ATTACHMENT B

The following Risk of Bias in Systematic Reviews (ROBIS) assessments were commissioned by the National Health and Medical Research to assess some of the conditions not examined in synthesis in the review of Western Herbal Medicine as part of the Natural Therapies Review. These conditions were diabetes/impaired glucose tolerance and upper respiratory tract infections (URTI). The ROBIS assessments were completed by independent reviewing company, KSR Evidence in October and November 2024 and can be found in this attachment as well as on the KSR website. To locate the reports on the KSR website, search by the KSR number in the tables below.

Citations for which a ROBIS was sought - URTI

Reference	KSR ID number
Anheyer, D.; Cramer, H.; Lauche, R.; Saha, F. J.; Dobos, G. Herbal medicine in children with respiratory tract infection: systematic review and meta-analysis, Acad Pediatr 2018;18(1):8-19.	KSRA35873
Antonelli, M.; Donelli, D.; Firenzuoli, F. Ginseng integrative supplementation for seasonal acute upper respiratory infections: a systematic review and meta-analysis, Complement Ther Med 2020;52:102457.	KSRA139188
David, S.; Cunningham, R. Echinacea for the prevention and treatment of upper respiratory tract infections: a systematic review and meta-analysis, Complement Ther Med 2019;44:18-26.	KSRA107797
Hawkins, J.; Baker, C.; Cherry, L.; Dunne, E. Black elderberry (Sambucus nigra) supplementation effectively treats upper respiratory symptoms: a meta-analysis of randomized, controlled clinical trials, Complement Ther Med 2019;42:361-65.	KSRA89929
Hoang, M.P.; Chitsuthipakorn, W.; Snidvongs, K. Herbal medicines for allergic rhinitis: a systematic review and meta-analysis, Curr Allergy Asthma Rep 2021;21(4):25.	KSRA166893
Wieland, L.S.; Piechotta, V.; Feinberg, T.; Ludeman, E.; Hutton, B.; Kanji, S.; Seely, D.; Garritty, C. Elderberry for prevention and treatment of viral respiratory illnesses: a systematic review, BMC Complement Med Ther 2021;21(1):112.	KSRA168001

Citations for which a ROBIS was sought – Diabetes, insulin resistance and metabolic syndrome

Reference	KSR ID number
Asbaghi, O.; Fouladvand, F.; Moradi, S.; Ashtary-Larky, D.; Choghakhori, R.; Abbasnezhad, A. Effect of green tea extract on lipid profile in patients with type 2 diabetes mellitus: a systematic review and meta-analysis, Diabetes Metab Syndr 2020;14(4):293-301.	KSRA132308

Barzkar, F.; Baradaran, H.R.; Khamseh, M.E.; Vesal Azad, R.; Koohpayehzadeh, J.; Moradi, Y. Medicinal plants in the adjunctive treatment of patients with type-1 diabetes: a systematic review of randomized clinical trials, J Diabetes Metab Disord 2020;19(2):1917-29.	KSRA147938
Deyno, S.; Eneyew, K.; Seyfe, S.; Tuyiringire, N.; Peter, E.L.; Muluye, R.A.; Tolo, C.U.; Ogwang, P.E. Efficacy and safety of cinnamon in type 2 diabetes mellitus and pre-diabetes patients: a meta-analysis and meta-regression, Diabetes Res Clin Pract 2019;156:107815.	KSRA114925
Huang, F. Y.; Deng, T.; Meng, L. X.; Ma, X. L. Dietary ginger as a traditional therapy for blood sugar control in patients with type 2 diabetes mellitus: a systematic review and meta-analysis, Medicine 2019;98(13):e15054.	KSRA101991
Jamali, N.; Jalali, M.; Saffari-Chaleshtori, J.; Samare-Najaf, M.; Samareh, A. Effect of cinnamon supplementation on blood pressure and anthropometric parameters in patients with type 2 diabetes: a systematic review and meta-analysis of clinical trials, Diabetes Metab Syndr 2020;14(2):119-25.	KSRA127474
Namazi, N.; Khodamoradi, K.; Khamechi, S. P.; Heshmati, J.; Ayati, M. H.; Larijani, B. The impact of cinnamon on anthropometric indices and glycemic status in patients with type 2 diabetes: a systematic review and meta-analysis of clinical trials, Complement Ther Med 2019;43(April):92-101.	KSRA97728
Tabrizi, R.; Nowrouzi-Sohrabi, P.; Hessami, K.; Rezaei, S.; Jalali, M.; Savardashtaki, A.; Shahabi, S.; Kolahi, A.-A.; Sahebkar, A.; Safiri, S. Effects of Ginkgo biloba intake on cardiometabolic parameters in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of clinical trials, Phytother Res 2021;35(1):246-55.	KSRA149376
Ziaei, R.; Foshati, S.; Hadi, A.; Kermani, M.A.H.; Ghavami, A.; Clark, C.C.T.; Tarrahi, M.J. The effect of nettle (urtica dioica) supplementation on the glycemic control of patients with type 2 diabetes mellitus: a systematic review and meta-analysis, Phytother Res 2020;34(2):282-94.	KSRA121207

KSR Number: KSRA35873

Herbal medicine in children with respiratory tract infection: systematic review and meta-analysis

Anheyer, D. Cramer, H. Lauche, R. Saha, F. J. Dobos, G.

Acad Pediatr 2018;18(1):8-19 Full text options PubMed 28610802

Publication year: 2018 Added to database: November 13, 2017

Risk of Bias Assessment

Overall summary: High risk of bias in the review

Bottom Line

The authors concluded that provided a standardized medication is available, Pelargonium sidoides can be considered as an adjunctive option for RTI in children. No recommendation for the preventive use of Echinacea could be made so far. These findings need cautious consideration due to some weaknesses in the performance of this systematic review.

Risk of Bias Assessment

Overall summary

High risk of bias in the review

Only randomized controlled trials (RCTs) in English or German published as full articles were included. Embase was not searched separately. Methods additional to database searching were not mentioned. The number of reviewers for title and abstract screening was not mentioned.

A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	No
B. Was the relevance of identified studies to the reviews research question appropriately considered?	Yes
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes
Risk of bias in the review	**High**

Details of Review

Number of studies	11
Number of participants	2181
Last search date	12 Feb 2015
Review type	Intervention
Objective	To assess the effects of herbal medicines compared with no treatment, placebo, or other medication in the treatment of respiratory tract infection (RTI) in children and adolescents.
Population	Children and adolescents (age 0–18 years) diagnosed with respiratory tract infections (RTIs).
Interventions	Herbal medicines.
Comparator	No treatment, placebo, or any pharmaceutical medication.
Outcome	Not specified, any outcome.
Study design	Randomised trials.

Results

This review was supported by a grant from the Karl and Veronica-Carstens Foundation. Participants' mean age ranged from 1.6 years to 12.7 years, with a median of 6.8 years. The gender ratio ranged from 47.5% to 71.4% for male (median 51.5%) and 28.6% to 52.5% for female (median 48.5%) participants. Race was only reported in 1 RCT. Children were diagnosed with nonspecific acute RTI, acute bronchitis, otitis media, tonsillitis (without indication for antibiotic treatment), common cold, and RTI with an additional existing chronic disease. Four studies assessed the preventive and therapeutic effects of Echinacea on RTIs. Although one study indicated that Echinacea might help reduce the frequency of RTIs, two studies showed contradictory results. Specifically, one trial involving Echinacea in liquid form did not demonstrate significant differences in illness duration or severity between the Echinacea and placebo groups. Another study examined a combination of Echinacea with osteopathic manipulative treatment but found no reduction in otitis media cases, suggesting limited preventive potential. In terms of safety, three studies reported adverse reactions to Echinacea, with one study showing a marginally higher risk of acute otitis media and rashes. Despite generally mild side effects, the evidence for Echinacea's efficacy and safety was insufficient to support its recommendation for RTI prevention or treatment. Pelargonium sidoides (EPs7630): Six studies focused on EPs7630's effects on RTI symptoms, particularly for acute bronchitis. In contrast to the mixed findings for Echinacea, meta-analysis of EPs7630 data demonstrated a positive response rate, suggesting moderate efficacy. This efficacy analysis yielded a risk ratio (RR) of 2.56 with an estimated number needed to treat (NNT) of 8, indicating that one child in every eight treated would benefit from symptom relief compared to placebo. For safety, EPs7630 presented no increased risk of adverse effects in children compared to placebo, with an RR of 1.06 in the safety meta-analysis. This finding suggests that EPs7630 is generally safe for pediatric use, assuming the product is a standardized, licensed formulation, which is more widely available in Europe than in the United States.

Full Risk of Bias Assessment

Domain 1: Study Eligibility Criteria

High

Only randomized controlled trials (RCTs) in English or German published as full articles were included. Observational and non-randomized studies or those not published as full articles in peer-reviewed journals were excluded. Participants were children and adolescents aged 0–18 years diagnosed with respiratory tract infections (RTIs). Studies with participants beyond this age range were only included if data specific to children and adolescents were available separately. Interventions: studies comparing herbal medicines to either no treatment, a placebo, or pharmaceutical medication were eligible. Herbal drugs that were solely homeopathic or exclusively part of traditional Chinese medicine (which may contain animal or mineral ingredients) were excluded.

1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Yes
1.2 Were the eligibility criteria appropriate for the review question?	Yes
1.3 Were eligibility criteria unambiguous?	Probably yes
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Probably yes
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	No
Concerns regarding specification of study eligibility criteria	**High**

Domain 2: Identification and Selection of Studies

Unclear

PubMed, Scopus, and the Cochrane Central Register of Controlled Trials (Central) were searched. Embase was not searched separately. Methods additional to database searching were not mentioned. The number of reviewers for title and abstract screening was not mentioned. Full papers were screened by three independent reviewers. The PubMed search strategy was presented and appeared adequate. Language restrictions were already addressed in ROBIS domain 1.

2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	No
2.2 Were methods additional to database searching used to identify relevant reports?	No information
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Yes
2.4 Were restrictions based on date, publication format, or language appropriate?	Probably yes
2.5 Were efforts made to minimise error in selection of studies?	No information
Concerns regarding identification and selection of studies	**Unclear**

Domain 3: Data Collection and Study Appraisal

Low

Data extraction and risk of bias assessments were performed by two independent reviewers. The Cochrane RoB 1 checklist was used for risk of bias assessment. Study characteristics were presented in a table.

3.1 Were efforts made to minimise error in data collection?	Yes
3.2 Were sufficient study characteristics considered for both review authors and readers to be able to interpret the results?	Yes
3.3 Were all relevant study results collected for use in the synthesis?	Probably yes
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes
3.5 Were efforts made to minimise error in risk of bias assessment?	Yes
Concerns regarding methods used to collect data and appraise studies	**Low**

Domain 4: Synthesis and Findings

Low

If at least three studies addressed a specific outcome, a meta-analysis was conducted with a random effects model. For dichotomous outcomes, risk ratios (RRs) with 95% confidence intervals (CI) were calculated by comparing the event risk in the experimental group to that in the control group. When data were missing, attempts were made to obtain information from the study authors. In trials with multiple arms (e.g., testing different herbal doses against one control), groups were combined to create a pooled estimate. Heterogeneity among studies was assessed with I^2 statistics, the chi-square test determined if observed differences could be due to chance, $P \leq 0.10$ suggesting significant heterogeneity. Sensitivity analyses were conducted to assess robustness, examining the impact of high versus low bias in selection, performance, detection, and attrition. Sensitivity analyses also helped identify sources of heterogeneity when statistical variation was high. Since fewer than ten studies were included in each meta-analysis, publication bias could not be assessed.

4.1 Did the synthesis include all studies that it should?	Yes
4.2 Were all pre-defined analyses reported or departures explained?	Yes
4.3 Was the synthesis appropriate given the degree of similarity in the research questions, study designs and outcomes across included studies?	Yes
4.4 Was between-study variation minimal or addressed in the synthesis?	Probably yes
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Probably yes
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Probably yes
Concerns regarding synthesis and findings	**Low**

Abstract

Background: Herbal medicines are particularly regarded as an alternative or complement to conventional pharmaceuticals in the treatment and prevention of respiratory tract infections (RTIs). Therefore, the purpose of this review was to identify evidence for herbal therapy in the treatment of RTIs concerning effectiveness and safety. Methods: Medline/PubMed, Scopus, and the Cochrane Library were searched through February 12, 2015. Randomized controlled trials that compared herbal therapy with no treatment, placebo, or any pharmaceutical medication in children and adolescents (age 0 to 18 years) with RTI were eligible. Results: Eleven trials with 2181 participants were included. No clear evidence for Echinacea (4 trials) or an herbal compound preparation (1 trial) in preventing RTI symptoms was found. Meta-analysis revealed evidence for efficacy (responder rates: risk ratio [RR], 2.56; 95% confidence interval [CI], 1.54-4.26; P < .01; heterogeneity: I ² = 38%; chi-square = 9.63; P = .14) and safety (patients with adverse events: RR, 1.06; 95% CI, 0.42-2.66; P = .9; heterogeneity: I ² = 72%; chi-square = 10.64; P = .01) of Pelargonium sidoides in treating RTI symptoms compared with placebo (6 trials). Conclusions: Because of conflicting evidence in the included studies no concrete conclusion on effects of Echinacea could be drawn so far. In the case of Pelargonium sidoides, meta-analysis revealed moderate evidence for efficacy and safety in the treatment of RTIs in children.

KSR Number: KSRA139188

Ginseng integrative supplementation for seasonal acute upper respiratory infections: a systematic review and meta-analysis

Antonelli, M. Donelli, D. Firenzuoli, F.

Complement Ther Med 2020;52:102457 Full text options PubMed 32951718

Publication year: 2020 Added to database: July 23, 2020

Risk of Bias Assessment

Overall summary: High risk of bias in the review

Bottom Line

The authors concluded that limitations of existing evidence don’t allow to draw conclusions on the topic. Nevertheless, it is not excluded that ginseng supplementation in adjunct to influenza vaccination and standard care might be useful for SAURIs prevention and management in healthy adult subjects, but further high-quality trials are needed to support this hypothesis.These findings need cautious interpretation as some relevant studies may have been missed.

Risk of Bias Assessment

Overall summary

High risk of bias in the review

Only articles published in English, French, Spanish, Italian, or Portuguese in scientific journals were considered. Full search strategies were reported and appeared sub-optimal. Methods additional to database searching were not reported.

A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	Probably no
B. Was the relevance of identified studies to the reviews research question appropriately considered?	Yes
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes
Risk of bias in the review	**High**

Details of Review

Number of studies	10
Number of participants	2058
Last search date	26 May 2020
Review type	Intervention
Objective	To assess the effects of ginseng supplementation for the prevention and/or treatment of seasonal acute upper respiratory infections (SAURIs).
Population	Patients (any age) with SAURIs (such as influenza or common cold), reporting at least a respiratory symptom like runny nose, sneezing, cough, sore throat, nasal or sinus congestion, in combination with at least a systemic symptom like fever, chills, myalgia, fatigue, headache.
Interventions	Oral administration of any extract obtained from ginseng (Panax ginseng, Panax notoginseng, or Panax quinquefolius) at any dosage over a well defined period (regardless of its duration).
Comparator	Any type of control (placebo, no treatment) or comparison (treatment-as-usual, other therapies), including no comparison.
Outcome	Duration, severity, and type of symptoms; incidence of SAURIs during the study period; adverse events.
Study design	Any study involving humans, both clinical trials and observational studies.

