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Liver-protectant and cardiovascular-protectant effects of *Nigella sativa*: a meta-analysis

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ABSTRACT

Objective A significant amount of evidence has lately revealed that individuals with non-alcoholic fatty liver diseases (NAFLD) are at high risk of cardiovascular diseases, which is the primary cause of death in patients. This study is to evaluate liver- and cardiovascular-protectant effects of *Nigella sativa* (*N. sativa*).

Methods The meta-analysis was performed using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The literature review was conducted in June 2022 with papers retrieved from the PubMed, ScienceDirect, and Cochrane Library websites from January 2010 to December 2021. The Review Manager version 5.3 was applied for the statistical analysis of parameters like aspartate transaminase (AST) and alanine transaminase (ALT) levels, lipid profil, blood glucose level, weight, and body mass index (BMI).

Results The results showed that *N. sativa* could significantly decrease the AST ($P = 0.009$) and ALT ($P < 0.05$) levels in research subjects. Subjects in the *N. sativa* group had a significant higher cure rate of fatty liver than those in the placebo group ($P = 0.000\,1$). In addition, lipid profile, blood pressure, and fasting blood glucose of subjects all significantly reduced in the *N. sativa* group ($P < 0.05$). However, the comparison of body weight and BMI between the *N. sativa* group and placebo group did not show significant difference ($P > 0.05$).

Conclusion *N. sativa* did have certain liver-protectant and cardiovascular-protectant effects on patients with NAFLD or chronic liver diseases (CLD), despite the insignificant comparison of body weight and BMI between the *N. sativa* group and the placebo group.

1 Introduction

It is thought that there are 1.5 billion cases of chronic liver disease (CLD) globally. Non-alcoholic fatty liver disease (NAFLD) is the leading cause of prevalent diseases (59%), followed by hepatitis B virus (HBV, 29%), hepatitis C virus (HCV, 9%), and acute liver diseases (ALD, 2%). Only 1% of patients with liver illness are the

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consequence of other conditions such as primary biliary cholangitis, primary sclerosing cholangitis, alpha-1 antitrypsin deficiency, Wilson's disease, and autoimmune hepatitis [1]. CLD is a continuous process of inflammation, destruction, and regeneration of liver parenchyma that eventually leads to liver fibrosis and cirrhosis.

It has been supported by a significant amount of evidence that individuals with NAFLD are also at high risk of cardiovascular disease, a primary cause of death in patients [2]. It is well-known that NAFLD is in close relation to the onset of or death from CLD. The severer the NAFLD is, the higher risk both fatal and non-fatal cardiovascular events could occur. The cardiovascular events (CVE) resulted from NAFLD include left ventricular dysfunction, atherosclerotic cardiovascular disease, abnormalities of the cardiac conduction system, and ischemic stroke. As suggested in some epidemiological or clinical studies, NAFLD could trigger the onset of the CVE no matter whether the conventional cardiovascular risk factors present or not [3-5].

For centuries, traditional Chinese medicine (TCM) has been widely utilized in the treatment of hepatic disorders such as NAFLD in Asia. Its holistic approach and syndrome-differentiated treatment of NAFLD has shown its advantages in handling this complicated metabolic condition. *Nigella sativa* (*N. sativa*) is a plant largely grown in western China, particularly in Xinjiang province. As a medicinal herb, *N. sativa* has been included in every edition of the *Pharmacopoeia of The People's Republic of China*. The seeds of *N. sativa* are extensively used in traditional Uyghur medicine to treat edema, urinary calculus, and bronchial asthma [6, 7]. *N. sativa* is considered an important medicine in TCM practice. Apart from the seeds, the oil of *N. sativa* has also been used for a long time to treat a variety of illnesses. The main active components in the extract of *N. sativa* include thymoquinone, thymohydroquinone, dithymoquinon, and thymol. P-cymene is the primary component of its oil, which makes up almost 30% of the weight of *N. sativa* [8]. *N. sativa* appears to be safe in ameliorating liver steatosis, liver damage, and fatty liver transformation in NAFLD patients and reducing CVE by lowering the levels of C-reactive protein and lipid peroxidation, according to a number of experimental and clinical research. *N. sativa* was also able to decrease levels of liver enzymes and play a preventive role by treating liver inflammation [9, 10]. Although many studies on the effects of *N. sativa* in the treatment of patients with NAFLD or CVE have emerged in recent years, most of them are single-centered with just a small sample size and their results to be debated. In this meta-analysis study, the liver- and cardiovascular-protectant effects of *N. sativa* were evaluated in order to offer evidence-based suggestions for clinical practice or on adjuvant therapies in this regard.

