

ANTIHYPERTENSIVE EFFECTS OF *NIGELLA SATIVA*: WEIGHING THE EVIDENCE

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ABSTRACT

Objective: Hypertension causes 7.5 million deaths annually worldwide. Antihypertensive drugs cause side effects, potentially leading to non-adherence, hence uncontrolled hypertension and increased risk of cardiovascular morbidity and mortality. Therefore, there has been increasing interest in alternative pharmacological treatments for hypertension, one of which is black cumin, or *Nigella sativa*, a traditional medicine that has been empirically used. This evidence-based case report aims to evaluate the current evidence for the effectiveness of *Nigella sativa* in reducing blood pressure in a mildly hypertensive patient.

Methods: A literature search was performed on MEDLINE, TRIP Database, Clinical Key, ScienceDirect, and DynaMed, using the keywords “nigella sativa”, “hypertension”, and “blood pressure” with all their synonyms and related terms. The included studies were two systematic reviews and two clinical trials, which were then critically appraised.

Results: Out of the four studies, three were considered valid. In terms of importance, Sahebkar *et al.* showed a reduction of the weighted mean difference (WMD) by *Nigella sativa*: -3.26 mmHg, 95% CI: -5.10, -1.42, $I^2 = 59%$ for systolic blood pressure and WMD: -2.80 mmHg, 95% CI: -4.28, -1.32, $I^2 = 60%$ for diastolic blood pressure. Badar *et al.* concluded that *Nigella sativa* significantly reduced systolic and diastolic blood pressure compared with the control group. Two studies were considered applicable to our patient in question.

Conclusion: The current evidence for the effect of *Nigella sativa* in lowering blood pressure is limited. However, one study gives strong evidence for significant antihypertensive effects of *Nigella sativa*. In mild hypertension, *Nigella sativa* could be one of the therapeutic options.

Keywords: Hypertension, Blood pressure, *Nigella sativa*, Black seed, Black cumin

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INTRODUCTION

Hypertension, or high blood pressure, is a condition in which elevated pressure persists within the blood vessels. The pressure in the blood vessels is created by blood flow that forces against the inner walls of the vessels. The latest data from the World Health Organization shows that hypertension is estimated to cause 7.5 million deaths annually or about 12.8% of all deaths worldwide. It also causes 57 million disability adjusted life years (DALYs) or about 3.7% of total DALYs [1]. The prevalence of this non-communicable disease is rising in developing countries, and in Indonesia, which is the fourth most populous country in the world. The burdens of diabetes, heart disease, stroke, and hypertension have increased in the past 20 y. According to Indonesian Basic Health Research (or Riset Kesehatan Dasar), the prevalence of hypertension in Indonesia was 25.8% in 2013. According to Sample Registration System Indonesia, hypertension with complications accounted for about 5.3% of all deaths in Indonesia in 2014, making it the fifth highest cause of death [2, 3]. Moreover, the burden of hypertension also comes from the low rate of diagnosis and treatment. Only 1/3 of patients with hypertension have been diagnosed, while only 0.7% of those diagnosed with hypertension are taking antihypertensive medications [3].

Currently, the available treatments for hypertension include various classes of antihypertensive drugs, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, and thiazide-type diuretics [4]. In a prospective cohort study in the United States, side effects of antihypertensive drugs occurred in 85% of the patients, resulting in non-adherence of 34.5% of patients to the treatments.[5] Such non-adherence is believed to be the main cause of uncontrolled hypertension, which then increases the risk of heart failure, stroke, and mortality [6, 7] The adverse effects of these drugs along with the relatively high costs, have contributed to the rising interest in herbal treatment for hypertension [8].

Nigella sativa, also known as black cumin, black seed, habitus sauda, or jintan hitam in Indonesia, is a traditional medicine that has been used

in various medical conditions since hundreds of years ago [9]. Preclinical and clinical studies have suggested *N. sativa* as antioxidants and diuretic agents, and its effects in reducing sympathetic activities, lowering lipids, increasing nitric oxide production to prevent arterial rigidity, reducing appetite and many others, all of which contribute to its potential use as an antihypertensive agent [10-12]. However, despite its empirical use through generations, the scientific evidence on the antihypertensive effects of *N. sativa* is somehow limited and often inconsistent. Therefore, this evidence-based case report aims to critically analyze and weigh the available evidence for the effects of *N. sativa* on alleviating hypertension.

