes	Ginseng	Blood glucose, insulin, lipid profile, serum and oxidative stress markers
Barzkar 2020 (263)	meta-analysis	Diabetes (type 1)	Cinnamon, Fenugreek, Combination	Blood glucose indices
Hajizadeh-Sharafabad 2020 (264)	meta-analysis	Diabetes	Chamomile	Metabolic parameters
Heshmati 2020 (265)	meta-analysis	Diabetes	Lemon balm	Cardiometabolic outcomes
Jalali 2020a (266)	meta-analysis	Diabetes	Cinnamon	Blood pressure
Jamali 2020 (267)	meta-analysis	Diabetes	Cinnamon	Blood pressure and anthropometric parameters
Jamali 2020a (268)	meta-analysis	Diabetes	Cinnamon	Lipid profiles
Tabrizi 2020 (269)	meta-analysis	Diabetes	Ginkgo	Cardiometabolic parameters
Xiao 2020 (270)	meta-analysis	Diabetes	Psyllium	Weight, body mass index, lipid profile, and glucose metabolism
Ziaei 2020a (271)	meta-analysis	Diabetes	Nettle	Glycaemic control
Akbari 2019 (272)	meta-analysis	Metabolic Syndrome and related disorders	Turmeric	Weight loss
Huang 2019a (273)	meta-analysis	Diabetes	Ginger	Glycaemic control
Namazi 2019 (274)	meta-analysis	Diabetes	Cinnamon	Weight, body mass index, lipid profile, and glucose metabolism
Asbaghi 2019a (275)	meta-analysis	Diabetes	Green tea	CRP and oxidative stress
Deyno 2019 (276)	meta-analysis	Diabetes and Impaired glucose tolerance	Cinnamon	Blood glucose and lipid profiles
Rocha 2019 (277)	meta-analysis	Diabetes	Cranberry, Bilberry	Glycaemic control
Shabani 2019 (278)	meta-analysis	Diabetes	Garlic	Lipid profile and glucose parameters
Yuan 2019 (279)	meta-analysis	Metabolic disorders	Turmeric	Blood Lipids
Zhang 2019 (280)	meta-analysis	Diabetic kidney disease	Astragalus	Kidney markers
Tabrizi 2018 (281)	meta-analysis	Diabetes	Turmeric	Lipid profile and Glycaemic control
Zhu 2018 (282)	meta-analysis	Diabetes and Metabolic disorders	Ginger	Glucose control, insulin sensitivity, and lipid profile

Review ID	Method of analysis	Population [a]	Intervention [b]	Outcomes [d]
Altobelli 2021 (283)	meta-analysis	Umbrella review (incl. diabetes)	Turmeric	Glycaemic and lipid profiles
Asbaghi 2021 (284)	meta-analysis	Umbrella review (incl. diabetes)	Saffron	Inflammatory markers
Asbaghi 2021a (285)	meta-analysis	Umbrella review (incl. diabetes)	Green tea	Glycaemic control
Askari 2021 (94)	meta-analysis	Umbrella review (incl. diabetes)	Garlic	Oxidative stress biomarkers
Atefi 2021 (286)	meta-analysis	Umbrella review (incl. diabetes)	Barberry	Blood pressure
Azizi 2021 (95)	meta-analysis	Umbrella review (incl. diabetes)	Black cumin	Liver function
Ghassab-Abdollahi 2021 (6)	meta-analysis	Umbrella review (incl. diabetes)	Black cumin	Oxidative stress and inflammatory biomarkers
Karimi 2021 (228)	meta-analysis	Umbrella review (incl. diabetes)	Saffron	Liver function
Koushki 2021 (96)	meta-analysis	Umbrella review (incl. diabetes)	Garlic	Inflammatory markers
Kutbi 2021 (287)	meta-analysis	Metabolic disease (incl. diabetes)	Cinnamon	Weight, body mass index, lipid profile, and glucose metabolism
Montazeri 2021 (7)	meta-analysis	Umbrella review (incl. diabetes)	Black cumin	Inflammatory markers
Moradi 2021 (288)	meta-analysis	Umbrella review (incl. diabetes)	Artichoke	Blood pressure
Morvaridzadeh 2021 (9)	meta-analysis	Umbrella review (incl. diabetes)	Ginger	Oxidative stress biomarkers
Mousavi 2021 (225)	meta-analysis	Umbrella review (incl. diabetes)	Saffron	Liver function
Shekarchizadeh-Esfahani 2021 (289)	meta-analysis	Umbrella review (incl. diabetes & impaired glucose tolerance)	Cinnamon	Liver function
Ardiana 2020 (10)	meta-analysis	Umbrella review (incl. diabetes)	Black cumin	Oxidative stress and inflammatory biomarkers
Askari 2020 (290)	meta-analysis	Umbrella review (incl. diabetes)	Ginger	Oxidative stress and inflammatory biomarkers
Askarpour 2020 (291)	meta-analysis	Umbrella review (incl. diabetes)	Fenugreek	Blood lipids and body weight
Clark 2020 (292)	meta-analysis	Umbrella review (incl. diabetes)	Psyllium	Blood pressure
Ghaderi 2020 (76)	meta-analysis	Umbrella review (incl. diabetes)	Saffron	Mental health and C-reactive protein
Ghavami 2020 (97)	meta-analysis	Umbrella review (incl. diabetes)	Ginseng	Liver function
Hadi 2020 (293)	meta-analysis	Umbrella review (incl. diabetes & impaired glucose tolerance)	Cinnamon	Blood pressure
Hallajzadeh 2020 (15)	meta-analysis	Umbrella review (incl. diabetes & impaired glucose tolerance)	Black cumin, Combination	Glycaemic control, lipid profiles, inflammatory and oxidative stress biomarkers
Jalali 2020 (16)	meta-analysis	Umbrella review (incl. diabetes)	Ginger	Inflammatory and oxidative stress biomarkers

Review ID	Method of analysis	Population [a]	Intervention [b]	Outcomes [d]
Jalili 2020 (294)	meta-analysis	Umbrella review (incl. diabetes)	Artichoke	Glycaemic control
Khodamoradi 2020 (295)	meta-analysis	Umbrella review (incl. diabetes)	Fenugreek	Cardiometabolic Risk Factors
Miraghajani 2020 (296)	meta-analysis	Umbrella review (incl. diabetes)	Ginseng	Anthropometric indices and body composition
Mirzavandi 2020 (99)	meta-analysis	Umbrella review (incl. diabetes)	Garlic	Inflammatory markers
Mohit 2020 (17)	meta-analysis	Umbrella review (incl. diabetes)	Black cumin	Inflammatory and oxidative stress biomarkers
Morvaridzadeh 2020 (297)	meta-analysis	Umbrella review (incl. diabetes)	Ginger	Inflammatory markers
Mousavi 2020 (298)	meta-analysis	Umbrella review (incl. diabetes & impaired glucose tolerance)	Cinnamon	Blood pressure
Mousavi 2020a (299)	meta-analysis	Umbrella review (incl. diabetes & impaired glucose tolerance)	Cinnamon	Anthropometric indices and body composition
Mousavi 2020b (300)	meta-analysis	Umbrella review (incl. diabetes & impaired glucose tolerance)	Turmeric	Anthropometric indices and body composition
Pourmasoumi 2020 (301)	meta-analysis	Umbrella review (incl. diabetes)	Cranberry	Cardiometabolic Risk Factors
Rahmani 2020 (302)	meta-analysis	Umbrella review (incl. diabetes)	Saffron	Glycaemic control and waist circumference
Razmpoosh 2020 (101)	meta-analysis	Umbrella review (incl. diabetes)	Black cumin	Liver and kidney parameters
Renfan 2020 (303)	meta-analysis	Umbrella review (incl. diabetes)	Green tea	Blood pressure
Roshanravan 2020a (304)	meta-analysis	Umbrella review (incl. diabetes)	Saffron	Glycaemic indices, lipid profiles,
Safari 2020 (305)	meta-analysis	Umbrella review (incl. diabetes)	Barberry	Glycaemic indices
Xu 2020 (102)	meta-analysis	Umbrella review (incl. diabetes)	Green tea	Lipid profiles
Yazdanpanah 2020 (306)	meta-analysis	Umbrella review (incl. diabetes & impaired glucose tolerance)	Cinnamon	Anthropometric indices and body composition
Ziaei 2020 (103)	meta-analysis	Umbrella review (incl. diabetes & impaired glucose tolerance)	Ginseng	Lipid profiles
Alizadeh 2019 (307)	meta-analysis	Umbrella review (incl. diabetes & impaired glucose tolerance)	Turmeric	Oxidative stress enzymes
Asbaghi 2019 (308)	meta-analysis	Umbrella review (incl. diabetes)	Saffron	Blood glucose and lipid profiles
Askari 2019 (104)	meta-analysis	Umbrella review (incl. diabetes)	Black cumin	Glycaemic control
Clark 2019 (309)	meta-analysis	Umbrella review (incl. diabetes & impaired glucose tolerance)	Turmeric	Adiponectin
Hadi 2019 (105)	meta-analysis	Umbrella review (incl. diabetes)	Turmeric	Blood pressure