Results

This research work was not funded. In one trial, study population was composed of patients with Chronic Lymphocytic Leukemia (CLL); in all the other included RCTs, participants were healthy subjects with no relevant comorbidities. Influenza vaccination status of participants varied across included studies: in four trials, subjects were recruited only if not vaccinated against the flu in the past 3 or 6 months; in three studies, patients were all vaccinated; in the remaining included RCTs, flu vaccination status was heterogeneous with only some participants being vaccinated. In seven studies P. quinquefolius was administered to participants, whereas in three trials P. ginseng was given to patients. No included study investigated the effects of P. notoginseng on SAURIs. In two studies, one group of participants was administered the ginseng extract given to the main intervention group but at a low-dose regimen. In one trial, intervention groups were given two different types of ginseng extracts named “GS-3K8” and “GINST” respectively. In all but one RCTs, intervention was administered daily for 8–16 weeks, whereas in one trial, ginseng was only given to patients at the onset of respiratory symptoms for a few days, thus only testing its therapeutic but not its preventive efficacy. The most commonly chosen dosage of P. quinquefolius extract for adults was 200 mg twice a day; the daily dose was adjusted in children depending on their weight, never exceeding the upper threshold of 26 mg/kg. For P. ginseng extracts, the recommended dose was 3 g a day in two studies, while no information about this detail was retrievable for the other included trial. The meta-analysis explored the effects of ginseng-based interventions on both the risk of developing infections and the duration of disease symptoms. For the first meta-analysis, which assessed infection risk across nine trials involving 1,550 participants, the results showed that ginseng interventions significantly reduced the likelihood of developing an infection. This finding, expressed as a relative risk (RR) of 0.69 with a 95% confidence interval between 0.52 and 0.90, indicated a favorable outcome for ginseng. A closer look at the type of ginseng used revealed that P. ginseng had a more pronounced effect in reducing infection risk compared to P. quinquefolius, as the pooled risk for P. ginseng studies was 0.50, while P. quinquefolius studies showed a relative risk closer to neutral at 0.84. The analysis also examined the impact of study quality, finding no significant difference between studies with high and low risk of bias, suggesting that the overall effect of ginseng was consistent across different levels of study rigor. A leave-one-out analysis, which excluded a trial involving non-healthy participants, still supported the benefit of ginseng, with the relative risk slightly adjusted to 0.65. In the second meta-analysis, which looked at the duration of disease symptoms across seven trials with a total of 1,152 participants, the ginseng intervention was associated with a reduction in symptom duration, although this result was not statistically significant. The mean difference in days was -2.58, with a confidence interval spanning -5.40 to 0.24, indicating that while there was a trend toward reduced duration, the evidence was not conclusive. Excluding a trial with a high risk of bias did not substantially change the outcome, but removing a trial that involved non-healthy subjects resulted in a statistically significant mean reduction of -3.11 days. When both of these trials were excluded, the result approached statistical significance with a mean reduction of -3.66 days. Overall, while ginseng interventions demonstrated a clear benefit in lowering infection risk, particularly with P. ginseng, the evidence on symptom duration was less robust, showing potential but not consistent results across all analyses.

Full Risk of Bias Assessment

Domain 1: Study Eligibility Criteria

Unclear

The eligibility criteria for the review included studies evaluating the efficacy of ginseng for preventing or treating seasonal acute upper respiratory infections (SAURIs). The review considered studies with any population of patients with SAURIs, defined by respiratory symptoms like runny nose or sore throat, alongside systemic symptoms such as fever or fatigue. The intervention required was oral administration of any ginseng extract (e.g., Panax ginseng, Panax notoginseng, or Panax quinquefolius) at any dosage, but excluded multicomponent remedies unless ginseng made up at least 90% of the formulation. The review accepted any control or comparison, such as placebo or other therapies, and focused on primary outcomes related to the efficacy of ginseng in reducing symptom duration, severity, and incidence of SAURIs, as well as safety outcomes on adverse events. Eligible studies included clinical trials and observational studies involving humans, while preclinical studies with animal or cellular models were excluded. Only articles published in English, French, Spanish, Italian, or Portuguese in scientific journals were considered, regardless of publication date.

1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Yes
1.2 Were the eligibility criteria appropriate for the review question?	Yes
1.3 Were eligibility criteria unambiguous?	Yes
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Yes
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Probably no
Concerns regarding specification of study eligibility criteria	**Unclear**

Domain 2: Identification and Selection of Studies

High

PubMed, EMBASE, Web of Science, Scopus, and the Cochrane Library were searched. Additional sources were ClinicalTrials.gov, the European Union Clinical Trials Register, the Chinese Clinical Trial Registry, and Google Scholar. Full search strategies were reported and appeared sub-optimal. Inclusion screening was by two independent reviewers. Methods additional to database searching were not reported.

2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Yes
2.2 Were methods additional to database searching used to identify relevant reports?	No information
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Probably no
2.4 Were restrictions based on date, publication format, or language appropriate?	Yes
2.5 Were efforts made to minimise error in selection of studies?	Yes
Concerns regarding identification and selection of studies	**High**

Domain 3: Data Collection and Study Appraisal

Low

Data extraction was by one reviewer and checked by a second reviewer. Risk of bias was assessed with the Cochrane RoB 2 tool by two reviewers.

3.1 Were efforts made to minimise error in data collection?	Probably yes
3.2 Were sufficient study characteristics considered for both review authors and readers to be able to interpret the results?	Yes
3.3 Were all relevant study results collected for use in the synthesis?	Probably yes
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes
3.5 Were efforts made to minimise error in risk of bias assessment?	Probably yes
Concerns regarding methods used to collect data and appraise studies	**Low**

Domain 4: Synthesis and Findings

Low

The relative risk (RR) was used as the measure of effect size to assess the risk of infection over the study period. This analysis employed the Mantel-Haenszel method to weight each trial, applying a continuity correction when necessary. A L'Abbé plot was used to visually present results. The meta-analysis focused on the duration of disease symptoms in days among infected participants, used the mean difference (MD) to combine data and the inverse variance method for weighting. These results were displayed in a forest plot. For both meta-analyses, a random-effects model was applied, with adjustments using the Hartung-Knapp-Sidik-Jonkman method. Heterogeneity was assessed with the I^2 statistic. The synthesis used aggregated data from each trial arm, and studies with three arms were treated as two separate comparisons (each intervention versus control). Risk of publication bias was evaluated for the first meta-analysis using a funnel plot, Egger's test, and the trim-and-fill method, but this approach was not feasible for the second meta-analysis due to fewer studies. Additionally, the p-curve method was applied in both analyses to check for potential "p-hacking" and confirm that the studies were appropriately powered to detect true effects. Both qualitative and quantitative subgroup analyses were conducted based on variables like ginseng species, specific pathogens, and study design. A separate analysis distinguished studies with a high versus low risk of bias. Finally, a leave-one-out analysis excluded a study involving sub-healthy individuals with chronic leukemia to focus on data from studies involving healthy participants only.

4.1 Did the synthesis include all studies that it should?	Yes
4.2 Were all pre-defined analyses reported or departures explained?	Yes
4.3 Was the synthesis appropriate given the degree of similarity in the research questions, study designs and outcomes across included studies?	Yes
4.4 Was between-study variation minimal or addressed in the synthesis?	Yes
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Yes
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Yes
Concerns regarding synthesis and findings	**Low**

Abstract

Background: The aim of the review was to assess whether ginseng can be a useful supplementation for seasonal acute upper respiratory infections (SAURIs). Method(s): All clinical studies investigating ginseng efficacy for the treatment or prevention of SAURIs were included in the review. Medline, EMBASE, Web of Science, Scopus, Cochrane Library, Google Scholar were systematically screened for relevant articles up to May 26th, 2020. The risk of bias was assessed with the Cochrane tool (RoB 2). Result(s): Nine articles (describing ten trials about P. ginseng or P. quinquefolius) were included in the review. Evidence globally indicated some useful activity of intervention when administered in adjunct to influenza vaccination. The results of our quantitative synthesis suggested a significant effect on SAURIs incidence (RR = 0.69 [95 % C.I. 0.52 to 0.90], $p < 0.05$), as well as a significant reduction of their duration if only studies with healthy individuals were included in the analysis (MD=-3.11 [95 % C.I.-5.81 to -0.40], $p < 0.05$). However, the risk of bias was high-to-unclear for most included trials, and publication bias couldn't be excluded. Discussion(s): Limitations of existing evidence don't allow to draw conclusions on the topic. Nevertheless, it is not excluded that ginseng supplementation in adjunct to influenza vaccination and standard care might be useful for SAURIs prevention and management in healthy adult subjects, but further high-quality trials are needed to support this hypothesis. Other: This research was not funded. The protocol was registered in PROSPERO under the following code: CRD42020156235.

KSR Number: KSRA132308

Effect of green tea extract on lipid profile in patients with type 2 diabetes mellitus: a systematic review and meta-analysis

Asbaghi, O. Fouladvand, F. Moradi, S. Ashtary-Larky, D. Choghakhori, R. Abbasnezhad, A.

Diabetes Metab Syndr 2020;14(4):293-301 Full text options PubMed 32289742

Publication year: 2020 Added to database: April 30, 2020

Risk of Bias Assessment

Overall summary: High risk of bias in the review

Bottom Line

The authors concluded that the supplementary intake of green tea extract may improve lipid profile by reducing serum TG concentrations in patients with T2DM. Furthermore, long-term GTE intervention may reduce serum triglyceride and total cholesterol concentrations.These findings should be considered with caution as some relevant studies may have been missed.

Risk of Bias Assessment

Overall summary

High risk of bias in the review

Embase was not mentioned. Keywords were provided but not a full search strategy.

A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	Probably no
B. Was the relevance of identified studies to the reviews research question appropriately considered?	Probably yes
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Probably yes
Risk of bias in the review	**High**

Details of Review

Number of studies	7
Number of participants	512
Last search date	August 2019
Review type	Intervention
Objective	To assess the effects of green tea extract (GTE) in improving the lipid profile of type 2 diabetes mellitus (T2DM) patients.
Population	Patients with type 2 diabetes mellitus (T2DM).
Interventions	Green tea supplementation.
Comparator	Not specified, "control group".
Outcome	Lipid profile (HDL-C, LDL-C, triglyceride or total cholesterol).
Study design	Randomised trials.

Results

No funding was reported for this review. The mean age of patients ranged from 50.2 to 64.9 years. Included studies were conducted between 2008 and 2019 in Japan, Iran, Taiwan and Mexico. The number of subjects in the intervention group was 300 and in the control group was 212. The mean BMI of participants ranged from 24 to 30.4 kg/m2. All the studies were performed on both sexes. Trial duration ranged from 4 to 16 weeks and daily dose of GTE varied between 400 and 10000 mg/d. In assessing the effect of GTE supplementation on TG levels, the authors reviewed seven studies, encompassing ten effect sizes and a total of 512 participants (300 in the intervention group and 212 in the control group). The pooled results using a random-effects model indicated that GTE supplementation significantly reduced TG serum concentrations, with a weighted mean difference (WMD) of 12.79 mg/dL (95% CI: 24.74 to 0.84; p = 0.036; I^2 = 69.8%, p = 0.000), suggesting substantial heterogeneity. To explore this variability, the authors conducted a subgroup analysis based on dose (less than 800 mg/day vs. 800 mg/day or more) and intervention duration (up to 8 weeks vs. longer than 8 weeks). Results showed a significant reduction in TG concentrations for doses of 800 mg/day or more (WMD: 3.52 mg/dL, 95% CI: 4.09 to 2.94, p < 0.001) and for interventions lasting longer than 8 weeks (WMD: 26.82 mg/dL, 95% CI: 45.33 to 8.32, p = 0.004). For serum TC concentrations, data from seven trials with nine effect sizes, totaling 512 subjects (300 intervention and 212 controls), indicated no significant overall effect of GTE supplementation. The pooled WMD was 6.81 mg/dL (95% CI: 15.13 to 1.52, p = 0.109; I^2 = 83.0%, p = 0.000), demonstrating high heterogeneity. However, subgroup analysis revealed that GTE doses below 800 mg/day (WMD: 14.25 mg/dL, 95% CI: 23.70 to 4.80, p = 0.003) and intervention durations longer than 8 weeks (WMD: 11.14 mg/dL, 95% CI: 20.93 to 1.34, p = 0.026) were associated with a significant reduction in TC concentrations. Regarding LDL levels, the pooled analysis of six studies with seven effect sizes (469 participants, including 277 in the intervention group and 192 in the control group) showed no significant effect of GTE supplementation on LDL concentrations, with a WMD of 0.37 mg/dL (95% CI: 4.13 to 3.40, p = 0.849; I^2 = 46.5%, p = 0.082). Subgroup analysis based on dose and intervention duration similarly revealed no significant changes in LDL concentrations. For HDL concentrations, data from six trials with five effect sizes (469 participants, including 277 intervention and 192 control subjects) showed no significant effect of GTE supplementation on HDL levels. The pooled WMD was 3.10 mg/dL (95% CI: 10.16 to 3.95, p = 0.389; I^2 = 95.4%, p = 0.000), and no significant effect was observed in the subgroup analysis. The authors assessed publication bias using Egger’s linear regression test, finding no evidence of publication bias for LDL (p = 0.670) and HDL (p = 0.943) concentrations. However, significant publication bias was detected for studies analyzing TG (p < 0.001) and TC (p = 0.007) concentrations.

Full Risk of Bias Assessment

Domain 1: Study Eligibility Criteria

Low

All human RCTs (either parallel or cross-over designs) which reported the effect of GTE on lipid profile (HDL-C, LDL-C, triglyceride or total cholesterol) in patients with T2DM were included. RCTs with treatment duration less than 2 weeks, and studies without any comparing control group were excluded.

1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Yes
1.2 Were the eligibility criteria appropriate for the review question?	Yes
1.3 Were eligibility criteria unambiguous?	Probably yes
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Probably yes
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes
Concerns regarding specification of study eligibility criteria	**Low**

Domain 2: Identification and Selection of Studies

High

Web of Science, PubMed, and Scopus databases were searched. Embase was not mentioned. Keywords were provided but not a full search strategy. The authors also checked reference lists and citations. Study selection was by two independent reviewers.

2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Probably no
2.2 Were methods additional to database searching used to identify relevant reports?	Probably yes
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	No information
2.4 Were restrictions based on date, publication format, or language appropriate?	Yes
2.5 Were efforts made to minimise error in selection of studies?	Yes
Concerns regarding identification and selection of studies	**High**

Domain 3: Data Collection and Study Appraisal

Low

Data extraction and risk of bias assessments were done by two independent reviewers. Risk of bias was assessed with the Cochrane RoB 1 tool. Study details were presented in tables.

3.1 Were efforts made to minimise error in data collection?	Yes
3.2 Were sufficient study characteristics considered for both review authors and readers to be able to interpret the results?	Yes
3.3 Were all relevant study results collected for use in the synthesis?	Yes
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes
3.5 Were efforts made to minimise error in risk of bias assessment?	Yes
Concerns regarding methods used to collect data and appraise studies	**Low**

Domain 4: Synthesis and Findings

Low

To assess the effect size on lipid profiles, the mean change and standard deviation for both intervention and control (comparison) groups were extracted. A random effects model was applied to calculate the weighted mean differences (WMDs) with 95% confidence intervals (CIs). Cochran's Q test and the I^2 statistic were used to examine between-study heterogeneity. Subgroup analysis, based on intervention dose and duration, was conducted to explore possible sources of heterogeneity, and between-subgroup heterogeneity was assessed using a fixed effect model. Sensitivity analysis involved removing each study individually to recalculate the pooled estimates. To identify potential publication bias, Begg's rank correlation test and Egger's regression asymmetry test were performed.

4.1 Did the synthesis include all studies that it should?	Yes
4.2 Were all pre-defined analyses reported or departures explained?	Yes
4.3 Was the synthesis appropriate given the degree of similarity in the research questions, study designs and outcomes across included studies?	Probably yes
4.4 Was between-study variation minimal or addressed in the synthesis?	Probably yes
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Probably yes
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Probably yes
Concerns regarding synthesis and findings	**Low**

Abstract

Background: Previous studies have indicated controversial results regarding the efficacy of green tea extract (GTE) in improving the lipid profile of type 2 diabetes mellitus (T2DM) patients. We aimed to conduct a systematic review and meta-analysis to pool data from randomized controlled trials (RCTs). Method(s): A systematic search was performed in Web of Science, PubMed, and Scopus databases, without any language and time restriction until August 2019, to retrieve the RCTs which examined the effects of GTE on serum concentrations of high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG) or total cholesterol (TC) in T2DM patients. Meta-analyses were carried out using a random effects model. I2 index was used to evaluate the heterogeneity. Result(s): Initial search yielded 780 publications. Of these, seven studies were eligible. The supplementary intake of GTE improved lipid profile by reducing serum TG concentrations in patients with T2DM. Meanwhile, subgroup analyses based on duration of interventions (<=8 and > 8 weeks) and intervention dosage (<=800 and > 800 mg/day) showed that the GTE supplementation longer than 8 weeks and in doses >800 mg/day resulted in a significant decrease in serum TG concentrations. Furthermore, intervention longer than 8 weeks with doses lower than 800 mg/day resulted in a significant reduction in serum TC concentrations. Conclusion(s): In conclusion, present systematic review and meta-analysis revealed that the supplementary intake of GTE may improve lipid profile by reducing serum concentrations of TG in patients with T2DM. Furthermore, the results of our stratified analyses suggested that long-term GTE intervention may reduce serum concentrations of TG and TC.