2 Materials and methods

2.1 Literature retrieval

This meta-analysis study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. The literature was retrieved from Cochrane, Sciencedirect, and PubMed websites. The keywords used for literature retrieval were NAFLD, cardiovascular diseases, cardiovascular risk, and *N. sativa*. All randomized control trials (RCTs) from January 2010 to December 2021 were included. We searched the included study in June 2022.

2.2 Inclusion and exclusion criteria

Studies were included if they: (i) were RCTs; (ii) used placebo in comparison to the effects of *N. sativa;* (iii) reported at least one of the following outcomes: changes in AST and ALT levels, lipid profile and blood glucose level. Studies were excluded if they: (i) reported none of the outcomes mentioned in the inclusion criteria (iii) above; (ii) were untraceable or not digital data; (iii) were non-RCTs; (iv) combined the use of other drugs or supplements. The authors independently screened the studies, extracted relevant data, and discussed each outcome.

2.3 Outcome and study quality

Study results such as cure rates, medication outcomes, recurrence rates, and adverse events were extracted for evaluation. The Jadad score with a scale ranging from 0 point to 5 points was applied for determining the quality of the RCTs. When the score was > 4, the study was considered high quality; when between 3 and 4, moderate quality; when < 3, low quality [12]. Finally, the criteria designed by the Oxford Center for Evidence-Based Medicine were used to assess the level of evidence base of each study [13].

2.4 Statistical analysis

Review Manager version 5.3 was used to statistically analyze each parameter. The data type was dichotomous or categorical, and expressed as odd ratio (OR), and continous data was mean difference (MD) with a 95% confidence interval (CI). Furthermore, the Cochrane Chi-squared test and inconsistency (I^2) were used to examine the heterogeneity of the studies. $P < 0.05$ was considered statistically significant; hence, the heterogeneity was significant when $I^2 > 50\%$.

3 Results

3.1 Baseline characteristics

A total of 60 related articles were obtained through literature retrieval. After screening, 11 articles left. In the

remained articles, as many as 681 patients were enrolled, with 340 in the *N. sativa* group and 341 in the placebo group, as shown in Figure 1.

Table 1 shows the characteristics of the included studies. The level of evidence base was 1b for nine RCTs. All included studies had a high quality, with the Jadad scores of either 4 or 5. Table 2 presents the scores of the quality assessment.

3.2 Liver-protectant effects

3.2.1 The ALT level Figure 2 shows nine articles [9, 10, 14-20] with 287 patients in the *N. sativa* group and 289 in the placebo group. The ALT level in the *N. sativa* group significantly reduced (MD – 6.46; 95% CI, – 12.92 to – 0.01; $P < 0.05$) in the nine articles, with a reasonably high heterogeneity ($I^2 = 96\%$).

3.2.2 The AST level Figure 3 shows that nine studies [9, 10, 14-20] had reported a significant decrease in the AST level in the *N. sativa* group (MD – 6.56; 95% CI, – 11.49 to – 1.63; $P = 0.009$), with a reasonably high heterogeneity ($I^2 = 92\%$).

3.2.3 Cure rates of fatty liver As shown in Figure 4, the cure rates of fatty liver were compared between the *N. sativa* group and the placebo group in three studies [10, 16, 20].