Review ID	Method of analysis	Population [a]	Intervention [b]	Outcomes [d]
Hadi 2019a (310)	meta-analysis	Umbrella review (incl. diabetes)	Barberry	Lipid profiles
Hallajzadeh 2019 (106)	meta-analysis	Umbrella review (incl. diabetes)	Turmeric	Endothelial function
Hasani 2019 (311)	meta-analysis	Umbrella review (incl. diabetes)	Ginger	Blood pressure
Huang 2019 (312)	meta-analysis	Umbrella review (incl. diabetes & impaired glucose tolerance)	Turmeric	Glycaemic control
Mohammadi 2019 (108)	meta-analysis	Umbrella review (incl. diabetes)	Ginseng	Inflammatory biomarkers
Pourmasoumi 2019 (226)	meta-analysis	Umbrella review (incl. diabetes)	Saffron	Cardiovascular risk factors
Saboori 2019 (109)	meta-analysis	Umbrella review (incl. diabetes)	Ginseng	C-reactive protein
Tabrizi 2019(313)	meta-analysis	Umbrella review (incl. diabetes)	Turmeric	Inflammatory and oxidative stress biomarkers
Taghizadeh 2019 (314)	meta-analysis	Umbrella review (incl. diabetes)	Garlic	C-reactive protein
White 2019 (315)	meta-analysis	Umbrella review (incl. diabetes)	Turmeric	Inflammatory markers
de Melo 2018 (316)	meta-analysis	Impaired glucose tolerance	Turmeric	Glycaemic control
Golzarand 2018 (317)	meta-analysis	Umbrella review (incl. diabetes)	Green tea	Anthropometric indices
Jovanovski 2018 (110)	meta-analysis	Umbrella review (incl. diabetes)	Psyllium	Lipid profiles
Khan 2018 (318)	meta-analysis	Umbrella review (incl. diabetes)	Psyllium	Blood pressure
Mousavi 2018 (114)	meta-analysis	Umbrella review (incl. diabetes)	Black cumin	Obesity indices
Namazi 2018 (319)	meta-analysis	Umbrella review (incl. diabetes)	Black cumin	Obesity indices
Pourmasoumi 2018 (320)	meta-analysis	Umbrella review (incl. diabetes)	Ginger	Lipid profiles
Qin 2018 (321)	meta-analysis	Umbrella review (incl. diabetes)	Turmeric	Oxidative stress
Sahebkar 2018 (322)	meta-analysis	Umbrella review (incl. diabetes)	Artichoke	Lipid profiles
Daryabeygi-Khotbehsara 2017 (323)	meta-analysis	Diabetes	Black cumin	--
Demmers 2017 (324)	meta-analysis	Impaired glucose tolerance	Turmeric, Ginkgo, Ginseng, Fenugreek	--
Emami 2017 (325)	meta-analysis	Umbrella review (incl. diabetes)	Garlic	--
Haghighatdoost 2017 (116)	meta-analysis	Umbrella review (incl. diabetes)	Green tea	--
Mohammadi-Sartang 2017 (118)	meta-analysis	Umbrella review (incl. diabetes)	Linseed	--
Si 2017 (326)	meta-analysis	Umbrella review (incl. diabetes)	Turmeric	--
Wang 2017 (327)	meta-analysis	Diabetes	Garlic	--
Derosa 2016 (328)	meta-analysis	Umbrella review (incl. diabetes)	Turmeric	--

Review ID	Method of analysis	Population [a]	Intervention [b]	Outcomes [d]
Dick 2016 (329)	meta-analysis	Umbrella review (incl. diabetes)	Aloe	--
Gong 2016 (330)	meta-analysis	Diabetes & impaired glucose tolerance	Fenugreek	--
Gui 2016 (331)	meta-analysis	Diabetes	Ginseng	--
Guo-Chong 2016 (332)	meta-analysis	Umbrella review (incl. diabetes)	Linseed	--
He 2016 (333)	meta-analysis	Umbrella review (incl. diabetes)	Oats	--
Komishon 2016 (334)	meta-analysis	Umbrella review (incl. diabetes)	Ginseng	--
Mazidi 2016 (335)	meta-analysis	Umbrella review (incl. diabetes)	Ginger	--
Qi-feng 2016 (336)	meta-analysis	Diabetes	Ginseng	--
Sahebkar 2016b (227)	meta-analysis	Umbrella review (incl. diabetes)	Turmeric	--
Sahebkar 2016c (123)	meta-analysis	Umbrella review (incl. diabetes)	Black cumin	--
Suksomboon 2016 (337)	meta-analysis	Diabetes & impaired glucose tolerance	Aloe	--
Ursoniu 2016 (68)	meta-analysis	Umbrella review (incl. diabetes)	Linseed	--
Yiyi 2016 (338)	meta-analysis	Impaired glucose tolerance	Aloe	--
Hou 2015 (339)	meta-analysis	Umbrella review (incl. diabetes)	Garlic	--
Khalesi 2015 (127)	meta-analysis	Umbrella review (incl. diabetes)	Linseed	--
Yarmolinsky 2015 (128)	meta-analysis	Umbrella review (incl. diabetes)	Green tea	--
Zhu 2015 (340)	meta-analysis	Umbrella review (incl. diabetes)	Cranberry	--
Khalesi 2014 (341)	meta-analysis	Umbrella review (incl. diabetes)	Green tea	--
Kwak 2014 (342)	meta-analysis	Umbrella review (incl. diabetes)	Garlic	--
Liu 2014 (343)	meta-analysis	Umbrella review (incl. diabetes)	Green tea	--
Neelakantan 2014 (344)	meta-analysis	Umbrella review (incl. diabetes)	Fenugreek	--
Onakpoya 2014 (131)	meta-analysis	Umbrella review (incl. diabetes)	Green Tea	--
Sahebkar 2014 (345)	meta-analysis	Umbrella review (incl. diabetes)	Turmeric	--
Shishtar 2014 (346)	meta-analysis	Umbrella review (incl. diabetes & impaired glucose tolerance)	Ginseng	--
Allen 2013 (347)	meta-analysis	Umbrella review (incl. diabetes)	Cinnamon	--
Shergis 2013 (133)	meta-analysis	Umbrella review (incl. diabetes)	Ginseng	--
Akilen 2012 (348)	meta-analysis	Umbrella review (incl. diabetes)	Cinnamon	--

Review ID	Method of analysis	Population [a]	Intervention [b]	Outcomes [d]
Gibb 2012 (349)	meta-analysis	Umbrella review (incl. diabetes & impaired glucose tolerance)	Psyllium	--
Leach 2012a (350)	meta-analysis	Diabetes	Cinnamon	--
Paul 2011 (351)	meta-analysis	Umbrella review (incl. diabetes & impaired glucose tolerance)	Cinnamon	--
Shojaii 2011a (352)	meta-analysis	Diabetes	Garlic, Ginkgo, Psyllium, St Mary's thistle, Green tea, Fenugreek	--
Suksomboon 2011 (353)	meta-analysis	Diabetes	Cinnamon, St Mary's thistle, Fenugreek	--
Baker 2008 (354)	meta-analysis	Umbrella review (incl. diabetes)	Cinnamon	--
Pham 2007 (355)	meta-analysis	Diabetes	Cinnamon	--
Lopresti 2021 (192)	descriptive	Umbrella review (incl. diabetes)	Withania	--
Matias 2021 (229)	descriptive	Umbrella review (incl. diabetes with peripheral nephropathy)	Turmeric	--
Anh 2020 (37)	descriptive	Diabetes	Ginger	--
Ashkar 2020 (356)	descriptive	Insulin resistance and PCOS	Aloe, Chamomile	--
Chan 2020 (357)	descriptive	Umbrella review (incl. diabetes)	Garlic	--
Emamat 2020 (358)	descriptive	Umbrella review (incl. diabetes)	Garlic	--
Giannoulaki 2020 (359)	descriptive	Diabetes or metabolic syndrome	Saffron	--
Mahmoodi 2020 (360)	descriptive	Diabetes	Black cumin	--
Tandon 2020 (193)	descriptive	Umbrella review (incl. diabetes)	Withania	--
Wal 2020 (361)	descriptive	Hypertension (incl. diabetes)	Cranberry	--
Hamdan 2019 (362)	descriptive	Diabetes	Black cumin	--
Hekmatpou 2019 (363)	descriptive	Wound healing (incl. diabetes)	Aloe	--
Hariri 2018 (364)	descriptive	Umbrella review (incl. diabetes)	Turmeric	--
Costello 2016 (365)	descriptive	Diabetes	Cinnamon	--
Lee 2016 (366)	descriptive	Umbrella review (incl. diabetes)	Red Ginseng	--
Mohtashami 2016 (154)	descriptive	Umbrella review (incl. diabetes)	Black cumin	--
Vaughn 2016 (367)	descriptive	Umbrella review (incl. diabetes, skin health)	Turmeric	--
Heshmati 2015 (368)	descriptive	Umbrella review (incl. diabetes)	Black cumin	--
Choi 2013 (369)	descriptive	Umbrella review (incl. diabetes)	Ginseng	--

Review ID	Method of analysis	Population [a]	Intervention [b]	Outcomes [d]
Rashidi 2013 (370)	descriptive	Diabetes	Garlic, Green tea, Psyllium, St Mary's thistle, Fenugreek, Nettle, Aloe	--
Kim 2011 (371)	descriptive	Diabetes	Red Ginseng	--
Lee 2011 (372)	descriptive	Umbrella review (incl. diabetes)	Ginseng	--
Mehri 2011 (373)	descriptive	Diabetes	Nettle	--
Shojaii 2011 (352)	descriptive	Umbrella review (incl. diabetes)	Cinnamon, Ginkgo, Black cumin, Psyllium, St Mary's thistle, Green tea, Fenugreek	--
Ulbricht 2011b (374)	descriptive	Umbrella review (incl. diabetes)	Gymnema	--
Kirkham 2009 (375)	descriptive	Diabetes	Cinnamon	--
Nahas 2009 (376)	descriptive	Diabetes	Cinnamon, Gymnema, Fenugreek, Green tea	--
Hasani-Ranjbar 2008 (377)	individual study results	Diabetes	St Mary's thistle, Psyllium, Garlic	--
Dugoua 2007 (378)	descriptive	Diabetes	Cinnamon	--
Leach 2007 (379)	descriptive	Diabetes	Gymnema	--
Buettner 2006 (380)	individual study results	Umbrella review (incl. diabetes)	Ginseng	--
Shekelle 2005 (381)	descriptive	Diabetes	Fenugreek	--
Yeh 2003 (382)	descriptive	Diabetes	Ginseng, Gymnema, St Mary's thistle, Fenugreek	--
Vogler 1999 (383)	descriptive	Umbrella review (incl. diabetes)	Ginseng	--
Vogler 1999a (384)	descriptive	Umbrella review (incl. diabetes)	Aloe	--

Abbreviations: CAM, complementary and alternative medicine

Notes:

N = Number of RCTs meeting our PICO criteria; k = total number of RCTs identified by systematic review.

a. Systematic review with no population restrictions were eligible for inclusion if they presented data that evaluated participants with diabetes.

b. Systematic reviews were eligible for inclusion if they presented data that examined the effectiveness of eligible WHMs (see Appendix A8).

c. Systematic review with no comparator restrictions were eligible for inclusion if they presented data that compared WHM with control (placebo or no intervention) or another intervention.

d. Outcomes assessed or listed by the systematic review.

e. Study ID of eligible RCTs that met the PICO criteria of this overview.