KSR Number: KSRA147938

Medicinal plants in the adjunctive treatment of patients with type-1 diabetes: a systematic review of randomized clinical trials

Barzkar, F. Baradaran, H.R. Khamseh, M.E. Vesal Azad, R. Koohpayehzadeh, J. Moradi, Y.

J Diabetes Metab Disord 2020;19(2):1917-29 Full text options PubMed 33520869

Publication year: 2020 Added to database: October 06, 2020

Risk of Bias Assessment

Overall summary: Unclear risk of bias in the review

Bottom Line

The authors concluded that there is insufficient evidence to draw conclusions about the efficacy of fenugreek, Berberine/Silymarine compound capsule, oral fig leaf decoction and cinnamon for glycemic control in type 1 diabetes. In addition, the evidence is inconclusive regarding the optimal doses and methods of preparations of these herbs and their safety in these patients. These findings should be considered with some caution as relevant studies may have been missed.

Risk of Bias Assessment

Overall summary

Unclear risk of bias in the review

This was a well performed systematic review only let down by (reporting of) the search strategies. Keywords were provided and appeared to only search in title and abstract without MeSH terms. No full search strategies were provided.

A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	Probably no
B. Was the relevance of identified studies to the reviews research question appropriately considered?	Yes
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes
Risk of bias in the review	**Unclear**

Details of Review

Number of studies	4
Number of participants	177
Last search date	October 2019
Review type	Intervention
Objective	To assess the effectiveness and safety of herbal medicine in patients with type 1 diabetes.
Population	Children and adults with type 1 diabetes .
Interventions	Any type of herbal medicines including extract from herbs, single herb or a compound of herbs alone or along with Insulin.
Comparator	"Placebo that should have been a drug without an effect on blood glucose levels."
Outcome	Glycemic control (as measured by glycated hemoglobin levels (HbA1c) and fasting blood glucose levels); adverse events (for example liver toxicity, kidney damage). Diabetes complications (for example, neuropathy, retinopathy, nephropathy, sexual dysfunction); health-related quality-of-life; all-cause mortality; costs.
Study design	Randomised trials.

Results

This work was supported by the Iran University of Medical Sciences (IUMS). The four included trials investigated the effects of (a) Cinnamomum zeylanicum (cinnamon) capsules, (b) Ficus carica (fig) leaf decoction, (c) Berberis aristata/Sylibum marianum capsules, and (d) Trigonella foenumgraecum (fenugreek) powder added to bread on glycemic control in patients with type 1 diabetes, compared to control groups. The studies included different age groups: the cinnamon trial involved 72 adolescents (mean age: 14 ± 1.4 years), the fenugreek trial included 10 adults (mean age: 22.7 ± 2.7 years), the Berberis/Sylibum study included 85 adults (mean age: 29.8 ± 7.2 years), and the fig-leaf study included 10 adults (mean age: 29 ± 2.2 years). Study lengths and designs varied across the trials. The authors rated the evidence quality for fenugreek as low to very low across outcomes, with only one trial examining 20 patients. In this trial, the fenugreek group showed a significant increase in mean urinary glucose and fasting plasma glucose after 10 days, although there was a slight improvement in glucose tolerance indices. Six patients in the fenugreek group reported minor gastrointestinal adverse effects, while none were reported in the placebo group. One trial compared fig leaf decoction to a placebo in patients with type 1 diabetes. The quality of evidence varied by outcome. There were no statistically significant differences in HbA1c or fasting plasma glucose between groups, although glucose tolerance improved significantly in the fig leaf group compared to placebo. Insulin dosage was reduced to avoid hypoglycemia, though the incidence of hypoglycemic events was similar between groups. The quality of evidence for cinnamon use in type 1 diabetes was low, based on a single trial with 57 participants. There were no statistically significant effects on HbA1c, insulin dosage, or hypoglycemic episodes associated with cinnamon use. One trial evaluated the effect of a B. aristata/S. marianum combination on glycemic control and adverse events in type 1 diabetes. There is moderate certainty that this combination may provide a slight improvement in fasting plasma glucose, though the certainty of evidence for its effects on HbA1c, postprandial glycemia, and adverse events is low. While some outcomes showed statistically significant improvements from baseline, there was no significant difference in improvement between the treatment and control groups.

Full Risk of Bias Assessment

Domain 1: Study Eligibility Criteria

Low

This systematic review included only randomized controlled trials in children and adults diagnosed with type 1 diabetes, with diagnosis criteria based on standards in place at the time of each study. The review considered any form of herbal medicine, including extracts from single herbs, individual herbs, or herbal compounds, either alone or in combination with insulin. There were no restrictions on the mode of administration or method of preparation for the herbal medicines. Studies that combined medicinal herbs with other therapies (e.g., holistic approaches like cupping or acupuncture) were excluded. Control interventions involved a placebo, specifically one without effects on blood glucose levels. Outcomes: Glycemic control, measured by glycated hemoglobin (HbA1c) and fasting blood glucose levels; adverse events, such as liver toxicity or kidney damage. Secondary Outcomes: Complications related to diabetes (e.g., neuropathy, retinopathy, nephropathy, sexual dysfunction), health-related quality of life, all-cause mortality, and costs.

1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Yes
1.2 Were the eligibility criteria appropriate for the review question?	Yes
1.3 Were eligibility criteria unambiguous?	Yes
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Yes
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes
Concerns regarding specification of study eligibility criteria	**Low**

Domain 2: Identification and Selection of Studies

Unclear

The Cochrane Library, MEDLINE, EMBASE, AMED (Allied and Complementary Medicine Database), Google Scholar and CINAHL were searched. Keywords were provided and appeared to only search in title and abstract without MeSH terms. No full search strategies were provided. Citation and reference lists tracking was performed for all of the retrieved studies. Authors of relevant identified studies and other experts (authors of reviews) were contacted in order to obtain additional references, unpublished trials, or ongoing trials. Study selection was by two independent reviewers.

2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Yes
2.2 Were methods additional to database searching used to identify relevant reports?	Yes
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Probably no
2.4 Were restrictions based on date, publication format, or language appropriate?	Yes
2.5 Were efforts made to minimise error in selection of studies?	Yes
Concerns regarding identification and selection of studies	**Unclear**

Domain 3: Data Collection and Study Appraisal

Low

Two authors independently abstracted relevant population and intervention characteristics using standard data extraction templates. The Cochrane Risk of Bias tool was used to assess risk of bias within studies. Two authors assessed risk of bias independently. Study characteristics were presented in tables.

3.1 Were efforts made to minimise error in data collection?	Yes
3.2 Were sufficient study characteristics considered for both review authors and readers to be able to interpret the results?	Yes
3.3 Were all relevant study results collected for use in the synthesis?	Yes
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes
3.5 Were efforts made to minimise error in risk of bias assessment?	Yes
Concerns regarding methods used to collect data and appraise studies	**Low**

Domain 4: Synthesis and Findings

Low

Mean differences were used to analyze the effect sizes of continuous outcomes. The effect sizes for dichotomous data were expressed in terms of relative risks or odds ratio. The analysis was narrative.

4.1 Did the synthesis include all studies that it should?	Probably yes
4.2 Were all pre-defined analyses reported or departures explained?	Yes
4.3 Was the synthesis appropriate given the degree of similarity in the research questions, study designs and outcomes across included studies?	Yes
4.4 Was between-study variation minimal or addressed in the synthesis?	Probably yes
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	No information
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Probably yes
Concerns regarding synthesis and findings	**Low**

Abstract

Propose: This study aims to systematically review the randomized controlled trials that address the effectiveness and safety of herbal medicine in patients with type 1 diabetes. Method(s): The Cochrane Library (latest issue); MEDLINE (until recent); EMBASE (until recent); AMED (Allied and Complementary Medicine Database) (until recent); and CINHAL (until recent) were searched electronically for the identification of trials until October 2019. Articles were initially screened based on title and abstract and then by full text by two independent authors. References of retrieved studies were hand-searched for further studies. Risk of bias was assessed according to the Cochrane handbook of systematic reviews of interventions. The results were summarized into GRADE (grading of recommendations, assessment, development and evaluation) tables. No meta-analysis was applicable as only one study was found for each intervention. Result(s): Four RCTs were finally included in the systematic review with an overall moderate quality of conduct and low quality of reporting. The sample sizes were very small. The results of these RCTs show that cinnamon pills and Berberine/Silymarine compound capsules may decrease blood glucose indices from baseline, while fenugreek seeds and fig leaf decoction do not show any statistically significant effect. Conclusion(s): The evidence is scarce and no recommendations can be made based on current evidence. Further trials with more rigorous methodology and stronger quality of reporting are needed to make conclusions.

KSR Number: KSRA107797

Echinacea for the prevention and treatment of upper respiratory tract infections: a systematic review and meta-analysis

David, S. Cunningham, R.

Complement Ther Med 2019;44:18-26 Full text options PubMed 31126553

Publication year: 2019 Added to database: July 24, 2019

Risk of Bias Assessment

Overall summary: High risk of bias in the review

Bottom Line

The authors concluded that whilst echinacea appears to be safe in the short term the claims that preparations of this plant can reduce the incidence or duration of URTIs remain to be convincingly shown. The result in the meta-analysis for echinacea in the prevention of URTIs is diminished by the likely presence of selective reporting, publication bias and methodological heterogeneity of the included studies. These findings need cautious interpretation as some relevant studies may have been missed.

Risk of Bias Assessment

Overall summary

High risk of bias in the review

Any trials not reported in the English language were excluded. The search strategy was presented and appeared sub-optimal.

A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	No
B. Was the relevance of identified studies to the reviews research question appropriately considered?	Yes
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes
Risk of bias in the review	**High**

Details of Review

Number of studies	29
Number of participants	Not reported
Last search date	Not reported, likely 2018
Review type	Intervention
Objective	To assess the current evidence from double-blind randomised placebo-controlled trials for the safety and efficacy of echinacea preparations in the prevention and treatment of upper respiratory tract infections (URTIs).
Population	Healthy populations of any age.
Interventions	Echinacea preparations.
Comparator	Placebo preparations.
Outcome	Duration of the URTI. The number of individuals who experienced at least one adverse event (AE).
Study design	Randomised double-blind placebo-controlled trials.

Results

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. The selected studies were categorised based on outcomes: nine contributed to the meta-analysis for prevention, seven for duration, and 16 for safety. A total of 11 studies were included in a narrative summary due to their lack of quantitative data for a meta-analysis. Most studies used natural infection as the experimental condition, while two trials involved experimental virus inoculation. The intervention across studies varied; 16 trials tested echinacea monotherapy (with different species such as E. purpurea, E. angustifolia, and E. pallidae), while seven studies used mixed echinacea preparations. Different plant parts, extraction techniques, and standardization processes were employed, reflecting significant methodological diversity. Subgroup and sensitivity analyses served as checks on the robustness of results, especially given the wide variability in methodologies and patient demographics. The meta-analysis on echinacea for preventing URTIs yielded a pooled risk ratio (RR) of 0.78 (95% CI 0.68–0.88), indicating a moderate and statistically significant reduction in URTI incidence in the echinacea groups. Study heterogeneity, as measured by the I^2 statistic, was moderate at 45%. For the duration of URTIs, the meta-analysis showed a mean difference of -0.12 days (95% CI 0.93–1.22), suggesting that echinacea had no meaningful impact on the duration of URTIs. In this case, study heterogeneity was high, with an I^2 of 97%. Regarding safety, the analysis resulted in an overall RR of 1.11 (95% CI 0.94–1.31), showing no statistically significant difference in adverse events between the echinacea and control groups, and study heterogeneity was low, with an I^2 of 0%.The narrative suggests that while some studies showed echinacea to be beneficial, others did not, and overall, methodological inconsistencies challenge the drawing of definitive conclusion.

Full Risk of Bias Assessment

Domain 1: Study Eligibility Criteria

High

The authors included any randomised double-blind placebo-controlled trial using an echinacea preparation to prevent or treat URTIs. Trials conducted from 1980 to the present day in populations of any age were considered and both peer-reviewed and unpublished trial reports were allowed. The authors excluded any trials where patient populations were not otherwise healthy; for example, those suffering from asthma. They also excluded any trials not reported in the English language.

1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Yes
1.2 Were the eligibility criteria appropriate for the review question?	Yes
1.3 Were eligibility criteria unambiguous?	Yes
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Yes
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	No
Concerns regarding specification of study eligibility criteria	**High**

Domain 2: Identification and Selection of Studies

High

The authors searched MEDLINE, EMBASE, CAB extracts, Web of Science, Cochrane DARE, clinicaltrials.gov and the WHO ICTRP. A search strategy was presented and appeared sub-optimal. They also reverse searched systematic reviews. In addition academics and study sponsors of registered trials were contacted where the authors were unable to find a report of the trial. Study selection was by two independent reviewers.The restriction to English papers was already addressed in ROBIS domain 1.

2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Yes
2.2 Were methods additional to database searching used to identify relevant reports?	Yes
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Probably no
2.4 Were restrictions based on date, publication format, or language appropriate?	Yes
2.5 Were efforts made to minimise error in selection of studies?	Yes
Concerns regarding identification and selection of studies	**High**

Domain 3: Data Collection and Study Appraisal

Low

Risk of bias was assessed with the Cochrane RoB 1 tool. Data extraction was by two independent reviewers.

3.1 Were efforts made to minimise error in data collection?	Yes
3.2 Were sufficient study characteristics considered for both review authors and readers to be able to interpret the results?	Yes
3.3 Were all relevant study results collected for use in the synthesis?	Yes
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes
3.5 Were efforts made to minimise error in risk of bias assessment?	Yes
Concerns regarding methods used to collect data and appraise studies	**Low**

Domain 4: Synthesis and Findings

Low

The authors provided a narrative summary for trials that lacked data suitable for quantitative synthesis, summarizing the results relevant to their review questions. Due to considerable methodological heterogeneity among the included studies, they primarily discussed findings based on the random-effects model, though the fixed-effects model was also shown for comparison. For binary outcomes, the authors used the "metabin" function, which employs the Mantel-Haenszel method for pooling and the DerSimonian-Laird estimator for tau². For continuous outcomes, they used the "metacont" function, applying inverse variance weighting and the same estimator. The authors assessed between-study heterogeneity using the I^2 statistic and included studies reporting zero adverse events in both groups using a continuity correction of 0.5, following Cheng et al. (2011). For potential biases across studies, they visually inspected funnel plots for asymmetry in each meta-analysis, applying the linear regression test for asymmetry when appropriate. The authors also considered selective reporting and publication bias risks in the literature. Following their protocol, they performed subgroup analyses for adults and children and conducted unplanned sensitivity analyses for further insights.

4.1 Did the synthesis include all studies that it should?	Yes
4.2 Were all pre-defined analyses reported or departures explained?	Yes
4.3 Was the synthesis appropriate given the degree of similarity in the research questions, study designs and outcomes across included studies?	Yes
4.4 Was between-study variation minimal or addressed in the synthesis?	Probably yes
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Probably yes
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Probably yes
Concerns regarding synthesis and findings	**Low**

Abstract

Background: Echinacea preparations are commonly used to prevent and treat upper respiratory tract infection.; Objective(s): To assess current evidence for the safety and efficacy of echinacea containing preparations in preventing and treating upper respiratory tract infection. Data sources: MEDLINE, EMBASE, CAB extracts, Web of Science, Cochrane DARE, clinicaltrials.gov and the WHO ICTRP - 1980 to present day. Eligibility criteria: Randomised double-blind placebo-controlled trials using an echinacea preparation to prevent or treat upper respiratory tract infections. Participants and interventions: Participants who are otherwise healthy of any age and sex. We considered any echinacea containing preparation. Study appraisal and synthesis methods: We used the Cochrane collaborations tool for quality assessment of included studies and performed three meta-analyses; on the prevention, duration and safety of echinacea.; Result(s): For the prevention of upper respiratory tract infection using echinacea we found a risk ratio of 0.78 [95% CI 0.68-0.88], for the treatment of upper respiratory tract infection using echinacea we found a mean difference in average duration of -0.45 [95% 1.85-0.94] days, finally for the safety meta-analyses we found a risk ratio of 1.09 [95% CI 0.95-1.25].; Limitation(s): The limitations of our review include the clinical heterogeneity - for example many different preparations were tested, the risk of selective reporting, deviations from our protocol and lack of contact with study authors.; Conclusion(s): Our review presents evidence that echinacea might have a preventative effect on the incidence of upper respiratory tract infections but whether this effect is clinically meaningful is debatable. We did not find any evidence for an effect on the duration of upper respiratory tract infections. Regarding the safety of echinacea no risk is apparent in the short term at least. The strength of these conclusions is limited by the risk of selective reporting and methodological heterogeneity. Implications of key findings: Based on the results of this review users of echinacea can be assured that echinacea preparations are safe to consume in the short term however they should not be confident that commercially available remedies are likely to shorten the duration or effectively prevent URTI. Researchers interested in the potential preventative effects of echinacea identified in this study should aim to increase the methodological strength of any further trials. PROSPERO ID: CRD42018090783.