Clinical question

A 45-year-old man participated in a blood pressure screening program. His blood pressure reading was 130/90 mmHg. He and his immediate family had no history of cardiovascular diseases. The patient was interested to know if he could use *N. sativa* supplements to control his blood pressure.

MATERIALS AND METHODS

A search of literatures was performed on September 15th to 16th, 2018 on MEDLINE, TRIP Database, Clinical Key, ScienceDirect, and DynaMed. The keywords used were “nigella sativa”, “hypertension” and “blood pressure” with all their synonyms and related terms. Table 1 below shows the terminology used in each database during the search.

The eligible articles were clinical trials, systematic reviews and meta-analyses with blood pressure (systolic and diastolic) as one of the outcomes of the study, limited to studies in human and published in English in the last 5 y. All guidelines and review articles were excluded. The search strategy is illustrated in fig. 1. After screening the literatures and reading the full texts, therapy articles or systematic reviews were critically appraised with consensus of all authors based on the guideline established by the Center of Evidence-Based Medicine, University of Oxford.

Table 1: Search terms used in the five databases

Database	Terminology	Hits	Selected
MEDLINE	((hypertension) OR blood pressure) AND nigella sativa) AND ((Review[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR Controlled Clinical Trial[ptyp] OR Clinical Trial[ptyp]) AND "last 5 y"[PDat])	15	3
Trip database	(hypertension)(nigella sativa)(blood pressure)	13	0
ClinicalKey	((Nigella sativa) OR 'blood pressure') AND 'nigella sativa'	21	0
ScienceDirect	TITLE-ABSTR-KEY("hypertension" OR "blood pressure") AND TITLE-ABSTR-KEY (nigella sativa)	6	0
DYNAMED	((Nigella sativa) OR 'blood pressure') AND 'nigella sativa'	3	1

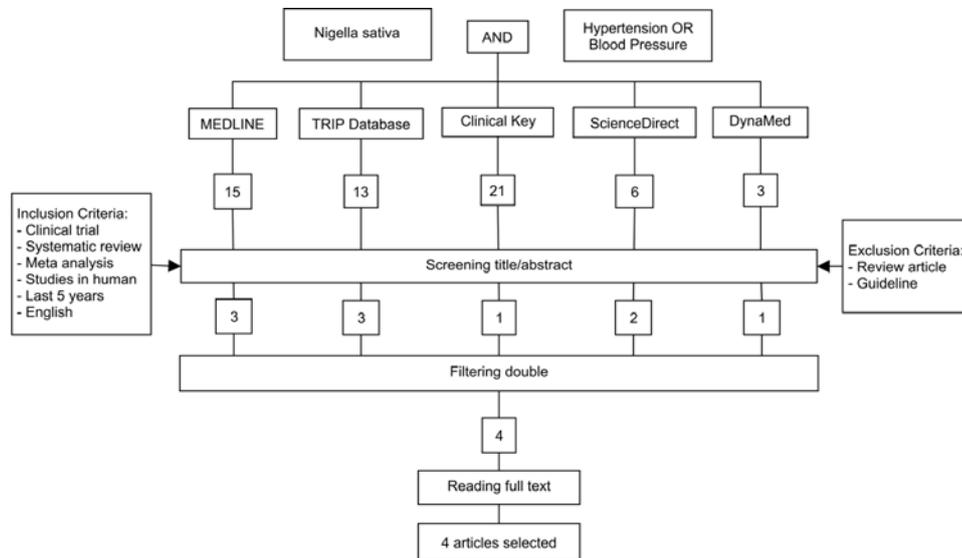


Fig. 1: Flowchart of the search strategy

RESULTS

Following the literature search, four articles were found to be eligible for this evidence-based case report [13–16] the design and summary of the articles can be found in table 2.

These two articles are prospective cohort studies with a level of evidence of 2b. The study by Badar A, *et al.* [13] has a larger sample

size and longer duration compared with the study by Rizka A, *et al.* [14]. The former is a single-blind non-randomized clinical trial, whereas the latter is a double-blind randomized controlled trial. The remaining two articles chosen are systematic reviews, the critical appraisal of which is explained in table 4. The review by Sahebkar A, *et al.* [15] includes a meta-analysis, while the review by Mohtashami A, *et al.* does not [16].

