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Review Article

Potential Effects of Nigella Sativa Supplementation in Coronary Heart Disease and other Cardiovascular Diseases

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ABSTRACT

Coronary heart disease (CHD) or coronary artery disease (CAD) is considered one of the world-wide leading causes of death and is characterized by either stenosis or occlusion of coronary arteries leading to myocardial ischemia or infarction respectively. Prevention of risk factors, improvement in biomarker levels and control of CHD are described as a strategic plan for Saudi Vision 2020-2030. Given the beneficial healthy effects of Nigella sativa (N. sativa), and since it is known that the anti-inflammatory and antioxidant effects of N. sativa are interconnected, the objective of this review is to compile and elucidate the potential role of N. sativa and its highly potential component thymoquinone (TQ) in CHD and other cardiovascular diseases. Since studies are rare for understanding the mode of action of N. sativa and TQ, the present review and articles for previous studies were searched through PubMed/Medline, Web of Science, Scopus, and Google Scholar databases using relevant keywords. The available randomized clinical trials (RCTs) that examined the effect of N. sativa supplementation on CHD and other cardiovascular diseases were mainly included. Serum parameters, including mainly the inflammatory markers, lipid profile, serum creatinine, leptin, resistin, ESR, hsCRP, vitamin D and other clinical, pathophysiological and biochemical factors, are discussed in association with the N. sativa supplementation in patients with CHD and other cardiovascular diseases. The present review helps understand the beneficial effects of N. sativa in coronary heart disease and other cardiovascular diseases and explores the underlying mechanisms explaining how N. sativa reverts cardiovascular complications back towards normality.

1. INTRODUCTION

The World Health Organization (WHO) data shows 17.9 million people die due to cardiovascular disease (CVD) each year, and dyslipidaemia is considered the most important atherosclerotic risk factor leading to CVD progression is significantly associated with more than half of the cases with ischemic heart disease world-wide (The World Health Report, 2002; Gupta et al., 2017). Non-HDL-C has been given much importance than determining low-density lipoprotein cholesterol (LDL-C) since non-high-density lipoprotein cholesterol (non-HDL-C) determinations provide a better picture of the association of CHD risk (Liu et al., 2006).

Prevention of risk factors, improvement in biomarker levels and control of CHD have been employed as strategies for Saudi Vision 2020-2030. The present review and innovative descriptions would provide information about the effect of N. sativa in controlling CHD.

Plants as medicine have been used as a therapeutic intervention for a variety of diseases because of their valuable activities as a natural therapy for more than 4000 years (Fong, 2002; Dattner, 2003; Oskouei et al., 2018). N. sativa., black seed or black cumin, is an annual herb and a herbaceous plant used as a traditional remedy in Arab countries, Iran and India, and is about 8-10 inches in height and highly cherished medicinal species belonging to the Ranunculaceae family a dicotyledonous bushy plant with specific characteristics of white or pale to dark blue coloured solitary and self-pollinating flowers, pinnate and segmented leaves and capsule fruits with numerous trigonal seeds (Akram & Afzal, 2016). Seeds of N. sativa give a specific aroma, a bitter and peppery taste (Sturtevant & Hedrick, 1972; Gharby et al., 2015) and are used in herbal medicines. The name of N. sativa was derived from the appearance of its small (1-5 mg in weight) dark grey to black colour seeds (Kokoska et al., 2008). Fruit capsules of N. sativa open and the black seeds are dispersed in the air (Schleicher & Saleh, 1998). The N.

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sativa oil and thymoquinone (TQ) in black seed decrease arterial blood pressure and heart rate and have beneficial effects on CAD, stroke and peripheral vascular disorders (Leong et al., 2013). N. sativa causes cardiac depression through central mechanisms of the vasomotor centre in the medulla and sympathetic outflow towards the periphery rather than to nitric oxide or eicosanoid (Leong et al., 2013).