KSR Number: KSRA114925

Efficacy and safety of cinnamon in type 2 diabetes mellitus and pre-diabetes patients: a meta-analysis and meta-regression

Deyno, S. Eneyew, K. Seyfe, S. Tuyiringire, N. Peter, E.L. Muluye, R.A. Tolo, C.U. Ogwang, P.E.

Diabetes Res Clin Pract 2019;156:107815 Full text options PubMed 31425768

Publication year: 2019 Added to database: November 08, 2019

Risk of Bias Assessment

Overall summary: High risk of bias in the review

Bottom Line

The authors concluded that cinnamon significantly reduced elevated FBG and HOMA-IR compared to placebo. However, there is no significant reduction in HbA1c and lipid profiles levels between cinnamon treated and placebo-treated T2DM patients or pre-diabetes patients. These findings need cautious interpretation due to some methodological issues with this review.

Risk of Bias Assessment

Overall summary

High risk of bias in the review

Embase was not mentioned. Some keywords were provided but no full search strategies. The number of reviewers involved in data extraction was not mentioned.

A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	Probably no
B. Was the relevance of identified studies to the reviews research question appropriately considered?	Yes
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes
Risk of bias in the review	**High**

Details of Review

Number of studies	16
Number of participants	1098
Last search date	Not reported
Review type	Intervention
Objective	To assess the efficacy of cinnamon for the treatment of patients with type 2 diabetes mellitus (T2DM) and pre-diabetes patients.
Population	T2DM patients or pre-diabetes patients aged 18 years and older of either gender.
Interventions	Cinnamon.
Comparator	Placebo.
Outcome	Fasting blood glucose (FBG), HbA1c, insulin level, LDL, HDL, TC, BMI, Homeostatic model assessment of insulin resistance (HOMA-IR), Alanine aminotransferase (ALT), and Aspartate aminotransferase (AST).
Study design	Randomised trials.

Results

This research had no specific grant from funding. However, the support from World Bank project, PHARMBIOTRAC, was crucial. The strength of the cinnamon used for the treatment ranged from 1 g to 14.4 g. The follow-up period ranged from one month to four months. Three studies were conducted in adults with T2DM patients either on oral antihyperglycemic agents or recently diagnosed T2DM. Some of the studies had background oral hypoglycemic as standard treatment while others do not have or have not provided evidence on the background therapy. Fifteen studies investigated the impact of cinnamon on fasting blood glucose (FBG), finding a reduction compared to placebo, with a weighted mean difference (WMD) of -0.545 mmol/L (95% CI: -0.910, -0.18) and high heterogeneity (I^2 = 83.6%). Four studies reported on HOMA-IR, showing a reduction in insulin resistance (WMD -0.714; 95% CI: -1.388, -0.040, I^2 = 84.4%). Eight studies assessing insulin levels found a reduction (WMD -0.964; 95% CI: -1.97, -0.042, I^2 = 55.4%). For other health markers like HbA1c, LDL, HDL, total cholesterol (TC), triglycerides (TG), and BMI, no significant differences were observed between cinnamon and placebo groups. Heterogeneity across studies was considerable, ranging from 55.4% to 86.0%, and meta-regression analyses showed no significant factors that could explain this variability. Safety outcomes indicated that cinnamon was generally well-tolerated, with no significant changes in liver function markers (AST and ALT) in the studies that assessed these parameters. The two studies revealed WMD respectively as 0.27 (95% CI: -3.20, 3.74), I2 = 58% and 3.5 (95% CI: -3.43, 10.44), I2 = 63%.

Full Risk of Bias Assessment

Domain 1: Study Eligibility Criteria

Low

The inclusion criteria for this meta-analysis were: (1) randomized controlled trials (RCTs) involving patients with type 2 diabetes (T2DM) or pre-diabetes; (2) participants aged 18 years or older, of any gender; and (3) studies with a minimum follow-up duration of four weeks for both primary and secondary outcomes. The review excluded non-randomized trials, cross-sectional studies, case series, case reports, studies on participants younger than 18, and studies not involving T2DM patients.

1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Yes
1.2 Were the eligibility criteria appropriate for the review question?	Yes
1.3 Were eligibility criteria unambiguous?	Yes
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Yes
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes
Concerns regarding specification of study eligibility criteria	**Low**

Domain 2: Identification and Selection of Studies

High

PubMed, Web of Science, SCOPUS, CINAHL, and the Cochrane library were searched. Embase was not mentioned. Some keywords were provided but no full search strategies. The reference list of all identified studies was searched for additional studies. Unpublished studies were searched in Google and Google Scholar. Ongoing clinical trials were also searched through clinicaltrials.gov. Two independent reviewers conducted the title and abstract screening in duplicate.

2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Probably no
2.2 Were methods additional to database searching used to identify relevant reports?	Yes
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	No information
2.4 Were restrictions based on date, publication format, or language appropriate?	Yes
2.5 Were efforts made to minimise error in selection of studies?	Yes
Concerns regarding identification and selection of studies	**High**

Domain 3: Data Collection and Study Appraisal

Unclear

Two independent reviewers using standardized Cochrane risk of bias tool for a randomized clinical trial assessed the risk of bias. The number of reviewers involved in data extraction was not mentioned. Study characteristics and risk of bias findings were presented in tables.

3.1 Were efforts made to minimise error in data collection?	No information
3.2 Were sufficient study characteristics considered for both review authors and readers to be able to interpret the results?	Yes
3.3 Were all relevant study results collected for use in the synthesis?	Yes
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes
3.5 Were efforts made to minimise error in risk of bias assessment?	Yes
Concerns regarding methods used to collect data and appraise studies	**Unclear**

Domain 4: Synthesis and Findings

Unclear

Publication bias was assessed using Egger's test. For all continuous variables in this study, the inverse variance-weighted method was applied to pool the weighted mean differences along with their 95% confidence intervals (CIs). Clinical and methodological heterogeneity were evaluated using the Chi-square test and I^2 statistics. Due to substantial heterogeneity among the studies, a random-effects model (REM) was employed to calculate the pooled mean difference and 95% CIs, following the DerSimonian and Laird method. Subgroup analyses and meta-regression were conducted to explore potential sources of heterogeneity. The authors showed some issues with wrongly reporting significance, when one considers the 95% CIs of some of the estimates. E.g. "Four studies reported HOMA-IR and metaanalysis revealed significant reduction in WMD (-0.714 (95% CI: 1.388, -0.040), I2 = 84.4.1%). (...) Eight studies evaluated effect on insulin (IU/mL) and found non-significant insulin reduction (-0.964[95% CI: -1.97, -0.042]." In the first example probably a minus sign is missing, what is wrong in the second example is unclear.

4.1 Did the synthesis include all studies that it should?	Yes
4.2 Were all pre-defined analyses reported or departures explained?	Probably yes
4.3 Was the synthesis appropriate given the degree of similarity in the research questions, study designs and outcomes across included studies?	Probably yes
4.4 Was between-study variation minimal or addressed in the synthesis?	Yes
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Probably yes
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Probably yes
Concerns regarding synthesis and findings	**Unclear**

Abstract

INTRODUCTION: Cinnamon has been used as a dietary component and in the management of diabetes mellitus. This study systematically reviewed and synthesized evidence on the efficacy of cinnamon for the treatment of type 2 diabetes mellitus (T2DM) and pre-diabetes patients.; METHODS: Databases of Web of Sciences, the Cochrane library, PubMed, CINAHL and SCOPUS were searched. Stata version 13 (College Station, Texas 77845 USA) and RevMan var. 5.3 software were used for meta-analysis. Heterogeneity was assessed using Chi-square and I2 tests.; RESULTS: Sixteen randomized controlled studies were included in the meta-analysis. Cinnamon significantly reduced fasting blood glucose (FBG) and homeostatic model assessment for insulin resistance (HOMA-IR) level compared to placebo with weighted mean difference (WMD) of -0.545 (95% CI: -0.910, -0.18) mmol/L, I2=83.6% and -0.714(-1.388, -0.04), I2=84.4% respectively. There was no significant change in weighted mean difference of glycosylated hemoglobin A1C (HbA1c) % and lipid profiles (mmol/L). Meta-regression did not show any factor significantly affecting the treatment response.; CONCLUSION: Cinnamon reduced FBG and HOMA-IR, level in T2DM and pre-diabetes patients compared to placebo. High heterogeneity observed among included studies warrants further clinical trials after standardization of cinnamon formulation.

KSR Number: KSRA89929

Black elderberry (Sambucus nigra) supplementation effectively treats upper respiratory symptoms: a meta-analysis of randomized, controlled clinical trials

Hawkins, J. Baker, C. Cherry, L. Dunne, E.

Complement Ther Med 2019;42:361-65 Full text options PubMed 30670267

Publication year: 2019 Added to database: January 28, 2019

Risk of Bias Assessment

Overall summary: High risk of bias in the review

Bottom Line

The authors reporeted that supplementation with a standardised elderberry extract is effective at reducing the total duration and severity of upper respiratory symptoms, as compared to a placebo group. The effect of elderberry supplementation is larger among cases of the flu than the common cold, but supplementation successfully reduces the symptoms regardless of underlying cause. These findings need cautious consideration given the methodological issues identified for this review.

Risk of Bias Assessment

Overall summary

High risk of bias in the review

Some keywords were provided, but no full search strategies. The number of reviewers involved in the study selection was not mentioned. Embase was not mentioned. The number of reviewers involved in risk of bias assessment was not mentioned. Publication bias was analysed using an Egger's analysis, a funnel plot, and Tweedie's Trim and Fill, even though only 4 studies were included.

A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	No
B. Was the relevance of identified studies to the reviews research question appropriately considered?	Yes
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes
Risk of bias in the review	**High**

Details of Review

Number of studies	4
Number of participants	180
Last search date	September 2018
Review type	Intervention
Objective	To assess the effects of elderberry supplementation for upper respiratory symptoms and to analyse moderator variables of vaccination status and underlying pathology that may influence that total effect size.
Population	People with upper respiratory symptoms.
Interventions	Elderberry supplementation as the primary intervention.
Comparator	Unspecified control group. Placebo.
Outcome	Upper respiratory symptoms. Self-reporting instruments to measure upper respiratory symptoms ranging from fever to sinus congestion. Visual analog scale (VAS). Total duration of upper respiratory symptoms.
Study design	Randomised trials.

Results

This work was supported by the Franklin Institute of Wellness research department. This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Four clinical trials involving 180 participants were included. These participants were divided into elderberry treatment and control groups. The findings indicate that elderberry supplementation significantly reduces the duration of upper respiratory symptoms, with a large mean effect size of 1.717 (95% CI: 0.840 to 2.593), supporting elderberry’s efficacy in symptom management. However, there was notable heterogeneity among studies. The analysis looked at two key moderating factors: the type of viral infection (influenza vs. common cold) and participants' flu vaccination status. Three of the four studies focused on elderberry's effects on influenza-related symptoms, while one examined its impact on symptoms consistent with the common cold. The results show elderberry is more effective at treating influenza symptoms, yielding a mean effect size of 2.074 (95% CI: 1.323 to 2.824), compared to a moderate effect size of 0.662 (95% CI: -0.096 to1.421) for the common cold. Although elderberry was effective in both cases, it appears more potent against influenza, though the authors advise caution due to the limited number of studies on common cold symptoms. Regarding flu vaccination, two studies involved participants who had not been vaccinated, while the other two had mixed flu vaccination statuses. The analysis found no significant difference in elderberry’s effectiveness based on vaccination status, with similar effect sizes observed among vaccinated and non-vaccinated groups.

Full Risk of Bias Assessment

Domain 1: Study Eligibility Criteria

Low

No search limitations or publication date limitations were used. Studies to be included were randomized trials with human subjects. Studies conducted on primates or other animals were excluded. This analysis was restricted to studies that used elderberry supplementation as the primary intervention with upper respiratory symptoms as the primary outcome. There was no restriction on the cause of these symptoms or a requirement for a diagnosis from the symptoms. Studies on elderberry supplementation with outcomes including cytokines, anti-inflammatory activity, or its effects on lipid profiles are available in the literature but were not included in the analyses.

1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Yes
1.2 Were the eligibility criteria appropriate for the review question?	Yes
1.3 Were eligibility criteria unambiguous?	Yes
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Yes
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes
Concerns regarding specification of study eligibility criteria	**Low**

Domain 2: Identification and Selection of Studies

High

PubMed, Google Scholar, and Science Direct were searched. To identify any unpublished papers, including dissertations and rejected papers, the authors also manually searched the citation section of published studies, related papers and presentations, and herbal medicine databases. Some keywords were provided, but no full search strategies. The number of reviewers involved in the study selection was not mentioned.

2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Probably no
2.2 Were methods additional to database searching used to identify relevant reports?	Yes
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	No information
2.4 Were restrictions based on date, publication format, or language appropriate?	Yes
2.5 Were efforts made to minimise error in selection of studies?	No information
Concerns regarding identification and selection of studies	**High**

Domain 3: Data Collection and Study Appraisal

Unclear

Data extraction was by by two authors, results were compared for inter-coder reliability. Reliability was found to be 100%. The Downs and Black checklist was used to assess bias within each of the four studies. Only the over all mean score was presented. The number of reviewers involved in risk of bias assessment was not mentioned.

3.1 Were efforts made to minimise error in data collection?	Yes
3.2 Were sufficient study characteristics considered for both review authors and readers to be able to interpret the results?	Yes
3.3 Were all relevant study results collected for use in the synthesis?	Yes
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes
3.5 Were efforts made to minimise error in risk of bias assessment?	No information
Concerns regarding methods used to collect data and appraise studies	**Unclear**

Domain 4: Synthesis and Findings

High

Standardised differences in means were calculated using the duration of symptoms and the symptom severity score. A random effects model was used due to clear heterogeneity of the studies (I-squared = 83.12). Publication bias was analysed using an Egger's analysis, a funnel plot, and Tweedie's Trim and Fill, even though only 4 studies were included. To evaluate the potential for vaccination status to influence the duration of upper respiratory symptoms, the moderator of vaccine status was used to conduct an additional analysis. To evaluate a potential difference in effect size due to the cause of the upper respiratory symptoms, a moderator analysis comparing the underlying condition was conducted.

4.1 Did the synthesis include all studies that it should?	Yes
4.2 Were all pre-defined analyses reported or departures explained?	Probably yes
4.3 Was the synthesis appropriate given the degree of similarity in the research questions, study designs and outcomes across included studies?	Probably no
4.4 Was between-study variation minimal or addressed in the synthesis?	Probably yes
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Probably no
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Probably no
Concerns regarding synthesis and findings	**High**

Abstract

Upper respiratory symptoms are often treated with over the counter drugs, antibiotics, and antiviral medications. Due to concerns about safety and efficacy, there is a demand for an alternative solution. Black elderberry (Sambucus nigra) has been used to treat cold and flu symptoms, but there are no large-scale studies or meta-analyses. This meta-analysis quantifies the effects of elderberry supplementation and evaluates moderators including vaccination status and the underlying pathology. This analysis included a total of 180 participants and evaluates moderators such as vaccination status and cause of the upper respiratory symptoms. Supplementation with elderberry was found to substantially reduce upper respiratory symptoms. The quantitative synthesis of the effects yielded a large mean effect size. These findings present an alternative to antibiotic misuse for upper respiratory symptoms due to viral infections, and a potentially safer alternative to prescription drugs for routine cases of the common cold and influenza.

KSR Number: KSRA166893

Herbal medicines for allergic rhinitis: a systematic review and meta-analysis

Hoang, M.P. Chitsuthipakorn, W. Snidvongs, K.

Curr Allergy Asthma Rep 2021;21(4):25 Full text options PubMed 33768322

Publication year: 2021 Added to database: April 16, 2021

Risk of Bias Assessment

Overall summary: Unclear risk of bias in the review

Bottom Line

THe authors concluded that HMs improved nasal symptoms, ocular symptoms, and disease-specific QOL when compared to placebo. Beneficial effects of HMs were similar to standard treatments but only revealed in a short-term treatment, less than 12 weeks. In general, HM is considered safe. In practice, standard treatments such as antihistamines and intranasal corticosteroids should be considered for a long-term treatment. These findings should be considered with caution as some relevant details were missing in this review.