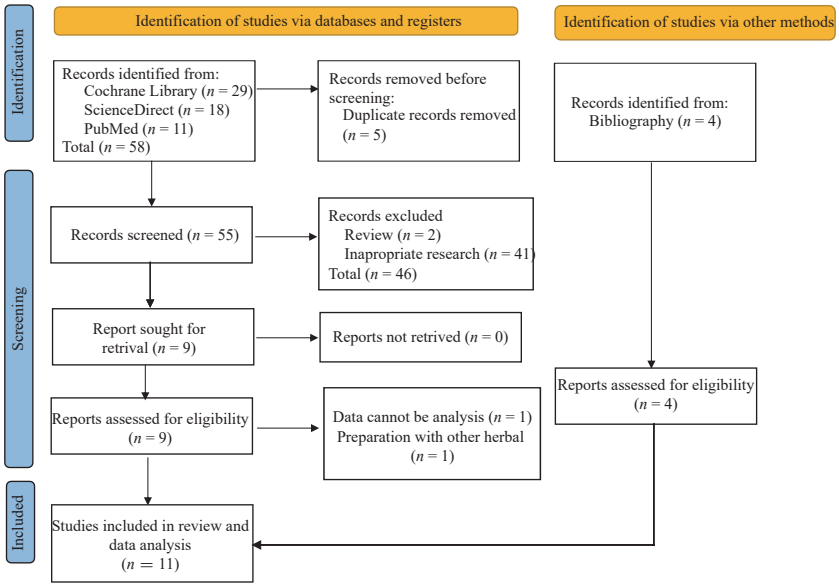

Figure 1 Article screening using PRISMA flowchart

Table 1 Baseline characteristics of the included studies

Study	Intervention	Preparation	Country	Study design	LE	Jadad scale	Case (*n*)	
							N. sativa	Placebo
Darand 2019 [9]	*N. sativa* vs placebo (500 mg rice starch)	Capsule	Iran	RCT	1b	5	22	21
Datau 2010 [14]	*N. sativa* vs placebo (wheat flour)	Capsule	Indonesia	RCT	1b	4	19	20
Huseini 2013 [15]	*N. sativa* vs placebo (150 mL mineral oil)	Oil	Iran	RCT	1b	5	35	35
Hussain 2017 [16]	*N. sativa* vs placebo (micro crystalline cellulose)	Capsule	Pakistan	RCT	1b	3	35	35
Khonche 2019 [10]	*N. sativa* vs placebo (2.5 mL mineral oil, 1.25 mL honey, and 1.25 mL water in each 5 mL of the mixture)	Oil	Iran	RCT	1b	5	60	60
Kooshki 2019 [8]	*N. sativa* vs placebo (medium-chain triglyceride oils in lunch and dinner)	Oil	Iran	RCT	1b	4	27	23
Mohtashami 2011 [17]	*N. sativa* vs placebo (mineral oil)	Oil	Iran	RCT	1b	4	35	35
Rashidmayvan 2019 [18]	*N. sativa* vs placebo (1 g of paraffin oil once a day)	Oil	Iran	RCT	1b	4	22	22
Razmpoosh 2020 [19]	*N. sativa* vs placebo (paraffin oil)	Capsule	Iran	RCT	1b	5	19	20
Shavakhi 2015 [20]	*N. sativa* vs placebo (cumin capsule thirice a day)	Capsule	Iran	RCT	1b	5	40	41
Shoaei-Hagh 2021 [21]	*N. sativa* vs placebo (sunflower oil)	Oil	Iran	RCT	1b	5	26	29

LE, level of evidence base; 1b, the results of the level of evidence base of the RCTs.

Table 2 Jadad scores of the included studies

Study	Randomization	Blinding	Withdrawal or dropout	Jadad scale
Darand 2019 [9]	2	2	1	5
Datau 2010 [14]	1	2	1	4
Huseini 2013 [15]	2	2	1	5
Hussain 2017 [16]	2	2	1	5
Khonche 2019 [10]	2	2	0	4
Kooshki 2019 [8]	2	2	0	4
Mohtashami 2011 [17]	2	2	0	4
Rashidmayvan 2019 [18]	2	2	1	5
Razmpoosh 2020 [19]	2	2	1	5
Shavakhi 2015 [20]	2	2	1	5
Shoaei-Hagh 2021 [21]	2	2	1	5

Randomization: 1 point; additional 1 point would be given if the randomization method was appropriate (e.g. computer generated). Blinding: 1 point; additional 1 point would be given if the blinding method was appropriate (e.g. indetical placebo). Withdrawal: 0 is the score point for study that not in critheria of Jadad score, and additional 1 point would be given if the number of withdrawal was clear and the reasons stated.

