OVERVIEW OF Western herbal medicines for preventing and treating health conditions

Appendices D to H

prepared by

**HT**ANALYSTS

for

National Health and Medical Research Council

NHMRC | Natural Therapies Working Committee

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Reportinformation

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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](#_ENREF_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](#_ENREF_2)).

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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

# 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.

## Digestive disorders

## Nervous system

### Anxiety

#### 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](#_ENREF_76), [77](#_ENREF_77), [174-180](#_ENREF_174)) 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](#_ENREF_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](#_ENREF_182)) 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](#_ENREF_189), [190](#_ENREF_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](#_ENREF_149), [160](#_ENREF_160), [191-205](#_ENREF_191)) 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‑18 Process flow for prioritising systematic reviews: Anxiety

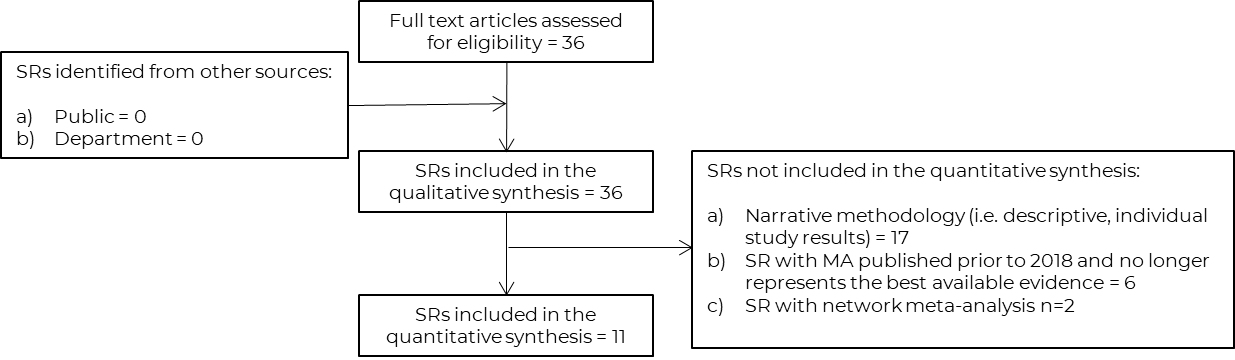


Table D‑25 PICO criteria of included systematic reviews: Anxiety

| Review ID | Method of analysis | Population a | Intervention b | Comparator c | Outcomes d | N | Study ID e |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Ghaderi 2020 ([76](#_ENREF_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](#_ENREF_181)) | Individual results | Neuropsychiatric disorders | Passionflower | Not specified | Anxiety, sleep quality | 1  (k=9) | Akhondzadeh 2001 |
| Shinjyo 2020 ([77](#_ENREF_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](#_ENREF_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](#_ENREF_175)) | meta-analysis | Anxiety, Insomnia | Chamomile | Placebo | Anxiety, insomnia, sleep quality | 2  (k=12) | Mao 2016, Amsterdam 2009 |
| Marx 2019 ([176](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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 |
| Brondino 2013 ([182](#_ENREF_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](#_ENREF_183)) | meta-analysis | Generalised anxiety disorder | Any (incl. complementary and alternative medicines) | Placebo | Anxiety (HAM-A) | 1 (k=21) | Connor 2002 |
| Miyasaka 2007 ([184](#_ENREF_184)) | meta-analysis (Cochrane) | Anxiety disorders | Passionflower | Placebo, no intervention, psychotherapy or other | Anxiety, Side effects | 1  (k=2) | Akhondzadeh 2001 |
| Miyasaka 2006 ([185](#_ENREF_185)) | meta-analysis (Cochrane) | Anxiety disorders | Valerian | Placebo, no intervention, psychotherapy | Anxiety, Side effects | 1  (k=1) | Andreatini 2002 |
| Witte 2005 ([186](#_ENREF_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](#_ENREF_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](#_ENREF_188)) | meta-analysis | Anxiety | Kava | Placebo | Any efficacy or safety outcome | -- | -- |
| Lopresti 2022 ([191](#_ENREF_191)) | descriptive | Umbrella review (any condition) | Any single herb, spice, plant or extract | Not specified | stress response biomarkers | -- | -- |
| Lopresti 2021 ([192](#_ENREF_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](#_ENREF_193)) | descriptive | Umbrella review (any condition) | Withania [ashwagandha] | Any | Any efficacy or safety outcome | -- | -- |
| Kim 2018 ([149](#_ENREF_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 |
| Sarris 2018 ([194](#_ENREF_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](#_ENREF_195)) | descriptive | Anxiety | Withania [ashwagandha] | Not specified | Stress/anxiety | 3  (k=5) | Khyati 2014, Auddy 2008, Andrade 2000 |
| Miroddi 2013 ([160](#_ENREF_160)) | descriptive | Umbrella review (any condition) | Passionflower | Not specified | Any efficacy or safety outcome | -- | -- |
| Sarris 2013 ([196](#_ENREF_196)) | descriptive | Anxiety, OCD, phobias | Plant-based medicine | Not specified | Anxiolytic activity (stress biomarkers) | 0 (k=21) | -- |
| Perry 2012 ([197](#_ENREF_197)) | descriptive | Umbrella review (any condition) | Lavender | Not specified | Stress/anxiety | 2 (k=15) | Kasper 2010, Woelk 2010 |
| Sarris 2012 ([198](#_ENREF_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](#_ENREF_199)) | descriptive | Generalised anxiety disorder, neurocognition | Kava | Not specified | Any efficacy or safety outcome | -- | -- |
| Lakhan 2010 ([200](#_ENREF_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](#_ENREF_201)) | descriptive | Stress conditions | Adaptogenic herbs | Not specified | Not specified | -- | -- |
| Sarris 2009 ([202](#_ENREF_202)) | descriptive | Mood and anxiety disorders | Kava, St John's wort | Not specified | Any efficacy or safety outcome (anxiety, depression) | -- | -- |
| Sarris 2007 ([203](#_ENREF_203)) | descriptive | Psychiatric disorders | Herbal medicines (oral) | Not specified | Any efficacy and safety outcome | -- | -- |
| Ernst 2006 ([204](#_ENREF_204)) | descriptive | Anxiety | Herbal preparations (oral) | Not specified | Anxiety | -- | -- |
| Jorm 2004 ([205](#_ENREF_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‑19 Critical appraisal summary: review author's judgements about each AMSTAR-2 item for each included systematic review – Anxiety



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

Table D‑26 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

#### 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‑27 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. |
| 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

#### 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‑28 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](#_ENREF_206), [207](#_ENREF_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; I2 = 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; I2 = 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; I2 = 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; I2=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; I2=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](#_ENREF_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; I2=0%) (GRADE: Low) and the SF-36 MCS (MD 10.19; 95% CI 5.78, 14.61; p < 0.001; I2=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; I2 = 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; I2 = 78.5%).

Figure D‑20 Forest plot of comparison: WHM vs placebo: Symptoms of anxiety – anxiety\*



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

Figure D‑21 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).

### Depression and mood disorders

#### 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](#_ENREF_76), [88](#_ENREF_88), [176](#_ENREF_176), [209-214](#_ENREF_209)) 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](#_ENREF_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](#_ENREF_216)) 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](#_ENREF_106), [191](#_ENREF_191), [225-228](#_ENREF_225)) 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](#_ENREF_71), [82](#_ENREF_82), [149](#_ENREF_149), [194](#_ENREF_194), [202](#_ENREF_202), [203](#_ENREF_203), [229-248](#_ENREF_229)) 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‑22 Process flow for prioritising systematic reviews: Depression and mood disorders

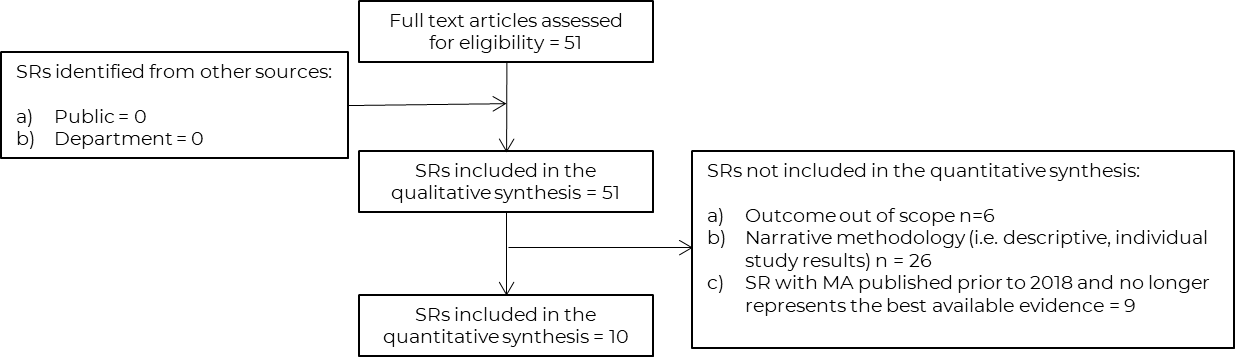


Table D‑29 PICO criteria of included systematic reviews: Depression and mood disorders

| Review ID | Method of analysis | Population a | Intervention b | Comparator c | Outcomes d | N | Study ID e |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Firoozeei 2021 ([88](#_ENREF_88)) | Meta-analysis | Umbrella review (any condition) | Lavender | Any | Depressive symptoms | 1 (k=17) | Araj-Khodaei 2020 |
| Karimi 2021 ([228](#_ENREF_228)) | Meta-analysis | Umbrella review (any condition) | Saffron | Placebo | Liver function | (k=12) | -- |
| Mousavi 2021 ([225](#_ENREF_225)) | Meta-analysis | Umbrella review (any condition) | Saffron | Not specified | Liver enzymes | (k=9) | -- |
| Wang 2021 ([209](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_106)) | Meta-analysis | Depression | Turmeric | Not specified | Endothelial function | (k=10) | -- |
| Khaksarian 2019 ([212](#_ENREF_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](#_ENREF_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, Akhondzadeh 2005, Noorbala 2005, Akhondzadeh 2004 |
| Pourmasoumi 2019 ([226](#_ENREF_226)) | Meta-analysis | Depression | Saffron | Not specified | Cardiovascular risk factors | (k=10) | -- |
| Toth 2019 ([213](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_149)) | Descriptive | Umbrella review (any condition) | Plant extracts administered orally (ginkgo biloba) | Not specified | Sleep quality | 1  (k=46) | Hemmeter 2001 |
| McCloskey 2018 ([230](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_216)) | Meta-analysis | Depression | St John's wort | SSRI | Depressive symptoms, anxiety, clinical global impression | (k=27) | -- |
| Ng 2017a ([217](#_ENREF_217)) | Meta-analysis | Depression | Turmeric | -- | -- | -- | -- |
| Asher 2017 ([218](#_ENREF_218)) | Meta-analysis | Major depressive disorder | CAMS: St John's wort | -- | -- | -- |  |
| Al-Karawi 2016 ([219](#_ENREF_219)) | Meta-analysis | Major depressive disorder | Turmeric | -- | -- | -- | -- |
| Apaydin 2016 ([215](#_ENREF_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](#_ENREF_220)) | Meta-analysis | Depression | St John's wort | SSRI | Depressive symptoms, anxiety, clinical global impression | k=27 | -- |
| Sahebkar 2016b ([227](#_ENREF_227)) | Meta-analysis | Depression | Turmeric | Not specified | TNF-alpha | -- | -- |
| Linde 2009 ([221](#_ENREF_221)) | Meta-analysis | Depression | St John's wort | -- | -- | -- | -- |
| Whiskey 2001 ([222](#_ENREF_222)) | Meta-analysis | Depression | St John's wort | -- | -- | -- | -- |
| Williams 2000 ([223](#_ENREF_223)) | Meta-analysis | Depression | St John's wort | -- | -- | -- | -- |
| Kim 1999 ([224](#_ENREF_224)) | Meta-analysis | Depression | St John's wort | -- | -- | -- | -- |
| Lopresti 2022 ([191](#_ENREF_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](#_ENREF_232)) | Descriptive | Major Depressive disorder | St John's wort | Placebo or other | Depressive symptomatology, quality of life, adverse effects | (k=35) | -- |
| Hausenblas 2015 ([82](#_ENREF_82)) | Descriptive | Umbrella review (any condition) | Saffron | Placebo or other | Psychological and behavioural outcomes | 6 (k=12) | -- |
| Hausenblas 2013 ([233](#_ENREF_233)) | individual study results | Major Depressive disorder | Saffron | Placebo or other | Any efficacy or safety outcome | 5 (k=5) | -- |
| Dhingra 2012 ([234](#_ENREF_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](#_ENREF_235)) | individual study results | Depression (mild-moderate) | Saffron, Lavender, Rhodiola | Placebo or other | Any efficacy or safety outcome | (k=9) | -- |
| Hung 2011 ([236](#_ENREF_236)) | individual study results | Umbrella review (any condition) | Rhodiola | Placebo or other | Any efficacy or safety outcome | (k=11) | -- |
| Sarris 2011a ([237](#_ENREF_237)) | Descriptive | Depression, Anxiety, Insomnia | Herbal medicines (Lavender, Saffron, St John's wort) | Any | Any efficacy or safety outcome | -- | -- |
| Ulbricht 2011 ([71](#_ENREF_71)) | Descriptive | Umbrella review (any condition) | Saffron | Placebo or other intervention | -- | -- | -- |
| Ulbricht 2011a ([238](#_ENREF_238)) | Descriptive | Umbrella review (any condition) | Rhodiola | Placebo or other | Any efficacy or safety outcome | -- | -- |
| Sarris 2009 ([202](#_ENREF_202)) | Descriptive | Mood and anxiety disorders | Kava, St John's wort | Not specified | Any efficacy or safety outcome (anxiety, depression) | -- | -- |
| Morgan 2008 ([239](#_ENREF_239)) | Descriptive | Depressive disorders | Ginseng, Lavender, Saffron, St John's wort | -- | -- | -- | -- |
| Gahlsdorf 2007 ([240](#_ENREF_240)) | Descriptive | Depression (mild-moderate) | St John's wort | -- | -- | -- | -- |
| Sarris 2007 ([203](#_ENREF_203)) | Descriptive | Psychiatric disorders | Herbal medicines (oral)^ | Not specified | Any efficacy and safety outcome | -- | -- |
| Clement 2006 ([241](#_ENREF_241)) | Descriptive | Depression (mild-moderate) | St John's wort | -- | -- | -- | -- |
| Jorm 2006 ([242](#_ENREF_242)) | Descriptive | Depression (children & adults) | Complementary treatments (St John's wort) | -- | -- | -- | -- |
| Frazer 2005 ([243](#_ENREF_243)) | Descriptive | Depression (older people) | St John's wort | -- | -- | -- | -- |
| Jorm 2002 ([244](#_ENREF_244)) | Descriptive | Depression | Ginkgo | -- | -- | -- | -- |
| Gaster 2000 ([245](#_ENREF_245)) | Descriptive | Depression | St John's wort | -- | -- | -- | -- |
| Stevinson 1999 ([246](#_ENREF_246)) | Descriptive | Depression | St John's wort | -- | -- | -- | -- |
| Volz 1997 ([247](#_ENREF_247)) | Descriptive | Depression | St John's wort | -- | -- | -- | -- |
| Ernst 1995 ([248](#_ENREF_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‑23 Critical appraisal summary: review author's judgements about each AMSTAR-2 item for each included systematic review – Depression and mood disorders