Risk of Bias Assessment

Overall summary

Unclear risk of bias in the review

Some keywords were presented but not a full search strategy. Only overall results of the risk of bias assessment were presented. Different HMs were pooled together.

A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	No
B. Was the relevance of identified studies to the reviews research question appropriately considered?	Yes
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes
Risk of bias in the review	**Unclear**

Details of Review

Number of studies	32
Number of participants	2,697
Last search date	9 Feb 2020
Review type	Intervention
Objective	To assess the effects of herbal medicines (HM) therapy in patients with allergic rhinitis (AR).
Population	Patients who had characteristic clinical symptoms of allergic rhinitis and allergies were confirmed by either skin prick test (SPT) or serum IgE test.
Interventions	H erbal medicines in any formulation (decoction, tablet, pill, powder, herbal patch, and nasal spray/drop). Duration of treatment was at least 1 week.
Comparator	HM versus placebo, versus standard treatment (antihistamines and intranasal corticosteroids), and HM plus standard treatment versus standard treatment alone.
Outcome	Nasal symptoms, ocular symptoms, disease specific quality of life (QOL), objective measurement for nasal patency, and adverse events.
Study design	Randomized controlled trials.

Results

Funding was not mentioned. The review included 19 RCTs on perennial allergic rhinitis (PAR) patients and 12 on seasonal allergic rhinitis (SAR) patients, with one study including both PAR and SAR cases. Four RCTs focused on patients under 18. Oral herbal medicine (HM) was used in 26 RCTs, intranasal spray or oil inhalation in 3 RCTs, and external herbal patch or moxibustion in 3 RCTs. Treatment duration ranged from 1 to 16 weeks. Comparisons included HM versus placebo in 27 RCTs and HM versus standard treatment in 3 RCTs. Four studies used antihistamines, and one used a combination of intranasal corticosteroid spray and antihistamine. Total Nasal Symptom Score (TNSS): Sixteen randomized controlled trials (RCTs) evaluated TNSS. When treatment duration was four weeks or less, HM was significantly more effective than placebo (Standardized Mean Difference (SMD) -0.68; 95% CI −0.98 to −0.38). At four to twelve weeks, HM continued to show benefits over placebo but to a lesser extent (SMD -0.22; 95% CI −0.4 to −0.05). However, when the treatment extended beyond twelve weeks, the benefits diminished, and there was no significant difference from placebo. Comparisons between HM and standard treatments revealed no significant differences, indicating similar efficacy. Individual Nasal Symptoms: Four key symptoms—sneezing, rhinorrhea, nasal obstruction, and itching—were assessed. In trials up to four weeks, HM showed benefits over placebo across all symptoms. Beyond four weeks, however, only nasal obstruction showed a continued benefit. Comparisons with standard treatments showed similar outcomes for both HM and standard therapy. Total Ocular Symptom Score (TOSS): Nine RCTs assessed ocular symptoms, such as itchy and watery eyes. For treatments lasting four weeks or less, HM showed a reduction in TOSS compared to placebo. Beyond this duration, HM did not demonstrate significant advantages over placebo, suggesting a time-dependent effect on ocular symptoms. Quality of Life (QOL): Using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), ten RCTs assessed how HM impacted patients' disease-specific QOL. HM improved QOL scores more than placebo in treatments lasting up to twelve weeks, with noticeable declines in effect for longer treatment durations. Comparisons with standard treatments also demonstrated similar QOL improvements for HM and conventional therapy. Objective Measurements for Nasal Patency: In trials evaluating nasal airflow resistance and other objective measures of nasal patency, HM did not significantly outperform placebo. This outcome suggests that HM’s benefits are more perceptible in symptom relief rather than in measurable changes in airflow. Adverse Events: Nine RCTs reported on adverse events, including common issues like headache, dry mouth, and gastrointestinal disturbances. The incidence of adverse effects was comparable between HM and both placebo and standard treatments, underscoring HM’s favorable safety profile. Specific side effects, such as diarrhea and mild liver toxicity, were rare. Overall, HM showed substantial benefits in alleviating nasal and ocular symptoms, and improving quality of life in AR patients, particularly for shorter treatments (up to 12 weeks). Long-term use, however, may lead to tachyphylaxis, where the efficacy decreases, especially in perennial allergic rhinitis (PAR) cases after four weeks.

Full Risk of Bias Assessment

Domain 1: Study Eligibility Criteria

Low

This review included randomized controlled trials (RCTs) on allergic rhinitis (AR) patients of any age, following ARIA diagnostic criteria. AR diagnosis was confirmed by skin prick test (SPT) or serum IgE test. Herbal medicine (HM) treatments, in various forms (e.g., decoctions, tablets, nasal sprays), were included with a minimum treatment duration of one week and no upper limit. Comparisons focused on HM versus placebo, HM versus standard treatment, and HM combined with standard treatment versus standard treatment alone. Standard treatments included antihistamines and intranasal corticosteroids. Outcomes assessed were nasal and ocular symptoms, disease-specific quality of life (QOL), nasal patency, and adverse events. Studies on homeopathy, immunotherapy, synthetic extracts, conference abstracts, and crossover studies with insufficient washout periods were excluded.

1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Yes
1.2 Were the eligibility criteria appropriate for the review question?	Yes
1.3 Were eligibility criteria unambiguous?	Yes
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Yes
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes
Concerns regarding specification of study eligibility criteria	**Low**

Domain 2: Identification and Selection of Studies

Unclear

PubMed and EMBASE were searched. Additional sources were manually searched for published and unpublished trials. Some keywords were presented but not a full search strategy. Inclusion screening was by two independent reviewers.

2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Probably yes
2.2 Were methods additional to database searching used to identify relevant reports?	Yes
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	No information
2.4 Were restrictions based on date, publication format, or language appropriate?	Yes
2.5 Were efforts made to minimise error in selection of studies?	Yes
Concerns regarding identification and selection of studies	**Unclear**

Domain 3: Data Collection and Study Appraisal

Unclear

Data extraction and risk of bias assessment was by two independent reviewers. The Cochrane RoB 1 tool was used, but only overall results were presented.

3.1 Were efforts made to minimise error in data collection?	Yes
3.2 Were sufficient study characteristics considered for both review authors and readers to be able to interpret the results?	Probably no
3.3 Were all relevant study results collected for use in the synthesis?	Yes
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes
3.5 Were efforts made to minimise error in risk of bias assessment?	Yes
Concerns regarding methods used to collect data and appraise studies	**Unclear**

Domain 4: Synthesis and Findings

Unclear

Herbal medicines (HMs) were categorized into subgroups based on their effects, with similar-effect HMs pooled together. An HM could belong to multiple subgroups if it had multiple effects. For analysis, risk ratio (RR) and 95% confidence interval (CI) were used for dichotomous data, while continuous data were presented as mean difference (MD) or standardized mean difference (SMD) with standard deviation (SD) and 95% CI. Subgroup analyses considered AR subtypes, study quality, and mechanism of effects. If baseline-to-endpoint change data was unavailable, final scores were used, and missing SDs were imputed where possible. Treatment effect discrepancies across trials were assessed using heterogeneity (I^2), with values indicating low (<40%), moderate (40-60%), or substantial (>60%) heterogeneity. A fixed-effect model was applied for low heterogeneity, and a random-effects model for high heterogeneity to ensure conservative estimates. Different HMs were pooled together.

4.1 Did the synthesis include all studies that it should?	Yes
4.2 Were all pre-defined analyses reported or departures explained?	Yes
4.3 Was the synthesis appropriate given the degree of similarity in the research questions, study designs and outcomes across included studies?	Yes
4.4 Was between-study variation minimal or addressed in the synthesis?	Probably no
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Probably yes
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Probably yes
Concerns regarding synthesis and findings	**Unclear**

Abstract

PURPOSE OF REVIEW: To assess the effects of herbal medicine (HM) therapy in various durations and analyze the effects of HM separately by mechanism of action in the treatment of allergic rhinitis (AR).; RECENT FINDINGS: Thirty-two studies were included (2,697 patients, mean age 34.6 years). For the <= 4 weeks of treatment duration, HM brought greater benefits over placebo in reduction of total nasal symptoms score (standardized mean difference (SMD) -0.68; 95% confidence interval (CI) -0.98, -0.38; p <0.01) and improvement in Rhinoconjunctivitis Quality of Life Questionnaire score (SMD -0.53; 95% CI -0.81, -0.25; p <0.01). For the 4-12 weeks duration, total nasal symptoms score (SMD -0.22; 95%CI -0.4, -0.05; p =0.01) and Rhinoconjunctivitis Quality of Life Questionnaire score (SMD -0.48; 95% CI -0.89, -0.06; p =0.03) favored the HM. However, HM therapy for longer than 12 weeks was related to tachyphylaxis and showed no benefit over placebo in any outcomes. There was no difference between the HM and standard treatment on symptoms improvement. Anti-allergic effect, anti-inflammatory effect, anti-leukotriene effect, and anti-histaminic effect of HM were revealed. HM was safe and their adverse effects were comparable placebo. HM therapy is safe and provides better results than placebo in improving nasal symptoms and disease-specific quality of life in patients with AR. Its beneficial effects are demonstrated only in less than 12 weeks of treatment.; TRIAL REGISTRATION: PROSPERO ID: CRD42020168367.

KSR Number: KSRA101991

Dietary ginger as a traditional therapy for blood sugar control in patients with type 2 diabetes mellitus: a systematic review and meta-analysis

Huang, F. Y. Deng, T. Meng, L. X. Ma, X. L.

Medicine 2019;98(13):e15054 Full text options PubMed 30921234

Publication year: 2019 Added to database: April 30, 2019

Risk of Bias Assessment

Overall summary: High risk of bias in the review

Bottom Line

The authors concluded that this analysis involving patients with T2DM showed no significant difference in fasting blood sugar with ginger consumption. However, dietary ginger significantly improved HbA1c from baseline to follow-up showing that this natural medicine might have an impact on glucose control over a longer period of time in patients with T2DM.These findings need cautious consideration as there were methodological issues with this review.

Risk of Bias Assessment

Overall summary

High risk of bias in the review

Only English-published trials were searched for. Some keywords were reported but no full search strategies. The number of reviewers involved in study selection was not reported. Methods additional to database searching were not mentioned. The number of reviewers involved in risk of bias assessment was not specifically mentioned. Risk of bias assessment was carried out "with reference to the criteria suggested by the Cochrane Collaboration." Risk of bias was presented only as "grade B" for all included studies.

A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	No
B. Was the relevance of identified studies to the reviews research question appropriately considered?	Yes
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes
Risk of bias in the review	**High**

Details of Review

Number of studies	8
Number of participants	454
Last search date	July 2018
Review type	Intervention
Objective	To assess the effects of ginger consumption on fasting blood sugar (FBS) and glycated hemoglobin (HbA1c) at baseline versus at follow-up in T2DM patients.
Population	Patients with type 2 diabetes mellitus (T2DM).
Interventions	Ginger supplement.
Comparator	Control group wiithout ginger.
Outcome	Fasting blood sugar (FBS) and glycated hemoglobin (HbA1c).
Study design	Randomized trials.

Results

No funding or sponsorship was received for the publication of this article. Eight randomized trials, totaling 454 participants, were included. Of these, 245 were assigned to a ginger supplementation group, and 209 served as controls. Participants had HbA1c levels ranging from 6.90% to 8.40% and were generally middle-aged (mean ages between 45.2 and 55.2 years). Trials were evaluated and received a moderate quality rating, assessed by Cochrane's criteria. All the participants were patients with T2DM who were either assigned to ginger therapy (1600– 4000mg daily) or to a control group. Fasting blood sugar and HbA1c were assessed at baseline versus at follow-up to observe for any significant change. A follow-up time period of 8 to 12 weeks was considered relevant to this meta-analysis. In examining fasting blood sugar (FBS) changes from baseline to follow-up among participants consuming ginger (1600–4000 mg daily), results indicated no statistically significant change. The weighted mean difference (WMD) in FBS was 1.38 with a 95% confidence interval (CI) ranging from -0.53 to 3.30 (P = .16). This lack of statistical significance suggests that ginger consumption does not meaningfully impact daily blood glucose levels in the short term. For the 209 participants who did not consume ginger, FBS changes from baseline were also not significant, with a WMD of -0.27 and a 95% CI from -5.09 to 4.54 (P = .91). This result aligns with the ginger group, showing no major daily blood sugar differences in the control. Significant effects were observed in HbA1c, a marker of long-term glucose control, among participants consuming ginger. In a subgroup of 215 individuals, HbA1c levels showed a statistically significant improvement from baseline to follow-up, with a WMD of 0.46 and a 95% CI between 0.09 and 0.84 (P = .02). This outcome suggests that ginger supplementation may contribute positively to long-term glucose regulation. For control participants, HbA1c measurements from baseline to follow-up were not significantly different. The WMD for HbA1c was -0.23, with a 95% CI from -0.60 to 0.14 (P = .22). This indicates that, in the absence of ginger, long-term glucose levels remained relatively unchanged in this cohort. Overall, while ginger consumption did not significantly affect FBS, it was associated with a moderate but significant improvement in HbA1c, indicating potential benefits in long-term glucose management for T2DM patients.

Full Risk of Bias Assessment

Domain 1: Study Eligibility Criteria

Low

The following inclusion criteria were considered: Randomized trials involving patients with T2DM; Trials comparing FBS and HbA1c in participants who were assigned to a ginger and a control group; Trials reporting FBS and HbA1c at baseline and at follow-up. Nonrandomized trials, systematic reviews, meta-analyses, and case studies were excluded.

1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Yes
1.2 Were the eligibility criteria appropriate for the review question?	Yes
1.3 Were eligibility criteria unambiguous?	Yes
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Yes
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes
Concerns regarding specification of study eligibility criteria	**Low**

Domain 2: Identification and Selection of Studies

High

MEDLINE (PubMed), Embase, the Cochrane Central database, and www.ClinicalTrials.gov were searched for English-published trials. Some keywords were reported but no full search strategies. The number of reviewers involved in study selection was not reported. Methods additional to database searching were not mentioned.

2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Yes
2.2 Were methods additional to database searching used to identify relevant reports?	No information
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	No information
2.4 Were restrictions based on date, publication format, or language appropriate?	No
2.5 Were efforts made to minimise error in selection of studies?	No information
Concerns regarding identification and selection of studies	**High**

Domain 3: Data Collection and Study Appraisal

High

Four authors were involved in data extraction, the number of reviewers involved in risk of bias assessment was not specifically mentioned. Risk of bias assessment was carried out "with reference to the criteria suggested by the Cochrane Collaboration." Risk of bias was presented only as "grade B" for all included studies.

3.1 Were efforts made to minimise error in data collection?	Probably yes
3.2 Were sufficient study characteristics considered for both review authors and readers to be able to interpret the results?	Probably yes
3.3 Were all relevant study results collected for use in the synthesis?	Probably yes
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Probably no
3.5 Were efforts made to minimise error in risk of bias assessment?	No information
Concerns regarding methods used to collect data and appraise studies	**High**

Domain 4: Synthesis and Findings

High

The data used in this analysis included the mean, standard deviation (SD), and participant count from each trial. For continuous variables, the weighted mean difference (WMD) and 95% confidence intervals (CI) were calculated, with analysis performed using RevMan 5.3 software. Heterogeneity was evaluated using the Q statistic test, considering results statistically significant if the P-value was ≤ 0.05. Additionally, heterogeneity was assessed with the I^2 test, where higher I^2 values indicated greater heterogeneity. Depending on the I^2 value, a fixed-effect model ($I^2 < 50\%$) or a random-effect model ($I^2 > 50\%$) was applied in the analysis.

