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The Effect of Nigella Sativa on Cardio-Metabolic Parameters: A Protocol for A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Among non-communicable diseases, cardiovascular diseases (CVDs) account for 44% of all deaths. Among natural alternatives, *Nigella sativa* (NS) exert beneficial effects on cardio-metabolic factors. This is the first systematic review and meta-analysis protocol aimed to identify all the findings relevant to the effects of NS on cardio-metabolic factors among adults. **Methods:** This study was prepared according to PRISMA-P checklist based on Cochrane Handbook for Systematic Reviews of Interventions. An initial literature search was conducted in various databases using MeSH terms and related synonyms. Trials examining the effects of NS versus control group were included. Main outcomes consisted of blood pressure, lipid and glycemic factors, and atherogenic indices. Seven reviewers independently evaluated titles and abstracts, reviewed full texts, extracted information, and assessed the risk of bias. Methodological quality of each randomized controlled trial was assessed using the Cochrane Handbook and the GRADE system, while Newcastle-Ottawa Quality Assessment Scale was used for non-randomized studies. Continuous data of homogeneous studies were meta-analyzed via STATA. Mean differences were calculated as the effect size with 95% CIs. Heterogeneity assessment, sensitivity analysis, and publication bias were performed. **Conclusion:** The quality of both randomized and non-randomized studies was assessed. The evidence from this study can provide information for future clinical trials.

Keywords: *Nigella sativa*; Cardio-Metabolic Factors; Systematic Review; Meta-Analysis; Insulin; Lipids; Glycemic Indices; Blood Pressure

Introduction

Non-communicable diseases, including cardiovascular diseases (CVDs), cancers, chronic respiratory diseases, and diabetes account for 72% of the mortality in the world. Among

them, CVDs have the highest death toll (44%) (Collins *et al.*, 2019). Meanwhile, cardio-metabolic factors are a collection of parameters associated with cardio-metabolic syndrome, such

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as hypertension, dyslipidemia, hyperglycemia and insulin resistance, and overweight and obesity. An important factor indicating the risk of cardio-metabolic disease is the atherogenic index (AIP). In fact, AIP is composed of triglycerides (TG) and high-density of lipoprotein cholesterol (HDL-C) and is commonly used as optimal indicator of dyslipidemia and associated diseases, including CVDs (Tan, 2019). On the other hand, insulin resistance has found to be associated with CVDs and even with other subclinical cardio-metabolic risk markers, such as hypertension, dyslipidemia, and central adiposity. In fact, insulin resistance is known as a common pathophysiological factor in cardio-metabolic disturbance affecting glucose intolerance, dyslipidemia and altered blood pressure parameters (Ramachandran *et al.*, 2007).

Meanwhile, there is a growing interest in finding safe and natural alternatives to common drugs used to treat any cardio-metabolic related disorders (Ezz *et al.*, 2011, Sahebkar *et al.*, 2016a). Among herbal medicine, *Nigella sativa* (NS) has been found to have beneficial effects on cardio-metabolic risk factors (Rouhi-Boroujeni *et al.*, 2015). The seeds of NS in the Ranunculaceae family grow in the Middle Eastern region and in the Western Asian countries. NS is known by different names, such as black seed, black cumin, caraway or Kalonji. Specific chemical analyses showed that NS consists of various components, including thymoquinone, which is the major active ingredient of NS, carvacrol, tanethole, and 4- terpineol, all of which have radical scavenging properties and anti-inflammatory activities (Ghosheh *et al.*, 1999, Padhye *et al.*, 2008).

Various effects of NS on lipid profile have been reported in several studies. Some evidence reported that supplementation with NS, significantly reduced serum concentrations of total cholesterol (TC), low density of lipoprotein cholesterol (LDL-C), and TG, while it led to an increase in HDL-C levels (Farzaneh *et al.*, 2014, Ibrahim *et al.*, 2014). It seems that the hypolipidemic effect of NS was the synergistic effect of its different ingredients, including thymoquinone, sterols, flavonoids, and high

content of polyunsaturated fatty acids (Ali and Blunden, 2003).

Several mechanisms are proposed to describe the hypolipidemic effect of NS, including the inhibition of de-novo cholesterol synthesis (Bamosa *et al.*, 1997), reducing insulin resistance and dyslipidemia through antioxidative action of thymoquinone, (Ismail *et al.*, 2010) and the inhibition of lipid peroxidation via antioxidant factors, such as phytosterols and flavonoids (de Jong *et al.*, 2003).