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

Table D‑30 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

#### 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‑31 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

#### 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‑32 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; I2 = 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; I2 = 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; I2 = 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](#_ENREF_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; I2 = 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; I2 = 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; I2 = 90%).

Figure D‑24 Forest plot of comparison: WHM vs placebo: Depression – depressive symptoms



Figure D‑25 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](#_ENREF_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; I2 = 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](#_ENREF_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; I2 = 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; I2 = 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](#_ENREF_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; I2 = 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](#_ENREF_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](#_ENREF_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).

### Insomnia

#### 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‑26 Process flow for prioritising systematic reviews: Insomnia

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Description automatically generated with medium confidence

Abbreviations: SR, systematic review

Table D‑33 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](#_ENREF_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](#_ENREF_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](#_ENREF_249)) | Descriptive | Insomnia | Alternative sedative medications (valerian) | Any | Any efficacy outcome | 1  (k=24) | Taibi 2009 |
| Tandon 2020 ([193](#_ENREF_193)) | Descriptive | No population restrictions | Withania | Any | Efficacy and safety | 1  (k=39) | Langade 2019 |
| Feizi 2019 ([250](#_ENREF_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](#_ENREF_175)) | Meta-analysis | Symptoms of anxiety, GAD, Insomnia, Sleep problems | Chamomile | Placebo | Anxiety, Insomnia, Sleep quality | 1  (k=12) | Zick 2011 |
| Kim 2018a ([149](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_162)) | Descriptive | Any | Hops, Combination | Any | Clinical efficacy, safety | -- | -- |
| Sarris 2011a ([237](#_ENREF_237)) | Descriptive | Depression, Anxiety, Insomnia | Herbal medicines (passionflower, valerian) | Any | Clinical efficacy, safety | -- | -- |
| Sarris 2011b ([253](#_ENREF_253)) | Descriptive | Insomnia | Complementary medicines (valerian, kava, combination) | Any | Clinical efficacy | -- | -- |
| Fernandez-San-Martin 2010 ([254](#_ENREF_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](#_ENREF_255)) | Descriptive | Insomnia or sleep problems | Valerian preparations | Any | Clinical efficacy, safety | -- | -- |
| Stevinson 2000 ([256](#_ENREF_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‑27 Critical appraisal summary: review author's judgements about each AMSTAR-2 item for each included systematic review – Insomnia



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

Table D‑34 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

#### 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‑35 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. |

#### 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‑36 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[[1]](#footnote-2) 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[[2]](#footnote-3) 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.

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](#_ENREF_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](#_ENREF_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](#_ENREF_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; I2 = 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; I2 = 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](#_ENREF_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; I2 = 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[[3]](#footnote-4) in people with insomnia (total 464 participants).

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

### Inflammatory bowel disease

#### 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‑1 Process flow for prioritising systematic reviews: Inflammatory bowel disease

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Description automatically generated with medium confidence

Abbreviations: SR, systematic review

Table D‑1 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](#_ENREF_6)) | Meta-analysis | Any | Nigella sativa | Placebo or no intervention | oxidative stress and inflammatory biomarkers | 1 (k=11) | Nikkhah-Bodaghi 2019 |
| Montazeri 2021 ([7](#_ENREF_7)) | Meta-analysis | Any | Nigella sativa | Placebo or no intervention | oxidative stress and inflammatory biomarkers | 1 (k=10) | Nikkhah-Bodaghi 2019 |
| Liu 2021 ([8](#_ENREF_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](#_ENREF_9)) | Meta-analysis | Any | Ginger | Placebo or no intervention | oxidative stress biomarkers | 1 (k=12) | Nikkhah-Bodaghi 2019 |
| Ardiana 2020 ([10](#_ENREF_10)) | Meta-analysis | Any | Nigella sativa | Placebo or no intervention | oxidative stress and inflammatory biomarkers | 1 (k=5) | Nikkhah-Bodaghi 2019 |
| Chandan 2020 ([11](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_16)) | Meta-analysis | Any | Ginger | Any | oxidative stress and inflammatory biomarkers | 1 (k=20) | Nikkhah-Bodaghi 2019 |
| Mohit 2020 ([17](#_ENREF_17)) | Meta-analysis | Any | Nigella sativa | Any | oxidative stress and inflammatory biomarkers | 1 (k=12) | Nikkhah-Bodaghi 2019 |
| Zheng 2020 ([18](#_ENREF_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](#_ENREF_19)) | Meta-analysis | Any | Nigella sativa | Any | C-reactive protein | 1 (k=5) | Nikkhah-Bodaghi2019 |
| Grammatikopoulou 2018 ([20](#_ENREF_20)) | Meta-analysis | UC | Curcumin | Any | Endoscopic remission, clinical response | (k=4) | Banerjee 2017, Kedia 2017, Lang 2015, Hanai 2006 |
| Iqbal 2018 ([21](#_ENREF_21)) | Meta-analysis | UC | Curcumin | Placebo | Endoscopic remission, clinical response | (k=3) | Banerjee 2017, Lang 2015, Singla 2014 |
| Restellini 2017 ([22](#_ENREF_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](#_ENREF_23)) | Meta-analysis | Collagenous colitis | Any (Boswellia) | Any (placebo) | Clinical response, histological response, QoL, adverse effects | 1 (k=12) | Madisch 2007 |
| Kim 2017 ([24](#_ENREF_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](#_ENREF_25)) | Descriptive | Crohn’s disease | Curcumin | Any | Inflammatory biomarkers, disease activity index | 0 (k=16) | no RCTs found |
| Simadibrata 2017 ([26](#_ENREF_26)) | Descriptive | UC | Curcumin | Placebo | Clinical remission/ maintenance | 3 (k=3) | Lang 2015, Singla 2014, Hanai 2006 |
| Langhorst 2015 ([27](#_ENREF_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](#_ENREF_28)) | Descriptive | UC & Crohn’s disease | Herbal medicine | Any | Clinical remission / maintenance | 8 (k=21) | Sandborn 2013, Krebs 2012, Holtmeier 2011, Omer 2007, Hanai 2006, Langmead 2004, Gerhardt 2001, Fernández-Bañares 1999 |
| Rahimi 2013 ([29](#_ENREF_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](#_ENREF_30)) | Individual study results | IBD | Curcumin | Any | Clinical remission / maintenance | 1 (k=1) | Hanai 2006 |
| Ernst 2008 ([31](#_ENREF_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‑2 Critical appraisal summary: overview author's judgements about each AMSTAR-2 item for each included systematic review – Inflammatory bowel disease



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

Table D‑2 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.

#### 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‑3 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. |
| 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. |

#### 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‑4 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](#_ENREF_32)). The minimal clinically important differences (MCID) for the UCDAI, CAI, or SCCAI have not been established ([35](#_ENREF_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; I2 = 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, I2 = 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; I2 = 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, I2 = 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; I2 = 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](#_ENREF_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[[4]](#footnote-5)) or ulcerative colitis (Fernández-Bañares 1999[[5]](#footnote-6)) 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, I2 = 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.

###### 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.

### Irritable bowel syndrome

#### 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.

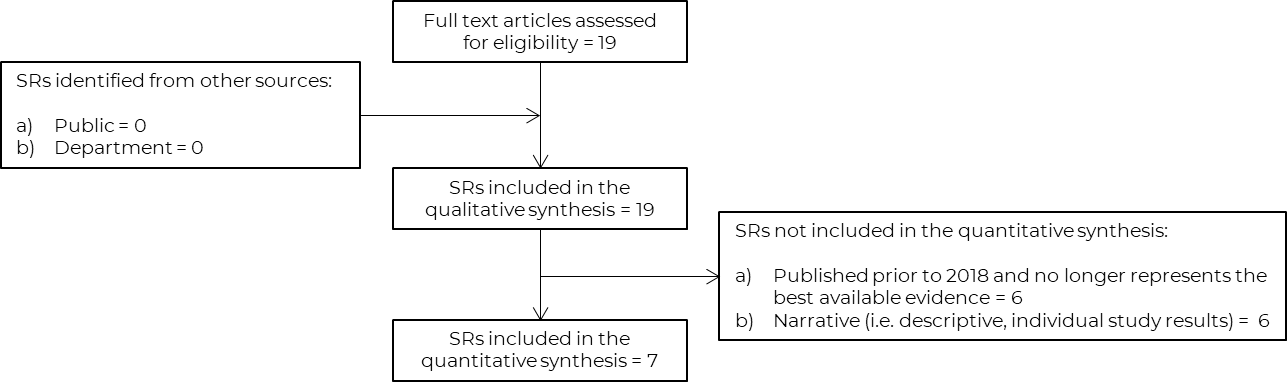
Six (6) other systematic reviews published prior to 2018 presented results in a meta-analysis (Lakhan 2015, Khanna 2014, Ford 2008, Huertas-Ceballos 2008, Liu 2006, Pittler 1998) but were not further assessed as the reviews were judged to no longer represent the best available evidence.