The cure rates of fatty liver of patients in the *N. sativa* group were markedly better than those in the placebo group (OR 4.76; 95% CI, 2.52 to 8.97; $P = 0.000\,1$). The heterogeneity of the comparison was as high as 75% (I^2 = 75%).

3.3 Cardiovascular-protectant effects

3.3.1 Blood pressure The results of systolic and diastolic pressures were compared between 139 patients in the *N. sativa* group and 145 patients in the placebo group in five studies [14, 15, 18, 19, 21]. The systolic blood pressure (MD – 3.32; 95% CI, – 5.43 to – 1.22; $P = 0.002$) and the diastolic blood pressure (MD – 4.23; 95% CI, – 6.49 to – 1.97; $P = 0.000\,2$) in the *N. sativa* group showed a significant decrease, with both heterogeneity equal to 41% (I^2 = 41%) (Figure 5 and 6).

3.3.2 Lipid profile Table 3 shows the results of lipid profile data. Lipid profile outcomes included triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), and total cholesterol. According to the results summarized from the studies, the TG, LDL, and total cholesterol markedly reduced, and the HDL significantly increased in the *N. sativa* group ($P < 0.05$). However, only the total cholesterol data showed a high heterogeneity ($I^2 = 82\%$), also the highest among all.

3.4 Fasting blood glucose

Figure 7 shows the data of fasting blood glucose comparison between 156 patients in the *N. sativa* group and 156 patients in the placebo group in six articles [8, 9, 14, 18, 19, 21]. The fasting blood glucose levels of patients were significantly lowered in the *N. sativa* group (MD – 6.45; 95% CI, – 9.80 to – 3.11; $P = 0.000\,2$), with a heterogeneity as low as 42% ($I^2 = 42\%$).