This systematic review was conducted on the effect of NS on lipid profile and glycemic indices in patients with diabetes and included seven trials in the final meta-analysis.

Although this meta-analysis included a few numbers of studies, the results demonstrated beneficial effects of NS on serum lipid profile. Notably, this meta-analysis assessed only those trials that were conducted among patients with diabetes (Daryabeygi-Khotbehsara *et al.*, 2017). Another previous meta-analysis published in 2015, assessed the effects of NS on lipid profile and included 17 randomized clinical trials (RCTs); the results reported that there was a significant relation between NS supplementation and TC and LDL-C (Sahebkar *et al.*, 2016a).

The therapeutic effects of NS on blood pressure, heart rate (Kazemipoor *et al.*, 2013, Mahdavi *et al.*, 2016), and oxidized LDL-C (Samani and Farrokhi, 2014) have been reported in several human studies. Most effects of NS on blood pressure or glycemic indices were reported to be due to various unsaturated fatty acids, including linolenic acid, linoleic acid, oleic acid, arachidonic, and eicosadienoic fatty acids in NS oil (Ma *et al.*, 2014). The effect of NS on blood pressure was also assessed in a systematic review and meta-analysis by Sahebkar (Sahebkar *et al.*, 2016b). This study included only 11 trials in the final meta-analysis. They reported that short-term treatment with NS powder can significantly reduce systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels. It should be noted that, the search terms in these two published meta-analysis were performed up to 2015 (Sahebkar *et*

al., 2016a, Sahebkar *et al.*, 2016b) and 2017 (Daryabeygi-Khotbehsara *et al.*, 2017) and further, they both included only RCTs. Hence, there are plenty of other published controlled trials with either randomized or non-randomized design assessing the efficacy of NS on any of the blood pressure or glycemic parameters (Al Dhaheri *et al.*, 2017, Algheshairy, 2018). Therefore, the present meta-analysis aimed to assess the effects of NS on all the anthropometric indices in detail with high numbers of studies (thirty-seven articles), which was registered at International Prospective Register of Systematic Reviews (PROSPERO) with the code CRD42020150929. (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=102222), anthropometric indices were not considered in the present meta-analysis and biochemical cardio-metabolic factors were included along with blood pressure parameters.

Regarding the relation between insulin levels and related disorders, altered insulin levels and insulin resistance have been found to be strongly associated with subclinical cardio-metabolic markers and various diseases (Ramachandran *et al.*, 2007). There are many trials reporting either positive or no association between NS and insulin concentrations and/or insulin resistance (Bamosa *et al.*, 2010, Heshmati *et al.*, 2015). However, none of the previous systematic reviews evaluated the effects of NS on either insulin levels or insulin resistance.

To the best of the authors' knowledge, there are no systematic reviews and meta-analysis that pooled the effect of NS supplementation on cardio-metabolic risk factors in adults. Thus, this meta-analysis protocol aimed to identify the relationship between NS and some cardio-metabolic parameters, including SBP, DBP, heart rate, AIP, and all the lipid profile and glycemic factors in previously published RCTs. The trials were conducted among populations with different health characteristics, such as patients with diabetes, metabolic syndrome, hyperlipidemia, hypertension, and coronary disease as well as overweight or obese and healthy participants.

Materials and Methods

Study design

The preferred reporting items for systematic reviews and meta-analyses protocol (PRISMA-P) guidelines was used for reporting the present systematic review and meta-analysis (Moher *et al.*, 2015). The PRISMA-P checklist is given in Additional **File 1**. Regarding the guidelines, this systematic review protocol was registered with the PROSPERO on September 15th, 2018 (Submitted Number 150929, September 15, 2019). Quantitative extracted data from included controlled clinical trials were meta-analyzed. Systematic review registration: https://www.crd.york.ac.uk/prospere/display_record.php?RecordID=150929 (CRD42020150929, on 25.2.2020).

Eligibility criteria

Patient and public involvement: All studies on adult's population were considered.

Types of studies: The study included controlled clinical human trials conducted among adults, with or without randomized design, consisting of any kinds of NS intervention compared to the control group. Self-controlled studies were also included. Studies with pre- and post-design or include NS with other products as their intervention, as well as studies without any control group were excluded. Animal, in-vitro, and in-vivo studies were also excluded.

Types of participants: Eligible participants in studies were human adults aged 18 years and older with any health status or disease characteristics.