Because of the beneficial, healthy effects of N. sativa, the present review was compiled to elucidate the potential role of N. sativa and its highly potential component TQ in CHD. The relevant published articles were searched through PubMed/Medline, Web of Science, Scopus, and Google Scholar databases using relevant keywords. The available randomized clinical trials (RCTs) that examined the effect of N. sativa supplementation on CHD and other cardiovascular diseases were mainly included.

2. CORONARY HEART DISEASE (CHD)

CAD or CHD is one of the worldwide leading causes of death. The World Health Organization (WHO) reports show that 46 % of deaths are due to CHD and 31% of deaths due to cardiovascular diseases across the globe. This situation may worsen in future since various uncontrollable risk factors, mainly diabetes, smoking, obesity, hypercholesterolemia, hypertension etc have been enormously increasing. Hence, future consequences of CAD might be quite alarming (Mack & Gopal, 2016). Changes produced by NSS supplementation in CHD and associated risks have been noticed in several studies (Dehkordi & Kamkhah, 2008; Seif, 2013; Haas et al., 2014; Al Asoom, 2017; Oskouei et al., 2018; Ghoreyshi et al., 2020), that emphasize to review the beneficial effects of N. sativa.

It is known that myocardial ischemia can trigger myocardial damage, life-threatening ventricular arrhythmias, and other damaging conditions. The ROS products may cause a decrease in antioxidant activity, lethal ventricular arrhythmias and tissue injury after reperfusion of the ischemic myocardium (Oskouei et al., 2018). ROS has potential significance in the pathophysiology of myocardial infarction (MI) (Rona, 1985; Ojha et al., 2012), and it has been investigated that post-ischemia ROS production and decrease in antioxidant task cause tissue dysfunction and ventricular arrhythmias (Moens et al., 2005). The N. sativa is promising for normalizing vascular inflammation and endothelial functions by affecting oxidative markers (Tavakoli-Rouzbehani et al., 2022), coronary angiogenesis (Al Asoom et al., 2017), reduction of C-reactive protein and lipid peroxidation (Kooshki et al., 2020).

It was found that N. sativa has antioxidant activity and revealed that postconditioning (PoC) for N. sativa can decrease ischemia-reperfusion injury by reducing the formation of ROS and leading to improvement in the myocardial oxidative stress conditions (Ghoreyshi et al., 2020). Kidney function dysfunction occurs with an increased risk for CVD (Hall, 1999). CVD risk is increased partly due to the higher prevalence of older age, diabetes, hypertension, oxidative stress and dyslipidemia (Culleton et al., 1999). Serum creatinine is also an indicator of insulin, hence, diabetes mellitus is associated with CAD (Rasouli et al., 2005; Harita et al., 2009; Hoseinin & Rasouli, 2009). Serum creatinine was found to be associated with pre-inflammatory markers such as Lp(a), apoAI and hsCRP (Rye et al., 2004; Onat et al., 2013), and independent relation with CAD (Onat et al., 2013). Elevated levels of leptin (Myers et al., 2010; Karbowska & Kochan, 2012) and resistin (Zhang et al., 2003; Reilly et al., 2005) were shown to be associated with increased BMI. This shows that these adipokines might have diagnostic importance in CHD with/ without obesity.

Accumulation of free radicals, membrane lipid peroxidation, and DNA damage mainly related to CHD and other atherosclerotic disorders (Violi et al., 2017; Pignatelli et al., 2018). It is further known that control of cellular detoxification of various exogenous toxins is carried out by Glutathione-S-transferases (GSTs) (Singh, 2015) that perform anti-oxidation activity and protect cells against oxidative stress and related DNA damage (Zhang et al., 2014). Whereas the N. sativa extract is considered a potent inducer of apo A-I gene expression, and hence, it has beneficial effects in treating dyslipidemia and CHD (Haas et al., 2014). Furthermore, it has been reported that N. sativa detoxifies through glutathione and GSTs, reduces aflatoxin (AF) () B1-DNA adducts, and protects against inhibition of DNA damage (Ates et al., 2021; Farshori et al., 2021). Several of the mentioned changes in CHD and cardiometabolic functions might be normalized via N. sativa supplementation (Ahmad et al., 2013; Haas et al., 2014; Shafiq et al., 2014; Asgary et al., 2015; Al Asoom et al., 2017; Kooshki et al., 2020; Razmpoosh et al., 2021; Shoaei-Hagh et al., 2021; Tavakoli-Rouzbehani et al., 2021, 2022; Emamat et al., 2022; Rashidmayvan et al., 2022).