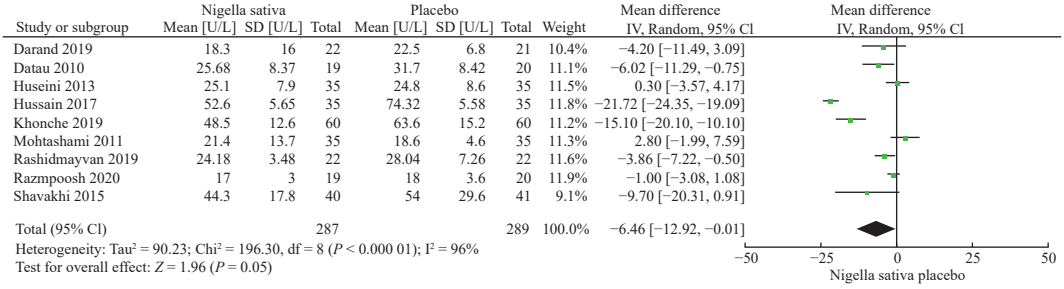

Figure 2 ALT forest plot

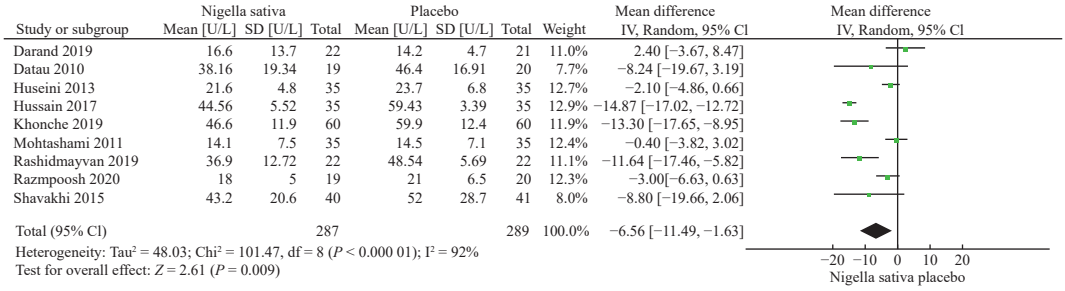

Figure 3 AST forest plot

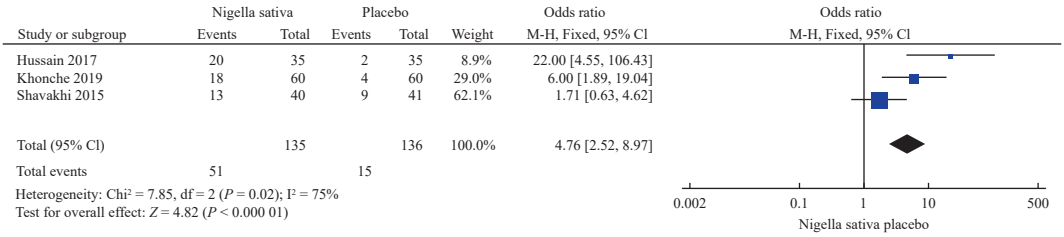

Figure 4 Cure rates forest plot

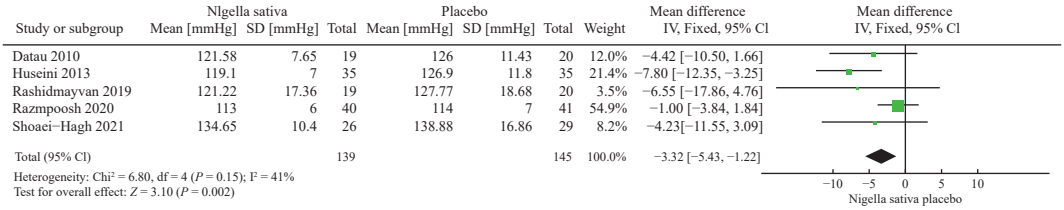

Figure 5 Systolic blood pressure forest plot

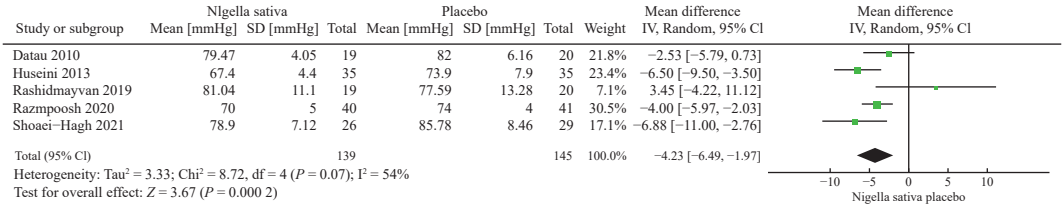

Figure 6 Diastolic blood pressure forest plot

Table 3 The results of lipid profile summarized from the included studies

Lipid profile	Case (*n*)		Study (*n*)	Pooled MD (Inverse variance)	*P* value	I^2 (%)	Favour
	N. sativa	Placebo					
TG	235	236	8	−12.14 [− 19.85 to − 4.43]	0.002 00	0	*N. sativa*
LDL	216	216	7	−6.27 [− 10.87 to − 1.74]	0.007 00	0	*N. sativa*
HDL	235	236	8	2.82 [− 1.81 to 3.84]	0.000 01	42%	Placebo
Total Cholestrol	156	156	6	−12.14 [− 19.85, − 4.43]	0.000 01	82%	*N. sativa*

TG, triglyceride; LDL, low density lipoprotein; HDL, high density lipoprotein; MD, mean difference; I^2, heterogeneity.