Table 2: Summary of the selected articles

	Badar, <i>et al.</i> (2017)	Rizka, <i>et al.</i> (2017)	Sahebkar, <i>et al.</i> (2016)	Mohtashami, <i>et al.</i> (2016)
Type of Studies	Non-randomized, single-blind clinical trial	Randomized, double-blind clinical trial	Systematic review and meta-analysis of randomized controlled trials	Systematic review of clinical trials
Subjects/Materials	Patients with type 2 diabetes and hypertension 57 patients in each group, total of 114	Advanced-age patients with hypertension 38 patients in each group, total of 76	Hypertensive and normotensive patients; pooled total of 860 patients 11 RCTs from PubMed, Medline, Cochrane Collaboration Library, SCOPUS, Web of Science, and Google Scholar	Patients with diabetes, patients with metabolic syndrome, patients with hyperlipidemia, patients with hypertension, and healthy subjects; pooled total of 1531
Intervention	<i>N. sativa</i> seeds: 500-mg oral capsules, 2 g/day for 12 mo	<i>N. sativa</i> seeds: 300-mg oral capsules, 2 times a day for 28 d	<i>N. sativa</i> oil (n=3) <i>N. sativa</i> powder (n=8)	<i>N. sativa</i> extract <i>N. sativa</i> oil <i>N. sativa</i> powder Dose of 200 mg to 5 g. Duration of 2 w to 6 mo
Control	Placebo (activated Charcoal capsules)	Placebo	Placebo (n=10) Standard treatment (n=1)	Not clear
Results	Significant decrease in SBP, DBP, and MAP	Clinically Significant decrease in SBP but not DBP	Short-term treatment with <i>N. sativa</i> significantly reduced SBP and DBP	<i>N. sativa</i> at different doses and for different durations can change various clinical and biochemical parameters, but less pronounced effect on blood pressure

RCTs, randomized controlled trials; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure, Out of the four articles chosen, two articles are original articles, the critical appraisal of which is shown in table 3.

Table 3: Critical appraisal of the two clinical trials

	Badar A, et al. (2017)	Rizka A, et al. (2017)
Level of evidence	2b	2b
Sample size	114	76
Length of treatment	12 mo	28 d
Validity	Randomization	-
	Group similarity	+
	Equal treatment	+
	Loss to follow-up (%)	15.8
	Drop-out (%)	N/A
	Blinding	Single
Importance	Changes in blood pressure (endpoint compared with baseline)	Systolic BP: 9.66 mmHg Diastolic BP: 3.51 mmHg
	P values (treatment vs placebo)	Systolic BP: 0.053 Diastolic BP: 0.024
		Systolic BP: 14.6 mmHg Diastolic BP: 3.9 mmHg
Applicability	Patient similarity	+
	Feasibility of treatment	+
	Benefits outweigh harm	+

+shown clearly in the article; - not being done; ? not stated clearly; levels of evidence based on Oxford Centre for Evidence-Based Medicine; BP: blood pressure

Table 4: Critical appraisal of the two systematic reviews

Validity	Sahebkar, et al. (2016)	Mohtashami, et al. (2016)
Did the systematic review address a relevant question?	Yes	Yes
Were the criteria used to select articles for inclusion appropriate?	Yes	Yes
Is it likely that important, relevant studies were missed?	No	No
Was the validity of the selected studies appraised?	Yes	No
Were the included studies sufficiently valid for the type of question asked?	Yes	No
Were the results of the selected studies similar to each other?	Yes	No
Importance		
What are the overall results of the meta-analysis?	Treatment with <i>N. sativa</i> has a significant effect on lowering systolic blood pressure (WMD: -3.26 mmHg, 95% CI: -5.10, -1.42, I ² = 59%) and diastolic blood pressure (WMD: -2.80 mmHg, 95% CI: -4.28, -1.32, I ² = 60%)	Four out of nine studies have shown that <i>N. sativa</i> can reduce blood pressure. The effect however was not significant in the other five trials
How precise were the results?	Precise, with 95% CI for reduced blood pressure after treatment with <i>N. sativa</i>	No statistical data were given in the review
Applicability		
Can the results be applied to our patient?	Yes	No
Were all the clinically important outcomes considered?	Yes	No
Do the benefits outweigh the harm?	Yes	Benefits cannot be concluded