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‑3 Process flow for prioritising systematic reviews: Irritable bowel syndrome



Abbreviations: SR, systematic review

Table D‑5 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](#_ENREF_37)) | Descriptive | Any | Ginger | No comparator restrictions | Any (IBSSS, ARRS) | 1 (k=109) | Tilburg 2014 |
| Black 2020 ([38](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_43)) | Meta-analysis | IBS | Curcumin | Control (placebo) | Global symptom improvement, HRQoL | 2 (k = 5) | Brinkhaus 2005, Portincasa 2016 |
| Anheyer 2017a ([44](#_ENREF_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](#_ENREF_45)) | Descriptive | Functional abdominal pain in children | Any (Peppermint) | Any | Pain, HRQoL, functional disability, adverse events | 1 (k=6) | Kline 2001 |
| Lakhan 2015 ([46](#_ENREF_46)) | Meta-analysis | Pain (includes IBS) | Zingiberaceae (Curcumin) | Any | Pain | 0 (k=8) | -- |
| Khanna 2014 ([47](#_ENREF_47)) | Meta-analysis | IBS | Peppermint | Control (placebo) | Global symptom improvement, Pain Adverse events | (k=5) | -- |
| Ruepert 2011 ([48](#_ENREF_48)) | individual study results | IBS | Bulking agents, antispasmodics, antidepressants (Psyllium) | Control (placebo) | Global symptom improvement, Pain | -- | -- |
| Shen 2009 ([49](#_ENREF_49)) | Descriptive | IBS | Peppermint, psyllium | -- | -- | -- | -- |
| Ford 2008 ([50](#_ENREF_50)) | Meta-analysis | IBS | Peppermint | -- | -- | -- | -- |
| Huertas-Ceballos 2008 ([51](#_ENREF_51)) | Meta-analysis | IBS and recurrent abdominal pain | Peppermint | -- | -- | -- | -- |
| Liu 2006 ([52](#_ENREF_52)) | Meta-analysis | IBS | Iberogast | -- | -- | -- | -- |
| Grigoleit 2005 ([53](#_ENREF_53)) | Descriptive | IBS | Peppermint | -- | -- | -- | -- |
| Jailwala 2000 ([54](#_ENREF_54)) | Descriptive | IBS | Peppermint | -- | -- | -- | -- |
| Pittler 1998 ([55](#_ENREF_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‑4 Critical appraisal summary: review author's judgements about each AMSTAR-2 item for each included systematic review – Irritable bowel syndrome



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

Table D‑6 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

#### 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‑7 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)  4 non-critical weaknesses in domains 7, 10, 13 & 14 | No meta-analysis  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

#### 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‑8 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[[6]](#footnote-7) 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.

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](#_ENREF_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[[7]](#footnote-8) 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](#_ENREF_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; I2 = 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; I2 = 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 < 0.000l; I2 = 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 < 0.0000l; I2 = 46%) were examined separate to those examining the effect of other WHMs (RR 1.48; 95% CI 0.84, 2.61; p = 0.17; I2 = 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; I2 = 74%). Statistical heterogeneity remained high (see Figure D‑6).

Figure D‑5 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 < 0.000l; I2 = 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‑6 Forest plot of comparison: WHM vs placebo: irritable bowel syndrome – Global improvement in IBS symptoms (sensitivity analysis)



###### 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[[8]](#footnote-9) 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.

### Gastro-oesophageal reflux disease

#### 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‑7 Process flow for prioritising systematic reviews: Gastro-oesophageal reflux disease

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Abbreviations: SR, systematic review

Table D‑9 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](#_ENREF_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‑10 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

#### 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‑8 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‑11 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

#### 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‑12 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](#_ENREF_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.

## Gynaecological/Reproductive

### Menstrual conditions (endometriosis, amenorrhea, dysmenorrhoea etc.)

#### 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.

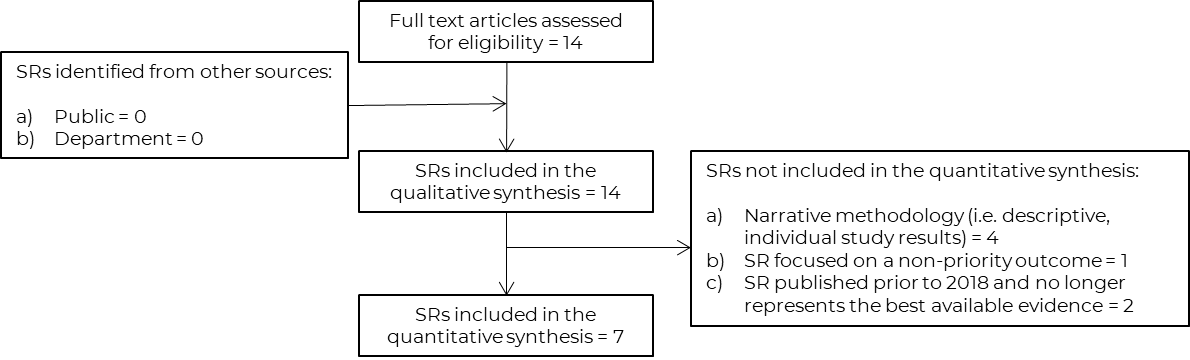
There were 6 reviews (Negi 2021, Mollazadeh 2020, Xu 2020, Pattanittum 2016, Chen 2016, Daily 2015) that presented results in a meta-analysis and were prioritised for critical appraisal and data extraction. Three reviews (Shinjyo 2020, Ursoniu 2016, Lakhan 2015) that presented results in a meta-analysis 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‑9 Process flow for prioritising systematic reviews: menstrual conditions



Abbreviations: SR, systematic review

Table D‑13 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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_37)) | Descriptive | No restriction | Ginger | Not specified | Blood loss | 1 (k=109) | Kashefi 2015 |
| Shinjyo 2020 ([63](#_ENREF_63)) | Meta-analysis | Sleep or related health problems | Valerian | Not specified | Not specified | 1 (k=60) | Mirabi 2011 |
| Pellow 2018 ([64](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_67)) | Descriptive | Heavy menstrual bleeding | Medicinal plant preparations | Placebo | Blood loss | 1 (k=3) | Kashefi 2015 |
| Ursoniu 2016 ([68](#_ENREF_68)) | Meta-analysis | No restrictions | Flaxseed | Not clear | -- | -- | -- |
| Daily 2015 ([69](#_ENREF_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](#_ENREF_46)) | Meta-analysis | Any pain condition | Zingiberaceae family extracts | Placebo | Pain | 1 (k=8) | Rahnama 2012 |
| Terry 2011 ([70](#_ENREF_70)) | Descriptive | Any pain condition | Ginger | Placebo or other intervention | -- | -- | -- |
| Ulbricht 2011 ([71](#_ENREF_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‑10 Critical appraisal summary: review author's judgements about each AMSTAR-2 item for each included systematic review – menstrual conditions



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

Table D‑14 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

#### 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‑15 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. |

#### 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‑16 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)[[9]](#footnote-10), 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](#_ENREF_72)). The median absolute MCID on a VAS scale in people with chronic pain is reported to be 20 mm (IQR 15–30) ([73](#_ENREF_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; I2 = 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; I2 = 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; I2 = 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](#_ENREF_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).

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](#_ENREF_75)). The measure also includes a present pain intensity index measured using a VAS for pain (0-10)[[10]](#footnote-11). 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](#_ENREF_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; I2 = 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[[11]](#footnote-12) (Kashefi 2014) or non-steroidal anti-inflammatory drugs[[12]](#footnote-13) (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.

### Premenstrual disturbances

#### 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‑17 List of herbs assessed in the identified primary studies: Premenstrual disturbances

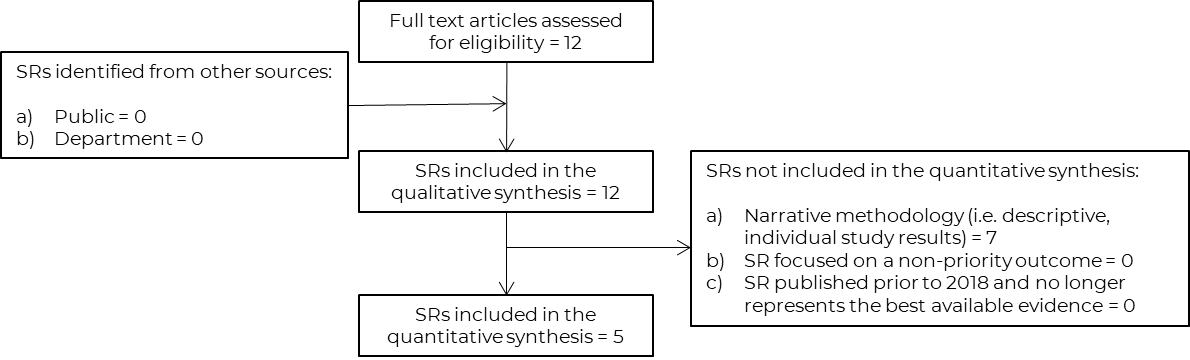
|  |  |
| --- | --- |
| WHM identified in included studies | Matched to Tier 1 list of WHM: Gynaecological / reproductive disorders a |
| Chamomile (Matricaria recruitica) | X |
| Chaste tree (Vitex agnus castus) | ✓ |
| Ginkgo (Ginkgo biloba) | X |
| Saffron (Crocus sativus) | X |
| St John's wort (Hypericum 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‑11 Process flow for prioritising systematic reviews: Premenstrual disturbances



Abbreviations: SR, systematic review

Table D‑18 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](#_ENREF_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](#_ENREF_77)) | Meta-analysis | Sleep problems and associated disorders | Valerian | Placebo | Sleep problems, Anxiety | 1 (k=60) | Behboodi Moghadam Z 2016 |
| Csupor 2019 ([78](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_82)) | Descriptive | Any\*\* | Saffron | Placebo OR other intervention | PMS symptoms, depression | 1 (k=12) | Agha-Hosseini 2008 |
| Su Hee 2014  ([83](#_ENREF_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](#_ENREF_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 |
| Dante 2011 ([85](#_ENREF_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](#_ENREF_71)) | Descriptive | Any | Saffron | Placebo OR other intervention | Any effectiveness OR safety outcomes | -- | -- |
| Whelan 2009 ([86](#_ENREF_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‑12 Critical appraisal summary: review author's judgements about each AMSTAR-2 item for each included systematic review – Premenstrual disturbances



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

#### 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‑19 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

#### 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‑20 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[[13]](#footnote-14), Mousavi 2015, Schellenberg 2012, Zamani 2012, Risoleti 2011j, 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[[14]](#footnote-15)) 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; I2=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; I2 high risk, 86%; I2moderate 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.

###### 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; I2 = 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; I2 = 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[[15]](#footnote-16) or the included systematic reviews.

The pooled results from one systematic review (Verkaik 2017n) 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; I2 = 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[[16]](#footnote-17).

The pooled results from one systematic review (Verkaik 2017n) 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; I2=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.

##### 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.

### Symptoms of menopause

#### 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](#_ENREF_76), [77](#_ENREF_77), [87-92](#_ENREF_87)) 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](#_ENREF_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.

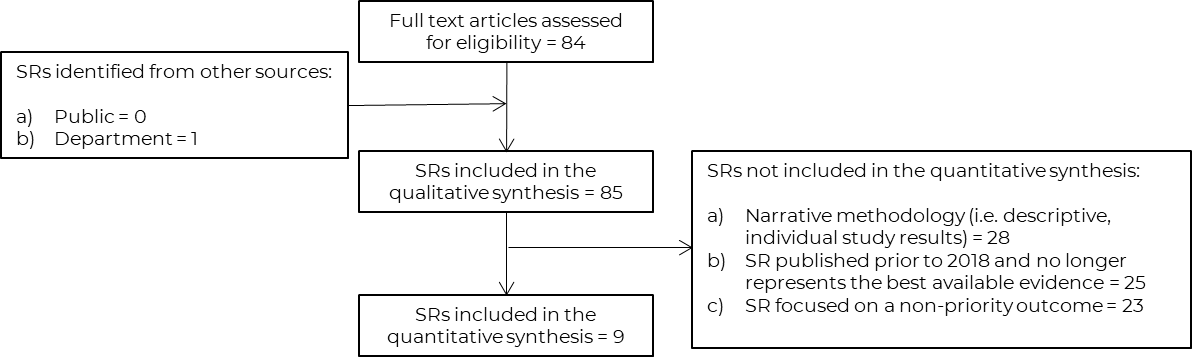
A further 23 systematic reviews ([15](#_ENREF_15), [94-115](#_ENREF_94)) that were published in 2018 or after were not considered further as they did not report on outcomes considered critical or important for this review (Askari 2021, Azizi 2021, Koushki 2021, Ghavami 2020, Hallajzadeh 2020, Kanadys 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](#_ENREF_68), [116-140](#_ENREF_116)) 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](#_ENREF_141)), 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‑13 Process flow for prioritising systematic reviews: Symptoms of menopause