-- Systematic review not assessed. Due to time an resource constraints.

D4.1.2 Critical appraisal

Not assessed.

D4.1.3 Effects of intervention

Outcomes considered by the NTWC to be critical or important for decision-making in people with diabetes are listed in Table D-39.

Table D-39 Outcomes considered by the NTWC to be critical or important for decision-making: Diabetes and impaired glucose tolerance

Outcome domain	Measured with	Consensus rating	Data available for comparison 1 or 2	Review ID
				Not assessed
Glycaemic control	HbA1c, fasting blood glucose	7	Not assessed	Not assessed
Body composition	Waist circumference, waist to hip ratio	7	Not assessed	Not assessed
HRQoL	SF-36 or similar	7	Not assessed	Not assessed
Patient reported improvement	Global assessment	7	Not assessed	Not assessed
Depression	BDI, HAM-D or measure of emotional function	6	Not assessed	Not assessed

Abbreviations: BDI, Beck depression inventory, HAM-D, Hamilton depression rating scale; HbA1c, percent glycated haemoglobin; HRQoL, Health-related quality of life; SF-36 36-item short form

Notes:

✓ A study result is available for inclusion in the synthesis.

X A study result is NOT available for inclusion because the systematic review does not adequately report the results (data were incomplete). It is unclear if the primary study reported complete data. Due to time and resource constraints, only the information presented in the systematic review is reported.

? The systematic review did not assess this outcome, it is unclear if the outcome was assessed by the primary studies included in the SR. Due to time and resource constraints, only the information presented in the systematic review is reported.

-- The systematic review did not assess this outcome. The outcome was (probably) not assessed by the included primary studies (for reasons unrelated to the *p*-value, magnitude or direction of the results).

Comparison 1 (vs placebo)

Not assessed.

Comparison 2 (vs inactive control)

Not assessed.

Comparison 3 (vs other)

Not assessed.

D4.2 Metabolic syndrome

D4.2.1 List of reviews

A summary of the PICO criteria of the eligible systematic reviews is provided in Table D-41.

A list of herbs included in the identified studies is provided in Table D-40.

There were 48 reviews that were published in 2018 or after that presented results in a meta-analysis and were prioritised for critical appraisal and data extraction. Of these, 12 reviews (103, 226, 272, 279, 281, 282, 287, 312, 385-388) were focused on people with metabolic syndrome or those at risk of cardiovascular disease, with the other 36 reviews (6, 7, 15, 76, 97, 99, 102, 104, 105, 107-110, 176, 284, 286, 288, 293, 294, 296, 298, 300, 301, 305-310, 313, 315, 317, 319, 321, 389, 390) being umbrella reviews that included primary studies in people with other conditions (the reviews were focused on a specified herb or outcome).

There were 9 other reviews (68, 118, 123, 124, 127, 326, 328, 332, 341) that presented results in a meta-analysis but were published prior to 2018 and were judged to no longer represent the best available evidence. Another 12 reviews (154, 162, 191, 357-359, 364, 369, 391-394) provided a descriptive or narrative review of individual study results, but in the absence of data were not considered further.

Given the time and resource constraints further assessment of these reviews was not able to be performed. NTWC was not involved in selection of which prioritised conditions were completed versus not completed (see NHMRC process report for additional information).

Table D-40 List of herbs included in the identified studies: Metabolic syndrome

WHM identified in included studies	Matched to Tier 1 list of WHM: Endocrine and metabolic [a]
Aloe (Aloe spp.)	X
Artichoke (Cynara scolymus)	X
Astragalus (Astragalus membranaceous, Euphorbia)	X
Barberry (Berberis vulgaris)	X
Bilberry (Vaccinium myrtillus)	X
Black cumin (Nigella sativa)	X
Capsicum/ Cayenne (Capsicum minimum)	X
Chamomile (Matricaria recruitica)	X
Cinnamon (Cinnamomum zeylanicum / C. cassia)	X
Cranberry (Vaccinium macrocarpon)	X
Fenugreek (Trigonella foenum-graecum, Euphrasia officinalis)	✓
Garlic (Allium sativum)	X
Ginger (Zingiber officinale)	X
Ginkgo (Ginkgo biloba)	X
Ginseng (Panax ginseng)	✓
Green tea (Centella asiatica, Camillia sinensis)	X
Gymnema (Gymnema sylvestre)	✓
Hops (Humulus lupulus)	X
Lemon balm (Melissa officinalis)	X
Linseed (Tilia spp.)	X
Nettle (Urtica dioica)	X
Oats (Avena sativa)	X
Psyllium (Plantago ovata)	X
Saffron (Crocus sativus)	X
St Mary's thistle (Ulmus rubra)	X
Turmeric (Curcuma longa)	X
Withania (Withania somnifera)	✓

Abbreviations: WHM, Western herbal medicine

✓ = yes; X = no
See Appendix A6.3 - Tier 1 herb list was considered in GRADE. Eligibility was based on the herb list in Appendix A8

Table D-41 PICO criteria of included systematic reviews: Metabolic syndrome

Review ID	Method of analysis	Population [a]	Intervention [b]	Outcomes [d]
Kutbi 2021 (287)	meta-analysis	Metabolic disorders	Cinnamon	Lipid profile, blood pressure, glucose metabolism and anthropometrics
Jang 2020 (385)	meta-analysis	Metabolic syndrome	Capsicum	Lipid profile, body weight and cardiovascular risk factors
Li 2020 (386)	meta-analysis	Metabolic syndrome and obesity	Green tea	Lipid profile, blood pressure, glucose metabolism and anthropometrics
Roshanravan 2020 (387)	meta-analysis	Metabolic syndrome	Barberry	Glycaemic control and lipid profile
Ziaei 2020 (103)	meta-analysis	Metabolic syndrome	Ginseng	Lipid profile
Akbari 2019 (272)	meta-analysis	Metabolic syndrome	Turmeric	Body weight and composition
Azhdari 2019 (388)	meta-analysis	Metabolic syndrome	Turmeric	Lipid profile, blood pressure, glucose metabolism and anthropometrics
Huang 2019 (312)	meta-analysis	At risk of cardiovascular disease (incl. metabolic syndrome)	Turmeric	Glycaemic control
Pourmasoumi 2019 (226)	meta-analysis	At risk of cardiovascular disease (incl. metabolic syndrome)	Saffron	Lipid profile, blood pressure, glucose metabolism and anthropometrics
Yuan 2019 (279)	meta-analysis	Metabolic disorders	Turmeric	Lipid profiles
Tabrizi 2018 (281)	meta-analysis	Metabolic syndrome	Turmeric	Glycaemic control and lipid profiles
Zhu 2018 (282)	meta-analysis	Diabetes and Metabolic syndrome	Ginger	Glycaemic control
Asbaghi 2021 (284)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Saffron	Inflammatory markers
Atefi 2021 (286)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Barberry	Blood pressure
Ghassab-Abdollahi 2021 (6)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Black cumin, Turmeric	Oxidative stress and inflammatory biomarkers
Montazeri 2021 (7)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Black cumin	Oxidative stress and inflammatory biomarkers
Moradi 2021 (288)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Artichoke	Blood pressure
Shekarchizadeh-Esfahani 2021 (389)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Garlic	Serum adiponectin and leptin
Ghaderi 2020 (76)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Saffron	Mental health and C-reactive protein
Ghavami 2020 (97)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Ginseng	Liver function
Hadi 2020 (293)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Cinnamon	Blood pressure

Review ID	Method of analysis	Population [a]	Intervention [b]	Outcomes [d]
Hallajzadeh 2020 (15)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Black cumin	Glycaemic control, lipid profiles, oxidative stress and inflammatory biomarkers
Jalili 2020 (294)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Artichoke	Glycaemic control
Miraghajani 2020 (296)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Ginseng	Anthropometric indices and body composition
Mirzavandi 2020 (99)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Garlic	Inflammatory markers
Mousavi 2020 (298)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Cinnamon	Blood pressure
Mousavi 2020a (300)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Turmeric	Body weight, body mass index and waist circumference
Payab 2020 (390)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Green tea, Black cumin	Lipid profile, anthropometric indices and body composition
Pourmasoumi 2020 (301)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Cranberry	Cardiovascular metabolic risk factors
Safari 2020 (305)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Barberry	Glycaemic control
Xu 2020 (102)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Green tea	Lipid profile
Yazdanpanah 2020 (306)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Cinnamon	Body weight and composition
Alizadeh 2019 (307)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Turmeric	Oxidative stress markers
Asbaghi 2019 (308)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Saffron	Blood glucose and lipid profile
Askari 2019 (104)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Black cumin	Glycaemic control
Clark 2019 (309)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Turmeric	Adiponectin levels
Hadi 2019 (105)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Turmeric	Blood pressure
Hadi 2019a (310)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Barberry	Lipid profile
Hernandez-Garcia 2019 (107)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Ginseng	Lipid profile
Marx 2019 (176)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Saffron	Depression and anxiety
Mohammadi 2019 (108)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Ginseng	Inflammatory biomarkers
Saboori 2019 (109)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Ginseng	C-reactive protein
Tabrizi 2019 (313)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Turmeric	Oxidative stress and inflammatory biomarkers
White 2019 (315)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Turmeric	Inflammatory biomarkers
Golzarand 2018 (317)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Green tea	Anthropometric indices
Jovanovski 2018 (110)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Psyllium	Lipid profiles