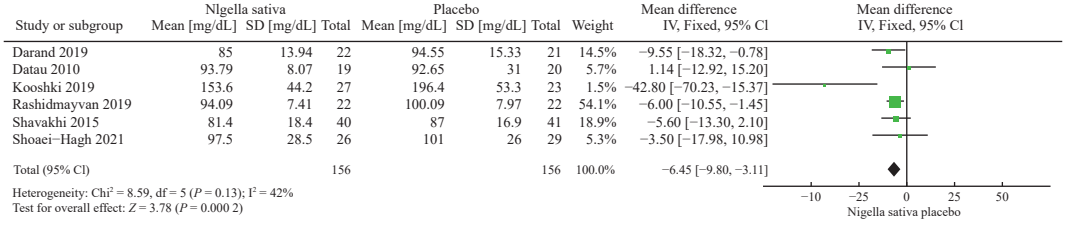

Figure 7 Fasting blood glucose forest plot

3.5 BMI and body weight measurement

Four articles [15, 16, 18, 20] reported the comparisons of BMI measurement between the two groups, without significant differences observed (MD − 0.49; 95% CI, − 1.47 to 0.49; P = 0.33) or heterogeneity reported (I^2 = 0%). Three papers [14, 16, 17] reported the results of comparisons of body weight measurement between the two groups, still without significant differences found (MD − 4.89; 95% CI, − 10.96 to 1.18; P =0.11) but that a heterogeneity as high as 70% (I^2 = 70%) (Figure 8 and 9).

4 Publication bias and funnel plot

There was no publication bias shown via Egger's test in TG (P = 0.59), LDL (P = 0.74), HDL (P = 0.10), systolic blood pressure (P = 0.15), fasting blood glucose (P = 0.13), or BMI (P = 0.81). Based on Egger's test, the AST, ALT, cure rate of fatty liver, total cholesterol, diastolic blood pressure, and body weight all showed $P \geqslant 0.05$. Figure 10 shows a symmetrical funnel plot that suggests low heterogeneity. However, different ethnic standards and interventions could lead to high heterogeneity.