Abbreviations: SR, systematic review

Table D‑21 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](#_ENREF_94)) | meta-analysis | Umbrella review (any condition) | Garlic | Placebo OR other intervention | Oxidative stress (antioxidant biomarkers) | 0  (k=12) | -- |
| Azizi 2021 ([95](#_ENREF_95)) | meta-analysis | Umbrella review (any condition) | Black cumin | Placebo OR other intervention | Liver enzyme levels | 0  (k=8) | -- |
| Castelo-Branco 2021 ([87](#_ENREF_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](#_ENREF_88)) | meta-analysis | Umbrella review (any condition) | Lavender | Placebo OR other intervention | Depression | 1  (k=17) | Kamalifard 2017 |
| Kanadys 2021 ([89](#_ENREF_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](#_ENREF_96)) | meta-analysis | Umbrella review (any condition) | Garlic | Placebo OR other intervention | Inflammatory mediators | 0 (k=10) | -- |
| Ghaderi 2020 ([76](#_ENREF_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](#_ENREF_97)) | meta-analysis | Umbrella review (any condition) | Ginseng | Placebo OR other intervention | Liver enzymes | 0 k=14) | -- |
| Hallajzadeh 2020 ([15](#_ENREF_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](#_ENREF_98)) | meta-analysis | Symptoms of menopause | Red clover | Placebo OR other intervention | Lipid profiles | 0 (k=10) | -- |
| Mirzavandi 2020 ([99](#_ENREF_99)) | meta-analysis | Umbrella review (any condition) | Garlic | Placebo OR other intervention | Inflammatory markers | 0 (k=17) | -- |
| Moosavian 2020 ([100](#_ENREF_100)) | meta-analysis | Umbrella review (any condition) | Garlic | Placebo OR other intervention | Oxidative stress markers | 0 (k=7) | -- |
| Razmpoosh 2020 ([101](#_ENREF_101)) | meta-analysis | Umbrella review (any condition) | Black cumin | Placebo OR other intervention | Liver and kidney parameters | 0 (k=19) | -- |
| Shinjyo 2020 ([77](#_ENREF_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](#_ENREF_102)) | meta-analysis | Umbrella review (any condition) | Green tea | Placebo OR other intervention | Lipid profile | 0  (k=27) | -- |
| Ziaei 2020 ([103](#_ENREF_103)) | meta-analysis | Menopause | Ginseng | Placebo OR other intervention | Lipid profile | 0 (k=27) | -- |
| Askari 2019 ([104](#_ENREF_104)) | meta-analysis | Umbrella review (any condition) | Black cumin | Placebo OR other intervention | Glycaemic control | 0  (k=17) | -- |
| Ghorbani 2019 ([90](#_ENREF_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](#_ENREF_105)) | meta-analysis | Umbrella review (any condition) | Turmeric | Placebo OR other intervention | Blood pressure modulation (SBP, DBP) | 0 (k=11) | -- |
| Hallajzadeh 2019 ([106](#_ENREF_106)) | meta-analysis | Umbrella review (any condition) | Turmeric | Placebo OR other intervention | Endothelial function | 0 (k=10) | -- |
| Hernandez-Garcia 2019 ([107](#_ENREF_107)) | meta-analysis | Umbrella review (any condition) | Ginseng | Placebo OR other intervention | Lipid profile | 0 (k=18) | -- |
| Mohammadi 2019 ([108](#_ENREF_108)) | meta-analysis | Umbrella review (any condition) | Ginseng | Placebo OR other intervention | Inflammatory markers | 0 (k=8) | -- |
| Saboori 2019 ([109](#_ENREF_109)) | meta-analysis | Umbrella review (any condition) | Ginseng | Placebo OR other intervention | C-reactive protein | 0 (k=9) | -- |
| Shahmohammadi 2019 ([91](#_ENREF_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](#_ENREF_110)) | meta-analysis | Umbrella review (any condition) | Psyllium | Placebo OR other intervention | Lipid profile | 0 (k=28) | -- |
| Khadivzadeh 2018 ([111](#_ENREF_111)) | meta-analysis | Symptoms of menopause | Red clover , Fenugreek, Schisandra, Combination | Placebo OR other intervention | Sleep dysfunction | 0 (k=12) | -- |
| Liu 2018 ([112](#_ENREF_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](#_ENREF_113)) | meta-analysis | Symptoms of menopause | Red clover | Placebo OR other intervention | Lipid profile | 0 (k=12) | -- |
| Mousavi 2018 ([114](#_ENREF_114)) | meta-analysis | Umbrella review (any condition) | Black cumin | Placebo OR other intervention | Obesity indices (BMI, WC, weight) | 0 (k=13) | -- |
| Najafi 2018 ([92](#_ENREF_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](#_ENREF_115)) | meta-analysis | Symptoms of menopause | Flaxseed, Red clover | Placebo OR other intervention | Maturation of vaginal epithelial cells | 0 (k=13) | -- |
| Haghighatdoost 2017 ([116](#_ENREF_116)) | meta-analysis | Umbrella review (any condition) | Green tea | -- | Plasma adiponectin levels | -- | -- |
| Kapoor 2017 ([117](#_ENREF_117)) | meta-analysis | Umbrella review (any condition) | Green tea | -- | Fat oxidation | -- | -- |
| Mohammadi-Sartang 2017 ([118](#_ENREF_118)) | meta-analysis | Umbrella review (any condition) | Linseed | -- | Body weight, composition | -- | -- |
| Myers 2017 ([119](#_ENREF_119)) | meta-analysis | Symptoms of menopause | Red clover | -- | Hot flushes | -- | -- |
| Sarri 2017 ([120](#_ENREF_120)) | Network meta-analysis | Symptoms of menopause | Black cohosh, Red clover, Valerian | -- | Vasomotor symptoms | -- | -- |
| Franco 2016 ([93](#_ENREF_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](#_ENREF_121)) | meta-analysis | Symptoms of menopause | Red clover | -- | Hot flushes, hormone levels | -- | -- |
| Li 2016 ([122](#_ENREF_122)) | meta-analysis | Women with breast cancer | Black cohosh | -- | Hot flushes | -- | -- |
| Sahebkar 2016 ([123](#_ENREF_123)) | meta-analysis | Umbrella review (any condition) | Black cumin | -- | Lipid profiles | -- | -- |
| Sahebkar 2016b ([124](#_ENREF_124)) | meta-analysis | Umbrella review (any condition) | Black cumin | -- | Blood pressure | -- | -- |
| Ursoniu 2016 ([68](#_ENREF_68)) | meta-analysis | Umbrella review (any condition) | Linseed | -- | Blood pressure | -- | -- |
| Chen 2015a ([125](#_ENREF_125)) | meta-analysis | Symptoms of menopause | Oral phytoestrogens (incl. Red clover) | -- | Symptoms, Hot flushes | -- | -- |
| Ghazanfarpour 2015 ([126](#_ENREF_126)) | meta-analysis | Symptoms of menopause | Red clover | -- | Hot flushes, hormone levels | -- | -- |
| Khalesi 2015 ([127](#_ENREF_127)) | meta-analysis | Umbrella review (any condition) | Linseed | -- | Blood pressure | -- | -- |
| Yarmolinsky 2015 ([128](#_ENREF_128)) | meta-analysis | Umbrella review (any condition) | Green tea | -- | Blood pressure | -- | -- |
| Gartoulla 2014 ([129](#_ENREF_129)) | meta-analysis | Symptoms of menopause | Red clover | -- | Hot flushes | -- | -- |
| Liu 2014 ([130](#_ENREF_130)) | meta-analysis | Symptoms of menopause | St John's wort, Combination | -- | Symptom | -- | -- |
| Onakpoya 2014 ([131](#_ENREF_131)) | meta-analysis | Umbrella review (any condition) | Green tea | -- | Blood pressure, lipid profile | -- | -- |
| Lethaby 2013 ([132](#_ENREF_132)) | meta-analysis (Cochrane) | Symptoms of menopause | Red clover | -- | Vasomotor symptoms | -- | -- |
| Shergis 2013 ([133](#_ENREF_133)) | meta-analysis | Umbrella review (any condition) | Panax ginseng | -- | Any efficacy measure | -- | -- |
| Leach 2012 ([134](#_ENREF_134)) | meta-analysis (Cochrane) | Symptoms of menopause | Black cohosh | -- | Symptoms | -- | -- |
| Hooper 2010 ([135](#_ENREF_135)) | meta-analysis | Symptoms of menopause | Red clover | -- | Breast density | -- | -- |
| Shams 2010 ([136](#_ENREF_136)) | meta-analysis | Symptoms of menopause | Black cohosh, Combination | -- | Symptoms | -- | -- |
| Jacobs 2009 ([137](#_ENREF_137)) | meta-analysis | Symptoms of menopause | Red clover | -- | Symptoms | -- | -- |
| Coon 2007 ([138](#_ENREF_138)) | meta-analysis | Symptoms of menopause | Red clover | -- | Hot flushes | -- | -- |
| Tempfer 2007 ([139](#_ENREF_139)) | meta-analysis | Symptoms of menopause | Red clover | -- | Symptoms | -- | -- |
| Nelson 2006 ([140](#_ENREF_140)) | meta-analysis | Symptoms of menopause | Red clover | -- | Hot flushes | -- | -- |
| Koliji 2021 ([141](#_ENREF_141)) | descriptive | Symptoms of menopause | Ginseng, Fenugreek, Red clover, Black cohosh, Schisandra, Black cumin, Combination | -- | Sexual function | -- | -- |
| Lopresti 2021 ([142](#_ENREF_142)) | descriptive | Umbrella review (any) | Black cohosh, Ginseng, | -- | -- | -- | -- |
| Ebrahimi 2020 ([143](#_ENREF_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](#_ENREF_144)) | descriptive | Symptoms of menopause | Liquorice, Chamomile | -- | Vaginal atrophy | -- | -- |
| Darand 2019 ([145](#_ENREF_145)) | descriptive | Infertility | Black cumin | -- | Sexual function, hormone levels | -- | -- |
| Dizavandi 2019 ([146](#_ENREF_146)) | descriptive | Symptoms of menopause | Linseed, Fenugreek, Red clover | -- | Vaginal atrophy, dyspareunia | -- | -- |
| Niazi 2019 ([147](#_ENREF_147)) | descriptive | Symptoms of menopause | Fenugreek, Liquorice, Red clover, Ginseng, Ginkgo, Red clover | -- | Sexual function | -- | -- |
| Roozbeh 2019 ([148](#_ENREF_148)) | descriptive | Menopause | Lavender | -- | Sleep, sexual function, vasomotor, psychological, physical symptoms | -- | -- |
| Kim 2018a ([149](#_ENREF_149)) | descriptive | Umbrella review (any) | Valerian, St John's wort | -- | Sleep quality, anxiety | -- | -- |
| Fattah 2017 ([150](#_ENREF_150)) | descriptive | Symptoms of menopause | Hops, Kava, Red clover | -- | Depression, anxiety | -- | -- |
| Thaung Zaw 2017 ([151](#_ENREF_151)) | descriptive | Umbrella review (any) | Red clover, Black cohosh | -- | Cognition, executive function, memory | -- | -- |
| Abdi 2016 ([152](#_ENREF_152)) | descriptive | Symptoms of menopause | Red clover | -- | Bone mineral density | -- | -- |
| Ghazanfarpour 2016 ([153](#_ENREF_153)) | descriptive | Symptoms of menopause | Black cohosh, Aniseed, Red clover, Valerian , St John's wort, Sage, Linseed, Fenugreek | -- | Hot flushes | -- | -- |
| Mohtashami 2016 ([154](#_ENREF_154)) | descriptive | Umbrella review (any) | Black cumin | -- | Blood parameters, antropometrics | -- | -- |
| Ismail 2015 ([155](#_ENREF_155)) | descriptive | Symptoms of menopause | Black cohosh, St John's wort, Red clover | -- | Symptoms | -- | -- |
| Ulbricht 2015 ([156](#_ENREF_156)) | descriptive | Umbrella review (any) | Black cohosh | -- | Clinical efficacy | -- | -- |
| Thomas 2014 ([157](#_ENREF_157)) | descriptive | Symptoms of menopause | Red clover | -- | Symptoms, hot flushes | -- | -- |
| Dew 2013 ([158](#_ENREF_158)) | descriptive | Symptoms of menopause | Linseed | -- | Symptoms, bone health | -- | -- |
| Kim 2013 ([159](#_ENREF_159)) | descriptive | Symptoms of menopause | Ginseng | -- | Symptoms | -- | -- |
| Miroddi 2013 ([160](#_ENREF_160)) | descriptive | Umbrella review (any) | Passionflower | -- | Clinical efficacy | -- | -- |
| Laakmann 2012 ([161](#_ENREF_161)) | descriptive | Symptoms of menopause | Black cohosh | -- | Symptoms | -- | -- |
| Ulbricht 2012 ([162](#_ENREF_162)) | descriptive | Umbrella review (any) | Hops | -- | Clinical efficacy | -- | -- |
| Clement 2011 ([163](#_ENREF_163)) | descriptive | Symptoms of menopause | Red clover, Combination | -- | Cognition | -- | -- |
| Borrelli 2008 ([164](#_ENREF_164)) | individual study results | Symptoms of menopause | Black cohosh | -- | Symptoms | -- | -- |
| Booth 2006 ([165](#_ENREF_165)) | descriptive | Symptoms of menopause | Red clover | -- | Symptoms | -- | -- |
| Krebs 2004 ([166](#_ENREF_166)) | individual study results | Symptoms of menopause | Red clover | -- | Symptoms | -- | -- |
| Huntley 2003 ([167](#_ENREF_167)) | descriptive | Symptoms of menopause | Black cohosh, Red clover, Ginseng | -- | Symptoms | -- | -- |
| Borrelli 2002 ([168](#_ENREF_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‑14 Critical appraisal summary: review author's judgements about each AMSTAR-2 item for each included systematic review – Symptoms of menopause