Review ID	Method of analysis	Population [a]	Intervention [b]	Outcomes [d]
Namazi 2018 (319)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Black cumin	Body weight and composition
Qin 2018 (321)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Turmeric	Oxidative stress
Mohammadi-Sartang 2017 (118)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Linseed	Body weight and composition
Si 2017 (326)	meta-analysis	Cardiovascular risk factors (incl. metabolic syndrome)	Turmeric	Lipid profiles
Derosa 2016 (328)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Turmeric	Circulating IL-6
Guo-Chong 2016 (332)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Linseed	C-reactive protein
Sahebkar 2016 (123)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Black cumin	Lipid profiles
Sahebkar 2016b (328)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Turmeric	Circulating IL-6
Sahebkar 2016c (124)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Black cumin	Blood pressure
Ursoniu 2016 (68)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Linseed	Blood pressure
Khalesi 2015 (127)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Linseed	Blood pressure
Khalesi 2014 (341)	meta-analysis	Umbrella review (incl. metabolic syndrome)	Green tea	Blood pressure
Lopresti 2021 (191)	individual study results	Umbrella review (incl. metabolic syndrome)	Ginseng	Stress biomarkers
Ponticelli 2021 (391)	descriptive	Diabetes, Inflammation, and Metabolic Syndrome	Hops	Lipid profile, blood pressure, glucose metabolism and inflammatory biomarkers
Chan 2020 (357)	descriptive	Umbrella review (incl. metabolic syndrome)	Garlic	Blood pressure and lipid profiles
Eisvand 2020 (392)	descriptive	Metabolic syndrome	Ginkgo	Lipid profile, blood pressure, glucose metabolism and body weight
Emamat 2020 (358)	descriptive	Umbrella review (incl. metabolic syndrome)	Garlic	Vascular function
Giannoulaki 2020 (359)	descriptive	Diabetes and Metabolic Syndrome	Saffron	Lipid profile, blood pressure, glucose metabolism
Smith 2020 (393)	descriptive	Umbrella review (incl. metabolic syndrome)	Ginseng	Testosterone concentrations
Jane 2019 (394)	descriptive	Umbrella review (incl. metabolic syndrome)	Psyllium, Oats	Obesity-related disease risk factors
Hariri 2018 (364)	descriptive	Umbrella review (incl. metabolic syndrome)	Turmeric	Anthropometric indices
Mohtashami 2016 (154)	descriptive	Umbrella review (incl. metabolic syndrome)	Black cumin	Blood parameters and anthropometric indices
Choi 2013 (369)	descriptive	Umbrella review (incl. metabolic syndrome)	Ginseng	Any
Ulbricht 2012 (162)	descriptive	Umbrella review (incl. metabolic syndrome)	Hops combination	Any

Abbreviations: CAM, complementary and alternative medicine

Notes:
N = Number of RCTs meeting our PICO criteria; k = total number of RCTs identified by systematic review.
a. Systematic review with no population restrictions were eligible for inclusion if they presented data that evaluated participants with metabolic syndrome.
b. Systematic reviews were eligible for inclusion if they presented data that examined the effectiveness of eligible WHMs (see Appendix A8).
c. Systematic review with no comparator restrictions were eligible for inclusion if they presented data that compared WHM with control (placebo or no intervention) or another intervention.
d. Outcomes assessed or listed by the systematic review.
e. Study ID of eligible RCTs that met the PICO criteria of this overview.
-- Systematic review not assessed. The outcome domain was not critical or important for this overview OR a more recent SR nominated as best available is included.

D4.2.2 Critical appraisal

Not assessed.

D4.2.3 Effects of intervention

Outcomes considered by the NTWC to be critical or important for decision-making in people with metabolic syndrome are listed in Table D-42.

Table D-42 Outcomes considered by the NTWC to be critical or important for decision-making: Metabolic syndrome

Outcome domain	Measured with	Consensus rating	Data available for comparison 1 or 2	Review ID
				Not assessed
Glycaemic control	HbA1c, fasting blood glucose	7	Not assessed	Not assessed
Body composition	Waist circumference, waist to hip ratio	7	Not assessed	Not assessed
HRQoL	SF-36 or similar	7	Not assessed	Not assessed
Patient reported improvement	Global assessment	7	Not assessed	Not assessed
Depression	BDI, HAM-D or measure of emotional function	6	Not assessed	Not assessed

Abbreviations: BDI, Beck depression inventory, HAM-D, Hamilton depression rating scale; HbA1c, percent glycated haemoglobin; HRQoL, Health-related quality of life; SF-36 36-item short form

Notes:

✓ A study result is available for inclusion in the synthesis.

X A study result is NOT available for inclusion because the systematic review does not adequately report the results (data were incomplete). It is unclear if the primary study reported complete data. Due to time and resource constraints, only the information presented in the systematic review is reported.

? The systematic review did not assess this outcome, it is unclear if the outcome was assessed by the primary studies included in the SR. Due to time and resource constraints, only the information presented in the systematic review is reported.

-- The systematic review did not assess this outcome. The outcome was (probably) not assessed by the included primary studies (for reasons unrelated to the *p*-value, magnitude or direction of the results).

Comparison 1 (vs placebo)

Not assessed.

Comparison 2 (vs inactive control)

Not assessed.

Comparison 3 (vs other)

Not assessed.

D5 Immune mediated

D5.1 Fatigue conditions (post viral fatigue, ME/CFS etc.)

D5.1.1 List of reviews

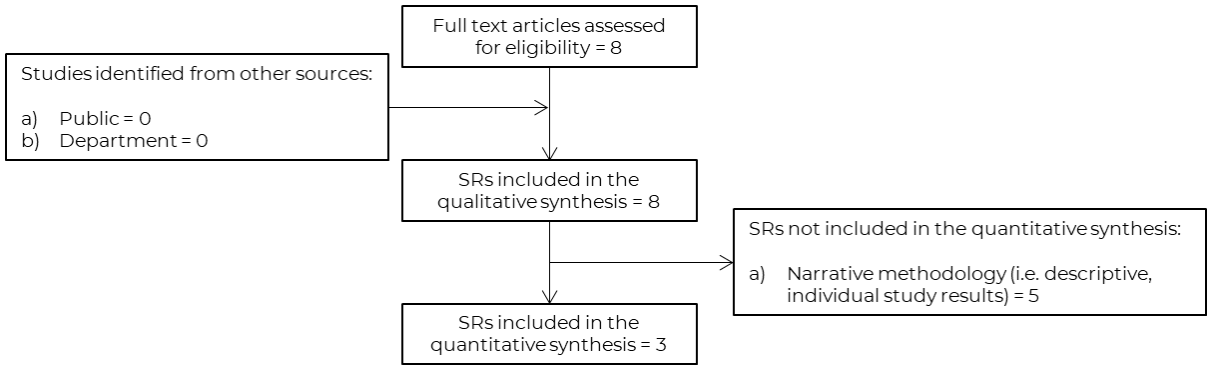
A summary of the PICO criteria of eligible systematic reviews is provided in Table D-44.

A list of herbs included in the identified studies is provided in Table D-43 .

There were 3 reviews (Bach 2016, Jin 2020, Kim 2020) that presented results in a meta-analysis and were prioritised for critical appraisal and data extraction. The other 5 reviews (Alraek 2011, Arring 2018, Ogawa-Ochiai 2018, Lopresti 2021, Provino 2010) provided a descriptive or narrative review or individual study results, noting that results were too heterogeneous to conduct a meaningful meta-analysis. These reviews were checked for additional studies and results, but in the absence of data were not considered further.

Figure D-28 outlines the selection process of the final included systematic reviews. Review details, including all outcome domains and measures reported by the included reviews, are provided in Appendix F1. Outcome data for critical or important outcomes are provided in Appendix F2.

Figure D-28 Process flow for prioritising systematic reviews: Fatigue conditions



Abbreviations: SR, systematic review

Table D-43 List of herbs assessed in the identified primary studies: Fatigue conditions

WHM identified in included studies	Matched to Tier 1 list of WHM: Immune system disorders [a]
Ginseng (Panax ginseng)	X
Siberian ginseng (Eluthero coccus senticosus)	X

Abbreviations: WHM, Western herbal medicine
✓ = yes; X = no
a. See Appendix A6.3 - Tier 1 herb list was considered in GRADE. Eligibility was based on the herb list in Appendix A8

Table D-44 PICO criteria of included systematic reviews: Fatigue conditions

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]	N	Study ID [e]
Lopresti 2021 (191)	Descriptive	No population restrictions	Oral use of herbs, spices, plants, fruits, vegetables, or their extracts used as a mono preparation	Placebo or control	Stress biomarkers	--	No studies in fatigue conditions
Jin 2020 (395)	Meta-analysis	Chronic fatigue syndrome or healthy adults after exercise	Panax ginseng	Placebo or vehicle treatment	Not specified	5 (k=8)	Hartz 2004, Hyeong-Geug 2013, Kim 2016, Lee 2016, La Gal 1996
Kim 2020 (396)	Meta-analysis	Chronic fatigue syndrome or idiopathic chronic fatigue	Any type of herbal medicine	Placebo, waitlist, or active treatment group	Not specified	1 (k=22)	Hartz 2004
Arring 2018 (397)	Descriptive	No population restrictions	Panax ginseng American ginseng	No comparator restrictions	Safety, Fatigue	2 (k=10)	La Gal 1996, Kim 2013
Ogawa-Ochiai 2018 (398)	Descriptive	No population restrictions	Panax ginseng	Not specified	Frailty and aging-related symptoms	1 SR (k=31)	Bach 2016 (see below)
Bach 2016 (399)	Meta-analysis	No population restrictions	Ginseng	Placebo	Fatigue severity, Physical performance	2 (k=12)	Kim 2013, Etemadifar 2013
Alraek 2011 (400)	Descriptive	Chronic fatigue syndrome	Any CAM *	Not specified	Not specified	1 (k=26)	Hartz 2004
Provino 2010 (201)	Descriptive	No population restrictions	Adaptogenic herbs (including Withania, ginseng, liquorice, rhodiola)	No comparator restrictions	Stress biomarkers, fatigue	0 (k=12)	No studies in fatigue conditions

Abbreviations: CAM, complementary and alternative medicine

Notes:

N = Number of RCTs meeting our PICO criteria; k = total number of RCTs identified by systematic review.

a. Systematic review with no population restrictions were eligible for inclusion if they presented data that evaluated participants with fatigue conditions.

b. Systematic reviews were eligible for inclusion if they presented data that examined the effectiveness of eligible WHMs (see Appendix A8).

c. Systematic review with no comparator restrictions were eligible for inclusion if they presented data that compared WHM with control (placebo or no intervention) or another intervention.

d. Outcomes assessed or listed by the systematic review.

e. Study ID of eligible RCTs that met the PICO criteria of this overview.

-- Systematic review not assessed. The outcome domain was not critical or important for this overview OR a more recent SR nominated as best available is included.

* Except acupuncture and complex herbal medicines.