3. NIGELLA SATIVA

Nigella sativa has been considered an herb having healing properties. Hence, it has been in use for centuries as an anti-inflammatory, hypotensive, immune-potentiating and has various other uses as a remedy and benefits for health (Akram & Afzal, 2016). The N. sativa is mostly distributed in Southern Europe, North Africa, and Asia Minor. Its originating countries are in the south and east Mediterranean Sea to India, Pakistan and Iran (Gharby et al., 2015). Furthermore, N. sativa has an amazing rich religious and historical background (Goreja, 2003).
N. sativa was used as a condiment and spice product (Cheikh-Rouhou et al., 2008; Kiralan et al., 2014; Maulidiani et al., 2015), for preparing dietary supplements and functional cosmetics (Kiralan et al., 2014; Pop et al., 2018) and for various medical disorders (Tariq, 2008; Bocşan et al., 2018; Mousavi et al., 2018; Neag et al., 2018). For obtaining information about the effect of N. sativa supplementation on obesity and obesity indices, a systematic review and meta-analysis were conducted to systematically review the available randomized clinical trials (RCTs) to see the effects of N. sativa on bodyweight (BW), body mass index (BMI), and waist circumference

(WC) in adults (Mousavi et al., 2018). A significant effect of N. sativa supplementation on BW and BMI was found in adults. However, the effect of N. sativa supplementation on WC was not found to be significant in this meta-analysis (Mousavi et al., 2018).

It has been documented that N. sativa has more than a hundred compounds (Khan et al., 2016; Pop et al., 2018) and is used in a mixture form or bioactive metabolites (Gilani et al., 2001; Ait Mbarek et al., 2007; Ahmad et al., 2013, 2021) shows potential health benefits. The curative and therapeutic features of N. sativa and its large number of components/ compounds, presenting N. sativa as a cytoprotective medicinal plant used for the prevention and treatment of many complicated diseases, and functional and disease-related effects of N. sativa were reviewed in detail (Khan et al., 2016). A comprehensive review of the pharmacological effects and mode of action of various components was described for various clinical conditions and disorders (Pop et al., 2018). The crude extracts of NSS were found to have spasmolytic and bronchodilator properties in their organic components, possibly by blocking the calcium channels (Gilani et al., 2001). While studying to determine in vitro and in vivo anti-cancer effect of NSS extracts in mouse models, it was revealed that the administration of NSS into the tumour site caused inhibition of the incidence of liver metastasis development and resultantly led to improvement in survival (Ait Mbarek et al., 2007). The NSS has been widely used as an antihypertensive, diuretic, liver tonic, appetite stimulant, anti-diarrheal, antibacterial, analgesic, antidiabetic, immunomodulator, anti-inflammatory, bronchodilator, spasmolytic, hepato-protective, gastro-protective, reno-protective, antioxidant, and having a variety of other effects (Ahmad et al., 2013, 2021). Owing to the significant involvement of oxidative stress and dyslipidemia in CHD, the hypolipidemic effect of N. sativa. administration was investigated in diet-induced hypercholesterolemia (Fatima et al., 2007). Significantly reduced levels of TC, triglyceride and LDL-C and elevated levels of HDL-C were investigated. Furthermore, beneficial effects were seen for serum levels of glucose, alanine transaminase (ALT), aspartate transaminase (AST) and the antioxidant glutathione (GSH), which suggested the cardioprotective and antiatherogenic effects of dietary N. sativa supplementation in experimentally induced hypercholesterolemia (Fatima et al., 2007).

