OVERVIEW OF WESTERN HERBAL MEDICINES FOR PREVENTING AND TREATING HEALTH CONDITIONS

EVIDENCE EVALUATION REPORT

prepared by

HTANALYSTS

for

National Health and Medical Research Council

NHMRC | Natural Therapies Working Committee

Canberra ACT 2601

SEPTEMBER 2024

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Dates

This evidence evaluation report and accompanying technical reports received approval from the National Health and Medical Research Council (NHMRC) Natural Therapies Working Committee (NTWC) on 20 November 2024.

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

History

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

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

This evidence evaluation report has been developed by **HT**ANALYSTS in conjunction with NHMRC, NTWC, and NTREAP. It describes the main body of evidence related to the effect of western herbal medicines for preventing and treating health conditions. Supplementary data are provided in Appendices A to H. All associated materials have been developed in a robust and transparent manner in accordance with relevant best practice standards (2-5).

Funding

This work is paid for by the Australian Government Department of Health and Aged Care (via NHMRC) under Official Order 2019-20P026.

Acknowledgements

Thanks to the members of the Department's NTREAP and NHMRC's NTWC for their advice and comments throughout the creation of this document. PRACI data was provided by Dr Amie Steel at UTS. Membership and other details of the Panel and Committee can be found at:

https://www.health.gov.au/committees-and-groups/natural-therapies-review-expert-advisory-panel

https://www.nhmrc.gov.au/about-us/leadership-and-governance/committees/natural-therapies-working-committee

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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
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
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

Plain language summary

What was the aim of this review?

The aim of this overview was to identify eligible studies and assess whether they demonstrate that Western herbal medicines (WHMs) are effective in preventing and/or treating certain injuries, diseases, medical conditions, or pre-clinical conditions relevant to the Australian population. Western herbalism is the practice of plant-based medicine, originating from Europe, the United Kingdom and North America. Herbalists use plants and unrefined plant extracts to create medicines that target individual body systems, with the aim of treating the underlying cause of disease.

This review is targeted for the Australian Government Department of Health and Aged Care (formerly Department of Health) to assist in their Natural Therapies Review, which is designed to determine whether certain natural therapies, including Western herbalism, have enough evidence of effectiveness to be considered re-eligible for private health insurance rebates. This review is not designed to be a complete review of all studies published for WHMs, nor is it intended to inform decisions about whether an individual or practitioner should use Western herbalism, individual herbs, extracts of herbs or combinations of herbs.

Key messages

For the populations (or conditions) assessed, individual WHMs probably provide people who use them with some benefit for some outcomes, when compared with people given a placebo (i.e. something that looks identical to the intervention but is designed to have no therapeutic effect). In general, the evidence assessed in this review was rated moderate or low certainty. Very few results were found comparing the use of WHM to an inactive control (e.g. waitlist), and those that were found were of very low certainty.

What was studied in the review?

This overview identified reviews using a planned literature search, with no limit on publication date. To make the overview more manageable, the overview only assessed studies for certain conditions or groups of people. These priority conditions and groups were decided based on Australian survey information and from seeking expert advice about the reasons why people in Australia commonly seek to use WHMs and the types of conditions seen by Western herbalists. To be included in the overview, herbs had to be on the list of core herbal medicines used by the Naturopaths & Herbalists Association of Australia, but eligibility was not based on specific pairings of herbs and conditions. Included studies needed to compare the results of people who use WHMs to a group of people who did not. Assessment of cost effectiveness, safety and studies of healthy populations was not included in this overview.

Studies published in languages other than English were listed in an evidence inventory, but not included in the assessment. Studies that compared WHMs with another intervention (active comparator) were also listed but were mostly not included in the main analysis because different studies used different comparators and outcome measures, which did not meet the criteria planned in the protocol. Results comparing the effects of WHM to an evidence-based treatment for depression were included as there were several studies evaluating the same evidence-based treatment in that population (a pre-specified criterion for presenting results).

Studies were assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework. GRADE is a method to assess how confident (or certain) systematic review authors can be that the results reported (estimates of effect) in studies are correct. The assessment made by the reviewer is then described as either:

- high certainty – meaning the authors have a lot of confidence that the true effect is similar to the estimated effect
- moderate certainty – meaning that the true effect is probably close to the estimated effect
- low certainty – meaning the true effect might be markedly different from the estimated effect

- very low certainty – meaning the true effect is probably markedly different from the estimated effect. Reviewers' confidence in the result was so limited that interpretation was not provided.

What studies did we identify in this review?

Using a planned approach, 8761 citations from 9 databases were collected and examined, including 658 publications submitted by the public via the Department's public call for evidence.

Out of 8761 citations screened, 402 reviews covering 16 prioritised conditions, were assessed in the evidence evaluation. A further 199 reviews were awaiting classification and 39 reviews had been registered but were not completed at the time the search was conducted for this review. Evidence from 270 RCTs, covering 11 conditions, were extracted from the reviews and are included in the results. Although prioritisation focused on conditions seen and herbs used by Western herbalists in Australia, we did not evaluate if the herbal preparation (e.g. liquid extracts, herbs, tablet or capsule) or dose prescribed in eligible studies correlated with that typically prescribed by Western herbalists in Australia for that condition. The treatment provider was often not specified. Few studies continued for more than 6-months.

What were the main results of the review?

The evidence provides moderate to low certainty that using WHMs is more effective than not using WHMs for most of the conditions and outcomes assessed in this review. There were 3 conditions for which the evidence also provides moderate to very low certainty that using WHMs has little (to no) benefit for some outcomes assessed in this review. There were 2 conditions assessed in this review where the effect of using WHMs is unknown (reflux and dermatitis/eczema). Because of the overall large volume of evidence, 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). The Natural Therapies Working Committee (NTWC) was not involved in selection of which prioritised conditions were completed versus not completed (see NHMRC process report for additional information). Compared with placebo:

The evidence provides moderate certainty that WHM probably:

- reduces pain intensity in people with menstrual conditions (dysmenorrhoea etc.) (7 RCTs, 601 participants) [WHM included ginger, cinnamon, valerian root or fenugreek]
- increases global improvement in people with premenstrual disturbances (6 RCTs, 839 participants) [WHM included chaste tree berry]
- increases clinical remission in people with inflammatory bowel disease (14 RCTs, 974 participants) [WHM included green tea extract, curcumin, Boswellia, aloe vera gel, Wormwood, St Mary's thistle or Andrographis]
- increases the proportion of people who achieve global improvement of symptoms in people with irritable bowel syndrome (19 RCTs, 1279 participants) [WHM included peppermint oil, curcumin + fennel, Carmint + Psyllium, anise oil, aloe vera juice, ginger or St Jonh's wort]
- improves symptom severity in people with symptoms of menopause (16 RCTs, 1680 participants) [WHM included black cohosh extract, alone or in combination with St John's wort or red clover]
- reduces depressive symptoms in people with depression (33 RCTs, 3910 participants) [WHM included curcumin, saffron or St John's wort]
- reduces anxiety in people with anxiety (20 RCTs, 2087 participants) [WHM included valerian root, kava, Passiflora, saffron, chamomile, ginkgo biloba or lavender].

The evidence provides low certainty evidence that WHM may:

- reduce overall symptoms (8 RCTs, 1133 participants), depressive symptoms (5 RCTs 613 participants) and anxiety (2 RCTs, 208 participants) in people with premenstrual disturbances [WHM included chaste tree]
- reduce anxiety and improve emotional functioning in people with depression (5 RCTs, 397 participants) [WHM included curcumin or saffron]

- reduce disease severity (3 RCTs, 183 participants) and increase patient-reported improvement (1 RCT, 70 participants) in people with acne [WHM included green tea-oral, green tea-topical]
- increase the proportion with clinical improvement (8 RCTs, 403 participants) in people with inflammatory bowel disease [WHM included green tea extract or curcumin]
- reduce pain (7 RCTs, 606 participants) and increase clinical improvement of symptoms (3 RCTs, 236 participants) in people with irritable bowel syndrome [WHM included peppermint oil or aloe vera juice]
- reduce depressive symptoms (2 RCTs, 129 participants), and improve overall symptoms (3 RCTs, 670 participants) and emotional functioning (2 RCTs, 508 participants) in people with anxiety [WHM included lavender, saffron, or chamomile]
- improve physical functioning (2 RCTs 508 participants) and sleep quality (2 RCTs, 382 participants) in people with anxiety [WHM included lavender]
- reduce symptoms of fatigue (3 RCTs, 185 participants) in people with chronic fatigue conditions [WHM included Siberian ginseng or panax ginseng]
- reduce hot flush frequency (14 RCTs, 1355 participants) in people with symptoms of menopause [WHM included black cohosh, red clover, valerian, valerian root, St John's wort or St John's wort + chaste tree].

The evidence provides moderate certainty that WHM probably has little (to no) effect on:

- sexual functioning in people with symptoms of menopause (7 RCTs, 887 participants) [WHM included ginseng, withania (ashwagandha), red clover or ginseng]
- sleep quality in people with insomnia (5 RCTs, 946 participants) [WHM included chamomile, valerian or kava].

The evidence provides low certainty that WHM may result in little (to no) change in:

- disease activity in people with inflammatory bowel disease (2 RCTs, 151 participants) [WHM included curcumin]
- symptoms of anxiety in people with insomnia (2 RCTs, 425 participants) [WHM included kava, valerian or chamomile].

Results compared to inactive control (e.g. waitlist) were also examined, but for the majority of conditions there were no results found. For 2 populations (inflammatory bowel disease, menstrual conditions) the evidence was very uncertain.

Results compared to active control were examined for one condition. Here, the evidence provides moderate certainty that WHM (St John's wort) is probably comparable to antidepressants for improving symptoms of depression in people with depression.

Implications for health policy and research

This review assesses the evidence for certain conditions and groups of people to inform the Australian Government about health policy decisions for private health insurance rebates. The review does not cover all the reasons that people use WHMs, or the reasons practitioners prescribe WHMs and is not intended to inform individual choices about using Western herbalism, individual herbs, extracts of herb or combinations of herbs.

The results of this review indicate that WHMs may be useful for some conditions and outcomes and not useful for others. Whether the individual herbs used in the primary studies for a condition correlate with those typically prescribed by Western herbalists in Australia is not known. A number of studies focussed on the effect of WHMs in people who received treatment for 12 weeks or less, so it is difficult to conclude the possible benefits of WHMs in people who continue to use WHMs for more than 12 weeks. It is unknown whether the effects of WHMs continue once people stop using WHMs. This review listed but did not assess WHMs versus other interventions for most conditions, so no comment can be made on whether WHMs are better or worse than other interventions.

Future research could be improved by studies of WHMs versus placebo or inactive control including outcomes that are considered critical or important for decision-making. Importantly, clinical trials that focus on the broader research question about the effectiveness of Western herbalism as a health service are needed.

How up to date is this review?

Searches were conducted from the earliest date included in the databases until 22 April 2021. Systematic reviews published after this date are not included in this review.

Executive summary

Background

Western herbalism is the practice of plant-based medicine, originating from Europe, the United Kingdom and North America. Herbalists use plants and unrefined plant extracts to create medicines that target individual body systems, with the aim of treating the underlying cause of disease.

In 2015, an overview of systematic reviews conducted for the Australian Government identified no systematic reviews containing evidence evaluating Western herbalism as a health service. The review noted that while there is a large body of research on the effects of individual herbal agents and remedies, the study of the real-life practice and outcomes of herbalism as a health service is a relatively new area of research that has yet to be addressed in systematic reviews. The current overview assesses the effectiveness of individual Western herbal medicines (WHMs), aiming to focus on WHMs prescribed by Western herbalists in Australia and conditions treated by Western herbalists in Australia.

Objectives

The objective of this overview is to evaluate the effectiveness of Western herbal medicines in individuals with a described injury, or to treat or prevent disease, medical condition or preclinical condition, including primary prevention in at-risk individuals, on outcomes that align with the reasons why consumers seek to use WHMs in Australia. This information will be used by the Australian Government in deciding whether to reinclude Western herbalism as eligible for private health insurance rebates, after Western herbalism was excluded in 2019. This overview is not designed to assess all the reasons that people use WHMs, or the reasons herbalists prescribe WHMs and is not intended to inform individual choices about using Western herbalism, individual herbs, extracts of herb or combinations of herbs.

Search methods

Literature searches were conducted in EMBASE, MEDLINE, EMCARE, PsycINFO, AMED, CINAHL, EMB reviews, PAHO, and PUBMED to identify relevant systematic reviews published from database inception to 22 April 2021. The public was also invited by the Department of Health and Aged Care (formerly Department of Health) to submit references of published research evidence. There were no limits on language of publication or date of publication in the search.

Selection criteria

Systematic reviews of randomised controlled trials (RCTs), quasi-RCTs and non-randomised studies that examined the effectiveness of WHMs compared to control (or another intervention, where applicable) were eligible for inclusion. Systematic reviews that included a single RCT or that included both RCTs and NRSIs were eligible; however, only evidence from the RCTs (and quasi-RCTs) were considered. Systematic reviews that did not report study eligibility criteria or did not conduct a comprehensive search of the literature (i.e. searched less than 2 databases) were not included. There were no limits on the type of herbal preparation (i.e. capsule, tablet, liquid extract, tea etc.), however, the herbal preparation (individual herb or combination product) must be used by Western herbalists in Australia and be administered orally, sublingually or be topically applied. Eligibility was not based on specific pairings of herbs and conditions.

RCTs (and quasi-RCTs) in people of any age with any injury, disease, medical condition or preclinical condition were eligible for inclusion. Studies examining WHMs in individuals at-risk, but not studies assessing at-risk populations in general, were also eligible for inclusion. The search was not restricted by comparators, however the 2 main comparators of interest for this review were WHMs versus placebo and WHMs versus control (including no intervention, waitlist, or usual care, if considered inactive). The tertiary comparator of interest was WHMs versus other interventions (inclusive of non-WHMs (i.e. Chinese and Ayurvedic formulations) and usual care if considered active). The search did not use outcomes to screen reviews for eligibility. Reviews were not excluded based on country of origin, however reviews published in a language other than English were not translated and were not included in the synthesis but were listed in an inventory for completeness.

Data collection and analysis

To ensure the overview was most relevant to the Australian population, populations were prioritised without knowledge of potential studies to ensure unbiased prioritisation. In determining the priority conditions for inclusion in the analysis and synthesis of the review, the National Health and Medical Research Council (NHMRC) Natural Therapies Working Committee (NTWC) were guided by relevant patient or practitioner reported Australian survey data (where available) and expert advice from The Department's Natural Therapies Review Expert Advisory Panel (NTREAP). Prioritisation was conducted after initial searching and screening process, but before data extraction.

After population prioritisation, a blinded outcome prioritisation process was undertaken by NTWC (with input from NTREAP). The outcome prioritisation process was developed based on published core outcome sets and systematic reviews in the priority populations, after the included studies were identified. As part of the process, NTWC (with advice from NTREAP) were asked to specify up to 7 'critical' or 'important' outcomes for inclusion in the analysis and synthesis of the overview. Where a study did not report a prioritised outcome for that population or condition, this was noted as an evidence gap in the overview. For outcome domains, NTWC were guided by GRADE methodology, scoring outcome domains on a scale of 0 (of limited importance for decision making) to 9 (critical for decision making). Harms and cost effectiveness measures were out of scope.

Data collection was performed by 2 researchers, the first collected data using data extraction forms and the second checked the forms for completeness and accuracy. Critical appraisal of the eligible reviews was conducted using A MeaSurement Tool to Assess systematic Reviews (AMSTAR-2).

In the data analysis and synthesis for each prioritised population, the overall certainty of evidence for a maximum of 7 critical or important outcomes were reported in GRADE summary of findings tables, with corresponding evidence statements assigned to each outcome. Data were assessed for reported outcomes at 'end of treatment' and reported minimal clinically important differences (MCID) or minimal important difference (MID) (where available). In instances where MCID were unavailable, effect estimates were assessed using a threshold of (1) small (mean difference [MD] <10% of the scale) (2) moderate (MD between 10% to 20% of the scale), or (3) large (MD more than 20% of the scale). If the effect was quantified using a standardised mean difference (SMD), we used Cohen's guidance for interpreting the magnitude of the SMD, where 0.2 represents a small difference, 0.5 is moderate, and 0.8 is large.

Main results

A total of 854 systematic reviews were identified as eligible for inclusion in this overview. Of these, 402 systematic reviews covering 16 conditions were considered in the evidence evaluation. For the synthesis 270 RCTs covering 11 prioritised conditions compared WHMs with placebo and 5 RCTs covering 2 prioritised conditions compared WHMs with inactive control (no intervention, wait list or usual care) were considered. Because of the large volume of evidence, it was not feasible to consider the evidence regarding 4 of the 16 prioritised conditions (diabetes, impaired glucose tolerance, metabolic syndrome, upper respiratory tract infections). Systematic reviews for these 4 conditions were not critically appraised or included in synthesis (see Appendix D). The Natural Therapies Working Committee (NTWC) was not involved in selection of which prioritised conditions were completed versus not completed (see NHMRC process report for additional information). Results for most studies of prioritised conditions with active comparators are presented in Appendix F2, but not in the synthesis, as the wide range of comparators and outcomes did not allow for synthesis as planned in the protocol. Studies comparing WHM to an active treatment in people with depression are included in the main report because the comparator was sufficiently homogenous across studies to support synthesis and the comparator represents an accepted, evidence-based 'gold standard' of care for the population in question.

At the time of the search, an additional 199 systematic reviews were awaiting classification, and an additional 39 reviews were recorded as ongoing (registered but not published at the time of the search). Of the reviews awaiting classification, 113 were not published in English and 42 were conference abstracts with the remaining 44 reviews not able to be retrieved and therefore not assessed. Of the ongoing reviews, 39 were registered on PROSPERO or a protocol had been published but results not reported at the time of search. There is no reason to suspect that the results of the reviews would differ substantially from those already included in this overview.

Due to a lack of studies that focus on Western herbalism as a practice, the overview has focused on individual herbal medicines. Although prioritisation focused on conditions seen, and herbs used by Western herbalists in Australia there was no specific matching of herbs and conditions, and extrapolation of the effect of these interventions may or may not reflect Western herbalism as a practice in Australia. Given the broad nature of the overview, it is difficult to specify if the included primary studies examined the individual WHM delivered in a manner that would be considered applicable to the Australian context. The primary studies identified by the reviews were often conducted over a 6 to 12-week time-period, with some studies examining the effect of the WHM for a slightly longer timeframe (24 weeks). Few, if any, provided any longer-term data (WHM administered for longer than 52 weeks).

Studies were assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework. GRADE combines information to assess overall how certain systematic review authors can be that the estimates of the effect (reported across a study/s for each critical or important outcome) are correct. High certainty means the authors have a lot of confidence that the true effect is similar to the estimated effect. Moderate certainty means that the true effect is probably close to the estimated effect. Low certainty means the true effect might be markedly different from the estimated effect. Very low certainty means the true effect is probably markedly different from the estimated effect.

This review evaluated 11 prioritised conditions for which there was evidence about the effect of WHM on an outcome considered critical or important by NTWC.

Compared with placebo, the evidence provides:

- moderate certainty evidence that WHM probably results in:
    - a large improvement in pain intensity in people with menstrual conditions (7 RCTs, 601 participants) [WHM included ginger, cinnamon, valerian root or fenugreek]
    - a large increase in patient-reported improvement in people with premenstrual disturbances (6 RCTs, 839 participants) [WHM included chaste tree berry]
    - a moderate increase in the proportion with clinical remission in people with inflammatory bowel disease (14 RCTs, 974 participants) [WHM included green tea extract, curcumin, Boswellia, aloe vera gel, Wormwood, St Mary's thistle or Andrographis]

  - a moderate increase in the proportion with clinical improvement in people with irritable bowel syndrome (19 RCTs, 1279 participants) [WHM included peppermint oil, curcumin + fennel, Carmint + Psyllium, anise oil, aloe vera juice, ginger or St Jonh's wort]
  - a moderate improvement in symptom severity in people with symptoms of menopause (16 RCTs, 1680 participants) [WHM included black cohosh extract, alone or in combination with St John's wort or red clover]
  - a moderate reduction in depressive symptoms in people with depression (33 RCTs, 3910 participants) [WHM included curcumin, saffron or St John's wort]
  - a slight reduction in anxiety in people with anxiety (20 RCTs, 2087 participants) [WHM included valerian root, kava, Passiflora, saffron, chamomile, ginkgo biloba or lavender].

- low certainty evidence that WHM may result in:
  - a large reduction in depressive symptoms (5 RCTs, 613 participants) and anxiety (2 RCTs, 208 participants), and a large improvement in overall symptoms (8 RCTs, 1133 participants) in people with premenstrual disturbances [WHM included chaste tree]
  - a large reduction in anxiety (5 RCTs, 397 participants) and a slight improvement in emotional functioning (2 RCTs, 358 participants) in people with depression [WHM included curcumin or saffron]
  - a large reduction in disease severity (3 RCTs, 183 participants) and a large increase in patient-reported improvement (1 RCT, 70 participants) in people with acne [WHM included green tea-oral, green tea-topical]
  - a moderate increase in the proportion with a clinical response (8 RCTs, 403 participants) in people with inflammatory bowel disease [WHM included green tea extract or curcumin]
  - a moderate reduction in pain intensity (7 RCTs, 606 participants) and a slight increase in clinical improvement (3 RCTs, 236 participants) in people with irritable bowel syndrome [WHM included peppermint oil or aloe vera juice]
  - a moderate reduction in depressive symptoms (2 RCTs, 129 participants), and a moderate improvement in global improvement (3 RCTs, 670 participants) and emotional functioning (2 RCTs, 508 participants) in people with anxiety [WHM included lavender, saffron, or chamomile]
  - a slight improvement in physical functioning (2 RCTs 508 participants) and sleep quality (2 RCTs, 382 participants) in people with anxiety [WHM included lavender]
  - a moderate reduction in symptoms of fatigue (3 RCTs, 185 participants) in people with chronic fatigue conditions [WHM included Siberian ginseng or panax ginseng]
  - a slight reduction in hot flush frequency (14 RCTs, 1355 participants) in people with symptoms of menopause [WHM included black cohosh, red clover, valerian, valerian root, St John's wort or St John's wort + chaste tree].

- moderate certainty evidence that WHM probably results in little (to no) change in:
  - sexual functioning in people with symptoms of menopause (7 RCTs, 887 participants) [WHM included ginseng, withania (ashwagandha), red clover or ginseng]
  - sleep quality in people with insomnia (5 RCTs, 946 participants) [WHM included chamomile, valerian or kava].

- low certainty evidence that WHM may result in little (to no) change in:
  - clinical improvement in people with inflammatory bowel disease (2 RCTs, 151 participants) [WHM included curcumin]
  - symptoms of anxiety in people with insomnia (2 RCTs, 425 participants) [WHM included kava, valerian or chamomile].

The evidence provides very low certainty of the effect of WHM compared with placebo for 6 critical or important outcomes prioritised for analysis in this overview (across 4 conditions: menstrual conditions, symptoms of menopause, depression and acne). For these outcomes, the true effect is probably markedly different from the estimated effect, with more studies needed to determine the true effect. There were 2 conditions assessed in this review where the effect of using WHMs is unknown (reflux and dermatitis/eczema) due to a lack of meaningful data.

Of the 104 outcomes prioritised as critical or important in this overview, there were no studies found reporting on 43 of those outcomes and therefore, the effect of WHM on these outcomes is unknown. The effect of WHM for 27 outcomes across 4 conditions was not assessed due to the volume of evidence. There are numerous systematic reviews examining the effect of WHM on these conditions, but preliminary data suggests the results are limited to one or 2 outcomes per condition.

Compared with inactive control (no intervention, waitlist, usual care [if inactive]), there were no results found for the majority of conditions. For 2 populations (IBD, menstrual conditions) the evidence was very uncertain.

Compared to active control, results for one condition show that WHM (St John's wort) is probably comparable to antidepressants for improving symptoms of depression in people with depression. Results for all other conditions versus active control were listed but not assessed because they did not meet prespecified criteria.

An assessment of harms of WHM was not conducted for this overview, as it was out of scope of this overview to assess adverse effects of WHM.

Overall, the evidence suggests that WHM probably provides people with some benefit for a range of outcomes considered critical or important by the NTWC, when compared with placebo. There remain many outcomes for which the benefits are unknown.

Limitations

This overview is limited to analysis of conditions prioritised by NTWC, who were guided by relevant patient and/or practitioner reported Australian survey data (where available) and expert advice from NTREAP during the prioritisation process, therefore this report may not cover all the reasons people seek to use WHMs. Because of the large volume of evidence, it was not feasible to consider the evidence regarding 4 of the 16 prioritised conditions (diabetes, impaired glucose tolerance, metabolic syndrome, upper respiratory tract infections). The NTWC was not involved in selection of which prioritised conditions were completed versus not completed (see NHMRC process report for additional information).

The outcomes assessed in this overview were limited to those deemed critical or important by NTWC for each priority condition. This meant that most conditions were limited to evidence that assessed 1 to 3 of the critical or important outcomes, with two conditions (reflux and dermatitis/eczema) having no useable evidence for critical or important outcomes.

Examination of the effectiveness of WHMs compared with other active interventions was not conducted, except in one condition, due to the wide variety of active comparators, outcomes, and conditions across these studies. It is unknown whether the results of these studies would influence the overall conclusions of this overview.

An additional limitation of this overview is that it has focused on individual herbal medicines, rather than Western herbalism as a health service because of the lack of evidence for the latter. Evidence was synthesised for herbs which met the criteria, but sub-group analysis by single or combination of herbs was generally not conducted. Clinical herbalists are trained to create unique herbal prescriptions for patients, and, as with many complementary therapies, herbalism applies a holistic approach to healthcare, and is often used in conjunction with conventional medicine (6). Whether the individual herbs identified in the primary studies for a condition correlate with that typically prescribed by Western herbalists in Australia is not known. As per protocol, detailed descriptions and follow-up about the herbal preparation (e.g., liquid extracts, herbs, tablet or capsule) used within the primary studies was not pursued.

Conclusions

The evidence provides moderate to low certainty that using WHMs is more effective than not using WHMs for many of the prioritised conditions and outcomes assessed in this review. For a few conditions and outcomes, the evidence provides moderate to very low certainty that using WHMs has little (to no) benefit.

1 Background

In 2015, a review of Western herbalism as a health service commissioned by NHMRC found no clear evidence demonstrating its efficacy in treating any clinical condition (6). The 2015 Overview was underpinned by an overview of systematic reviews that focused solely on the effects of Western herbalism as a health service and were published in the English language between 2008 to May 2013. Systematic reviews examining the therapeutic effects of individual herbs were excluded, as were systematic reviews of Chinese and Ayurvedic herbal medicines. In this Overview, the evidence evaluation was not limited by publication date and a broader, more comprehensive search of the literature was undertaken. Specifically, individual herbal medicines on List A of the core herbal medicines used by the Naturopaths & Herbalists Association of Australia (NHAA; previously National Herbalists Association of Australia), a peak professional association representing appropriately qualified Western herbalists and naturopaths using herbal medicines as their primary treatment modality, were included as were combination herbal medicines that included *at least 1* herb from List A, in combination with other herbal ingredients listed on the Therapeutic Goods Administration (TGA) permissible ingredients list. The updated review also included studies that assessed these core herbal medicines for primary prevention. Like the 2015 Overview, systematic reviews evaluating the effectiveness of Chinese and Ayurvedic herbal medicines were excluded, as these remain outside the scope of this review. Eligible comparisons were Western herbal medicines (WHMs) (individual or combination) versus placebo, WHMs (individual or combination) versus inactive control (no intervention) and WHMs (individual or combination) versus other interventions. Studies not published in the English language were not translated, and databases in languages other than English were not searched.

1.1 Description of the condition

Western herbalism is the main form of herbal medicine practised in Australia (7, 8). A Western herbalist engages in extemporaneous compounding of herbs for therapeutic purposes for individuals under their care (8). Today, the practice of Western herbalism includes a holistic treatment framework based on treating individuals within a wider social, emotional, economical, spiritual and cultural framework and, like naturopathy, adherence to the principle of 'first do no harm' (9). Western herbalists may practise out of various settings including the home, clinical practices and multimodality centres. A survey of Western herbalists in Australia indicated that most practitioners (97%) have access to a herbal dispensary within their clinic (10).

Western herbalism is practised for a range of reasons to improve general health and wellbeing, as well as to treat a variety of clinical and preclinical conditions. Brief summaries of the populations and conditions identified and prioritised for inclusion are provided in Section 4.

1.2 Description of the intervention

Western herbalism is a traditional system of plant-based medicine derived primarily from Europe, the United Kingdom and North America (9). While medicinal plants from other herbal traditions, such as Traditional Chinese Medicine and Ayurvedic Medicine can be utilised by Western herbalists, the clinical application of Western herbalism is distinct from these traditions. Western herbal medicine uses plants and plant material to create medicines to help prevent or treat various illnesses. These materials may use some or all parts of a plant such as flowers, roots, stems and rhizomes, fruits and seeds, leaves and bark. WHMs are administered in various preparations including liquid herbal extracts such as tinctures or fluid extracts, oral tablets or capsules, or through topical application, for example, via poultices, creams and pessaries. Most commonly, liquid herbal extracts are prepared using an alcohol solvent, however, glycerol can be used as an alternative, when alcohol-based preparations may not be appropriate (e.g. when prescribing to children). Medicinal herbs can also be extracted in water, and this is commonly referred to as "tea" (9).

In Australia, the regulation of herbal medicines differs depending upon the form, preparation and dosage of the herbal medicine. The TGA regulates some medicinal herbal products (tablets, capsules and liquid extracts), including through a list of permissible ingredients for products listed on the Australian Register of Therapeutic Goods (ARTG). Others, such as raw plant materials (dried or fresh) used in teas, are unregulated beyond the guidelines applied to all food substances (8, 9); with the exception of herbal medicines listed as a scheduled substance on the Australian poisons standard (11).

A survey of Western herbalists in Australia indicated that the most common preparation of herbs prescribed was liquid extracts (90%), followed by dried preparations such as teas (4.3%) and tablets and capsules (3.8%) (10). These preparations are usually dispensed as either an individualised mixture of one or multiple herbs or dispensed as proprietary formulae such as premanufactured tablets/capsules. Individual consumers also have access to some premanufactured herbal products through pharmacies, supermarkets and health food stores (10).

1.3 How the intervention might work

It is thought that chemical constituents found in plants used for herbal medicine act in a similar manner to pharmaceutical ingredients, noting that some pharmaceutical ingredients were originally derived from plants (e.g. salicylic acid in aspirin). Like pharmaceutical ingredients, the chemical constituents in medicinal plants are thought to work on a cellular level within the body. However, unlike a pharmaceutical medicine, which often uses purified or manufactured chemical constituents, herbal medicine utilises the 'whole plant' inclusive of the variety of chemical constituents present in its natural form. Western herbalists therefore use unrefined plant extracts (i.e. fluid extracts, teas, creams etc.) containing several different chemical constituents which are thought to work together synergistically, suggesting that the effect of the 'whole plant' is greater than the sum total of the effects of its individual constituents (12). Western herbalists also claim that toxicity is reduced when 'whole plants' are used instead of purified chemical constituents. Western herbalists claim that this synergy also applies to combinations of plants and claim that combining herbs improves clinical efficacy and reduces adverse effects (12).

Western herbalism emphasises the effects of herbs on individual body systems, with the aim of treating the underlying cause of disease. Herbs may be used for, but not limited to, their supposed anti-inflammatory, haemostatic, expectorant, antispasmodic and immuno-stimulatory properties.

1.4 Why it is important to do this review

In Australia, complementary therapies, including Western herbalism, are most often used in conjunction with conventional medicine and other strategies for maintaining good health and wellness. For this reason, it is important to synthesise the evidence for the effectiveness of WHMs, to enable consumers, health care providers and policy makers to make informed decisions about care. The Australian Government will use this review to assist in deciding whether to reinclude Western herbalism as eligible for private health insurance rebates.

The 2015 Overview identified no systematic reviews containing evidence evaluating Western herbalism as a health service. The review noted that while there is a large body of research on the effects of individual herbal agents and remedies, the study of the real life practice and outcomes of herbalism as a health service is a relatively new area of research that has yet to be addressed in systematic reviews (6).

2 Objectives

To conduct an overview of systematic reviews to evaluate the effectiveness of WHMs in individuals with a described injury, disease, medical condition or preclinical condition, including disease prevention in at-risk individuals. The overview will compile the evidence from systematic reviews of RCTs and quasi-RCTs.

The questions for the overview were as follows:

1. What is the effectiveness of WHM compared to placebo on outcomes considered critical or important among individuals with any condition, pre-condition, injury or risk factor?
2. What is the effectiveness of WHM compared to an inactive control (no intervention, waitlist or usual care [if considered inactive]) on outcomes considered critical or important among individuals with any condition, pre-condition, injury or risk factor?
3. What evidence exists examining the effectiveness of WHM compared to active comparators (including usual care if considered active) on outcomes considered critical or important among individuals with any condition, pre-condition, injury or risk factor?

The intent is to evaluate the evidence representative of the populations (or conditions) commonly seen by Western herbalists in Australia, the intervention(s) commonly used by the herbalists, and outcomes that align with the reasons why people use Western herbs and/or herbalists prescribe WHMs.

Table 1 lists the populations (or conditions) identified and considered in this overview. A prespecified prioritisation process aimed at making best use of the available evidence is described in Appendix A6.

Prioritised populations are listed below, grouped into similar “umbrella” populations groups:

- Digestive disorders
    - Inflammatory bowel diseases
    - Irritable bowel syndrome
    - Gastro-oesophageal reflux disease
- Gynaecological/reproductive
    - Menstrual conditions (e.g. endometriosis, amenorrhea, dysmenorrhoea etc.)
    - Premenstrual disturbances
    - Menopause (symptoms of)
- Nervous system
    - Anxiety (incl. symptoms and disorders)
    - Depressive/mood disorders
    - Insomnia
- Endocrine/metabolic
    - Diabetes
    - Impaired glucose tolerance
    - Metabolic syndrome
- Immune system
    - Fatigue conditions (post viral fatigue, ME/CFS etc.)
    - Upper respiratory tract infections
    - Dermatitis & eczema
    - Acne

3 Methods

Methods used to conduct the evidence evaluation were based on that described in the *Cochrane Handbook for Systematic Reviews of Interventions* (13) and relevant sections in the Joanna Briggs Institute Reviewer's manual (14). Covidence (www.covidence.org), a web-based platform for producing systematic reviews, was used for screening citations and recording decisions made. EndNote and Microsoft Excel were used for managing citations and data extraction, respectively. Where appropriate, RevMan 5.4 (15) was used for the main analyses and GRADEpro GDT software (www.gradepro.org) was used to record decisions and derive an overall assessment of the certainty of evidence for each outcome guided by GRADE methodology (5).

The criteria for determining the eligibility of reviews were predefined, with the approved protocol registered on the international prospective register of systematic reviews (PROSPERO: CRD42021243337).

Eligible herbs were the individual herbal medicines on List A of the core herbal medicines used by the NHAA for inclusion in the Western herbal medicine curriculum (See Appendix A8), or combination herbal preparations that include at least one herb from List A in combination with other herbal medicines listed on the TGA list of permissible ingredients. Specific herb-populations pairings were not required for inclusion.

Eligible reviews were assigned to an appropriate International Classification of Disease (ICD-11) category based on the primary clinical condition(s) assessed in the review. Reviews that were outcome focused (i.e. included studies in various populations), were listed as umbrella reviews, with each condition assessed within the primary studies of the review listed.

Populations and up to 7 critical or important outcomes were prioritised to inform the data synthesis for the systematic review on the effects of WHMs for preventing and treating health conditions. Throughout the population and outcome prioritisation process, NTWC remained blinded to the screening results (i.e. number of studies identified) and characteristics of included studies (e.g. study design, size, quality) to prevent any influence on decision-making (see **Appendix A6**). For prioritised conditions, the review quality was assessed, appropriate data were extracted into data extraction tables, and the results summarised into appropriate categories according to identified populations, conditions and comparators. Within each condition, eligible reviews are listed according to the publication year (more recent first). If there were multiple reviews published in the same year, they are ordered alphabetically within that year.

Summary of Findings tables included results for up to 7 critical or important outcomes prioritised by NTWC, who were guided by the GRADE framework (see Appendix A6.2 and Appendix B4).

Further details on the methods and approach used to conduct the evidence evaluation are provide in Appendix A and B of the Technical Report, which outline the following:

- Appendix A1 search methods
- Appendix A2 search strategy
- Appendix A3 search results
- Appendix A4 review selection criteria
- Appendix A5 selection of reviews (inclusion decisions)
- Appendix A6 refining the research questions
- Appendix A7 summary of screening results
- Appendix A8 list of core herbal medicines
- Appendix B1 overlap tables
- Appendix B2 critical appraisal and risk of bias process
- Appendix B3 data extraction processes
- Appendix B4 data analysis and synthesis
- Appendix B5 evidence statements

4 Results

4.1 Description of studies

4.1.1 Flow of studies

The literature was searched on 22 April 2021 to identify relevant studies published from database inception to the literature search date. Search details and results of the search are provided in **Appendix A1 – A5** and application of the study selection criteria are provided in **Appendix C1** and **Appendix C2**.

A PRISMA flow diagram summarising the search and screening results is provided in Figure 1. The PRISMA flow diagram shows the number of citations at each stage of search and screening process, including: the initial search; studies considered irrelevant based on the title and/or abstract; studies found not to be relevant when reviewed at full text; studies which met the eligibility criteria for inclusion in the review and the number of studies that were in considered in the analysis for prioritised conditions.

The search retrieved 920 citations corresponding to 850 systematic reviews that were eligible for inclusion. There were 4 additional systematic reviews (not retrieved in the search) that were identified and included from the Department's public call for evidence (see Included studies), the remaining studies provided from the Department's call were already identified in the search and screened for eligibility. A further 199 reviews are awaiting classification (see Studies awaiting classification) and 39 protocols for reviews were registered (see Ongoing studies).

4.1.2 Excluded studies

There were 875 citations screened at full text that were excluded for not meeting the reviews eligibility criteria. Of these, 217 reviews were of an intervention(s) that was out of scope (e.g. focused on nutraceuticals, pharmaceuticals or herbs not on List A), 245 had a study design out of scope (e.g. the systematic review did not include RCTs or the review was not underpinned by a systematic search), 180 were a publication type out of scope (e.g. were opinion pieces, editorials or commentaries, or were reviews that focused on pharmacokinetics or pharmacodynamics of the intervention), 17 reviews were in a population out of scope (e.g. healthy participants not at risk), 14 reviews were of outcomes out of scope (e.g. focus was toxicity or cost). As per Cochrane guidelines, details of citations which are likely to be considered eligible but are not, are presented in **Appendix C1**. Note that some studies may have been out of scope for more than 1 reason, but only 1 reason is listed for each.

4.1.3 Studies awaiting classification

Completed reviews identified as potentially eligible for inclusion that could not be retrieved, translated or provided insufficient or inadequate data, are listed in the *Characteristics of studies awaiting classification* tables (see **Appendix C4**). This includes 42 conference proceedings with incomplete information about the study (**Appendix C4.1**), 113 systematic reviews published in languages other than English (**Appendix C4.2**) that are possibly eligible for inclusion (pending translation into English), and 44 reviews that were not able to be retrieved (**Appendix C4.3**).

Among the 199 systematic reviews awaiting classification, there were 67 reviews that covered a priority population (43 were in a language other than English). The reviews appeared comparable to those included in the evidence synthesis with respect to the interventions and outcomes assessed.

4.1.4 Ongoing studies

Ongoing reviews that did not have published results at the time of the search are listed in the *Characteristics of ongoing studies* table (see **Appendix C5**). There were 39 reviews that were registered or had a published protocol. Among these, 11 reviews covered a priority population and appeared comparable to reviews included in the evidence synthesis with respect to the interventions and outcomes assessed.

4.1.5 Included studies

There were 854 systematic reviews identified as eligible for inclusion in the overview (see Figure 1). After prioritisation of the populations (or conditions) considered most relevant to the practise of Western herbal medicine in Australia (see **Appendix A6.1**), 402 reviews were considered in the evidence evaluation (qualitative synthesis). Because of the large volume of evidence, it was not feasible to complete critical appraisal and synthesis for 4 of the 16 prioritised conditions (diabetes, impaired glucose tolerance, metabolic syndrome, 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 (see 4.11, 4.12, 4.14 and Appendix D). The NTWC was not involved in selection of which prioritised conditions were completed versus not completed (see NHMRC process report for additional information).

An overview of the conditions identified and included in this overview is provided in Table 1.

For the main comparisons, systematic reviews that included RCTs comparing WHM with either a placebo or an inactive control (no intervention, waitlist or usual care, if considered inactive), were considered for quantitative synthesis. Those that included NTWC prioritised critical and important outcome domains and measures, were included in the final analysis. The prioritised outcome domains are highlighted in a blue box in **Appendix F1**. Systematic reviews that included RCTs comparing WHM with other active comparators are included in qualitative descriptions in the report, but results from these studies were not included in the main report, except in the case of depression because the comparator was sufficiently homogenous across studies to support synthesis and the comparator represents an accepted, evidence-based 'gold standard' of care for the population in question.

There were 452 systematic reviews that met the eligibility criteria for this review but were not included in the evidence evaluation. This is because they were either conducted in populations (or conditions) not prioritised by NTWC for analysis or synthesis (396 reviews) or they were conducted in populations that were of lower priority (56 reviews). These systematic reviews are listed in an inventory titled *Citation details of systematic reviews of low and non-priority populations* (**Appendix C3**).

Appendix D provides descriptions of the included reviews, including a summary of the PICO criteria, a summary of the critical appraisal (quality) assessment and results of the data synthesis for the main comparison. Detailed descriptions of the included systematic reviews and the primary studies found within can be found in **Appendix E1**.