4.1 Did the synthesis include all studies that it should?	Yes
4.2 Were all pre-defined analyses reported or departures explained?	Probably yes
4.3 Was the synthesis appropriate given the degree of similarity in the research questions, study designs and outcomes across included studies?	Probably yes
4.4 Was between-study variation minimal or addressed in the synthesis?	Probably yes
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	No information
4.6 Were biases in primary studies minimal or addressed in the synthesis?	No information
Concerns regarding synthesis and findings	**High**

Abstract

BACKGROUND: Ancient medical practitioners used to encourage dietary supplements and herbal medicine for the treatment of type 2 diabetes mellitus (T2DM). Ginger (Zingiber officinale), is a nontoxic spice with negligible side effects, and is considered safe by the food and drug administration. In this analysis, we aimed to systematically compare fasting blood sugar (FBS) and glycated hemoglobin (HbA1c) at baseline versus at follow-up in T2DM patients who consumed and who did not consume ginger. METHODS: A literature search was carried out through MEDLINE, Embase, the Cochrane Central, and www.ClinicalTrials.gov for English-published trials comparing glucose parameters in T2DM patients who were assigned to ginger consumption versus a control group. All the participants were patients with T2DM who were either assigned to ginger therapy (1600- 4000 mg daily) or to a control group. FBS and HbA1c were assessed in the ginger and control groups, respectively, from baseline to follow-up to observe any significant change. Weight mean difference (WMD) with 95% confidence intervals (CI) was calculated to represent the analysis which was carried out by the RevMan 5.3 software. RESULTS: Eight randomized trials consisting of a total number of 454 participants with T2DM were included in this analysis. At first, FBS was compared in patients with T2DM from baseline prior to ginger consumption until follow-up after ginger consumption. The results showed no significant difference in FBS (WMD: 1.38, 95% CI: [-0.53-3.30]; P = .16). For the T2DM patients who did not consume ginger, no significant difference in FBS was observed (WMD: -0.27, 95% CI: [-5.09-4.54]; P = .91). However, a significantly improved HbA1c from baseline to follow-up was observed in those participants with ginger consumption (WMD: 0.46, 95% CI: [0.09-0.84]; P = .02) whereas in the control group, no significant difference in HbA1c was observed (WMD: -0.23, 95% CI: [-0.60-0.14]; P = .22). CONCLUSION: This analysis involving patients with T2DM showed no significant difference in FBS with ginger consumption. However, dietary ginger significantly improved HbA1c from baseline to follow-up showing that this natural medicine might have an impact on glucose control over a longer period of time in patients with T2DM.

KSR Number: KSRA127474

Effect of cinnamon supplementation on blood pressure and anthropometric parameters in patients with type 2 diabetes: a systematic review and meta-analysis of clinical trials

Jamali, N. Jalali, M. Saffari-Chaleshtori, J. Samare-Najaf, M. Samareh, A.

Diabetes Metab Syndr 2020;14(2):119-25 Full text options PubMed 32032898

Publication year: 2020 Added to database: February 27, 2020

Risk of Bias Assessment

Overall summary: High risk of bias in the review

Bottom Line

The authors concluded that cinnamon supplementation significantly decreased the SBP and DBP; however, it did not affect body weight (BW), body mass index (BMI) and waist circumference (WC). These findings need cautious consideration due to methodological weaknesses of this review.

Risk of Bias Assessment

Overall summary

High risk of bias in the review

Keywords were provided but no full search strategies. The number of reviewers involved in the study selection was not mentioned. The Jadad scale was used for quality assessment of clinical trials. Studies scoring 3 of the 5 points were considered high-quality studies. This is an outdated tool. The number of reviewers involved in the risk of bias assessment was not mentioned.

A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	No
B. Was the relevance of identified studies to the reviews research question appropriately considered?	Yes
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes
Risk of bias in the review	**High**

Details of Review

Number of studies	9
Number of participants	623
Last search date	22 August 2019
Review type	Intervention
Objective	To assess the effect of cinnamon supplementation on the SBP and DBP and anthropometric parameters in patients with type 2 diabetes.
Population	Patients with type 2 diabetes.
Interventions	Cinnamon supplementation.
Comparator	Not specified, presumably placebo.
Outcome	SBP or DBP, body weight (BW), body mass index (BMI) and waist circumference (WC).
Study design	Clinical trials.

Results

This study was performed without any specific funding. Study sample sizes ranged from 19 to 69 participants in the intervention group and 3 to 69 subjects in the control group. The mean age of the subjects in the intervention and control groups ranged from 52.1 to 61.7 and 53.2 to 64.4, respectively. The duration of the interventions was 2 months in 4 studies and 3 months in the other 5 studies. The minimum dose of cinnamon supplementation among the studies was 1 g/d and the maximum was 4.5 g/d 8 (8.88%). Only one (11.1%) of the studies used cinnamon powder and the rest (88.8%) of trials used cinnamon supplements in the form of capsules. Cinnamon supplementation significantly decreased systolic blood pressure (SBP) in patients with type 2 diabetes (5 studies, overall standardized mean difference (SMD): -0.532, 95% CI: [-1.032, -0.033], P = 0.037). There was significant heterogeneity among the studies (I^2: 79.3%, P = 0.001), but no significant publication bias was found (P = 0.611). Cinnamon supplementation also significantly reduced diastolic blood pressure (DBP) in type 2 diabetic patients (5 studies, overall SMD: -0.681, 95% CI: [-1.297, -0.065], P = 0.030). There was high heterogeneity among the studies (I^2: 86.0%, P < 0.001), and no publication bias was detected (P = 0.784). Cinnamon supplementation did not result in a significant change in body weight (BW) compared to controls in patients with type 2 diabetes (7 studies, overall SMD: -0.309, 95% CI: [-0.793, 0.175], P = 0.211). Subgroup analysis based on the duration of the intervention also showed no significant change in BW following supplementation. Significant heterogeneity was observed among the studies (I^2: 85%, P < 0.001). Cinnamon supplementation had no significant effect on body mass index (BMI) (7 studies, overall SMD: -0.550, 95% CI: [-1.244, 0.144], P = 0.120). Subgroup analysis based on the duration of intervention also found no significant change in BMI. High heterogeneity was observed among the studies (I^2: 91.2%, P < 0.001). The overall analysis showed no significant effect of cinnamon supplementation on waist circumference (WC) (3 studies, overall SMD: -0.235, 95% CI: [-0.518, 0.047], P = 0.103). However, in the subgroup analysis based on duration, a significant reduction in WC was observed after 3 months of supplementation (2 studies, subtotal SMD: -0.389, 95% CI: [-0.756, -0.021], P = 0.038). No heterogeneity was found in this meta-analysis (I^2: 42.8%, P = 0.174).

Full Risk of Bias Assessment

Domain 1: Study Eligibility Criteria

Low

Inclusion criteria were: high-quality clinical trials; consumption of cinnamon in the form of supplement; participants with type 2 diabetes; and trials reporting at least one of the primary outcomes such as SBP or DBP and secondary ones, including body weight (BW), body mass index (BMI) and waist circumference (WC). Trials with healthy subjects or participants with other types of disorders were excluded from the study.

1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Yes
1.2 Were the eligibility criteria appropriate for the review question?	Yes
1.3 Were eligibility criteria unambiguous?	Yes
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Yes
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes
Concerns regarding specification of study eligibility criteria	**Low**

Domain 2: Identification and Selection of Studies

Unclear

PubMed, Embase, Scopus, Web of Science and Cochrane trials databases were searched. Keywords were provided but no full search strategies. Manual search of reference lists and Google Scholar was done to identify additional records. The number of reviewers involved in the study selection was not mentioned.

2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Yes
2.2 Were methods additional to database searching used to identify relevant reports?	Yes
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	No information
2.4 Were restrictions based on date, publication format, or language appropriate?	Yes
2.5 Were efforts made to minimise error in selection of studies?	No information
Concerns regarding identification and selection of studies	**Unclear**

Domain 3: Data Collection and Study Appraisal

High

Two independent researchers extracted the data. The Jadad scale was used for quality assessment of clinical trials. Studies scoring 3 of the 5 points were considered high-quality studies. This is an outdated tool. The number of reviewers involved in the risk of bias assessment was not mentioned.

3.1 Were efforts made to minimise error in data collection?	Yes
3.2 Were sufficient study characteristics considered for both review authors and readers to be able to interpret the results?	Probably yes
3.3 Were all relevant study results collected for use in the synthesis?	Probably yes
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Probably no
3.5 Were efforts made to minimise error in risk of bias assessment?	No information
Concerns regarding methods used to collect data and appraise studies	**High**

Domain 4: Synthesis and Findings

Low

Standard mean difference (SMD) and 95% confidence interval (CI) were used to evaluate the effect of cinnamon supplementation on the outcomes. In the case of significant heterogeneity, the authors used fixed or random effect models. They assessed the potential heterogeneity by using I2 index (50%) and P value (<=0.05). Potential publication bias was checked by Egger's regression test. Sensitivity analysis was performed to find the impact of each study on the pooled effect.

4.1 Did the synthesis include all studies that it should?	Yes
4.2 Were all pre-defined analyses reported or departures explained?	Yes
4.3 Was the synthesis appropriate given the degree of similarity in the research questions, study designs and outcomes across included studies?	Probably yes
4.4 Was between-study variation minimal or addressed in the synthesis?	Probably yes
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Probably yes
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Probably yes
Concerns regarding synthesis and findings	**Low**

Abstract

Background and aims: The present systematic review and meta-analysis was conducted to investigate the effect of cinnamon supplementation on blood pressure and anthropometric indices in patients with type 2 diabetes. Method(s): PubMed, Embase, Scopus, Web of Science and Cochrane Library were systematically searched to find relevant records up to 22 August 2019. Standard mean difference (SMD) and 95% confidence interval (CI) were used to evaluate the effect of cinnamon supplementation on the outcomes of this study. In the case of heterogeneity, fixed and random effect models were used. The obtained data were analyzed by Stata 13. After excluding irrelevant records, 9 eligible articles were included. Result(s): This meta-analysis found a significant reduction in systolic blood pressure (SBP) (SMD: -0.532, 95% CI: [-1.032, -0.033], P = 0.037) and diastolic blood pressure (DBP) (SMD: -0.681, 95% CI: [-1.297, -0.065], P = 0.030) of patients with type 2 diabetes following cinnamon supplementation. Based on the results of the present study, cinnamon supplementation had no significant effect on the body weight (BW) (SMD: -0.309, 95% CI: [-0.793, 0.175], P = 0.211), body mass index (BMI) (SMD: -0.550, 95% CI: [-1.244, 0.144], P = 0.120). and waist circumference (WC) (SMD: -0.235, 95% CI: [-0.518, 0.047], P = 0.103). Conclusion(s): Cinnamon supplementation significantly decreased SBP and DBP of patients with type 2 diabetes. Although cinnamon intake caused changes in anthropometric parameters, the observed changes were not statistically significant.

KSR Number: KSRA97728

The impact of cinnamon on anthropometric indices and glycemic status in patients with type 2 diabetes: a systematic review and meta-analysis of clinical trials

Namazi, N. Khodamoradi, K. Khamechi, S. P. Heshmati, J. Ayati, M. H. Larijani, B.

Complement Ther Med 2019;43(April):92-101 Full text options PubMed 30935562

Publication year: 2019 Added to database: March 13, 2019

Risk of Bias Assessment

Overall summary: High risk of bias in the review

Bottom Line

The authors concluded that supplementation with cinnamon can reduce serum levels of glucose with no changes in other glycemic parameters and anthropometric indices. However due to high heterogeneity, findings should be interpreted with great caution. The review had some methodological weaknesses.

Risk of Bias Assessment

Overall summary

High risk of bias in the review

Grey literature (e.g., theses, conference abstracts) was excluded. Risk of bias was assessed with the outdated Jadad scale. There was high heterogeneity which remained unexplained.

A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	Probably no
B. Was the relevance of identified studies to the reviews research question appropriately considered?	Yes
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes
Risk of bias in the review	**High**

Details of Review

Number of studies	18
Number of participants	1100
Last search date	31 February 2018 (!)
Review type	Intervention
Objective	To assess the effects of cinnamon on glycemic status and anthropometric indices in patients with type 2 diabetes.
Population	Patients with type 2 diabetes (T2DM).
Interventions	Any form of cinnamon (whole herb not effective components). Cinnamomum verum, Cinnamomum zeylanicum, Ceylon cinnamon.
Comparator	Placebo.
Outcome	Fasting blood sugar (FBS), weight, body mass index, Quetelet, glucose, insulin, HOMA-IR, insulin resistance, QUICKI, insulin sensitivity, HbA1c, diabetes, other glycemic status and anthropometric indices.
Study design	Randomised trials.

Results

Funding was not mentioned. The 18 trials, spanning 2003 to 2018, included 1,100 participants aged 46 to 63 from Asia, Europe, and the U.S. Participants received cinnamon in powder (15 trials) or extract form (2 trials), with one study not specifying the form used. Doses ranged from 1 to 6 grams per day for powder and 0.12 to 0.5 grams per day for extract, administered over 40 to 120 days. All trials used a randomized placebo-controlled design, with ten studies deemed high quality (Jadad score ≥ 3). Findings from Meta-Analysis Fasting Blood Sugar (FBS): The meta-analysis of 18 trials (21 effect sizes) indicated a significant reduction in FBS for the cinnamon group, with a weighted mean difference (WMD) of -19.26 mg/dL (95% CI: -28.08, -10.45), though heterogeneity was high (I^2 = 96.5%). Subgroup analysis suggested the reduction was more prominent in studies without dietary intervention (-19.21 mg/dL; 95% CI: -28.13, -10.29) and those conducted in Asia (-22.32 mg/dL; 95% CI: -29.75, -14.89). HbA1c: Among 14 effect sizes, cinnamon supplementation showed a non-significant reduction in HbA1c compared to placebo (WMD = -0.24%; 95% CI: -0.48, -0.01), with high heterogeneity (I^2 = 76.8%). Subgroup analyses across diet adherence, dosage, duration, and quality did not significantly impact these findings. Body Weight: Analysis of four datasets showed no significant reduction in body weight for the cinnamon group compared to placebo (WMD = -0.46; 95% CI: -1.87, 2.30), with no detected heterogeneity (I^2 = 0%). No significant differences emerged between the powder and extract forms of cinnamon on weight reduction. BMI: From five effect sizes, BMI changes were non-significant between cinnamon and placebo groups (WMD = -0.05 kg/m²; 95% CI: -0.52, 0.42), with low heterogeneity (I^2 = 0%). Waist Circumference (WC): Only two studies reported on WC, showing no significant reduction in WC after cinnamon supplementation (WMD = -0.53 cm; 95% CI: -3.96, 2.81; I^2 = 0%). Publication Bias and Sensitivity Analysis No publication bias was detected for FBS or HbA1c based on Begg's and Egger's tests. Sensitivity analyses showed that excluding any single trial did not significantly change the pooled effect sizes for each outcome, supporting the robustness of the findings. These results suggest cinnamon supplementation may modestly reduce FBS but does not significantly impact HbA1c, weight, BMI, or WC in type 2 diabetes patients. The high heterogeneity indicates variability across trials, highlighting a need for further research.

Full Risk of Bias Assessment

Domain 1: Study Eligibility Criteria

High

To be included, studies had to be randomized clinical trials (parallel or cross-over), include a placebo group, involve adult participants with type 2 diabetes, and measure FBS at both the beginning and end of the trial. Only studies examining whole cinnamon (not isolated components) were included, and sufficient statistical information had to be provided. Exclusions applied to non-clinical trials (e.g., animal studies), studies involving other diseases or healthy subjects, cinnamon combined with other ingredients, studies with children or athletes, and grey literature (e.g., theses, conference abstracts).

1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Yes
1.2 Were the eligibility criteria appropriate for the review question?	Yes
1.3 Were eligibility criteria unambiguous?	Yes
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Yes
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Probably no
Concerns regarding specification of study eligibility criteria	**High**

Domain 2: Identification and Selection of Studies

Low

PubMed/Medline, SCOPUS, Web of Sciences, EMBASE, and the Cochrane library were searched. Full search strategies were presented and appeared adequate. Reference lists of the relevant original articles, narrative reviews, systematic reviews and meta-analyses were hand searched. Two independent reviewers were involved in study selection.

2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Yes
2.2 Were methods additional to database searching used to identify relevant reports?	Yes
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Yes
2.4 Were restrictions based on date, publication format, or language appropriate?	Yes
2.5 Were efforts made to minimise error in selection of studies?	Yes
Concerns regarding identification and selection of studies	**Low**

Domain 3: Data Collection and Study Appraisal

Unclear

Two independent reviewers performed data extraction and risk of bias assessment. Risk of bias was assessed with the Jadad scale, which is outdated. Study characteristics were presented in tables.

3.1 Were efforts made to minimise error in data collection?	Yes
3.2 Were sufficient study characteristics considered for both review authors and readers to be able to interpret the results?	Probably yes
3.3 Were all relevant study results collected for use in the synthesis?	Yes
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Probably no
3.5 Were efforts made to minimise error in risk of bias assessment?	Yes
Concerns regarding methods used to collect data and appraise studies	**Unclear**

Domain 4: Synthesis and Findings

Unclear

Effect estimates were calculated as weighted mean differences (WMDs) with 95% confidence intervals (CIs) and combined using a random-effects model with the DerSimonian and Laird method. If mean changes were not provided, they were derived from baseline and endpoint values, with standard deviation (SD) calculated based on pre- and post-treatment SDs. For cases where standard error (SE) or median values were reported, conversions were applied to estimate SD. When data was only available in graphical form, plot digitizer software was used to extract values. Heterogeneity was evaluated using Cochran's Q and I^2 tests, with $I^2 > 50\%$ indicating high heterogeneity. Subgroup analysis was performed to explore sources of heterogeneity across various factors (e.g., age, dosage, duration, quality, species of cinnamon). Sensitivity analysis assessed the impact of each study on overall results. Publication bias was examined through funnel plots, Begg's and Egger's tests, with adjustments made using "trim and fill" methods if bias was detected. There was high heterogeneity which remained unexplained.