Figure D-29 Critical appraisal summary: review author's judgements about each AMSTAR-2 item for each included systematic review – Fatigue conditions

	Review ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
FATIGUE	Jin 2020	Y	PY	N	PY	N	Y	N	PY	Y	Y	Y	Y	Y	Y	Y	Y
	Kim 2020	Y	Y	N	PY	Y	Y	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y
	Bach 2016	Y	PY	N	PY	Y	Y	N	PY	PY	Y	Y	Y	Y	Y	N	Y

N = No; PY = Partial Yes, Y = Yes

D5.1.2 Critical appraisal

A summary of the quality of included systematic reviews is provided in Figure D-29 and Table D-45. The strengths or limitations of the included systematic reviews assessed against each AMSTAR-2 domain is provided in Appendix E1.

All 3 systematic reviews that included a meta-analysis (Jin 2020, Kim 2020, Bach 2016) were judged to probably provide an accurate and comprehensive summary of the available studies that address the question of interest (i.e. met, or partially met, AMSTAR-2 domains 4, 8, 9 and 11). The other 5 systematic reviews (Alraek 2011, Arring 2018, Ogawa-Ochiai 2018, Lopresti 2021, Provino 2010) had at least one critical flaw (did not meet domain 11) and were not further assessed.

Table D-45 Critical appraisal summary: Fatigue conditions

Review ID	Summary	Notes
Jin 2020	Three non-critical weaknesses in domains 3, 5 and 7.	Authors did not provide an explanation for only including RCTs, it is not clear if study selection was done in duplicate, and the review authors did not provide a list of excluded studies read at full text.
Kim 2020	One non-critical weakness in domain 3.	Authors did not provide an explanation for only including RCTs.
Bach 2016	Three non-critical weaknesses in domains 3, 7 and 15.	Authors did not provide an explanation for only including RCTs, the review authors did not provide a list of excluded studies read at full text and the authors did not perform graphical or statistical tests for publication bias/discuss the likelihood and magnitude of impact of publication bias.

Abbreviations: RCT, randomised controlled trial

D5.1.3 Effects of intervention

Outcomes considered by the NTWC to be critical or important for decision-making in people with fatigue conditions are listed in Table D-46.

Table D-46 Outcomes considered by the NTWC to be critical or important for decision-making: Fatigue conditions

Outcome domain	Measured with	Consensus rating	Data available for comparison 1 or 2	Review ID		
				Jin 2020	Kim 2020	Bach 2016
Fatigue	Any validated multi-dimensional measure of fatigue [a]	9	Yes	✓	✓	✓
Quality of life	SF-36 or other validated measure	8	No	X	?	?
Patient reported improvement	No measures reported in eligible reviews	7	No	?	?	?
Emotional functioning	MASQ or other validated measure	7	No	X	?	?
Physical functioning	No measures reported in eligible reviews	7	No	?	?	?
Sleep quality	No measures reported in eligible reviews	7	No	?	?	?
Thinking/ concentration	Any relevant sub-domain of fatigue scale	7	No	?	?	?

Abbreviations: MASQ, Mood and Anxiety Symptom Questionnaire; NRS, numerical rating scale; RPSF, Revised Piper Fatigue Scale; RVI, Rand vitality index; SF-36, Short-Form Health Survey; VAFS, Visual Analogue Fatigue Scale; VAS, visual analogue scale

Notes:

a. In the absence of multi-dimensional measures of fatigue, data were included from studies that used a single item-measures.

✓ A study result is available for inclusion in the synthesis.

X A study result is NOT available for inclusion because the systematic review does not adequately report the results (data were incomplete). It is unclear if the primary study reported complete data. Due to time and resource constraints, only the information presented in the systematic review is reported.
? The systematic review did not assess this outcome, it is unclear if the outcome was assessed by the primary studies included in the SR. Due to time and resource constraints, only the information presented in the systematic review is reported.
-- The systematic review did not assess this outcome. The outcome was (probably) not assessed by the included primary studies (for reasons unrelated to the *p*-value, magnitude or direction of the results).

Comparison 1 (vs placebo)

Seven (7) RCTs (Etemadifar 2013, Le Gal 1996, Hartz 2004, Hyeong-Geug 2013, Kim 2013, Kim 2016, Lee 2016) were found by the included systematic reviews that compared ginseng with placebo in people with fatigue conditions. Three (3) RCTs (Etemadifar 2013, Hartz 2004, Kim 2013) contributed data relevant to one critical or important outcome. It is unclear if the RCTs assessed or reported the other critical or important outcomes. Data were missing from 4 RCTs (Gal 1996, Hyeong-Geug 2013, Kim 2016, Lee 2016) (total 539 participants) that could have contributed data but there was insufficient information in the reviews to make an assessment.

There were no studies awaiting classification or ongoing that compared WHMs with placebo in people with fatigue conditions.

Fatigue

Three (3) RCTs (total 185 participants) measured fatigue with various scales (modified Fatigue Impact Scale [FIS], Checklist Individual Strength [CIS], Numeric Rating Scale [NRS], Rand Index of Vitality [RVI] at the end of treatment (between 4 and 12 weeks).

The modified FIS provides an assessment of the perceived impact of fatigue in terms of physical, cognitive, and psychosocial functioning over the previous 4 weeks. It consists of 21 questions and is summarised to a total score ranging from 0 (no fatigue) to 84 (severe fatigue). The CIS comprises 20 items on a 7-point Likert scale, divided into four subscales: fatigue severity, concentration, motivation, and physical activity. A higher score indicates more complaints. The RVI consists of 4 questions that measure vitality, energy level, and fatigue and is intended to be a measure of subjective well-being. The NRS is a segmented version of a visual analogue scale that is administered verbally or graphically. The 11-point scale ranges from 0 (representing no fatigue) to 10 (representing fatigue as bad as you can imagine).

Pooled results suggest little to no improvement in fatigue in the WHM group compared to placebo (SMD –0.36; 95% CI –0.71, 0.00; $p = 0.05$) (*GRADE: Low*). No sensitivity analysis was performed examining the impact of studies at high risk of bias as none of the included RCTs were judged to be at high risk of bias.

Data were incomplete for 4 other RCTs (total 539 participants), of which 2 (Gal 1996, Lee 2016) were reported to show an effect ($p < 0.05$) favouring WHM and 2 (Kim 2016, Hyeong-Geug 2013) were reported to show no difference between groups ($p > 0.05$).

Quality of life

One RCT (total 52 participants) measured quality of life with the SF-36 at the end of treatment (4 weeks), but the data were incomplete and not able to be included in the evidence synthesis. The study was reported to show no difference between groups ($p > 0.05$).

The SF-36 is a multidimensional generic measure of HRQoL that comprises 36-items assessing eight domains: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. Total scores for each domain are summarised on a scale from 0 (worse) to 100 (best) and are standardised to reflect a general population mean of 50 and standard deviation of 10. The MCID for the SF-36 is estimated to be around 2 to 4 points for the general population (i.e. ~0.5 of the SD) (208).

Emotional functioning

One RCT (total 96 participants) measured emotional wellbeing with the Mood and Anxiety Symptom Questionnaire (MASQ) at the end of treatment (8 weeks), but the data was incomplete and not able to be included in the evidence synthesis. The study was reported to show an effect ($p < 0.05$) favouring WHM.

The MASQ assesses a range of symptoms relevant to depression and anxiety (401). There are 3 scales that measure general distress: mixed symptoms (15 items), anxious symptoms (11 items), and depressive symptoms (12 items), one anxiety-specific scale: anxious arousal (17 items), and one depression specific scale: anhedonic depression (22 items). Higher scores reflect greater levels of symptomatology.

Comparison 2 (vs inactive control)

There were no studies found by the included systematic reviews that compared WHM with inactive control (no intervention, waitlist or usual care) in people with fatigue conditions.

Comparison 3 (vs other)

There were no studies found by the included systematic reviews that compared WHM with other interventions in people with fatigue conditions.

D5.2 Upper respiratory tract infection

D5.2.1 List of reviews

A summary of the PICO criteria of the eligible systematic reviews is provided in Table D-48.

A list of herbs included in the identified studies is provided in Table D-47.

There were 7 reviews (402-408) published in 2018 or after that presented results in a meta-analysis and were prioritised for critical appraisal and data extraction. There were 10 other reviews (133, 409-417) that presented results in a meta-analysis but were published prior to 2018 and were judged to no longer represent the best available evidence. These reviews, along with 10 other reviews (372, 418-426) that provided a descriptive or narrative review or individual study results, were to be checked for additional studies and results, for inclusion in the evidence synthesis.

Due to time and resource constraints further assessment of these reviews was not able to be performed. NTWC was not involved in selection of which prioritised conditions were completed versus not completed (see NHMRC process report for additional information).

Table D-47 List of herbs included in the identified studies: Upper respiratory tract infection

WHM identified in included studies	Matched to Tier 1 list of WHM: Immune system disorders [a]
Herbal combination	X
Andrographis (Andrographis paniculata)	✓
Astragalus (Astragalus membranaceous)	✓
Black cumin (Nigella sativa)	X
Cinnamon (Cinnamomum zeylanicum / C. cassia)	X
Echinacea (Echinacea spp.)	✓
Elder (Sambucus nigra)	✓
Garlic (Allium sativum)	✓
Ginger (Zingiber officinale)	X
Ginseng (Panax ginseng)	X
Green tea (Camillia sinensis)	X
Ivy (Hedera helix)	X

Abbreviations: WHM, Western herbal medicine

✓ = yes; X = no

a. See Appendix A6.3 - Tier 1 herb list was considered in GRADE. Eligibility was based on the herb list in Appendix A8

Table D-48 PICO criteria of included systematic reviews: Upper respiratory tract infections