It was noted that most of the beneficial effects of NSS are due to thymoquinone, that is a major bioactive component in NSS (Ahmad et al., 2013; Srinivasan, 2018; Mazaheri et al., 2019; Majdalawieh et al., 2021). : The main constituents of N. sativa NS have been extensively reported previously (Mamun& Absar, 2018). These are : 30-40 % crude fat (fixed and volatile oil containing a wide range of fatty acids such as linoleic, oleic, linolenic and palmitic acids), 20-30 % crude protein, 5-10 % crude fibre and potassium, sodium, magnesium, phosphorus, calcium and other minerals.

The most important bioactive ingredients in N. sativa are thymoquinone, phytosterols, nigellone, vitamins, fatty acids and minerals (Amin et al., 2016; Mamun & Absar, 2018). It has been studied that most of the potential effects in N.sativa are due to main seed essential oil constituent thymoquinone (TQ) (an important active constituent in both volatile and fixed oil) (Cheikh-Rouhou et al., 2007; Ahmad et al., 2013; Gholamnezhad et al., 2016; Srinivasan, 2018; Oskouei et al., 2018; Mazaheri et al., 2019; Majdalawieh et al., 2021). N. sativa seeds contain monoterpenes, sesquiterpenes and derivatives (Pop et al., 2018), and indazole alkaloids, saponins (Mehta et al., 2009), cycloartenols (Mehta et al., 2009) and flavonoids (Mehta et al., 2009; Maulidiani et al., 2015). The biological activity of N. sativa is mainly due to volatile oil compounds, especially TQ (Burits & Bucar, 2000; Padhye et al., 2008). Hydrodistillation, microwave-assisted extraction, super critical fluid extraction, and the Botnick method are used for obtaining the essential oil of N. sativa (Liu et al., 2011; Botnick et al., 2012; Kalidasu et al., 2017). Whereas non-volatile compounds in N. sativa are isoquinoline alkaloids e.g. nigellicimine and pyrazol alkaloids, nigellidine and nigellicine, saponins, carbohydrates, fatty acids, proteins, fixed oils, phenolic compounds, and calcium, potassium and iron (Al-Gaby, 1998; Forouzanfar et al., 2014; Tavakkoli et al., 2017).

N. sativa has been found effective for the treatment of other conditions/ disorders, including: toothache, flatulence, as a choleretic, anti-spasmodic and uricosuric (Pourbakhsh et al., 2014), anti-inflammatory (Al-Ghamdi, 2001; Hajhashemi et al., 2004), anti-oxidant (Mansour et al., 2002; Kanter et al., 2006; Uz et al., 2008), anti-asthmatic, anti-diabetic, anticancer (Le et al., 2004; Ait Mbarek et al., 2007; Boskabady et al., 2010; Periasamy et al., 2016; Mollazadeh et al., 2017), analgesic (Bashir and Qureshi, 2010; Parvardeh et al., 2018), anti-tumor, and anti-tussive activities (Machmudah et al., 2005; Parvardeh et al., 2005; Ait Mbarek et al., 2007; Hosseinzadeh et al., 2008), anticonvulsant (Hosseinzadeh and Parvardeh, 2004), obesity, nasal congestion, back pain, hypertension, amenorrhea (Ziaee et al., 2012), infections, and intestinal worms (El-Dakhakhny, 1965; Schleicher and Saleh, 1998; Al-Rowais, 2002; Goreja, 2003), anti-microbial ((Kokoska et al., 2008; Forouzanfar et al., 2014; Rafati et al., 2014), hypoglycemic (Kaleem et al., 2006; Meddah et al., 2009) and antilipidemic/ anti-hyperlipidemic (Hawsawi et al., 2001; Bamosa et al., 2002; Ali et al., 2003; Kooti et al., 2016), metabolic (Meddah et al., 2009; Razavi et al., 2014; Hadi et al., 2016), dermatological (Boca, 2018), endocrine, immune, respiratory and cardiovascular (Hosseini et al., 2017; Tavakkoli et al., 2017), as a protective agent against ethanol induced toxicity (Hosseini et al., 2017); an anti-aging agent (Shahroudi et al., 2017) and a protective agent against natural or chemical toxins (Tavakkoli et al., 2017).