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

Table D‑22 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

#### 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‑23 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  4 non-critical weaknesses in domains 5, 7, 10 & 13 | Risk of bias of RCTs included in the review not reported.  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

#### 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‑24 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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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; I2 = 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; I2 = 75%) compared with those for red clover (SMD –0.48; 95% CI –0.99, –0.03; p = 0.07; I2 = 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; I2 = 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; I2 = 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‑15 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‑16 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; I2 = 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; I2 = 82%) compared with those for black cohosh (SMD –0.32; 95% CI –1.01, 0.38; p = 0.37; I2 = 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; I2 = 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; I2 = 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‑17 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](#_ENREF_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; I2 = 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 (I2 = 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; I2 = 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; I2 = 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; I2 = 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; I2 = 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; I2 = 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; I2 = 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; I2 = 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).

## Endocrine and metabolic

### Diabetes and impaired glucose tolerance

#### 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](#_ENREF_260)) 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](#_ENREF_6), [7](#_ENREF_7), [9](#_ENREF_9), [10](#_ENREF_10), [15-17](#_ENREF_15), [76](#_ENREF_76), [94-97](#_ENREF_94), [99](#_ENREF_99), [101-106](#_ENREF_101), [108-110](#_ENREF_108), [114](#_ENREF_114), [225](#_ENREF_225), [226](#_ENREF_226), [228](#_ENREF_228), [283-322](#_ENREF_283)).