Review ID	Method of analysis	Population [a]	Intervention [b]	Outcomes [d]
Snidvongs 2021 (402)	meta-analysis	Upper respiratory tract infection (allergic rhinitis)	Astragalus, Green tea, Cinnamon, Ginseng, Black cumin, Ginger	Any efficacy outcomes
Wieland 2021 (403)	meta-analysis	Upper respiratory tract infection (viral)	Elderberry	Any efficacy outcomes (incl. prevention)
Ang 2020 (404)	meta-analysis	Upper respiratory tract infection (COVID)	Herb, not specified	Any efficacy outcomes
Antonelli 2020 (405)	meta-analysis	Upper respiratory tract infection (seasonal, acute)	Ginseng	Any efficacy outcomes
David 2019 (406)	meta-analysis	Upper respiratory tract infection (viral)	Echinacea	Any efficacy outcomes (incl. prevention)
Hawkins 2019 (407)	meta-analysis	Upper respiratory tract infection (viral)	Elderberry	Any efficacy outcomes (incl. prevention)
Anheyer 2018 (408)	meta-analysis	Upper respiratory tract infection (children)	Echinacea	Any efficacy outcomes
Hu 2017 (409)	meta-analysis	Upper respiratory tract infection (acute, adults and children))	Andrographis	Symptom relief
Schapowal 2015 (410)	meta-analysis	Upper respiratory tract infection	Echinacea	Recurrence, complications
Wagner 2015 (411)	meta-analysis	Upper respiratory tract infection (cough)	Andrographis, Echinacea, Ivy, Combination	Any efficacy outcomes
Linde 2014 (412)	meta-analysis	Upper respiratory tract infection (common cold)	Echinacea	Any efficacy outcomes
Shergis 2013 (133)	meta-analysis	Umbrella review (incl. URTI)	Ginseng	Any efficacy outcomes
Seida 2011 (413)	meta-analysis	Upper respiratory tract infection (common cold)	Ginseng	Prevention
Pittler 2007 (414)	meta-analysis	Umbrella review (incl. URTI)	Garlic	Any efficacy outcomes
Shah 2007 (415)	meta-analysis	Upper respiratory tract infection (common cold)	Echinacea, Combination	Any efficacy outcomes (incl. prevention)
Schoop 2006 (416)	meta-analysis	Upper respiratory tract infection (rhinovirus)	Echinacea	Prevention
Poolsup 2004 (417)	meta-analysis	Upper respiratory tract infection (uncomplicated)	Andrographis	Any efficacy outcomes

Review ID	Method of analysis	Population [a]	Intervention [b]	Outcomes [d]
Sierocinski 2021 (418)	descriptive	Upper respiratory tract infection (acute)	Ivy, Combination	Any efficacy outcomes
Harnett 2020 (419)	individual study results	Upper respiratory tract infection (acute)	Elderberry	Any efficacy outcomes
Jin 2019 (420)	descriptive	Upper respiratory tract infection (chronic rhinosinusitis)	Herb, not specified	Any efficacy outcomes
Anushiravani 2018 (421)	descriptive	Upper respiratory tract infection (chronic rhinosinusitis)	Herb, not specified	Any efficacy outcomes
Reckhenrich 2018 (422)	descriptive	Upper respiratory tract infection (with cough)	Ivy	Any efficacy outcomes
Lissiman 2014 (423)	individual study results	Upper respiratory tract infection (common cold)	Garlic	Any efficacy outcomes
Chuan 2013 (424)	individual study results	Upper respiratory tract infection	Astragalus	Prevention
Lee 2011 (372)	descriptive	Umbrella review (incl. URTI)	Ginseng	Any efficacy outcomes
Guo 2007 (425)	descriptive	Umbrella review (incl. URTI)	Ginseng, Elderberry, Andrographis, Echinaecea	Any efficacy outcomes
Coon 2004 (426)	descriptive	Upper respiratory tract infection	Andrographis	Any efficacy outcomes

Abbreviations: CAM, complementary and alternative medicine

Notes:

N = Number of RCTs meeting our PICO criteria; k = total number of RCTs identified by systematic review.

a. Systematic review with no population restrictions were eligible for inclusion if they presented data that evaluated participants with URTI.

b. Systematic reviews were eligible for inclusion if they presented data that examined the effectiveness of eligible WHMs (see Appendix A8).

c. Systematic review with no comparator restrictions were eligible for inclusion if they presented data that compared WHM with control (placebo or no intervention) or another intervention.

d. Outcomes assessed or listed by the systematic review.

e. Study ID of eligible RCTs that met the PICO criteria of this overview.

-- Systematic review not assessed. The outcome domain was not critical or important for this overview OR a more recent SR nominated as best available is included.

D5.2.2 Critical appraisal

Not assessed

D5.2.3 Effects of intervention

Outcomes considered by the NTWC to be critical or important for decision-making in people with upper respiratory tract infections are listed in Table D-49.

Table D-49 Outcomes considered by the NTWC to be critical or important for decision-making: Upper respiratory tract infection

Outcome domain	Measured with	Consensus rating	Data available for comparison 1 or 2	Review ID
				Not assessed
HRQoL	SNOT-20 or similar (disease-specific)	7	Not assessed	Not assessed
Patient reported improvement	Wisconsin Upper Respiratory Symptom Survey-11	7	Not assessed	Not assessed
Symptom severity	Symptom severity score (or similar)	7	Not assessed	Not assessed
Treatment duration	Mean duration (days)	7	Not assessed	Not assessed
Disease severity	Lund-Mackay scoring (radiologic)	6	Not assessed	Not assessed
Infection frequency	As reported	6	Not assessed	Not assessed

Abbreviations: HRQoL, Health-related quality of life; SF-36 36-item short form; SNOT-20, sinonasal outcome test 20

Notes:

✓ A study result is available for inclusion in the synthesis.

X A study result is NOT available for inclusion because the systematic review does not adequately report the results (data were incomplete). It is unclear if the primary study reported complete data. Due to time and resource constraints, only the information presented in the systematic review is reported.

? The systematic review did not assess this outcome, it is unclear if the outcome was assessed by the primary studies included in the SR. Due to time and resource constraints, only the information presented in the systematic review is reported.

-- The systematic review did not assess this outcome. The outcome was (probably) not assessed by the included primary studies (for reasons unrelated to the *p*-value, magnitude or direction of the results).

Comparison 1 (vs placebo)

Not assessed.

Comparison 2 (vs inactive control)

Not assessed.

Comparison 3 (vs other)

Not assessed.

D5.3 Dermatitis or eczema

D5.3.1 List of reviews

A summary of the PICO criteria of the eligible systematic reviews is provided in Table D-50.

A list of herbs included in the identified studies is provided in Table D-51.

There were 2 systematic reviews (367, 427) that provided a narrative summary of primary study results examining the effect if WHM on people with dermatitis or eczema (Thandar 2017, Vaughn 2016). The reviews did not provide any meaningful data for inclusion in a meta-analysis (with both reviews simply noting the benefits or harms of the intervention). In the absence of data, no further assessment of these reviews was made.

Table D-50 PICO criteria of included systematic reviews: Dermatitis or eczema

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]
Thandar 2017 (427)	descriptive	atopic eczema	Any topical herb (St John's wort, Witch hazel, Chamomile, Liquorice, Combinations)	Placebo or active control	--
Vaughn 2016 (367)	descriptive	Any skin condition	Curcumin	Placebo or active control	--

Abbreviations: CAM, complementary and alternative medicine
Notes:
N = Number of RCTs meeting our PICO criteria; k = total number of RCTs identified by systematic review.
a. Systematic review with no population restrictions were eligible for inclusion if they presented data that evaluated participants with dermatitis or eczema.
b. Systematic reviews were eligible for inclusion if they presented data that examined the effectiveness of eligible WHMs (see Appendix A8).
c. Systematic review with no comparator restrictions were eligible for inclusion if they presented data that compared WHM with control (placebo or no intervention) or another intervention.
d. Outcomes assessed or listed by the systematic review.
e. Study ID of eligible RCTs that met the PICO criteria of this overview.
-- Systematic review not assessed. The outcome domain was not critical or important for this overview OR a more recent SR nominated as best available is included.

Table D-51 List of herbs included in the identified studies: Dermatitis or eczema

WHM identified in included studies	Matched to Tier 1 list of WHM: Immune system disorders [a]
Herbal combination	X
Chamomile (Matricaria recruitica)	X
Liquorice (Glycyrrhiza glabra)	X
Witch hazel (Hamamelis virginiana)	X

Abbreviations: WHM, Western herbal medicine
✓ = yes; X = no
a. See Appendix A6.3 - Tier 1 herb list was considered in GRADE. Eligibility was based on the herb list in Appendix A8

D5.3.2 Critical appraisal

Not assessed.

D5.3.3 Effects of intervention

Outcomes considered by the NTWC to be critical or important for decision-making in people with dermatitis and eczema conditions are listed in Table D-52.

Table D-52 Outcomes considered by the NTWC to be critical or important for decision-making: Dermatitis and eczema

Outcome domain	Measured with	Consensus rating	Data available for comparison 1 or 2	Review ID	
				Thandar 2017	Vaughn 2016
HRQoL	SF-36 or similar	8	No	X	X
Patient reported improvement	Global improvement score	8	No	X	X
Symptom severity	Modified SCORAD	7	No	X	X
Emotional functioning	SF-36 MCS (or similar)	7	No	X	X
Physical functioning	SF-36 PCS (or similar)	6	No	X	X
Pain	VAS (or similar)	6	No	X	X

Abbreviations: HRQoL, Health-related quality of life; MCS, mental component score; PCS, physical component score; SF-36 36-item short form; VAS, visual analogue scale

Notes:

✓ A study result is available for inclusion in the synthesis.

X A study result is NOT available for inclusion because the systematic review does not adequately report the results (data were incomplete). It is unclear if the primary study reported complete data. Due to time and resource constraints, only the information presented in the systematic review is reported.

? The systematic review did not assess this outcome, it is unclear if the outcome was assessed by the primary studies included in the SR. Due to time and resource constraints, only the information presented in the systematic review is reported.

-- The systematic review did not assess this outcome. The outcome was (probably) not assessed by the included primary studies (for reasons unrelated to the *p*-value, magnitude or direction of the results).

Comparison 1 (vs placebo)

No usable information provided by the identified reviews. The effect of WHM on people with dermatitis or eczema is unknown.

Comparison 2 (vs inactive control)

No usable information provided by the identified reviews. The effect of WHM on people with dermatitis or eczema is unknown.

Comparison 3 (vs other)

No usable information provided by the identified reviews. The effect of WHM on people with dermatitis or eczema is unknown.

D5.4 Acne

D5.4.1 List of reviews

A summary of the PICO criteria of the eligible systematic reviews is provided in Table D-53.

A list of herbs included in the identified studies is provided in Table D-54.

One review (Kim 2021) presented results in a meta-analysis and was prioritised for critical appraisal and data extraction. The other 4 reviews (Vaughn 2016, Tuong 2015, Ernst 2002, Vogler 1999) provided a narrative or descriptive review of individual studies but did not report any data. These reviews were checked for additional results, but in the absence of data were not considered further.