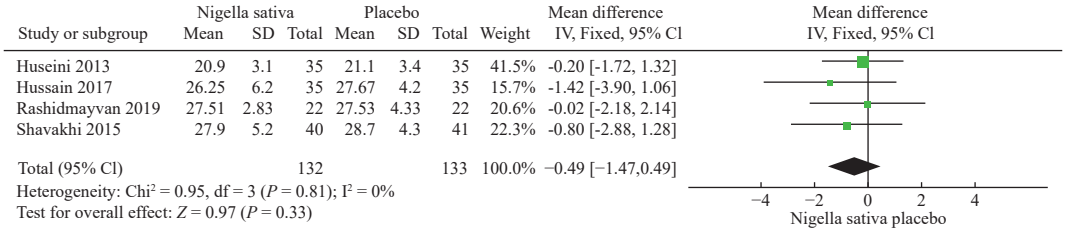

Figure 8 BMI forest plot

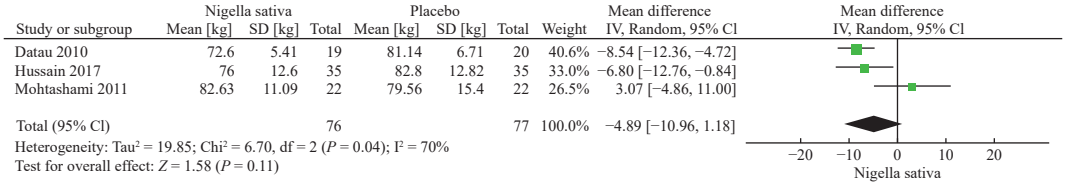

Figure 9 Body weight forest plot

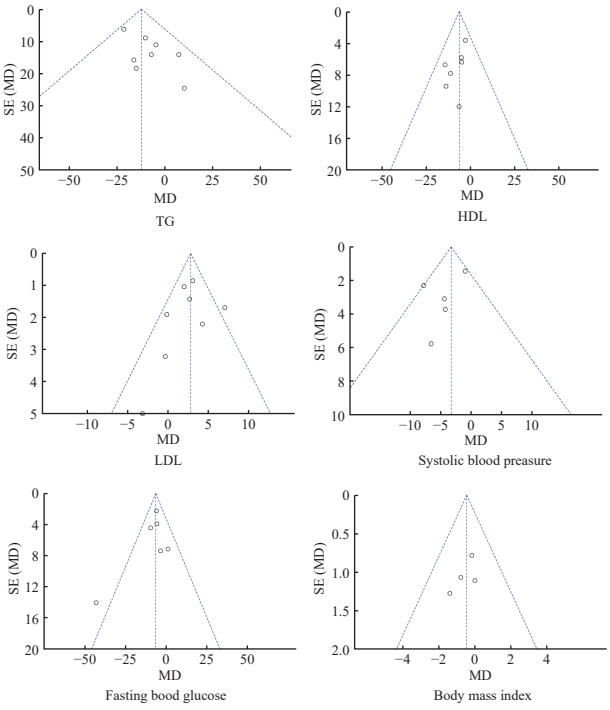

Figure 10 Funnel plot

5 Discussion

The *Ranunculaceae* family plant, known as *black seed* or *N. sativa*, grows abundantly around the world, particularly in Asia. It can be used both as a food and a medicinal herb. In the Islamic countries, the *N. sativa* seed is considered a divine medicine, as the prophet sallallahu alayhi wa sallam (SAW) had once emphasized its use. Bukhari depicts *N. sativa* a cure for all diseases. Major components of the *N. sativa* extract, including thymoquinone, dithymoquinone, thymol, and thymohydroquinone, are what forms the healing role of *N. sativa* [22-24]. Hence, we conducted a meta-analysis with the use of data retrieved from 11 RCTs with the Jaded scores ranging from 3 to 5 for the purpose of determining the hepato-protectant and cardiovascular-protectant effects of *N. sativa*. A high heterogeneity might be caused by insufficient samples or the use of different methods in each article.

It was found that *N. sativa* was effective in lowering the AST and ALT levels to protect the liver. Thymoquinone, a component of *N. sativa,* reduced the liver enzyme levels by inhibiting the oxidative stress pathway [25, 26]. Oxidative stress is one of the major causes of hepatic illnesses, which could lead to lipid peroxidation. Lipid peroxidation is manifested as hepatocyte injuries that are characterized by histological abnormalities in the liver and elevated levels of hepatic enzymes in the blood (ALT and AST). *N. sativa* extracts or its active components stimulate the cellular antioxidant systems and enhance the superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) activities as well as the gluthatione levels to relieve the oxidative stress and endoplasmic reticulum stress [26]. *N. sativa* compounds are also capable of alleviating hepatic inflammation by reducing the levels of anti-inflammatory factors such as interleukin-6 (IL-6), high-sensitivity C reactive protein (hs-CRP), tumor necrosis factor alpha (TNF-α), transforming growth factor β (TGF-β), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) , and increasing the levels of liver apoptosis markers [26-28].

The cure rate of fatty liver had a significant increase in the *N. sativa* group. It was because of the choleretic effects that the thymoquinone, monounsaturated fatty acids (MUFAs) (palmitoleic acid and oleic acid), polyunsaturated fatty acids (PUFAs) [linoleic acid (omega 6), linoleic acid (omega 3), and 11,13-eicosadecanoic acid] in the *N. sativa* had that reduced lipid accumulation in the liver [29-31]. Apart from the ability to alleviate fatty liver in patients, *N. sativa* could also prevent hepatic fibrosis by inhibiting TGF-β-induced activation of hepatic stellate cells, down-regulating the expressions of α-smooth

muscle actin, and activating the protein kinase phosphorylation of adenosine monophosphate. Some studies reported that *N. sativa* could promote the differentiation of endogenous stem cells to help the regeneration of the liver fibrotic tissues [32, 33].

Several studies have reported that *N. sativa* preparations could play an anti-dislipidemic role via lowering the TG, LDL, and total cholesterol levels, and elevating the HDL level [34, 35]. From this meta-analysis, the same result was obtained. In addition, omega-3 fatty acid content of *N. sativa* oil was found to be able to prevent the very-low-density lipoprotein cholestrol (VLDL-C) formation and apolipoprotein-B100, which could also reduce TG and LDL levels in the serum. Moreover, n-3 PUFAs, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are naturally-formed strong ligands of peroxisome proliferator-activated receptor α (PPAR-α) with the ability to facilitate fatty acid β-oxidation through a pathway that is mediated by PPAR-α , thus lowering the substrate consumption by triglyceride synthesis [36]. Such a physiological process could prevent the onset of cardiocerebrovascular events that might progress to atherosclerosis, thereby reducing the risks of atherogenic incidents in patients and protecting them from having fatty liver related diseases.