Owing to the design of the single-blind, non-randomized clinical trial by Badar, et al. [13], its validity is weaker compared with the double-blind, randomized controlled trial by Rizka, et al. [14]. Nevertheless, the validity of the study by Rizka, et al. [14] is also limited by the unknown significance in group similarity and the short duration of treatment. In both clinical trials, those lost to follow-up or dropping out were below 20%, and thus had little effect on their validity. The changes in systolic and diastolic blood pressures at the end of the trial compared with the baseline were taken into account to determine the clinical importance. Only the change in systolic blood pressure of more than 10 mmHg in the study by Rizka et al. [14] was of clinical importance. Meanwhile, the P values of differences in the systolic and diastolic blood pressures between the treatment group and the placebo group were considered to determine its statistical significance. Only the P value for the difference in diastolic blood pressure in the study by Badar et al. [13] was less than 0.05, and thus statistically significant. Overall, both studies were weak in

validity as only one out of four parameters was met in each study. Both clinical trials were considered to be applicable though because of their apparent feasibility of treatment and the benefits over the reported harms. Moreover, the study by Badar, et al. [13] was considered stronger with a higher patient similarity and a narrower range of age and blood pressures. In the study by Rizka, et al. [14], the patients were elderly with a mean systolic blood pressure of 160 mmHg, which was higher than that in the study by Badar, et al.

The meta-analysis by Sahebkar, et al. [15] was valid, relevant, important, and applicable to our question and showed a level of evidence of 1a. Sahebkar, et al. [15] included all valid studies (RCTs, published before 30 August 2015) to determine the effect of *N. sativa* on lowering blood pressure. The study analyzed differences in blood pressure reduction using I² index and X² statistics, measuring inter-study heterogeneity. Each study included in the meta-analysis was assessed for publication bias using Egger's test and no bias was

found. Importance was met with -3.26 mmHg, 95% CI: $-5.10, -1.42$, $I^2 = 59\%$ for SBP and weighted mean difference: -2.80 mmHg, 95% CI: $-4.28, -1.32$, $I^2 = 60\%$ for DBP. Meanwhile, we concluded that the systematic review by Mohtashami, *et al.* [16] was not valid or applicable to our question. The study was not focused on blood pressure but rather on blood parameters and anthropometric indices. Mohtashami, *et al.* [16] was unable to make a conclusion on the effects of *N. sativa* on reducing blood pressure because of the different characteristics across the selected studies.

DISCUSSION

Considering the validity components, the clinical study by Badar, *et al.* [13] may not suffice. Although there was group similarity in this study, the groups were not assigned randomly. Together with the single-blind design, this poses a notable risk of bias in the study thereby reducing its validity. Meanwhile, the study by Rizka, *et al.* [14] claimed to have comparable baseline characteristics in the two groups, there were no statistical data presented to indicate statistical significance. While this may decrease the validity of the study to a certain extent, it could still be more valid with its double-blind design than the study by Badar, *et al.* [13]

In terms of importance, both clinical trials seemed weak as only one out of four parameters favored the treatment using *N. sativa*. Notably however, in both studies, changes in blood pressure and the P values of difference between the treatment group and placebo were the only values available for appraisal of importance. The relative risk and the number needed to treat could not be obtained without any data on the event rates. Both studies only presented the mean values of systolic and diastolic blood pressure in the treatment and placebo groups, without specifying the number of events of hypertension in each group. This means that the ratio of benefit and harm in the treatment using *Nigella sativa* cannot be quantified. These inevitably result in a suboptimal appraisal of the importance of these clinical trials. As for their applicability, both studies presented adequate evidence in favor of using *N. sativa* in patients with hypertension, mainly because of the feasibility and safety. *N. sativa* is easily found in Indonesia and has been empirically used in Indonesia as dietary supplements [17]. The reported adverse events in both studies were minimal, hence strengthening their applicability. The study by Rizka, *et al.* [14] is, however, less applicable to our question because their patients were elderly with a mean SBP of 160 mmHg. Our patient is a middle-aged man with mild hypertension of SBP of 130 mmHg. The difference in blood pressures may be clinically significant and may affect the translation of the results to our patient.