Types of intervention: Any types of NS supplement (oil or powder or foods containing NS) with any names of NS supplements, including black seed or black cumin, caraway or Kalonji, and cuminum.

Information sources

Three reviewers searched electronic databases, including PubMed, Scopus, ISI Web of Science and the Cochrane Central Register of Controlled Trials for peer review literature, up to June, 2020.

The search strategy includes related keywords of NS supplement. Grey literature was also performed via the 'GREY MATTERS' checklists from the Canadian Agency for Drugs and Technologies in Health (CADTH). No language restrictions was considered and the searches were performed again just before the final analysis.

Search strategy

An initial literature search was conducted using MeSH terms and synonyms of NS using "OR" BOOLEAN operator between them. The full search strategy is given in Additional **File 2**.

Study records

Data management and selection process: Data collection was done according to the PRISMA flow diagram for reporting systematic reviews and meta-analyses and a PRISMA diagram was filled to report the numbers of studies selected at different levels of assessment (Liberati *et al.*, 2009). All reviewers met and compared their screening for at least two times to share and compare their results, after screening. Records with 95% mutual concordance were included.

Data extraction: Seven authors performed the screening of the studies according to the inclusion and exclusion criteria. All reviewers met and compared their screening at least two times to discuss and compare their results. They finally included records with 95% mutual concordance. Authors also performed data extraction independently for each study using a standardized form of Cochrane Data Collection for Randomized Controlled Trials. The extracted data consisted of baseline characteristics of the study, including the authors' names, publication year, and the region of published article. Moreover, the data included methodological quality and the design of each study, including pilot, non-randomized (quasai), and randomized full trials; characteristics of trial participants, including total participants, age, health status and disease characteristics, type of NS supplement, and duration of the intervention. Furthermore, outcome measures and their definitions and units; the drop-out and completion rates; the

measurement tools, and the final analysis with or without adjusted variables and the per-protocol or intention-to-treat analysis were among the extracted data. The data were entered separately for studies that had more than one outcome measure in order to conduct individual analysis. The accuracy of the extracted data was revised by two other reviewers and any disagreement was resolved through group discussion.

Outcomes

Main outcomes included blood pressure parameters, including SBP, DBP; lipid profile, including LDL-C, HDL-C, TG, TC, very low density of lipoprotein cholesterol (VLDL-C); AIP and oxidized-LDL; glycemic indices, including fasting plasma glucose, insulin levels, hemoglobin A1c, insulin resistance, and insulin sensitivity.

In summary, according to the PICOS (population, intervention, comparator, and outcomes) components, the population was adults; the intervention was all types of NS; the comparator was the control or placebo groups; the outcomes were cardiometabolic factors which were defined in detail above; and the design of studies was randomized controlled trials.

Quality assessment

Cochrane collaboration's tool was used to assess the potential risk of bias in the eligible studies (Higgins *et al.*, 2019). Cochrane Collaboration's tool included selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete data outcome), and reporting bias (selective outcome reporting) evaluated for the qualitative assessment. At the end, studies that have a low risk of bias for all domains will be regarded as good quality, and studies will have a fair quality if one criterion or 2 criteria are categorized as unclear risk of bias. If 2 studies or more have a high risk or unclear risk of bias, the studies will be regarded as poor quality.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach

was used to assess the quality of evidence for each outcome according to the domains, including risk of bias, publication bias, imprecision of results, heterogeneity, and indirectness of evidence and finally, the quality of evidence was categorized as very low, low, moderate, and high (Guyatt *et al.*, 2011, GuyattGH, 2008). Newcastle-Ottawa Quality Assessment Scale was used to evaluate the quality of nonrandomized studies based on three criteria, including selection of study groups, comparability of study groups, and ascertainment of either the exposure or outcome of interest (DerSimonian and Laird, 1986, Wells *et al.*, 2015).

Ethics approval and consent for participate

The ethics and feasibility of the present study is registered at the Department of Nutrition, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, (NO. IR.SSU.SPH.Rev-980616). Consent for publication is not applicable for the present systematic review protocol.

Data analysis

The differences in mean change values from baseline to the end of the intervention period of studies and the corresponding standard deviations (SDs) for intervention and control groups were extracted to be used as the effect size for meta-analysis. The weighted mean difference (WMD) and its corresponding 95% confidence intervals (CIs) were calculated using the random effects model 41. The STATA software (Version 14.2, College Station, Texas, USA) was used as the principal tool for meta-analysis.