A further 42 reviews ([68](#_ENREF_68), [116](#_ENREF_116), [118](#_ENREF_118), [123](#_ENREF_123), [127](#_ENREF_127), [128](#_ENREF_128), [131](#_ENREF_131), [133](#_ENREF_133), [227](#_ENREF_227), [323-355](#_ENREF_323)) 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](#_ENREF_37), [154](#_ENREF_154), [192](#_ENREF_192), [193](#_ENREF_193), [229](#_ENREF_229), [352](#_ENREF_352), [356-384](#_ENREF_356)) 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](#_ENREF_260)) | meta-analysis | Diabetes | Green tea | Lipid profiles |
| Asbaghi 2020a ([261](#_ENREF_261)) | meta-analysis | Diabetes | Green tea | Adiponectin |
| Durg 2020 ([262](#_ENREF_262)) | meta-analysis | Diabetes | Ginseng | Blood glucose, insulin, lipid profile, serum and oxidative stress markers |
| Barzkar 2020 ([263](#_ENREF_263)) | meta-analysis | Diabetes (type 1) | Cinnamon, Fenugreek, Combination | Blood glucose indices |
| Hajizadeh-Sharafabad 2020 ([264](#_ENREF_264)) | meta-analysis | Diabetes | Chamomile | Metabolic parameters |
| Heshmati 2020 ([265](#_ENREF_265)) | meta-analysis | Diabetes | Lemon balm | Cardiometabolic outcomes |
| Jalali 2020a ([266](#_ENREF_266)) | meta-analysis | Diabetes | Cinnamon | Blood pressure |
| Jamali 2020 ([267](#_ENREF_267)) | meta-analysis | Diabetes | Cinnamon | Blood pressure and anthropometric parameters |
| Jamali 2020a ([268](#_ENREF_268)) | meta-analysis | Diabetes | Cinnamon | Lipid profiles |
| Tabrizi 2020 ([269](#_ENREF_269)) | meta-analysis | Diabetes | Ginkgo | Cardiometabolic parameters |
| Xiao 2020 ([270](#_ENREF_270)) | meta-analysis | Diabetes | Psyllium | Weight, body mass index, lipid profile, and glucose metabolism |
| Ziaei 2020a ([271](#_ENREF_271)) | meta-analysis | Diabetes | Nettle | Glycaemic control |
| Akbari 2019 ([272](#_ENREF_272)) | meta-analysis | Metabolic Syndrome and related disorders | Turmeric | Weight loss |
| Huang 2019a ([273](#_ENREF_273)) | meta-analysis | Diabetes | Ginger | Glycaemic control |
| Namazi 2019 ([274](#_ENREF_274)) | meta-analysis | Diabetes | Cinnamon | Weight, body mass index, lipid profile, and glucose metabolism |
| Asbaghi 2019a ([275](#_ENREF_275)) | meta-analysis | Diabetes | Green tea | CRP and oxidative stress |
| Deyno 2019 ([276](#_ENREF_276)) | meta-analysis | Diabetes and Impaired glucose tolerance | Cinnamon | Blood glucose and lipid profiles |
| Rocha 2019 ([277](#_ENREF_277)) | meta-analysis | Diabetes | Cranberry, Bilberry | Glycaemic control |
| Shabani 2019 ([278](#_ENREF_278)) | meta-analysis | Diabetes | Garlic | Lipid profile and glucose parameters |
| Yuan 2019 ([279](#_ENREF_279)) | meta-analysis | Metabolic disorders | Turmeric | Blood Lipids |
| Zhang 2019 ([280](#_ENREF_280)) | meta-analysis | Diabetic kidney disease | Astragalus | Kidney markers |
| Tabrizi 2018 ([281](#_ENREF_281)) | meta-analysis | Diabetes | Turmeric | Lipid profile and Glycaemic control |
| Zhu 2018 ([282](#_ENREF_282)) | meta-analysis | Diabetes and Metabolic disorders | Ginger | Glucose control, insulin sensitivity, and lipid profile |
| Altobelli 2021 ([283](#_ENREF_283)) | meta-analysis | Umbrella review (incl. diabetes) | Turmeric | Glycaemic and lipid profiles |
| Asbaghi 2021 ([284](#_ENREF_284)) | meta-analysis | Umbrella review (incl. diabetes) | Saffron | Inflammatory markers |
| Asbaghi 2021a ([285](#_ENREF_285)) | meta-analysis | Umbrella review (incl. diabetes) | Green tea | Glycaemic control |
| Askari 2021 ([94](#_ENREF_94)) | meta-analysis | Umbrella review (incl. diabetes) | Garlic | Oxidative stress biomarkers |
| Atefi 2021 ([286](#_ENREF_286)) | meta-analysis | Umbrella review (incl. diabetes) | Barberry | Blood pressure |
| Azizi 2021 ([95](#_ENREF_95)) | meta-analysis | Umbrella review (incl. diabetes) | Black cumin | Liver function |
| Ghassab-Abdollahi 2021 ([6](#_ENREF_6)) | meta-analysis | Umbrella review (incl. diabetes) | Black cumin | Oxidative stress and inflammatory biomarkers |
| Karimi 2021 ([228](#_ENREF_228)) | meta-analysis | Umbrella review (incl. diabetes) | Saffron | Liver function |
| Koushki 2021 ([96](#_ENREF_96)) | meta-analysis | Umbrella review (incl. diabetes) | Garlic | Inflammatory markers |
| Kutbi 2021 ([287](#_ENREF_287)) | meta-analysis | Metabolic disease (incl. diabetes) | Cinnamon | Weight, body mass index, lipid profile, and glucose metabolism |
| Montazeri 2021 ([7](#_ENREF_7)) | meta-analysis | Umbrella review (incl. diabetes) | Black cumin | Inflammatory markers |
| Moradi 2021 ([288](#_ENREF_288)) | meta-analysis | Umbrella review (incl. diabetes) | Artichoke | Blood pressure |
| Morvaridzadeh 2021 ([9](#_ENREF_9)) | meta-analysis | Umbrella review (incl. diabetes) | Ginger | Oxidative stress biomarkers |
| Mousavi 2021 ([225](#_ENREF_225)) | meta-analysis | Umbrella review (incl. diabetes) | Saffron | Liver function |
| Shekarchizadeh-Esfahani 2021 ([289](#_ENREF_289)) | meta-analysis | Umbrella review (incl. diabetes & impaired glucose tolerance) | Cinnamon | Liver function |
| Ardiana 2020 ([10](#_ENREF_10)) | meta-analysis | Umbrella review (incl. diabetes) | Black cumin | Oxidative stress and inflammatory biomarkers |
| Askari 2020 ([290](#_ENREF_290)) | meta-analysis | Umbrella review (incl. diabetes) | Ginger | Oxidative stress and inflammatory biomarkers |
| Askarpour 2020 ([291](#_ENREF_291)) | meta-analysis | Umbrella review (incl. diabetes) | Fenugreek | Blood lipids and body weight |
| Clark 2020 ([292](#_ENREF_292)) | meta-analysis | Umbrella review (incl. diabetes) | Psyllium | Blood pressure |
| Ghaderi 2020 ([76](#_ENREF_76)) | meta-analysis | Umbrella review (incl. diabetes) | Saffron | Mental health and C-reactive protein |
| Ghavami 2020 ([97](#_ENREF_97)) | meta-analysis | Umbrella review (incl. diabetes) | Ginseng | Liver function |
| Hadi 2020 ([293](#_ENREF_293)) | meta-analysis | Umbrella review (incl. diabetes & impaired glucose tolerance) | Cinnamon | Blood pressure |
| Hallajzadeh 2020 ([15](#_ENREF_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](#_ENREF_16)) | meta-analysis | Umbrella review (incl. diabetes) | Ginger | Inflammatory and oxidative stress biomarkers |
| Jalili 2020 ([294](#_ENREF_294)) | meta-analysis | Umbrella review (incl. diabetes) | Artichoke | Glycaemic control |
| Khodamoradi 2020 ([295](#_ENREF_295)) | meta-analysis | Umbrella review (incl. diabetes) | Fenugreek | Cardiometabolic Risk Factors |
| Miraghajani 2020 ([296](#_ENREF_296)) | meta-analysis | Umbrella review (incl. diabetes) | Ginseng | Anthropometric indices and body composition |
| Mirzavandi 2020 ([99](#_ENREF_99)) | meta-analysis | Umbrella review (incl. diabetes) | Garlic | Inflammatory markers |
| Mohit 2020 ([17](#_ENREF_17)) | meta-analysis | Umbrella review (incl. diabetes) | Black cumin | Inflammatory and oxidative stress biomarkers |
| Morvaridzadeh 2020 ([297](#_ENREF_297)) | meta-analysis | Umbrella review (incl. diabetes) | Ginger | Inflammatory markers |
| Mousavi 2020 ([298](#_ENREF_298)) | meta-analysis | Umbrella review (incl. diabetes & impaired glucose tolerance) | Cinnamon | Blood pressure |
| Mousavi 2020a ([299](#_ENREF_299)) | meta-analysis | Umbrella review (incl. diabetes & impaired glucose tolerance) | Cinnamon | Anthropometric indices and body composition |
| Mousavi 2020b ([300](#_ENREF_300)) | meta-analysis | Umbrella review (incl. diabetes & impaired glucose tolerance) | Turmeric | Anthropometric indices and body composition |
| Pourmasoumi 2020 ([301](#_ENREF_301)) | meta-analysis | Umbrella review (incl. diabetes) | Cranberry | Cardiometabolic Risk Factors |
| Rahmani 2020 ([302](#_ENREF_302)) | meta-analysis | Umbrella review (incl. diabetes) | Saffron | Glycaemic control and waist circumference |
| Razmpoosh 2020 ([101](#_ENREF_101)) | meta-analysis | Umbrella review (incl. diabetes) | Black cumin | Liver and kidney parameters |
| Renfan 2020 ([303](#_ENREF_303)) | meta-analysis | Umbrella review (incl. diabetes) | Green tea | Blood pressure |
| Roshanravan 2020a ([304](#_ENREF_304)) | meta-analysis | Umbrella review (incl. diabetes) | Saffron | Glycaemic indices, lipid profiles, |
| Safari 2020 ([305](#_ENREF_305)) | meta-analysis | Umbrella review (incl. diabetes) | Barberry | Glycaemic indices |
| Xu 2020 ([102](#_ENREF_102)) | meta-analysis | Umbrella review (incl. diabetes) | Green tea | Lipid profiles |
| Yazdanpanah 2020 ([306](#_ENREF_306)) | meta-analysis | Umbrella review (incl. diabetes & impaired glucose tolerance) | Cinnamon | Anthropometric indices and body composition |
| Ziaei 2020 ([103](#_ENREF_103)) | meta-analysis | Umbrella review (incl. diabetes & impaired glucose tolerance) | Ginseng | Lipid profiles |
| Alizadeh 2019 ([307](#_ENREF_307)) | meta-analysis | Umbrella review (incl. diabetes & impaired glucose tolerance) | Turmeric | Oxidative stress enzymes |
| Asbaghi 2019 ([308](#_ENREF_308)) | meta-analysis | Umbrella review (incl. diabetes) | Saffron | Blood glucose and lipid profiles |
| Askari 2019 ([104](#_ENREF_104)) | meta-analysis | Umbrella review (incl. diabetes) | Black cumin | Glycaemic control |
| Clark 2019 ([309](#_ENREF_309)) | meta-analysis | Umbrella review (incl. diabetes & impaired glucose tolerance) | Turmeric | Adiponectin |
| Hadi 2019 ([105](#_ENREF_105)) | meta-analysis | Umbrella review (incl. diabetes) | Turmeric | Blood pressure |
| Hadi 2019a ([310](#_ENREF_310)) | meta-analysis | Umbrella review (incl. diabetes) | Barberry | Lipid profiles |
| Hallajzadeh 2019 ([106](#_ENREF_106)) | meta-analysis | Umbrella review (incl. diabetes) | Turmeric | Endothelial function |
| Hasani 2019 ([311](#_ENREF_311)) | meta-analysis | Umbrella review (incl. diabetes) | Ginger | Blood pressure |
| Huang 2019 ([312](#_ENREF_312)) | meta-analysis | Umbrella review (incl. diabetes & impaired glucose tolerance) | Turmeric | Glycaemic control |
| Mohammadi 2019 ([108](#_ENREF_108)) | meta-analysis | Umbrella review (incl. diabetes) | Ginseng | Inflammatory biomarkers |
| Pourmasoumi 2019 ([226](#_ENREF_226)) | meta-analysis | Umbrella review (incl. diabetes) | Saffron | Cardiovascular risk factors |
| Saboori 2019 ([109](#_ENREF_109)) | meta-analysis | Umbrella review (incl. diabetes) | Ginseng | C-reactive protein |
| Tabrizi 2019([313](#_ENREF_313)) | meta-analysis | Umbrella review (incl. diabetes) | Turmeric | Inflammatory and oxidative stress biomarkers |
| Taghizadeh 2019 ([314](#_ENREF_314)) | meta-analysis | Umbrella review (incl. diabetes) | Garlic | C-reactive protein |
| White 2019 ([315](#_ENREF_315)) | meta-analysis | Umbrella review (incl. diabetes) | Turmeric | Inflammatory markers |
| de Melo 2018 ([316](#_ENREF_316)) | meta-analysis | Impaired glucose tolerance | Turmeric | Glycaemic control |
| Golzarand 2018 ([317](#_ENREF_317)) | meta-analysis | Umbrella review (incl. diabetes) | Green tea | Anthropometric indices |
| Jovanovski 2018 ([110](#_ENREF_110)) | meta-analysis | Umbrella review (incl. diabetes) | Psyllium | Lipid profiles |
| Khan 2018 ([318](#_ENREF_318)) | meta-analysis | Umbrella review (incl. diabetes) | Psyllium | Blood pressure |
| Mousavi 2018 ([114](#_ENREF_114)) | meta-analysis | Umbrella review (incl. diabetes) | Black cumin | Obesity indices |
| Namazi 2018 ([319](#_ENREF_319)) | meta-analysis | Umbrella review (incl. diabetes) | Black cumin | Obesity indices |
| Pourmasoumi 2018 ([320](#_ENREF_320)) | meta-analysis | Umbrella review (incl. diabetes) | Ginger | Lipid profiles |
| Qin 2018 ([321](#_ENREF_321)) | meta-analysis | Umbrella review (incl. diabetes) | Turmeric | Oxidative stress |
| Sahebkar 2018 ([322](#_ENREF_322)) | meta-analysis | Umbrella review (incl. diabetes) | Artichoke | Lipid profiles |
| Daryabeygi-Khotbehsara 2017 ([323](#_ENREF_323)) | meta-analysis | Diabetes | Black cumin | -- |
| Demmers 2017 ([324](#_ENREF_324)) | meta-analysis | Impaired glucose tolerance | Turmeric, Ginkgo, Ginseng, Fenugreek | -- |
| Emami 2017 ([325](#_ENREF_325)) | meta-analysis | Umbrella review (incl. diabetes) | Garlic | -- |
| Haghighatdoost 2017 ([116](#_ENREF_116)) | meta-analysis | Umbrella review (incl. diabetes) | Green tea | -- |
| Mohammadi-Sartang 2017 ([118](#_ENREF_118)) | meta-analysis | Umbrella review (incl. diabetes) | Linseed | -- |
| Si 2017 ([326](#_ENREF_326)) | meta-analysis | Umbrella review (incl. diabetes) | Turmeric | -- |
| Wang 2017 ([327](#_ENREF_327)) | meta-analysis | Diabetes | Garlic | -- |
| Derosa 2016 ([328](#_ENREF_328)) | meta-analysis | Umbrella review (incl. diabetes) | Turmeric | -- |
| Dick 2016 ([329](#_ENREF_329)) | meta-analysis | Umbrella review (incl. diabetes) | Aloe | -- |
| Gong 2016 ([330](#_ENREF_330)) | meta-analysis | Diabetes & impaired glucose tolerance | Fenugreek | -- |
| Gui 2016 ([331](#_ENREF_331)) | meta-analysis | Diabetes | Ginseng | -- |
| Guo-Chong 2016 ([332](#_ENREF_332)) | meta-analysis | Umbrella review (incl. diabetes) | Linseed | -- |
| He 2016 ([333](#_ENREF_333)) | meta-analysis | Umbrella review (incl. diabetes) | Oats | -- |
| Komishon 2016 ([334](#_ENREF_334)) | meta-analysis | Umbrella review (incl. diabetes) | Ginseng | -- |
| Mazidi 2016 ([335](#_ENREF_335)) | meta-analysis | Umbrella review (incl. diabetes) | Ginger | -- |
| Qi-feng 2016 ([336](#_ENREF_336)) | meta-analysis | Diabetes | Ginseng | -- |
| Sahebkar 2016b ([227](#_ENREF_227)) | meta-analysis | Umbrella review (incl. diabetes) | Turmeric | -- |
| Sahebkar 2016c ([123](#_ENREF_123)) | meta-analysis | Umbrella review (incl. diabetes) | Black cumin | -- |
| Suksomboon 2016 ([337](#_ENREF_337)) | meta-analysis | Diabetes & impaired glucose tolerance | Aloe | -- |
| Ursoniu 2016 ([68](#_ENREF_68)) | meta-analysis | Umbrella review (incl. diabetes) | Linseed | -- |
| Yiyi 2016 ([338](#_ENREF_338)) | meta-analysis | Impaired glucose tolerance | Aloe | -- |
| Hou 2015 ([339](#_ENREF_339)) | meta-analysis | Umbrella review (incl. diabetes) | Garlic | -- |
| Khalesi 2015 ([127](#_ENREF_127)) | meta-analysis | Umbrella review (incl. diabetes) | Linseed | -- |
| Yarmolinsky 2015 ([128](#_ENREF_128)) | meta-analysis | Umbrella review (incl. diabetes) | Green tea | -- |
| Zhu 2015 ([340](#_ENREF_340)) | meta-analysis | Umbrella review (incl. diabetes) | Cranberry | -- |
| Khalesi 2014 ([341](#_ENREF_341)) | meta-analysis | Umbrella review (incl. diabetes) | Green tea | -- |
| Kwak 2014 ([342](#_ENREF_342)) | meta-analysis | Umbrella review (incl. diabetes) | Garlic | -- |
| Liu 2014 ([343](#_ENREF_343)) | meta-analysis | Umbrella review (incl. diabetes) | Green tea | -- |
| Neelakantan 2014 ([344](#_ENREF_344)) | meta-analysis | Umbrella review (incl. diabetes) | Fenugreek | -- |
| Onakpoya 2014 ([131](#_ENREF_131)) | meta-analysis | Umbrella review (incl. diabetes) | Green Tea | -- |
| Sahebkar 2014 ([345](#_ENREF_345)) | meta-analysis | Umbrella review (incl. diabetes) | Turmeric | -- |
| Shishtar 2014 ([346](#_ENREF_346)) | meta-analysis | Umbrella review (incl. diabetes & impaired glucose tolerance) | Ginseng | -- |
| Allen 2013 ([347](#_ENREF_347)) | meta-analysis | Umbrella review (incl. diabetes) | Cinnamon | -- |
| Shergis 2013 ([133](#_ENREF_133)) | meta-analysis | Umbrella review (incl. diabetes) | Ginseng | -- |
| Akilen 2012 ([348](#_ENREF_348)) | meta-analysis | Umbrella review (incl. diabetes) | Cinnamon | -- |
| Gibb 2012 ([349](#_ENREF_349)) | meta-analysis | Umbrella review (incl. diabetes & impaired glucose tolerance) | Psyllium | -- |
| Leach 2012a ([350](#_ENREF_350)) | meta-analysis | Diabetes | Cinnamon | -- |
| Paul 2011 ([351](#_ENREF_351)) | meta-analysis | Umbrella review (incl. diabetes & impaired glucose tolerance) | Cinnamon | -- |
| Shojaii 2011a ([352](#_ENREF_352)) | meta-analysis | Diabetes | Garlic, Ginkgo, Psyllium, St Mary's thistle, Green tea, Fenugreek | -- |
| Suksomboon 2011 ([353](#_ENREF_353)) | meta-analysis | Diabetes | Cinnamon, St Mary's thistle, Fenugreek | -- |
| Baker 2008 ([354](#_ENREF_354)) | meta-analysis | Umbrella review (incl. diabetes) | Cinnamon | -- |
| Pham 2007 ([355](#_ENREF_355)) | meta-analysis | Diabetes | Cinnamon | -- |
| Lopresti 2021 ([192](#_ENREF_192)) | descriptive | Umbrella review (incl. diabetes) | Withania | -- |
| Matias 2021 ([229](#_ENREF_229)) | descriptive | Umbrella review (incl. diabetes with peripheral nephropathy) | Turmeric | -- |
| Anh 2020 ([37](#_ENREF_37)) | descriptive | Diabetes | Ginger | -- |
| Ashkar 2020 ([356](#_ENREF_356)) | descriptive | Insulin resistance and PCOS | Aloe, Chamomile | -- |
| Chan 2020 ([357](#_ENREF_357)) | descriptive | Umbrella review (incl. diabetes) | Garlic | -- |
| Emamat 2020 ([358](#_ENREF_358)) | descriptive | Umbrella review (incl. diabetes) | Garlic | -- |
| Giannoulaki 2020 ([359](#_ENREF_359)) | descriptive | Diabetes or metabolic syndrome | Saffron | -- |
| Mahmoodi 2020 ([360](#_ENREF_360)) | descriptive | Diabetes | Black cumin | -- |
| Tandon 2020 ([193](#_ENREF_193)) | descriptive | Umbrella review (incl. diabetes) | Withania | -- |
| Wal 2020 ([361](#_ENREF_361)) | descriptive | Hypertension (incl. diabetes) | Cranberry | -- |
| Hamdan 2019 ([362](#_ENREF_362)) | descriptive | Diabetes | Black cumin | -- |
| Hekmatpou 2019 ([363](#_ENREF_363)) | descriptive | Wound healing (incl. diabetes) | Aloe | -- |
| Hariri 2018 ([364](#_ENREF_364)) | descriptive | Umbrella review (incl. diabetes) | Turmeric | -- |
| Costello 2016 ([365](#_ENREF_365)) | descriptive | Diabetes | Cinnamon | -- |
| Lee 2016 ([366](#_ENREF_366)) | descriptive | Umbrella review (incl. diabetes) | Red Ginseng | -- |
| Mohtashami 2016 ([154](#_ENREF_154)) | descriptive | Umbrella review (incl. diabetes) | Black cumin | -- |
| Vaughn 2016 ([367](#_ENREF_367)) | descriptive | Umbrella review (incl. diabetes, skin health) | Turmeric | -- |
| Heshmati 2015 ([368](#_ENREF_368)) | descriptive | Umbrella review (incl. diabetes) | Black cumin | -- |
| Choi 2013 ([369](#_ENREF_369)) | descriptive | Umbrella review (incl. diabetes) | Ginseng | -- |
| Rashidi 2013 ([370](#_ENREF_370)) | descriptive | Diabetes | Garlic, Green tea, Psyllium, St Mary's thistle, Fenugreek, Nettle, Aloe | -- |
| Kim 2011 ([371](#_ENREF_371)) | descriptive | Diabetes | Red Ginseng | -- |
| Lee 2011 ([372](#_ENREF_372)) | descriptive | Umbrella review (incl. diabetes) | Ginseng | -- |
| Mehri 2011 ([373](#_ENREF_373)) | descriptive | Diabetes | Nettle | -- |
| Shojaii 2011 ([352](#_ENREF_352)) | descriptive | Umbrella review (incl. diabetes) | Cinnamon, Ginkgo, Black cumin, Psyllium, St Mary's thistle, Green tea, Fenugreek | -- |
| Ulbricht 2011b ([374](#_ENREF_374)) | descriptive | Umbrella review (incl. diabetes) | Gymnema | -- |
| Kirkham 2009 ([375](#_ENREF_375)) | descriptive | Diabetes | Cinnamon | -- |
| Nahas 2009 ([376](#_ENREF_376)) | descriptive | Diabetes | Cinnamon, Gymnema, Fenugreek, Green tea | -- |
| Hasani-Ranjbar 2008 ([377](#_ENREF_377)) | individual study results | Diabetes | St Mary's thistle, Psyllium, Garlic | -- |
| Dugoua 2007 ([378](#_ENREF_378)) | descriptive | Diabetes | Cinnamon | -- |
| Leach 2007 ([379](#_ENREF_379)) | descriptive | Diabetes | Gymnema | -- |
| Buettner 2006 ([380](#_ENREF_380)) | individual study results | Umbrella review (incl. diabetes) | Ginseng | -- |
| Shekelle 2005 ([381](#_ENREF_381)) | descriptive | Diabetes | Fenugreek | -- |
| Yeh 2003 ([382](#_ENREF_382)) | descriptive | Diabetes | Ginseng, Gymnema, St Mary's thistle, Fenugreek | -- |
| Vogler 1999 ([383](#_ENREF_383)) | descriptive | Umbrella review (incl. diabetes) | Ginseng | -- |
| Vogler 1999a ([384](#_ENREF_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.