Figure 1 Literature screening results: Western herbal medicines, systematic reviews

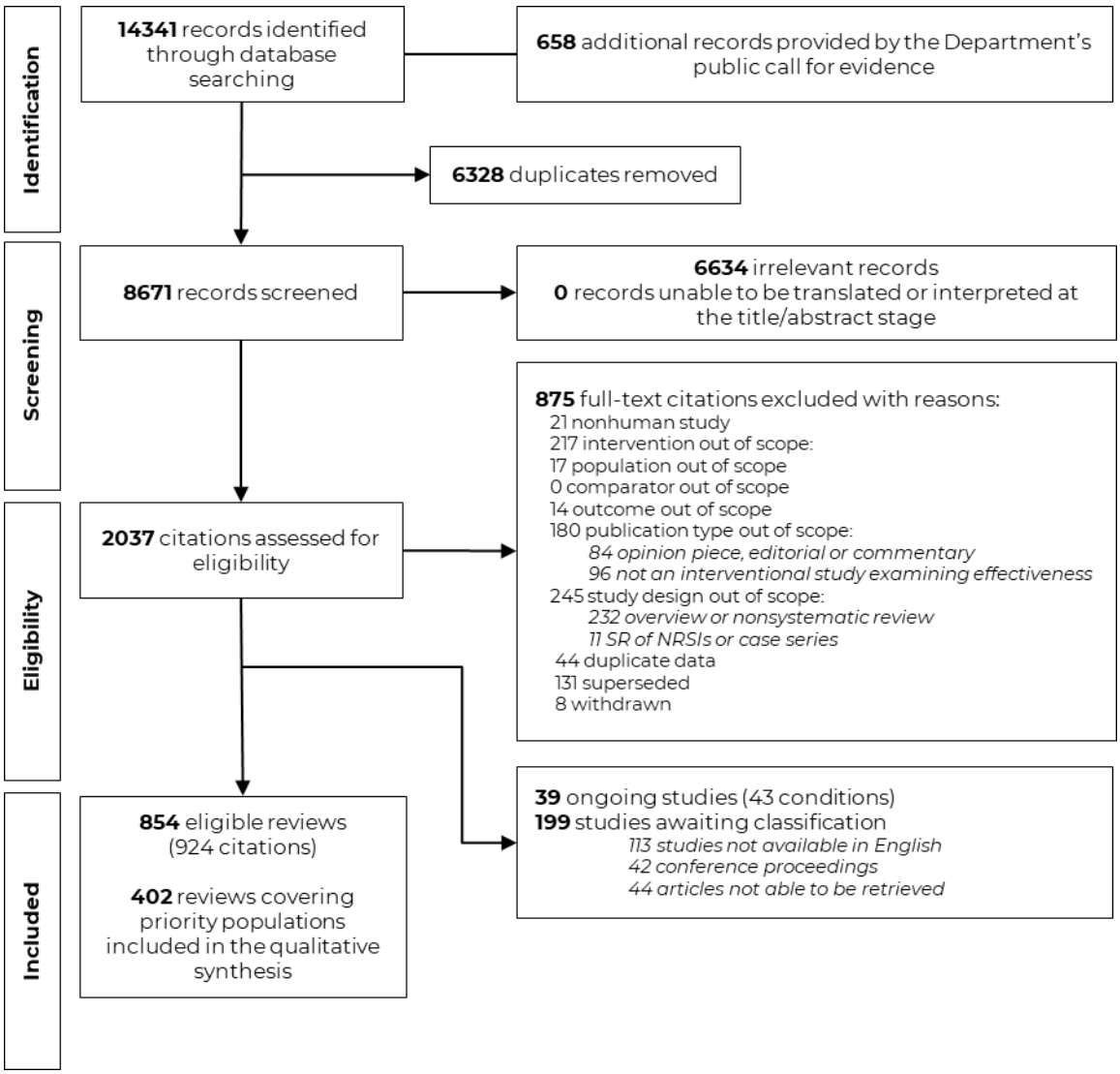


Table 1 List of populations (conditions) identified and considered in this review

ICD-11	POPULATION	# reviews including studies in the population		
		No	Low priority	High priority
01 Certain infectious and parasitic diseases				
	Anogenital warts	2		
	Athlete's foot	1		
	Candidiasis	2		
	Herpes	1		
	Herpes	2		
	HIV	3		
	Tuberculosis	5		
	Viral hepatitis	6		
02 Neoplasms				
	Cancer (inclusive of cancer prevention, cancer fatigue, cancer pain, and insomnia, radiotoxicity or nausea/vomiting associated with cancer) Cancers covered include: blood, breast, colorectal, gastrointestinal, head and neck, liver, lung, ovarian, prostate, skin & stomach.	77		
03 Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism				
	platelet aggregation	1		
	Thalassaemia	2		
04 Diseases of the immune system				
	Chronic fatigue			**5**
	Systemic lupus erythematosus	3		
05 Endocrine, nutritional and metabolic diseases				
	Diabetes			**163**[b]
	Dyslipidaemia	13		
	Hashimoto's disease		4	
	Hypercholesterolaemia	51		
	Hyperlipidaemia	1		
	Hypothyroidism		1	
	Impaired glucose tolerance			**15**[b]
	Latent hyperprolactinemia	1		
	Metabolic syndrome			**70**[b]
	Overweight/obese	89		
	Polycystic ovary syndrome		18	
06 Mental and behavioural disorders				
	Adjustment disorder	1		
	Anxiety disorders			**36**

ICD-11	POPULATION	# reviews including studies in the population		
		No	Low priority	High priority
	Symptoms of anxiety			**6**
	Bodily distress disorders	2		
	Mood disorder, depression including bipolar			**56**
	Neurocognitive decline, inclusive of Alzheimer's and nervous impairment	59		
	Neurodevelopmental disorders	10		
	Obsessive compulsive disorders	8		
	Post-traumatic stress disorder	1		
	Schizophrenia	24		
	Smoking cessation	1		
	Substance disorders	4		
07 Sleep-wake disorders				
	Bruxism	2		
	Insomnia			**15**
	Restless legs syndrome	1		
	Sleep disturbance		7	
08 Diseases of the nervous system				
	Cerebrovascular diseases	6		
	Epilepsy	1		
	Migraine	4		
	Multiple sclerosis	7		
	Neuropathic pain	1		
	Parkinson's disease	3		
	Polyneuropathy	3		
	Post viral olfactory dysfunction	1		
	Stroke (recovery)	3		
	Tardive dyskinesia	3		
09 Disease of the visual system				
	Blepharitis	1		
	Diabetic retinopathy	2		
	Dry eye syndrome	1		
	Glaucoma	4		
	Macular degeneration	2		
	Ocular hypertension	1		
10 Diseases of the ear or mastoid process				
	Hearing loss	1		

ICD-11	POPULATION	# reviews including studies in the population		
		No	Low priority	High priority
	Otitis media	2		
	Tinnitus	4		
11 Diseases of the circulatory system				
	Angina	6		
	Cardiovascular disease	2		
	Claudication, intermittent	1		
	Coronary artery disease	30		
	Heart failure	3		
	Hypertension	43		
	Mitral valve disease	1		
	Myocardial infarction	4		
	Peripheral artery disease	9		
	Raynaud's syndrome	2		
	Venous insufficiency	8		
12 Diseases of the respiratory system				
	Acute respiratory distress syndrome	1		
	Asthma		10	
	Bronchitis	2		
	Chronic obstructive pulmonary disease	3		
	Cystic fibrosis	1		
	Idiopathic pulmonary fibrosis	1		
	Upper respiratory tract infection			**28** [b]
13 Diseases of the digestive system				
	Anal fissure	1		
	Constipation (children, hospital, palliative care, postpartum)		13	
	Dental conditions (incl. Caries, Gingivitis. Periodontitis	13		
	Dumping syndrome	1		
	Functional Dyspepsia		3	
	Gastritis	4		
	Gastro-oesophageal reflux disease			**1**
	H. pylori infection &/or stomach ulcers	5		
	Haemorrhoids	1		
	Hepatic fibrosis or cirrhosis	6		
	Infantile colic	2		
	Inflammatory bowel diseases			**26**

ICD-11	POPULATION	# reviews including studies in the population		
		No	Low priority	High priority
	Irritable bowel syndrome			**19**
	Non-alcoholic fatty liver disease	50		
	Oral ulcerative disorders, Oral submucous fibrosis, Oral leukoplakia	12		
	Small intestinal bacterial overgrowth		1	
	Steatosis	2		
14 Diseases of the skin				
	Acne			**5**
	Alopecia	7		
	Dermatitis & eczema			**2**
	Keratosis	2		
	Onychomycosis	1		
	Oral lichen planus	13		
	Pigmentation	5		
	Pruritus (including Uraemic pruritis)	6		
	Psoriasis		12	
	Radiodermatitis, cancer	2		
15 Diseases of the musculoskeletal system or connective tissue				
	Arthropathies	62		
	Back pain	6		
	Fibromyalgia	3		
	Osteopathies	2		
16 Diseases of the genitourinary system				
	Amenorrhea			**1**
	Benign prostatic hyperplasia	10		
	Certain specific disorders of breast	3		
	Chronic kidney disease	14		
	Dysmenorrhoea			**11**
	Infertility		14	
	Oligozoospermia	2		
	Menopause			**87**
	Menstruation			**3**
	Premenstrual disturbances			**12**
	Primary vesicoureteral reflux	1		
	Urinary tract infection	12		
17 Conditions related to sexual health				

ICD-11	POPULATION	# reviews including studies in the population		
		No	Low priority	High priority
	Erectile dysfunction	14		
	Sexual dysfunction	5		
18 Pregnancy, childbirth or the puerperium				
	Breastfeeding		7	
	Childbirth	3		
	Postpartum	2		
	Pre-eclampsia	1		
	Pregnancy	13		
	Pregnancy, nausea/vomiting	9		
20 Developmental anomalies				
	Neurofibromatosis	1		
21 Symptoms, signs or clinical findings, not elsewhere classified				
	Digestive complaints		3	
	Halitosis	1		
	Postoperative, nausea/vomiting	4		
	Postoperative, pain	3		
	Postoperative, wound healing	2		
	Radiculopathy	1		
	Taste disorder	1		
22 Injury, poisoning or certain other consequences of external causes				
	Altitude sickness	4		
	Wound healing (burns, postoperative, pressure ulcer)	5		
	Pruritus, chemical	1		
	Spinal cord injury	1		
24 Factors influencing health status or contact with health services				
	Abdominal aortic aneurysm repair	1		
	Care involving dialysis	3		
	Postoperative, nausea/vomiting	1		
	Preoperative	1		
	Stress		6	
	TOTAL[a]	**99**	**867**	**564**

Abbreviations: ICD-11, International Statistical Classification of Diseases and Related Health Problems 11th Revision;

a. Numbers reflect the population considered within the systematic review and not the number of included reviews (i.e. umbrella reviews that considered more than one population are counted more than once).

b. critical appraisal and synthesis not completed. See section 4.1.5 Included studies.

4.2 Inflammatory bowel disease

4.2.1 Description of the condition

Inflammatory bowel disease (IBD) encompasses a group of conditions characterised by chronic inflammation in the intestinal tract. The most common chronic immune-mediated IBDs are Crohn's disease and ulcerative colitis (16). Crohn's disease is characterised by inflammation of the full thickness of the bowel wall and primarily affects the ileum and colon but may involve other parts of the digestive tract (17). Ulcerative colitis causes inflammation of the inner lining of the colon and rectum (18). About 5-15% of patients with IBD affecting the colon have features of both conditions (19). The cause of IBD remains unknown, with genetic, infectious and environmental factors assumed to play a role in dysregulating intestinal immunity, leading to gastrointestinal injury (19). Common symptoms of IBD include bloody diarrhoea, abdominal pain, constipation and weight loss.

The global incidence of IBD has rapidly accelerated as the prevalence has risen to more than 0.3% of the population in several nations, including North America, Europe and Australia (20). There are approximately 75,000 Australians living with IBD and over 1,622 new cases diagnosed each year (776 with Crohn's disease and 846 with ulcerative colitis) (19). Diagnosis can occur at any age, but commonly occurs during adolescence and early adulthood, leading to lifelong management and treatment (19). The disease burden for individuals living with IBD is high, and can involve multiple hospitalisation, the need for multidisciplinary care, significant psychological impacts and inadequate responsiveness to disease deterioration and reduced quality of life (21). In 2012, total hospital costs attributed to IBD were estimated to be $100 million, which continues to rise as prevalence continues to accelerate (21).

Management of IBD varies according to disease severity and other factors (e.g. age at diagnosis) but the main goal of therapy is centred on achieving clinical and/or patient-reported remission[a] using immunomodulators, steroids, biologic agents, or surgical interventions (18, 19, 22). Other treatments may focus on relieving acute disease symptoms, improving pain management or preventing hospitalisation. Guidelines do not routinely recommend complementary therapies for IBD noting the limited evidence-base; but, due to adverse effects associated with long-term use of pharmacological therapies, many people with IBD seek out complementary therapies (including herbal and dietary supplements) to provide symptomatic relief (e.g. peppermint oil for bloating, abdominal pain) or to assist with inducing or maintaining remission by promoting anti-inflammatory effects (e.g. curcumin) (19, 22, 23).

4.2.2 Description of reviews

There were 26 citations (24-49) corresponding to 26 systematic reviews (Ghassab-Abdollahi 2021, Montazeri 2021, Liu 2021, Morvaridzadeh 2021, Ardiana 2020, Chandan 2020, Coelho 2020, Goulart 2020, Goulart 2020a, Hallajzadeh 2020, Jalali 2020, Mohit 2020, Zheng 2020, Tavakoly 2019, Grammatikopoulou 2018, Iqbal 2018, Restellini 2017, Kafil 2017, Kim 2017, Schneider 2017, Simadibrata 2017, Langhorst 2015, Ng 2013, Rahimi 2013, Kumar 2012, Ernst 2008) identified in the literature search that evaluated the effectiveness of WHMs in people with IBD. There were no additional reviews identified in the Department's public call for evidence (see Appendix C2), 3 systematic reviews (50-52) awaiting classification (see Appendix C4) and one ongoing review (53) (see Appendix C5).

A summary of the PICO criteria of the 26 eligible systematic reviews is provided in Appendix D1.1.1.

The populations eligible for inclusion in the reviews were participants with ulcerative colitis (Chandan 2020, Goulart 2020, Zheng 2020, Grammatikopoulou 2018, Iqbal 2018, Simadibrata 2017), Crohn's disease (Schneider 2017), collagenous colitis (Kafil 2017), or participants with any form of IBD (Liu 2021, Coelho 2020, Goulart 2020a, Restellini 2017, Kim 2017, Langhorst 2015, Ng 2013, Rahimi 2013, Kumar 2012).

[a] e.g. absence of rectal bleeding and return to normal bowel habit in UC or a reduction in inflammatory markers such as C-reactive protein in Crohn's disease

Nine (9) reviews had no population restrictions but searched for studies that focused on the effect of a single herb (Boswellia) for any clinical condition (Ernst 2008) or included studies that measured oxidative stress and/or inflammatory biomarkers as an outcome (Ghassab-Abdollahi 2021, Montazeri 2021, Morvaridzadeh 2021, Ardiana 2020, Hallajzadeh 2020, Jalali 2020, Mohit 2020, Tavakoly 2019).

Seven (7) systematic reviews (Liu 2021, Chandan 2020, Coelho 2020, Goulart 2020, Zheng 2020, Grammatikopoulou 2018, Iqbal 2018) were prioritised for critical appraisal and data extraction as they were published in 2018 or after and presented results in a meta-analysis. Three (3) other reviews (Kafil 2017, Kim 2017, Langhorst 2015) identified additional RCTs and were included in the qualitative synthesise. Review details, including outcome domains and measures, and the risk of bias of eligible RCTs are provided in Appendix F1.

4.2.3 Description of studies

Within the eligible systematic reviews, there were 27 RCTs that met our PICO criteria (see Appendix F1). Of these, 20 RCTs were conducted in people with ulcerative colitis (active or quiescent), 6 RCTs were in people with Crohn's disease and one RCT was in people with collagenous colitis.

An overlap table of the RCTs within the included systematic reviews is shown in Table 2.

The RCTs used different herbs[b] (see Appendix D1.1.1) and doses to either induce or maintain disease remission with the intervention period ranging from 4 weeks up to 12 months. Ten (10) of the 12 identified herbs matched to the Tier 1 herbs included in the Western herbal medicine curriculum for the Digestive system (i.e. most commonly taught in Australian curriculum for this condition; see Appendix A6.3).The studies were conducted in a variety of countries including Canada, China, Cyprus, Germany, Hong Kong, India, Iran, Israel, Japan, Romania, Ukraine, the UK and the US with sample sizes ranging from 20 to 224 participants (total 1613 participants).

There were 22 RCTs that examined the effect of WHM compared with placebo (Kumar 2019, Sadeghi 2019, Sugimoto 2019, Masoodi 2018, Shapira 2018, Banerjee 2017, Kedia 2017, Lang 2015, Rastegarpanah 2015, Singla 2014, Dryden 2013, Sandbom 2013, Suskind 2013, Holtmeier 2011, Shivakumar 2011, Sandbom 2010, Madisch 2007, Omer 2007, Hanai 2006, Langmead 2004, Atkinson 2002, Hallert 1991), usually delivered as an adjunct to standard therapy (e.g. mesalazine, 5- aminosalicylic acid or corticosteroids). Two (2) RCTs (Krebs 2012, Fernandez-Banares 1999) examined the effect of WHM compared with no intervention and 3 RCTs (Langhorst 2013, Tang 2011, Gerhardt 2001) examined the effect of WHM compared with standard therapy (i.e. mesalazine).

Results for the Primary Comparison: WHM versus placebo and Secondary Comparison: WHM versus inactive control (no intervention, waitlist, usual care [if inactive]) are provided in the Summary of Findings tables (see Section 4.2.5). Results for the Tertiary Comparison (versus active comparators) are provided in Appendix F2.

4.2.4 Risk of bias

Risk of bias assessment for the eligible RCTs as summarised by included systematic reviews are provided in Appendix F1.

The reviews by Kim 2017, Kafil 2017 and Coelho 2020 were used to inform the evidence synthesis as they used the Cochrane Collaboration's risk of bias assessment tool (54) to asses bias within the included RCTs and provided the most comprehensive information to make a judgement.

Several of the eligible RCTs (Kumar 2019, Sugimoto 2019, Shapira 2018, Dryden 2013, Suskind 2013, Krebs 2012, Atkinson 2002, Fernández-Bañares 1999) were judged by the included systematic reviews to be at overall high risk of bias.

[b] Including curcumin, boswellia, green tea extract, St Mary's thistle

Table 2 List of included systematic reviews and overlap with eligible RCTs (per outcome): Inflammatory bowel disease

Review ID	Best available [a]	Prioritised outcome domain [b]	Study ID: Kumar 2019	Sadeghi 2019	Sugimoto 2019	Masoodi 2018	Shapira 2018	Banerjee 2017	Kedia 2017	Lang 2015	Rastegarpanah 2015	Singla 2014	Dryden 2013	Langhorst 2013	Sandbom 2013	Suskind 2013	Krebs 2012	Holtmeier 2011	Shivakumar 2011	Tang 2011	Sandborn 2010	Madisch 2007	Omer 2007	Hanai 2006	Langmead 2004	Atkinson 2002	Gerhardt 2001	Fernandez-Banares 1999	Hallert 1991
Liu 2021	†	Patient reported improvement	Y	--	Y	Y	--	Y	Y	Y	Y	Y	Y	--	--	--	--	--	--	--	--	--	--	Y	--	--	--	--	--
Chandan 2020	✓		--	--	--	Y	--	Y	Y	Y	--	Y	--	--	--	--	--	--	Y	--	--	--	--	Y	--	--	--	--	--
Coelho 2020	†		--	Y	--	Y	#	#	Y	Y	--	Y	--	--	--	#	--	--	--	--	--	--	--	Y	--	#	--	--	--
Goulart 2020	✓		--	Y	#	Y	--	#	Y	Y	--	#	--	--	--	--	--	--	--	--	--	--	--	#	--	--	--	--	--
Zheng 2020	✓		--	--	--	Y	--	Y	Y	Y	--	Y	--	--	--	--	--	--	--	--	--	--	--	Y	--	--	--	--	--
Grammatikopoulou 2018	✓		--	--	--	--	--	Y	Y	Y	--	--	--	--	--	--	--	--	--	--	--	--	--	Y	--	--	--	--	--
Iqbal 2018	†		--	--	--	--	--	Y	--	Y	--	Y	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Kafil 2017	†		--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	Y	--	--	--	--	--	--	--
Kim 2017	✓		--	--	--	--	--	--	--	Y	Y	--	Y	--	Y	--	Y	Y	--	--	Y	--	Y	Y	Y	--	--	Y	Y
Langhorst 2015	†		--	--	--	--	--	--	--	--	Y	Y	--	Y	Y	--	Y	Y	--	Y	--	--	Y	Y	Y	--	Y	Y	--
Schnieder 2017	*		--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Simadibrata 2017	*		--	--	--	--	--	--	--	Y	--	Y	--	--	--	--	--	--	--	--	--	--	--	Y	--	--	--	--	--
Ng 2013	*		--	--	--	--	--	--	--	--	--	--	--	--	Y	--	Y	Y	--	--	--	--	Y	Y	Y	--	Y	Y	--
Rahimi 2013	*		--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	Y	--	--	--	--	--	--	--	Y	--
Kumar 2012	*		--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	Y	--	--	--	--	--
Ernst 2008	*		--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	Y	--	--

Abbreviations: RCT, randomised controlled trial

Notes:

a. Best available information means the systematic review meets AMSTAR-2 domains 4, 8, 9, & 11 (see Appendix B1 [Framework for selecting the systematic review from which to extract data]).

b. Only critical or important outcome domains with available data included here (see Appendix D1.1.3)

✓ Systematic review meets (or partially meets) prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

† Systematic review meets (or partially meets) some, but not all, prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).
X Systematic review does not meet prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).
* Systematic review not assessed. A study result is available and reported in another systematic review nominated as the best available evidence.
Y RCT is included in the systematic review, meets our PICO criteria & a study result is reported for the listed outcome measure [result available]
RCT is included in the systematic review, meets our PICO criteria but a study result is not available for the listed outcome measure as the SR did not include it in their data synthesis due to high risk of bias or heterogeneity [data are incomplete; result may be available in another SR]
-- RCT is not included in systematic review.

4.2.5 Summary of findings and evidence statement

4.2.5.1 Primary Comparison (vs placebo)

There were 22 RCTs found by the included systematic reviews that compared WHM with placebo in people with IBD. 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 (no data reported) and one RCT (Hallert 1991) did not report results prior to crossover so were not able to be used in the synthesis.

WHM compared to placebo for Inflammatory bowel disease

Patient or population: Inflammatory bowel disease
Setting: Community
Intervention: WHM (curcumin, green tea extract, boswellia, wormwood, St Mary's thistle, andrographis) delivered as an adjunct to standard therapy
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with WHM				
Clinical improvement assessed with: CDAI, UCDAI or other Scale: range varies (higher is worse) follow-up: range 4 to 24 weeks	-	SMD **0.37 SD lower^** (0.77 lower to 0.04 higher)	-	151 (2 studies) †	⨁⨁◯◯ LOW [a,b,c,d,e]	WHM may result in little to no difference in disease activity in people with IBD.
Clinical response assessed with: CDAI, UCDAI (response rate) Scale: % with change in score by n points follow-up: range 4 to 24 weeks	342 per 1,000	**567 per 1,000** (393 to 824)	**RR 1.66** (1.15 to 2.41)	403 (8 RCTs) ††	⨁⨁◯◯ LOW [a,b,c,e,f]	WHM may result in a clinical response in people with IBD. #
Clinical remission assessed with: CDAI, UCDAI (remission rate) Scale: % achieve score indicating inactive disease follow-up: range 4 to 24 weeks	326 per 1,000	**503 per 1,000** (405 to 620)	**RR 1.54** (1.24 to 1.90)	974 (14 RCTs) †††	⨁⨁⨁◯ MODERATE [a,b,c,e,g]	WHM probably results in maintenance of clinical remission in people with IBD. #
Pain	-	-	-	(0 studies)	-	The effect of WHM on pain in people with IBD is unknown.
HRQoL	-	-	-	(0 studies) **	-	The effect of WHM on HRQoL in people with IBD is unknown.
Emotional functioning	-	-	-	(0 studies) ***	-	The effect of WHM on emotional functioning in people with IBD is unknown.

WHM compared to placebo for Inflammatory bowel disease

Patient or population: Inflammatory bowel disease

Setting: Community

Intervention: WHM (curcumin, green tea extract, boswellia, wormwood, St Mary's thistle, andrographis) delivered as an adjunct to standard therapy

Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with WHM				
Physical functioning	-	-	-	(0 studies)	-	The effect of WHM on physical functioning in people with IBD is unknown.
Stool quality/ frequency	-	-	-	(0 studies)	-	The effect of WHM on stool quality or frequency in people with IBD is unknown.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

^ As a rule of thumb, an SMD of 0.2 represents a small difference, 0.5 is moderate, and 0.8 is a large difference (55).
# A 25% relative risk improvement was considered important (i.e. RR > 1.25).

† Data from 20 RCTs (> 1100 participants) not included here because results were not adequately reported [missing information].
†† Data from 14 RCTs (> 763 participants) not included here because results were not adequately reported [missing information].
††† Data from 8 RCTs (> 192 participants) not included here because results were not adequately reported [missing information].
** Data from 4 RCTs (236 participants) not included here because results were not adequately reported [missing information].
*** Data from one RCT (40 participants) not included here because results were not adequately reported [missing information].

CDAI: Crohn's disease activity index; **CI:** confidence interval; **RR:** risk ratio; **UCDAI:** ulcerative colitis disease activity index; **WHM:** Western herbal medicine

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. Certainty of evidence not downgraded.
b. No serious inconsistency. Certainty of evidence not downgraded.
c. No serious indirectness. The available evidence is in people with inflammatory bowel disease and is directly generalisable to the Australian population with few caveats. The herbs used in the identified studies are comparable to those commonly used in Australia (>80% matched) or could be sensibly applied. Certainty of evidence not downgraded.
d. Serious imprecision. Wide confidence intervals (upper and lower bound overlaps with both large and no important difference). Certainty of evidence downgraded.
e. Publication bias suspected. There is a strong suspicion of non-reporting of results likely related to the *p* value, direction or magnitude of effect. Certainty of evidence downgraded.
f. Serious imprecision. Wide confidence intervals (lower bound overlaps with no important difference). Certainty of evidence downgraded.
g. No serious imprecision. Certainty of evidence not downgraded.

4.2.5.2 Secondary Comparison (vs inactive control)

There were 2 RCTs found by the included systematic reviews that compared WHM with no intervention in people with either Crohn's disease (Krebs 2012[c]) or ulcerative colitis (Fernández-Bañares 1999[d]). The RCTs contributed data relevant to one outcome. The available evidence is summarised below.

WHM compared to inactive control for Inflammatory bowel disease

Patient or population: Inflammatory bowel disease
Setting: Community
Intervention: WHM (wormwood, psyllium seed) delivered as an adjunct to standard therapy
Comparison: Control (no intervention)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Control	Risk with WHM				
Clinical improvement	-	-	-	(0 studies)	-	The effect of WHM on clinical improvement in people with IBD is unknown.
Clinical response	-	-	-	(0 studies)	-	The effect of WHM on clinical response in people with IBD is unknown.
Clinical remission assessed with: CDAI, UCDAI Scale: % achieve set score indicating inactive disease follow-up: range 4 to 52 weeks	553 per 1,000	**1,000 per 1,000** (260 to 1,000)	**RR 1.82** (0.47 to 7.02)	87 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,d,e]	The evidence is very uncertain about the effect to WHM on clinical remission in people with IBD. #
Pain	-	-	-	(0 studies)	-	The effect of WHM on pain in people with IBD is unknown.
HRQoL	-	-	-	(0 studies) **	-	The effect of WHM on HRQoL in people with IBD is unknown.
Emotional functioning	-	-	-	(0 studies) **	-	The effect of WHM on emotional functioning in people with IBD is unknown.
Physical functioning	-	-	-	(0 studies)	-	The effect of WHM on physical functioning in people with IBD is unknown.
Stool quality/ frequency	-	-	-	(0 studies)	-	The effect of WHM on stool quality or frequency in people with IBD is unknown.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
^ As a rule of thumb, an SMD of 0.2 represents a small difference, 0.5 is moderate, and 0.8 is a large difference (55).
# A 25% relative risk reduction/increase was considered important (i.e. RR < 0.75 or RR > 1.25).

** Data from one RCT (20 participants) not included here because results were not adequately reported [missing information].

CDAI: Crohn's disease activity index; **CI:** confidence interval; **RR:** risk ratio; **UCDAI:** ulcerative colitis disease activity index; **WHM:** Western herbal medicine

[c] delivered as an adjunct to corticosteroids

[d] delivered alone or as an adjunct to mesalazine

WHM compared to inactive control for Inflammatory bowel disease

Patient or population: Inflammatory bowel disease
Setting: Community
Intervention: WHM (wormwood, psyllium seed) delivered as an adjunct to standard therapy
Comparison: Control (no intervention)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Control	Risk with WHM				

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanation

a. No serious risk of bias. Certainty of evidence not downgraded.
b. Serious inconsistency. Statistical heterogeneity is high (I^2 = 77%). Certainty of evidence downgraded.
c. No serious indirectness. The available evidence is in people with inflammatory bowel disease and is directly generalisable to the Australian population with few caveats. The herbs used in the identified studies are comparable to those commonly used in Australia and can be sensibly applied. Certainty of evidence not downgraded.
d. Very serious imprecision. Wide confidence intervals (upper and lower bound overlaps with both large and no important difference). Certainty of evidence downgraded 2 levels.
e Publication bias not suspected. Certainty of evidence not downgraded.

4.2.5.3 Tertiary Comparison (vs active control)

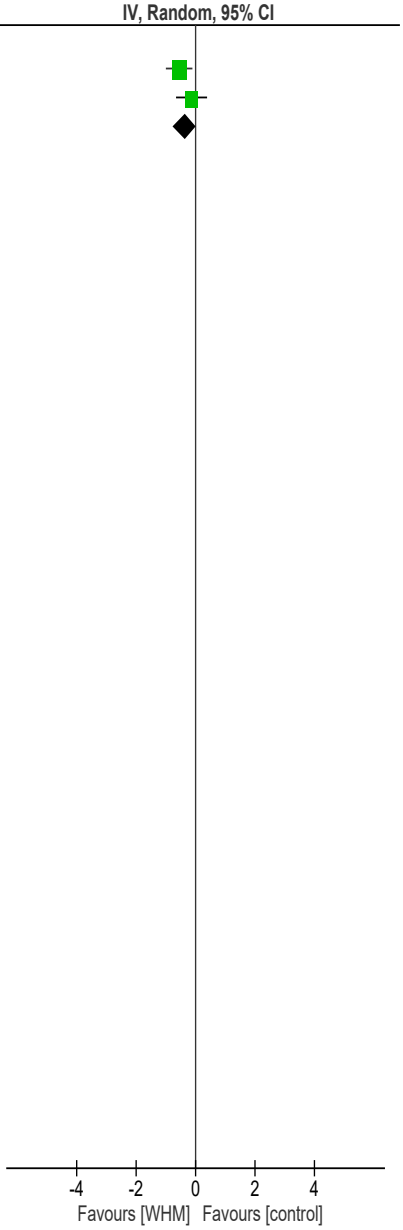
There were 3 RCTs found by the included systematic reviews that compared WHM with active comparators (mesalazine) in people with Crohn's disease (1 RCT) or ulcerative colitis (2 RCTs) and contributed data relevant to at least one critical or important outcome (see Appendix F2).

4.2.6 Forest plots

Outcome results related to people with inflammatory bowel disease are presented in Figure 2 (disease activity index), Figure 3 (clinical response), and Figure 4 (clinical remission).

Figure 2 Forest plot of comparison: WHM vs placebo: Inflammatory bowel disease – disease activity index

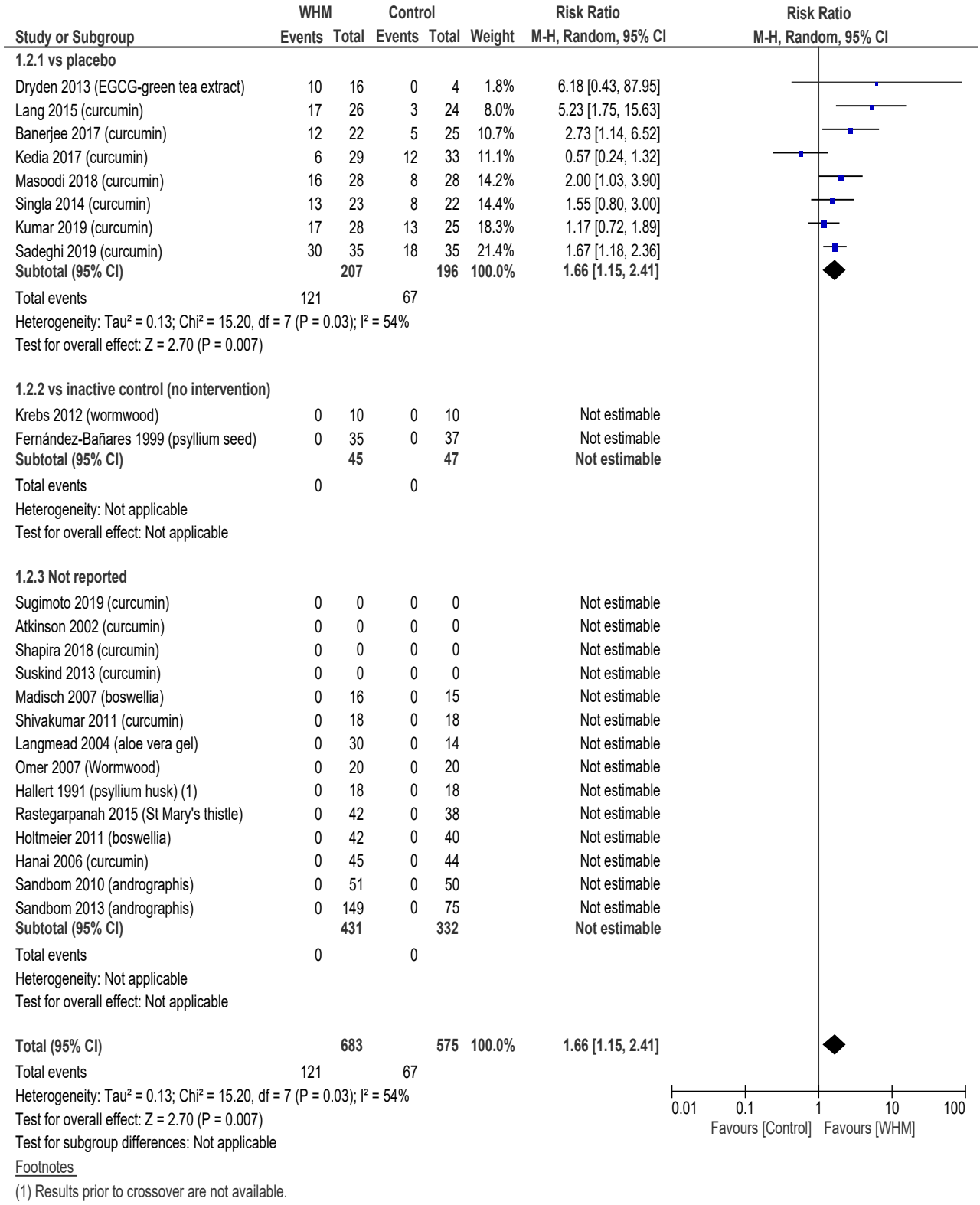
Study or Subgroup	WHM Mean	WHM SD	WHM Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 vs placebo								
Hanai 2006 (curcumin) (1)	1	2	45	2.2	2.3	44	55.2%	-0.55 [-0.98, -0.13]
Kedia 2017 (curcumin) (2)	3.4	3.1	29	3.8	2.8	33	44.8%	-0.13 [-0.63, 0.37]
Subtotal (95% CI)			**74**			**77**	**100.0%**	**-0.37 [-0.77, 0.04]**
Heterogeneity: Tau² = 0.03; Chi² = 1.57, df = 1 (P = 0.21); I² = 36%								
Test for overall effect: Z = 1.76 (P = 0.08)								
1.1.2 vs inactive control (no intervention)								
Fernández-Bañares 1999 (psyllium seed)	0	0	30	0	0	37		Not estimable
Krebs 2012 (wormwood)	0	0	10	0	0	10		Not estimable
Subtotal (95% CI)			**40**			**47**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
1.1.3 Not reported								
Atkinson 2002 (curcumin)	0	0	0	0	0	0		Not estimable
Banerjee 2017 (curcumin)	0	0	22	0	0	25		Not estimable
Dryden 2013 (EGCG-green tea extract)	0	0	15	0	0	4		Not estimable
Hallert 1991 (psyllium husk)	0	0	18	0	0	18		Not estimable
Holtmeier 2011 (boswellia)	0	0	42	0	0	40		Not estimable
Kumar 2019 (curcumin)	0	0	28	0	0	25		Not estimable
Lang 2015 (curcumin)	0	0	26	0	0	24		Not estimable
Langmead 2004 (aloe vera gel)	0	0	30	0	0	14		Not estimable
Madisch 2007 (boswellia)	0	0	16	0	0	15		Not estimable
Masoodi 2018 (curcumin)	0	0	28	0	0	28		Not estimable
Omer 2007 (Wormwood)	0	0	20	0	0	20		Not estimable
Rastegarpanah 2015 (St Mary's thistle)	0	0	42	0	0	38		Not estimable
Sadeghi 2019 (curcumin)	0	0	35	0	0	35		Not estimable
Sandbom 2010 (andrographis)	0	0	51	0	0	50		Not estimable
Sandbom 2013 (andrographis)	0	0	149	0	0	75		Not estimable
Shapira 2018 (curcumin)	0	0	51	0	0	50		Not estimable
Shivakumar 2011 (curcumin)	0	0	18	0	0	18		Not estimable
Singla 2014 (curcumin)	0	0	23	0	0	22		Not estimable
Sugimoto 2019 (curcumin)	0	0	0	0	0	0		Not estimable
Suskind 2013 (curcumin)	0	0	0	0	0	0		Not estimable
Subtotal (95% CI)			**614**			**501**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Footnotes
(1) DAI
(2) UCDAI

Abbreviations: DAI, disease activity index, UCDAI, Ulcerative colitis disease activity index

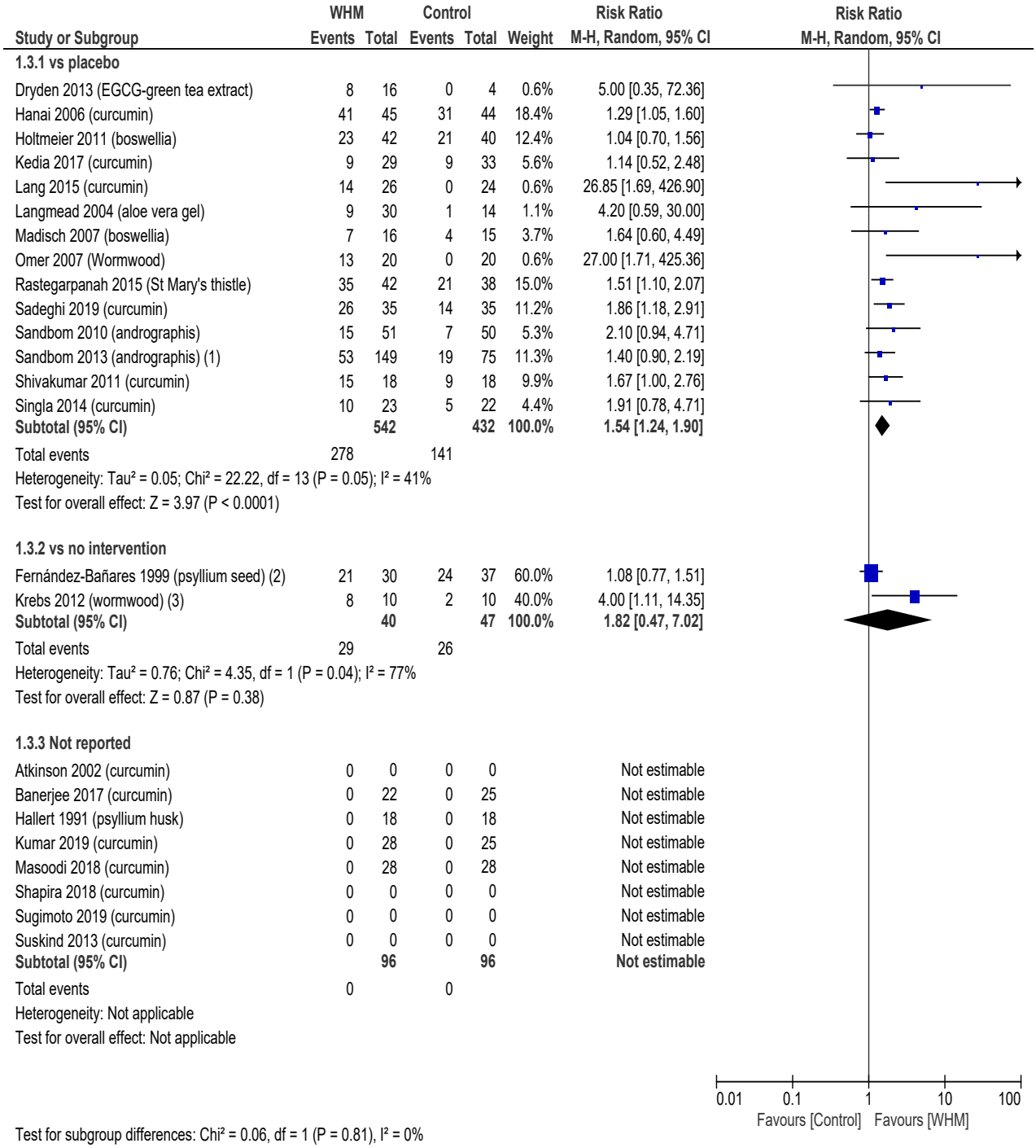
Figure 3 Forest plot of comparison: WHM vs placebo: Inflammatory bowel disease – Clinical response in disease activity (response rate)



Footnotes

(1) Results prior to crossover are not available.

Figure 4 Forest plot of comparison: WHM vs placebo: Inflammatory bowel disease – Clinical remission (remission rate)



Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%

Footnotes

(1) Data from Kim 2017 (inverted)

(2) Data from Kim 2017 (inverted)

(3) Data from Kim 2017 (inverted)

Note: Kim 2017 reports the proportion of participants *who fail to achieve* (or maintain) remission. The data are "inverted" in our evidence synthesis to correlate with other reviews that report the proportion of participants *who achieve* (or maintain) remission.

4.3 Irritable bowel syndrome

4.3.1 Description of the condition

Irritable bowel syndrome (IBS) is a symptom-based condition associated with abdominal pain or discomfort and changes in bowel habits that persist over an extended period. Individuals with IBS also experience bowel sensitivity, causing uneven contractions, pain and bloating (56, 57). IBS presents with similar symptoms to several other gastrointestinal diseases and is often confused with inflammatory bowel disease (IBD), as both IBS and IBD can affect the oesophagus, intestines and stomach (58). General symptoms include abdominal pain, bloating, constipation, diarrhoea, and flatulence (56, 59). The cause of IBS is not well understood; however, altered gut motility, an imbalance of 'good' and 'bad' bacteria and a slightly inflamed or 'leaky' gut are thought to be involved (60). Certain foods may induce IBS symptoms prompting affected individuals to modify their diet (60). Episodes of gastroenteritis, chronic stress and food poisoning may also trigger IBS and worsen IBS in individuals experiencing periods of high stress (59).

Approximately 10-15% of the global population are affected by IBS, with 1 in 5 people experiencing IBS at some time in their lives (56, 59). In Australia, up to 30% of the population are thought to have IBS, which is diagnosed more frequently in females than males (59). IBS is a chronic condition that can substantially reduce the quality of life and work productivity and has been associated with indirect costs (e.g. loss of income), imposing a substantial burden on individuals with IBS (61).

Treatment for IBS typically includes a modified diet (e.g. low FODMAP[e], increased consumption of soluble fibre) combined with symptom management (62). Complementary and alternative therapies that aim to provide anti-inflammatory effects, such as peppermint (*Mentha piperita*) and Psyllium *(Plantago ovata)* are popular herbal medicines used for reducing abdominal pain, inflammation and relieving constipation (61, 63).

4.3.2 Description of reviews

There were 19 citations (64-83) corresponding to 19 SRs identified in the literature search that evaluated the effectiveness of WHMs in people with IBS (Anh 2020, Black 2020, Hawrelak 2020, Tan 2020, Alammar 2019, Hong 2018, Ng 2018, Anheyer 2017a, Korterink 2015, Lakhan 2015, Khanna 2014, Ruepert 2011, Shen 2009, Ford 2008, Huertas-Ceballos 2008, Liu 2006, Grigoleit 2005, Jailwala 2000, Pittler 1998). No additional reviews were identified in the Department's public call for evidence (see Appendix C2). There were 6 reviews awaiting classification (84-89) (see Appendix C4) and one ongoing review (90) (see Appendix C5).

A summary of the PICO criteria of eligible systematic reviews is provided in Appendix D1.2.1.

The populations eligible for inclusion in the reviews were participants with IBS (Black 2020, Hawrelak 2020, Alammar 2019, Hong 2018, Ng 2018, Khanna 2014, Ruepert 2011, Shen 2009, Ford 2008, Huertas-Ceballos 2008, Liu 2006, Grigoleit 2005, Jailwala 2000, Pittler 1998) or participants with functional gastrointestinal disorders (Tan 2020, Anheyer 2017a, Korterink 2015). Two reviews had no population restrictions but searched for studies that focused on the effect of a single herb (ginger) for any clinical condition (Anh 2020) or presented results where pain was measured as an outcome (Lakhan 2015).

Six (6) systematic reviews (Black 2020, Hawrelak 2020, Tan 2020, Alammar 2019, Hong 2018, Ng 2018) were prioritised for critical appraisal and data extraction as they were published in 2018 or after and presented results in a meta-analysis. One other review (Anheyer 2017a) identified an additional RCT and was included in the qualitative synthesis.

Review details, including outcome domains and measures, and the risk of bias of eligible RCTs are provided in Appendix F1.

4.3.3 Description of studies

Within the eligible systematic reviews, there were 40 RCTs that met our PICO criteria (see Appendix F1). Of these, 19 RCTs (Weerts 2019, Cash 2016, Mosaffa-Jahromi 2016[f], Alam 2013, Merat 2009, Cappello 2007,

[e] Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols.

[f] The RCT had a second intervention group (curcumin and fennel oil combination).

Capanni 2005, Kline 2001, Liu 1997, Schneider 1990, Carling 1989, Lawson 1988, Lech 1988, Weiss 1988, Wildgrube 1988, Nash 1986, Dew 1984, Evans 1982, Rees 1979) were focused on the use of peppermint oil to relieve symptoms of IBS. Another 21 RCTs (Portincasa 2016, Shulman 2016, Brown 2015, Storsrud 2015, Tilburg 2014, Bortolotti 2011, Hutchings 2011, Saito 2010, Bijkerk 2009, Davis 2006, Vejdani 2006, Brinkhaus 2005, Bundy 2004, Madisch 2004, Pedersen 1998, Jalihal 1990, Prior 1987, Nigam 1984, Arthurs 1983, Longstreth 1981, Ritchie 1979) examined the effect of a variety of WHMs[g] (see Appendix D1.1.1). Five (5) of the 13 identified herbs (~38%) were matched to the Tier 1 herbs included in the Western herbal medicine curriculum for the Digestive system (i.e. most commonly taught in Australian curriculum for this condition; see Appendix A6.3).

An overlap table of the RCTs within the included systematic reviews is shown in Table 3 (peppermint oil) and Table 4 (WHMs other than peppermint)[h].

All included RCTs examined the effect of WHM compared with placebo and were conducted in a variety of countries including Bangladesh, China, Germany, India, Iran, Italy, Sweden, the Netherlands, UK or the US with participants generally diagnosed using the Rome I-IV criteria, Manning diagnostic criteria, Kruis criteria or via detailed clinical examination. Sample sizes ranged from 20 to 208 (total 2040 participants). Several RCTs had crossover designs with a washout period defined as recurrence of active IBS symptoms (Dew 1984, Rees 1979), after at least 1 week (Carling 1989, Schneider 1990) or not reported (Hutchings 2011).

Results for the Primary Comparison: WHM versus placebo are provided in the Summary of Findings tables (see Section 4.3.5). Additional details are provided in Appendix F2. There were no studies found for the Secondary Comparison: WHM versus inactive control (no intervention, waitlist, usual care [if inactive]) and no results available for the Tertiary Comparison (versus active comparators).

4.3.4 Risk of bias

Risk of bias assessment for the eligible RCTs as summarised by included systematic reviews are provided in Appendix F1.

All reviews used the Cochrane Collaboration's risk of bias assessment tool (54) to assess bias within the included RCTs and provided comprehensive information to make a judgement.

Several of the eligible RCTs were consistently judged by the included systematic reviews to be at high risk of bias relating to selection bias (Portincasa 2016), attrition bias (Bortolotti 2011, Hutchings 2011, Cappello 2007, Davis 2006, Vejdani 2006, Kline 2001, Liu 1997, Schneider 1990, Lawson 1988, Lech 1988, Weiss 1988) or outcome reporting (Merat 2010, Arthurs 1983, Cappani 2005, Longstreth 1981).