The review by Sahebkar, *et al.* [15] was shown to be valid because of its focus on the question asked, appropriate inclusion criteria, similar results between studies, and good coverage of the included studies. Eleven studies were included, ranging from treatment duration of 4–12 w with both hypertensive and normotensive patients. No publication bias was identified in all 11 studies. Random effect models were used when comparing with a control group, concluding that the group receiving *N. sativa* had a mean decrease of 3.26 and 2.80 mmHg in systolic and diastolic blood pressures, respectively. The effect was also found to be important in lowering blood pressure in human, but the reduction of 3.26/2.80 mmHg was not clinically significant in controlling hypertension. Besides, the study was conducted in a heterogeneous population with patient differences in demographics and baseline clinical characteristics. It was also limited by the short duration of the included studies, which only ranged from 4 to 12 w, and hence was not indicative for the effect of long-term use of *N. sativa*.

In contrast, the systematic review made by Mohtashami, *et al.* [16] demonstrated low validity. This judgment was based on the lack of information about how the authors concluded the effects of each included trial. Moreover, no statistical data were provided by Mohtashami, *et al.* [16] making results in the study less important.

Among the four studies considered, we concluded that the meta-analysis by Sahebkar, *et al.* [15] was the strongest evidence available for our research question owing to its relatively high validity, importance, and applicability.

Unfortunately, the mechanism of how *N. sativa* reduces blood pressure is not well defined. Several factors can be assumed to play a role in this mechanism based on the components of *N. sativa*. Thymoquinone acts on serotonergic and muscarinic receptors, thymol acts on calcium ion channels, and other components induce diuretic effects through mediating signaling pathways [18–20]. Thymoquinone, flavonoids, and polyphenols also have antioxidant activity that dilates blood vessels by nitric oxide production [21–23]. Furthermore, *N. sativa* also lowers blood pressure via the diuretic effect; the effect of a dose of 5 mg/kg of *N. sativa* was comparable with that of furosemide, a frequently used diuretic. This diuretic effect helps to decrease blood pressure through reduction of electrolytes and water content, thus reducing cardiac output [24]. However, these results were obtained in a strict, laboratory-controlled environment; hence, their proposed mechanisms must be interpreted with caution. The exact mechanism of action of *N. sativa* is therefore still indefinite.

The limitation of this study is that in the appraisal of the importance of the clinical trials, the relative risk and the number needed to treat could not be assessed owing to the lack of data of the event rates in the two clinical trials. The data were unpublished and we have yet to be in correspondence with the authors of these studies for the relevant data. In general, we have also found that the use of *N. sativa* in alleviating high blood pressure is relatively unexplored, resulting in the limited number of studies available. We hope that this study will prompt more clinical trials on the use of *N. sativa* in treating hypertension, which will help to determine its effects on blood pressure and its safety during long-term use.

As for the patient in our case, the recommended management based on the 2017 ACC/AHA guidelines is nonpharmacologic therapy and re-evaluation in 3–6 mo after starting therapy [4]. Nonpharmacologic therapy may include a combination of changes in diet and physical activity. As for the use of *N. sativa* supplements to control hypertension, we have to explain to the patient that the current evidence is still limited, despite a favorable tendency towards the antihypertensive effects. The patient can also be educated on the importance of a balanced diet, physical activity, and routine health check-up.

CONCLUSION

In conclusion, the current evidence for the use of *N. sativa* in lowering blood pressure is still limited, with the strongest evidence for its significant antihypertensive effect from a meta-analysis of RCTs. Other clinical trials also suggested clinically significant decreases in systolic blood pressure. Considering its benefits of alleviating hypertension and its relatively few reported side effects, further research is encouraged to achieve a better understanding of the use of *N. sativa* as antihypertensive treatment and to provide high-quality evidence to support healthcare policies and clinical decisions. This should benefit millions of people affected by hypertension and cardiovascular diseases worldwide.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICTS OF INTERESTS

There is no conflict of interest in the preparation and publication of this study.

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