Assessment of heterogeneity and publication bias and sensitivity analysis: The heterogeneity among studies was tested using Cochran's Q test and the I-squared tests (Higgins and Thompson, 2002). If the heterogeneity presents, sub-group analyses based on different parameters were performed to identify the source of heterogeneity. The publication bias was conducted with the Begg's funnel plots and Egger's tests (Higgins and Thompson, 2002). Sensitivity analysis was used to evaluate the robustness of the results (Egger *et*

al., 2008). Two-sided P -values < 0.05 were considered as statistically significant. The participants were analyzed according to a group allocated to them, regardless of whether they received the intervention.

Discussion

This systematic review and meta-analysis provided an updated and comprehensive synthesis of studies reporting the effect of NS on cardio-metabolic parameters. Intervention studies can provide the strongest evidence for the validity of final outcomes which is the strength of performing this meta-analysis. Previously, a few review studies were published investigating the effect of NS on some related parameters, though, the results were limited to specific population (Daryabeygi-Khotbehsara *et al.*, 2017) or specific designs of trials (Sahebkar *et al.*, 2016a, Sahebkar *et al.*, 2016b). Accordingly, performing this systematic review and meta-analysis comprehensively identified and summarized the effects of NS supplementation on different clinical and biochemical parameters in healthy or unhealthy individuals. Furthermore, the results of this systematic review created a comprehensive vision among either therapists or patients on the NS effectiveness.

Conflict of interest

The authors declare that they have no competing interests.

Funding statement

This research is funded by the Department of Nutrition, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran (NO. 970619-1). The university will control implementation of the study in accordance with the approved protocol.

Authors' contributions

Nadjarzadeh A is the guarantor. Razmpoosh E and Mirzavandi F drafted the manuscript. All authors contributed to the development of the selection criteria, the risk of bias assessment strategy, and data extraction criteria. Sadeqi N, Safi S, and Salehi-Abargouei A selected publications

and assessed the eligibility and quality. The other reviewers (Abdollahi N and Salehi-Abargouei A) collaborated with Razmpoosh E to revise the completed tasks. Salehi-Abargouei A and Razmpoosh E introduced statistical expertise. All authors read, provided feedback, and approved the final manuscript.

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References

- Al Dhaheri A, Al Khatib D & Jarrar A** 2017. The Effect of Black Seed Powder on Blood Glycaemia, Blood Lipidemia and Body Composition on Adults at Risk for Cardiovascular Diseases. In *Annals of Nutrition and Metabolism*, pp. 913-913. Kargar Allschwilerstrasse 10, CH-4009 BASEL, SWITZERLAND.
- Algheshairy RM** 2018. The control of type 2 diabetes with specific references to Nigella sativa seed and Ajwa dates. Manchester Metropolitan University.
- Ali B & Blunden G** 2003. Pharmacological and toxicological properties of Nigella sativa. *Phytotherapy Research*. **17** (4): 299-305.
- Bamosa AO, Ali BA & Sowayan S** 1997. Effect of oral ingestion Nigella sativa seeds on some blood parameters. *Saudi pharmaceutical journal*. **5**: 126-129.
- Bamosa AO, Kaatabi H, Lebdaa FM, Elq A & Al-Sultanb A** 2010. Effect of Nigella sativa seeds on the glycemic control of patients with type 2 diabetes mellitus. *Indian journal of physiology and pharmacology*. **54** (4): 344-354.
- Collins T, Mikkelsen B & Axelrod S** 2019. Interact, engage or partner? Working with the private sector for the prevention and control of noncommunicable diseases. *Cardiovascular diagnosis and therapy*. **9** (2): 158.
- Daryabeygi-Khotbehsara R, Golzarand M, Ghaffari MP & Djafarian K** 2017. Nigella sativa improves glucose homeostasis and serum lipids in type 2 diabetes: A systematic review and meta-analysis. *Complementary therapies in medicine*. **35**: 6-13.
- de Jong A, Plat J & Mensink RP** 2003. Metabolic effects of plant sterols and stanols. *Journal of nutritional biochemistry*. **14** (7): 362-369.
- DerSimonian R & Laird N** 1986. Meta-analysis in clinical trials. *Controlled clinical trials*. **7** (3): 177-188.
- Egger M, Davey-Smith G & Altman D** 2008. Systematic reviews in health care: meta-analysis in context. John Wiley & Sons.
- Ezz HSA, Khadrawy YA & Noor NA** 2011. The neuroprotective effect of curcumin and Nigella sativa oil against oxidative stress in the pilocarpine model of epilepsy: a comparison with valproate. *Neurochemical research*. **36** (11): 2195.
- Farzaneh E, Nia FR, Mehrtash M, Mirmoeini FS & Jalilvand M** 2014. The effects of 8-week Nigella sativa supplementation and aerobic training on lipid profile and VO2 max in sedentary overweight females. *International journal of preventive medicine*. **5** (2): 210.
- Ghosheh OA, Houdi AA & Crooks PA** 1999. High performance liquid chromatographic analysis of the pharmacologically active quinones and related compounds in the oil of the black seed (Nigella sativa L.). *Journal of pharmaceutical and biomedical analysis*. **19** (5): 757-762.
- Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P & Knottnerus A** 2011. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *Journal of clinical epidemiology*. **64** (4): 380-382.
- GuyattGH O** 2008. Ratingquality of evidence and strength of recommendations. GRADE: going from evidence to recommendations. *British medical journal*. **336** (7652): 1049-1051.
- Heshmati J, Namazi N, Memarzadeh M-R, Taghizadeh M & Kolahdooz F** 2015. Nigella sativa oil affects glucose metabolism and lipid concentrations in patients with type 2 diabetes:

- A randomized, double-blind, placebo-controlled trial. *Food research international*. **70**: 87-93.
- Higgins J, et al.** 2019. Cochrane handbook for systematic reviews of interventions. John Wiley & Sons.
- Higgins J & Thompson S** 2002. Quantifying heterogeneity in a meta- analysis. *Statistics in medicine*. **21** (11): 1539-1558.
- Ibrahim RM, et al.** 2014. A randomised controlled trial on hypolipidemic effects of *Nigella Sativa* seeds powder in menopausal women. *Journal of translational medicine*. **12** (1): 82.
- Ismail M, Al-Naqeep G & Chan KW** 2010. *Nigella sativa* thymoquinone-rich fraction greatly improves plasma antioxidant capacity and expression of antioxidant genes in hypercholesterolemic rats. *Free radical biology and medicine*. **48** (5): 664-672.
- Kazemipoor M, Hajifaraji M, Haerian BS, Mosaddegh MH & Cordell GA** 2013. Antiobesity effect of caraway extract on overweight and obese women: a randomized, triple-blind, placebo-controlled clinical trial. *Evidence-based complementary and alternative medicine*. **2013**.
- Liberati A, et al.** 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Annals of internal medicine*. **151** (4): W-65-W-94.
- Ma Y, et al.** 2014. Lipoprotein lipase variants interact with polyunsaturated fatty acids for obesity traits in women: replication in two populations. *Nutrition, metabolism and cardiovascular diseases*. **24** (12): 1323-1329.
- Mahdavi R, Namazi N, Alizadeh M & Farajnia S** 2016. *Nigella sativa* oil with a calorie-restricted diet can improve biomarkers of systemic inflammation in obese women: A randomized double-blind, placebo-controlled clinical trial. *Journal of clinical lipidology*. **10** (5): 1203-1211.
- Moher D, et al.** 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews*. **4** (1): 1.
- Padhye S, Banerjee S, Ahmad A, Mohammad R & Sarkar FH** 2008. From here to eternity-the secret of Pharaohs: Therapeutic potential of black cumin seeds and beyond. *Cancer therapy*. **6** (b): 495.
- Ramachandran A, Snehalatha C, Yamuna A, Murugesan N & Narayan KV** 2007. Insulin resistance and clustering of cardiometabolic risk factors in urban teenagers in southern India. *Diabetes care*. **30** (7): 1828-1833.
- Rouhi-Boroujeni H, Rouhi-Boroujeni H, Heidarian E, Mohammadizadeh F & Rafieian-Kopaei M** 2015. Herbs with anti-lipid effects and their interactions with statins as a chemical anti-hyperlipidemia group drugs: A systematic review. *ARYA atherosclerosis*. **11** (4): 244.
- Sahebkar A, Beccuti G, Simental-Mendía LE, Nobili V & Bo S** 2016a. *Nigella sativa* (black seed) effects on plasma lipid concentrations in humans: A systematic review and meta-analysis of randomized placebo-controlled trials. *Pharmacological research*. **106**: 37-50.
- Sahebkar A, et al.** 2016b. A systematic review and meta-analysis of randomized controlled trials investigating the effects of supplementation with *Nigella sativa* (black seed) on blood pressure. *Journal of hypertension*. **34** (11): 2127-2135.
- Samani KG & Farrokhi E** 2014. Effects of cumin extract on oxLDL, paraoxanase 1 activity, FBS, total cholesterol, triglycerides, HDL-C, LDL-C, Apo A1, and Apo B in the patients with hypercholesterolemia. *International journal of health sciences*. **8** (1): 39.
- Tan CX** 2019. Virgin avocado oil: An emerging source of functional fruit oil. *Journal of functional foods*. **54**: 381-392.
- Wells GA, et al.** 2015. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses.