4. NIGELLA SATIVA AND CARDIOVASCULAR DISEASES

Studies carried out in acute and chronic models reveal that the anti-inflammatory and antioxidant effects of N. sativa are interconnected (Halliwell et al., 1988; Stadtman, 2004). Cardiovascular disease is a leading cause of death worldwide (Prabhakaran et al., 2016). It is mainly

related to the factors of increased serum cholesterol levels, hypertension, smoking, increased LDL/ LDL oxidation, high platelet aggregation, etc. (Rahman & Lowe, 2006) and oxidative stress relating to hypertension, atherosclerosis, heart failure, ischemia-reperfusion and cardiac hypertrophy (Cave et al., 2006).

The mechanism of BP lowering effects of N. sativa in humans has shown a reduction in both systolic and diastolic BP (Sahebkar et al., 2016). The antihypertensive effect of N. sativa in humans and animals is quite convincing (Khattab & Nagi, 2007; Dehkordi & Kamkhah, 2008). N. sativa enhances Na+, K+, and Cl- excretion (Zaoui et al., 2000) and the thymol extracts cause negative inotropic activity on canine and guinea pig-isolate cardiac preparations (Szentandrássy et al., 2004). TQ helps improve endothelial functions by decreasing oxidative stress and improving the expression of eNOS (Ahmad et al., 2013).

The N. sativa has been shown to lower serum cholesterol in animal models and has beneficial effects for treating dyslipidemia (Haas et al., 2014). N. sativa affects the lipid profile by reducing serum LDL cholesterol, total cholesterol and triglycerides and increases HDL cholesterol (Li et al., 2004; Nadir et al., 2010; Shafiq et al., 2014) and has beneficial effects in hypercholesterolemia (Sabzghabaee et al., 2012) with decrease in triglyceride and LDL-cholesterol levels and an increase in HDL-cholesterol (Bhatti et al., 2009). The ameliorative actions of N. sativa are on dyslipidemia or hyperlipidemia (Asgary et al., 2015).

It was revealed that N. sativa oil causes improvement in vascular nitric oxide (NO) and flow-mediated dilation (FMD) (Emamat et al., 2022). However, further studies are required to confirm the influence of N. sativa oil on vascular inflammation (Table 1). Several related reports are given in Table 1. Use of N. sativa oil as medication in CVD patients with hypertension but no hepatic, renal or patient-reported adverse effects showed antihypertensive effects and beneficial control of glucose and lipid metabolism (Shoaei-Hagh et al., 2021). Another report did not find any apparent beneficial effects of N. sativa oil administration for the duration of eight weeks (1000 mg/day) in patients with non-alcoholic fatty liver disease (NAFLD) (Rashidmayvan et al., 2022). Higher doses for longer duration may clarify the effect N. sativa. Beneficial effects of N. sativa supplementation in adults with obesity and overweight status lead to the overall improvement in CVD risk factors (Razmpoosh et al., 2021).

Table 1: Selected representative reports on the potential effects of N. sativa supplementation in CHD and other cardiovascular diseases/ risk factors.