4.1 Did the synthesis include all studies that it should?	Yes
4.2 Were all pre-defined analyses reported or departures explained?	Yes
4.3 Was the synthesis appropriate given the degree of similarity in the research questions, study designs and outcomes across included studies?	Yes
4.4 Was between-study variation minimal or addressed in the synthesis?	Probably no
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Probably yes
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Probably yes
Concerns regarding synthesis and findings	**Unclear**

Abstract

Background and aims: There is some evidence regarding the positive effects of cinnamon on metabolic status in patients with type 2 diabetes (T2DM). However, they are conflicting. In the present study, we aimed to systematically review the effects of cinnamon on glycemic status and anthropometric indices in patients with T2DM. Method(s): Five electronic databases including PubMed/Medline, SCOPUS, Web of Sciences, EMBASE, and the Cochrane library were searched until 31 February 2018 with no language limitation. Randomized clinical trials that examined the effects of cinnamon on at least fasting blood sugar (FBS) were included. Other glycemic parameters and anthropometric indices were also extracted. A random effects model with DerSimonian and Laird method was used for pooling the effect sizes. Result(s): Finally, 18 studies were included in the meta-analysis. Supplementation with cinnamon reduced FBS by -19.26 mg/dL (95% CI: -28.08, -10.45; I²:96.5%; p = 0.0001) compared to placebo. However, the effects of cinnamon on HbA1C (-0.24%; 95% CI: -0.48, -0.01; I²: 76.8%, p = 0.0001), body weight (-0.46, 95%CI: -1.87, 2.30; I²:0%; p = 0.79), body mass index (WMD: -0.05 kg/m2; 95% CI: -0.52, 0.42; I²: 0%; p = 0.91), and waist circumference (WMD: -0.53 cm; 95% CI: -3.96, 2.81; I²: 0%; p = 0.66) were not significant. Additionally, cinnamon did not change the serum levels of insulin and insulin resistance significantly. Conclusion(s): Supplementation with cinnamon can reduce serum levels of glucose with no changes in other glycemic parameters and anthropometric indices. However, due to high heterogeneity findings should be interpreted with great caution.

KSR Number: KSRA149376

Effects of Ginkgo biloba intake on cardiometabolic parameters in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of clinical trials

Tabrizi, R. Nowrouzi-Sohrabi, P. Hessami, K. Rezaei, S. Jalali, M. Savardashtaki, A. Shahabi, S. Kolahi, A.-A. Sahebkar, A. Safiri, S.

Phytother Res 2021;35(1):246-55 Full text options PubMed 33090588

Publication year: 2021 Added to database: October 21, 2020

Risk of Bias Assessment

Overall summary: High risk of bias in the review

Bottom Line

The authors concluded that GKB supplementation significantly improves HDL-cholesterol, but also increases HbA1c levels. However, they were not able to show any significant change in other lipidemic, glycemic and blood pressure variables. Due to uncertainties related to the limited number of studies, it is too early to conclude whether GKB has any potential effects on the cardiometabolic factors in patients with T2DM or not. These findings need cautious consideration as non-English studies may have been missed.

Risk of Bias Assessment

Overall summary

High risk of bias in the review

Only studies in English were included. The number of reviewers involved in the risk of bias assessment was not mentioned.

A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	Probably no
B. Was the relevance of identified studies to the reviews research question appropriately considered?	Probably yes
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes
Risk of bias in the review	**High**

Details of Review

Number of studies	7
Number of participants	768
Last search date	2 Sep 2019
Review type	Intervention
Objective	To assess the effects of Ginkgo biloba intake on cardiometabolic parameters in patients with type 2 diabetes mellitus.
Population	Patients with type 2 diabetes mellitus (T2DM).
Interventions	Gingko biloba (GKB) supplements.
Comparator	Not specified.
Outcome	Cardiometabolic parameters such as glycemic control, lipid profile, systolic and diastolic blood pressure. Lipid profile factors (triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol), and glycemic indices (FBS, HbA1c).
Study design	Parallel design clinical trials.

Results

The review was supported by Social Determinants of Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran (No. 21619). The analysis included seven clinical trials, covering 768 participants, to evaluate whether GKB supplementation could modulate these cardiometabolic parameters. The analysis found that GKB had no statistically significant impact on fasting blood sugar (FBS), with a weighted mean difference (WMD) of -4.15 mg/dL (95% CI: -8.99, 0.70; p = .094). However, a slight but significant increase in HbA1c levels was observed, with a WMD of 0.26% (95% CI: 0.02, 0.50; p = .034). This suggests that while GKB may not lower blood sugar levels significantly in T2DM patients, it may slightly elevate HbA1c levels. In terms of lipid profiles, GKB supplementation showed a positive effect on HDL cholesterol levels, with a WMD of 1.99 mg/dL (95% CI: 0.19, 3.79; p = .030), suggesting an improvement in this lipid parameter. However, GKB did not significantly affect triglycerides (WMD = 13.56 mg/dL, 95% CI: -3.20, 30.32; p = .113), total cholesterol (WMD = -18.74 mg/dL, 95% CI: -44.24, 6.76; p = .150), or LDL cholesterol (WMD = -9.50 mg/dL, 95% CI: -26.60, 7.60; p = .276). These results indicate that while GKB may have a modest benefit on HDL cholesterol, it does not significantly impact other lipid levels in patients with T2DM. Regarding blood pressure, GKB supplementation showed no significant effects on either systolic (WMD = -0.90 mmHg, 95% CI: -3.05, 1.26; p = .416) or diastolic blood pressure (WMD = -0.79 mmHg, 95% CI: -2.16, 0.57; p = .256). This suggests that GKB is unlikely to be beneficial in managing blood pressure in T2DM patients. Subgroup analyses were performed to explore the potential sources of heterogeneity by age (over or under 60 years), type of intervention (GKB alone or with other drugs), and duration of treatment (over or under 10 months). These analyses, however, did not reveal any significant differences that could explain the variations in study outcomes. Additionally, sensitivity analyses showed that removing individual studies did not significantly alter the results, indicating the stability of the findings. The authors also checked for publication bias, which was not significant for the primary outcomes, suggesting a low risk of bias in the included studies.

Full Risk of Bias Assessment

Domain 1: Study Eligibility Criteria

High

Papers were included if they met the following criteria: (a) parallel-design clinical trials published in English, (b) studies reporting sufficient data on the effects of GKB on at least one of the following parameters—lipid profile factors (triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol), glycemic indices (FBS, HbA1c), and blood pressure (SBP, DBP)—in patients with diagnosed type 2 diabetes for a duration of more than one month. Exclusion criteria were: (a) studies conducted on animals, (b) trials lacking essential data, (c) papers without an appropriate control group, and (d) studies published as conference abstracts, book chapters, editorials, patents, dissertations, or brief reports, or those reporting insufficient data on outcome changes from baseline at the study's end.

1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Yes
1.2 Were the eligibility criteria appropriate for the review question?	Yes
1.3 Were eligibility criteria unambiguous?	Yes
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Yes
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	No
Concerns regarding specification of study eligibility criteria	**High**

Domain 2: Identification and Selection of Studies

Low

PubMed, Embase, Scopus, Web of Science, Google Scholar and the Cochrane Library were searched. A Pubmed strategy was presented and appeared adequate. Reference lists were checked for additional studies. It was implied that study selection was by two reviewers.

2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Yes
2.2 Were methods additional to database searching used to identify relevant reports?	Yes
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Yes
2.4 Were restrictions based on date, publication format, or language appropriate?	Yes
2.5 Were efforts made to minimise error in selection of studies?	Probably yes
Concerns regarding identification and selection of studies	**Low**

Domain 3: Data Collection and Study Appraisal

Unclear

Data extraction was by two reviewers. The number of reviewers involved in the risk of bias assessment was not mentioned. Risk of bias was assessed with the Cochrane RoB 1 tool. Study characteristics were presented in tables.

3.1 Were efforts made to minimise error in data collection?	Probably yes
3.2 Were sufficient study characteristics considered for both review authors and readers to be able to interpret the results?	Yes
3.3 Were all relevant study results collected for use in the synthesis?	Yes
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes
3.5 Were efforts made to minimise error in risk of bias assessment?	No information
Concerns regarding methods used to collect data and appraise studies	**Unclear**

Domain 4: Synthesis and Findings

Low

Heterogeneity among studies was assessed using the I^2 statistic ($I^2 > 50\%$) and p-values (< .05). When heterogeneity was present, fixed- or random-effects models were applied to pool weighted mean differences (WMDs) with 95% confidence intervals (CIs), following Chang et al. Subgroup analysis was conducted based on mean age (above or below 60 years), intervention type (GKB + other drug vs. GKB alone), and treatment duration (over or under 10 months) to explore possible sources of heterogeneity. Sensitivity analyses were performed by excluding each trial individually to evaluate its impact on the pooled effect. Potential publication bias was assessed using Egger's test.

4.1 Did the synthesis include all studies that it should?	Yes
4.2 Were all pre-defined analyses reported or departures explained?	Probably yes
4.3 Was the synthesis appropriate given the degree of similarity in the research questions, study designs and outcomes across included studies?	Probably yes
4.4 Was between-study variation minimal or addressed in the synthesis?	Probably yes
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Probably yes
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Probably yes
Concerns regarding synthesis and findings	**Low**

Abstract

Ginkgo biloba (GKB) may have a beneficial effect on cardiometabolic parameters in type 2 diabetes mellitus (T2DM), but the data is inconsistent. Therefore, the current systematic review and meta-analysis of clinical trials was conducted to assess the influence of GKB on cardiometabolic parameters in T2DM. Several online databases such as PubMed, Embase, Scopus, Web of Sciences, Google Scholar and Cochrane Library were systematically searched from inception up to September 2, 2019. Heterogeneity across included studies was assessed using the Cochran's Q statistic and I2 index. To pool weighted mean differences (WMDs) and the corresponding 95% confidence intervals (CIs) as summary effect size, we selected fixed or random-effects model according to the result of heterogeneity. Seven studies comprising 768 subjects were included in the present meta-analysis which resulted in a significant effect of GKB on hemoglobin A1c (HbA1c) (WMD = 0.26, 95% CI = [0.02, 0.50], p =.034) and serum HDL-cholesterol levels (WMD = 1.99, 95% CI = [0.19, 3.79], p =.030) with no significant publication bias. GKB can significantly modulate HbA1c and HDL-cholesterol levels. However, due to uncertainties related to the limited number of studies, it is too early to conclude whether GKB has any potential effects on the cardiometabolic factors in patients with T2DM or not.

KSR Number: KSRA168001

Elderberry for prevention and treatment of viral respiratory illnesses: a systematic review

Wieland, L.S. Piechotta, V. Feinberg, T. Ludeman, E. Hutton, B. Kanji, S. Seely, D. Garritty, C.

BMC Complement Med Ther 2021;21(1):112 Full text options PubMed 33827515

Publication year: 2021 Added to database: April 21, 2021

Risk of Bias Assessment

Overall summary: Low risk of bias in the review

Bottom Line

The authors concluded that elderberry is a promising intervention for reducing the severity and duration of influenza and the common cold, and it does not appear associated with serious adverse effects. However, the current evidence base is limited in both size and quality. This was a well performed systematic review.

Risk of Bias Assessment

Overall summary

Low risk of bias in the review

This was a well performed systematic review with low risk of bias in all four ROBIS domains.

A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	Yes
B. Was the relevance of identified studies to the reviews research question appropriately considered?	Yes
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes
Risk of bias in the review	**Low**

Details of Review

Number of studies	5
Number of participants	883
Last search date	11 June 2020
Review type	Intervention
Objective	To assess the benefits and harms of elderberry for the prevention and treatment of viral respiratory infections, and to assess the relationship between elderberry supplements and negative health impacts associated with overproduction of proinflammatory cytokines.
Population	People not yet diagnosed with the common cold, influenza, or an infection due to a novel coronavirus for prevention; and people diagnosed (by any criterion) with the common cold, influenza, or a novel coronavirus infection for treatment studies.
Interventions	Elderberry supplements. Black elderberry (Sambucus nigra; also known as European elderberry), other species of Sambucus with similar characteristics (e.g., Sambucus ebulus, Sambucus canadensis).
Comparator	No supplements, placebo, or other active interventions. Different formulation, dose, or schedule of elderberry.
Outcome	Number of new cases of infection, severity of illness, total duration of illness, adverse events / harms, time to improvement in viral illness, total duration of viral illness, incidence of hospitalizations, duration of hospitalization, requency of intubation and ventilation, mortality. Cases of systemic sepsis, cases of multi-organ failure, and expression of cytokines, including interferons (IFNs), interleukins (ILs), chemokines, colony-stimulating factors (CSFs), c-reactive protein (CRP) and tumor necrosis factor (TNF-alpha) in vivo.
Study design	Randomized controlled trials. For overproduction of pro-inflammatory cytokines, also cohort studies, controlled before-and-after studies, interrupted time series, case-control studies, and case reports.

Results

Two authors were supported by the National Center for Complementary and Integrative Health (NCCIH) of the National Institutes of Health (NIH), USA. In terms of prevention, one RCT (312 participants) focused on elderberry's potential to reduce the incidence of the common cold. This study compared elderberry to a placebo in a population traveling internationally. Results showed that elderberry did not significantly decrease the risk of developing cold symptoms (risk ratio [RR] 0.69), with 8% of participants in the elderberry group and 11% in the placebo group reporting cold symptoms. However, for participants who did develop colds, elderberry use was associated with a shorter average duration by about two days and slightly reduced symptom severity. The authors rated the evidence as low certainty due to concerns over bias and the imprecision of effect estimates, particularly given the small sample sizes. For treatment, three RCTs evaluated elderberry's effects on influenza symptoms. Two studies examined a proprietary elderberry extract (Sambucol) compared to placebo, while a third tested a different elderberry formulation. Combined, these studies involved 151 participants, including both adults and children with confirmed influenza A or B. Elderberry appeared to reduce the average duration of influenza symptoms by nearly three days compared to placebo, showing quicker recovery at two and three days into the illness. Additionally, elderberry users reported less severe symptoms over the course of their illness. Although promising, these studies were small, with some risk of bias in participant selection and outcome reporting, leading to low certainty in the evidence. One study (64 participants) measured the duration and severity of symptoms individually but did not provide data for an overall illness duration metric, limiting the comparability of findings across trials. Across all three studies, no serious adverse events were reported in either the elderberry or placebo groups; however, given the limited reporting on minor side effects, the authors could not draw firm conclusions on the full safety profile. An additional trial assessed a combined elderberry-echinacea product (Echinaforce Hotdrink) in comparison to oseltamivir (Tamiflu) in a sample of 473 participants with influenza symptoms. Results showed that oseltamivir had a slight edge in recovery time at the one-day mark, but by five days, there was little difference in the number of participants recovered. Interestingly, fewer adverse events and complications were observed in the herbal product group. This suggests elderberry, particularly in combination products, may offer a viable alternative to antiviral medications, although the certainty of these findings is low due to risk of bias and limited event numbers. The review also examined elderberry's effects on cytokine production. The authors identified three ex vivo studies with a total of 51 participants who received elderberry and subsequently had cytokine levels measured. One RCT administered elderberry for 12 weeks to postmenopausal women and found no significant differences in plasma cytokines (CRP, TNF-alpha, IL-6) between the elderberry and placebo groups. A separate study of 22 healthy volunteers who drank elderberry tea daily for 30 days found reductions in IL-1 and CRP, but little to no effect on IL-6 and TNF-alpha. Finally, a comparative study tested a single dose of elderberry against diclofenac (a nonsteroidal anti-inflammatory drug) and noted that elderberry produced similar but less potent anti-inflammatory effects, with a temporary reduction in cytokine levels that tapered off by eight hours post-administration.