Another significant result found in this study was that the blood pressure of patients was decreased in the *N. sativa* group. This might be explained by the mechanism that the thymol in *N. sativa* could block the L-type calcium (Ca^{2+}) ion channels, thus preventing sarcoplasmic reticulum from releasing Ca^{2+} and vasodilating the blood vessels to lower the blood pressure [37]. Studies on angiotensin II-induced hypertensive rat models showed that *N. sativa* could have antihypertensive effects by counteracting the role of angiotensin via thymoquinone antagonizing the elevated systolic blood pressure and mean arterial pressure in angiotensin II [38, 39].

That fasting blood glucose lowered in the *N. sativa* group was another significant finding in this study. It is known that the continuous elevation of blood glucose would produce numerous reactive oxygen species (ROS) to encourage oxidative stress, resulting in increased insulin resistance and β-cell dysfunction, which ultimately accelerates the development of diabetes complications. Due to the lack of free-radical quenching enzymes, oxidative stress can readily destroy pancreatic beta-cells, resulting in decreased insulin output. Thymoquinone, an important antioxidant present in *N. sativa*, has the ability to neutralize free radicals. It might lessen oxidative stress and encourage the growth of pancreatic β-cell integrity, improving insulin secretion in the process [40].

Our study reported no significant difference in the comparison of BMI and body weight between the *N. sativa* and the placebo groups, which is contrary to the results from previous studies. SAFI et al. [41] suggested that *N. sativa* significantly reduce body weight, BMI, and waist circumference. Moreover, smaller appetite, less hungry feeling or even satiety could be the consequence of the administration of *N. sativa*. This might be caused by interactions of the different ingredients in *N. sativa*. In addition to a large quantity of thymoquinone, *N. sativa* oil also contains a large amount of fatty acids such as linolenic acid and palmitic acid. ASOOM et al. [42] used 800 mg/kg of powdered *N. sativa* in an effort to show its' effect in decreasing the rat weight but failed. It is recommended that a larger amount of *N. sativa* powder or extracts should be used to investigate whether *N. sativa* could decrease body weight.

6 Conclusion

In this meta-analysis study, *N. sativa* was found to play hepato-protectant and cardiovascular-protectant roles by mitigating the liver enzyme level, cure rate of fatty liver, lipid profile, blood pressure, and fasting blood glucose level. But no significant differences were observed in the comparison of body weight and BMI between patients receiving *N. sativa* and those placebos. However, these data from the existing RCTs are still insufficient, resulting in failure to predict the potential outcomes after receiving *N. sativa*. Therefore, extensive follow-up investigations are necessary to tackle the issue. Apart from this, studies on *N. sativa* are still limited, more studies should be carried out to reduce the heterogeneity.

Competing interests

The authors declare no conflict of interest.

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黑孜然的肝脏保护和心血管保护作用：一项荟萃分析

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【摘要】目的 有大量证据揭示，非酒精性脂肪性肝病患者是心血管疾病的高危人群，而心血管疾病是此类患者死亡的首要原因。本研究旨在评价黑孜然对肝脏和心血管保护作用。**方法** 采用 PRISMA 指南进行荟萃分析，于 2022 年 6 月在 PubMed、ScienceDirect、Cochrane Library 网站分别检索 2010 年 1 月至 2021 年 12 月发表的相关文献。应用 Review Manager 软件（5.3 版）对天冬氨酸转氨酶和丙氨酸转氨酶水平、血脂、血糖、体重和体重指数等指标进行统计学分析。**结果** 黑孜然能显著降低研究对象的天冬氨酸转氨酶（$P = 0.009$）和丙氨酸转氨酶（$P < 0.05$）水平。同时，黑孜然组受试者脂肪肝治愈率显著高于安慰剂组（$P = 0.000\ 1$）。此外，黑孜然组受试者的血脂、血压、空腹血糖均显著降低（$P < 0.05$）。然而，黑孜然组与安慰剂组的体重和体重指数无显著差异（$P > 0.05$）。**结论** 尽管黑孜然组和安慰剂组的体重和体重指数差异不显著，但黑孜然对非酒精性脂肪性肝病或慢性肝病患者确实具有一定的肝脏保护和心血管保护作用。

【关键词】保肝药；保心药；黑孜然；血脂；肝酶；脂肪肝