Cardiovascular diseases (CVD)	Type of study	Investigations
CVD risk factors	Randomized controlled trial	N. sativa (NS) oil improves vascular nitric oxide (NO) and flow-mediated dilation (FMD) (Emamat et al., 2022).
Hypertension with CVD risk factors	Randomized, double-blind, placebo-controlled-trial	Use of N. sativa seeds oil showing antihypertensive effects, and beneficial effects on glucose control and lipid metabolism in hypertensive patients (Shoaei-Hagh et al., 2021).
Cardiometabolic outcomes in patients with non-alcoholic fatty liver	Randomized double-blind, placebo-controlled-trial	No favourable effect of N.sativa oil (NSO) (1000 mg/day for 8 weeks) on cardiometabolic measures in non-alcoholic fatty liver disease (NAFLD) (Rashidmayvan et al., 2022).
CVD risk factors in obese and overweight women	Crossover, double-blind, placebo-controlled randomized trial	Beneficial effects of N.S supplements among adults with obesity to prevent possible cardiovascular diseases. (Razmpoosh et al., 2021
Cardiovascular disease risk factors in patients with type 2 diabetes mellitus	Double-blind randomized clinical-trial	The NSO supplement has cardiovascular protective effects in patients with diabetes type-2 (T2DM), by improving the lipid profile, glycemia, and by reducing the C-reactive protein level and the lipid peroxidation (Kooshki et al., 2020)
Coronary artery disease	Randomized, double-blind, placebo-controlled clinical-trial	It suggests a potential beneficiary effect of NS on the metabolic parameters in CAD patients including improvements in anthropometric indices, blood pressure, and FBS (Tavakoli-Rouzbehani et al., 2021)
	randomized, double-blind, placebo-control clinical-trial	NSO supplementation demonstrated a potential beneficial effect on endothelial function by reducing ICAM-1, VCAM-1 levels & affecting oxidative markers. (Tavakoli-Rouzbehani et al., 2022)
Coronary heart disease CHD) prevention	Experimental animal-study	It demonstrated an increase in VEGF and a decrease of the VWF in the hearts of Nigella-fed

		and exercise-trained rats. This might indicate the potentiality for induction of coronary angiogenesis via long-term administration of NS and exercise training. (Al Asoom et al., 2017)
Hyperlipidemia/ dyslipidemia and CHD	Comparative animal-study	NS & simvastatin showed comparable effects in treatment of hyperlipidemia. NS showed protective role in terms of hepatic dysfunction and can be used as a cholesterol lowering agent (Muneera et al., 2015)
	Cell line study for Inducing apolipoprotein A-I gene expression	NSS is a potent inducer of apo A-I gene expression, presumably by enhancing PPARα/RXRα expression. It has beneficial effects in treating dyslipidemia and CHD (Haas et al., 2014)

Beneficial effects of N. sativa supplementation was obtained in patients with type-2 diabetes mellitus having cardiovascular disease risks by improving the lipid profile and glycemia and decreasing lipid peroxidation and C-reactive protein (CRP) (Kooshki et al., 2020). The patients with CAD revealed beneficial effects of N. sativa on anthropometric indices, fasting blood sugar (FBS), blood pressure (BP) and metabolic parameters (Tavakoli-Rouzbehani et al., 2021). It was found that the N. sativa oil supplementation showed beneficial effect on endothelial cells that decreased intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion protein 1 (VCAM-1) levels and affected oxidative markers and hence influencing the oxidative markers (Tavakoli-Rouzbehani et al., 2022). CHD prevention was achieved by producing coronary angiogenesis with long-term N. sativa supplementation (Al Asoom et al., 2017). Treatment of Hyperlipidemia/ dyslipidemia with CAD was obtained using N. sativa supplementation (Haas et al., 2014; Muneera et al., 2015) (Table-1).

Table 1 provides the following further information that some of the potential RCTs conducted for the duration of two months with the daily oral dosages of NSS oil having beneficial effects via:
Improving the vascular nitric oxide (NO) activity and brachial flow-mediated dilation (FMD) without significant change in intracellular adhesion molecule-1 (ICAM-1) and vascular cellular adhesion molecule-1 (VCAM-1) levels in patients with CVD risk factors (Emamat et al., 2022).
Significantly reducing SBP, DBP, total cholesterols (TC), and low-density lipoprotein (LDL), malondialdehyde (MDA) and fasting blood sugar (FBS), and significantly increasing high-density lipoprotein (HDL) and glutathione reductase (GR) (Shoaei-Hagh et al., 2021).
Increasing serum HDL-C and reducing levels of LDL-C, TC/HDL-C ratio, serum glutamic-oxaloacetic transaminase and systolic blood pressure, though without any considerable effect on diastolic blood pressure measures. (Razmpoosh et al., 2021).