The other RCTs where judged to be at low risk of bias (11 RCTs: Weerts 2019, Cash 2016, Mosaffa-Jahromi 2016, Storsrud 2015, Merat 2010, Saito 2010, Bijkerk 2009, Madisch 2004, Lawson 1988, Dew 1984, Rees 1979) or have unclear risk of bias (14 RCTs: Shulman 2016, Brown 2015, Tilburg 2014, Alam 2013, Brinkhaus 2005, Pedersen 1998, Jalihal 1990, Carling 1989, Wildgrube 1988, Prior 1987, Nash 1986, Nigam 1984, Evans 1982, Ritchie 1979).

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

[h] The overlap tables were separated for ease of presentation. As per protocol, to investigate potential sources of heterogeneity, primary studies could be stratified (if needed) based on the type of herb.

Table 3 List of included systematic reviews and overlap with eligible RCTs (per outcome): Irritable bowel syndrome (peppermint oil)

Review ID	Best available [a]	Prioritised outcome domain [b]	Study ID																	
			Weerts 2019	Cash 2016	Mosaffa-Jahromi 2016 [c]	Alam 2013	Merat 2009	Cappello 2007	Capanni 2005	Kline 2001	Liu 1997	Schneider 1990	Carling 1989	Lawson 1988	Lech 1988	Weiss 1988	Wildgrube 1988	Nash 1986	Dew 1984	Evans 1982	Rees 1979
Black 2020	✓	Global symptom improvement	?	?	?	--	!	?	?	--	!	--	--	--	?	--	--	--	--	--	--
Hawrelak 2020	✓		--	?	?	?	?	Y	Y	Y	Y	?	Y	?	Y	Y	?	Y	!	?	Y
Tan 2020	✓		--	--	Y	--	Y	Y	--	--	!	--	--	--	--	--	--	--	--	--	--
Alammar 2019	✓		--	Y	--	!	!	Y	Y	--	!	!	!	--	Y	Y	--	--	Y	--	Y
Black 2020	✓	Abdominal pain	?	?	!	--	?	!	!	--	?	--	--	--	!	--	--	--	--	--	--
Hawrelak 2020	✓		--	?	Y	?	?	?	!	Y	!	?	!	?	!	?	?	!	Y	?	!
Tan 2020	✓		--	--	?	--	?	?	--	--	Y	--	--	--	--	--	--	--	--	--	--
Alammar 2019	✓		--	Y	--	!	Y	!	Y	--	Y	Y	!	--	Y	!	--	--	!	--	!
Anheyer 2017a	†		--	--	--	--	--	--	--	?	--	--	--	--	--	--	--	--	--	--	--
Koterink 2015	*		--	--	--	--	--	--	--	?	--	--	--	--	--	--	--	--	--	--	--
Hawrelak 2020	✓	Bloating etc.	--	?	Y	?	?	?	!	!	!	?	!	?	!	?	?	!	!	?	!
Hawrelak 2020	✓	Emotional functioning	--	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!	!
Hawrelak 2020	✓	Stool frequency/ bowel transit time	--	?	!	?	?	?	!	!	!	?	Y	?	Y	?	?	!	Y	?	Y
Hawrelak 2020	✓	HRQoL	--	!	?	!	?	!	!	!	!	!	!	!	!	!	!	!	!	!	!

Abbreviations: HRQoL, health-related quality of life; IBS, irritable bowel syndrome; RCT, randomised controlled trial

Notes:

a. Best available information means the systematic review meets AMSTAR-2 domains 4, 8, 9, & 11 (see Appendix B1 [Framework for selecting the systematic review from which to extract data]).

b. Only critical or important outcome domains with available data included here (see Appendix D1.1.3)

c. RCT has two intervention arms (peppermint oil and anise oil)

✓ Systematic review meets (or partially meets) prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

† Systematic review meets (or partially meets) some, but not all, prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

X Systematic review does not meet prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

* Systematic review not assessed. A study result is available and reported in another systematic review nominated as the best available evidence.

Y RCT is included in the systematic review, meets our PICO criteria & a study result is reported for the listed outcome measure [result available].

? RCT is included in the systematic review & meets our PICO criteria, but a study result is not available for the listed outcome [data is incomplete; result may be available in another SR]

! RCT is included in the systematic review, but the SR indicates the study does not measure (or report) the listed outcome [not measured]

-- RCT is not included in systematic review.

Table 4 List of included systematic reviews and overlap with eligible RCTs (per outcome): Irritable bowel syndrome (WHM other than peppermint oil)

Review ID	Best available [a]	Prioritised outcome domain [b]	Study ID																				
			Mosaffa-Jahromi 2016 [c]	Portincasa 2016	Shulman 2016	Brown 2015	Storsrud 2015	Tilburg 2014	Bortolotti 2011	Hutchings 2011	Saito 2010	Bijkerk 2009	Davis 2006	Vejdani 2006	Brinkhaus 2005	Madisch 2004	Pedersen 1998	Jalihal 1990	Prior 1987	Nigam 1984	Arthurs 1983	Longstreth 1981	Ritchie 1979
Anh 2020	†	Global symptom improvement	?	--	--	--	--	?	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Black 2020	✓		!	--	--	--	--	--	--	--	--	!	--	--	--	--	--	?	?	?	?	?	?
Hawrelak 2020	✓		?	?	--	!	?	?	!	?	?	--	?	!	?	?	?	--	--	--	--	--	--
Tan 2020	✓		Y	Y	--	--	Y	Y	--	--	?	--	Y	?	--	--	--	--	--	--	--	--	--
Black 2020	✓	Abdominal pain	?	--	--	--	--	--	--	--	--	?	--	--	--	--	--	!	?	!	!	!	!
Hawrelak 2020	✓		?	?	--	!	!	?	?	!	?	--	?	?	?	?	!	--	--	--	--	--	--
Tan 2020	✓		?	?	--	--	?	?	--	--	?	--	?	!	--	--	--	--	--	--	--	--	--
Anheyer 2017a	†		--	--	?	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Lakhan 2015	†		--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Hong 2018	✓	Patient reported improvement	--	--	--	--	Y	--	--	Y	--	--	Y	--	--	--	--	--	--	--	--	--	--
Ng 2018	†		--	?	--	--	--	--	--	--	--	--	--	--	?	--	--	--	--	--	--	--	--
Hawrelak 2020	✓	Health-related quality of life	?	?	--	!	!	!	!	?	!	--	?	!	!	!	!	--	--	--	--	--	--
Hong 2018	✓		--	--	--	--	!	--	--	?	--	--	!	--	--	--	--	--	--	--	--	--	--
Ng 2018	†		--	?	--	--	--	--	--	--	--	--	--	--	!	--	--	--	--	--	--	--	--
Hawrelak 2020	✓	Emotional functioning	!	?	--	!	?	!	!	!	!	--	!	!	?	!	!	--	--	--	--	--	--
Hong 2018	✓		--	--	--	--	?	--	--	!	--	--	!	--	--	--	--	--	--	--	--	--	--
Hawrelak 2020	✓	Bloating etc.	?	?	--	?	!	!	?	!	?	--	?	?	!	!	!	--	--	--	--	--	--
Hawrelak 2020	✓	Stool frequency/ bowel transit time	?	?	--	?	Y	!	?	!	?	--	!	!	!	!	!	--	--	--	--	--	--

Abbreviations: HRQoL, health-related quality of life; IBS, irritable bowel syndrome, RCT, randomised controlled trial; WHM, Western herbal medicine

Notes:

a. Only critical or important outcome domains with available data included here (see Appendix D1.2.3).

b. Best available information means the systematic review meets AMSTAR-2 domains 4, 8, 9, & 11 (see Appendix B1 [Framework for selecting the systematic review from which to extract data]).

c. RCT has two intervention arms (peppermint oil and anise oil).

✓ Systematic review meets (or partially meets) prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

† Systematic review meets (or partially meets) some, but not all, prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

X Systematic review does not meet prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).
* Systematic review not assessed. A study result is available and reported in another systematic review nominated as the best available evidence.
Y RCT is included in the systematic review, meets our PICO criteria & a study result is reported for the listed outcome measure [result available].
? RCT is included in the systematic review & meets our PICO criteria, but a study result is not available for the listed outcome [data are incomplete; result may be available in another SR]
! RCT is included in the systematic review, but the SR indicates the study does not measure (or report) the listed outcome [not measured]
-- RCT is not included in systematic review.

4.3.5 Summary of findings and evidence statement

4.3.5.1 Primary Comparison (vs placebo)

There were 40 RCTs found by the included systematic reviews that compared WHM 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 2 critical or important outcomes.

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) could have contributed data but there was insufficient information reported by the primary studies or the included systematic reviews to make an assessment.

WHM compared to placebo for Irritable bowel syndrome

Patient or population: Irritable bowel syndrome
Setting: Community
Intervention: WHM (peppermint oil, aloe vera, turmeric, psyllium, St John's wort, capsicum, ginger, anise oil, senna or fixed dose herbal combinations)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with WHM				
Clinical improvement assessed with: IBS-SSS, GSRS or other Scale: range varies (higher is worse) follow-up: range 4 to 20 weeks	-	SMD **0.44 SD lower^** (0.70 lower to 0.18 lower)	-	236 (3 studies) †	⊕⊕◯◯ LOW [a,b,c,d,e]	WHM may result in a slight reduction IBS symptom severity with people with IBS.
Clinical response assessed with: IBS-SSS, GSRS or other (response rate) Scale: % with change in score by n points follow-up: range 4 to 24 weeks	285 per 1,000	**508 per 1,000** (391 to 665)	**RR 1.78** (1.37 to 2.33)	1279 (19 RCTs) ††	⊕⊕⊕◯ MODERATE [c,f,g,h,i]	WHM probably results in a clinical response in people with IBS.
Abdominal pain (response rate) follow-up: range 2 to 18 weeks	271 per 1,000	**501 per 1,000** (406 to 617)	**RR 1.85** (1.50 to 2.28)	606 (7 RCTs) †††	⊕⊕◯◯ LOW [b,c,h,e,j]	WHM may result in an improvement in abdominal pain in people with IBS.
Health-related quality of life	-	-	-	(0 RCTs) **	-	The effect of WHM on quality of life in people with IBS is unknown.
Emotional functioning	-	-	-	(0 RCTs) ***	-	The effect of WHM on emotional functioning in people with IBS is unknown.
Bloating, distention or cramping	-	-	-	(0 RCTs) ****	-	The effect of WHM on bloating, distension or cramping in people with IBS is unknown.

WHM compared to placebo for Irritable bowel syndrome

Patient or population: Irritable bowel syndrome
Setting: Community
Intervention: WHM (peppermint oil, aloe vera, turmeric, psyllium, St John's wort, capsicum, ginger, anise oil, senna or fixed dose herbal combinations)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with WHM				
Stool frequency or quality	-	-	-	(0 RCTs) *****	-	The effect of WHM on stool frequency or quality in people with IBS is unknown.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

^ As a rule of thumb, an SMD of 0.2 represents a small difference, 0.5 is moderate, and 0.8 is a large difference (55).
# A 25% relative risk reduction/increase was considered important (i.e. RR < 0.75 or RR > 1.25).

† Data from 22 RCTs (1606 participants) [not reported] not included here because results were not adequately reported [missing information].
†† Data from 6 RCTs (563 participants) not included here because results were not adequately reported [missing information]. 3 RCTs suggest an effect favouring WHM and 3 RCTs suggest there is no important difference between groups.
††† Data from 13 RCTs (983 participants) not included here because results were not adequately reported [missing information]. 9 RCTs suggest an effect favouring WHM and 4 RCTs suggest there is no difference between groups.
** Data from 4 RCTs (411 participants) not included here because results were not adequately reported [missing information]. 2 RCTs suggest an effect favouring WHM and 2 RCTs suggest there is no difference between groups.
*** Data from 2 RCTs (144 participants) not included here because results were not adequately reported [missing information]. Both RCTs suggest there is no difference between groups.
**** Data from 6 RCTs (243 participants) not included here because results were not adequately reported [missing information]. 4 RCTs suggest an effect favouring WHM and 2 RCTs suggest there is no difference between groups.
***** Data from 9 RCTs (518 participants) not included here because results were not adequately reported [missing information]. 2 RCTs suggest an effect favouring WHM and 5 RCTs suggest there is no difference between groups. Data were not reported for 2 RCTs.

CI: confidence interval; **GSRS:** gastrointestinal rating scale; **IBS:** irritable bowel syndrome; **IBS-SSS:** IBS symptom severity scale; **RR:** risk ratio; **WHM:** Western Herbal Medicine

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanation

a. No serious risk of bias. One RCT contributing >40% of data at high risk of bias. In a sensitivity analysis, the size and direction of effect did not materially change (SMD –0.39; 95% CI –0.75, –0.04; p = 0.03; I^2 = 0%). Certainty of evidence not downgraded.
b. No serious inconsistency. Certainty of evidence not downgraded.
c. No serious indirectness. The available evidence is in people with irritable bowel syndrome and is directly generalisable to the Australian population with few caveats. The herbs used in the identified studies are comparable to those commonly used in Australia (~38%) or could be sensibly applied. Certainty of evidence not downgraded.
d. Serious imprecision. Wide confidence intervals (upper and lower bounds overlap with both moderate and no important difference). Certainty of evidence downgraded.
e. Publication bias suspected. There is a strong suspicion of non-reporting of results likely related to the p value, direction or magnitude of effect. Certainty of evidence downgraded.
f. Serious risk of bias. 8 RCTs contributing ~40% of data at high risk of bias that overstates the size of the effect. Certainty of evidence downgraded.
g. No serious inconsistency. Statistical heterogeneity (I^2=67%) judged likely to be related to differences in study characteristics (e.g. differences in the intervention, participants, setting). Certainty of evidence not downgraded.
h. No serious imprecision. Certainty of evidence not downgraded.
i. Publication bias not detected. Certainty of evidence not downgraded.

j. Serious risk of bias. 6 RCTs contributing >90% of data were at high risk of bias that overstates the size of the effect. Certainty of evidence downgraded.

4.3.5.2 Secondary Comparison (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 [if inactive]) in people with IBS. The effect of WHM compared with inactive control in people with IBS is unknown.

4.3.5.3 Tertiary Comparison (vs active control)

There were 2 RCTs found by the included systematic reviews that compared WHM with active comparators, but individual study data were not provided (see Appendix F2).

4.3.6 Forest plots

Outcome results related to people with irritable bowel syndrome are presented in Figure 5 (symptom severity), Figure 6 (global symptom improvement), and Figure 7 (abdominal pain).

Figure 5 Forest plot of comparison: WHM vs placebo: Irritable bowel syndrome – Symptom severity

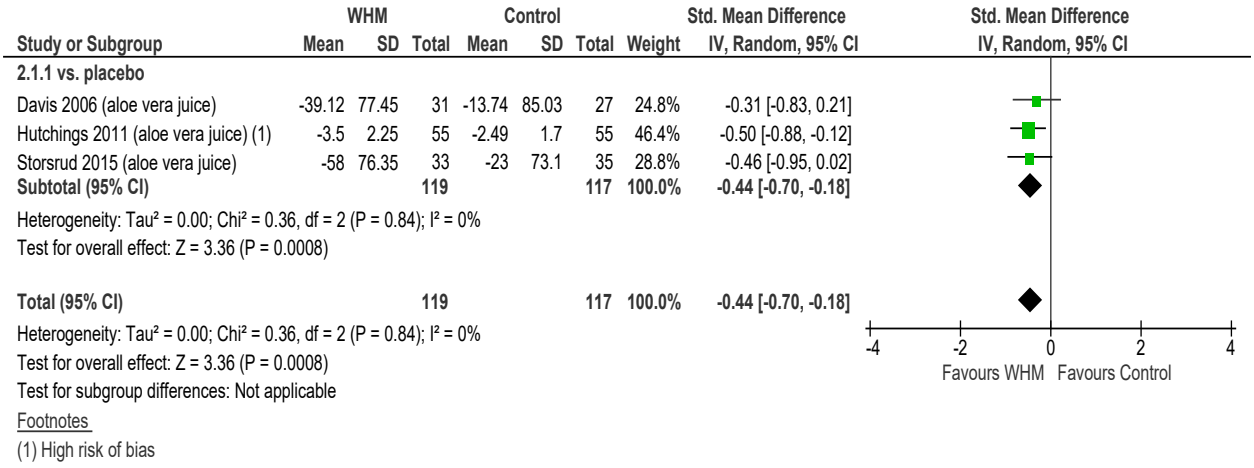
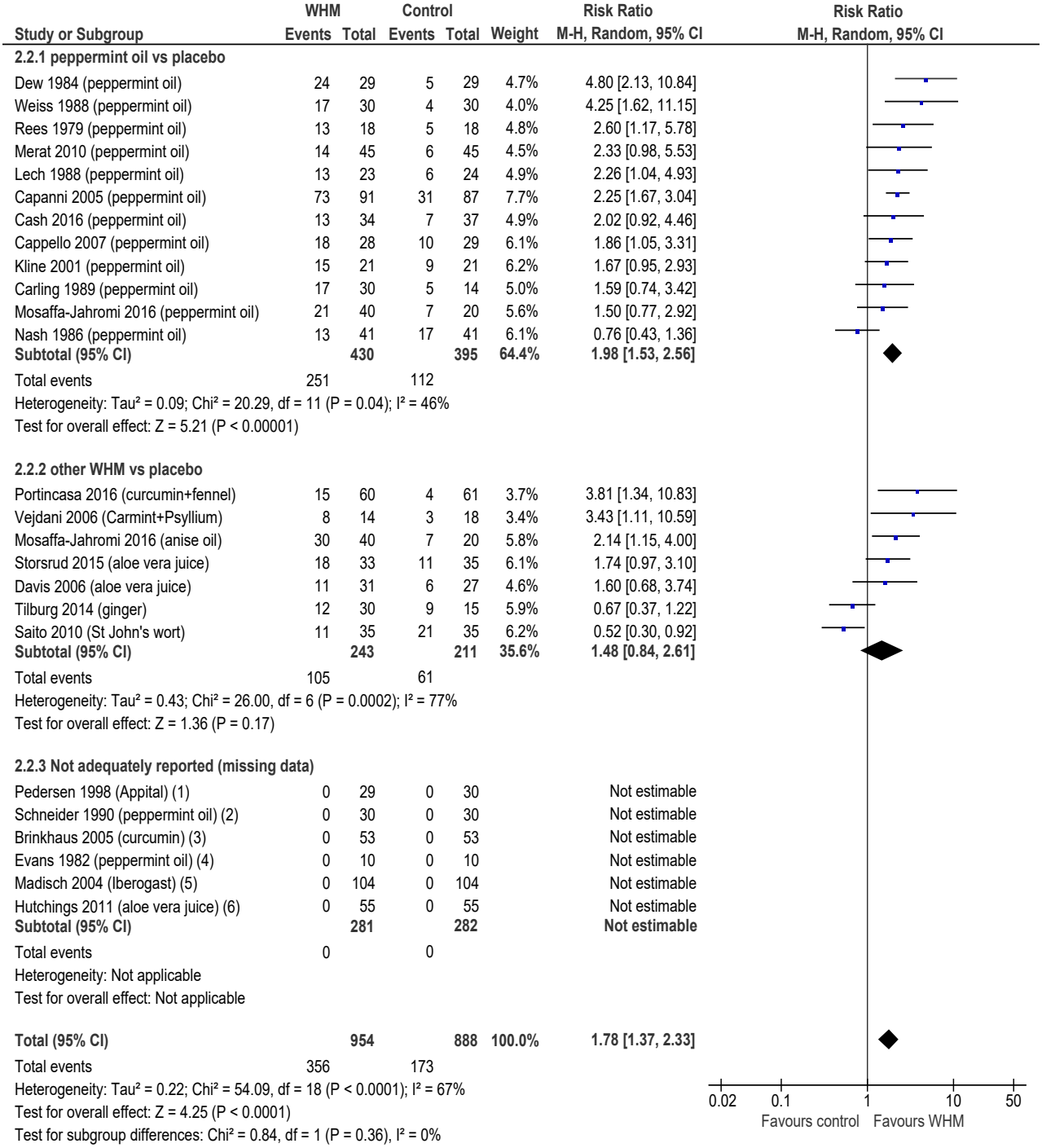


Figure 6 Forest plot of comparison: WHM vs placebo: Irritable bowel syndrome – Global improvement in IBS symptoms (response rate*)

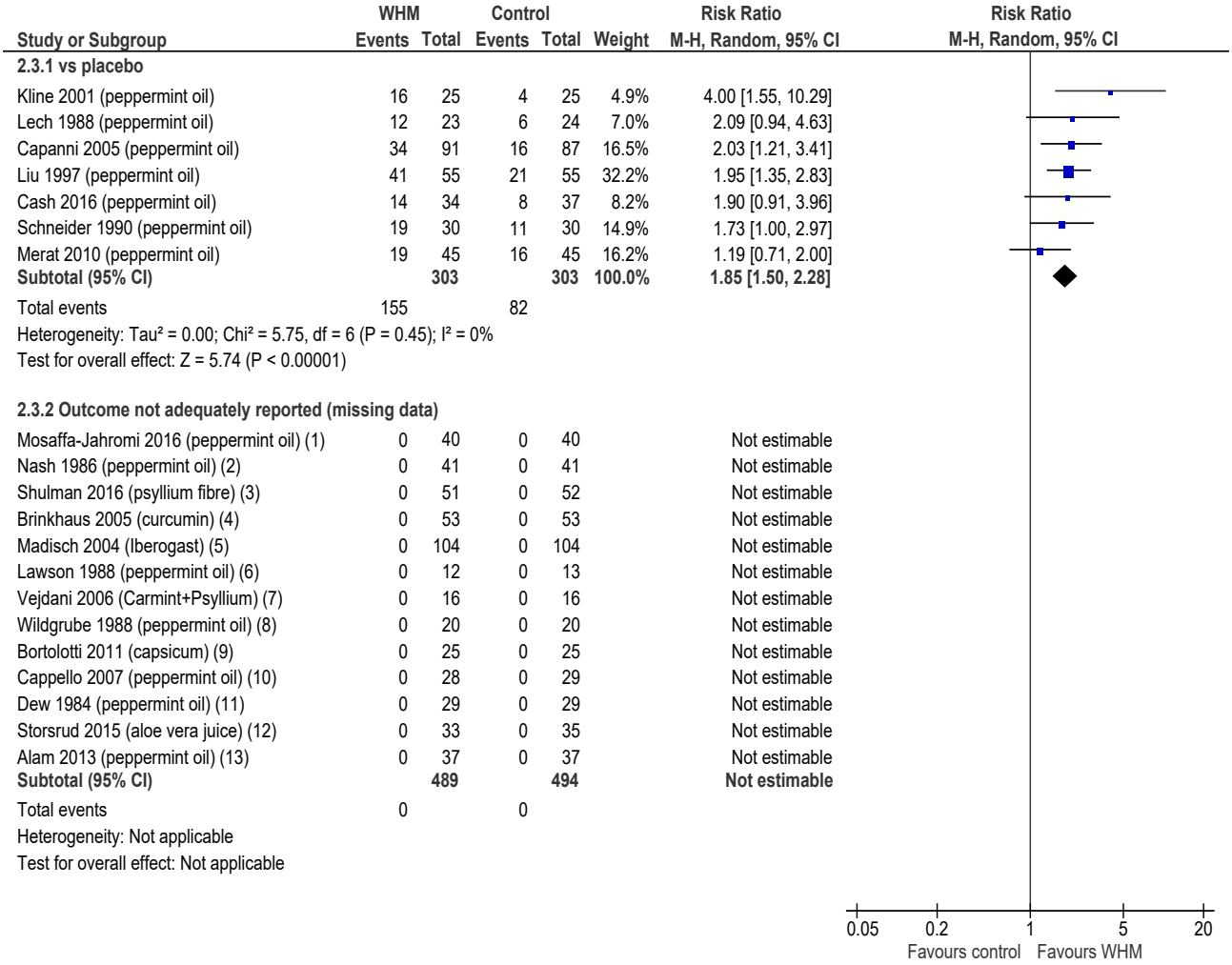


Footnotes

(1) SR authors reported no important difference between groups (p=0.081) but no other data provided.
(2) SR authors reported an important difference between groups (p=0.002) but no other data provided.
(3) SR authors reported no important difference between groups (p>0.05) but no other data provided.
(4) SR authors reported an important difference between groups (p<0.005) but no other data provided.
(5) SR authors reported an important difference between groups (p=0.001) but no other data provided.
(6) SR authors reported no important difference between groups (p>0.05) but no other data provided.

* the proportion of participants who achieved a global improvement in IBS symptoms.

Figure 7 Forest plot of comparison: WHM vs placebo: Irritable bowel syndrome – Abdominal pain (response rate*)



Footnotes

(1) SR authors reported an important difference between groups (p<0.001) but no other data provided.
(2) SR authors reported no important difference between groups (p>0.05) but no other data provided.
(3) SR authors reported an important difference between groups (p<0.05) but no other data provided.
(4) SR authors reported no important difference between groups (p>0.05) but no other data provided.
(5) SR authors reported an important difference between groups (p=0.0009) but no other data provided.
(6) SR authors reported no important difference between groups (p>0.05) but no other data provided.
(7) SR authors reported an important difference between groups (p=0.016) but no other data provided.
(8) SR authors reported an important difference between groups (p<0.05) but no other data provided.
(9) SR authors reported no important difference between groups (p>0.05) but no other data provided.
(10) SR authors reported no important difference between groups (p=0.05) but no other data provided.
(11) SR authors reported an important difference between groups (p<0.001) but no other data provided.
(12) SR authors reported an important difference between groups (p=0.011) but no other data provided.
(13) SR authors reported an important difference between groups (p<0.05) but no other data provided.

* the proportion of participants who achieved improvement in abdominal pain symptoms

4.4 Gastro-oesophageal reflux disease

4.4.1 Description of the condition

Gastro-oesophageal reflux disease (GORD) is a condition where the stomach contents are squeezed back into the oesophagus, resulting in symptoms of heartburn, regurgitation, ulcers and further complications such as peptic oesophagitis (91). GORD occurs when there is a defective function of the lower oesophagus sphincter, leading to excessive stomach acid exposure in the oesophagus (91, 92). The pathogenesis of GORD is multifactorial, with no definite cause for the disease's development. Risk factors for GORD include smoking, obesity, use of non-steroidal anti-inflammatory drugs or aspirin, and a low socioeconomic background (93). The general implications of developing GORD are based on lower oesophageal sphincter (LES) dysregulation, transient LES relaxation and impaired oesophageal acid clearance (91, 94).

Globally, approximately 1 in 6 individuals experience GORD symptoms (93), with reports of GORD being more frequent in men than in women (91). In Australia, approximately 11.6% of the population has been diagnosed with GORD. Undiagnosed prevalence of GORD is estimated at 10-20% of the general population (95).

GORD has a significant impact on quality of life, with most people diagnosed with GORD requiring long term management. Medications that slow or stop acid production in the stomach such as antacids, H2-receptor antagonists or proton pump inhibitors (PPI) are commonly used when diet and lifestyle adjustments are ineffective. Acid suppression is an effective form of therapy but does not cure the condition and there are concerns about overuse of PPIs for long term management of GORD (92, 95). To mitigate adverse effects, diet and lifestyle changes remain an important tool in the management of GORD. Common herbal medicines used to manage symptoms of heartburn include chamomile, ginger, liquorice root, lemon balm and milk thistle.

4.4.2 Description of reviews

There was one citation (96) corresponding to one systematic review (Sadeghi 2020) identified in the literature search that examined the effectiveness of WHM in people with GORD. No additional systematic reviews were identified in the Department's public call for evidence (see Appendix C2). There was one review (97) awaiting classification (see Appendix C4) and no ongoing reviews (see Appendix C5).

A summary of the PICO criteria of the eligible systematic reviews is provided in Appendix D1.3.1.

Sadeghi 2020 investigated the effectiveness of herbal medicines in people with GORD. Of the 13 RCTs identified by the systematic review, one RCT (Moeini 2016) met our PICO criteria. The other RCTs examined other herbal medicines not on List A (e.g. Chinese, Ayurvedic) (see Appendix A8).

4.4.3 Description of studies

Within the eligible systematic reviews, there was one RCT that met our PICO criteria (see Appendix F1). Moeini 2016 evaluated the gastroprotective effects of hawthorn compared with placebo in 80 participants with GORD. Treatment duration was 4 weeks. The RCT was reported to assess the severity of symptoms, but no usable data were provided. Hawthorn is not on the list of herbs included in the Western herbal medicine curriculum for the Digestive system (i.e. most commonly taught in Australian curriculum for this condition; see Appendix A6.3).

An overlap table of the RCTs within the included systematic reviews is shown in Table 5.

Result for the Primary Comparison: WHM vs placebo are provided in Section 4.4.5.

There were no studies found for the Secondary Comparison: WHM vs inactive control (no intervention, waitlist, usual care [if inactive]) or the Tertiary Comparison (versus active comparators).

4.4.4 Risk of bias

Risk of bias assessment for the eligible RCTs as summarised by included systematic reviews are provided in Appendix F1.

Moeini 2016 was assessed by Sadeghi 2020 using the Cochrane Collaboration's risk of bias assessment tool (54). The RCT was judged to be at high risk of bias for 3 domains (allocation concealment, performance bias and detection bias). Risk of bias was unclear for random sequence generation and selective reporting and the study was at low risk of bias for incomplete outcome data.

Table 5 List of included systematic reviews and overlap with eligible RCTs (per outcome): Gastro-oesophageal reflux disease

Review ID	Best available [a]	Prioritised outcome domain [b]	Study ID
			Moeini 2016
Sadeghi 2020	✓	GORD symptoms	?
		Regurgitation	?

Abbreviations: RCT, randomised controlled trial

Notes:

a. Best available information means the systematic review meets AMSTAR-2 domains 4, 8, 9, & 11 (see Appendix B1 [Framework for selecting the systematic review from which to extract data]).

b. Only critical or important outcome domains with available data included here (see Appendix D1.1.3)

✓ Systematic review meets (or partially meets) prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

? RCT is included in the systematic review & meets our PICO criteria, but a study result is not available for the listed outcome [data is incomplete; result may be available in another SR].

4.4.5 Summary of findings and evidence statement

4.4.5.1 Primary Comparison (vs placebo)

One RCT (Moeini 2016) was found by the included systematic review (Sadeghi 2020) that compared hawthorn with placebo in people with GORD. The RCT could have contributed data to at least one outcome (symptom severity), but the systematic review authors did not adequately report data for inclusion in the synthesis.

In the absence of usable data, the effect of WHM compared with placebo on the following outcomes in people with GORD is unknown:

- GORD symptoms (heartburn, oesophagitis, (silent) acid reflux, dysphagia and belching)
- Pain
- HRQoL
- Emotional functioning
- Physical functioning
- Patient reported improvement
- Regurgitation

4.4.5.2 Secondary Comparison (vs inactive control)

No studies were found by the included systematic reviews that compared WHM with an inactive control in people with GORD. Therefore, the effect of WHM compared with inactive control (no intervention, waitlist or usual care [if inactive]) on the prioritised outcomes in people with GORD is unknown.

4.4.5.3 Tertiary Comparison (vs active control)

No studies found. The effect of WHM compared with active controls on the prioritised outcomes in people with GORD is unknown.

4.5 Menstrual conditions

4.5.1 Description of the condition

Menstrual conditions is an umbrella term used in this overview to encompass a range of disorders characterised by pain in the pelvic region and irregularities in the menstrual cycle such as dysmenorrhoea, amenorrhea and endometriosis. Lifestyle, dietary patterns, environment and genetic factors may influence the risk of menstrual conditions. Dysmenorrhoea has several underlying causes that can be classified as either primary or secondary (98). Primary dysmenorrhoea describes painful menstrual bleeding, with some surveys reporting that it is experienced by 50-90% of people with menstrual cycles. Secondary dysmenorrhoea is attributed to underlying pelvic conditions such as endometriosis or fibroids in females who have menstruated previously (98). Amenorrhoea is the absence of menstruation, commonly due to a lack of hormonal function in the ovaries, which may result in infertility (99). The most common causes of amenorrhoea include polycystic ovarian syndrome, hypothalamic amenorrhoea, ovarian failure and hyperprolactinemia (99). Endometriosis is a chronic inflammatory condition characterised by abnormal growth of endometrial-like tissue outside the uterine cavity (100). The aetiology behind endometriosis is not known.

The prevalence of moderate to severe dysmenorrhoea is estimated to affect 44.2% of Australian women aged 18 to 39 (101). At the same time, amenorrhoea not due to pregnancy, lactation or menopause affects between 3% and 4% of females (99). Endometriosis affects 10-15% of all females of reproductive age and 70% of females with chronic pelvic pain (102). Typically, the diagnosis of endometriosis is often delayed, impairing the quality of life for many females, and resulting in unnecessary pain and, in some cases, infertility.

Therapeutic options for most menstrual conditions include nonsteroidal anti-inflammatory drugs and hormonal contraceptives (98). The primary aim of treatment is to provide symptomatic relief and improve quality of life by reducing pain and discomfort. A variety of WHM such as withania, chamomile, curcumin, ginger, lavender and peppermint are suggested to help relieve symptoms associated with menstrual conditions, but specific treatments or recommendations are lacking (103, 104).

4.5.2 Description of reviews

There were 14 citations (64, 73, 105-116) corresponding to 14 systematic reviews identified in the literature search that evaluated WHMs in people with menstrual conditions (Negi 2021, Anh 2020, Mollazadeh 2020, Shinjyo 2020, Xu 2020, Pellow 2018, Chen 2016, Javan 2016, Pattanittum 2016, Ursoniu 2016, Daily 2015, Lakhan 2015, Terry 2011, Ulbricht 2011). No additional reviews were identified through the Department's public call for evidence (see Appendix C2). There were 2 reviews awaiting classification (117, 118) that were not in English (see Appendix C4) and no ongoing reviews (see Appendix C5).

A summary of the PICO criteria of included reviews is provided in Appendix D2.1.1.

The populations eligible for inclusion in the reviews were participants with dysmenorrhoea (Negi 2021, Xu 2020, Pellow 2018, Chen 2016, Pattanittum 2016, Daily 2015), heavy menstrual bleeding (Javan 2016) or prespecified gynaecologic and pelvic conditions (Mollazadeh 2020). Two reviews (Lakhan 2015, Terry 2011) included studies of participants with any pain condition and 3 reviews (Anh 2020, Ursoniu 2016, Ulbright 2011) had unclear or no population restrictions but presented RCTs of participants with dysmenorrhoea or amenorrhoea. One umbrella review (Shinjyo 2020) searched for studies of participants with sleep or related health problems and included a study of participants with dysmenorrhoea.

Six (6) systematic reviews (Negi 2021, Anh 2020, Chen 2016, Daily 2015, Lakhan 2015, Terry 2011) searched for evidence on ginger or zingiberaceae family extracts, 3 reviews searched for evidence on medicinal plant preparations (Pellow 2018, Javan 2016) or dietary supplements (Pattanittum 2016), one review searched for evidence on cinnamon, ginger or fennel (Xu 2020), and one review searched for evidence on Chaste tree (vitex) (Mollazadeh 2020), valerian root (Shinjyo 2020), saffron (Ulbricht 2011) or flaxseed (Ursoniu 2016).

Seven (7) systematic reviews (Negi 2021, Mollazadeh 2020, Xu 2020, Pellow 2018, Chen 2016, Pattanittum 2016, Daily 2015) included evidence from at least one RCT that met our PICO criteria and presented a study result available for inclusion in the synthesis. These reviews were prioritised for critical appraisal and data extraction.

Review details, including outcome domains and measures, and the risk of bias of eligible RCTs are provided in Appendix F1.

4.5.3 Description of studies

Within the eligible systematic reviews, there were 24 RCTs that met our PICO criteria (see Appendix F1). The RCTs used different herbs[i] (see Appendix D2.1.1) and doses with the intervention period ranging from one to 3 menstrual cycles. Most studies were focused on measuring pain intensity among females with moderate to severe dysmenorrhoea, and one study measured blood loss among females with heavy menstrual bleeding. All but 4 of the RCTs were conducted in secondary or tertiary school students at learning institutions in Iran or India; the settings of 4 RCTs (Abadi 2020, Pakniat 2019, Rad 2018, Gupta 2013) were not specified.

An overlap table of the RCTs that met our PICO criteria from the included systematic reviews is shown in Table 6.

There were 15 RCTs that examined the effect of WHM versus placebo. Two RCTs (Shobeiri 2014, Sah Hosseini 2005) tested the effect of chaste tree on heavy menstrual bleeding and the other 13 RCTs examined the use of ginger (Abadi 2020, Jenabi 2013, Kashefi 2014, Rahnama 2012, Rahnama 2010), cinnamon (Jahangirifar 2018, Jaafarpour 2015, Akhavan Amjadi 2009), fenugreek (Heshmati 2016, Younesy 2014, Akbari 2012) or valerian root (Mirabi 2011, Dolation 2010) on pain intensity. Of these, only one herb (chaste tree) is listed as a Tier 1 herb included in the Western herbal medicine curriculum for Gynaecological / reproductive disorders (i.e. most commonly taught in Australian curriculum for this condition; see Appendix A6.3).

Three (3) RCTs tested the effect of WHM against no treatment on pain intensity, with 2 RCTs (Modaress 2011, Jenabi 2010) examining the use of chamomile and one RCT (Gupta 2013) examining the use of ginger. The remaining 6 RCTs compared the effect of WHM against an active comparator; being either progressive muscle relaxation (Halder 2012) or non-steroidal anti-inflammatory drugs[j] (Pakniat 2019, Rad 2018, Shirvani 2015, Jenabi 2012, Ozgoli 2009).

In total, 14 RCTs (Pakniat 2019, Jahangirifar 2018, Rad 2018, Jaafarpour 2015, Kashefi 2014, Shobeiri 2014, Gupta 2013, Jenabi 2013, Akbari 2012, Jenabi 2012, Rahnama 2012, Modaress 2011, Dolation 2010, Jenabi 2010) had adequately reported results available for inclusion in the evidence synthesis. The other 10 RCTs (Abadi 2020, Heshmati 2016, Shirvani 2015, Younesy 2014, Halder 2012, Mirabi 2011, Rahnama 2010, Akhavan Amjadi 2009, Ozgoli 2009, Sah Hosseini 2005) had results that were not adequately reported by the included systematic reviews.

Results for the Primary Comparison: WHM vs placebo and the Secondary Comparison: WHM vs inactive control (no intervention, waitlist, usual care [if inactive]) are provided in the Summary of Findings tables (see Section 4.5.5). Additional details are provided in Appendix F2. Results for the Tertiary Comparison (versus active comparators) are provided in Appendix F2.

4.5.4 Risk of bias

Risk of bias assessment for the eligible RCTs as summarised by included systematic reviews are provided in Appendix F1.

The reviews by Mollazadeh 2019, Pattanittum 2016 and Daily 2015 were used to inform the evidence synthesis as they used the Cochrane Collaboration's risk of bias assessment tool (54) to asses bias within the included RCTs and provided the most comprehensive information to make a judgement. Four (4) RCTs (Kashefi 2014, Jenabi 2013, Akbari 2012, Dolation 2010) were judged to be at low risk of bias while 8 RCTs (Shirvani 2015, Shobheiri 2014, Halder 2012, Rahnama 2012, Modaress 2011, Jenabi 2010, Ozgoli 2009, Sah Hosseini 2005) were judged to be at high risk of bias in at least one domain.

[i] Chaste tree is the only herb studied in the included RCTs that is on the core list of herbs included in the WHM curriculum for menstrual conditions (see Appendix A6.3).

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

Table 6 List of included systematic reviews and overlap with eligible RCTs (per outcome): Menstrual conditions

Review ID	Best available [a]	Prioritised outcome domain [b]	Study ID																								
			Abadi 2020	Pakniat 2019	Jahangirifar 2018	Rad 2018	Heshmati 2016	Jaafarpour 2015	Shirvani 2015	Kashefi 2014	Shobeiri 2014	Younesy 2014	Gupta 2013	Jenabi 2013	Akbari 2012	Halder 2012	Jenabi 2012	Rahnama 2012	Mirabi 2011	Modaress 2011	Dolation 2010	Jenabi 2010	Rahnama 2010	Akhavan Amjadi 2009	Ozgoli 2009	Sah Hosseini 2005
Negi 2021	✓	Pain intensity	!	Y	--	Y	--	--	!	Y	--	--	--	Y	--	--	--	Y	--	--	--	--	--	--	!	--
Xu 2020	✓		--	Y	?	--	--	?		Y	--	--	--	Y	--	--	--	Y	--	--	--	--	--	--	--	--
Pellow 2018	†		--	--	--	--	?	--	--	Y	--	?	--	Y	--	--	--	Y	?	--	--	--	--	--	?	--
Chen 2016	✓		--	--	--	--	--	--	X	Y	--	--	--	Y	--	!	--	Y	--	--	--	--	--	--	!	--
Pattanittum 2016	✓		--	--	--	--	--	--	--	Y	--	--	--	Y	Y	--	Y	Y	--	Y	Y	Y	?	!	--	--
Daily 2015	✓		--	--	--	--	--	--	X	Y	--	--	Y	Y	--	!	--	Y	--	--	--	--	--	--	!	--
Mollazadeh 2020	✓	Patient-reported blood loss	--	--	--	--	--	--	--	--	Y	--	--	--	--	--	--	--	--	--	--	--	--	--	--	!

Abbreviations: RCT, randomised controlled trial

Notes:

a. Best available information means the systematic review meets AMSTAR-2 domains 4, 8, 9, & 11 (see Appendix B1 [Framework for selecting the systematic review from which to extract data]).

b. Only critical or important outcome domains with available data included here (see Appendix D1.1.3)

✓ Systematic review meets (or partially meets) prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

† Systematic review meets (or partially meets) some, but not all, prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

Y RCT is included in the systematic review, meets our PICO criteria & a study result is reported for the listed outcome measure [result available].

? RCT is included in the systematic review & meets our PICO criteria, but a study result is not available for the listed outcome [data are incomplete; result may be available in another SR]

! RCT is included in the systematic review, but the SR indicates the study does not measure (or report) the listed outcome [not measured]

-- RCT is not included in systematic review.

4.5.5 Summary of findings and evidence statements

4.5.5.1 Primary Comparison (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, 7 RCTs (Akbari 2012, Dolation 2010, Jenabi 2013, Kashefi 2014, Rahnama 2012) contributed data relevant to one outcome (pain intensity) and one RCT (Shobeiri 2014) contributed data relating to blood loss. Another 5 RCTs did not contribute any data because their results were not adequately reported, either by the primary study or the included systematic reviews.

Western herbal medicine compared to placebo for menstrual conditions

Patient or population: Menstrual conditions
Setting: Community
Intervention: WHM (ginger, cinnamon, fenugreek, valerian, chaste tree, German chamomile)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with WHM				
Pain intensity assessed with: VAS, SF-MPQ Scale: 0 to 10 cm (higher is worse) follow-up: range 1 to 3 menstrual cycles	The mean pain score was **6.09 cm**	**MD 2.34** cm lower (2.92 lower to 1.76 lower)	--	601 (7 RCTs) †	⊕⊕⊕◯ MODERATE a,b,c,d,e	WHM probably results in a large reduction in pain intensity in people with menstrual conditions **
Global improvement (patient-reported)	-	-	--	(0 studies)	--	The effect of WHM on patient-reported improvement in people with menstrual conditions is unknown
Health-related quality of life	-	-	--	(0 studies)	--	The effect of WHM on quality of life in people with menstrual conditions is unknown
Emotional functioning	-	-	--	(0 studies)	--	The effect of WHM on emotional functioning in people with menstrual conditions is unknown
Physical functioning	-	-	-	(0 studies)	--	The effect of WHM on physical functioning in people with menstrual conditions is unknown
Menstrual regularity	-	-	-	(0 studies)	--	The effect of WHM on menstrual regularity in people with menstrual conditions is unknown
Patient-reported blood loss assessed with: Higham score Scale: 0 to >21 (higher is worse) follow-up: 1 menstrual cycle	The mean Higham score was **24.6 points**	**MD 1.0** point higher (5.32 lower to 7.32 higher)	--	60 (1 RCT) ††	⊕◯◯◯ VERY LOW f,g,h,i,j	The evidence is very uncertain about the effect of WHM on patient-reported blood loss in people with menstrual conditions

Western herbal medicine compared to placebo for menstrual conditions

Patient or population: Menstrual conditions
Setting: Community
Intervention: WHM (ginger, cinnamon, fenugreek, valerian, chaste tree, German chamomile)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with WHM				

* **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

** MCID of 1.0 cm in females with endometriosis (74). MCID is not established in people with primary dysmenorrhoea.
† Data from 4 RCTs (total 396 participants) not included here because results were not adequately reported [missing information]. All 4 RCTs suggested an effect favouring WHM.
†† Data from one RCT (total 60 participants) not included here because results were not adequately reported [missing information].