Figure D-30 outlines the selection process of the final included systematic reviews. Review details, including all outcome domains and measures reported by the included reviews, are provided in Appendix F1. Outcome data for critical or important outcomes are provided in Appendix F2.

Table D-53 PICO criteria of included systematic reviews: Acne

Review ID	Method of analysis	Population [a]	Intervention [b]	Comparator [c]	Outcomes [d]	N	Study ID [e]
Kim 2021 (428)	Meta-analysis	Acne vulgaris	Green tea (extract or consumption)	Placebo (ethanol 3%)	Acne lesion count or measure of disease severity	5 (k=9)	Waranuch 2019, Lu 2016, Yoon 2013, Sharquie 2008, Sharquie 2006
Vaughn 2016 (367)	Umbrella review; descriptive	Skin health (acne)	Curcumin (oral/topical combination*)	Placebo	Major outcomes (Leed's technique)	1 (k=18)	Lalla 2001
Tuong 2015 (429)	Umbrella review; descriptive	Dermatologic conditions (acne vulgaris)	Polyphenols (green tea)	Any (no comparator)	Any (acne lesion count)	1 (k=17)	Jung 2012
Ernst 2002 (430)	Umbrella review; descriptive	Dermatologic conditions (acne)	Any CAM (tea tree oil)	Any (5% benzoyl peroxide)	Any (improvement)	2 (k=51)	Fulton 1990, Basset 1990
Vogler 1999 (384)	Umbrella review; descriptive	Any (acne)	Aloe vera	Any	Any	1	Fulton 1990

Abbreviations: CAM, complementary or alternative medicine; RCT, randomised controlled trial

Notes:

N = Number of RCTs meeting our PICO criteria; k = total number of RCTs identified by systematic review.

a. Systematic review with no population restrictions were eligible for inclusion if they presented data that evaluated participants with insomnia or sleep problems.

b. Systematic reviews were eligible for inclusion if they presented data that examined the effectiveness of eligible WHMs (see Appendix A8).

c. Systematic review with no comparator restrictions were eligible for inclusion if they presented data that compared WHM with control (placebo or no intervention) or another intervention.

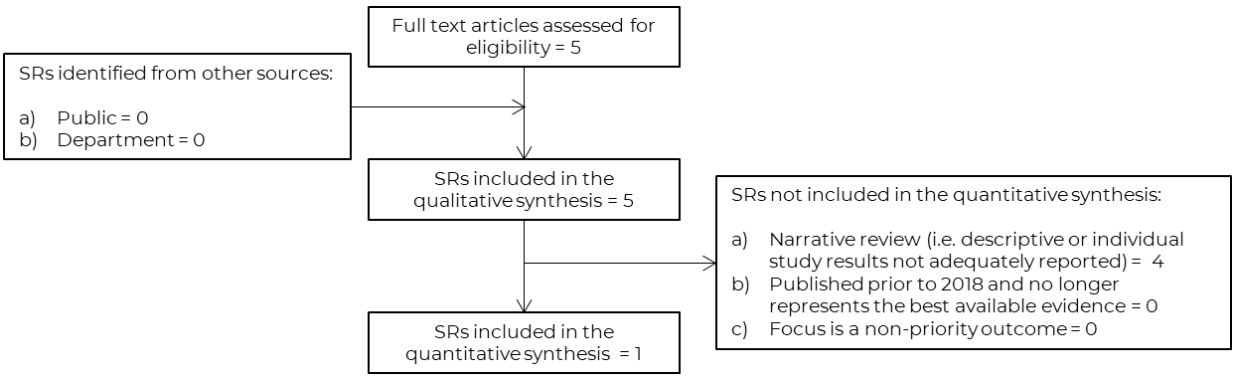
d. Outcomes assessed or listed by the systematic review. Grey highlight = nonpriority outcome; Blue highlight = critical or important outcome

e. Study ID of eligible RCTs that met the PICO criteria of this overview.

-- Systematic review not assessed. The outcome domain was not critical or important for this overview OR a more recent SR nominated as best available is included.

* *Curcuma longa, Aloe spp., Withania somnifera, Piper longum, Hemidesmus indicus, and other not on List A (Azardirachta indica, Linn, Terminalia arjuna, T. chebula*)

Figure D-30 Process flow for prioritising systematic reviews: Acne



Abbreviations: SR, systematic review

Table D-54 List of herbs included in the identified studies: Acne

WHM identified in included studies	Matched to Tier 1 list of WHM: Immune system disorders [a]
Herbal combination (curcumin + others*)	X
Aloe vera (Aloe spp.)	X
Green tea (Camellia sinensis)	X
Tea tree oil (Melaleuca alternifolia)	X

Abbreviations: WHM, Western herbal medicine

✓ = yes; X = no

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

a. See Appendix A6.3 - Tier 1 herb list was considered in GRADE. Eligibility was based on the herb list in Appendix A8

D5.4.2 Critical appraisal

A summary of the quality of included systematic reviews is provided in Figure D-31 and Table D-55. The strengths or limitations of the included systematic reviews assessed against each AMSTAR-2 domain is provided in Appendix E1.

One systematic review (Kim 2021) that included a meta-analysis was judged to probably provide an accurate and comprehensive summary of the available studies that address the question of interest (i.e. met, or partially met, AMSTAR-2 domains 4, 8, 9 and 11). The other 4 systematic reviews (Vaughn 2016, Tuong 2015, Ernst 2002, Volger 1999) had at least one critical flaw (did not meet domain 11) and were not further assessed.

Figure D-31 Critical appraisal summary: review author's judgements about each AMSTAR-2 item for each included systematic review – Acne

	Review ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
ACNE	Kim 2021	N	N	N	PY	Y	Y	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y

N = No; PY = Partial Yes, Y = Yes

Table D-55 Critical appraisal summary: Acne

Review ID	Summary	Notes
Kim 2021	3 non-critical weakness in domains 1, 2 and 3.	The authors did not adequately define the research question, adequately report inclusion and exclusion criteria or explain the study selection criteria.

D5.4.3 Effects of intervention

Outcomes considered by the NTWC to be critical or important for decision-making in people with acne are listed in Table D-56.

Table D-56 Outcomes considered by the NTWC to be critical or important for decision-making: Acne

Outcome domain	Measured with	Consensus rating	Data available for comparison 1 or 2	Review ID Kim 2021
Patient reported improvement	Change in acne lesion count (Leed's technique)	8	Yes	✓
HRQoL	SF-36 or similar	7	No	--
Emotional functioning	SF-36 mental component score (or similar)	7	No	--
Physical functioning	SF-36 physical component score (or similar)	6	No	--
Disease severity score	Acne severity index	6	Yes	✓

Abbreviations: HRQoL, Health-related quality of life; SF-36 36-item short form; VAS, visual analogue scale
Notes:
✓ A study result is available for inclusion in the synthesis.
X A study result is NOT available for inclusion because the systematic review does not adequately report the results (data were incomplete). It is unclear if the primary study reported complete data. Due to time and resource constraints, only the information presented in the systematic review is reported.
? The systematic review did not assess this outcome, it is unclear if the outcome was assessed by the primary studies included in the SR. Due to time and resource constraints, only the information presented in the systematic review is reported.
-- The systematic review did not assess this outcome. The outcome was (probably) not assessed by the included primary studies (for reasons unrelated to the *p*-value, magnitude or direction of the results).

Comparison 1 (vs placebo)

Three RCTs (Lu 2016, Sharquie 2006, Yoon 2013) were found by the included systematic review that compared green tea with placebo in people with acne vulgaris. All three RCTs contributed data relevant to at least one critical or important outcomes. One RCT (Yoon 2013) investigated two different concentrations of green tea extract (1% EGCG and 5% EGCG) using a split-face trial design[q]; hence was considered as two separate studies in the analysis. One other RCT (Lalla 2001) was identified that compared a curcumin-based herbal combination with placebo in people with acne vulgaris. Data for this study (total 53 participants) were not adequately reported, therefore was not able to be included in the evidence synthesis.

Patient reported improvement

One RCT (total 35 participants; [70 split-face]) reported patient-assessment of improvement measured using a visual analogue scale (VAS) at the end of treatment (8 weeks) (Yoon 2013). The other 2 RCTs (total 113 participants) did not measure this outcome.

The VAS is subjective tool that can be used to measure a variety of outcomes. It is measured on a continuous scale (cm) from 0 to 10, with higher scores indicating a worse outcome. Pooled results suggest a significant improvement in acne in the WHM group compared with placebo (MD –4.61; 95% CI –5.98, –3.23; $p < 0.00001$; $I^2 = 80\%$) (*GRADE: Low*).

Disease severity

Three RCTs (total 181 participants) reported a global assessment of acne severity measured using the Leeds revised technique or based on acne lesion count at the end of treatment (range 4 to 8 weeks) (Lu 2016, Sharquie 2006, Yoon 2013 (2 comparison groups)).

[q] participants used intervention on one half of face, and placebo on the other half.

The Leeds revised acne grading system reflects both inflammatory (papules, pustules, nodules, cysts) and noninflammatory (comedones [blackheads and whiteheads]) acne lesions using a series of colour photographs ranked in order of severity (431). Acne lesion counts can be used to guide grading of acne severity (from mild[r] to severe[s]) (432) and are based on a count of the number of inflammatory or noninflammatory lesions. As all studies reported acne lesion counts, this measure was used in the evidence synthesis.

Pooled results suggested an effect that favours the WHM group compared to placebo for inflammatory lesions (SMD –3.59; 95% CI –5.96, –1.20; $p = 0.03$; $I^2 = 96\%$) (*GRADE: Low*) but not noninflammatory lesions (SMD –0.73; 95% CI –6.44, 4.99; $p = 0.80$; $I^2 = 99\%$) (*GRADE: Very low*). However, there was substantial heterogeneity observed in both results.

A sensitivity analysis that removed one RCT (Lu 2016) examining the effect of oral decaffeinated green tea extract (other RCTs used a topical application), the heterogeneity did not materially change for the inflammatory lesion count (SMD –4.56; 95% CI –6.42, –2.71; $p < 0.0001$; $I^2 = 85\%$); but was notably improved for the noninflammatory lesion count (SMD –3.56; 95% CI –4.35, –2.78; $p < 0.00001$; $I^2 = 0\%$), with the direction of effect also changed.