Additional File 1: PRISMA-P checklist

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	page 1 1a	Identify the report as a protocol of a systematic review
Update	page 1 1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	page 1 2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:	page 6	
Contact	page 1 3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	page 13 3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review: funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	page 46	Describe the rationale for the review in the context of what is already known
Objectives	page 7 7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	page 7-88	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	page 8 9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	page 9 10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	page 9 11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Additional File 2: Search Strategy

Pubmed	Cuminum*[Title/Abstract] OR cuminum[MeSH] OR cumin*[Title/Abstract] OR copticum*[Title/Abstract] OR caraway*[Title/Abstract] OR Carum*[Title/Abstract] OR carum[MeSH] OR carvi*[Title/Abstract] OR carvus*[Title/Abstract] OR copticum*[Title/Abstract] OR Ajowan*[Title/Abstract] OR Thymoquinon*[Title/Abstract] OR Thymoquinone[MeSH] OR NS*[Title/Abstract] OR NS[MeSH] OR Kalonjus*[Title/Abstract] OR Kalonji*[Title/Abstract] OR Black seed*[Title/Abstract] OR TQ*[Title/Abstract]
Cochrane, Central Register for Controlled Trials	"Cuminum" in Title, Abstract, Keywords in Trials' or "thymoquinone" in Title, Abstract, Keywords in Trials' or "cumin" in Title, Abstract, Keywords in Trials' or "NS" in Title, Abstract, Keywords in Trials' or "ajowan" in Title, Abstract, Keywords in Trials' or "black seed" in Title, Abstract, Keywords in Trials' or "carvi" in Title, Abstract, Keywords in Trials' or "copticum" in Title, Abstract, Keywords in Trials' or "carum" in Title, Abstract, Keywords in Trials' or "carvus" in Title, Abstract, Keywords in Trials' or "carvus" in Title, Abstract, Keywords in Trials' or "Kalonjus" in Title, Abstract, Keywords in Trials' or "kalonji" in Title, Abstract, Keywords in Trials'
ISI Web of Knowledge	TI=(cuminum*) OR TI=(cumin*) OR TI=(cyminum*) OR TI=(copticum*) OR TI=(caraway*) OR TI=(carumO) OR TI=(carvi) OR TI=(carvus) OR TI=(ajowan*) OR TI=(Thymoquinon*) OR TI=(NS*) OR TI=(Kalonjus) OR TI=(Kalonji) OR TI=(Black seed*) OR TS=(cuminum*) OR TS=(cumin*) OR TS=(cyminum*) OR TS=(copticum) OR TS=(copticum*) OR TS=(caraway*) OR TS=(carum*) OR TS=(carvi) OR TS=(carvus) OR TS=(ajowan*) OR TS=(Thymoquinon*) OR TS=(NS*) OR TS=(Kalonjus) OR TS=(Kalonji) OR TS=(Black seed*)
Scopus	TITLE-ABS-KEY (cuminum*) OR TITLE-ABS-KEY (cumin*) OR TITLE-ABS-KEY (cyminum*) OR TITLE-ABS-KEY (copticum*) OR TITLE-ABS-KEY (caraway*) OR TITLE-ABS-KEY (Carum*) OR TITLE-ABS-KEY (carvi*) OR TITLE-ABS-KEY (carvus*) OR TITLE-ABS-KEY (Ajowan*) OR TITLE-ABS-KEY (Thymoquinon*) OR TITLE-ABS-KEY (NS*) OR TITLE-ABS-KEY (Kalonjus*) OR TITLE-ABSKEY (Kalonji*)
Google Scholar	allintitle: Kalonji OR cuminum OR cumin OR caraway OR Carum OR carvi OR copticum OR Ajowan OR Thymoquinone OR NS OR kalonjus OR Kalonji OR Black seed