CI: confidence interval; **MD:** mean difference; **SF-MPQ:** short-form McGill Pain Questionnaire; **VAS:** visual analogue scale

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. One RCT (< 10% weight) at high risk of bias that does not materially influence the estimate of effect. Certainty of evidence not downgraded.
b. Serious inconsistency. Point estimates vary and confidence intervals of some studies do not overlap. Substantial statistical heterogeneity (I^2 = 90%) that cannot be explained. Certainty of evidence downgraded.
c. No serious indirectness. The available evidence is in students in Iran or India with moderate to severe dysmenorrhoea and can be sensibly applied to the Australian population. It is possible that the herbs used in the studies are contrary to what is prescribed in Australia, but the evidence could be sensibly applied. Certainty of evidence not downgraded.
d. No serious imprecision. Certainty of evidence not downgraded.
e. Publication bias not suspected. Missing data from 4 RCTs (396 participants) that could have contributed data to this outcome, all of which reported an effect favouring WHM. Certainty of evidence not downgraded.
f. Serious risk of bias. One study (100% weight) at high risk of bias. Certainty of evidence downgraded.
g. Inconsistency not assessed. One study contributing data. Certainty of evidence not downgraded.
h. No serious indirectness. The available evidence is in students in Iran with heavy menstrual bleeding and can be sensibly applied to the Australian population. The herb used in the study (chaste tree berry) is matched to what is likely used in Australia. Certainty of evidence not downgraded.
i. Very serious imprecision. Single study. Wide confidence intervals (upper and lower bounds overlap with both a large and no important difference). Certainty of evidence downgraded 2 levels.
j. Publication bias not suspected. Certainty of evidence not downgraded.

4.5.5.2 Secondary Comparison (vs inactive control)

There were 3 RCTs (Gupta 2013, Jenabi 2010, Modaress 2011) found by the included systematic reviews that compared WHM with control (no treatment) in people with dysmenorrhea or heavy menstrual bleeding that contributed data relevant to one outcome (pain intensity). The available evidence is summarised below.

Western herbal medicine compared to inactive control for menstrual conditions

Patient or population: Menstrual conditions
Setting: Community
Intervention: Western herbal medicine
Comparison: inactive control (no treatment)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Control	Risk with WHM				
Pain intensity assessed with: VAS, NRS, SF-MPQ Scale: 0 to 10 cm (higher is worse) follow-up: range 2 to 3 menstrual cycles	The mean pain score was **5.14**	**MD 2.29** lower (4.49 lower to 0.09 lower)	--	304 (3 RCTs)	⊕◯◯◯ VERY LOW a,b,c,d,e	The evidence is very uncertain about the effect of WHM on pain intensity in people with menstrual conditions **
Global improvement (patient-reported)	-	-	--	(0 studies)	--	The effect of WHM on patient-reported improvement in people with menstrual conditions is unknown
Health-related quality of life	-	-	--	(0 studies)	--	The effect of WHM on quality of life in people with menstrual conditions is unknown
Emotional functioning	-	-	--	(0 studies)	--	The effect of WHM on emotional functioning in people with menstrual conditions is unknown
Physical functioning	-	-	-	(0 studies)	--	The effect of WHM on physical functioning in people with menstrual conditions is unknown
Menstrual regularity	-	-	-	(0 studies)	--	The effect of WHM on menstrual regularity in people with menstrual conditions is unknown
Patient-reported blood loss	-	-	-	(0 studies)	--	The effect of WHM on patient-reported blood loss in people with menstrual conditions is unknown

* **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
** MCID of 1.0 cm in females with endometriosis (74). MCID is not established in people with primary dysmenorrhoea.

CI: confidence interval; **MD:** mean difference; **NRS:** numeric rating scale; **SF-MPQ:** short-form McGill Pain Questionnaire; **VAS:** visual analogue scale

Western herbal medicine compared to inactive control for menstrual conditions

Patient or population: Menstrual conditions
Setting: Community
Intervention: Western herbal medicine
Comparison: inactive control (no treatment)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Control	Risk with WHM				

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Serious risk of bias. Three studies (100% weight) at high risk of bias. Certainty of evidence downgraded.
b. Serious inconsistency. Point estimates vary and confidence intervals of some studies do not overlap. Substantial statistical heterogeneity (I^2 = 89%) that cannot be explained. Certainty of evidence downgraded.
c. No serious indirectness. The available evidence is in students in Iran with moderate to severe dysmenorrhoea and can be sensibly applied to the Australian population. It is possible that the herbs used in the studies are contrary to what is prescribed in Australia, but the evidence could be sensibly applied. Certainty of evidence not downgraded.
d. Serious imprecision. Wide confidence intervals (upper and lower bounds overlap with both large and no important difference). Certainty of evidence downgraded.
e. Publication bias not suspected. Certainty of evidence not downgraded.

4.5.5.3 Tertiary Comparison (vs active control)

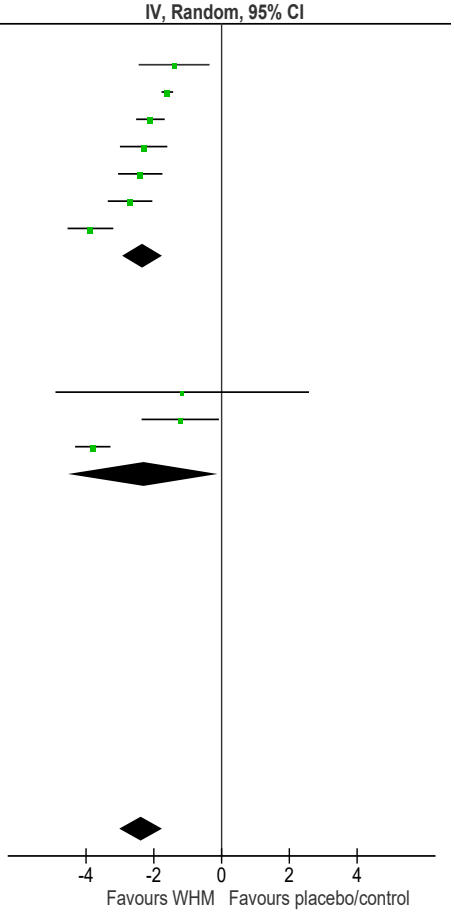
There were 7 RCTs found by the included systematic reviews that compared WHM with active comparators in people with dysmenorrhea or heavy menstrual bleeding. The comparators included progressive muscle relaxation, nutritional supplements, or non-steroidal anti-inflammatory drugs (see Appendix F2).

4.5.6 Forest plots

Outcome results related to people with menstrual conditions are presented in Figure 8 (pain intensity) and Figure 9 (patient-reported blood loss).

Figure 8 Forest plot of comparison: WHM vs placebo or control: Menstrual conditions - pain intensity (VAS)

Study or Subgroup	WHM Mean	WHM SD	WHM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
3.1.1 WHM vs placebo								
Rahnama 2012 (ginger)	4.6	2.6	59	6	2.7	46	9.3%	-1.40 [-2.42, -0.38]
Jahangirifar 2018 (cinnamon) (1)	4.492	0.2913	30	6.092	0.2913	28	12.3%	-1.60 [-1.75, -1.45]
Jaafarpour 2015 (cinnamon) (2)	3.992	0.8896	38	6.092	0.8896	38	11.8%	-2.10 [-2.50, -1.70]
Jenabi 2013 (ginger)	4.81	1.7	35	7.11	1.12	34	10.8%	-2.30 [-2.98, -1.62]
Dolation 2010 (valerian root)	2	1.4	51	4.4	1.8	49	11.0%	-2.40 [-3.03, -1.77]
Akbari 2012 (fenugreek)	3.3	1.3	51	6	1.9	50	11.0%	-2.70 [-3.34, -2.06]
Kashefi 2014 (ginger)	3.08	1.52	47	6.95	1.67	45	10.9%	-3.87 [-4.52, -3.22]
Subtotal (95% CI)			**311**			**290**	**77.3%**	**-2.34 [-2.92, -1.76]**
Heterogeneity: Tau² = 0.52; Chi² = 61.03, df = 6 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 7.90 (P < 0.00001)								
3.1.2 WHM vs control (no intervention)								
Jenabi 2010 (chamomile) (3)	5.94	6.01	40	7.1	10.39	40	2.3%	-1.16 [-4.88, 2.56]
Gupta 2013 (ginger) (4)	2.91	2.45	34	4.13	2.12	30	8.9%	-1.22 [-2.34, -0.10]
Modaress 2011 (chamomile)	0.4	0.9	80	4.2	2.1	80	11.5%	-3.80 [-4.30, -3.30]
Subtotal (95% CI)			**154**			**150**	**22.7%**	**-2.29 [-4.49, -0.09]**
Heterogeneity: Tau² = 2.93; Chi² = 18.33, df = 2 (P = 0.0001); I² = 89%								
Test for overall effect: Z = 2.04 (P = 0.04)								
3.1.3 Missing data (not adequately reported by the SR)								
Rahnama 2010 (ginger) (5)	0	0	59	0	0	46		Not estimable
Younesy 2014 (fenugreek) (6)	0	0	51	0	0	50		Not estimable
Heshmati 2016 (peppermint) (7)	0	0	46	0	0	44		Not estimable
Mirabi 2011 (valerian root) (8)	0	0	51	0	0	49		Not estimable
Subtotal (95% CI)			**207**			**189**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Total (95% CI)			**672**			**629**	**100.0%**	**-2.38 [-3.01, -1.76]**
Heterogeneity: Tau² = 0.82; Chi² = 118.29, df = 9 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 7.48 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%								



Footnotes

(1) Data imputed using the placebo group mean from other RCTs

(2) Data imputed using the placebo group mean from other RCTs

(3) SF-MPQ (0-10)

(4) NRS (0-10)

(5) SR authors reported an important difference between groups (p<0.01) but no other data provided.

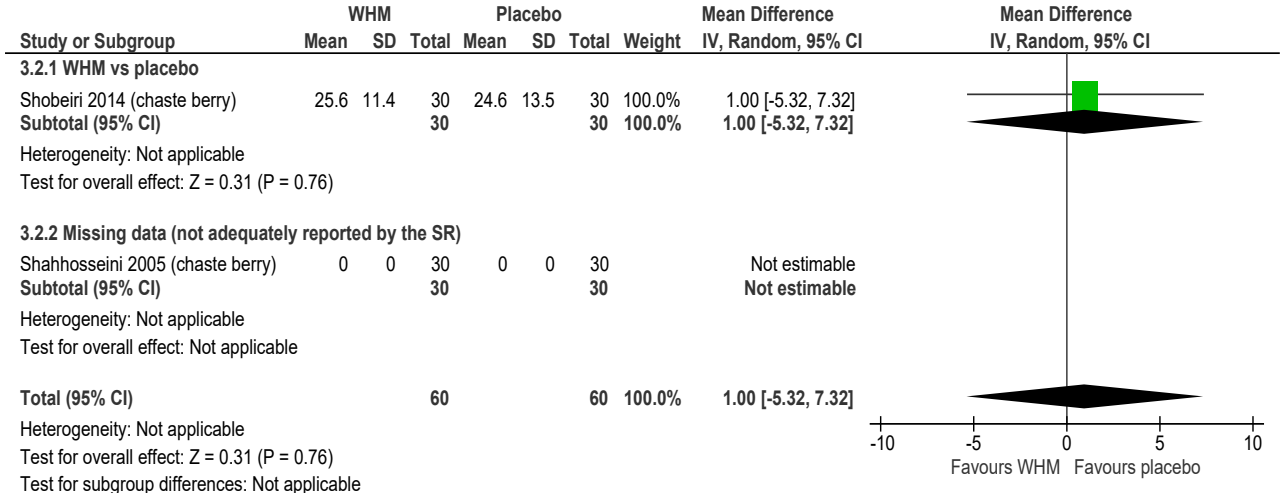
(6) SR authors reported an important difference between groups (p<0.001) but no other data provided.

(7) SF-MPQ; SR authors reported an important difference between groups (p=0.008) but no other data provided.

(8) SR authors reported an important difference between groups (p<0.001) but no other data reported.

Abbreviations: SF-MPQ, short-form McGill Pain Questionnaire; VAS, visual analogue score.

Figure 9 Forest plot of comparison: WHM vs placebo: Menstrual conditions – menstrual blood loss (Higham score)



4.6 Premenstrual disturbances

4.6.1 Description of the condition

Premenstrual disturbances encompasses disorders associated with menstruation that affect the psychological and emotional wellbeing of females of reproductive age (119). Specifically, premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD). PMS is characterised by psychological and somatic symptoms during the luteal phase of the menstrual cycle (119). PMDD is a severe form of PMS, with emotional, behavioural and physical symptoms that can be extreme and sometimes disabling (120). PMS and PMDD are cyclic in pattern, occurring prior to menstruation and typically resolving after the menstrual period. There are no definite causes of PMS and PMDD, although it is posited that reproductive hormones, genetics and psychosocial symptoms such as anxiety and stress or a combination of factors are potential contributors to the aetiology and development of PMS and PMDD (121-123).

Up to 80% of individuals who have menstrual cycles experience some form of PMS (123). Up to 90% of women experience at least 1 symptom of PMS in most months, and 50% experience several symptoms each month. An estimated 20-40% of premenopausal women may experience moderately severe symptoms of PMS. Furthermore, approximately 2-9% of premenopausal women experience disabling symptoms; individuals with disabling symptoms may be considered to have premenstrual dysphoric disorder (PMDD), the severe form of PMS (123).

Current treatments are aimed toward symptomatic relief, with treatment options guided by PMS severity. Conservative management includes regular exercise, relaxation techniques, vitamin and mineral supplementation (e.g., Vitamin B6 and calcium) and cognitive behavioural therapy (121, 122). For more severe presentations, combined oral contraceptives, antidepressants (selective serotonin reuptake inhibitors) and hormone agonists gonadotrophin-releasing hormone) may be prescribed (121, 122). Complementary and alternative medicines, including herbal medicines such as chaste tree berry, ginkgo biloba, St John's wort and curcumin are also suggested to be beneficial in treating premenstrual disturbances (121), however they are not currently recommended in routine clinical practice (121-123).

4.6.2 Description of reviews

There were 12 citations (116, 124-134) corresponding to 12 systematic reviews (Ghaderi 2020, Shinjyo 2020, Csupor 2019, Khalesi 2019, Cerqueira 2017, Verkaik 2017, Hausenblas 2015, Su Hee 2014, van Die 2013, Dante 2011, Ulbricht 2011, Whelan 2009) identified in the literature search that evaluated the effectiveness of WHMs in people with premenstrual disturbances. There were no additional reviews identified in the Department's public call for evidence (see Appendix C2). There was one review (135) awaiting classification (see Appendix C4) and no ongoing reviews (see Appendix C5).

A summary of the PICO criteria of the 12 eligible systematic reviews is provided in Appendix D2.2.1.

Eight (8) reviews searched specifically for studies in people with PMS (Csupor 2019, Khalesi 2019, Su Hee 2014, van Die 2013, Dante 2011), both PMS or PMDD (Cerqueira 2017, Verkaik 2017, Whelan 2009), or any female reproductive disorder (van Die 2013). Two (2) reviews were focused on the effectiveness of a specific herb across any clinical condition (Hausenblas 2015, Ulbricht 2011), and 2 reviews were focused on the effect of a specific herb on specific outcomes, being either sleep-related health problems (Shinjyo 2020) or mental health and inflammatory biomarkers (Ghaderi 2020).

There were 4 systematic reviews that searched for evidence on chaste tree berry (Csupor 2019, Cerqueira 2017, Verkaik 2017, van Die 2013), 3 reviews searched for evidence specific to saffron (Ghaderi 2020, Hausenblas 2015, Ulbricht 2011), and one review assessed the evidence specific to either chamomile (Khalesi 2019) or valerian (Shinjyo 2020). Three (3) reviews did not specify the herbal medicine of interest (Su Hee 2014, Dante 2011, Whelan 2009).

Five (5) systematic reviews (Ghaderi 2020, Shinjyo 2020, Csupor 2019, Verkaik 2017, van Die 2013) were prioritised for critical appraisal and data extraction as they presented results in a meta-analysis. Review details, including outcome domains and measures, and the risk of bias of eligible RCTs are provided in Appendix F1.

4.6.3 Description of studies

Within the eligible systematic reviews, there were 29 RCTs that met our PICO criteria (see Appendix F1). The studies examined the effect of several herbs including chaste tree berry, chamomile, St John's wort, ginkgo biloba, saffron and valerian. Of these, only one herb (chaste tree) is listed as a Tier 1 herb included in the Western herbal medicine curriculum for Gynaecological / reproductive disorders (i.e. most commonly taught in Australian curriculum for this condition; see Appendix A6.3).

An overlap table of the RCTs that met our PICO criteria from the included systematic reviews is shown in Table 7.

The RCTs were conducted in a variety of countries including China (Ma 2012, He 2009), Germany (Shellenberg 2012, Shellenberg 2001, Lauritzen 1997), Iran (Zamani 2012, Pakgohar 2009, Agha-Hoesseini 2008), Italy (Ciotta 2011, Di Pierro 2009), Turkey (Atmaca 2003) the United Kingdom (Turner 1993) or not specified. Sample sized ranged from 47 to 268 (total 5749 participants), with the interventions being delivered over various time periods (8 weeks to 3 months) (or not specified).

There were 18 RCTs that examined the effect of WHM compared with placebo (Najafi 2018, Behboodi Moghadam 2016, Kaplanoglu 2015[k], Mousavi 2015, Schellenberg 2012, Zamani 2012, Risoleti 2011[k], Canning 2010, Ma 2010, He 2009, Ozgoli 2009, Pakgohar 2009, Agha-Hosseini 2008, Hicks 2004, Delavar 2002, Schellenberg 2001, Tamborini 1993, Turner 1993).

There were 13 RCTs examined the effect of WHM compared with an active comparator (Kaplanoglu 2015[k], Sharifi 2014, Karimian 2013, Salehi 2013[l], Ciotta 2011, Modaress 2011, Risoleti 2011[k], Masumeh 2010, Di Pierro 2009, Scaldarella 2008, Atmaca 2003, Onaran 2003, Lauritzen 1997) being either mefenamic acid (NSAID), magnesium oxide, pyridoxine-HCL (vitamin B6), oral contraceptive pill or fluoxetine.

Results for the Primary Comparison: WHM versus placebo are provided in the Summary of Findings tables (see Section 4.6.5).

There were no studies found for the Secondary Comparison: WHM versus inactive control (no intervention, waitlist, usual care [if inactive]). Additional details are provided in Appendix F2. Results for the Tertiary Comparison (versus active comparators) are provided in Appendix F2.

4.6.4 Risk of bias

Risk of bias assessment for the eligible RCTs as summarised by included systematic reviews are provided in Appendix F1.

The reviews by Verkaik 2017 and van Die 2013 were used to inform the evidence synthesis as they used the Cochrane Collaboration's risk of bias assessment tool (54) to asses bias within the included RCTs and provided the most comprehensive information to make a judgement.

There were 8 RCTs (Salehi 2013, Schellenberg 2012, Zamani 2012, Ma 2010, He 2009, Pakgohar 2009, Atmaca 2003, Schellenberg 2001) with some concerns of bias, as the information provided was unclear.

Eleven (11) RCTs (Kaplanoglu 2015, Mousavi 2015, Cioatta 2011, Risoleti 2011, Di Pierro 2009, Pakgohar 2009, Scaldarella 2008, Onaran 2003, Delavar 2002, Lauritzen 1997, Turner 1993) were judged to be at high risk of bias in at least one domain. Information about risk of bias for the other 10 RCTs were not provided.

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

[l] Study included three treatment groups: WHM and 2 active controls.

Table 7 List of included systematic reviews and overlap with eligible RCTs (per outcome): Premenstrual disturbances

Review ID	Best available [a]	Prioritised outcome domain [b]	Study ID																												
			Najafi 2018	Behboodi Moghadam 2016	Kaplanoglu 2015	Mousavi 2015	Sharifi 2014	Karimian 2013	Salehi 2013	Schellenberg 2012	Zamani 2012	Modaress 2011	Ciotta 2011	Risoleti 2011	Canning 2010	Ma 2010	Masumeh 2010	Di Pierro 2009	He 2009	Pakgohar 2009	Ozgoli 2009	Agha-Hosseini 2008	Scaldarella 2008	Hicks 2004	Atmaca 2003	Onaran 2003	Delvar 2002	Schellenberg 2001	Lauritzen 1997	Tamborini 1993	Turner 1993
Csupor 2019	✓	PMS Symptoms	--	--	--	--	--	--	--	Y	--	--	--	--	--	--	--	--	Y	--	--	--	--	--	--	--	--	Y	--	--	--
Khalesi 2019	†		?	--	--	--	?	?	--	--	--	?	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Verkaik 2017	✓		--	--	?	?	--	--	?	?	?	--	?	?	--	--	--	?	?	?	--	--	?	--	?	?	?	?	?	--	?
Cerqueira 2017	*		--	--	--	--	--	--	--	?	Y	--	Y	--	--	Y	--	--	Y	--	--	--	--	--	Y	--	--	Y	Y	--	--
Hausenblas 2015	*		--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	?	--	--	--	--	--	--	--	--	--
Su Hee 2014	*		--	--	--	--	--	--	--	--	?	--	--	--	?	?	?	--	?	--	?	?	--	?	?	--	--	--	--	--	--
Van Die 2013	✓		--	--	--	--	--	--	--	--	Y	--	Y	--	--	Y	--	Y	Y	Y	--	--	--	--	Y	--	--	Y	Y		Y
Dante 2011	*		--	--	--	--	--	--	--	--	--	--	--	--	?	?	--	--	?	--	?	?	--	?	?	--	--	?	?	?	?
Ulbricht 2011	*		--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Whelan 2009	*		--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	?		?	?	--	--	?	?	?	?
Ghaderi 2020	✓	Depression	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	Y	--	--	--	--	--	--	--	--	--
Shinjyo 2020	✓	Anxiety	--	Y	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

Abbreviations: RCT, randomised controlled trial

Notes:

a. Best available information means the systematic review meets AMSTAR-2 domains 4, 8, 9, & 11 (see Appendix B1 [Framework for selecting the systematic review from which to extract data]).

b. Only critical or important outcome domains with available data included here (see Appendix D1.1.3)

✓ Systematic review meets (or partially meets) prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

† Systematic review meets (or partially meets) some, but not all, prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

* Systematic review not assessed. A study result is available and reported in another systematic review nominated as the best available evidence.

Y RCT is included in the systematic review, meets our PICO criteria & a study result is reported for the listed outcome measure [result available].

? RCT is included in the systematic review & meets our PICO criteria, but a study result is not available for the listed outcome [data are incomplete; result may be available in another SR]

! RCT is included in the systematic review, but the SR indicates the study does not measure (or report) the listed outcome [not measured]

-- RCT is not included in systematic review.

4.6.5 Summary of findings and evidence statements

4.6.5.1 Primary Comparison (vs placebo)

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

Five (5) 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.

Western herbal medicine compared to placebo for premenstrual disturbances

Patient or population: Premenstrual disturbances (PMS or PMDD)
Setting: Community
Intervention: WHM (chaste tree)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with WHM				
PMS Symptoms assessed with: PMSD, MDQ, DSR, PMS-VAS follow-up: range 2 to 6 menstrual cycles	-	**SMD 1.31 SD lower** (1.82 lower to 0.8 lower) ^	-	1133 (8 RCTs)†	⨁⨁◯◯ LOW [a,b,c,d,e]	WHM may result in a large reduction in PMS symptom severity in people with premenstrual disturbances.
Global improvement (patient-reported) assessed with: PMS-VAS, PMSD, DSR (response rate) follow-up: range 2 to 6 menstrual cycles	316 per 1,000	**626 per 1,000** (481 to 816)	**RR 1.98** (1.52 to 2.58) #	839 (6 RCTs) ††	⨁⨁⨁◯ MODERATE [c,d,e,f,g]	WHM probably results in a large improvement in PMS symptoms in people with premenstrual disturbances.
Depression assessed with: VAS, BDI, MDQ-negative affect follow-up: range 2 to 6 menstrual cycles	-	**SMD 1.02 SD lower** (1.67 lower to 0.38 lower) ^	-	613 (5 RCTs) †††	⨁⨁◯◯ LOW [b,c,d,e,f]	WHM may result in a large improvement in depressive symptoms in people with premenstrual disturbances.
Anxiety assessed with: VAS follow-up: range 3 to 6 menstrual cycles	-	**SMD 1.44 SD lower** (1.91 lower to 0.97 lower) ^	-	208 (2 RCTs) ††††	⨁⨁◯◯ LOW [c,d,e,g,h]	WHM may result in a large improvement in anxiety in people with premenstrual disturbances.

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

Western herbal medicine compared to placebo for premenstrual disturbances

Patient or population: Premenstrual disturbances (PMS or PMDD)
Setting: Community
Intervention: WHM (chaste tree)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with WHM				
Emotional functioning	-	-	-	(0 studies)	--	The effect of WHM on emotional functioning in people with premenstrual disturbances is unknown.
Physical functioning	-	-	-	(0 studies)	--	The effect of WHM on physical functioning in people with premenstrual disturbances is unknown.
Health-related quality of life	-	-	-	(0 studies)	--	The effect of WHM on quality of life in people with premenstrual disturbances is unknown.

* **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
^ As a rule of thumb, an SMD of 0.2 represents a small difference, 0.5 is moderate, and 0.8 is a large difference (55).
# A 25% relative risk reduction/increase was considered important (i.e. RR < 0.75 or RR > 1.25).

† Data from one RCT (total 67 participants) (SMD –0.96; 95% –1.38, –0.54) not added to the pooled analysis. Data from 5 other RCTs (~400 participants) not included here due to inadequate reporting [missing information].
†† Data from 9 other RCTs (~735 participants) not included here due to inadequate reporting [missing information].
††† Data from one RCT (total 47 participants) (SMD 6.23; 95% CI 5.21, 7.25) not able to be added to the pooled analysis. Data from 12 other RCTs (~990 participants) not included here due to inadequate reporting [missing information].
†††† Data from one RCT (total 100 participants) (SMD 1.9; 95% CI 1.44, 2.39) not added to the pooled analysis. Data from 15 other RCTs (~1290 participants) not included due to inadequate reporting [missing information].

BDI: Beck depression inventory; **CI:** confidence interval; **DSR:** daily symptom rating scale; **MD:** mean difference; **MDQ:** menstrual distress questionnaire; **PMDD:** premenstrual dysphoric disorder; **PMS:** premenstrual syndrome; **PMSD:** PMS daily diary'; **VAS:** visual analogue scale

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. Sensitivity analysis suggest studies at overall high risk of bias do not materially influence the estimate of effect. Certainty of evidence not downgraded.
b. Serious inconsistency. Point estimates vary and confidence intervals of some studies do not overlap. Substantial statistical heterogeneity (I^2 > 90%) that cannot be explained. Certainty of evidence downgraded.
c. No serious indirectness. The available evidence is in people with PMS or PMDD and is directly generalisable to the Australian population with few caveats. The herbs used in the identified studies are comparable to those commonly used in Australia and can be sensibly applied. Certainty of evidence not downgraded.
d. No serious imprecision. Certainty of evidence not downgraded.
e. Publication bias suspected. There is a strong suspicion of non-reporting of results likely related to the *p* value, direction or magnitude of effect. Certainty of evidence downgraded.
f. No serious risk of bias. One study contributing <15% of data at high risk of bias. In a sensitivity analysis, the size and direction of effect did not materially change. Certainty of evidence not downgraded.
g. No serious inconsistency. Certainty of evidence not downgraded.
h. Serious risk of bias. One study contributing >50% of data at high risk of bias. Certainty of evidence downgraded.

4.6.5.2 Secondary Comparison (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 premenstrual disturbances. In the absence of evidence, the effect of WHM compared with control on the prioritised outcomes is unknown.

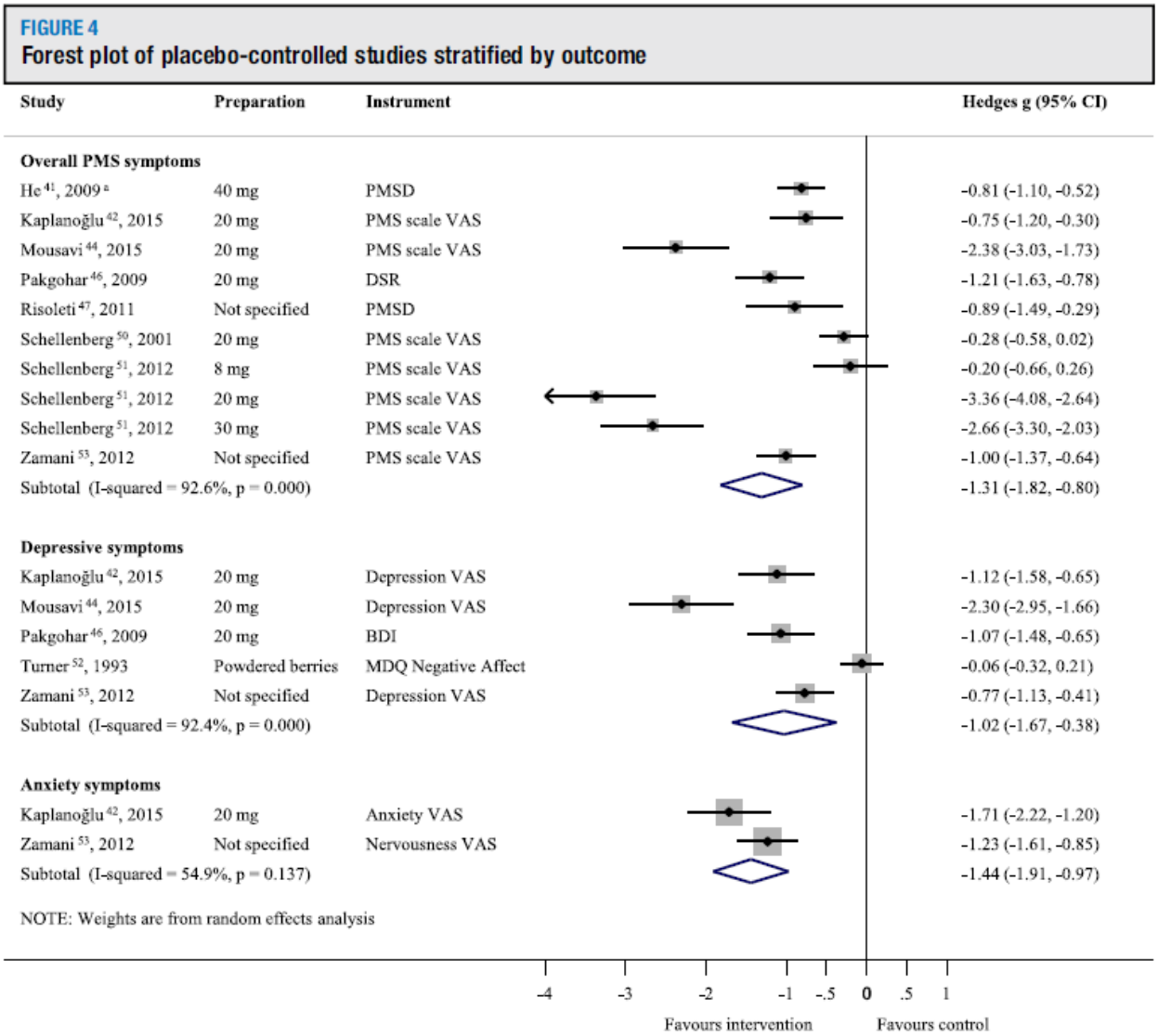
4.6.5.3 Tertiary Comparison (vs active control)

There were 13 RCTs found by the included systematic reviews that compared WHM with active comparators, of which 9 had data adequately reported by the included systematic reviews (see Appendix F2).

4.6.6 Forest plots

Outcome results related to people with premenstrual disturbances are presented in Figure 10 (PMS symptoms, anxiety, depression) and Figure 11 (patient reported improvement).

Figure 10 Forest plot of comparison: WHM vs placebo: Premenstrual disturbances - PMS symptoms, anxiety, depression



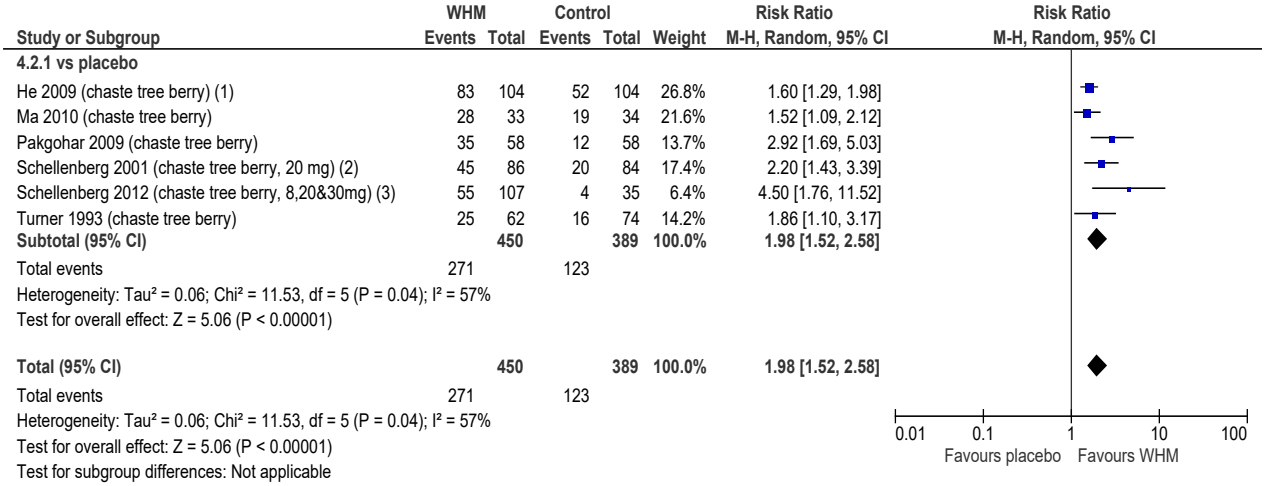
Treatment effect of *Vitex agnus castus* (N=9; 17 effect sizes) are expressed in Hedges g and 95% confidence intervals (CI). The blue diamond reflects the weighted treatment effect. Area of gray square reflects the weight each comparison contributes to the meta-analysis. Abbreviations of the instruments used: PMSD (PMS diary); PMS scale VAS (PMS visual analog scale); DSR (Daily Symptom Report); Depression VAS (visual analog scale); BDI (Beck Depression Inventory); MDQ (Mood Disorders Questionnaire); Anxiety VAS (visual analog scale); Nervousness VAS (visual analog scale). [a]To avoid the inclusion of multiple outcomes in the analysis the results of the study by He[41] assessed using the Premenstrual Tension Self-Rating Scale were excluded from this subset.

BDI, Beck Depression Inventory; *DSR*, Daily Symptom Report; *MDQ*, Moos Menstrual Distress Questionnaire; *PMS*, premenstrual syndrome; *PMSD*, premenstrual syndrome diary; *VAS*, visual analog scale.

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

Source: Verkaik, Kamperman (129)

Figure 11 Forest plot of comparison: WHM vs placebo: Premenstrual disturbances – patient reported improvement



Footnotes

(1) minimum 60% improvement in symptom diary score

(2) minimum 50% decrease in total symptom score

(3) minimum 50% decrease in total symptom score

4.7 Symptoms of menopause

4.7.1 Description of the condition

Natural menopause is defined as the permanent cessation of menses and is a normal process of ageing that is typically confirmed after menstrual periods have been absent for 12 months (136-139). Symptoms of menopause are characterised by the pathological changes that occur during the transition period (perimenopause) and are related to the gradual loss of ovarian follicular function and decline in circulating blood oestrogen levels (136, 140). Perimenopause is estimated to last around 4 years and is the period when troublesome symptoms such as hot flushes[n], headache, sleep disturbance, lack of concentration, depressed mood, atrophic genital changes and bone loss can begin, with women who experience a longer transition period more likely to seek help (139). Women with artificial menopause, induced after the surgical removal of ovaries, or through interventions such as chemotherapy or radiation therapy, are also more likely to experience bothersome or disabling symptoms of menopause (138); as are women who experience premature (before 40 years of age) or early menopause (aged between 40 and 45 years) (137).

Natural menopause is estimated to occur between the ages of 47 and 53 years, with education, lifestyle factors (such as smoking, high physical activity), and ethnicity reported to play a role (137, 141, 142). Globally, between 2% and 3.7% of women are estimated to experience premature menopause and between 7.6% and 12.2% of women are estimated to undergo early menopause (141, 143), which places them at increased risk of chronic conditions later in life. In Australia, natural menopause is estimated to occur at a mean age of 52 years (142), with about 1.2% of women undergoing premature menopause and 5.8% experiencing early menopause (141).

Treatment and management of troublesome and disruptive symptoms associated with menopause centre on minimising the effects of declining oestrogen levels through hormone replacement therapy (136, 144-146). Other treatments may focus on managing or preventing specific symptoms such as localised oestrogen cream for vaginal atrophy, blood pressure medications for hot flushes, antidepressants for mood changes, or calcium and Vitamin D for bone loss (144, 146-148). Given the risks associated with long-term hormone replacement therapy (e.g., thromboembolic or coronary events, breast cancer) (138, 144-146), and the variability of symptom severity, many women experiencing mild or moderate symptoms of menopause seek lifestyle and behavioural therapies as an alternative. These include acupuncture (149), herbal medicines (150), relaxation therapies (151) and exercise therapies (152). The Australasian Menopause Society notes that the evidence for the effectiveness of lifestyle or behavioural changes is mixed and limited (144), but note that some may improve general wellbeing and help women manage their symptoms.

4.7.2 Description of reviews

There were 85 citations (33, 113, 124, 125, 150, 153-233) corresponding to 85 systematic reviews identified in the literature search that evaluated the effectiveness of WHMs in people with symptoms of menopause. One additional review (180) was identified in the Department's public call for evidence (see Appendix C2). There were 17 reviews awaiting classification (see Appendix C4) and 2 ongoing reviews (see Appendix C5).

A summary of the PICO criteria of included reviews is provided in Appendix D2.3.1.

The populations eligible for inclusion in the reviews were often specific to those experiencing symptoms associated with menopause in either the perimenopausal or postmenopausal period (or both), with studies in participants with early menopause (natural or associated with treatment for cancer) also eligible for inclusion.

A large number of the identified systematic reviews were umbrella reviews that included at least one study in people with symptoms of menopause, but which focused on the effect of a specific WHM on a particular outcome that was often considered not critical or important for this Overview (such as lipid profiles, liver function, blood pressure, or measures of obesity). These reviews included evidence relating to the following WHMs: black cumin, black cohosh, garlic, ginseng, green tea, linseed, psyllium and turmeric.

[n] We use the Australian language of hot flushes throughout instead of the American hot flashes.

Nine (9) systematic reviews (Castelo-Branco 2021, Firoozeei 2021, Kanadys 2021, Ghaderi 2020, Shinjyo 2020, Ghorbani 2019, Shahmohammadi 2019, Najafi 2018a, Franco 2016) were prioritised for critical appraisal and data extraction as they presented results in a meta-analysis and were considered the best available evidence. Six (6) reviews (Castelo-Branco 2021, Kanadys 2021, Ghorbani 2019, Shahmohammadi 2019, Najafi 2018a, Franco 2016) were focused on symptoms associated with menopause and 3 reviews (Firoozeei 2021 Ghaderi 2020, Shinjyo 2020) searched for studies specific to a WHM (saffron, lavender, valerian root).

Review details, including outcome domains and measures, and the risk of bias of eligible RCTs are provided in Appendix F1.

4.7.3 Description of studies

Within the eligible systematic reviews there were 42 RCTs that met our PICO criteria (see Appendix F1). All 42 RCTs examined the effect of WHM compared with placebo[°].

Ten (10) other RCTs (Wang 2019, Zhang 2015, Chen 2014, Xi 2014, Huang 2013, Chen 2013, Sun 2012, Bai 2007, Nappi 2005, Liske 2002) were identified by one review (Castelo-Branco 2021) that examined the effect of black cohosh compared with an active comparator (hormone therapy, vitamins/minerals, fluoxetine or other antidepressants). The review provided limited information about these studies; therefore, they were not considered further in this overview.

An overlap table of the RCTs that met our PICO criteria from the included systematic reviews is shown in Table 8.

The studies examined the effect of several herbs including: withania (ashwagandha; Chung 2015), black cohosh (Jiang 2015, Shahnazi 2013, Li 2011, Newton 2006, Pockaj 2006, Frei-Kleiner 2005, Osmers 2005, Jacobson 2001, Stoll 1987), fennel (black cumin) (Ghazanfarpour 2018, Rahimi Kian 2017), fenugreek (Shamshad Begum 2016, Steels 2017), panax ginseng (Oh 2010, Kim 2009, Dongre 2015, Wiklund 1999), hops (Aghamiri 2016), Kava (Warnecke 1991, Warnecke 1990); red clover (Lambert 2017, Clifton-Bligh 2015, Shakeri 2015, Lipovac 2012, del Giorno 2010, Hidalgo 2005, Atkinson 2004, Tice 2003, Jeri 2002, van de Weijer 2002, Baber 1999, Knight 1999), saffron (Kashani 2018), St John's wort (Abdali 2010), valerian root (Jenabi 2017, Mirabi 2011), or a combination of St John's wort with either black cohosh (Chung 2007, Uebelhack 2006) or chaste tree berry (van Die 2009). Of these, only 2 herbs (black cohosh and chaste tree) are marked as a Tier 1 herb included in the Western herbal medicine curriculum for Gynaecological / reproductive disorders (i.e. most commonly taught in Australian curriculum for this condition; see Appendix A6.3).

The RCTs were conducted in a variety of countries including Austria (Lipovac 2012), Australia (Clifton-Bligh 2015, van Die 2009, Baber 1999, Knight 1999), Brazil (del Giorno 2010), Ecuador (Ehsanpour 2012, Hidalgo 2005), Denmark (Lambert 2017), Germany (Warnecke 1991, Warnecke 1990), India (Dongre 2015), Iran (Kashani 2018, Kamalifard 2017, Shakeri 2015, Shahnazi 2013, Abdali 2010), Korea (Chung 2015, Oh 2010, Kim 2009, Chung 2007), the Netherlands (van de Weijer 2002), Peru (Jeri 2002), Sweden (Wiklund 1999), Switzer land (Frei-Kleiner 2005), the United Kingdom (Atkinson 2004), and the United States (Newton 2006, Pockaj 2006, Tice 2003). The country setting was not specified for 25 studies (Ghazanfarpour 2018, Jenabi 2017, Rahimi Kian 2017, Steels 2017, Aghamiri 2016, Shamshad 2016, Jiang 2015, Charandabi 2013, Mirabi 2013, Li 2011, Geller 2009, Uebelhack 2006, Osmers 2005, Jacobson 2001, Stoll 1987). Sample sized ranged from 24 to 384 participants (total > 1200 participants), with the interventions being delivered over various time periods (8 weeks to 24 months) (or not specified).

Results for the Primary Comparison: WHM versus placebo are provided in the Summary of Findings tables (see Section 4.7.5).

There were no studies found for the Secondary Comparison: WHM versus inactive control (no intervention, waitlist, usual care [if inactive]) or the Tertiary Comparison (versus active comparators), therefore there are no additional details to provide in Appendix F2.

[°] One RCT (Kamalifard 2017) also included an 'active' intervention group (bitter orange).