#### Critical appraisal

Not assessed.

#### 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.

### Metabolic syndrome

#### 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](#_ENREF_103), [226](#_ENREF_226), [272](#_ENREF_272), [279](#_ENREF_279), [281](#_ENREF_281), [282](#_ENREF_282), [287](#_ENREF_287), [312](#_ENREF_312), [385-388](#_ENREF_385)) were focused on people with metabolic syndrome or those at risk of cardiovascular disease, with the other 36 reviews ([6](#_ENREF_6), [7](#_ENREF_7), [15](#_ENREF_15), [76](#_ENREF_76), [97](#_ENREF_97), [99](#_ENREF_99), [102](#_ENREF_102), [104](#_ENREF_104), [105](#_ENREF_105), [107-110](#_ENREF_107), [176](#_ENREF_176), [284](#_ENREF_284), [286](#_ENREF_286), [288](#_ENREF_288), [293](#_ENREF_293), [294](#_ENREF_294), [296](#_ENREF_296), [298](#_ENREF_298), [300](#_ENREF_300), [301](#_ENREF_301), [305-310](#_ENREF_305), [313](#_ENREF_313), [315](#_ENREF_315), [317](#_ENREF_317), [319](#_ENREF_319), [321](#_ENREF_321), [389](#_ENREF_389), [390](#_ENREF_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](#_ENREF_68), [118](#_ENREF_118), [123](#_ENREF_123), [124](#_ENREF_124), [127](#_ENREF_127), [326](#_ENREF_326), [328](#_ENREF_328), [332](#_ENREF_332), [341](#_ENREF_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](#_ENREF_154), [162](#_ENREF_162), [191](#_ENREF_191), [357-359](#_ENREF_357), [364](#_ENREF_364), [369](#_ENREF_369), [391-394](#_ENREF_391)) 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](#_ENREF_287)) | meta-analysis | Metabolic disorders | Cinnamon | Lipid profile, blood pressure, glucose metabolism and anthropometrics |
| Jang 2020 ([385](#_ENREF_385)) | meta-analysis | Metabolic syndrome | Capsicum | Lipid profile, body weight and cardiovascular risk factors |
| Li 2020 ([386](#_ENREF_386)) | meta-analysis | Metabolic syndrome and obesity | Green tea | Lipid profile, blood pressure, glucose metabolism and anthropometrics |
| Roshanravan 2020 ([387](#_ENREF_387)) | meta-analysis | Metabolic syndrome | Barberry | Glycaemic control and lipid profile |
| Ziaei 2020 ([103](#_ENREF_103)) | meta-analysis | Metabolic syndrome | Ginseng | Lipid profile |
| Akbari 2019 ([272](#_ENREF_272)) | meta-analysis | Metabolic syndrome | Turmeric | Body weight and composition |
| Azhdari 2019 ([388](#_ENREF_388)) | meta-analysis | Metabolic syndrome | Turmeric | Lipid profile, blood pressure, glucose metabolism and anthropometrics |
| Huang 2019 ([312](#_ENREF_312)) | meta-analysis | At risk of cardiovascular disease (incl. metabolic syndrome) | Turmeric | Glycaemic control |
| Pourmasoumi 2019 ([226](#_ENREF_226)) | meta-analysis | At risk of cardiovascular disease (incl. metabolic syndrome) | Saffron | Lipid profile, blood pressure, glucose metabolism and anthropometrics |
| Yuan 2019 ([279](#_ENREF_279)) | meta-analysis | Metabolic disorders | Turmeric | Lipid profiles |
| Tabrizi 2018 ([281](#_ENREF_281)) | meta-analysis | Metabolic syndrome | Turmeric | Glycaemic control and lipid profiles |
| Zhu 2018 ([282](#_ENREF_282)) | meta-analysis | Diabetes and Metabolic syndrome | Ginger | Glycaemic control |
| Asbaghi 2021 ([284](#_ENREF_284)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Saffron | Inflammatory markers |
| Atefi 2021 ([286](#_ENREF_286)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Barberry | Blood pressure |
| Ghassab-Abdollahi 2021 ([6](#_ENREF_6)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Black cumin, Turmeric | Oxidative stress and inflammatory biomarkers |
| Montazeri 2021 ([7](#_ENREF_7)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Black cumin | Oxidative stress and inflammatory biomarkers |
| Moradi 2021 ([288](#_ENREF_288)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Artichoke | Blood pressure |
| Shekarchizadeh-Esfahani 2021 ([389](#_ENREF_389)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Garlic | Serum adiponectin and leptin |
| Ghaderi 2020 ([76](#_ENREF_76)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Saffron | Mental health and C-reactive protein |
| Ghavami 2020 ([97](#_ENREF_97)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Ginseng | Liver function |
| Hadi 2020 ([293](#_ENREF_293)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Cinnamon | Blood pressure |
| Hallajzadeh 2020 ([15](#_ENREF_15)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Black cumin | Glycaemic control, lipid profiles, oxidative stress and inflammatory biomarkers |
| Jalili 2020 ([294](#_ENREF_294)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Artichoke | Glycaemic control |
| Miraghajani 2020 ([296](#_ENREF_296)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Ginseng | Anthropometric indices and body composition |
| Mirzavandi 2020 ([99](#_ENREF_99)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Garlic | Inflammatory markers |
| Mousavi 2020 ([298](#_ENREF_298)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Cinnamon | Blood pressure |
| Mousavi 2020a ([300](#_ENREF_300)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Turmeric | Body weight, body mass index and waist circumference |
| Payab 2020 ([390](#_ENREF_390)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Green tea, Black cumin | Lipid profile, anthropometric indices and body composition |
| Pourmasoumi 2020 ([301](#_ENREF_301)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Cranberry | Cardiovascular metabolic risk factors |
| Safari 2020 ([305](#_ENREF_305)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Barberry | Glycaemic control |
| Xu 2020 ([102](#_ENREF_102)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Green tea | Lipid profile |
| Yazdanpanah 2020 ([306](#_ENREF_306)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Cinnamon | Body weight and composition |
| Alizadeh 2019 ([307](#_ENREF_307)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Turmeric | Oxidative stress markers |
| Asbaghi 2019 ([308](#_ENREF_308)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Saffron | Blood glucose and lipid profile |
| Askari 2019 ([104](#_ENREF_104)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Black cumin | Glycaemic control |
| Clark 2019 ([309](#_ENREF_309)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Turmeric | Adiponectin levels |
| Hadi 2019 ([105](#_ENREF_105)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Turmeric | Blood pressure |
| Hadi 2019a ([310](#_ENREF_310)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Barberry | Lipid profile |
| Hernandez-Garcia 2019 ([107](#_ENREF_107)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Ginseng | Lipid profile |
| Marx 2019 ([176](#_ENREF_176)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Saffron | Depression and anxiety |
| Mohammadi 2019 ([108](#_ENREF_108)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Ginseng | Inflammatory biomarkers |
| Saboori 2019 ([109](#_ENREF_109)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Ginseng | C-reactive protein |
| Tabrizi 2019 ([313](#_ENREF_313)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Turmeric | Oxidative stress and inflammatory biomarkers |
| White 2019 ([315](#_ENREF_315)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Turmeric | Inflammatory biomarkers |
| Golzarand 2018 ([317](#_ENREF_317)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Green tea | Anthropometric indices |
| Jovanovski 2018 ([110](#_ENREF_110)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Psyllium | Lipid profiles |
| Namazi 2018 ([319](#_ENREF_319)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Black cumin | Body weight and composition |
| Qin 2018 ([321](#_ENREF_321)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Turmeric | Oxidative stress |
| Mohammadi-Sartang 2017 ([118](#_ENREF_118)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Linseed | Body weight and composition |
| Si 2017 ([326](#_ENREF_326)) | meta-analysis | Cardiovascular risk factors (incl. metabolic syndrome) | Turmeric | Lipid profiles |
| Derosa 2016 ([328](#_ENREF_328)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Turmeric | Circulating IL-6 |
| Guo-Chong 2016 ([332](#_ENREF_332)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Linseed | C-reactive protein |
| Sahebkar 2016 ([123](#_ENREF_123)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Black cumin | Lipid profiles |
| Sahebkar 2016b ([328](#_ENREF_328)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Turmeric | Circulating IL-6 |
| Sahebkar 2016c ([124](#_ENREF_124)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Black cumin | Blood pressure |
| Ursoniu 2016 ([68](#_ENREF_68)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Linseed | Blood pressure |
| Khalesi 2015 ([127](#_ENREF_127)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Linseed | Blood pressure |
| Khalesi 2014 ([341](#_ENREF_341)) | meta-analysis | Umbrella review (incl. metabolic syndrome) | Green tea | Blood pressure |
| Lopresti 2021 ([191](#_ENREF_191)) | individual study results | Umbrella review (incl. metabolic syndrome) | Ginseng | Stress biomarkers |
| Ponticelli 2021 ([391](#_ENREF_391)) | descriptive | Diabetes, Inflammation, and Metabolic Syndrome | Hops | Lipid profile, blood pressure, glucose metabolism and inflammatory biomarkers |
| Chan 2020 ([357](#_ENREF_357)) | descriptive | Umbrella review (incl. metabolic syndrome) | Garlic | Blood pressure and lipid profiles |
| Eisvand 2020 ([392](#_ENREF_392)) | descriptive | Metabolic syndrome | Ginkgo | Lipid profile, blood pressure, glucose metabolism and body weight |
| Emamat 2020 ([358](#_ENREF_358)) | descriptive | Umbrella review (incl. metabolic syndrome) | Garlic | Vascular function |
| Giannoulaki 2020 ([359](#_ENREF_359)) | descriptive | Diabetes and Metabolic Syndrome | Saffron | Lipid profile, blood pressure, glucose metabolism |
| Smith 2020 ([393](#_ENREF_393)) | descriptive | Umbrella review (incl. metabolic syndrome) | Ginseng | Testosterone concentrations |
| Jane 2019 ([394](#_ENREF_394)) | descriptive | Umbrella review (incl. metabolic syndrome) | Psyllium, Oats | Obesity-related disease risk factors |
| Hariri 2018 ([364](#_ENREF_364)) | descriptive | Umbrella review (incl. metabolic syndrome) | Turmeric | Anthropometric indices |
| Mohtashami 2016 ([154](#_ENREF_154)) | descriptive | Umbrella review (incl. metabolic syndrome) | Black cumin | Blood parameters and anthropometric indices |
| Choi 2013 ([369](#_ENREF_369)) | descriptive | Umbrella review (incl. metabolic syndrome) | Ginseng | Any |
| Ulbricht 2012 ([162](#_ENREF_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.