Full Risk of Bias Assessment

Domain 1: Study Eligibility Criteria

Low

This systematic review included studies focused on preventing or treating viral respiratory infections—specifically the common cold, influenza, and novel coronavirus infections (e.g., SARS, MERS, COVID-19). Studies for prevention required participants who had not yet been diagnosed, while treatment studies included diagnosed individuals. Bacterial infections and non-specified viral respiratory infections (except as symptoms of colds, influenza, or coronavirus) were excluded. There were no restrictions on age, gender, comorbidities, or settings. Elderberry studies included any species of the plant and evaluated all forms, doses, and delivery methods, with some studies considering elderberry alone and others with additional herbal components. Comparators included no intervention, placebo, or various elderberry doses, forms, and non-elderberry controls. Outcomes for prevention studies were infection rates, severity, illness duration, and adverse effects, while treatment outcomes included recovery time, duration, hospitalization metrics, mortality, and adverse effects. Outcomes also tracked cytokine-related adverse effects, such as systemic sepsis and cytokine expression markers. For studies assessing elderberry's impact on infections, only randomized controlled trials (RCTs) were included. For cytokine-related risks, any study design (RCTs, cohort studies, case reports, etc.) was considered to comprehensively assess elderberry's association with cytokine production and risk factors, especially concerning conditions like cytokine storm.

1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Yes
1.2 Were the eligibility criteria appropriate for the review question?	Yes
1.3 Were eligibility criteria unambiguous?	Yes
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Yes
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes
Concerns regarding specification of study eligibility criteria	**Low**

Domain 2: Identification and Selection of Studies

Low

The authors searched six databases (MEDLINE (PubMed), CENTRAL, EMBASE, CABI, Science Citation Index, and International Pharmaceutical Abstracts), four research registers (WHO COVID-19 Global Research Database, LIT-COVID, Center for Disease Control and Prevention COVID-10 Research Article Database, and Clinicaltrials.gov), and two preprint sites (MedRixv, BioRxiv). A full search strategy was presented and appeared adequate. The authors also checked the reference lists of related systematic reviews and the reference lists of all included studies. Inclusion screening was done by two independent reviewers.

2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Yes
2.2 Were methods additional to database searching used to identify relevant reports?	Yes
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Yes
2.4 Were restrictions based on date, publication format, or language appropriate?	Yes
2.5 Were efforts made to minimise error in selection of studies?	Yes
Concerns regarding identification and selection of studies	**Low**

Domain 3: Data Collection and Study Appraisal

Low

Data extraction was done by one author and checked by a second author. Two authors used the Cochrane RoB 1.0 criteria to independently assess the risk of bias for each included RCT. The same authors used the Cochrane Effective Practice and Organisation of Care (EPOC) criteria to assess the risk of bias for controlled before-and-after (CBA) and interrupted time series (ITS) studies. Study characteristics were presented in tables.

3.1 Were efforts made to minimise error in data collection?	Yes
3.2 Were sufficient study characteristics considered for both review authors and readers to be able to interpret the results?	Yes
3.3 Were all relevant study results collected for use in the synthesis?	Yes
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes
3.5 Were efforts made to minimise error in risk of bias assessment?	Yes
Concerns regarding methods used to collect data and appraise studies	**Low**

Domain 4: Synthesis and Findings

Low

The authors used risk ratios (RR) for dichotomous data and mean differences (MD) for continuous data, with 95% confidence intervals (CI) estimated for all effect sizes. To evaluate the presence and extent of heterogeneity, the authors used visual inspection of forest plots, chi-square statistical tests (with $p \leq 0.1$), and the I^2 statistic. Subgroup analyses were planned by types of viral illness (e.g., influenza versus the common cold), study population demographics (e.g., adults versus children), clinical characteristics (e.g., baseline severity of illness, vaccination status), and elderberry characteristics (e.g., dose, delivery method) if sufficient data were available to identify potential sources of heterogeneity. Sensitivity analyses were also planned to exclude studies with high risks of bias in selection, outcome assessment, or loss to follow-up. Finally, the authors intended to assess reporting biases using funnel plots if a comparison included at least 10 trials; however, no analysis contained more than two trials.

4.1 Did the synthesis include all studies that it should?	Yes
4.2 Were all pre-defined analyses reported or departures explained?	Yes
4.3 Was the synthesis appropriate given the degree of similarity in the research questions, study designs and outcomes across included studies?	Yes
4.4 Was between-study variation minimal or addressed in the synthesis?	Yes
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Yes
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Yes
Concerns regarding synthesis and findings	**Low**

Abstract

BACKGROUND: Elderberry has traditionally been used to prevent and treat respiratory problems. During the COVID-19 pandemic, there has been interest in elderberry supplements to treat or prevent illness, but also concern that elderberry might overstimulate the immune system and increase the risk of 'cytokine storm'. We aimed to determine benefits and harms of elderberry for the prevention and treatment of viral respiratory infections, and to assess the relationship between elderberry supplements and negative health impacts associated with overproduction of pro-inflammatory cytokines.; METHODS: We conducted a systematic review and searched six databases, four research registers, and two preprint sites for studies. Two reviewers independently assessed studies for inclusion, extracted data from studies, assessed risk of bias using Cochrane tools, and evaluated certainty of estimates using GRADE. Outcomes included new illnesses and the severity and duration of illness.; RESULTS: We screened 1187 records and included five randomized trials on elderberry for the treatment or prevention of viral respiratory illness. We did not find any studies linking elderberry to clinical inflammatory outcomes. However, we found three studies measuring production of cytokines ex vivo after ingestion of elderberry. Elderberry may not reduce the risk of developing the common cold; it may reduce the duration and severity of colds, but the evidence is uncertain. Elderberry may reduce the duration of influenza but the evidence is uncertain. Compared to oseltamivir, an elderberry-containing product may be associated with a lower risk of influenza complications and adverse events. We did not find evidence on elderberry and clinical outcomes related to inflammation. However, we found evidence that elderberry has some effect on inflammatory markers, although this effect may decline with ongoing supplementation. One small study compared elderberry to diclofenac (a nonsteroidal anti-inflammatory drug) and provided some evidence that elderberry is as effective or less effective than diclofenac in cytokine reduction over time.; CONCLUSIONS: Elderberry may be a safe option for treating viral respiratory illness, and there is no evidence that it overstimulates the immune system. However, the evidence on both benefits and harms is uncertain and information from recent and ongoing studies is necessary to make firm conclusions.

KSR Number: KSRA121207

The effect of nettle (urtica dioica) supplementation on the glycemic control of patients with type 2 diabetes mellitus: a systematic review and meta-analysis

Ziaei, R. Foshati, S. Hadi, A. Kermani, M.A.H. Ghavami, A. Clark, C.C.T. Tarrahi, M.J.

Phytother Res 2020;34(2):282-94 Full text options PubMed 31802554

Publication year: 2020 Added to database: January 09, 2020

Risk of Bias Assessment

Overall summary: High risk of bias in the review

Bottom Line

The authors concluded that their findings tentatively support the use of nettle as an antidiabetic plant and suggest that nettle supplementation can be effective in controlling fasting blood sugar in T2DM patients. These findings need cautious interpretation as some relevant studies may have been missed.

Risk of Bias Assessment

Overall summary

High risk of bias in the review

Embase was not mentioned. Keywords were provided but no full search strategies.

A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	Probably no
B. Was the relevance of identified studies to the reviews research question appropriately considered?	Yes
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Yes
Risk of bias in the review	**High**

Details of Review

Number of studies	8
Number of participants	401
Last search date	June 2019
Review type	Intervention
Objective	To assess the effect of nettle supplementation on markers of glycemic status in adults with type 2 diabetes mellitus (T2DM).
Population	Adults with type 2 diabetes mellitus (T2DM).
Interventions	Nettle supplementation.
Comparator	Placebo.
Outcome	Fasting blood sugar (FBS) concentrations, insulin levels, homeostasis model assessmentestimated insulin resistance index (HOMA-IR), and glycosylated hemoglobin percentage.
Study design	Randomised trials.

Results

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This meta-analysis included eight trials. Among them, six trials reported the effect of nettle on fasting blood sugar (FBS), three trials on glycosylated hemoglobin, three on the HOMA-IR index, and three on insulin levels. The studies included in this analysis were published between 2012 and 2017. All trials followed a parallel design and were conducted in Iran, with participants ranging in age from 41 to 57 years. Two studies focused exclusively on male participants and two on female participants, while the remaining four trials included both genders. The nettle dosage administered varied between 1.5 and 10 g/day, and the duration of interventions ranged from 8 to 12 weeks. Baseline BMI data showed that all studies examined overweight and obese participants. In some trials, there were three intervention groups (nettle alone, nettle with aerobic training, and aerobic training with placebo) along with a placebo group. The authors combined the results of the nettle and placebo groups as one study, and those of the nettle plus aerobic training and placebo plus aerobic training groups as another study. Among eight studies included in the systematic review, five were categorized as good quality, one was fair quality, and two were low quality. Overall, six studies with nine treatment arms, including a total of 306 participants, examined the effect of nettle supplementation on fasting blood sugar (FBS). Based on a random-effects model, the authors found that nettle supplementation significantly reduced FBS (WMD: −18.01 mg/dl, 95% CI: −30.04 to −5.97, $p < .001$) compared to the control group, with substantial between-study heterogeneity ($I^2 = 94.6\%$, $p < .001$). Neither the mean age nor BMI of participants accounted for this heterogeneity; however, participant gender appeared to explain some variability. Studies involving both genders showed a greater reduction in FBS (WMD: −40.71 mg/dl, 95% CI: −60.85 to −20.58) compared to studies focusing on men (WMD: −7.91 mg/dl, 95% CI: −12.08 to −3.74) or women (WMD: −8.61 mg/dl, 95% CI: −14.17 to −3.05) alone. Sensitivity analysis, removing each study one at a time, indicated that the effect of nettle on FBS remained consistent. Three trials, with a total of 186 participants, assessed the impact of nettle supplementation on glycosylated hemoglobin. The pooled effect size indicated no significant effect of nettle on glycosylated hemoglobin (WMD: −0.77%, 95% CI: −1.77 to 0.22, $p = .12$). Although between-study heterogeneity was significant ($I^2 = 83.0\%$, $p < .001$), the limited number of eligible studies prevented subgroup analysis. Sensitivity analysis showed that the removal of any single study did not influence the overall effect. A pooled analysis of three studies (four treatment arms) with 145 participants found no significant effect of nettle supplementation on the HOMA-IR index (WMD: −0.22, 95% CI: −0.83 to 0.40, $p = .49$). Significant between-study heterogeneity was observed ($I^2 = 69.2\%$, $p < .02$), but subgroup analysis was not feasible due to the limited number of studies. Sensitivity analysis indicated that the results were stable, with no substantial change when individual studies were removed. Three trials involving 143 participants evaluated the effect of nettle on insulin concentration. The meta-analysis showed no significant effect of nettle supplementation on insulin levels (WMD: 0.83, 95% CI: −0.26 to 1.92, $p = .13$). Between-study heterogeneity was high ($I^2 = 89.4\%$, $p < .001$), but subgroup analysis was again restricted by the number of studies. Sensitivity analysis confirmed that the findings remained stable when individual studies were excluded. An assessment of publication bias through funnel plot analysis revealed no evidence of bias across studies investigating FBS, glycosylated hemoglobin, HOMA-IR, and insulin.

Full Risk of Bias Assessment

Domain 1: Study Eligibility Criteria

Low

The authors included RCTs (either parallel or cross-over designs) that examined the effects of nettle supplementation on adults (age ≥18 years old) with T2DM. Studies were excluded if they (1) supplemented nettle in combination with any other drugs, minerals, or botanicals (unless a separate arm controlled the effect of the mixed substance); (2) were publications with duplicate data; (3) contained trials with follow up duration less than 4 weeks; and (4) were studies without sufficient data.

1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Yes
1.2 Were the eligibility criteria appropriate for the review question?	Yes
1.3 Were eligibility criteria unambiguous?	Yes
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Yes
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes
Concerns regarding specification of study eligibility criteria	**Low**

Domain 2: Identification and Selection of Studies

High

PubMed, Scopus, ISI Web of Science, and the Cochrane Library were searched. Embase was not mentioned. Keywords were provided but no full search strategies. Electronic searches were complemented by hand searches of the reference lists of eligible articles and email correspondences with authors for additional data, where relevant. Study selection was by two independent reviewers.

2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Probably no
2.2 Were methods additional to database searching used to identify relevant reports?	Yes
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	No information
2.4 Were restrictions based on date, publication format, or language appropriate?	Yes
2.5 Were efforts made to minimise error in selection of studies?	Yes
Concerns regarding identification and selection of studies	**High**

Domain 3: Data Collection and Study Appraisal

Low

Data extraction was conducted by two authors, independently. The Cochrane risk of bias tool (RoB 1) was used. Quality assessment was also undertaken by two authors independently, and any discrepancies were resolved through discussion with a third, independent researcher. Study characteristics were presented in tables.

3.1 Were efforts made to minimise error in data collection?	Yes
3.2 Were sufficient study characteristics considered for both review authors and readers to be able to interpret the results?	Yes
3.3 Were all relevant study results collected for use in the synthesis?	Yes
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes
3.5 Were efforts made to minimise error in risk of bias assessment?	Yes
Concerns regarding methods used to collect data and appraise studies	**Low**

Domain 4: Synthesis and Findings

Low

To determine the overall effect size, the authors used the weighted mean difference (WMD) and standard deviation (SD) for fasting blood sugar (FBS), glycosylated hemoglobin, insulin levels, and the HOMA-IR index between the intervention and control groups. For studies that did not report mean changes directly in both groups, they calculated it by subtracting the baseline value from the post-intervention data. Additionally, if only baseline and final SD values were available, the authors imputed the SD for net changes using the method proposed by Follmann et al. (1992) with a correlation coefficient of 0.5. Given that the included RCTs were conducted across varied settings, a random effects model was applied for all meta-analyses. Study heterogeneity was assessed with the I-squared (I^2) index, considering heterogeneity statistically significant if $p < .01$ or $I^2 > 50\%$. Subgroup analyses were performed based on participants' gender, baseline BMI, and mean age to evaluate the impact of these factors on outcomes. Sensitivity analyses, using the leave-one-out method (removing one trial at a time and recalculating effect size), were conducted to examine the robustness of the findings. Publication bias was assessed through graphical (funnel plots) and statistical methods (Egger's regression test).

4.1 Did the synthesis include all studies that it should?	Yes
4.2 Were all pre-defined analyses reported or departures explained?	Yes
4.3 Was the synthesis appropriate given the degree of similarity in the research questions, study designs and outcomes across included studies?	Probably yes
4.4 Was between-study variation minimal or addressed in the synthesis?	Probably yes
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Probably yes
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Probably yes
Concerns regarding synthesis and findings	**Low**

Abstract

Type 2 diabetes mellitus (T2DM) is a major health problem, worldwide, that is associated with increased morbidity and mortality. Several randomized controlled clinical trials (RCTs) have investigated the effect of nettle (Urtica dioica) supplementation on markers of glycemic status in patients with T2DM, with conflicting results. Therefore, the present study assessed the effect of nettle on some glycemic parameters in patients with T2DM. A comprehensive search was conducted in PubMed, Scopus, Cochrane Library, and Web of Science, from database inception up to June 2019, to identify RCTs investigating the effect of nettle supplementation on glycemic markers, including fasting blood sugar (FBS) concentrations, insulin levels, homeostasis model assessment-estimated insulin resistance index, and glycosylated hemoglobin percentage in adults with T2DM. The Cochrane Collaboration tool was used to assess the methodological quality of the included studies. Results of this meta-analysis were reported based on the random effects model. Eight RCTs, comprising 401 participants, were included in the present systematic review and meta-analysis. Based on the Cochrane Collaboration risk of bias tool, five studies were considered as good quality, one was fair, and two studies were poor, respectively. The results of the meta-analysis revealed a significant reduction in FBS concentrations (weighted mean difference [WMD]: -18.01 mg/dl, 95% confidence interval [CI]: -30.04 to -5.97, $p < .001$, $I2 = 94.6\%$) following nettle supplementation. However, no significant reduction was observed in insulin levels (WMD: 0.83 Hedges' g, 95% CI: -0.26 to 1.92, $p = .13$, $I2 = 89.4\%$), homeostasis model assessment-estimated insulin resistance index (WMD: -0.22, 95% CI: -0.83 to 0.40, $p = .49$, $I2 = 69.2\%$), or glycosylated hemoglobin percentage (WMD: -0.77%, 95% CI: -1.77 to 0.22, $p = .12$, $I2 = 83.0\%$). The findings of the present study suggest that nettle supplementation may be effective in controlling FBS for T2DM patients. However, further studies are needed to confirm the veracity of these results.