Table 8 List of included systematic reviews and overlap with eligible RCTs (per outcome): Symptoms of menopause

Review ID	Best available [a]	Prioritised outcome domain [b]	Study ID: Ghazanfarpour 2018	Kashani 2018	Jenabi 2017	Kamalifard 2017	Lambert 2017	Rahimi Kian 2017	Steels 2017	Aghamiri 2016	Shamshad 2016	Chung 2015	Clifton-Bligh 2015	Dongre 2015	Jiang 2015	Shakeri 2015	Charandabi 2013	Mirabi 2013	Shanazi 2013	Ehsanpour 2012	Lipovac 2012	Li 2011	Abdali 2010	del Giorno 2010	Oh 2010	Geller 2009	Kim 2009	Van Die 2009	Chung 2007	Newton 2006 (BC)	Pockaj 2006	Uebelhack 2006	Frei-Kliener 2005	Hidalgo 2005	Osmers 2005	Atkinson 2004	Tice 2003	Jeri 2002	van de Weijer 2002	Jacobson 2001 (BC)	Baber 1999	Knight 1999	Wiklund 1999	Stoll 1987
Castelo-Branco 2021 [c]	✓	Symptom Severity	--	--	--	--	--	--	--	--	--	--	--	--	!	--	--	--	--	--	--	?	--	--	--	--	--	--	--	--	--	?	--	--	?	--	--	--	--	!	--	--	--	?
Kanadys 2021	✓		--	--	--	--	Y	--	--	--	--	--	Y	--	--	Y	--	--	--	--	Y	--	--	Y	--	--	--	--	--	--	--	--	--	Y	--	Y	!	!	Y	--	Y	Y	--	--
Castelo-Branco 2021 [c]	✓	Hot flushes	--	--	--	--	--	--	--	--	--	--	--	--	!	--	--	--	--	--	--	?	--	--	--	--	--	--	--	--	--	!	--	--	?	--	--	--	--	?	--	--	--	!
Kanadys 2021	✓		--	--	--	--	Y	--	--	--	--	--	Y	--	--	Y	--	--	--	--	Y	--	--	Y	--	--	--	--	--	--	--	--	--	Y	--	Y	Y	Y	Y	--	Y	Y	--	--
Shinjyo 2020	✓		--	--	?	--	--	--	--	--	--	--	--	--	--	--	--	?	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Franco 2016	✓		--	--	--	--	--	--	--	--	--	?	--	--	?	--	?	--	Y	--	Y	--	?	--	--	--	--	?	?	Y	Y	--	Y	--	--	Y	Y	Y	Y	--	Y	Y	--	--
Ghorbani 2019	✓	Sexual function	--	--	--	--	--	--	--	--	--	Y	--	Y	--	--	--	--	--	--	--	--	--	--	Y	--	Y	--	--	--	--	--	--	--	--	--	--	--	--	--	--	Y	--
Najafi 2018a	†		--	--	--	--	--	?	?	--	?	--	--	--	--	?	--	--	--	?	--	--	--	--	?	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Castelo-Branco 2021 [c]	✓	HRQoL	--	--	--	--	--	--	--	--	--	--	--	--	?	--	--	--	--	--	--	!	--	--	--	--	--	--	--	--	--	!	--	--	!	--	--	--	--	!	--	--	--	!
Ghorbani 2019	✓		--	--	--	--	--	--	--	--	--	!	--	!	--	--	--	--	--	--	--	--	--	--	!	--	!	--	--	--	--	--	--	--	--	--	--	--	--	--	--	Y	--
Ghorbani 2019	✓	Emotional functioning	--	--	--	--	--	--	--	--	--	!	--	!	--	--	--	--	--	--	--	--	--	--	!	--	!	--	--	--	--	--	--	--	--	--	--	--	--	--	--	Y	--
Shahmohammadi 2019	✓		!	--	--	--	Y	Y	Y	!	!	--	--	--	--	Y	Y	--	--	Y	!	--	--	--	--	!	--	--	--	--	--	--	--	!	--	--	Y	--	--	--	--	--	--	--

Table 8 List of included systematic reviews and overlap with eligible RCTs (per outcome): Symptoms of menopause (cont'd)

Review ID	Best available [a]	Prioritised outcome domain [b]	Study ID: Chazanfarpour 2018	Kashani 2018	Jenabi 2017	Kamalifard 2017	Lambert 2017	Rahimi Kian 2017	Steels 2017	Aghamiri 2016	Shamshad 2016	Chung 2015	Clifton-Bligh 2015	Dongre 2015	Jiang 2015	Shakeri 2015	Charandabi 2013	Mirabi 2013	Shanazi 2013	Ehsanpour 2012	Lipovac 2012	Li 2011	Abdali 2010	del Giorno 2010	Oh 2010	Geller 2009	Kim 2009	Van Die 2009	Chung 2007	Newton 2006 (BC)	Pockaj 2006	Uebelhack 2006	Frei-Kliener 2005	Hidalgo 2005	Osmers 2005	Atkinson 2004	Tice 2003	Jeri 2002	van de Weijer 2002	Jacobson 2001 (BC)	Baber 1999	Knight 1999	Wiklund 1999	Stoll 1987
Castelo-Branco 2021 [c]	✓	Depression	--	--	--	--	--	--	--	--	--	--	--	--	!	--	--	--	--	--	--	!	--	--	--	--	--	--	--	--	--	?	--	--	!	--	--	--	--	!	--	--	--	!
Firoozeei 2021	✓		--	--	--	Y	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Ghaderi 2020	✓		--	?	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Shahmoham madi 2019	✓		Y	--	--	--	!	!	!	Y	Y	--	--	--	--	!	!	--	--	!	Y	--	--	--	--	!	--	--	--	--	--	--	--	Y	--	--	Y	--	--	--	--	--	--	--
Castelo-Branco 2021 [c]	✓	Anxiety	--	--	--	--	--	--	--	--	--	--	--	--	!	--	--	--	--	--	--	!	--	--	--	--	--	--	--	--	--	!	--	--	!	--	--	--	--	!	--	--	--	?
Shahmoham madi 2019	✓		Y	--	--	--	!	!	!	Y	Y	--	--	--	--	!	!	--	--	!	Y	--	--	--	--	Y	--	--	--	--	--	--	--	!	--	--	Y	--	--	--	--	--	--	--

Abbreviations: BC, includes breast cancer patients; QoL, quality of life; RCT, randomised controlled trial

Notes:

a. Only critical or important outcome domains with available data reported here (see Appendix D1.1)

b. Best available information means the systematic review meets AMSTAR-2 domains 4, 8, 9, & 11 (see Framework for selecting the systematic review from which to extract data [Appendix B1]).

c. 10 RCTs comparing black cohosh with an active comparator not included here: Wang 2019, Zhang 2015, Chen 2014, Xi 2014, Huang 2013, Chen 2013, Sun 2012, Bai 2007, Nappi 2005, Liske 2002

✓ Systematic review meets (or partially meets) prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

† Systematic review meets (or partially meets) some, but not all, prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

X Systematic review does not meet prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

* Systematic review not assessed. A study result is available and reported in another systematic review nominated as the best available evidence.

Y RCT is included in the systematic review, meets our PICO criteria & a study result is available for inclusion in the synthesis.

? RCT is included in the systematic review & meets our PICO criteria, but the systematic review does not adequately report the results. Due to time and resource constraints, only the information presented in the systematic review is reported.

! RCT is included in the systematic review but does not measure the listed outcome.

-- RCT is not included in systematic review.

4.7.4 Risk of bias

Risk of bias assessment for the eligible RCTs as summarised by included systematic reviews are provided in Appendix F1.

Five (5) reviews (Castelo-Branco 2021, Firoozeei 2021, Kanadys 2021, Ghorbani 2019, Franco 2016) used the Cochrane Collaboration's risk of bias assessment tool (54) to asses bias within the included RCTs and provided comprehensive information to make a judgement. The other reviews assessed quality of the RCTs using the Jaded Scale (234) or the Oxford Centre for Evidence-Based Medicine Checklist .

Twelve (12) RCTs (Kamalifard 2017, Lambert 2017, Clifton-Bligh 2015, Dongre 2015, Shakeri 2015, del Giorno 2010, Newton 2006, Uebelhack 2006, Osmers 2005, Atkinson 2004, Tice 2003, Stoll 1987) were judged by the review authors to be at overall low risk of bias. There were concerns of bias in 6 RCTs (Jiang 2015, Charandabi 2013, Shanazi 2013, Pockaj 2006, Jacobson 2001, Wiklund 1999) and for 15 RCTs (Chung 2015, Aghamiri 2016, Lipovac 2012, Li 2011, Abdali 2010, Oh 2010, Kim 2009, van Die 2009, Chung 2007, Frei-Kleiner 2005, Hidalgo 2005, Jeri 2002, van de Weijer 2002, Knight 1999, Baber 1999) the risk of bias was high (mostly related to attrition bias or selective reporting of results).

Risk of bias information for 12 RCTs (Ghazanfarpour 2018, Kashani 2018, Jenabi 2017, Rahimi Kian 2017, Steels 2017, Shamshad Begum 2016, Mirabi 2013, Ehsanpour 2012, Geller 2009, Warnecke 1991, Warnecke 1990) were incomplete, and were assumed to have some concerns of bias.

4.7.5 Summary of findings and evidence statements

4.7.5.1 Primary Comparison (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 10 RCTs did not contribute any data because their results were not adequately reported, either by the primary study or the included systematic reviews.

Western herbal medicine compared to placebo for symptoms of menopause

Patient or population: Symptoms of menopause
Setting: Community
Intervention: WHM (black cohosh, red clover, withania/ashwagandha, fenugreek, valerian, St John's wort, chaste tree berry)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with WHM				
Symptom severity assessed with: GCS, KMI, MRS follow-up: range 8 weeks to 24 months	-	**SMD 0.56 SD lower ^** (0.87 lower to 0.25 lower)	--	1680 (16 RCTs)	⊕⊕⊕◯ MODERATE a,b,c,d,e	WHM probably results in a reduction in symptom severity in people with symptoms of menopause.

Western herbal medicine compared to placebo for symptoms of menopause

Patient or population: Symptoms of menopause
Setting: Community
Intervention: WHM (black cohosh, red clover, withania/ashwagandha, fenugreek, valerian, St John's wort, chaste tree berry)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with WHM				
Hot flush daily frequency follow-up: range 8 weeks to 24 months	-	**SMD 0.46 SD lower ^** (0.80 lower to 0.12 lower)	--	1355 (14 RCTs) †	⊕⊕◯◯ LOW [c,e,f,g,h]	WHM may result in a slight reduction in hot flush daily frequency in people with symptoms of menopause
Sexual functioning assessed with: GCS, KMI, MRS, MenQoL, FSFI follow up: range 6 weeks to 16 weeks	-	**SMD 0.25 SD lower ^** (0.58 lower to 0.08 higher)	--	887 (7 RCTs) ††	⊕⊕⊕◯ MODERATE [c,e,h,i,j]	WHM probably results in little to no difference in sexual functioning in people with symptoms of menopause
Health-related quality of life	-	-	--	(0 studies)	--	The effect of WHM on quality of life in people with symptoms of menopause is unknown
Emotional functioning assessed with: GCS, KMI, MRS follow up: range 6 weeks to 12 weeks	-	**SMD 0.47 SD lower ^** (1.33 lower to 0.39 higher)	--	114 (2 RCTs) †††	⊕◯◯◯ VERY LOW [c,g,k,l,o]	The evidence is very uncertain about the effect of WHM on emotional functioning in people with symptoms of menopause
Depression assessed with: GCS, KMI, MRS, HAM-D follow up: range 8 weeks to 12 months	-	**SMD 0.26 SD lower ^** (1.00 lower to 0.48 higher)	--	585 (5 RCTs) ††††	⊕◯◯◯ VERY LOW [c,e,l,m,n]	The evidence is very uncertain about the effect of WHM on symptoms of depression in people with symptoms of menopause
Anxiety assessed with: GCS, KMI, MRS, HAM-A follow up: range 8 weeks to 12 months	-	**SMD 0.90 SD lower ^** (1.79 lower to 0.01 lower)	--	560 (5 RCTs) †††††	⊕◯◯◯ VERY LOW [c,e,l,m,n]	The evidence is very uncertain about the effect of WHM on anxiety in people with symptoms of menopause

Western herbal medicine compared to placebo for symptoms of menopause

Patient or population: Symptoms of menopause
Setting: Community
Intervention: WHM (black cohosh, red clover, withania/ashwagandha, fenugreek, valerian, St John's wort, chaste tree berry)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with WHM				

* **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
^ As a rule of thumb, an SMD of 0.2 represents a small difference, 0.5 is moderate, and 0.8 is a large difference (55).
# A 25% relative risk reduction/increase was considered important (i.e. RR < 0.75 or RR > 1.25).

† Data from 2 RCTs (total 128 participants) not included here because results were not adequately reported [missing information]. Both RCTs suggested an effect favouring WHM.
†† Data from 4 RCTs (total 365 participants) not included here because results were not adequately reported [missing information]. 2 RCTs suggested no difference between groups and 2 RCTs suggested an effect favouring the WHM.
††† Data from 4 RCTs (total 360 participants) not included here because results were not adequately reported [missing information]. All 4 RCTs suggested an effect favouring the WHM.
†††† Data from 3 RCTs (total 242 participants) not included here because results were not adequately reported [missing information]. All 3 RCTs suggested an effect favouring the WHM.
††††† Data from 3 RCTs (total 231 participants) not included here because results were not adequately reported [missing information]. 2 RCTs suggested an effect favouring the WHM, 1 RCT suggested no important difference between groups.

CI: confidence interval; **MD:** mean difference; **FSFI:** Female Sexual Function Index; **GAQ:** Global assessment questionnaire; **GCS:** Greene Climacteric Scale; **HAM-A:** Hamilton anxiety rating scale; **HAM-D:** Hamilton depression rating scale; **KMI:** Kupperman Menopausal Index; **MenQoL:** Menopause quality of life; **MRS**: Menopause Rating Scale, **SF-36:** 36-item short form health survey; **WHQ:** Women's health questionnaire; **PGWBI:** Psychological general well-being index.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. Five RCTs at high risk of bias (~30% weight) that do not seriously influence the estimate of effect. Certainty of evidence not downgraded.
b. No serious inconsistency. Point estimates vary and confidence intervals of some studies do not overlap. Substantial statistical heterogeneity (I^2 = 89%) that can be partially explained by difference in study characteristics. Certainty of evidence not downgraded.
c. No serious indirectness. The available evidence is in both perimenopausal or menopausal women and can be sensibly applied to the Australian population. The herbs used in the identified studies are comparable to those commonly used in Australia or could be sensibly applied. Certainty of evidence not downgraded.
d. Serious imprecision. Wide confidence intervals (upper and lower bounds overlap with both large and small important differences). Certainty of evidence downgraded.
e. Publication bias not suspected. Certainty of evidence not downgraded.
f. Serious risk of bias. 8 RCTs at high risk of bias (>50% weight) that likely overstate the size of effect. Certainty of evidence downgraded.
g. No serious inconsistency. Point estimates are consistent. Statistical heterogeneity is high (I^2 > 80%) but likely explained through differences in the PICO of included studies. Certainty of evidence not downgraded.
h. Serious imprecision. Wide confidence intervals (upper and lower bounds overlap with both important and no important difference). Certainty of evidence downgraded.
i. No serious risk of bias. Three RCTs at high risk of bias (~36% weight) that do not seriously influence the estimate of effect. Certainty of evidence not downgraded.
j. No serious inconsistency. Point estimate and confidence intervals of one study do not overlap. Statistical heterogeneity is high (I^2 = 78%) likely explained through differences in the PICO of included studies. Certainty of evidence not downgraded.
k. No serious risk of bias. Certainty of evidence not downgraded.
l. Very serious imprecision. Wide confidence intervals (upper and lower bounds overlap with both large and no important differences). Certainty of evidence downgraded 2 levels.

m. Serious risk of bias. Two RCTs at high risk of bias (~40% weight) that overstates the direction or size of the effect. Certainty of evidence downgraded.
n. No serious inconsistency. Point estimates vary and statistical heterogeneity is high (I^2 > 90%) but likely explained through differences in the PICO of included studies. Certainty of evidence not downgraded.
o. Publication bias suspected. Evidence is limited to 2 small trials. There is a strong suspicion of non-reporting of results likely related to the *p* value, direction or magnitude of effect. Certainty of evidence downgraded.

4.7.5.2 Secondary Comparison (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. In the absence of evidence, the effect of WHM compared with inactive control on the prioritised outcomes is unknown.

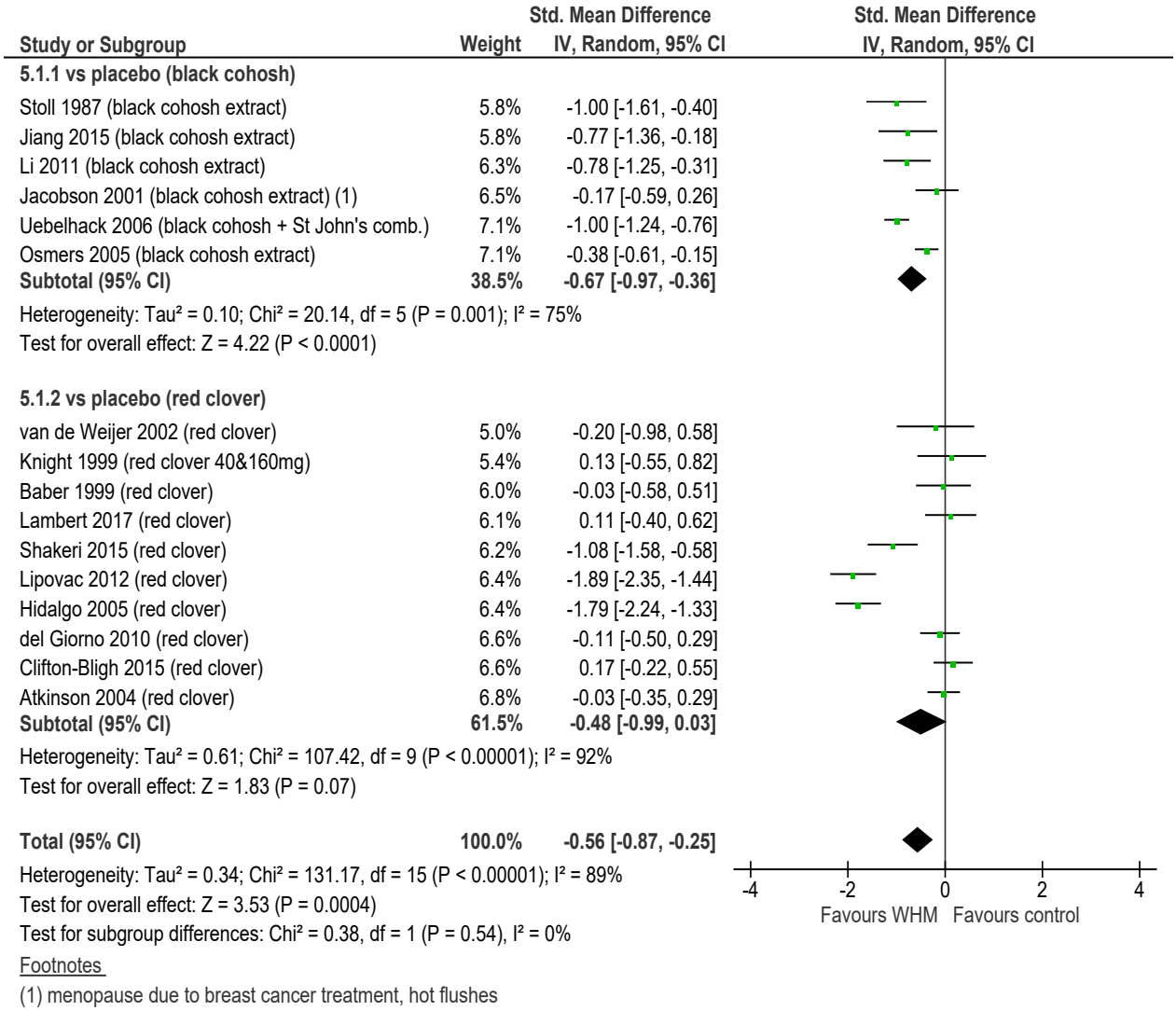
4.7.5.3 Tertiary Comparison (vs active control)

There were 11 RCTs found by the included systematic reviews that compared WHM with active comparators in people with symptoms of menopause, but details about these studies were lacking and no data were provided (see Appendix F2).

4.7.6 Forest plots

Outcome results related to people with symptoms of menopause are presented in Figure 12 (total symptoms), Figure 13 (hot flush daily frequency), Figure 14 (sexual functioning) and Figure 15 (emotional functioning, anxiety, depression)

Figure 12 Forest plot of comparison: WHM vs placebo: Symptoms of menopause - improvement in KMI, MRS or GCS total symptoms scores

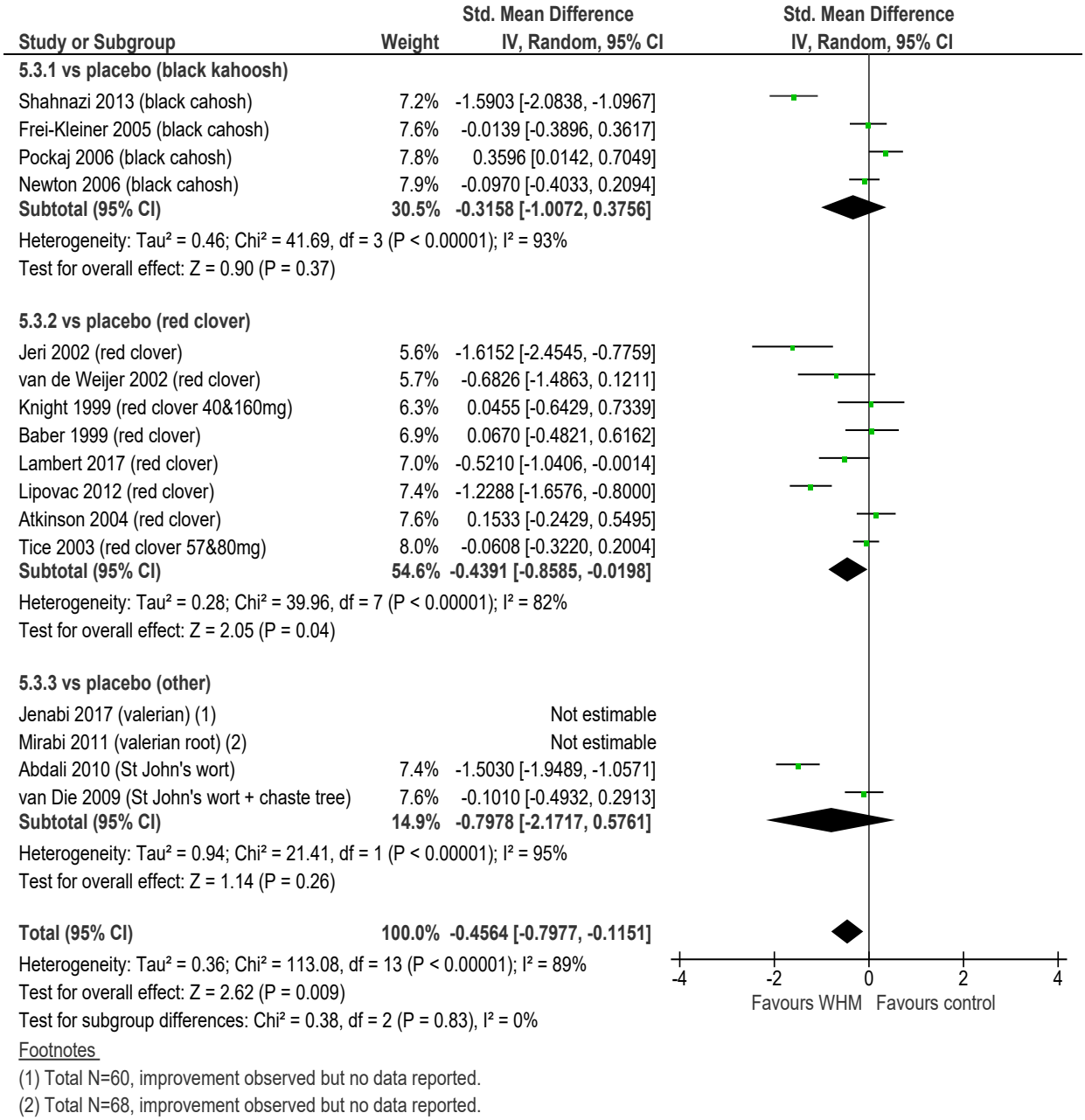


Footnotes

(1) menopause due to breast cancer treatment, hot flushes

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

Figure 13 Forest plot of comparison: WHM vs placebo: Symptoms of menopause – hot flush, daily frequency



Footnotes

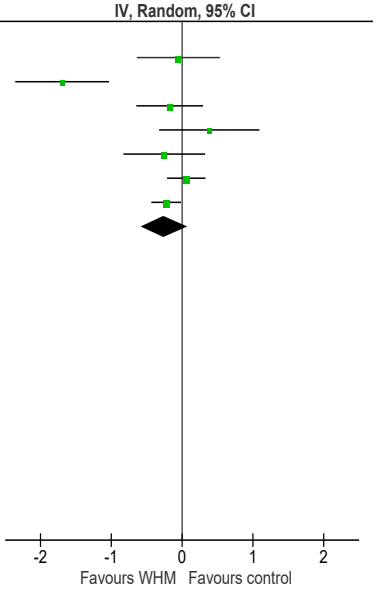
(1) Total N=60, improvement observed but no data reported.

(2) Total N=68, improvement observed but no data reported.

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

Figure 14 Forest plot of comparison: WHM vs placebo: Symptoms of menopause – sexual functioning

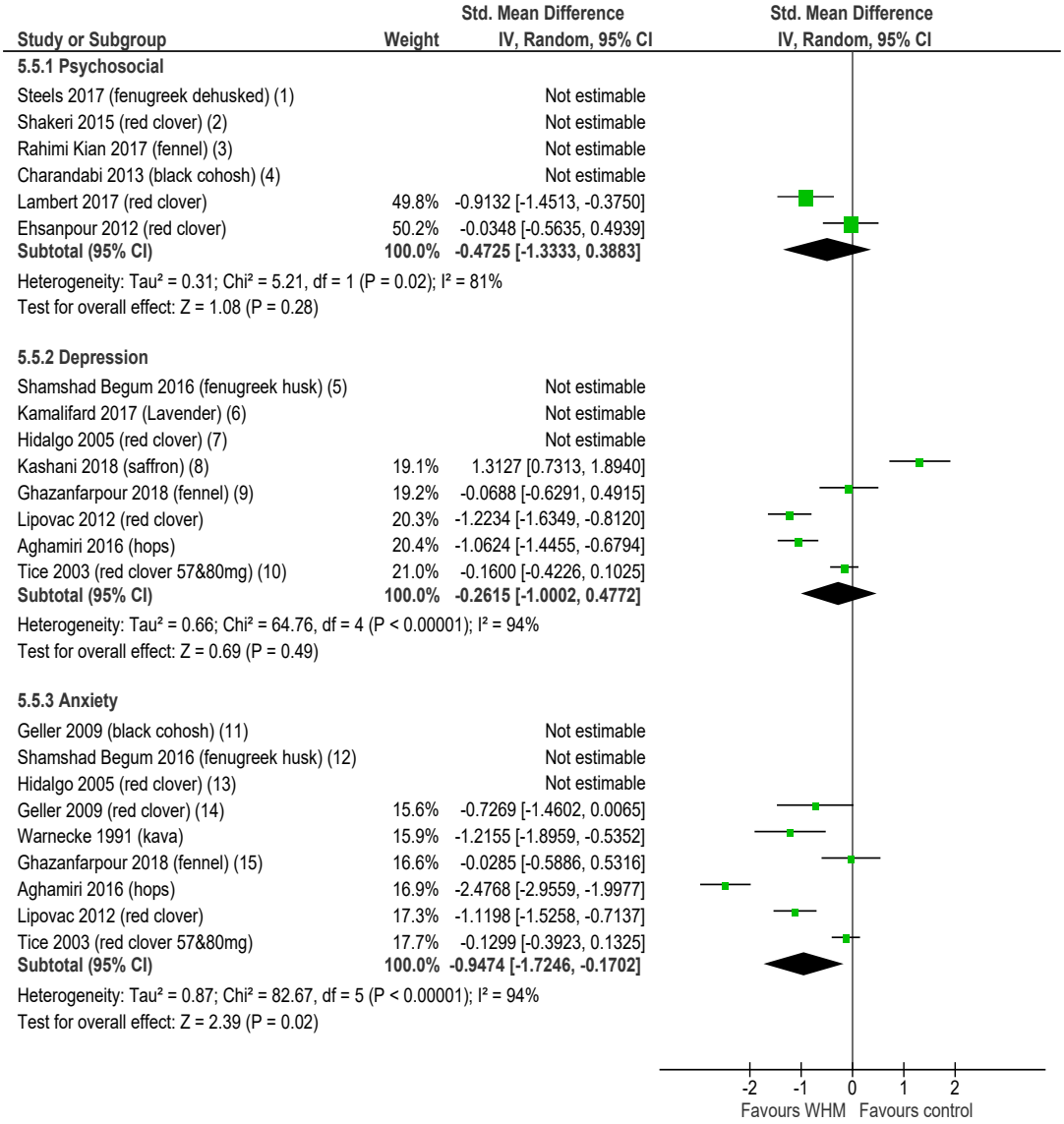
Study or Subgroup	WHM Mean	WHM SD	WHM Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.4.1 vs placebo								
Chung 2015 (ginseng)	-23.98	4.1	23	-23.78	3.28	23	12.7%	-0.05 [-0.63, 0.53]
Dongre 2015 (ashwaganda)	-23.86	2.02	25	-20.06	2.38	25	11.5%	-1.69 [-2.35, -1.04]
Ehsanpour 2012 (red clover)	-21.1	6.224	36	-20	6.224	36	14.7%	-0.17 [-0.64, 0.29]
Kim 2009 (ginseng)	-15.32	21.8001	24	-22.99	13.66	12	10.8%	0.38 [-0.32, 1.08]
Oh 2010 (ginseng)	-22.95	4.74	24	-21.68	5.16	24	12.9%	-0.25 [-0.82, 0.32]
Tice 2003 (red clover 57&80mg)	-19.8	3.394	167	-20	3.394	84	18.2%	0.06 [-0.20, 0.32]
Wiklund 1999 (ginseng)	-6.3	2.5	193	-5.8	1.9	191	19.1%	-0.22 [-0.43, -0.02]
Subtotal (95% CI)			**492**			**395**	**100.0%**	**-0.25 [-0.58, 0.08]**
Heterogeneity: Tau² = 0.14; Chi² = 26.75, df = 6 (P = 0.0002); I² = 78%								
Test for overall effect: Z = 1.47 (P = 0.14)								
5.4.2 missing outcome data								
Rahimi Kian 2017 (fennel) (1)	0	0	45	0	0	45		Not estimable
Shakeri 2015 (red clover) (2)	0	0	36	0	0	36		Not estimable
Shamshad Begum 2016 (fenugreek husk) (3)	0	0	44	0	0	44		Not estimable
Steels 2017 (fenugreek dehusked) (4)	0	0	59	0	0	56		Not estimable
Subtotal (95% CI)			**184**			**181**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								



Footnotes

(1) SR authors noted an effect favour the intervention (*p*=0.013) but no other information provided.
(2) SR authors noted an effect favour the intervention (*p*=0.09) but no other information provided.
(3) SR authors noted an effect favour the intervention (*p*<0.001) but no other information provided.
(4) SR authors noted an effect favour the intervention but no other information provided.

Figure 15 Forest plot of comparison: WHM vs placebo: Symptoms of menopause – emotional functioning, anxiety, depression



Footnotes

(1) missing data. Improved 25% vs 3% from baseline comparing fenugreek with placebo.
(2) SR authors report an effect favouring the intervention (p<0.0001) but no other data provided.
(3) SR authors report an effect favouring the intervention (p<0.001) but no other data provided.
(4) SR authors report an effect favouring the intervention (p<0.0001) but no other data provided.
(5) SR authors report an effect favouring the intervention (p<0.01) but no other data provided.
(6) Data not able to be included (missing information). SR authors report SMD -1.12 (-1.53, -0.70).
(7) missing data. Decrease from baseline of 60% vs 22% comparing red clover with placebo.
(8) Data calculated from WMD 3.38 (2.05, 4.71)
(9) SR authors report no important difference between groups (p=0.83) but no other data provided.
(10) SR authors report no difference between groups (p>0.05) but no other data provided.
(11) SR authors report no difference between groups (p=0.78) but no other data provided.
(12) SR authors report an effect favouring the intervention (p<0.01) but no other data provided.
(13) missing data. Decrease from baseline of 50% vs 11% comparing red clover with placebo.
(14) SR authors report an effect favouring the intervention (p=0.04) but no other data provided.
(15) SR authors report no difference between groups (p=0.83) but no other data provided.

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

4.8 Anxiety

4.8.1 Description of the condition

Anxiety is the most common mental health condition in Australia and the sixth largest contributor to burden of disease, with 1 in 4 people experiencing anxiety at some stage in their life (235, 236). While it is normal to feel anxious or stressed in certain situations, those with an anxiety disorder experience these symptoms more frequently and persistently without an obvious cause. These feelings of anxiety can impact their quality of life and day-to-day functioning (235). There are different types of anxiety presenting with different symptoms, including generalised anxiety disorder, social anxiety, specific phobias, and panic disorders.

Each type of anxiety disorder has its own features, however there are some common symptoms including excessive fear or worrying, panic attacks, racing heart, tightening of the chest, shortness of breath, and avoidance of situations that cause anxiety, which can impact on daily life.

Treatments for anxiety focus on controlling symptoms to minimise their impact on daily life. This can include psychological treatments such as Cognitive Behavioural Therapy, medical treatments such as antidepressants, or an anxiety management strategy (235). Research examining other psychotherapies including alternative herbal treatments has been identified, however more high-quality evidence and efficacy studies are needed to implement herbal therapies into routine clinical practice for managing anxiety (237).

4.8.2 Description of reviews

There were 36 citations (124, 125, 214, 225, 238-269) corresponding to 36 systematic reviews identified in the literature search that evaluated the effectiveness of WHMs in people with anxiety (Ghaderi 2020, Janda 2020, Sayed 2020, Shinjyo 2020, Donelli 2019, Hieu 2019, Marx 2019, Moller 2019, Yap 2019, Baric 2018, Ooi 2018, Smith 2018, Brondino 2013, Hidalgo 2007, Miyasaka 2007, Miyasaka 2006, Witte 2005, Pittler 2003, Pittler 2000, Lopresti 2021, Lopresti 2022, 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). No additional reviews were identified in the Department's public call for evidence (see Appendix C2). There were two systematic reviews awaiting classification (270, 271) that were published in a language other than English (see Appendix C4) and no ongoing reviews (see Appendix C5).

A summary of the PICO criteria of the included reviews is provided in Appendix D3.1.1.

The populations eligible for inclusion in the reviews were typically participants with anxiety or psychiatric conditions, with some reviews requiring participants be diagnosed with a specific anxiety disorder (Janda 2020, Donelli 2019, Hieu 2019, Marx 2019, Moller 2019, Baric 2018, Ooi 2018, Smith 2018, Sayed 2020, Yap 2019, Brondino 2013, Hidalgo 2007, Miyasaka 2007, Miyasaka 2006, Witte 2005, Pittler 2003, Pittler 2000, Sarris 2018, Pratte 2014, Sarris 2013, Sarris 2012, Sarris 2011, Lakhan 2010, Provino 2010, Sarris 2009, Sarris 2007, Ernst 2006, Jorm 2004). Other reviews had no population restrictions and were focused on the efficacy of a particular herb across various conditions (Ghaderi 2020, Lopresti 2021, Tandon 2020, Miroddi 2013) or presented results for RCTs where anxiety was measured as an outcome (Lopresti 2022, Lopresti 2021, Kim 2018, Perry 2012).

There were 10 reviews published in 2018 or after that were prioritised for critical appraisal and data extraction (Ghaderi 2020, Janda 2020, Shinjyo 2020, Donelli 2019, Hieu 2019, Marx 2019, Moller 2019, Baric 2018, Ooi 2018, Smith 2018). One review published prior to 2018 (Brondino 2013) was also included, Review details, including outcome domains and measures, and the risk of bias of eligible RCTs are provided in Appendix F1.

4.8.3 Description of studies

Within the eligible systematic reviews, there were 32 RCTs that met our PICO criteria, almost all of which examined the effect of WHM compared with placebo in participants with anxiety, either diagnosed as generalised anxiety disorder or having met a threshold indicative of symptoms of anxiety or stress. Studies in participants with acute anxiety associated with surgery or other conditions (e.g. childbirth, dental procedures) were not included here, but included with studies relating to the underlying condition (e.g. dysmenorrhea, insomnia).

An overlap table of the RCTs within the included systematic reviews is shown in Table 9.

There were 13 RCTs that focused on the effectiveness of kava (Savage 2015, Sarris 2013, Sarris 2009, Connor 2006, Geier 2004, Lehrl 2004, Boerner 2003, Gastpar 2003, Connor 2002, Malsch 2001, Singh 1998, Volz 1997, Kinzler 1991). The other WHMs considered by the included RCTs were Withania (Lopresti 2019, Kyati 2013, Auddy 2008, Andrade 2000), German chamomile (Amsterdam 2009, Mao 2016), ginkgo biloba (Woelk 2007), lavender oil (oral) (Kasper 2017, Kasper 2016, Kasper 2015, Kasper 2014, Kasper 2010, Woelk 2010), passiflora (Akhondzadeh 2001), rhodiola (Cropley 2015), saffron (Lopresti 2018, Jafarnia 2017, Mazidi 2016), and Valerian root (Andreatini 2002). Only 4 of these 9 herbs are marked as a Tier 1 herb included in the Western herbal medicine curriculum for Nervous system disorders (i.e. most commonly taught in Australian curriculum for this condition; see Appendix A6.3).

Many of the included RCTs were conducted in Germany (Kasper 2017, Kasper 2016, Kasper 2015, Kasper 2014, Kasper 2010, Woelk 2010, Woelk 2007, Boerner 2003), with other countries such as Australia (Lopresti 2018, Savage 2015, Sarris 2013, Sarris 2009), Brazil (Andreatini 2002), India (Lopresti 2019, Khyati 2013, Auddy 2008, Andrade 2000), Iran (Jafarnia 2017, Mazidi 2016, Akhonzadeh 2001) and the United States (Amsterdam 2009, Mao 2016, Connor 2006, Connor 2002) also represented. Sample sizes ranged from 24 to 539 (total >2500 participants).

Results for the Primary Comparison: WHM versus placebo are provided in the Summary of Findings tables (see Section 4.8.5).

There were no studies found for the Secondary Comparison: WHM versus inactive control (no intervention, usual care). Results for the Tertiary Comparison (versus active comparators) are provided in Appendix F2.

4.8.4 Risk of bias

Risk of bias assessment for the eligible RCTs as summarised by included systematic reviews are provided in Appendix F1.

Nine (9) reviews (Ghaderi 2020, Janda 2020, Sayad 2020, Donelli 2019, Hieu 2019, Moller 2019, Baric 2018, Ooi 2018, Brondino 2013) used the Cochrane Collaboration's risk of bias assessment tool (54) to asses bias within the included RCTs and provided comprehensive information to make a judgement. The other 2 reviews (Shinjyo 2020, Marx 2019) assessed quality of the RCTs using the Jadad Scale (234).

Many of the eligible RCTs were judged by the included systematic reviews to be at overall high risk of bias (Kasper 2017, Kasper 2016, Mao 2016, Kasper 2015, Woelk 2010, Amsterdam 2009, Connor 2006, Akhondzadeh 2001) with concerns of bias relating to non-blinding of participants, selective reporting and high rates of attrition. In most other studies, the risk of bias was unclear (Kasper 2014, Andreatini 2002, Connor 2002, Malsch 2001, Singh 1998, Volz 1997, Kinzler 1991) or not assessed (Lopresti 2018 Jafarnia 2017 Mazidi 2016, Cropley 2015, Sarris 2009, Geier 2004, Lehrl 2004, Gastpar 2003).

There were 8 RCTs judged to be at overall low risk of bias (Lopresti 2019, Khyati 2013, Sarris 2013, Kasper 2010, Auddy 2008, Woelk 2007, Boerner 2003, Andrade 2000).

Table 9 List of included systematic reviews and overlap with eligible RCTs (per outcome): Anxiety

Review ID	Best available [a]	Prioritised outcome domain [b]	Study ID: Lopresti 2019	Lopresti 2018	Jafarnia 2017	Kasper 2017	Kasper 2016	Keefe/Mao 2016 [c]	Mazidi 2016	Cropley 2015	Kasper 2015	Savage 2015 [d]	Kasper 2014	Khyati 2013	Sarris 2013	Kasper 2010	Woelk 2010	Amsterdam 2009	Sarris 2009	Auddy 2008	Woelk 2007	Connor 2006	Jacobs 2005 [e]	Geier 2004	Lehrl 2004	Boerner 2003	Castpar 2003	Andreatini 2002	Connor 2002	Akhondzadeh 2001	Malsch 2001	Andrade 2000	Singh 1998	Volz 1997	Kinzler 1991	Warnecke 1991 [f]	Warnecke 1990 [f]
Ghaderi 2020	✓	Anxiety	--	--	✓	--	--	--	✓	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Janda 2020	†		--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	✓	--	--	--	--	--	--
Sayed 2020	--		--	--	--	✓	✓	--	--	--	✓	--	✓	--	--	✓	✓	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Shinjyo 2020	✓		--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	✓	--	--	--	--	--	--	--	--
Donelli 2019	✓		--	--	--	✓	✓	--	--	--	✓	--	✓	--	--	✓	✓	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Hieu 2019	✓		--	--	--	--	--	✓	--	--	--	--	--	--	--	--	--	✓	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Lopresti 2019	--		?	--	--	--	--	--	--	--	--	--	--	?	--	--	--	--	--	?	--	--	--	--	--	--	--	--	--	--	?	--	--	--	--	--
Marx 2019	✓		--	✓	✓	--	--	--	✓	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Moller 2019	✓		--	--	--	--	✓	--	--	--	✓	--	--	--	--	✓	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Yap 2019	--		--	--	--	--	✓	--	--	--	✓	--	✓	--	--	✓	✓	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Baric 2018	✓		--	--	--	--	--	✓	--	--	--	--	✓	--	✓	--	✓	✓	--	--	--	--	--	--	--	✓	--	✓	✓	✓	✓	--	--	✓	--	--	--
Kim 2018	✓		--	--	--	--	--	--	--	--	?	--	--	--	--	?	--	--	--	--	--	--	?	--	--	?	--	--	--	--	--	--	--	--	--	--	--
Ooi 2018	✓		--	--	--	--	--	--	--	--	--	✓	--	--	✓	--	--	--	--	--	--	✓	--	--	--	✓	--	--	✓	--	--	--	--	--	--	--	--
Sarris 2018	--		--	--	--	--	--	?	--	?	--	--	--	--	?	--	--	?	?	--	?	--	--	--	--	?	--	--	--	?	--	--	--	--	--	--	--
Smith 2018	†		--	--	--	--	--	--	--	--	--	--	--	--	✓	--	--	--	✓	--	--	--	--	✓	✓	--	✓	--	✓	--	✓	--	--	--	--	--	--
Brondino 2013	✓		--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	✓	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Witte 2005	--		--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	✓	✓	--	--	--	--	✓	--	--	✓	✓	✓	--
Pittler 2003	--		--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	✓	✓	--	✓	--	✓	--	✓	--	✓	✓	✓	✓	✓

Table 9 List of included systematic reviews and overlap with eligible RCTs (per outcome): Anxiety (cont'd)

Review ID	Best available [a]	Prioritised outcome domain [b]	Lopresti 2019	Lopresti 2018	Jafarnia 2017	Kasper 2017	Kasper 2016	Keefe/Mao 2016 [c]	Mazidi 2016	Cropley 2015	Kasper 2015	Savage 2015 [d]	Kasper 2014	Khyati 2013	Sarris 2013	Kasper 2010	Woelk 2010	Amsterdam 2009	Sarris 2009	Auddy 2008	Woelk 2007	Connor 2006	Jacobs 2005 [e]	Geier 2004	Lehrl 2004	Boerner 2003	Gastpar 2003	Andreatini 2002	Connor 2002	Akhondzadeh	Malsch 2001	Andrade 2000	Singh 1998	Volz 1997	Kinzler 1991	Warnecke 1991 [f]	Warnecke 1990 [f]
Ghaderi 2020	✓	Depression	--	--	!	--	--	--	✓	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Donelli 2019	✓	Depression	--	--	--	!	?	--	--	--	!	--	?	--	--	!	!	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Hieu 2019	✓	Depression	--	--	--	--	--	!	--	--	--	--	--	--	--	--	--	!	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Marx 2019	✓	Depression	--	✓	!	--	--	--	?	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Hieu 2019	✓	CGI - severity	--	--	--	--	--	!	--	--	--	--	--	--	--	--	--	?	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Moller 2019	✓	CGI - global	--	--	--	--	✓	--	--	--	✓	--	--	--	--	✓	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Moller 2019	✓	HRQoL	--	--	--	--	?	--	--	--	!	--	--	--	--	?	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Janda 2020	†	Sleep quality	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	!	--	--	--	--	--	--	--
Shinjyo 2020	✓	Sleep quality	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	!	--	--	--	--	--	--	--	--	--
Hieu 2019	✓	Sleep quality	--	--	--	--	--	!	--	--	--	--	--	--	--	--	--	!	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Moller 2019	✓	Sleep quality	--	--	--	--	!	--	--	--	?	--	--	--	--	?	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--

Notes:
a. Only critical or important outcome domains with available data reported here (see Appendix D1.1)
b. Best available information means the systematic review meets AMSTAR-2 domains 4, 8, 9, & 11 (see Framework for selecting the systematic review from which to extract data [Appendix B1]).
c. Single RCT with short (8 week) and longer-term (34 weeks) data.
d. Protocol only. RCT complete but results not published.
e. Mixed population. RCT included in the evidence synthesis for insomnia.
f. RCT included in the evidence synthesis for women with symptoms of menopause.
✓ Systematic review meets (or partially meets) prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).
† Systematic review meets (or partially meets) some, but not all, prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).
X Systematic review does not meet prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).
Y RCT is included in the systematic review, meets our PICO criteria & a study result is available for inclusion in the synthesis.
? RCT is included in the systematic review & meets our PICO criteria, but the systematic review does not adequately report the results. Due to time and resource constraints, only the information presented in the systematic review is reported.
! RCT is included in the systematic review but does not measure the listed outcome.
-- RCT is not included in systematic review.

4.8.5 Summary of findings and evidence statements

4.8.5.1 Primary Comparison (vs placebo)

There were 30 RCTs found by the included systematic reviews that compared WHM with placebo in people with symptoms of anxiety. Of these, 21 RCTs contributed data relevant to 6 outcomes (anxiety, depression, global improvement, HRQoL-mental, HRQoL-physical, sleep quality) (Lopresti 2018, 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).

Two RCTs did not provide any data, either because the RCT results are not published (Savage 2015) or the study was discontinued (Connor 2006). Another 7 RCTs did not contribute any data because their results were not adequately reported , either by the primary study or by the systematic reviews (Lopresti 2019, Cropley 2015, Khyati 2013, Auddy 2008, Andrade 2000, Singh 1998, Kinzler 1991).