#### Critical appraisal

Not assessed.

#### 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.

## Immune mediated

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

#### 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

A black background with a black square

Description automatically generated with medium confidence

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 (Elutherococcus 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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_399)) | Meta-analysis | No population restrictions | Ginseng | Placebo | Fatigue severity, Physical performance | 2  (k=12) | Kim 2013, Etemadifar 2013 |
| Alraek 2011 ([400](#_ENREF_400)) | Descriptive | Chronic fatigue syndrome | Any CAM \* | Not specified | Not specified | 1 (k=26) | Hartz 2004 |
| Provino 2010 ([201](#_ENREF_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



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

#### 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

#### 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](#_ENREF_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](#_ENREF_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.

### Upper respiratory tract infection

#### 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](#_ENREF_402)) 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](#_ENREF_133), [409-417](#_ENREF_409)) 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](#_ENREF_372), [418-426](#_ENREF_418)) 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](#_ENREF_402)) | meta-analysis | Upper respiratory tract infection (allergic rhinitis) | Astragalus, Green tea, Cinnamon, Ginseng, Black cumin, Ginger | Any efficacy outcomes |
| Wieland 2021 ([403](#_ENREF_403)) | meta-analysis | Upper respiratory tract infection (viral) | Elderberry | Any efficacy outcomes (incl. prevention) |
| Ang 2020 ([404](#_ENREF_404)) | meta-analysis | Upper respiratory tract infection (COVID) | Herb, not specified | Any efficacy outcomes |
| Antonelli 2020 ([405](#_ENREF_405)) | meta-analysis | Upper respiratory tract infection (seasonal, acute) | Ginseng | Any efficacy outcomes |
| David 2019 ([406](#_ENREF_406)) | meta-analysis | Upper respiratory tract infection (viral) | Echinacea | Any efficacy outcomes (incl. prevention) |
| Hawkins 2019 ([407](#_ENREF_407)) | meta-analysis | Upper respiratory tract infection (viral) | Elderberry | Any efficacy outcomes (incl. prevention) |
| Anheyer 2018 ([408](#_ENREF_408)) | meta-analysis | Upper respiratory tract infection (children) | Echinacea | Any efficacy outcomes |
| Hu 2017 ([409](#_ENREF_409)) | meta-analysis | Upper respiratory tract infection (acute, adults and children)) | Andrographis | Symptom relief |
| Schapowal 2015 ([410](#_ENREF_410)) | meta-analysis | Upper respiratory tract infection | Echinacea | Recurrence, complications |
| Wagner 2015 ([411](#_ENREF_411)) | meta-analysis | Upper respiratory tract infection (cough) | Andrographis, Echinacea, Ivy, Combination | Any efficacy outcomes |
| Linde 2014 ([412](#_ENREF_412)) | meta-analysis | Upper respiratory tract infection (common cold) | Echinacea | Any efficacy outcomes |
| Shergis 2013 ([133](#_ENREF_133)) | meta-analysis | Umbrella review (incl. URTI) | Ginseng | Any efficacy outcomes |
| Seida 2011 ([413](#_ENREF_413)) | meta-analysis | Upper respiratory tract infection (common cold) | Ginseng | Prevention |
| Pittler 2007 ([414](#_ENREF_414)) | meta-analysis | Umbrella review (incl. URTI) | Garlic | Any efficacy outcomes |
| Shah 2007 ([415](#_ENREF_415)) | meta-analysis | Upper respiratory tract infection (common cold) | Echinacea, Combination | Any efficacy outcomes (incl. prevention) |
| Schoop 2006 ([416](#_ENREF_416)) | meta-analysis | Upper respiratory tract infection (rhinovirus) | Echinacea | Prevention |
| Poolsup 2004 ([417](#_ENREF_417)) | meta-analysis | Upper respiratory tract infection (uncomplicated) | Andrographis | Any efficacy outcomes |
| Sierocinski 2021 ([418](#_ENREF_418)) | descriptive | Upper respiratory tract infection (acute) | Ivy, Combination | Any efficacy outcomes |
| Harnett 2020 ([419](#_ENREF_419)) | individual study results | Upper respiratory tract infection (acute) | Elderberry | Any efficacy outcomes |
| Jin 2019 ([420](#_ENREF_420)) | descriptive | Upper respiratory tract infection (chronic rhinosinusitis) | Herb, not specified | Any efficacy outcomes |
| Anushiravani 2018 ([421](#_ENREF_421)) | descriptive | Upper respiratory tract infection (chronic rhinosinusitis) | Herb, not specified | Any efficacy outcomes |
| Reckhenrich 2018 ([422](#_ENREF_422)) | descriptive | Upper respiratory tract infection (with cough) | Ivy | Any efficacy outcomes |
| Lissiman 2014 ([423](#_ENREF_423)) | individual study results | Upper respiratory tract infection (common cold) | Garlic | Any efficacy outcomes |
| Chuan 2013 ([424](#_ENREF_424)) | individual study results | Upper respiratory tract infection | Astragalus | Prevention |
| Lee 2011 ([372](#_ENREF_372)) | descriptive | Umbrella review (incl. URTI) | Ginseng | Any efficacy outcomes |
| Guo 2007 ([425](#_ENREF_425)) | descriptive | Umbrella review (incl. URTI) | Ginseng, Elderberry, Andrographis, Echinaecea | Any efficacy outcomes |
| Coon 2004 ([426](#_ENREF_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.

#### Critical appraisal

Not assessed

#### 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.

### Dermatitis or eczema

#### 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](#_ENREF_367), [427](#_ENREF_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](#_ENREF_427)) | descriptive | atopic eczema | Any topical herb (St John's wort, Witch hazel, Chamomile, Liquorice, Combinations) | Placebo or active control | -- |
| Vaughn 2016 ([367](#_ENREF_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

#### Critical appraisal

Not assessed.

#### 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.

### Acne

#### 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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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.

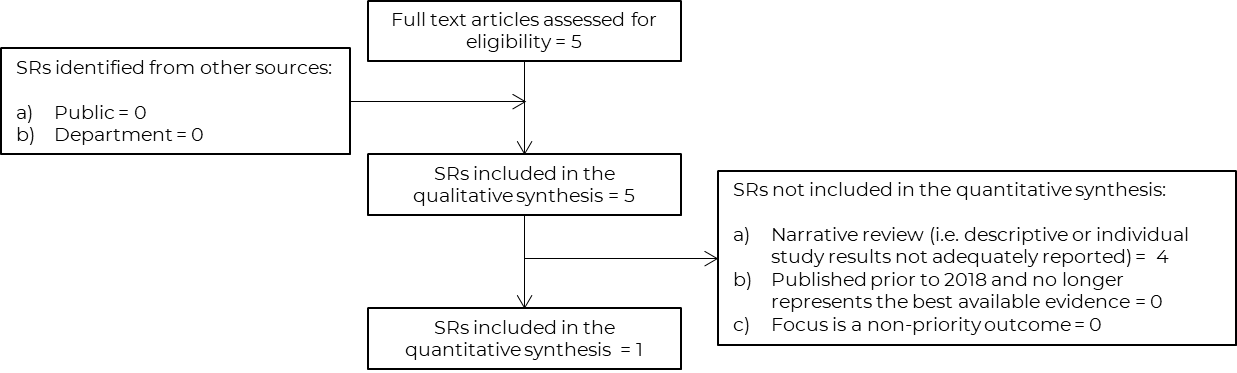
d. Outcomes assessed or listed by the systematic review. Grey highlight = nonpriority outcome; Blue highlight = critical or important outcome

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

#### 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



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. |

#### 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[[17]](#footnote-18); 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; I2 = 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)).

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](#_ENREF_431)). Acne lesion counts can be used to guide grading of acne severity (from mild[[18]](#footnote-19) to severe[[19]](#footnote-20)) ([432](#_ENREF_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; I2 = 96%) (GRADE: Low) but not noninflammatory lesions (SMD –0.73; 95% CI –6.44, 4.99; p = 0.80; I2 = 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; I2 = 85%); but was notably improved for the noninflammatory lesion count (SMD –3.56; 95% CI –4.35, –2.78; p < 0.00001; I2 = 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.

# 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.

## Systematic reviews

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

# 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.

## 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.

## 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).

# Differences between protocol & review

## 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.

## 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](https://htanalysts.sharepoint.com/:w:/r/Projects/Current_Projects/NHM17%20Natural%20therapies/08%20Draft/03%20Evidence%20review/Western%20herbalism/NHM17_WHM_TR-ABC_DRAFT.docx?d=w283d578d4fce4360bef8fede6ff92788&csf=1&web=1)), 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).

# 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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1. Valerian or combinations of the following: valerian and hops; Indian valerian, cabbage rose, spikenard, Heart-leaved moonseed, Withania, ginger, black pepper, liquorice, Convolvulus pluricalis [↑](#footnote-ref-2)
2. Not adequately described by the reviews. Assumed to be a simple visual analogue scale (scale range unknown) (higher is better). [↑](#footnote-ref-3)
3. zolpidem, oxazepam or diphenhydramine [↑](#footnote-ref-4)
4. delivered as an adjunct to corticosteroids [↑](#footnote-ref-5)
5. delivered alone or as an adjunct to mesalazine [↑](#footnote-ref-6)
6. Including peppermint oil, aloe vera, turmeric, psyllium, St John’s wort, capsicum, ginger, anise oil, senna or fixed dose herbal combinations [↑](#footnote-ref-7)
7. including pain or discomfort, diarrhoea, constipation, bloating, burping, rumbling, hunger pains, heartburn, nausea, acid reflux, gas, loose stools, hard stools, urgency, and incomplete emptying [↑](#footnote-ref-8)
8. Peppermint oil, fixed dose of lemon balm, peppermint oil & Coriandrum sativum, or fixed dose of horse chestnut, peppermint oil & Schinopsis lorentzii [↑](#footnote-ref-9)
9. or from 0 (no pain) to 10 (worst pain) on a 10-cm scale [↑](#footnote-ref-10)
10. Note the 0-10 score is reported by the RCT. [↑](#footnote-ref-11)
11. zinc sulphate [↑](#footnote-ref-12)
12. mefenamic acid, Ibuprofen or a fixed-combination NSAID (containing paracetamol, ibuprofen and caffeine).. [↑](#footnote-ref-13)
13. Study included three treatment groups: WHM, placebo and active control. [↑](#footnote-ref-14)
14. Pooled estimated were corrected for bias (i.e. Hedge’s g) and were results according to per protocol analysis. [↑](#footnote-ref-15)
15. It is assumed depression was included as part of a PMS symptoms diary (or VAS) and hence results should be available. [↑](#footnote-ref-16)
16. It is assumed anxiety was included as part of a PMS symptoms diary (or VAS) and hence results should be available. [↑](#footnote-ref-17)
17. participants used intervention on one half of face, and placebo on the other half. [↑](#footnote-ref-18)
18. <20 comedones, <15 inflammatory lesions, or total lesion count <30 [↑](#footnote-ref-19)
19. >5 pseudocysts, total comedones count >100, total inflammatory count >50; or total lesion count >125 [↑](#footnote-ref-20)