Comparison 2 (vs inactive control)

There was one RCT (Jung 2012) found by the eligible systematic reviews that compared WHM (green tea extract) with control (no intervention) in people with acne. The study results were not adequately reported, and retrieval of primary study results was not pursued.

Comparison 3 (vs other)

There were 2 RCTs found by the eligible systematic reviews that compared green tea or combination WHM (green tea extract, aloe and mangosteen) against an active comparator; being either 5% zinc sulphate (Sharquie 2008) or antibiotics (1% clindamycin) (Waranuch 2019) and contributed data to at least one critical or important outcome (disease severity). One other RCT (Basset 1990) comparing tea tree oil with benzoyl peroxide was identified, but there were no study results available for inclusion in the synthesis.

Data from these studies are presented in Appendix F2 Supplementary outcome data.

[r] <20 comedones, <15 inflammatory lesions, or total lesion count <30

[s] >5 pseudocysts, total comedones count >100, total inflammatory count >50; or total lesion count >125

Appendix E Critical appraisal forms

This appendix documents the critical appraisal made on systematic reviews that met the prespecified inclusion criteria for an overview of systematic reviews examining the effect of Western herbal medicines for preventing and treating any health condition.

E1 Systematic reviews

The methodological quality of included systematic reviews were assessed using the AMSTAR-2 quality assessment checklist (433).

Each question of the AMSTAR-2 was answered as 'yes', 'no', or 'partial yes'; with a 'yes' answer denoting a positive result. The overall quality of the systematic review was assessed, regardless of whether the systematic review was broader in scope than the clinical question posed in this Overview (i.e. includes other interventions or studies not eligible for inclusion).

It is noted that the AMSTAR-2 leads to a judgement of methodological quality (or limitations) of a systematic review, not a judgement about risk of bias of the body of evidence included within the systematic review.

Eligible reviews are listed for each priority population in order of ICD-11 category. Within the ICD-11 category studies are then listed by condition, then by publication date (most recent first).

A summary (by condition) is provided below. Full details are provided in *Appendix E1-WHM-AMSTAR-2* (see separate spreadsheet).

Appendix F Characteristics of included studies

This appendix documents the data extracted from systematic reviews that met the prespecified inclusion criteria for an overview of systematic reviews examining the effect of Western herbal medicine for preventing and treating any health condition.

All extracted data is presented, including that which was not synthesised in the main report.

F1 Study details

(see separate spreadsheet *Appendix F1- WHM-Study details*)

Appendix F1 lists the characteristics of each included review (for priority populations) in order of the umbrella populations. Reviews within each category are listed by publication year (most recent first) and then alphabetically.

For each review, the data extraction included (but was not limited to) the following characteristics: review objective, author affiliation, declared interests and source of funds, review method of analysis, eligibility criteria, date of documented search and databases searched, reported outcomes (including measurement method and timing), and risk of bias assessments of the included RCTs as reported by the review authors.

The PICOs of eligible RCTs meeting the inclusion criteria for this Overview are also listed, with studies reporting an outcome domain considered critical or important for inclusion in the review are highlighted, either with a blue box (meaning the RCT data was extracted from the systematic review) or a grey box (meaning the RCT data was extracted from another [more recent or higher quality] systematic review). Conversely, outcome domains and measures that were of limited importance are not highlighted.

F2 Supplementary outcome data

(see separate spreadsheet *Appendix F2- WHM-Outcome data*)

Appendix F2 lists the data extracted for critical or important outcomes reported by the identified systematic reviews (for priority populations) in order of the umbrella populations. Within each condition, reviews are listed by comparison (WHM vs placebo, WHM vs inactive control, WHM vs active control) with the study results per critical or important outcome measures that includes (but is not limited to) the following: outcome domain, timing, outcome measure, measure details, number of included participants, point estimates, p-value, direction of effect.

Data extracted is that reported by the review authors at the end of treatment (where possible) with footnotes included if further explanation was required (e.g. authors do not provide end-of treatment results therefore the mean change from baseline data are reported). The final column lists the risk of bias assessment for that outcome as made by the review authors (see Appendix F1).

Appendix G Differences between protocol & review

G1 Methods not implemented

To confirm combination herbal preparations are representative of WHM in Australia, a list of potentially relevant systematic reviews was to be supplied to a content expert for independent full text screening; however, no such reviews were identified. The expert was to confirm the appropriateness of the herbal combination/s as meeting the WHM eligibility criteria after examination of the systematic review (or primary studies within). Advice regarding the relevant grouping or subgrouping of the studies for analysis (with regards to the intervention) was also to be sought at this time.

It was intended that, if a review did not contain the required PICO information for a decision to be made regarding eligibility, the information was to be sought from the systematic review authors through an open-ended request. Given time and resource constraints, we did not contact authors for additional information regarding eligibility criteria.

G2 Changes from protocol

There were differences between the protocol and review relating to the following sections:

Inclusion decisions

Each citation (title and abstract) was to be screened by one evidence reviewer who was to discard ineligible SRs (marked as irrelevant and tagged with a reason for exclusion) and retain those with relevant data or information (marked as relevant or maybe). Where there was uncertainty regarding relevance, a decision was to be made through discussion with a second (lead) reviewer. After initial testing, it was agreed that a screening should be done independently by 2 reviewers. This was because, with the volume of eligible herbs (125 in total) and the variances in naming conventions (e.g. Latin vs common name), a large volume of irrelevant reviews were being marked as 'maybe'. With 2 reviewers independently screening citations, the lead reviewer was able to focus their attentions to resolving conflicts prior to retrieving full text articles (inter-rater reliability varied [Cohen's kappa ranged from 0.485 to 0.861]).

Studies identified in the literature search

RCTs in the systematic reviews were individually identified and recorded into an Excel spreadsheet and were arranged to determine the most recent systematic reviews (i.e. studies from 2018 onwards). The date restriction was implemented to identify systematic reviews reporting the most relevant RCTs for the prioritised population; this date restriction was not applied for populations with a small number of systematic reviews (i.e. less than 10). This pragmatic decision was made to identify the most relevant and recent systematic reviews encompassing a broad range of RCTs to maximise the available data for evidence synthesis.

It was intended that SRs judged to have critical flaws, then the primary studies would be retrieved to check and confirm data retrieved. Given time and resource constraints, we did not return to primary studies in any circumstance.

Selection of eligible and priority studies

If a systematic review reported a relevant population meeting the inclusion criteria, i.e. PICO (see Appendix A), but was not ranked as a priority, the systematic review would not be included throughout the data extraction process in full text. The rationale behind excluding these non-priority studies during the data extraction process was to identify the most relevant and recent systematic reviews, since extracting every systematic review for each population was not practical, as some systematic reviews identified the same RCTs. An additional selection filter was applied to identify eligible studies with outcomes ranked as a priority by NTWC; the primary reviewers took the eligible studies through data extraction.

For example, if a study met the predefined PICO criteria but were not a priority population (e.g. cardiovascular disease) as agreed upon by the NTWC, the study would not be data extracted. If a study met the predefined inclusion criteria and was a priority population (e.g. irritable bowel syndrome) as outlined by the NTWC and reported a prioritised outcome (e.g. global improvement), the systematic review would be included in data extraction.

Where additional assistance was required regarding eligibility for a combination herbal preparation, a content expert (Dr Erica McIntyre) was to be consulted – this was not required for the review of WHMs.

The primary study of interest was a systematic review of RCTs, with or without a meta-analysis. When it came to prioritising systematic review for inclusion in the evidence synthesis, systematic reviews without a meta-analysis were not considered in the first pass.

Data collection and risk of bias assessment process

The characteristics of all included SRs were to be extracted by one reviewer using a standard pre-tested data extraction and coding form. It was intended that the lead reviewer would then check all forms for completeness and accuracy. Similarly, the AMSTAR quality of each included SR was to be assessed by one reviewer, with the lead reviewer then checking and confirming all assessments made. Given time and resource constraint, and the time taken to complete this overview, data extraction forms and quality assessments were checked by a second reviewer, but it was not always the nominated lead reviewer.

Stratification of interventions

The protocol noted that systematic reviews were to be stratified (where possible) based on the type of herb and how the intervention is prepared (e.g. liquid herbal extracts such as tincture or fluid extracts, oral tablets or capsules, or topical application, for example, via poultices, creams and pessaries etc.). There were few cases where this was possible (see IBD and peppermint oil, Depression and St John's Wort, and Menopause and black cohosh or red clover).

Non-completion of 4 prioritised conditions

The protocol stated that included reviews would be critically appraised, appropriate data extracted into data extraction tables, and the results analysed and summarised into appropriate categories according to identified populations, interventions and comparators. Due to the overall large volume of evidence, time and resource constraints, and the time taken to complete this overview, it was not feasible to critically appraise and synthesise data for 4 of the 16 prioritised conditions (diabetes, impaired glucose tolerance, metabolic syndrome and upper respiratory tract infections) due to time and resource constraints. Reviews were screened for eligibility, information about population(s), intervention (specific herbs) and outcomes was tabulated, and reviews were prioritised for critical appraisal. NTWC was not involved in selection of which prioritised conditions were completed versus not completed (see NHMRC process report for additional information).

Appendix H Response to methodological review

Methodological review (or peer review) was conducted to appraise the methodological quality and assess the appropriateness of reporting for this overview (including appendices).

For reporting, the methodological review assessed the overview against the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Checklist (2020) and where applicable, the MECIR (Methodological Expectations of Cochrane Intervention Reviews) manual.

The methodological review also considered (where appropriate):

- Risk-of-bias for overviews of reviews (Ballard and Montgomery 2017)
- Chapter V on overviews from the Cochrane Handbook for Systematic Reviews of Interventions (updated 2022)
- GRADE guidance and GRADE working group criteria for determining whether the GRADE approach was used (GRADE handbook).

The overview (including appendices) has been updated to reflect the amendments suggested by methodological review and NHMRC's Natural Therapies Working Committee, where appropriate. In summary, updates included additional information and/or clarification of the Plain Language Summary, Executive Summary, Results sections and Appendices, including:

- A Summary of Findings Table added to the main report for the tertiary comparison for depression – the one case where there was sufficient quality evidence comparing to the same active comparator (an accepted, evidence-based 'gold standard' of care for the population in question).
- Statements about the results vs inactive comparators and vs active comparators were added to the summaries.

A detailed record of responses to all comments indicating changes that were made was provided to NHMRC together with the amended Report and Appendices documents.

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