Western herbal medicine compared to placebo for Symptoms of anxiety

Patient or population: Anxiety
Setting: Community
Intervention: WHM (kava, lavender, saffron, Withania, valerian, Passiflora, gingko biloba, German chamomile)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with WHM				
Anxiety assessed with: HAM-A, BAI, ASI, RCADS follow-up: range 3 weeks to 24 weeks	-	**SMD 0.43 SD lower ^** (0.59 lower to 0.28 lower)	--	2087 (20 RCTs) †	⨁⨁⨁◯ MODERATE a,b,c,d,e	WHM probably results in a slight reduction in anxiety in people with symptoms of anxiety
Depression assessed with: HAM-D, BDI, follow-up: range 8 weeks to 12 weeks	-	**SMD 0.58 SD lower ^** (0.93 lower to 0.22 lower)	--	129 (2 RCTs) ††	⨁⨁◯◯ LOW b,c,f,g,h	WHM may result in a reduction in depressive symptoms in people with symptoms of anxiety
Global improvement assessed with: CGI follow-up: range 8 weeks to 10 weeks	-	**SMD 0.49 SD lower ^** (0.81 lower to 0.17 lower)	--	670 (3 RCTs) †††	⨁⨁◯◯ LOW b,c,f,g,h	WHM may result in a reduction in overall symptoms in people with symptoms of anxiety
HRQoL - mental assessed with SF-36 (higher is better) scale range: 0 to 100 follow-up: 10 weeks	-	**MD 10.19 higher** (5.78 higher to 14.61 higher)	--	508 (2 RCTs)	⨁⨁◯◯ LOW b,c,f,g,h	WHM may result in an improvement in quality of life (emotional) in people with symptoms of anxiety #
HRQoL - physical assessed with SF-36 (higher is better) scale range: 0 to 100 follow-up: 10 weeks	-	**MD 7.32 higher** (3.88 higher to 10.77 higher)	--	508 (2 RCTs)	⨁⨁◯◯ LOW b,c,f,g,h	WHM may result in a slight improvement in quality of life (physical) in people with symptoms of anxiety #
Sleep quality assessed with PSQI scale range: 0 to 21 (higher is worse) follow-up: 10 weeks	-	**MD 1.36 lower** (2.28 lower to 0.44 lower)	--	382 (2 RCTs)	⨁⨁◯◯ LOW b,c,f,g,h	WHM may result in a slight improvement in sleep quality in people with symptoms of anxiety #

Western herbal medicine compared to placebo for Symptoms of anxiety

Patient or population: Anxiety
Setting: Community
Intervention: WHM (kava, lavender, saffron, Withania, valerian, Passiflora, gingko biloba, German chamomile)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with WHM				
Fatigue	-	-	--	(0 studies)	--	The effect of WHM on fatigue in people with symptoms of anxiety is unknown

* **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
^ As a rule of thumb, an SMD of 0.2 represents a small difference, 0.5 is moderate, and 0.8 is a large difference (55).
# Effect estimates were considered on three levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale).

† Data from 5 RCTs (total 390 participants) not included here because results were not adequately reported [missing information]. 3 RCTs suggested an effect favouring the WHM and 2 RCTs suggested no important difference.
†† Data from 2 RCTs (total 651 participants) not included here because results were not adequately reported [missing information].
††† Data from one RCT (total 57 participants) not included here because results were not adequately reported [missing information].

ASI: Anxiety Status Inventory; **BAI**: Beck Anxiety Inventory; **BDI**: Beck Depression Inventory; **CI:** confidence interval; **MD:** mean difference; **HAM-A:** Hamilton anxiety rating scale; **HAM-D:** Hamilton depression rating scale; **RCADS:** Revised Child Anxiety & Depression Scale; **SF-36:** 36-item short form health survey

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. Six RCTs at high risk of bias (~35% weight) that do not seriously influence the estimate of effect. Certainty of evidence not downgraded.
b. No serious inconsistency. Certainty of evidence not downgraded.
c. No serious indirectness. The available evidence is in people with diagnosed anxiety or symptoms of anxiety and can be sensibly applied to the Australian population. The herbs used in the identified studies are comparable to those commonly used in Australia or could be sensibly applied. Certainty of evidence not downgraded.
d. Serious imprecision. Wide confidence intervals (upper and lower bounds overlap with both moderate and small important differences). Certainty of evidence downgraded.
e. Publication bias not suspected. Certainty of evidence not downgraded.
f. No serious risk of bias. Certainty of evidence not downgraded.
g. Serious imprecision. Wide confidence intervals (upper and lower bounds overlap with both large and small important differences). Certainty of evidence downgraded.
h. Publication bias suspected. There is a strong suspicion of non-reporting of results likely related to the *p* value, direction or magnitude of effect. Certainty of evidence downgraded.

4.8.5.2 Secondary Comparison (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 anxiety. In the absence of evidence, the effect of WHM compared with inactive control on the prioritised outcomes is unknown.

4.8.5.3 Tertiary Comparison (vs active control)

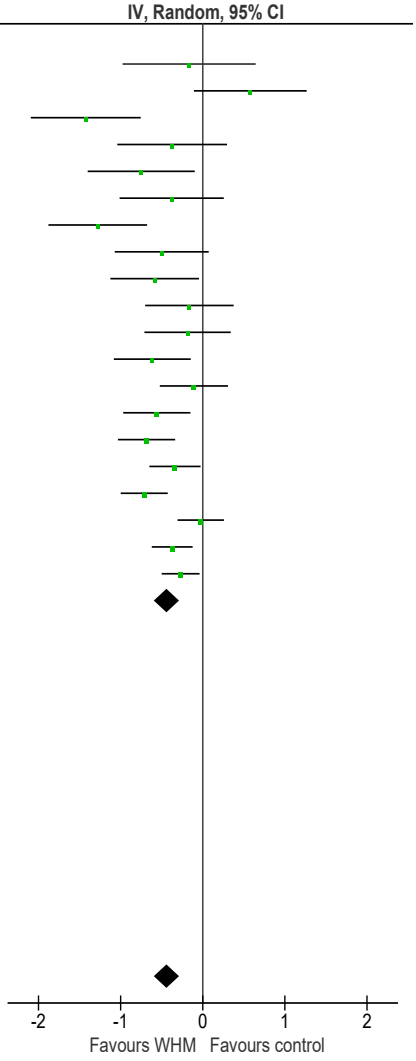
There were 6 RCTs found by the included systematic reviews that compared WHM with active comparators (see Appendix F2).

4.8.6 Forest plots

Outcome results related to people with symptoms of anxiety are presented in Figure 16 (anxiety), Figure 17 (depression) and Figure 18 (clinical global improvement). Forest plots for HRQoL and sleep quality are not provided as individual study data was not provided by the systematic review reporting the pooled results.

Figure 16 Forest plot of comparison: WHM vs placebo: Symptoms of anxiety – anxiety

Study or Subgroup	WHM Mean	WHM SD	WHM Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
6.1.1 Anxiety (HAM-A, unless noted)								
Andreatini 2002 (valerian root)	14.6	9.8	12	16	6.1	12	2.6%	-0.17 [-0.97, 0.64]
Connor 2002 (kava)	14.2	8.3	17	10.3	4.4	18	3.3%	0.58 [-0.10, 1.26]
Sarris 2009 (kava) (1)	11.26	4.47	29	19.5	7.26	18	3.4%	-1.42 [-2.09, -0.76]
Akhondzadeh 2001 (passiflora)	-5.5	0.75	18	-5.1	1.28	18	3.4%	-0.37 [-1.03, 0.29]
Jafarnia 2017 (saffron)	-0.9	2.4847	20	1	2.4847	20	3.5%	-0.75 [-1.39, -0.11]
Malsch 2001 (kava) (2)	-3	7.5	20	-0.6	4.6	20	3.6%	-0.38 [-1.00, 0.25]
Mazidi 2016 (saffron) (3)	-2.19	2.4592	30	1	2.4592	24	3.9%	-1.28 [-1.87, -0.69]
Geier 2004 (kava)	14.8	4.3	25	16.8	3.55	25	4.1%	-0.50 [-1.06, 0.06]
Amsterdam 2009 (chamomile)	-8.2	5.3329	28	-4.8	6.0841	29	4.4%	-0.59 [-1.12, -0.05]
Lehrl 2004 (kava) (4)	-10.6	7.3	34	-9.2	10	23	4.4%	-0.16 [-0.69, 0.37]
Sarris 2013 (kava)	14.03	7.01	27	15.26	6.2	31	4.5%	-0.18 [-0.70, 0.33]
Woelk 2007 (ginkgo biloba) (5)	-13.2423	8.5322	52	-7.8	9.2	30	5.0%	-0.61 [-1.07, -0.15]
Mao 2016 (chamomile)	1	4.5	46	1.5	4.7	47	5.6%	-0.11 [-0.51, 0.30]
Volz 1997 (kava)	9.7	9.9	52	15.2	9.6	48	5.7%	-0.56 [-0.96, -0.16]
Gastpar 2003 (kava) (6)	39	2.35	71	40.6	2.3	70	6.4%	-0.68 [-1.02, -0.34]
Kasper 2015 (lavender)	-12	7.8	86	-9.35	7.8	84	6.8%	-0.34 [-0.64, -0.04]
Kasper 2010 (lavender)	-16.01	8.63	104	-9.51	9.51	108	7.1%	-0.71 [-0.99, -0.43]
Kasper 2017 (lavender) (7)	-11.6	8.1	103	-11.4	8	102	7.2%	-0.02 [-0.30, 0.25]
Kasper 2014 (lavender)	-12.8	8.7	135	-9.5	9	136	7.6%	-0.37 [-0.61, -0.13]
Kasper 2016 (lavender)	-10.78	9	159	-8.35	9	156	7.8%	-0.27 [-0.49, -0.05]
Subtotal (95% CI)			**1068**			**1019**	**100.0%**	**-0.43 [-0.59, -0.28]**
Heterogeneity: Tau² = 0.07; Chi² = 48.92, df = 19 (P = 0.0002); I² = 61%								
Test for overall effect: Z = 5.57 (P < 0.00001)								
6.1.2 Outcome not adequately reported (missing data)								
Lopresti 2018 (saffron) (8)	0	0	38	0	0	37		Not estimable
Auddy 2006 (withania) (9)	0	0	100	0	0	30		Not estimable
Khyati 2013 (withania) (10)	0	0	44	0	0	42		Not estimable
Lopresti 2019 (withania) (11)	0	0	30	0	0	30		Not estimable
Andrade 2000 (withania) (12)	0	0	20	0	0	19		Not estimable
Subtotal (95% CI)			**232**			**158**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Total (95% CI)			**1300**			**1177**	**100.0%**	**-0.43 [-0.59, -0.28]**
Heterogeneity: Tau² = 0.07; Chi² = 48.92, df = 19 (P = 0.0002); I² = 61%								
Test for overall effect: Z = 5.57 (P < 0.00001)								
Test for subgroup differences: Not applicable								



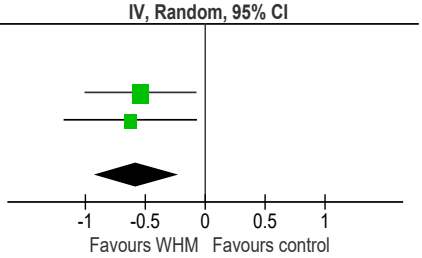
Footnotes

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

Figure 17 Forest plot of comparison: WHM vs placebo: Symptoms of anxiety – depression

Study or Subgroup	WHM Mean	WHM SD	WHM Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Kasper 2014 (lavender) (1)	0	0	222	0	0	114		Not estimable
Kasper 2016 (lavender) (2)	0	0	159	0	0	156		Not estimable
Lopresti 2018 (saffron)	-1.569	1.0428	38	-1	1.0428	37	58.8%	-0.54 [-1.00, -0.08]
Mazidi 2016 (saffron) (3)	-1.34	3.6888	30	1	3.6888	24	41.2%	-0.63 [-1.18, -0.07]
Total (95% CI)			**68**			**61**	**100.0%**	**-0.58 [-0.93, -0.22]**

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 3.19 (P = 0.001)



Footnotes
(1) not reported
(2) not reported
(3) BDI

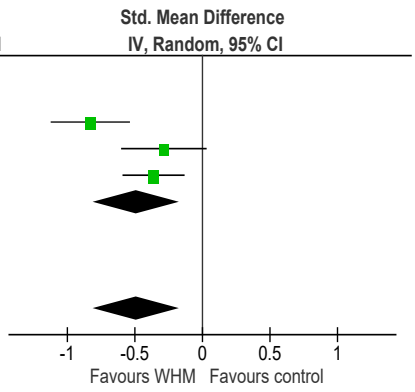
Figure 18 Forest plot of comparison: WHM vs placebo: Symptoms of anxiety – Global improvement

Study or Subgroup	WHM Mean	WHM SD	WHM Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
6.4.2 Item 2 - global change								
Amsterdam 2009 (chamomile) (1)	0	0	28	0	0	29		Not estimable
Kasper 2010 (lavender)	1.83	1.2	98	2.83	1.2	103	32.5%	-0.83 [-1.12, -0.54]
Kasper 2015 (lavender)	2.49	1.08	80	2.8	1.08	80	31.2%	-0.29 [-0.60, 0.03]
Kasper 2016 (lavender)	2.68	1.24	155	3.13	1.24	154	36.3%	-0.36 [-0.59, -0.14]
Subtotal (95% CI)			**361**			**366**	**100.0%**	**-0.49 [-0.81, -0.17]**

Heterogeneity: Tau² = 0.06; Chi² = 8.21, df = 2 (P = 0.02); I² = 76%
Test for overall effect: Z = 3.01 (P = 0.003)

Total (95% CI)			**361**			**366**	**100.0%**	**-0.49 [-0.81, -0.17]**

Heterogeneity: Tau² = 0.06; Chi² = 8.21, df = 2 (P = 0.02); I² = 76%
Test for overall effect: Z = 3.01 (P = 0.003)
Test for subgroup differences: Not applicable



Footnotes
(1) not reported

4.9 Depression

4.9.1 Description of the condition

Depression is a highly prevalent mood disorder having the third highest burden of all diseases in Australia (272), affecting 1 in every 16 Australians (273) and more than 300 million people worldwide (274). Depression is characterised by intense feeling of sadness that impact one's physical and mental health for extended periods of time. Those experiencing depression will often report symptoms of low mood, loss of interest or pleasure in most activities, sleep disturbances, changes in appetite or unintentional changes of weight, decreased energy, either slowed or agitated movement, decreased concentration and, in some cases, feelings of guilt, worthlessness and thought of suicide (275). Depressive symptoms can become chronic, leading to substantial impairment in an individual's ability to function in everyday life (276).

There are several different types of depressive disorders that are characterised by the specific symptoms experienced by the person, as well as the severity of the symptoms - either mild, moderate, or severe. Major depressive disorder is the most commonly diagnosed depressive disorder in Australia, however, several other types including bipolar disorder, cyclothymic disorder, dysthymic disorder and seasonal affective disorder are also recognised within the Australian healthcare context (277). A variety of social, psychological, and biological factors contribute to depression. In particular, people who have experienced adverse life events are at higher risk of developing depression. In Australia, females are more likely to be diagnosed (273).

There are many known and effective treatments for depression that are highly dependent on the severity and pattern of depressive episodes. Traditional treatments offered by health-care providers include psychological treatments such as behavioural activation, cognitive behavioural therapy and interpersonal psychotherapy, and/or antidepressant medication (274). Alternative interventions such as yoga, mindfulness, relaxation, breathing exercises and herbalism are becoming increasingly popular worldwide (278, 279).

4.9.2 Description of reviews

There were 51 citations (116, 124, 130, 156, 214, 242, 258, 266, 267, 280-315) corresponding to 51 systematic reviews identified in the literature search that evaluated the effectiveness of WHMs in people with depression. No additional reviews were identified in the Department's public call for evidence (see Appendix C2). There were 6 systematic reviews (316-321) awaiting classification that were published in a language other than English (see Appendix C4) and no ongoing reviews (see Appendix C5).

A summary of the PICO criteria of the eligible systematic reviews is provided in Appendix D3.2.1.

The populations eligible for inclusion in the reviews were often specific to those experiencing symptoms of depression or major depressive disorder, with many reviews also including people with depression associated with other underlying comorbidities (e.g. diabetes, coronary artery disease, symptoms of menopause). Other reviews had no population restrictions but had focused on the effect of a specific WHM and presented results that included at least one study in people with depression. Seventeen (17) reviews were focused on the evidence relating to St John's wort (Apaydin 2016, Ng 2017, Cui 2016, Maher 2016, Linde 2009, Sarris 2009, Gahlsdorf 2007, Clement 2006, Jorm 2006, Frazer 2005, Whiskey 2001, Gaster 2000, Williams 2000, Kim 1999, Stevinson 1999, Volz 1997, Ernst 1995).

The other reviews included evidence relating to saffron (Dai 2020, Ghaderi 2020, Khaksarian 2019, Marx 2019, Toth 2019, Yang 2018, Karimi 2021, Mousavi 2021, Pourmasoumi 2019, Hausenblas 2015, Hausenblas 2013, Ulbricht 2011), turmeric (Wang 2021, Fusar-Poli 2020, Hallajzadeh 2019, Sahebkar 2016c, Ng 2017a, Al-Karawi 2016, Matias 2021), lavender (Firoozeei 2021), rhodiola (Hung 2011, Ulbricht 2011a), gingko biloba (Jorm 2002) or any herbal or complementary medicine (Lopresti 2022, Asher 2017, Kim 2018a, McCloskey 2018, Sarris 2018, Yeung 2018, Dhingra 2012, Dwyer 2011, Sarris 2011a, Morgan 2008, Sarris 2007). Six (6) reviews (Lopresti 2022, Karimi 2021, Mousavi 2021, Hallajzadeh 2019, Pourmasoumi 2019, Sahebkar 2016c) were focused on outcomes not critical or important to this review (e.g. liver enzymes, stress biomarkers, endothelial function, cardiovascular risk factors).

Ten (10) systematic reviews (Firoozeei 2021, Wang 2021, Dai 2020, Fusar-Poli 2020, Ghaderi 2020, Khaksarian 2019, Marx 2019, Toth 2019, Yang 2018, Apaydin 2016) were prioritised for critical appraisal and data extraction as they presented results in a meta-analysis and were judged to provide the best available evidence. Review details, including outcome domains and measures, and the risk of bias of eligible RCTs are provided in Appendix F1.

4.9.3 Description of studies

Within the eligible systematic reviews, there were 64 RCTs that met our PICO criteria. Most primary studies were conducted in people with major depressive disorder (diagnosed according to DSM-IV criteria) or symptoms of depression that met a threshold pre-specified by the study investigators. Two RCTs (Kashani 2016, Tabeshpour 2017) were in people with post-partum depression, one RCT (Lingaerde 1999) was in people with seasonal affective disorder, and one RCT (Kell 2017) was in people with low mood but who did not have a diagnosis of depression. Studies in participants with depression associated with surgery (e.g. after cardiopulmonary bypass or percutaneous intervention), mixed with anxiety or other conditions were not included here. These studies are included with the evidence synthesis relating to the underlying condition (e.g. dysmenorrhea, menopause, metabolic syndrome).

An overlap table of the RCTs that met our PICO criteria from the included systematic reviews is shown in Table 10.

There were 35 RCTs that focused on the effectiveness of St John's wort in people with major depressive disorder that had been comprehensively reviewed by other systematic reviews (see Ng 2017, Apaydin 2016, Cui 2016). Due to time and resource constraints, studies assessing St John's wort were not individually considered in this Overview. Instead, the meta-analysis results presented by the best available systematic review (Apaydin 2016) are reported.

The other 29 RCTs considered WHMs such as saffron (Jelodar 2018, Ghajar 2017, Kashani 2016, Kell 2017, Tabeshpour 2017, Sahraian 2016, Talaei 2015, Kashani 2013, Modabbernia 2012, AkhondzadehBasti 2008, AkhondzadehBasti 2007, Moshiri 2006, Akhondzadeh 2005, Noorbala 2005, Akhondzadeh 2004), turmeric (Kanchanatawan 2018, Lopresti 2017, Panahi 2015, Yu 2015, Lopresti 2014, Sanmukhani 2014, Bergman 2013), lavender (Araj-Khodaei 2020, Nikfarjam 2017, Nikfarjam 2013, Akhondzadeh 2003), gingko (Lindgaerde 1999) and rhodiola (Mao 2015, Darbinyan 2007). Of these, only 2 (St John's wort and lavender) are marked as a Tier 1 herb included in the Western herbal medicine curriculum for Nervous system disorders (i.e. most commonly taught in Australian curriculum for this condition; see Appendix A6.3).

The majority of included studies (18) were conducted in Iran (Araj-Khodaei 2020, Jelodar 2018, Ghajar 2017, Kashani 2017, Nikfarjam 2017, Tabeshpour 2017, Sahraian 2016, Talaei 2015, Kashani 2013, Nikfarjam 2013, Modabbernia 2012, AkhondzadehBasti 2008, Akhondzadeh Basti 2007, Moshiri 2006, Akhondzadeh 2005, Noorbala 2005, Akhondzadeh 2004, Akhondzadeh 2003) with other countries such as Australia (Kell 2017, Lopresti 2017, Lopresti 2014), China (Yu 2015), India (Sanmukhani 2014), Israel (Panahi 2015, Bergman 2013) and Thailand (Kanchanatawan 2018) also represented. The country was not specified for 3 RCTs (Mao 2015, Darbinyan 2007 Lingaerde 1999). The interventions were typically delivered over 6 to 8 weeks.

Twenty-one (21) RCTs compared WHM with placebo (Jelodar 2018, Kanchanatawan 2018, Kell 2017, Lopresti 2017, Tabeshpour 2017, Sahraian 2016, Mao 2015, Talaei 2015, Panahi 2015, Yu 2015, Lopresti 2014, Sanmukhani 2014, Bergman 2013, Kashani 2013, Modabbernia 2012, Akhondzadeh Basti 2008, Darbinyan 2007, Moshiri 2006, Akhondzadeh 2005, Akhondzadeh 2003, Lingaerde 1999). Two RCTs compared WHM with an inactive control (Nikfarjam 2017, Nikfarjam 2013) but no data were provided. Seven (7) RCTs compared WHM directly with an active intervention (Araj-Khodaei 2020, Ghajar 2017, Kashani 2017, Akhondzadeh Basti 2007, Noorbala 2005, Akhondzadeh 2004, Akhondzadeh 2003).

Results for the Primary Comparison: WHM versus placebo are provided in the Summary of Findings tables (see Section 4.7.5).

There were no studies found for the Secondary Comparison: WHM versus inactive control (no intervention, usual care). Results for the Tertiary Comparison (versus active comparators) are provided in in the Summary of Findings tables and Appendix F2.

Table 10 List of included systematic reviews and overlap with eligible RCTs (per outcome): Depression

Review ID	Best available [a]	Prioritised outcome domain [b]	Study ID: Araj-Khodaei 2020	Jelodar 2018	Kanchanatawan 2018	Ghajar 2017	Kell 2017 [c]	Lopresti 2017	Nikfarjam 2017	Tabeshpour 2017 [d]	Kashani 2016 [d]	Sahraian 2016	Mao 2015	Talaei 2015	Panahi 2015	Yu 2015	Lopresti 2014	Sanmukhani 2014	Bergman 2013	Kashani 2013 [e]	Nikfarjam 2013	Modabbernia 2012	Akhondzadeh Basti 2008	Akhondzadeh Basti 2007	Darbinyan 2007	Moshiri 2006	Akhondzadeh 2005	Noorbala 2005	Akhondzadeh 2004	Akhondzadeh 2003 (lavender)	Lingaerde 1999 [f]
Firoozeei 2021	✓	Depressive symptoms	✓	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Wang 2021	✓		--	--	✓	--	--	✓	--	--	--	--	--	--	--	✓	✓	✓	✓	--	--	--	--	--	--	--	--	--	--	--	--
Dai 2020	✓		--	--	--	✓	--	--	--	✓	✓	--	--	--	--	--	--	--	--	--	--	--	--	✓	--	✓	✓	✓	--	--	--
Fusar-Poli 2020	✓		--	--	✓	--	--	✓	--	--	--	--	--	--	✓	✓	✓	✓	✓	--	--	--	--	--	--	--	--	--	--	--	--
Ghaderi 2020	✓		--	✓	--	--	!	--	--	✓	--	✓	--	✓	--	--	--	--	--	--	--	--	--	--	--	✓	✓	--	--	--	--
Khaksarian 2019	✓		--	--	--	--	--	--	--	--	✓	--	--	--	--	--	--	--	--	--	--	--	✓	✓	--	✓	✓	--	--	--	--
Marx 2019	✓		--	✓	--	✓	✓	--	--	✓	✓	✓	--	✓	--	--	--	--	--	✓	--	✓	--	✓	--	✓	✓	✓	✓	--	--
Toth 2019	✓		--	--	--	✓	--	--	--	✓	✓	--	--	--	--	--	--	--	--	--	--	--	--	✓	--	✓	✓	✓	✓	--	--
Yang 2018	✓		--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	✓	--	✓	✓	✓	✓	--	--
Matias 2021	*		--	--	?	--	--	?	--	--	--	--	--	--	?	?	?	?	?	--	--	--	--	--	--	--	--	--	--	--	--
McCloskey 2018	*		--	--	--	--	--	--	--	?	?	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Sarris 2018	*		--	--	--	--	--	--	?	--	--	--	?	--	--	--	--	--	--	--	?	--	--	--	?	--	--	--	--	?	?
Fusar-Poli 2020	✓	Anxiety	--	--	✓	--	--	✓	--	--	--	--	--	--	✓	!	✓	!	!	--	--	--	--	--	--	--	--	--	--	--	--
Ghaderi 2020	✓		--	!	--	--	!	--	--	!	--	!	--	✓	--	--	--	--	--	--	--	--	--	--	--	!	!	--	--	--	--
Marx 2019	✓		--	!	--	?	✓	--	--	!	!	!	--	✓	--	--	--	--	--	!	--	!	--	!	--	!	!	!	!	--	--
Fusar-Poli 2020	✓	CGI	--	--	!	--	--	!	--	--	--	--	--	--	!	!	!	!	!	--	--	--	--	--	--	--	--	--	--	--	--
Apaydin 2016	✓		35 RCTs examining the efficacy of St John's wort not included here																												

Abbreviations: CGI, Clinical global impression; RCT, randomised controlled trial; SR, systematic review

Notes:

a. Only critical or important outcome domains with available data reported here (see Appendix D1.1)

b. Best available information means the systematic review meets AMSTAR-2 domains 4, 8, 9, & 11 (see Framework for selecting the systematic review from which to extract data [Appendix B1]).

c. Participants described as being healthy adults with low mood.
d. Participants with postpartum depression.
e. Participants with major depression and sexual dysfunction attributed to fluoxetine use.
f. Participants with seasonal affective disorder.

✓ Systematic review meets (or partially meets) prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).
† Systematic review meets (or partially meets) some, but not all, prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).
X Systematic review does not meet prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).
* Systematic review not assessed. A study result is available and reported in another systematic review nominated as the best available evidence.
Y RCT is included in the systematic review, meets our PICO criteria & a study result is available for inclusion in the synthesis.
? RCT is included in the systematic review & meets our PICO criteria, but the systematic review does not adequately report the results. Due to time and resource constraints, only the information presented in the systematic review is reported.
! RCT is included in the systematic review but does not measure the listed outcome.
-- RCT is not included in systematic review.

4.9.4 Risk of bias

Risk of bias assessment for the eligible RCTs as summarised by included systematic reviews are provided in Appendix F1.

Most of the included systematic reviews used the Cochrane Collaboration's risk of bias assessment tool (54) to asses bias within the included RCTs and comprehensive information to make a judgement.

Five (5) RCTs were judged to be at low risk of bias (Kanchanatawan 2018, Ghajar 2017, Lopresti 2017, Lopresti 2014, Akhondzadeh 2004). There were some concerns of bias in 10 RCTs, as the information provided was missing or unclear (Jelodar 2018, Kashani 2017, Kell 2017, Tabeshpour 2017, Sahraian 2016, Kashani 2013, Modabbernia 2012, Akhondzadeh Basti 2007, Moshiri 2006, Noorbala 2005).

Eight (8) RCTs (Araj-Khodaei 2020, Panahi 2015, Talaei 2015, Yu 2015, Bergman 2013, Sanmukhani 2014, Akhondzadeh Basti 2008, Akhondzadeh 2005) were judged to be at high risk of bias in at least one domain. Information about risk of bias for the other 6 RCTs were not provided (Nikfarjam 2017, Mao 2015, Nikfarjam 2013, Darbinyan 2007, Akhondzadeh 2003, Lindgaerde 1999).

4.9.5 Summary of findings and evidence statements

4.9.5.1 Primary Comparison (vs placebo)

There were 21 RCTs found by the included systematic reviews that compared WHM (other than St Jonn's Wort) with placebo in people with depression (or symptoms of depression). Of these, 18 RCTs contributed data relevant to 2 outcomes (anxiety, depression). (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).

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

A further 16 RCTs comparing St John's wort with placebo provided data relevant to 3 outcomes (depression, emotional functioning and physical functioning).

Western herbal medicine compared to placebo for depression and mood disorders

Patient or population: Depression and mood disorders
Setting: Community
Intervention: WHM (saffron, curcumin, St John's wort)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with WHM				
Depression assessed with: HAM-D, BDI, HADS, MDRS, DASS-21 follow-up: range 6 weeks to 12 weeks	-	**SMD 0.60 SD lower ^** (0.89 lower to 0.31 lower)	--	1022 (17 RCTs)	⊕⊕⊕◯ MODERATE [a,b,c,d,e]	WHM probably results in a reduction in depressive symptoms in people with depression
		St John's Wort: SMD 0.49 SD lower ^ (0.74 lower to 0.23 lower)		2888 (16 RCTs)	⊕⊕⊕◯ MODERATE [h]	

Western herbal medicine compared to placebo for depression and mood disorders

Patient or population: Depression and mood disorders
Setting: Community
Intervention: WHM (saffron, curcumin, St John's wort)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with WHM				
Anxiety assessed with: HAM-A, BAI, STAI, DASS-21 follow-up: range 6 weeks to 12 weeks	-	**SMD 1.49 SD lower ^** (2.39 lower to 0.59 lower)	--	397 (5 RCTs) †	⨁⨁◯◯ LOW [c,d,e,f,g]	WHM may result in a large reduction in anxiety in people with depression
Stress assessed with: DASS-21 follow-up: range 6 weeks to 12 weeks	-	-	--	(0 studies) ††	--	The effect of WHM on stress in people with depression is unknown
HRQoL	-	-	--	(0 studies)	--	The effect of WHM on quality of life in people with depression is unknown
Emotional functioning assessed with: SF-36 MCS range: 0 to 100 (higher is better) follow-up: range 6 weeks to 12 weeks	-	- **St John's Wort: SMD 0.48 SD higher ^** (0.24 higher to 0.73 higher)	--	(0 studies) 358 (2 RCTs)	-- ⨁⨁◯◯ LOW [i]	WHM may result in a slight increase in emotional functioning in people with depression
Global improvement assessed with: CGI follow-up: range 6 weeks to 12 weeks	-	-	--	(0 studies) †††	--	The effect of WHM on global improvement in people with depression is unknown
Physical functioning assessed with: SF-36 PCS range: 0 to 100 (higher is better) follow-up: range 6 weeks to 12 weeks	-	- **St John's Wort: SMD 0.28 SD higher ^** (1.03 lower to 0.47 higher)	--	(0 studies) 358 (2 RCTs)	-- ⨁◯◯◯ VERY LOW [j]	The evidence is very uncertain about the effect of WHM on physical functioning in people with depression

Western herbal medicine compared to placebo for depression and mood disorders

Patient or population: Depression and mood disorders
Setting: Community
Intervention: WHM (saffron, curcumin, St John's wort)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with WHM				

* **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
^ As a rule of thumb, an SMD of 0.2 represents a small difference, 0.5 is moderate, and 0.8 is a large difference (55).

† Data from one RCT (total 66 participants) not included here because results were not adequately reported [missing information].
†† Data from one RCT (total 121 participants) not included here because results were not adequately reported [missing information].
††† Data from 2 RCTs (total 80 participants) not included here because results were not adequately reported [missing information].

BAI: Beck Anxiety Inventory; **BDI**: Beck Depression Inventory; **CI:** confidence interval; **DASS-21**: depression, anxiety, stress scale; **HADS:** Hospital anxiety and depression scale; **HAM-A:** Hamilton anxiety rating scale; **HAM-D:** Hamilton depression rating scale; **IDS-SR30**: Self-rated Inventory of Depressive Symptomatology; **MADRS**: Montgomery-Åsberg Depression Rating Scale; **MCS:** mental component score; **MD:** mean difference; **PCS:** physical component score;

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. Seven RCTs at high risk of bias (~40% weight) that do not seriously influence the estimate of effect. Certainty of evidence not downgraded.
b. No serious inconsistency. Statistical heterogeneity is high (I^2=78%) but likely explained by differences in PICO of included studies. Certainty of evidence not downgraded.
c. No serious indirectness. The available evidence is in people diagnosed with major depression or with symptoms of depression that can be sensibly applied to the Australian population. It is possible the herbs used in the identified studies are not comparable to those commonly used in Australia but they could be sensibly applied. Certainty of evidence not downgraded.
d. Serious imprecision. Wide confidence intervals (upper and lower bounds overlap with both large and small important differences). Certainty of evidence downgraded.
e. Publication bias not suspected. Certainty of evidence not downgraded.
f. No serious risk of bias. Certainty of evidence not downgraded.
g. Serious inconsistency. Statistical heterogeneity is high (I^2=93%) and confidence intervals of studies do not overlap. Certainty of evidence downgraded.
h. GRADE assessed by Apaydin 2016 (290) Downgraded for inconsistency (due to heterogeneity; direction of effects; no replication).
i. GRADE assessed by Apaydin 2016 (290) Downgraded for study limitations (no good quality study; effect not present when excluding poor quality studies; studies not designed or not powered to assess outcome).
j. GRADE assessed by Apaydin 2016 (290) Downgraded for inconsistency (due to heterogeneity; direction of effects; no replication) and study limitations (no good quality study; effect not present when excluding poor quality studies; studies not designed or not powered to assess outcome).

4.9.5.2 Secondary Comparison (vs inactive control)

There were no RCTs identified by the included systematic reviews that compared WHM with inactive control (no intervention, waitlist or usual care) in people with depression. In the absence of evidence, the effect of WHM compared with inactive control on the prioritised outcomes is unknown:

4.9.5.3 Tertiary Comparison (vs active control)

There were 6 RCTs found by the included systematic reviews that compared WHM (other than St John's Wort) with selective serotonin reuptake inhibitors (fluoxetine, citalopram) or a tricyclic antidepressant (imipramine) in people with depression (Araj-Khodaei 2020, Ghajar 2017, Kashani 2017, Akhondzadeh Basti 2007, Noorbala 2005, Akhondzadeh 2004). Five (5) RCTs contributed data relevant to one outcome.

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

Western herbal medicine compared to antidepressant for depression and mood disorders

Patient or population: Depression and mood disorders
Setting: Community
Intervention: WHM (saffron, lavender, St John's wort)
Comparison: selective serotonin reuptake inhibitors (fluoxetine, citalopram) or tricyclic antidepressants (imipramine)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with antidepressants	Risk with WHM				
Depression assessed with: HAM-D (higher is worse) follow-up: range 6 weeks to 8 weeks	-	**SMD 0.15 SD lower ^** (0.15 lower to 0.46 higher)	--	224 (5 RCTs) †	⨁⨁◯◯ LOW [a,b,c,d,e]	WHM probably results in a little to no difference in depressive symptoms in people with depression
		St John's Wort: SMD 0.03 SD higher ^ (0.15 lower to 0.21 higher)		2248 (14 RCTs)	⨁⨁⨁◯ MODERATE	
Anxiety assessed with: HAM-A follow-up: range 6 weeks to 8 weeks	-	**-**	--	(0 studies) ††	--	The effect of WHM on anxiety in people with depression is unknown
Stress assessed with: DASS-21 follow-up: range 6 weeks to 8 weeks	-	-	--	(0 studies)	--	The effect of WHM on stress in people with depression is unknown
HRQoL	-	-	--	(0 studies)	--	The effect of WHM on quality of life in people with depression is unknown
Emotional functioning assessed with: SF-36 MCS range: 0 to 100 (higher is better) follow-up: range 6 weeks to 12 weeks	-	-	--	(0 studies)	--	The evidence is very uncertain about the effect of WHM on emotional functioning in people with depression
		St John's Wort: SMD 0.11 SD lower ^ (0.15 lower to 0.38 higher)	--	216 (1 RCT)	⨁◯◯◯ VERY LOW [g]	
Global improvement assessed with: CGI follow-up: range 6 weeks to 12 weeks	-	-	--	(0 studies)	--	The effect of WHM on global improvement in people with depression is unknown

Western herbal medicine compared to antidepressant for depression and mood disorders

Patient or population: Depression and mood disorders
Setting: Community
Intervention: WHM (saffron, lavender, St John's wort)
Comparison: selective serotonin reuptake inhibitors (fluoxetine, citalopram) or tricyclic antidepressants (imipramine)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with antidepressants	Risk with WHM				
Physical functioning assessed with: SF-36 PCS range: 0 to 100 (higher is better) follow-up: range 6 weeks to 12 weeks	-	-	--	(0 studies)	--	The evidence is very uncertain about the effect of WHM on physical functioning in people with depression
		St John's Wort: SMD 0.35 SD higher ^ (0.01 higher to 0.70 higher)	--	153 (1 RCT)	⨁◯◯◯ VERY LOW [g]	

* **The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
^ As a rule of thumb, an SMD of 0.2 represents a small difference, 0.5 is moderate, and 0.8 is a large difference (55).

† Data from one RCT (total participants unclear) not included here because results were not adequately reported [missing information].
†† Data from one RCT (total 66 participants) not included here because results were not adequately reported [missing information].

CI: confidence interval; **HAM-D:** Hamilton depression rating scale; **HAM-A:** Hamilton anxiety rating scale; **MD:** mean difference;

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

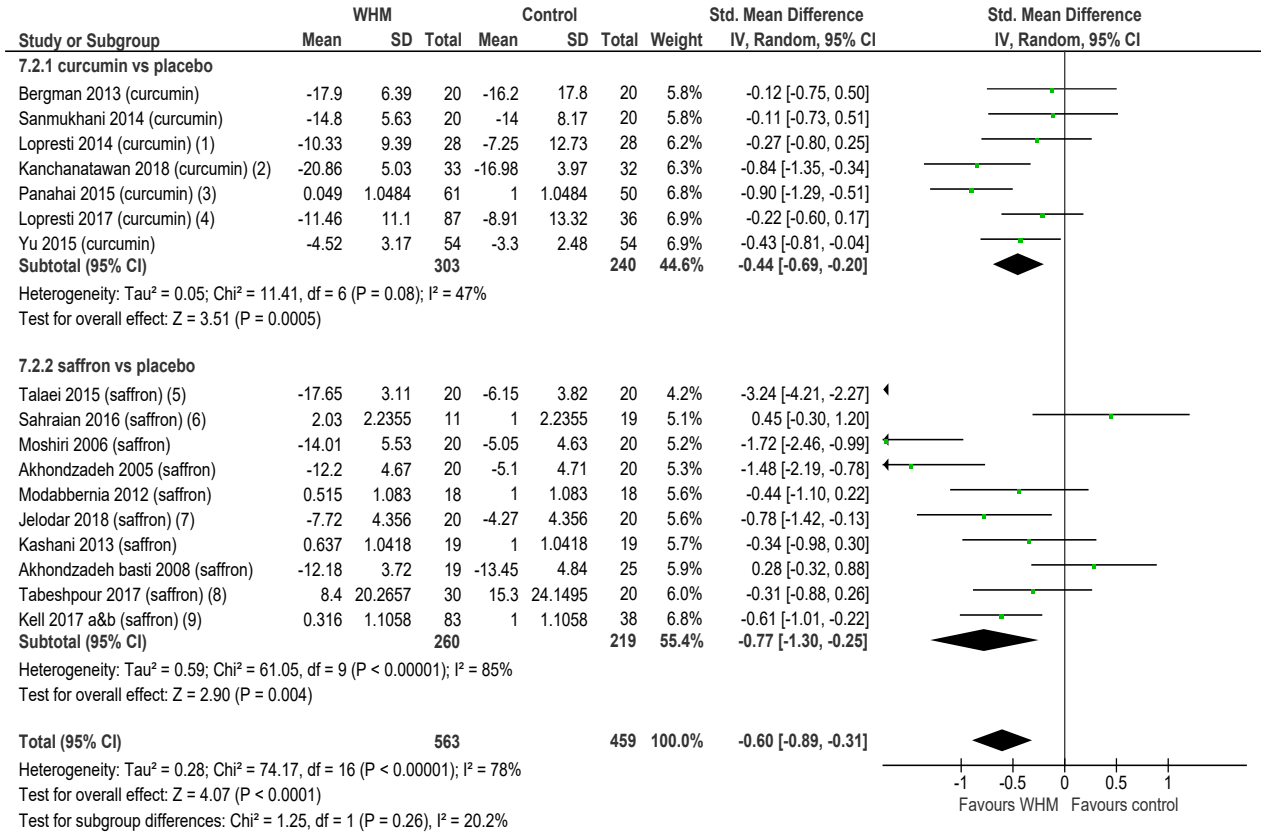
a. No serious risk of bias. Five RCTs at low or unclear risk of bias. Certainty of evidence not downgraded.
b. No serious inconsistency. Statistical heterogeneity is low (I^2=24%) Point estimate for one study does not overlap with the others, but likely explained by differences in PICO. Certainty of evidence not downgraded.
c. No serious indirectness. The available evidence is in people diagnosed with major depression, postpartum depression or mild-moderate depression that can be sensibly applied to the Australian population. It is possible the herbs used in the identified studies are not comparable to those commonly used in Australia, but they could be sensibly applied. Certainty of evidence not downgraded.
d. Very serious imprecision. Wide confidence intervals (upper and lower bounds overlap with both benefit and harms). Certainty of evidence downgraded 2 levels.
e. Publication bias not suspected. Certainty of evidence not downgraded.
f. GRADE assessed by Apaydin 2016 (290) Downgraded for inconsistency (due to heterogeneity; direction of effects; no replication).
g. GRADE assessed by Apaydin 2016 (290) Downgraded for inconsistency (due to heterogeneity; direction of effects; no replication) and study limitations (no good quality study; effect not present when excluding poor quality studies; studies not designed or not powered to assess outcome).

4.9.6 Forest plots

Outcome results related to people with depression compared with placebo are presented in Figure 19 (depressive symptoms – WHM other than St John's wort), Figure 20 (depressive symptoms – St John's wort), and Figure 21 (anxiety).

Outcome results related to people with depression compared with an active intervention are presented in Figure 22 (depressive symptoms – WHM other than St John's wort) and Figure 23 (depressive symptoms – St John's wort).

Figure 19 Forest plot of comparison: WHM vs placebo: Depression – depressive symptoms



Footnotes

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

Figure 20 Forest plot of comparison: St John's wort vs placebo: Depression – depressive symptoms

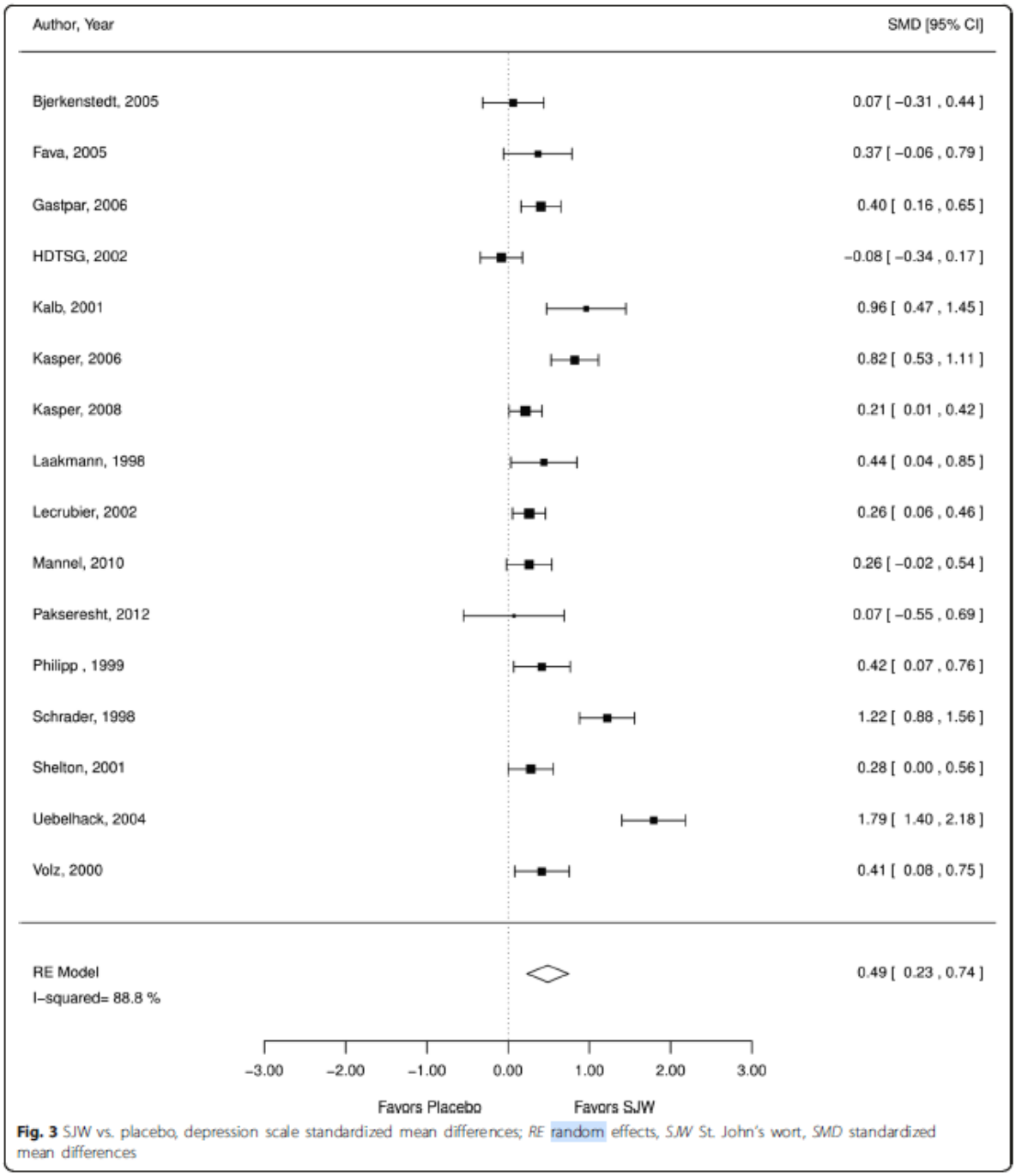
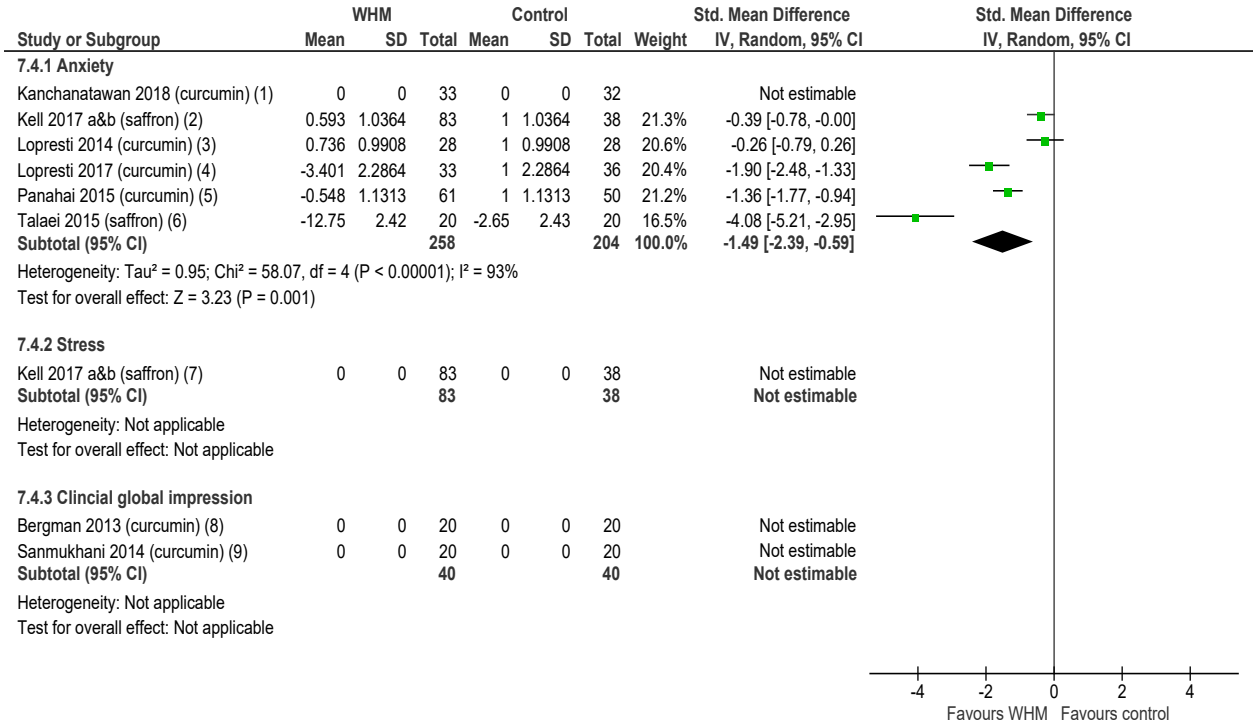


Fig. 3 SJW vs. placebo, depression scale standardized mean differences; *RE* random effects, *SJW* St. John's wort, *SMD* standardized mean differences

Source: Apaydin, Maher (290)

Figure 21 Forest plot of comparison: WHM vs placebo: Depression – anxiety, stress, and global improvement

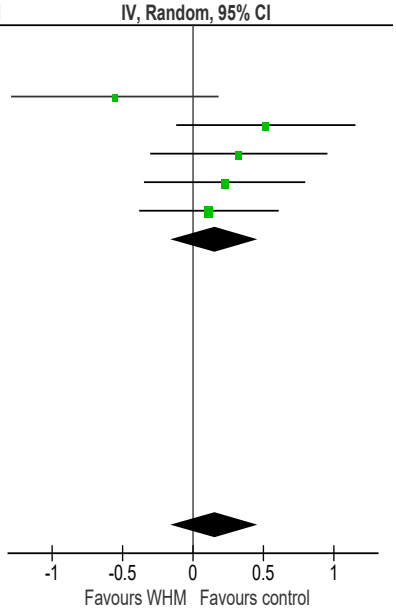


Footnotes

(1) HAM-A; missing data; NR
(2) DASS-21
(3) STAI
(4) STAI
(5) HADS-A
(6) BAI
(7) DASS-21; missing data; NR
(8) missing data, no difference observed between groups
(9) missing data, no difference observed between groups

Figure 22 Forest plot of comparison: WHM vs active intervention: Depression – depressive symptoms

Study or Subgroup	WHM Mean	WHM SD	WHM Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
7.5.1 Depression (HAM-D)								
Akhondzadeh 2004 (saffron)	-11.2	1.39	15	-10.41	1.38	15	14.5%	-0.55 [-1.29, 0.18]
Akhondzadeh Basti 2007 (saffron) (1)	-12	4.1	20	-13.5	4.91	20	18.7%	0.33 [-0.30, 0.95]
Araj-Khodaei 2020 (lavender) (2)	0	0	0	0	0	0		Not estimable
Ghajar 2017 (saffron) (3)	-10.13	5.9702	30	-11.27	2.9963	20	21.6%	0.22 [-0.34, 0.79]
Kashani 2016 (saffron) (4)	-7.5	1.97	32	-7.71	1.69	32	26.7%	0.11 [-0.38, 0.60]
Noorbala 2005 (saffron)	-12.2	4.67	20	-15	5.88	20	18.4%	0.52 [-0.11, 1.15]
Subtotal (95% CI)			**117**			**107**	**100.0%**	**0.15 [-0.15, 0.46]**
Heterogeneity: Tau² = 0.03; Chi² = 5.25, df = 4 (P = 0.26); I² = 24%								
Test for overall effect: Z = 0.98 (P = 0.32)								
7.5.2 Anxiety (HAM-A)								
Ghajar 2017 (saffron) (5)	0	0	33	0	0	33		Not estimable
Subtotal (95% CI)			**33**			**33**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Total (95% CI)			**150**			**140**	**100.0%**	**0.15 [-0.15, 0.46]**
Heterogeneity: Tau² = 0.03; Chi² = 5.25, df = 4 (P = 0.26); I² = 24%								
Test for overall effect: Z = 0.98 (P = 0.32)								
Test for subgroup differences: Not applicable								



Footnotes

(1) change from baseline

(2) Missing data, no difference between groups; SMD 0.57; 95% CI -0.12 to 1.26; p=0.877

(3) change from baseline

(4) change from baseline

(5) missing data; NR

Figure 23 Forest plot of comparison: St John's wort vs active intervention: Depression – depressive symptoms

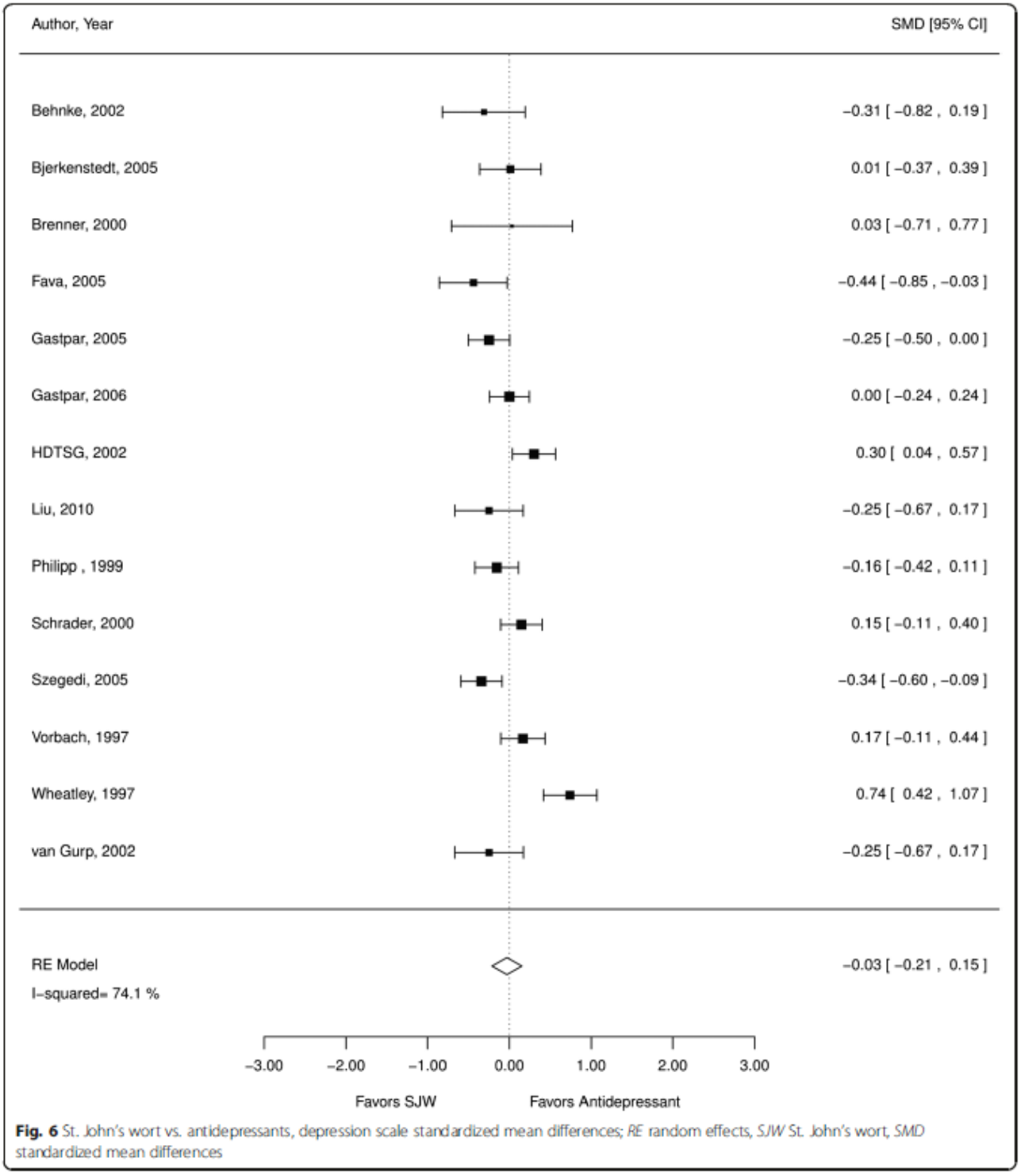


Fig. 6 St. John's wort vs. antidepressants, depression scale standardized mean differences; *RE* random effects, *SJW* St. John's wort, *SMD* standardized mean differences

Source: Apaydin, Maher (290)

4.10 Insomnia

4.10.1 Description of the condition

Sleep problems are common across the adult Australian population and can range from experiencing mild sleep disturbances each week to being diagnosed with clinical insomnia (322). Sleep problems and insomnia are characterised by an inability to fall asleep or lack of sleep which can cause daytime impairment. Insomnia can present in different forms such as onset insomnia, defined as difficulty initiating sleep, or maintenance insomnia, defined as difficulty maintaining sleep through the night or early awakening (323). In short term cases, precipitating factors such as shift work, stressors, or comorbid conditions may trigger insomnia. In other cases, insomnia is paired with hyperarousal which can distort sleep perception or interrupt sleep. If left untreated, maladaptive behaviours like daytime napping or sedative dependence may form alongside neurocognitive responses such as conditioned night-time arousal or cognitive alterations, eventually developing into chronic insomnia. If symptoms of sleeplessness and impaired daytime function occur ≥3 times a week for more than 3 months, patients are considered to have chronic insomnia disorder according to the International Classification of Sleep Disorders (ICSD-3) criteria (324).

In Australia, 14.8% of adults are reported to have chronic insomnia and 59.4% report sleep problems more than 3 times a week (322). Women are more likely to report chronic insomnia and daytime consequences than men. In both men and women, the prevalence of chronic insomnia increases with age; adults over 75 report the highest rates of chronic insomnia (23.1%) in Australia. Older people are also significantly more likely to report maintenance insomnia. Despite these significant numbers, less than 1/3 of people seek treatment. Even when treatment is initiated, it can take a relatively heterogenous approach (322).

Current treatment options for insomnia include pharmacological interventions, hormonal or herbal supplements (such as melatonin or valerian), and cognitive behavioural therapy (CBT) for insomnia. CBT is recommended for first line management for patients with insomnia since improvements can be maintained for up to 3 years and medications are only recommended for short term usage (322, 325). However, CBT can be time consuming (4-8 weeks) and limited by accessibility of clinicians. New evidence has suggests that exercise interventions and mindfulness based interventions can be helpful in improving sleep quality (325).

4.10.2 Description of reviews

There were 15 citations (107, 214, 227, 241, 255, 257, 304, 326-333) corresponding to 15 systematic reviews (Feizi 2019, Fernandez-San-Martin 2010, Hieu 2019, Kim 2018a, Leach 2015, Lopresti 2021, Sarris 2011, Sarris 2011b, Shinjyo 2020, Sys 2020, Stevinson 2000, Tandon 2020, Taibi 2007, Taslaman 2014, Ulbricht 2012) identified in the literature search that evaluated the effectiveness of WHMs in people with insomnia. There were no additional reviews identified in the Department's public call for evidence (see Appendix C2). There was one systematic review (334) awaiting classification (see Appendix C4) and no ongoing reviews (see Appendix C5).

A summary of the PICO criteria of the eligible systematic reviews is provided in Appendix D3.3.1.

The populations eligible for inclusion in the reviews was usually participants with insomnia or sleep problems (Shinjyo 2020, Sys 2020, Feizi 2019, Kim 2018a, Leach 2015, Taslaman 2014, Sarris 2011b, Fernandez-San-Martin 2010, Taibi 2007, Stevinson 2000). Two reviews also searched for studies in people with anxiety (Hieu 2019, Sarris 2011). Three reviews had no population restrictions but presented results where stress biomarkers were measured as an outcome (Lopresti 2021) or were focused on specific WHM (Tandon 2020, Ulbricht 2012) and included studies in people with insomnia.

Four (4) of the reviews (Shinjyo 2020, Hieu 2019, Leach 2015, Fernandez-San-Martin 2010) presented results in a meta-analysis and were prioritised for critical appraisal and data extraction. Review details, including outcome domains and measures, and the risk of bias of eligible RCTs are provided in Appendix F1.

4.10.3 Description of studies

Within the eligible systematic reviews, there were 13 RCTs that met our PICO criteria, examining the effects of a variety of herbs such as chamomile, valerian, kava, Withania or hops compared with placebo or other interventions among people with insomnia. Of these, 4 herbs (are marked as a Tier 1 herb included in the Western herbal medicine curriculum for Nervous system disorders (i.e. most commonly taught in Australian curriculum for this condition; see Appendix A6.3).

Eleven (11) RCTs compared WHM with placebo (Langade 2019, Taavoni 2011, Zick 2011, Taibi 2009, Koetter 2007, Oxman 2007, Jacobs 2005, Morin 2005, Coxeter 2003, Farag 2003, Donath 2000) and 3 RCTs (Maroo 2013, Morin 2005, Ziegler 2002) compared WHM with an active intervention.

The RCTs were conducted in a variety of countries including Australia (Coxeter 2003), Germany (Donath 2000, Ziegler 2002), Norway (Oxman 2007) and the United States (Jacobs 2005, Taibi 2009, Zick 2011) (or not specified). Sample sizes ranged from 6 to 405 (total 1562 participants), with the interventions being delivered over various time periods (range 14 days to 6 months).

An overlap table of the RCTs that met our PICO criteria from within the included systematic reviews is shown in Table 11.

Results for Primary Comparison: WHM versus placebo are provided in the Summary of Findings tables (see Section 4.10.5).

There were no studies found for the Secondary Comparison: WHM versus inactive control (no intervention, usual care). Results for the Tertiary Comparison (versus active comparators) are provided in Appendix F2.

Table 11 List of included systematic reviews and overlap with eligible RCTs (per outcome): Insomnia

Review ID	Best available [a]	Prioritised outcome domain [b]	Study ID												
			Langade 2019	Maroo 2013	Taavoni 2011	Zick 2011	Taibi 2009 #	Koetter 2007 ##	Oxman 2007	Jacobs 2005	Morin 2005	Coxeter 2003	Farag 2003	Ziegler 2002	Donath 2000
Lopresti 2021	†	Sleep quality	?	--	--	--	--	--	--	--	--	--	--	--	--
Shinjyo 2020	✓		--	Y	Y	--	Y	!	Y	Y	!	!	!	Y	Y
Sys 2020	†		--	--	--	--	?	--	--	--	--	--	--	--	--
Tandon 2020	†		?	--	--	--	--	--	--	--	--	--	--	--	--
Feizi 2019	†		--	--	--	?	--	--	?	--	--	?	--	--	?
Hieu 2019	✓		--	--	--	Y	--	--	--	--	--	--	--	--	--
Kim 2018a	†		--	--	--	?	?	--	?	--	--	?	--	?	?
Leach 2015	✓		--	--	--	Y	--	--	Y	Y	--	Y	--	!	Y
Fernandez-San-Martin 2010	✓		--	--	--	--	Y	!	Y	--	--	Y	--	--	Y
Lopresti 2021	†	Anxiety	?	--	--	--	--	--	--	--	--	--	--	--	--
Shinjyo 2020	✓		--	!	!	--	!	!	!	Y	!	!	!	!	!
Tandon 2020	†		?	--	--	--	--	--	--	--	--	--	--	--	--
Hieu 2019	✓		--	--	--	Y	--	--	--	--	--	--	--	--	--
Shinjyo 2020	✓	HRQoL	--	!	!	--	!	!	!	!	Y	!	!	!	!

Abbreviations: HRQoL, health-related quality of life; RCT, randomised controlled trial

a. Best available information means the systematic review meets AMSTAR-2 domains 4, 8, 9, & 11 (see Appendix B1 [Framework for selecting the systematic review from which to extract data]).

b. Only critical or important outcome domains with available data included here (see Appendix D1.1.3)

population described as with insomnia in some reviews, others suggest participants have menopause-related sleep problems.

Participants are diagnosed with insomnia according to ICD-10 criteria or are described as having a nonorganic sleep disorder.

✓ Systematic review meets (or partially meets) prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

† Systematic review meets (or partially meets) some, but not all, prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

X Systematic review does not meet prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

* Systematic review not assessed. A study result is available and reported in another systematic review nominated as the best available evidence.
Y RCT is included in the systematic review, meets our PICO criteria & a study result is available for inclusion in the synthesis.
? RCT is included in the systematic review & meets our PICO criteria, but the systematic review does not adequately report the results. Due to time and resource constraints, only the information presented in the systematic review is reported.
! RCT is included in the systematic review but does not measure the listed outcome.
-- RCT is not included in systematic review.

4.10.4 Risk of bias

Risk of bias assessment for the eligible RCTs as summarised by included systematic reviews are provided in Appendix F1.

Hieu 2019 and Leach 2015 used the Cochrane Collaboration risk of bias assessment tool to assess bias in the included RCTs (54), whereas Shinjyo 2020 and Fernandez-San-Martin 2010 used the Jaded Scale (234).

The majority of RCTs were reported as having unclear methodology, therefore most were judged to be at overall unclear risk of bias. Almost all were judged to be at high risk of bias relating to sponsorship bias.

4.10.5 Summary of findings and evidence statements

4.10.5.1 Primary Comparison (vs placebo)

There were 11 RCTs (found by the included systematic reviews that compared WHM 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 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.

WHM compared to placebo for insomnia

Patient or population: Insomnia
Setting: Community
Intervention: WHM (valerian or combination with hops or Withania, ginger, black pepper, liquorice)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with placebo	Risk with WHM				
Sleep quality assessed with: PSQI, ISI (higher is worse), VAS (higher is better) Follow-up: range 4 to 24 weeks	--	**SMD 0.12 lower ^** (0.24 lower to 0.21 higher)	--	946 (5 RCTs) †	⊕⊕⊕◯ MODERATE a,b,c,d,e	WHM probably results in little to no difference in sleep quality in people with insomnia.
Patient reported improvement	--	--	--	(0 studies)	--	The effect of WHM on global improvement in people with insomnia is unknown.
Health related quality of life	--	--	--	(0 studies) *	--	The effect of WHM on quality of life in people with insomnia is unknown.
Symptoms of depression	--	--	--	(0 studies) **	--	The effect of WHM on symptoms of depression in people with insomnia is unknown.

WHM compared to placebo for insomnia

Patient or population: Insomnia
Setting: Community
Intervention: WHM (valerian or combination with hops or Withania, ginger, black pepper, liquorice)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with placebo	Risk with WHM				
Symptoms of anxiety assessed with: STAI scale range: 20 to 80 (higher is worse) follow-up: 4 weeks	The mean STAI score was **40.8**	**MD 1.71 higher** (1.39 lower to 4.80 higher) ^^	--	425 (2 RCTs) ††	⊕⊕◯◯ LOW [a,b,c,d,f]	WHM may result in little to no difference in anxiety in people with insomnia. #
Physical functioning	--	--	--	(0 studies)	--	The effect of WHM on physical functioning in people with insomnia is unknown.
Fatigue	--	--	--	(0 studies) **	--	The effect of WHM on fatigue in people with insomnia is unknown.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
^ As a rule of thumb, an SMD of 0.2 represents a small difference, 0.5 is moderate, and 0.8 is a large difference (55).
^^ Effect estimates were considered on three levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale).

A cut point of 39-40 and above indicates symptoms are clinically significant (335).

† Data from 4 RCTs (total 284 participants) not included here because results were not adequately reported [missing information]. All 3 studies suggested no difference between groups.
†† Data from one RCT (total 606 participants) not included here because results were not adequately reported [missing information]. The study suggested an effect favouring WHM.
* Data from one RCT (total 184 participants) not included here because results were not adequately reported [missing information].
** Data from one RCT (total 34 participants) not included here because results were not adequately reported [missing information].

CI: confidence interval; **WHM:** Western Herbal Medicine

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. Certainty of evidence not downgraded.
b. Serious inconsistency. Point estimates do not overlap. High statistical heterogeneity (I^2 = 78%) that is not able to be explained. Certainty of evidence downgraded.
c. No serious indirectness. The available evidence is in people with insomnia and is directly generalisable to the Australian population with few caveats. The herbs used in the identified studies are comparable to those commonly used in Australia and can be sensibly applied. Certainty of evidence not downgraded.
d. No serious imprecision. Certainty of evidence not downgraded.
e. Publication bias not suspected. Certainty of evidence not downgraded.
f. Publication bias suspected. There is a strong suspicion of non-reporting of results likely related to the *p* value, direction or magnitude of effect. Certainty of evidence downgraded.

4.10.5.2 Secondary Comparison (vs inactive control)

There were no RCTs found by the included systematic reviews that compared WHM with control (no intervention, waitlist or usual care) in people with insomnia. In the absence of evidence, the effect of WHM compared with control on the prioritised outcomes in people with insomnia is unknown.

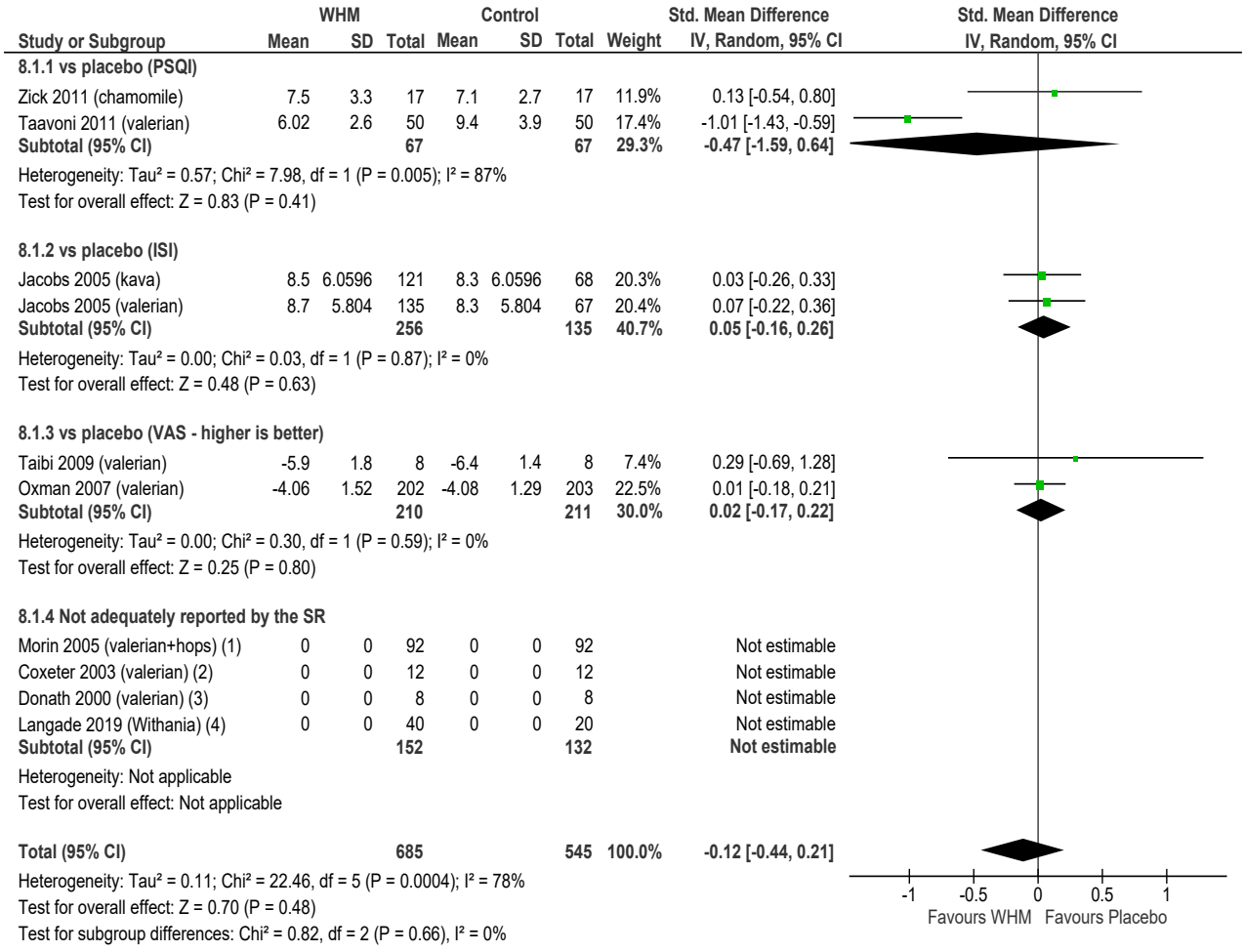
4.10.5.3 Tertiary Comparison (vs active control)

There were 3 RCTs found by the included systematic reviews that compared WHM with active comparators. Data from these studies are presented in Appendix F2.

4.10.6 Forest plots

Outcome results related to people with insomnia are presented in Figure 24 (sleep quality) and Figure 25 (anxiety).

Figure 24 Forest plot of comparison: WHM vs placebo: Insomnia – sleep quality



Footnotes

(1) SR authors report there was no important difference observed between groups. No data were provided.

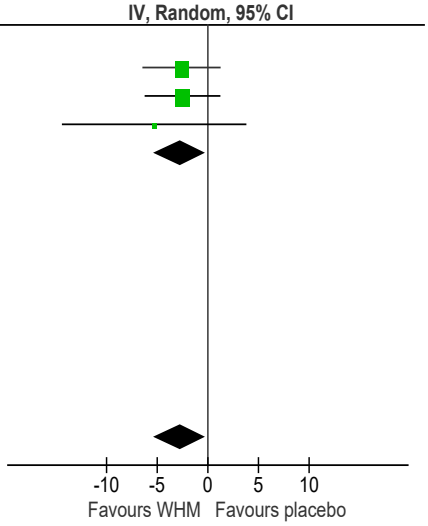
(2) SR authors report there was no important difference observed between groups. No data were provided.

(3) Hedges's g -0.11 (95% CI -0.82, 0.59). Data not able to be included due to missing information.

(4) SR authors report an effect favouring WHM (p<0.05). No other data were provided.

Figure 25 Forest plot of comparison: WHM vs placebo: Insomnia – anxiety

Study or Subgroup	WHM Mean	WHM SD	WHM Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
8.4.1 vs placebo (STAI)								
Jacobs 2005 (kava) (1)	11.8	12.3	121	14.4	12.9	67	44.6%	-2.60 [-6.39, 1.19]
Jacobs 2005 (valerian) (2)	11.9	11.9	135	14.4	12.9	68	47.6%	-2.50 [-6.16, 1.16]
Zick 2011 (chamomile)	35.5	11	17	40.8	15.5	17	7.8%	-5.30 [-14.33, 3.73]
Subtotal (95% CI)			**273**			**152**	**100.0%**	**-2.76 [-5.29, -0.24]**
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 2 (P = 0.85); I² = 0%								
Test for overall effect: Z = 2.14 (P = 0.03)								
8.4.4 Not adequately reported by the SR								
Langade 2019 (Withania) (3)	0	0	40	0	0	20		Not estimable
Subtotal (95% CI)			**40**			**20**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Total (95% CI)			**313**			**172**	**100.0%**	**-2.76 [-5.29, -0.24]**
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 2 (P = 0.85); I² = 0%								
Test for overall effect: Z = 2.14 (P = 0.03)								
Test for subgroup differences: Not applicable								



Footnotes

(1) Results are mean change from baseline.

(2) Results are mean change from baseline.

(3) SR authors report an effect favouring WHM (p<0.05). No other data were provided.

4.11 Diabetes and Impaired glucose tolerance

4.11.1 Description of the condition

Diabetes and impaired glucose tolerance were initially prioritised as separate conditions. However, it was found that systematic reviews and studies within them were often unclear whether the studies enrolled people with diabetes or impaired glucose tolerance or both (or metabolic disorder). Diabetes and impaired glucose tolerance are therefore combined here and in Appendix D.

Impaired glucose tolerance occurs when blood glucose levels are higher than normal but not high enough to meet the diagnostic criteria for diabetes (336). Impaired glucose tolerance is considered a high-risk factor for developing type 2 diabetes and cardiovascular disease (337-341). In Australia, the prevalence of impaired glucose tolerance is estimated to be 8.8% (342), with one in 6 Australians older than 25 years estimated to have pre-diabetes (impaired glucose intolerance and/or impaired fasting glucose) (336, 343).

Diabetes mellitus is a chronic metabolic disease characterised by elevated levels of blood glucose (hyperglycaemia) resulting from defects in insulin secretion, impaired insulin production, weakened response to insulin or absolute insulin deficiency (344). Insulin deficiency leads to hyperglycaemia organ complication, primarily blood vessels, eyes, nerves and kidneys (345). Classifying diabetes is critical for disease management. Common classifications of diabetes include type 1 diabetes, type 2 diabetes and gestational diabetes (occurs during pregnancy) (346). Clinical presentation and disease pathogenesis various among individuals, and may be influenced by environmental, lifestyle and genetic factors (345, 346).

Type 1 diabetes, also known as juvenile diabetes constitutes about 5-10% of all diabetes cases (347) and is caused by the auto-immune destruction of insulin-producing beta cells in the islets of Langerhans leading to little to no production of insulin (348, 349). The exact cause of Type 1 diabetes is unknown but risk factors include genetic predisposition and environmental triggers such as exposure to certain viruses (350, 351). Type 2 diabetes is the most common, making up 85-90% of all diabetes cases and usually occurs in adults over the age of 45 (352). It is characterised by insulin resistance and/or the gradual loss to produce enough insulin in the pancreas and is associated with modifiable lifestyle risk factors such as diet and exercise (352). Gestational diabetes is defined as an intolerance to glucose that is first diagnosed or has its onset during pregnancy. It is estimated to affect almost 5% of pregnancies in Australia and between 3% and 9% worldwide (353). Although some women will continue to have elevated glucose levels, gestational diabetes usually disappears after giving birth (354), however an estimated 40% are at risk of recurrence of gestational diabetes in a subsequent pregnancy and at increased risk of developing type 2 diabetes at later age (355).

An estimated 1.2 million Australians (4.9% of the total population) had diabetes in 2017–18, based on self-reported data from the Australian Bureau of Statistics (ABS) 2017–18 National Health Survey (356). However, this is likely to be an underestimate of the true prevalence given this does not include people with undiagnosed diabetes (356). Prevalence of diabetes in 2017-18 was higher in males (5.0%) than females (3.8%) and increases with age (356). High blood plasma glucose (including diabetes) was responsible for 4.3% of ill health and premature death in Australia and was the fifth leading risk factor contributing to ill health and premature death in 2018 (357)

Primary management of diabetes involves lifestyle modifications such as weight modifications, controlled diet and increased physical activity. Life-long treatment with insulin is needed for type 1 diabetes but may be required for managing type 2 diabetes (358, 359). The effects of complementary and alternative medicines on metabolic control are conflicting due to deficiencies in the robustness of evidence and issues with safety. However, few studies have shown positive effects of certain complementary therapies for diabetes management (360, 361).

4.11.2 Description of reviews

There were 166 citations (24, 25, 27, 28, 33-35, 64, 113, 124, 153, 154, 158, 159, 161, 163-166, 168, 169, 171, 172, 174, 178, 181, 183, 189, 193, 194, 197, 199, 219, 255, 257, 296, 362-490) corresponding to 166 systematic reviews identified in the literature search that evaluated the effectiveness of WHMs in people with diabetes and/or impaired glucose tolerance. No additional reviews were identified in the Department's public call for evidence (see Appendix C2). There were 14 systematic reviews awaiting classification (see Appendix C4) and 4 ongoing reviews (see Appendix C5).

A summary of the PICO criteria of the 166 eligible systematic reviews is provided in Appendix D4.1.1.

There were 23 reviews (362-384) that were published in 2018 or after, that presented results in a meta-analysis and focused on people with diabetes or metabolic disorders, that were to be prioritised for critical appraisal and data extraction. Another 66 reviews (24, 25, 27, 28, 33-35, 124, 153, 154, 158, 159, 161, 163-166, 168, 169, 171, 172, 174, 178, 385-427) were earmarked for assessment as they were umbrella reviews published in 2018 or after that presented results in a meta-analysis and included primary studies in people with diabetes or pre-diabetes. Many of these reviews were focused on one or 2 outcomes considered critical or important for this review (i.e. glycaemic control, body composition) but many were focused on outcomes not considered critical or important for this overview (such as lipid profiles, blood pressure, oxidative stress and inflammatory biomarkers; See appendix D).

The remaining 77 reviews (64, 113, 181, 183, 189, 193, 194, 197, 199, 219, 255, 257, 296, 428-490) were judged likely to no longer represent the best available evidence or likely to not adequately report data of included primary studies.

Given the time and resource constraints further assessment of these reviews was not able to be performed (see NHMRC process report for additional information).

4.12 Metabolic syndrome

4.12.1 Description of the condition

Metabolic syndrome is not a disease state, but a collective term used to describe risk factors frequently associated with cardiovascular diseases and type 2 diabetes (491). The risk factors correlated with metabolic syndrome include excessive waist circumference, lipid abnormalities, hypertension and elevated glucose levels (492). Precise definitions of metabolic syndrome vary but generally encompass its efficacy in identifying cardiovascular diseases and diabetes in people who may be suitable for preventive therapy but would otherwise not be treated (491).

In Australia, metabolic syndrome is becoming increasingly common due to the rise in obesity and sedentary lifestyle behaviours. The clinical diagnosis of metabolic syndrome has been used to predict individuals at risk of cardiovascular disease, diabetes and chronic kidney disease (491, 492). An estimated 33.5% of Australians aged over 12 have metabolic syndrome, with the prevalence higher in women than men (493).

Changes in lifestyle behaviour are essential preventative methods for managing chronic comorbidities and preventing metabolic conditions. Individuals who were obese are 6 times more likely to develop metabolic syndrome than individuals within a normal weight range (492). The effects of complementary and alternative medicines on metabolic control are conflicting due to deficiencies in the robustness of evidence.

4.12.2 Description of reviews

There were 70 citations (24, 25, 33, 113, 124, 159, 161, 164-166, 168, 170-172, 174, 183, 189, 190, 193, 219, 227, 242, 256, 374, 381, 383, 384, 386, 388, 390, 391, 397, 398, 400, 402, 404, 405, 409-414, 416-418, 420, 422, 424, 426, 431, 433, 437, 447, 463-465, 470, 475, 494-503) corresponding to 70 systematic reviews identified in the literature search that evaluated the effectiveness of WHMs in people with metabolic syndrome. No additional reviews were identified in the Department's public call for evidence (see Appendix C2). There were 3 systematic reviews awaiting classification (see Appendix C4) and no ongoing reviews (see Appendix C5).

A summary of the PICO criteria of the 70 eligible systematic reviews is provided in Appendix D4.2.1.

There were 12 reviews (165, 374, 381, 383, 384, 390, 416, 417, 494-497) that were published in 2018 or after that presented results in a meta-analysis and focused on people with metabolic syndrome or those at risk of cardiovascular disease, that were to be prioritised for critical appraisal and data extraction. Another 36 reviews (24, 25, 33, 124, 159, 161, 164, 166, 168, 170-172, 174, 242, 386, 388, 391, 397, 398, 400, 402, 404, 405, 409-414, 418, 420, 422, 424, 426, 498, 499) were earmarked for assessment as they were umbrella reviews published in 2018 or after that presented results in a meta-analysis and included primary studies in people with metabolic syndrome. Many of these reviews were focused on one or 2 outcomes considered critical or important for this review (i.e. glycaemic control, body composition) but many were focused on outcomes not considered critical or important for this overview (such as lipid profiles, blood pressure, oxidative stress and inflammatory biomarkers).

The remaining 21 reviews (113, 183, 189, 190, 193, 219, 227, 256, 431, 433, 437, 447, 463-465, 470, 475, 500-503) were judged likely to no longer represent the best available evidence or likely to not adequately report data of included primary studies.

Given the time and resource constraints, further assessment of these reviews was not able to be performed.

4.13 Fatigue conditions (postviral fatigue, ME/CFS etc.)

4.13.1 Description of the condition

Fatigue is defined as a constant feeling of tiredness and prolonged weariness that is not relieved by rest (504). The onset of fatigue may be acute or insidious, with chronic fatigue typically experienced with greater intensity and longer duration, impacting daily life, functional activity and quality of life (505). There are a broad range of factors contributing to the onset of fatigue, including underlying diseases and psychological, social and behavioural factors (504). Postviral fatigue, idiopathic fatigue and Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS) are conditions with limited understanding but are typically characterised by substantial fatigue following exertion, unsatisfactory rest or sleep and cognitive difficulties (506). Classified as a neurologic disorder, ME/CFS is a complex illness that can affect many parts of the body, including muscles, cardiac, immune, and digestive systems, and can be associated with a variety of additional symptoms such as orthostatic intolerance and fibromyalgia (507, 508). While the cause of ME/CFS is not known, many people with ME/CFS often develop symptoms after a viral infection, with postviral fatigue (including long COVID) presenting with a similar diverse range of symptoms (507).

Globally, ME/CFS prevalence is estimated to be around 1%, affecting approximately twice as many women as men (506). However, these estimates are dependent on the diagnostic methods and case definitions used. In Australia, an estimated 250,000 individuals are affected by ME/CFS, with 25% presenting with severe symptoms, ultimately becoming housebound or bedbound (506, 507).

Diagnosis for ME/CFS and other fatigue conditions is often overlooked and difficult to identify due to varied definitions and established clinical diagnostic criteria (509). Treatment guidelines for chronic fatigue are based on symptomatic management, routine follow-up with a general practitioner, and investigation of co-occurring conditions such as fibromyalgia and postural orthostatic tachycardia syndrome (510). Alternative medicines for fatigue are aimed towards symptomatic relief and improvement in quality of life, as traditional pharmaceutical treatments are not available (511, 512).

4.13.2 Description of reviews

There were 8 citations (256, 265, 513-518) corresponding to 8 systematic reviews (Alraek 2011, Arring 2018, Bach 2016, Jin 2020, Kim 2020, Lopresti 2021, Ogawa-Ochiai 2018, Provino 2010) identified in the literature search that evaluated the effectiveness of WHMs in people with fatigue conditions. There were no additional reviews identified in the Department's public call for evidence (see Appendix C2), no systematic reviews awaiting classification (see Appendix C4) and no ongoing reviews (see Appendix C5).

A summary of the PICO criteria of the 8 eligible systematic reviews is provided in Appendix D5.1.1.

The populations eligible for inclusion in the reviews were participants with chronic fatigue syndrome (Alraek 2011, Kim 2020, Jin 2020) or participants with fatigue (Arring 2018). Four reviews had no population restrictions but presented results where fatigue was measured as an outcome (Bach 2016, Lopresti 2021, Ogawa-Ochiai 2018, Provino 2010).

Three (3) of the reviews (Bach 2016, Jin 2020, Kim 2020) presented results in a meta-analysis and were prioritised for critical appraisal and data extraction. Review details, including outcome domains and measures, and the risk of bias of eligible RCTs are provided in Appendix F1.

4.13.3 Description of studies

Within the eligible systematic reviews, there were 7 RCTs that met our PICO criteria, all of which examined the effect of ginseng compared with placebo. The included RCTs were conducted in Korea (Kim 2013), Iran (Etemadifar 2013), the United States (Hartz 2004) or not specified (Kim 2016, Lee 2016, Hyeong-Geug 2013, Le Gal 1996) and examined the effects of panax ginseng (Kim 2016, Lee 2016, Etemadifar 2013, Hyeong-Geug 2013, Kim 2013, Le Gal 1996) or Siberian ginseng (Hartz 2004) among people with chronic fatigue (Kim 2013, Hartz 2004) or multiple sclerosis (Etemadifar 2013). Sample sizes ranged from 46 to 218 (total 724 participants). All 7 RCTs compared WHM with placebo, with treatment delivered over 4 weeks (Kim 2016, Lee 2016, Hyeong-Geug 2013, Kim 2013), 6 weeks (Le Gal 1996), 8 weeks (Hartz 2004) or 12 weeks (Etemadifar 2013).

An overlap table of the RCTs within the included systematic reviews is shown in Table 12.

Results for the Primary Comparison: WHM versus placebo are provided in the Summary of Findings tables (see Section 4.13.5). There were no studies found for the Secondary Comparison: WHM versus inactive control (no intervention, usual care [if inactive]) or the Tertiary Comparison (WHM versus active comparators). Additional details are provided in Appendix F2.

Table 12 List of included systematic reviews and overlap with eligible RCTs (per outcome): Fatigue conditions

Review ID	Best available*	Prioritised outcome domain	Study ID						
			Kim 2016	Lee 2016	Kim 2013	Etemadifar 2013	Hyeong-Geug 2013	Hartz 2004	Le Gal 1996
Jin 2020*	†	Fatigue	?	?	--	--	?	?	!
Kim 2020	✓		--	--	--	--	--	Y	--
Bach 2016	✓		--	--	Y	Y	--	--	--
Arring 2018	X		--	--	?	--	--	--	?
Alraek 2011	X		--	--	--	--	--	?	--
Provino 2010	X		--	--	--	--	--	--	--
Jin 2020*	†	Quality of Life	!	?	--	--	!	!	!
Jin 2020*	†	Emotional functioning	!	!	--	--	!	?	?
Lopresti 2021	X	Nil	--	--	--	--	--	--	--
Ogawa-Ochiai 2018	X	Nil	--	--	--	--	--	--	--

* Best available information means the systematic review meets AMSTAR-2 domains 4, 8, 9, & 11 (see Appendix B2 Framework for selecting the systematic review from which to extract data)

✓ Systematic review meets (or partially meets) prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

† Systematic review meets (or partially meets) some, but not all, prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

X Systematic review does not meet prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

* Jin 2020: The authors did not present results (only *p* values provided) for listed outcomes. A meta-analysis for 'Clinical effect' based on self-reported fatigue scales (fatigue score, fatigue severity or checklist of individual strength), but the threshold for 'Clinical effect' (dichotomous) was not specified. Due to time and resource constraints, retrieval of primary studies was not pursued.

Y RCT is included in the systematic review, meets our PICO criteria & a study result is available for inclusion in the synthesis.

? RCT is included in the systematic review, meets our PICO criteria, but the systematic review does not adequately report the results. Due to time and resource constraints, retrieval of primary studies was not pursued.

! RCT is included in the systematic review but does not measure the listed outcome.

-- RCT is not included in systematic review.

4.13.4 Risk of bias

None of the eligible RCTs were judged by the included systematic reviews to be at overall high risk of bias. Risk of bias assessments for the included RCTs as summarised by included systematic reviews are provided in Appendix F1.

Both Kim 2013 and Etemadifar 2013 were rated by Bach 2016 using the Jadad Scale (234). Kim 2013 met 4 out of the 5 items on the Jadad scale, with concerns about not "using identical placebo". Etemadifar 2013 met all 5 items on the Jadad scale.

Hartz 2004 was assessed by Kim 2020 using the Cochrane Collaboration's risk of bias assessment tool (54) and was judged to be at low risk of bias in the domains relating to selection, performance, detection and attrition bias. The study was judged to be at unclear risk of bias for selective outcome reporting.

4.13.5 Summary of findings and evidence statements

4.13.5.1 Primary Comparison (vs placebo)

Seven (7) RCTs (Etemadifar 2013, 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 outcome. Four (4) studies (Gal 1996, Hyeong-Geug 2013, Kim 2016, Lee 2016) could have contributed data but there was insufficient information in the reviews to make an assessment.

WHM compared to placebo for fatigue conditions

Patient or population: Fatigue conditions
Setting: Community
Intervention: WHM (ginseng)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with WHM				
Fatigue assessed with: various (higher is worse) follow-up: range 4 to 12 weeks	-	SMD **0.36 SD lower^** (0.71 lower to 0.00 lower)	-	185 (3 RCTs) †	⨁⨁◯◯ LOW [a,b,c,d,e]	WHM may result in little to no difference in fatigue severity in people with fatigue conditions
Quality of life assessed with: SF-36 (higher is best) scale range: 0 to 100 follow-up: 4 weeks	No results available for inclusion in the synthesis.		-	(0 studies) ††	-	The effect of WHM on health-related quality of life in people with fatigue conditions is unknown.
Patient reported improvement	No measures assessed in eligible reviews.		-	(0 studies)	-	The effect of WHM on patient reported improvement in people with fatigue conditions is unknown.
Emotional functioning assessed with: MASQ (higher is best) scale range: unclear follow-up: 8 weeks	No results available for inclusion in the synthesis.		-	(0 studies) †††	-	The effect of WHM on emotional functioning in people with fatigue conditions is unknown.
Physical functioning	No measures assessed in eligible reviews.		-	(0 studies)	-	The effect of WHM on physical functioning in people with fatigue conditions is unknown.
Sleep quality	No measures assessed in eligible reviews.		-	(0 studies)	-	The effect of WHM on sleep quality in people with fatigue conditions is unknown.
Thinking/ concentration	No measures assessed in eligible reviews.		-	(0 studies)	-	The effect of WHM on ability to concentration in people with fatigue conditions is unknown.

WHM compared to placebo for fatigue conditions

Patient or population: Fatigue conditions
Setting: Community
Intervention: WHM (ginseng)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with Placebo	Risk with WHM				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

^ As a rule of thumb, an SMD of 0.2 represents a small difference, 0.5 is moderate, and 0.8 is a large difference (55).

† Data from 4 RCTs (539 participants) not included here because results were not adequately reported [missing information]. The studies reported conflicting results.
†† Data from one RCT (52 participants) not included here because results were not adequately reported [missing information]. The study was reported to show no difference between groups ($p > 0.05$).
††† Data from one RCT (96 participants) not included here because results were not adequately reported [missing information]. The study was reported to show an effect ($p < 0.05$) favouring WHM.

CI: confidence interval; **MASQ:** Mood and anxiety symptom questionnaire; **RR:** risk ratio; **SF-36:** 36-item short form; **WHM:** Western Herbal Medicine

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. Certainty of evidence not downgraded.
b. No serious inconsistency. Certainty of evidence not downgraded.
c. No serious indirectness. The available evidence is in people with chronic fatigue or multiple sclerosis taking ginseng and is directly generalisable to the Australian population with few caveats. It is possible that the herbs used in the studies are contrary to what is prescribed in Australia, but the evidence can be sensibly applied. Certainty of evidence not downgraded.
d. Serious imprecision. Wide confidence intervals (lower bound overlaps with no important difference). Certainty of evidence downgraded.
E Publication bias suspected. There is a strong suspicion of non-reporting of results likely related to the *p* value, direction or magnitude of effect. Data were missing from 4 studies that reported conflicting results. Certainty of evidence downgraded.

4.13.5.2 Secondary Comparison (vs inactive control)

There were no studies found by the included systematic reviews that compared WHM with control (no intervention, waitlist or usual care) in people with fatigue conditions. In the absence of evidence, the effect of WHM compared with control (no intervention, waitlist or usual care) on the prioritised outcomes in people with fatigue conditions is unknown.

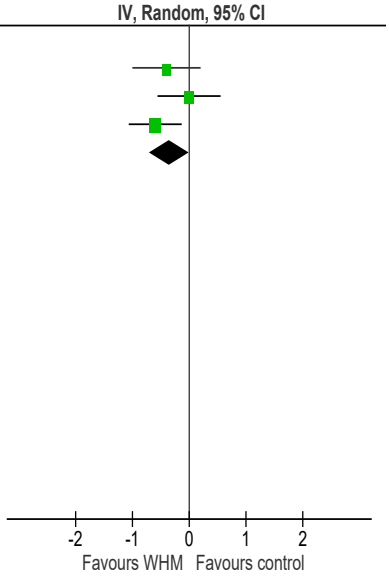
4.13.5.3 Tertiary Comparison (vs active control)

No studies found. The effect of WHM compared with active controls on the prioritised outcomes in people with fatigue conditions is unknown.

4.13.6 Forest plots

Outcomes results related to people with fatigue conditions is presented in Figure 26 (fatigue severity).

Figure 26 Forest plot of comparison: WHM vs placebo: Fatigue conditions – fatigue severity



Study or Subgroup	WHM Mean	WHM SD	WHM Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Fatigue (any measure)								
Hartz 2004 (siberian ginseng)	-11.8	3.93	26	-10.2	3.93	20	27.9%	-0.40 [-0.99, 0.19]
Etemadifar 2013 (panax ginseng)	23.65	12.8	26	23.69	12.94	26	31.5%	-0.00 [-0.55, 0.54]
Kim 2013 (panax ginseng)	41.8	13.2	58	48.8	7.3	29	40.6%	-0.60 [-1.05, -0.14]
Subtotal (95% CI)			**110**			**75**	**100.0%**	**-0.36 [-0.71, -0.00]**
Heterogeneity: Tau² = 0.03; Chi² = 2.73, df = 2 (P = 0.26); I² = 27%								
Test for overall effect: Z = 1.97 (P = 0.05)								
1.1.2 Outcome not adequately reported by the SR								
Gal 1996 (panax ginseng) (1)	0	0	109	0	0	109		Not estimable
Lee 2016 (panax ginseng) (2)	0	0	26	0	0	26		Not estimable
Kim 2016 (panax ginseng) (3)	0	0	72	0	0	77		Not estimable
Hyeong-Geug 2013 (panax ginseng) (4)	0	0	90	0	0	30		Not estimable
Subtotal (95% CI)			**297**			**242**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								

Test for subgroup differences: Not applicable

Footnotes

(1) Data from Jun 2020: Effect favouring ginseng (p=0.019) measure not specified.

(2) Data from Jun 2020: Effect favouring ginseng (p<0.01) with VAS; no important difference between groups (p>0.05) with Revised Piper Fatigue Scale

(3) Data from Jun 2020: no important difference between groups (p>0.05) with Checklist Individual Strength

(4) Data from Jun 2020: no important difference between groups (p>0.05) with Numeric rating scale

4.14 Upper respiratory tract infection

4.14.1 Description of the condition

Upper respiratory tract infections are an umbrella category of illnesses caused by various bacteria and viruses. URTIs generally affect the nose, sinuses, pharynx, larynx and large airways, involving swelling and self-limited irritation of the upper airways (519). The most common URTIs seen by primary care physicians include common cold, sinusitis, pharyngitis, epiglottitis and laryngotracheitis (520). Risk factors for acquiring URTIs include exposure to children and pets, individuals with a compromised autoimmune system, poor hand hygiene, being in crowded areas and seasonal influence (519, 521).

Globally, the burden of URTIs reached 17.2 billion people in 2019, with the incident number of cases increasing by 37 per cent between 1990 and 2019 (522). In Australia, URTIs are the most commonly managed respiratory problem in general practices, with 6 out of 100 visits relating to URTIs (523).

General treatment surrounds symptomatic relief, although antibiotics are given to treat infections of bacterial origin (524). Alternative medicines for treating URTIs have been reported for use as symptomatic treatment (525). However, further testing and review of high-quality evidence are needed to implement complementary and alternative medicines into routine clinical practice.

4.14.2 Description of studies

There were 27 citations (199, 478, 526-550) corresponding to 27 systematic reviews identified in the literature search that evaluated the effectiveness of WHMs in people with URTIs. No additional reviews were identified in the Department's public call for evidence (see Appendix C2). There were 3 systematic reviews awaiting classification (see Appendix C4) and one ongoing review (see Appendix C5).

A summary of the PICO criteria of the 27 eligible systematic reviews is provided in Appendix D5.2.1.

There were 7 reviews (526-532) published in 2018 or after that presented results in a meta-analysis that were to be prioritised for critical appraisal and data extraction. The other 20 reviews were earmarked for assessment as they were judged likely to no longer represent the best available evidence (199, 533-541) or did not adequately report data of included primary studies (478, 542-550).

Given time and resource constraints, further assessment of these reviews was not able to be performed.

4.15 Dermatitis and eczema

4.15.1 Description of the condition

Dermatitis is characterised by red, itchy rashes as a nonspecific response to inflammation of the skin. Some types of dermatitis are chronic (e.g. contact dermatitis and atopic dermatitis) (551). Contact dermatitis is caused by contact with external agents and can have an irritant or allergic cause. Around 70% of contact dermatitis cases are caused by an irritant (552). Atopic dermatitis also known as eczema, is an inflammatory skin condition characterised by dry, itchy and irritated skin, occurring more frequently in children than adults (553). It is not uncommon for patients to have both atopic dermatitis and contact dermatitis. Dermatitis and eczema can affect any area of the skin but often affects the face, behind the elbows and knees, wrists and ankles and are influenced by a combination of environmental and genetic factors (554, 555). Generally, there is usually no single trigger for an eczema flare (551).

The global incidence rate of dermatitis between 2007 and 2017 was 13.0%, whereas 2.4% of the population worldwide were affected with eczema (556, 557). In Australia, the estimated lifetime prevalence of atopic dermatitis is 16.4% (553). Overall, prevalence of eczema is higher in younger individuals than in older individuals, affecting approximately 30% of children and 10% of adults in Australia with infantile eczema affecting 1 in 5 children (551).

The primary treatments for dermatitis and eczema are aimed at reduced exposure to allergens and irritant topical agents (e.g. topical corticosteroids) and application of topical nonsteroidal treatments (e.g. pimecrolimus, tar preparations, crisaborole). Medicated dressings and herbal preparations may also be considered for some patients (558-560).

4.15.2 Description of studies

There were 2 citations (473, 561) corresponding to 2 systematic reviews identified in the literature search that evaluated the effectiveness of WHMs in people with dermatitis or eczema. No additional reviews were identified in the Department's public call for evidence (see Appendix C2). There were no systematic reviews awaiting classification (see Appendix C4) and no ongoing reviews (see Appendix C5).

Both reviews provided a narrative summary of primary study results examining the effect of WHM on people with dermatitis or eczema (Thandar 2017, Vaughn 2016). The reviews failed to 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 and the effect of WHM on dermatitis or eczema is unknown.

4.16 Acne

4.16.1 Description of the condition

Acne vulgaris is a chronic, inflammatory skin condition caused by a blockage of the hair follicle, increased sebum production, bacterial colonisation and inflammation (562). The condition generally develops during adolescence and may resolve during adulthood, predominately affecting more women than men (562, 563). Individuals begin to experience whiteheads, blackheads and inflamed pus-filled lesions in area of the body producing excess sebum, such as the face, chest or back. Other clinical variants of acne exist (e.g. acne conglobate and acne fulminans) but are rare in occurrence. These clinical variants are more severe and typically affect young males (564, 565).

The global prevalence of acne is estimated to be 9.4% of the population, predominantly affecting teenagers and young adults (566). In Australia, acne is considered almost universal in teenagers with an estimated prevalence of 93.3% in individuals aged 16 to 18 years (567). Acne can persist beyond adolescence with women typically more affected than men (568). There are many factors contributing to the cause of acne including hormonal changes often seen during puberty, environment, genetics and stress. Certain foods (e.g. whey protein, diets high in sugar) are suggested to contribute to the development of acne however robust evidence associating diet with acne is lacking (563, 569).

Current treatments for managing acne include improved face hygiene with soap-free face wash, the use of oil-free products and avoidance of triggers (e.g. oily substances, friction with clothes or other objects). Pharmacotherapies are also prescribed to clear severe acne and reduce scarring, this includes topical retinoids, antibiotics and oral isotretinoin (570). Individuals with acne also often use herbal medicines or other complementary medicines to avoid potential side effects associated with pharmacotherapies (360), with the aim of reducing inflammation, balancing hormones, restoring the skin's natural oils or reducing bacterial load.

4.16.2 Description of reviews

There were 5 citations (473, 490, 571-573) corresponding to 5 systematic reviews (Kim 2021, Vaughn 2016, Tuong 2015, Ernst 2002, Volger 1999) identified in the literature search that evaluated the effectiveness of WHM in people with acne. There were no additional reviews identified in the Department's public call for evidence (see Appendix C2), no systematic reviews awaiting classification (see Appendix C4) and no ongoing reviews (see Appendix C5).

A summary of the PICO criteria of the 5 eligible systematic reviews is provided in Appendix D5.4.1.

The populations eligible for inclusion in the reviews were participants with acne vulgaris (Kim 2021) or subjects diagnosed with a skin condition (Vaughn 2016, Tuong 2015, Ernst 2002). One review had no population restrictions but included a study in people with acne (Vogler 1999).

There was one review (Kim 2021) that presented results in a meta-analysis that was prioritised for critical appraisal and data extraction. Review details, including outcome domains and measures, and the risk of bias of eligible RCTs are provided in Appendix F1.

4.16.3 Description of studies

Within the eligible systematic reviews, there were 9 RCTs that met our PICO criteria. Five (5) RCTs examined the effect of WHM compared with placebo (Lu 2016, Yoon 2013, Sharquie 2006, Lalla 2001) or control (no intervention) (Jung 2012). The other 3 RCTs (Sahrquie 2008, Waranuch 2019, Basset 1990) compared WHM with an active intervention (e.g. 1% clindamycin gel, 5% benzoyl peroxide solution).

An overlap table of the RCTs within the included systematic reviews is shown in Table 2.

The RCTs were conducted in Taiwan, Iraq, South Korea or not specified and examined the effects of green tea extract[p] (Lu 2016, Yoon 2013, Jung 2012, Sharquie 2008, Sharquie 2006), tea tree oil (Bassett 1990), aloe vera (Fulton 1990) or an herbal combination containing green tea extract (Waranuch 2019) or curcumin (Lu 2001). Sample sizes ranged from 17 to 124 (total 488 participants). The interventions were administered over 4 (Waranuch 2019, Lu 2016, Lalla 2001), 8 (Yoon 2013, Jung 2012, Sharquie 2008, Sharquie 2006) or 12 weeks (Basset 1990) (or unclear Fulton 1990). None of the identified herbs matched to the Tier 1 herbs included in the Western herbal medicine curriculum for immune conditions (i.e. most commonly taught in Australian curriculum for this condition; see Appendix A6.3).

Results for the Primary Comparison: WHM versus placebo are provided in the Summary of Findings tables (see Section 4.16.5). There was one study found for the Secondary Comparison: WHM versus inactive control (no intervention, usual care [if inactive]), however it failed to provide any meaningful data for inclusion. Results for the Tertiary Comparison (versus active comparators) are provided in Appendix F2.

Table 13 List of included systematic reviews and overlap with eligible RCTs (per outcome): Acne

Review ID	Best available*	Prioritised outcome domain	Study ID								
			Waranuch 2019	Lu 2016	Yoon 2013	Jung 2012	Sharquie 2008	Sharquie 2006	Lalla 2001	Basset 1990	Fulton 1990
Kim 2021	✓	Disease improvement (acne lesion count)	Y	Y	Y	--	Y	Y	--	--	--
		Patient subjective assessment (VAS)	!	!	Y	--	!	!	--	--	--
Vaughn 2016	X	Disease improvement (Leed's score)	--	--	--	--	--	--	?	--	--
Tuong 2015	X	Disease improvement (acne lesion count)	--	--	--	?	--	--	--	--	--
Ernst 2002	X	Disease improvement (acne lesion count)	--	--	--	--	--	--	--	?	!
Vogler 1999	X	Disease improvement (acne lesion count)	--	--	--	--	--	--	--	--	!

Abbreviations: VAS, visual analogue scale

* Best available information means the systematic review meets AMSTAR-2 domains 4, 8, 9, & 11 (see Appendix B1 Framework for selecting the systematic review from which to extract data)

✓ Systematic review meets (or partially meets) prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

† Systematic review meets (or partially meets) some, but not all, prespecified critical AMSTAR-2 domains (4, 8, 9 & 11).

X Systematic review does not meet prespecified critical AMSTAR-2 domain 11 and was not further assessed.

Y RCT is included in the systematic review, meets our PICO criteria & a study result is available for inclusion in the synthesis.

? RCT is included in the systematic review, meets our PICO criteria, but the systematic review does not adequately report the results. Due to time and resource constraints, retrieval of primary studies was not pursued.

! RCT is included in the systematic review but does not measure the listed outcome.

-- RCT is not included in systematic review.

4.16.4 Risk of bias

Risk of bias assessment for the eligible RCTs as summarised by included systematic reviews are provided in Appendix F1.

Five RCTs were assessed by Kim 2021 using the Cochrane Collaboration's risk of bias assessment tool (54). The other RCTs were assessed using a 5- or 7-point Jadad scale (234).

Four RCTs (Lu 2019, Waranuch 2019, Yoon 2013, Lalla 2001) were at overall low risk of bias and in one RCT (Sharquie 2008) the risk of bias was unclear. The other 3 RCTs (Jung 2012, Fulton 19909, Sharquie 2008) were judged by the included systematic reviews to be at overall high risk of bias. An assessment of bias for one RCT (Bassett 1990) was not provided.

[p] epigallocatechin-3-gallate (EGCG)

4.16.5 Summary of findings and evidence statements

4.16.5.1 Primary Comparison (vs placebo)

There were 3 RCTs (Lu 2016, Sharquie 2006, Yoon 2013) found by the included systematic review that compared green tea with placebo in people with acne and contributed to data relevant to 2 of the 5 critical or important outcomes. One other RCT (Lalla 2001) did not contribute any data.

There were no studies awaiting classification or ongoing that compared WHM with placebo in people with acne.

WHM compared to placebo for Acne

Patient or population: Acne
Setting: Community
Intervention: WHM (green tea)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with control	Risk with WHM				
Patient reported improvement assessed with: VAS scale range: 0 to 10 (higher is worse) follow-up: 8 weeks	The mean change in VAS score was **1.2 points**	**MD 4.61 lower** (3.23 lower to 5.98 lower)	-	70 (1 RCT) †	⨁⨁◯◯ LOW [a,b,c,d,e]	WHM may result in a large improvement in global symptoms in people with acne. #
Quality of Life	-	-	-	(0 studies)	-	The effect of WHM on quality of life in people with acne is unknown.
Emotional functioning	-	-	-	(0 studies)	-	The effect of WHM on emotional functioning in people with acne is unknown.
Physical functioning	-	-	-	(0 studies)	-	The effect of WHM on physical functioning in people with acne is unknown.
Disease severity assessed with: inflammatory acne lesion count scale range: 0 to >150 (higher is worse) follow-up: range 4 to 8 weeks	-	**SMD 3.59 SD lower ^** (5.97 lower to 1.20 lower)	-	183 (3 RCTs) †	⨁⨁◯◯ LOW [a,b,c,d,e]	WHM may result in a large reduction in disease severity (inflammatory lesions) in people with acne.

WHM compared to placebo for Acne

Patient or population: Acne
Setting: Community
Intervention: WHM (green tea)
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Evidence statement
	Risk with control	Risk with WHM				
Disease severity assessed with: noninflammatory acne lesion count scale range: 0 to >150 (higher is worse) follow-up: range 4 to 8 weeks		**SMD 0.73 SD lower ^** (6.44 lower to 4.99 higher)	-	134 (2 RCTs) †	⨁◯◯◯ VERY LOW a,c,e,f,g	The evidence is very uncertain about the effect of WHM on disease severity (noninflammatory lesions) in people with acne.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

^ As a rule of thumb, an SMD of 0.2 represents a small difference, 0.5 is moderate, and 0.8 is a large difference (55).
# In the absence of an MCID, effect estimates were considered on three levels: small (MD <10% of the scale), moderate (MD between 10% to 20% of the scale) or large (MD more than 20% of the scale).

† One RCT was considered as 2 separate studies in this analysis as it examined different concentrations of green tea extract independently in a split-face trial design.

CI: confidence interval; **MD:** mean difference; **SD:** standard deviations; **SMD:** standardised mean difference; **VAS:** visual analogue scale; **WHM,** Western herbal medicine

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. No serious risk of bias. Certainty of evidence not downgraded.
b. Serious inconsistency. Substantial statistical heterogeneity (I^2 = 90%) that cannot be explained. Certainty of evidence downgraded.
c. No serious indirectness. The evidence is in people with acne vulgaris and is directly applicable to the Australian healthcare context with few caveats. It is possible that the herbs used in the studies are contrary to what is prescribed in Australia, but the evidence can be sensibly applied. Certainty of evidence not downgraded.
d. No serious imprecision. Certainty of evidence not downgraded.
e. Publication bias suspected. There is a strong suspicion of non-reporting of results likely related to the *p* value, direction or magnitude of effect. Certainty of evidence downgraded.
f. Very serious inconsistency. Point estimates vary and confidence intervals do not overlap. Substantial statistical heterogeneity (I^2 > 90%) that cannot be explained. Certainty of evidence downgraded 2 levels.
g. Serious imprecision. Wide confidence intervals (upper and lower bounds overlap with both large and no important differences). Certainty of evidence downgraded.

4.16.5.2 Secondary Comparison (vs inactive control)

There was one RCT found by the included systematic reviews that compared WHM with control (no intervention, waitlist, usual care [if inactive]) in people with acne. The review did not provide any usable data. In the absence of evidence, the effect of WHM compared with inactive control on the prioritised outcomes in people with acne is unknown.

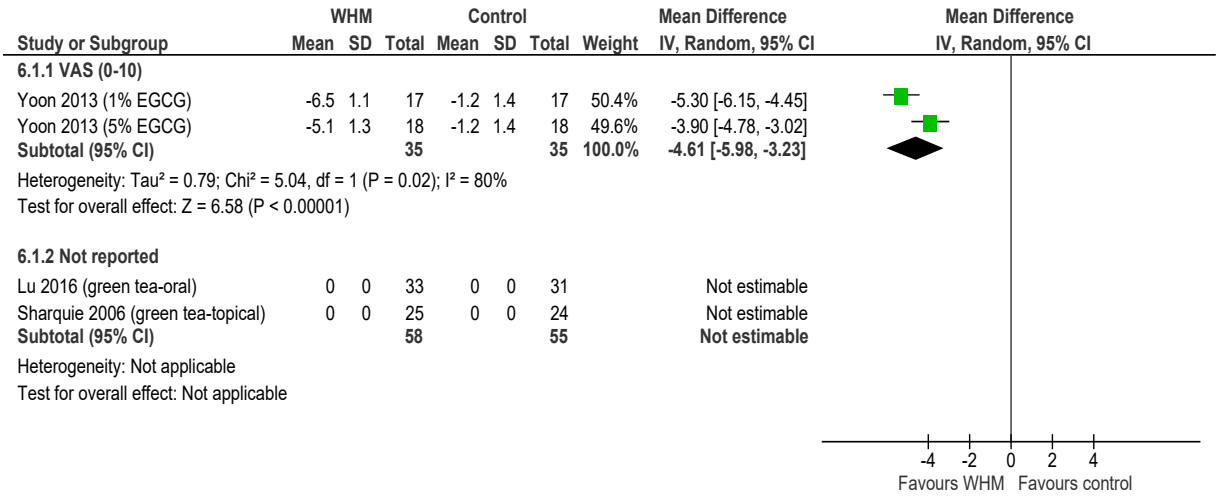
4.16.5.3 Tertiary Comparison (vs active control)

There were 4 studies found by the included systematic reviews that compared WHM with active comparators (see Appendix F2).

4.16.6 Forest plots

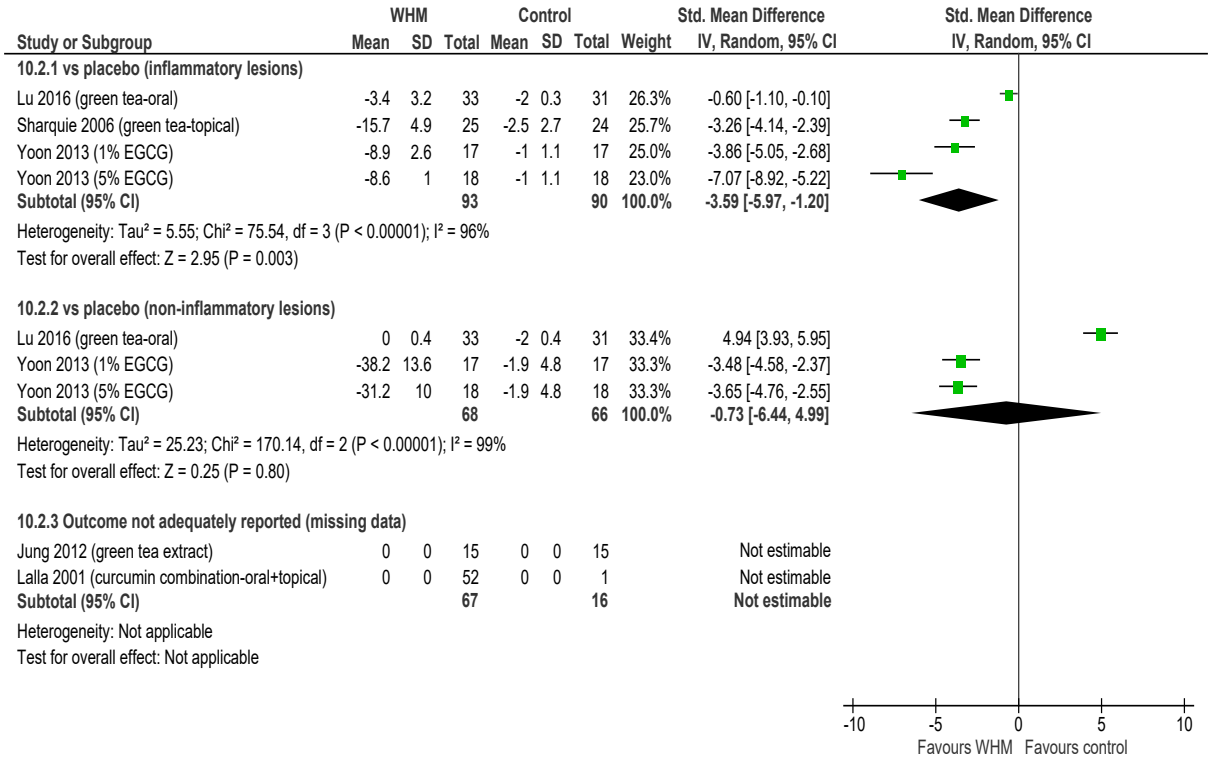
Outcomes results for people with acne is presented in Figure 27 (global improvement) and Figure 28 (disease severity).

Figure 27 Forest plot of comparison: WHM vs placebo: Acne vulgaris - Global improvement (patient reported)



Abbreviation: EGCG, epigallocatechin-3-gallate solution (green tea extract); VAS, visual analogue scale

Figure 28 Forest plot of comparison: WHM vs placebo: Acne vulgaris - Disease severity (acne lesion count)



Abbreviations: EGCG, epigallocatechin-3-gallate (green tea extract) solution

5 Discussion

5.1 Summary of main results

We conducted a systematic review of systematic reviews (an overview) to evaluate the effectiveness of WHM for 16 clinical or preclinical conditions prioritised (by NTWC) as most relevant to the practice of WHM in Australia. We identified 402 systematic reviews that reported on critical or important outcomes and were included in the qualitative synthesis. The 2 comparators of interest were placebo and 'inactive' control. Evidence from 270 RCTs covering 11 conditions are include in the final analysis for Primary Comparison: WHM versus placebo presented in the summary of findings tables. There were 5 RCTs found for Secondary Comparison: WHM versus 'inactive' control covering 2 conditions (inflammatory bowel disease, menstrual conditions).

For the Tertiary comparison: WHM versus 'active' control, studies of prioritised conditions are described in the results section and data presented in Appendix F2. For one population (depression), results are presented in a summary of findings table, as there were several studies evaluating the effects of the same (or similar) WHM compared with the same (or similar) evidence-based treatment (a pre-specified criterion for presenting results). No other priority populations are included in the synthesis or summary of findings tables, as the wide range of comparators and outcomes did not allow for synthesis as planned in the protocol.

Given time and resource constraints, critical appraisal and synthesis of the evidence for 4 of the 16 prioritised conditions (diabetes, impaired glucose tolerance, metabolic syndrome, and upper respiratory tract infections) were not able to be performed. The Natural Therapies Working Committee (NTWC) was not involved in selection of which prioritised conditions were completed versus not completed (see NHMRC process report for additional information).

Our confidence in the result from the body of evidence for each outcome was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework. GRADE combines information to assess overall how certain systematic review authors can be that the estimates of the effect (reported across a study/s for each critical or important outcome) are correct.

Certainty of evidence is interpreted as follows:

Certainty	Definition
High certainty	The authors have a lot of confidence that the true effect is similar to the estimated effect.
Moderate certainty	The true effect is probably close to the estimated effect.
Low certainty	The true effect may be markedly different from the estimated effect.
Very low certainty	The true effect is probably markedly different from the estimated effect

For 11 prioritised conditions there was moderate or low certainty evidence about the effect of WHM on at least one of the outcomes considered critical or important by NTWC. The overview found, that compared with placebo, the evidence provides:

- moderate certainty evidence that WHM probably results in:
    - a large improvement (>20%) in pain intensity in people with menstrual conditions (7 RCTs, 601 participants) [WHM included ginger, cinnamon, valerian root or fenugreek]
    - a large increase (>20%) in patient-reported improvement in people with premenstrual disturbances (6 RCTs, 839 participants) [WHM included chaste tree berry]
    - a moderate increase (10-20%) in the proportion with clinical remission in people with inflammatory bowel disease (14 RCTs, 974 participants) [WHM included green tea extract, curcumin, Boswellia, aloe vera gel, Wormwood, St Mary's thistle or Andrographis]
    - a moderate increase (10-20%) in the proportion with clinical improvement in people with irritable bowel syndrome (19 RCTs, 1279 participants) [WHM included peppermint oil, curcumin + fennel, Carmint + Psyllium, anise oil, aloe vera juice, ginger or St Jonh's wort]

  - a moderate improvement (10-20%) in symptoms severity in people with symptoms of menopause (16 RCTs, 1680 participants) [WHM included black cohosh extract, alone or in combination with St John's wort or red clover]
  - a moderate reduction (10-20%) in depressive symptoms in people with depression (33 RCTs, 3910 participants) [WHM included curcumin, saffron or St John's wort]
  - a slight reduction (<10%) in anxiety in people with anxiety (20 RCTs, 2087 participants) [WHM included valerian root, kava, Passiflora, saffron, chamomile, ginkgo biloba or lavender].

- low certainty evidence that WHM may result in:
  - a large reduction (>20%) in depressive symptoms (5 RCTs 613 participants) and anxiety (2 RCTs, 208 participants), and a large improvement (>20%) in overall symptoms (8 RCTs, 1133 participants) in people with premenstrual disturbances [WHM included chaste tree]
  - a large reduction (>20%) in anxiety (5 RCTs, 397 participants) and a slight improvement (<10%) in emotional functioning (2 RCTs, 3587 participants) in people with depression [WHM included curcumin or saffron]
  - a large reduction (>20%) in disease severity (3 RCTs, 183 participants) and a large increase (>20%) in patient-reported improvement (1 RCT, 70 participants) in people with acne [WHM included green tea-oral, green tea-topical]
  - a moderate increase (10-20%) in the proportion with a clinical response (8 RCTs, 403 participants) in people with inflammatory bowel disease [WHM included green tea extract or curcumin]
  - a moderate reduction (10-20%) in abdominal pain intensity (7 RCTs, 606 participants) and a slight (<10%) increase in clinical improvement (3 RCTs, 236 participants) in people with irritable bowel syndrome [WHM included peppermint oil or aloe vera juice]
  - a moderate reduction (10-20%) in depressive symptoms (2 RCTs, 129 participants), a moderate improvement (10-20%) in global improvement (3 RCTs, 670 participants) and emotional functioning (2 RCTs, 508 participants) in people with anxiety [WHM included lavender, saffron, or chamomile]
  - a slight improvement (<10%) in physical functioning (2 RCTs 508 participants) and sleep quality (2 RCTs, 382 participants) in people with anxiety [WHM included lavender]
  - a moderate reduction in symptoms of fatigue (3 RCTs, 185 participants) in people with chronic fatigue conditions [WHM included Siberian ginseng or panax ginseng]
  - a slight reduction (<10%) in hot flush frequency (14 RCTs, 1355 participants) in people with symptoms of menopause [WHM included black cohosh, red clover, valerian, valerian root, St John's wort or St John's wort + chaste tree].

- moderate certainty evidence that WHM probably results in little (to no) change in:
  - sexual functioning in people with symptoms of menopause (7 RCTs, 887 participants) [WHM included ginseng, withania (ashwagandha), red clover or ginseng]
  - sleep quality in people with insomnia (5 RCTs, 946 participants) [WHM included chamomile, valerian or kava].

- low certainty evidence that WHM may result in little (to no) change in:
  - clinical improvement in people with inflammatory bowel disease (2 RCTs, 151 participants) [WHM included curcumin]
  - symptoms of anxiety in people with insomnia (2 RCTs, 425 participants) [WHM included kava, valerian or chamomile].

The evidence provides very low certainty of the effect of WHM compared with placebo for 6 critical or important outcomes prioritised for analysis in this review (across 4 conditions: menstrual conditions, symptoms of menopause, depression and acne). For these outcomes, the true effect is probably markedly different from the estimated effect, with more studies needed to determine the true effect.

Of the 104 outcomes prioritised as critical or important in this review, there were no studies found reporting on 43 of those outcomes and therefore, the effect of WHM on these outcomes is unknown. There were 2 conditions assessed in this review where the effect of using WHMs is unknown (reflux and dermatitis/eczema). The effect of WHM for 27 outcomes across 4 conditions was not assessed due to the volume of evidence, time and resource constraints. There are numerous systematic reviews examining the effect of WHM on these conditions, but preliminary data suggest the results are limited to one or 2 outcomes per condition.

Results for WHM compared to inactive control (e.g. waitlist) were also examined, but for the majority of conditions there were no results found. For 2 populations (IBD, menstrual conditions) the evidence was very uncertain.

Compared to active control, results were examined for one condition. Here, the evidence provides moderate certainty that WHM (St John's wort) is probably comparable to antidepressants for improving symptoms of depression in people with depression. Results for all other conditions were listed but not assessed because they did not meet criteria prespecified in the protocol.

An assessment of harms of WHM was not conducted for this review, as it was out of scope of this review to assess adverse effects of WHM.

Overall, the evidence suggests that WHM may provide people with some benefit for a range of outcomes considered critical or important by the NTWC, when compared with placebo. There remain many outcomes for which the benefits are unknown.

5.2 Overall completeness and applicability of evidence

The practice of Western herbalism includes a holistic treatment framework that includes a wider social, emotional, economical, spiritual and cultural framework. In the absence of studies that focus on Western herbalism as a practice, the overview has focused on individual herbal medicines. Extrapolation of the effect of these interventions may or may not reflect Western herbalism as a practise, and given the broad nature of the overview, it is difficult to specify if the included primary studies examined the individual WHM delivered in a manner that would be considered applicable to the Australian context.

The identified systematic reviews could be categorised as being:

- a review that focused on the effect of a single herb (or herbal extract) on a single condition (e.g. a review of the effectiveness of St John's Wort on depression)
- an umbrella review that focused on the properties of a particular herb and its effectiveness across multiple conditions (e.g. effect of Nigella sativa across circulatory, endocrine and mental health conditions)
- an umbrella review that focused on a particular condition and examined the effectiveness of various interventions for that condition (e.g. a review of pharmacological and non-pharmacological interventions for insomnia)
- an umbrella review that focused on a particular outcome and searched for herbal medicines (or other intervention) shown to be effective for that outcome (e.g. herbal medicines that improve blood pressure).

This overview aimed to compile the evidence from systematic reviews of RCTs and quasi RCTs to assess the effectiveness of WHM in conditions prioritised by the NTWC. Only studies that assessed WHM versus placebo or WHM versus inactive control (no intervention, waitlist, usual care if considered inactive) were included in the synthesis. Studies of prioritised conditions with active comparators were not able to be included in the synthesis or summary of findings tables (except depression), as the wide range of comparators and outcomes did not allow for synthesis as planned in the protocol. There are 192 systematic reviews covering 4 conditions prioritised by the NTWC that have been earmarked for assessment, but given time and resources, critical appraisal and data synthesis were not completed.

There were 452 systematic reviews that met the eligibility criteria for the overview but were not included in the evidence evaluation. This is because they either examined the effects of WHMs in populations (or conditions) not prioritised by NTWC for analysis or synthesis (396 reviews) or they were conducted in populations that were of lower priority (56 reviews). These studies are listed in an inventory titled *Citation details of systematic reviews of low and non-priority populations* (Appendix C3).

Databases in languages other than English were not searched. Studies published in a language other than English (identified through English databases) were not translated and were not included in the synthesis but are listed in an inventory for completeness (Appendix C4.2). There were 124 reviews identified in a language other than English. There is no reason to suspect that the results of the reviews awaiting classification would differ substantially from those published in English or change the reviews overall conclusions.

The primary studies included within the eligible reviews were conducted in a range of countries including Australia, Brazil, Canada, China, Germany, Greece, India, Iran, Israel, New Zealand, South Korea, Spain, Sweden, the Netherlands, the United Kingdom and the United States. For some herbs, there tended to be a disproportionate number of studies from one region (e.g. many studies relating to effect of saffron were conducted in Iran, whereas studies in lavender extract were conducted in Germany). The primary studies identified by the reviews were often conducted over a 6 to 12-week time-period, with some studies examining the effect of the WHM for a slightly longer timeframe (24 weeks). Few, if any, provided any longer-term data (WHM administered for longer than 52 weeks).

The included primary studies were generally assumed to have provided a description of the condition and interventions examined in the study, however the reporting of this within the systematic reviews was often limited. This is because they often did not capture details about the participants comorbidities and did not provide complete details about the herbal product (such as mode of delivery, how often, how much etc.). The systematic reviews also often did not describe all the outcomes measured by the primary study (although it is possible this information was also missing from the primary study). There were also issues with determining if the data reported by the reviews were end of treatment scores, or differences in means from baseline. As per the protocol, we made no attempt to retrieve this information from the primary studies. For the outcomes with available evidence, it is considered unlikely this information would have impacted the overall conclusions of this review. However, it is possible that some of the outcomes with minimal or no information (i.e. the effect of WHM is uncertain or unknown) have been assessed by the primary studies, but the results have not been captured in the published systematic reviews. This may be because the results are not favourable to the intervention but, may also be because the reviews simply were not focused on that outcome. Among the 11 prioritised conditions for WHM versus placebo (not including the 5 conditions awaiting assessment), 45 (~58%) out of the 77 outcomes prioritised as critical or important for this overview were not reported by the included reviews.

Systematic reviews included in this overview are those published up until April 2021. At the time of the search, there were 199 reviews awaiting classification (67 in priority populations) and 39 ongoing reviews (11 in priority populations) that would meet the eligibility criteria for this overview. These reviews (awaiting classification and ongoing) appear comparable to those included in the evidence synthesis in terms of population, WHM and outcomes measured. There is no reason to suspect that the results of the reviews would differ substantially from those already included in this overview.

5.3 Certainty of the evidence

The certainty of evidence across outcomes was generally downgraded for issues with imprecision (related to sample size and wide confidence intervals that were compatible with both important benefit and little or no difference). In rare instances, the certainty of evidence was downgraded for inconsistency, when the effect estimates differed importantly across studies, as indicated by minimal or no overlap in the confidence intervals, and no clear explanation for statistical heterogeneity. We did not downgrade for indirectness, although in some cases note that the studies may not be directly applicable to the Australian healthcare context, meaning the delivery of the intervention or the participants included within the trial may have unknown factors that do not directly match the WHM as delivered in Australia.

The certainty of evidence was downgraded due to serious risk of bias when sensitivity analysis showed clear interaction between the effect estimates and the studies judged to be at high risk of bias. It is noted that we did not independently assess the risk of bias of the primary studies and instead relied upon the published systematic reviews to provide this information. At times, we noted disagreement between reviews with regards to risk of bias assessments for the same study, but as per protocol, did not return to the primary studies to conduct our own assessment.

5.4 Potential biases in the review process

To ensure transparency in the review process, we published the final NTWC-endorsed research protocol on PROSPERO. To capture the majority of reviews assessing the effectiveness of WHMs, we comprehensively searched multiple databases and did not apply date, language, population or outcome restrictions in our search. Screening was performed by 2 reviewers (independently). In addition, we provided detailed documentation of the inclusion criteria to avoid inconsistent application of study selection criteria and used standardised procedures for data collection and critical appraisal. Where possible, we have applied a methodological approach consistent with the *Cochrane Handbook for Systematic Reviews of Interventions* and other best practice methods.

Data collection was performed by two reviewers, the first collected data using data extraction forms and the second checked for completeness and accuracy in data extraction. Decisions regarding prioritisation of conditions and critical or important outcomes were made by the NTWC, with input from NTREAP, who were blinded to the number and details of the studies found.

While we have attempted to control for potential biases, some deviations from the protocol were necessary for pragmatic reasons. To ensure these deviations from protocol are clear, deviations and post-hoc decisions have been documented and explained in **Appendix G**.

5.5 Limitations

5.5.1 At review level

This overview was limited to the assessment of the evidence for certain conditions and groups of people to inform the Australian Government about health policy decisions for private health insurance rebates. This review was not designed to assess all the reasons that people seek out WHM, or the reasons practitioners prescribe WHM and was not intended to inform individual choices about Western herbalism, individual herbs, extracts of herb or combinations of herbs. Conditions were prioritised by NTWC, who were guided by relevant patient and/or practitioner reported Australian survey data (where available) and expert advice from NTREAP during the prioritisation process. The priority list was intended to represent the key conditions for which an individual would consult with a Western herbalist in Australia (not for which an individual would purchase over-the-counter herbal products). Given the large number of studies identified across a diverse range of conditions and as agreed *a priori*, the evidence synthesis was limited to 11 priority conditions. The breadth and diversity of conditions identified for inclusion in this overview means that it is possible that some interventions, conditions, outcome domains and outcome measures may have been misclassified or missed during the outcome prioritisation process.

In the absence of studies that focus on Western herbalism as a practice, the overview has focused on individual herbal medicines. This approach limits the ability to assess a key part of Western herbalism as a practice, being diagnosis and prescribing of the most appropriate individual herb (or herb combinations). Given the size of the overview, detailed descriptions and follow-up about the herbal preparation (e.g. liquid extracts, herbs, tablet or capsule) used within the primary studies was not pursued. The overview has therefore not considered whether the individual WHMs identified in the primary studies for a condition correlate with that typically prescribed by Western herbalists in Australia for that condition (in terms of herb(s), dose or preparation prescribed).

The 2 main comparators of interest were WHM compared to placebo or WHM compared to an inactive control (no intervention, waitlist or usual care) with the outcomes assessed limited to those deemed critical or important by NTWC for each condition. The available evidence was often limited to between one and 3 critical or important outcomes per condition. The effectiveness of WHM compared with other active comparators was not assessed for most conditions. Data from these studies are listed in Appendix F2. It is unknown whether the results of these studies would impact the overall conclusions of this review.

It was out of scope of the review to assess safety. Information regarding the sustainability of the effect is also unknown as the overview did not assess any follow-up data (noting neither did any of the included reviews).

Systematic reviews included in this overview are those published up until April 2021. It is likely there are numerous reviews that have been published after this search date and would meet the eligibility criteria for this overview. There is no reason to suspect that the results of the reviews would differ substantially from those already identified in this overview; however, it is possible a search for primary studies targeted to a defined condition would increase the certainty of evidence across some outcomes.

6 Authors' conclusions

6.1 Implications for health policy

This report was commissioned by the Australian Government as part of the Natural Therapies Review, with findings intended to inform decisions relating to whether private health insurance cover should be reinstated to WHM. As such, specific recommendations are not provided.

While there remains an absence of high certainty evidence about the effectiveness of individual WHMs compared with placebo for the 11 priority conditions and outcomes that align with the reasons why consumers commonly use WHMs in Australia, there is moderate to low certainty for certain individual WHMs to improve outcomes in a variety of common health conditions.

There are 7 conditions for which the evidence provides moderate certainty of benefit for at least one outcome (inflammatory bowel disease, irritable bowel syndrome, menstrual conditions, premenstrual disturbances, symptoms of menopause, anxiety, depression) and 2 conditions for which the evidence provides low certainty of benefit for at least one outcome (chronic fatigue, acne). In contrast, there was one condition where the evidence provides moderate and low certainty that WHM provides little to no benefit for 2 outcomes (insomnia). The effect of WHM is unknown in two conditions (GORD and dermatitis/eczema) due to lack of usable data. The effect of WHM for 4 of the 16 prioritised conditions (diabetes, impaired glucose tolerance, metabolic syndrome and upper respiratory tract infections) was not assessed due to the volume of evidence, time and resource constraints. The Natural Therapies Working Committee (NTWC) was not involved in selection of which prioritised conditions were completed versus not completed (see NHMRC process report for additional information).

6.2 Implications for research

Trials evaluating the effectiveness of individual WHMs compared with placebo are in abundance. However, the available evidence could be enhanced by measuring and reporting outcomes that are considered critical or important for decision-making in Australia. Many of the studies focused on the effect of WHM in participants who received treatment for 12 weeks or less, so it is possible the benefits of WHM may be more apparent in people who continue using the WHM for more than 12 weeks. Information about the sustainability of the effect would also be valuable. Most important, however, is the need for clinical trials that focus on the broader research question about the effectiveness of Western herbalism as a health service.

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