Decreasing the FBS, triglyceride, TC, LDL-C, serum hs-CRP, MDA and increasing HDL-C in the intervention group compared with the placebo group. (Kooshki et al., 2020).
Significantly reducing the weight, body mass index, waist circumference, hip circumference, waist-to-hip ratio, SBP, DBP, and FBS compared to the placebo group (Tavakoli-Rouzbehani et al., 2021).
Decreasing significantly the serum levels of VCAM-1, ICAM-1, and MDA while increasing the total antioxidant capacity (Tavakoli-Rouzbehani et al., 2022).
The experimental studies in rats showed the beneficial effects of N. sativa via:
Increasing significantly the levels of VEGF in rats (Al Asoom et al., 2017).
Improving significantly the lipid profile in rats (Muneera et al., 2015).

However, one major randomized, double-blind, placebo-controlled trial in patients with cardiometabolic complications along with non-alcoholic fatty liver disease (NAFLD) administered with NSS oil for eight weeks did not show statistically significant differences in serum levels of adiponectin, leptin and SBP and DBP (Rashidmayvan et al., 2022). Hence, it was suggested that further studies with higher dosages over a longer period to investigate whether this effect is dose- and time-dependent. A meta-analysis revealed that N. sativa supplementation in humans may be beneficial as an antioxidant via increasing the levels of superoxide dismutase (SOD) but shows no significant effect on the level of total antioxidant capacity (TAC) and MDA (Ardiana et al., 2020). There are other studies associated with the supplementation of N. sativa that did not reveal any significant change in the levels of MDA, TAC and glutathione peroxidase (GPx) (Kaatabi et al., 2015; Namazi et al., 2015; Hadi et al., 2016; Nikkhah-Bodaghi et al., 2019).

5. NIGELLA SATIVA AND CORONARY HEART DISEASE

The N. sativa has been shown to lower serum cholesterol in animal models and has beneficial effects in treating CHD via inducing apo A-1 gene expression by increasing the expression of PPARα/RXRα (Haas et al., 2014). The N. sativa seeds are used for natural therapy and prevention for ischemic heart disease with confirmed dyslipidemia as a risk factor (Asgary et al., 2015), leading to lipid-lowering effects of N. sativa to be due to the absorption of intestinal cholesterol absorption/drop in the synthesis of hepatic cholesterol and upregulation process for LDL receptors. An increase in vascular endothelial

growth factor (VEGF) and a decrease of the Von Willebrand factor (VWF) in the hearts of Nigella-fed rats indicated the potential induction of coronary angiogenesis by long-term N. sativa administration (Al Asoom, 2017). Beneficial effects of N. sativa on cardiac functioning have been shown in human and rat studies (Khattab & Nagi, 2007; Dehkordi & Kamkhah, 2008). Long-term treatment with N. sativa showed increased peak force of cardiac contraction, myocardial flow rate and rate of tension development that revealed positive cardiac adaptation for long-term N. sativa administration (El-Bahai et al., 2009). Structural remodelling of the myocardium for myocardial hypertrophy and increased diameter of cardiomyocytes was also demonstrated (Al-Asoom LI et al., 2014). Hypertrophied hearts were studied for the effect of N. sativa using histological and electrophysiological techniques (Al-Asoom LI et al., 2014), and it was shown that orally induced N. sativa for three months in rats revealed a protective effect of N. sativa against the ischemia-reperfusion insult in the rat hearts (Seif, 2013). The oxidative stress serves as a trigger for the damage of the heart during the process of oxidative reperfusion (I/R) injury, whereas PoC is used to decrease the resulting conditions of ischemia in reperfusion. Considering this known information, the well-known antioxidant activity of N. sativa was studied recently to investigate whether PoC for N. sativa can decrease ischemia-reperfusion injury via decreasing ROS (reactive oxygen species) formation (Ghoreyshi et al., 2020). The results showed antioxidant properties of N. sativa leading to NS-PoC ameliorating the cardiac activity in isolated heart during I/R in rat via improvement in the myocardial oxidative stress conditions (Ghoreyshi et al., 2020).

Studies carried out in the heart and various other organs and body systems confirming N. sativa as a potential treatment approach for ischemic disorders emphasize carrying out further studies and understanding the exact mechanism of action of N. sativa (Oskouei et al., 2018). The TQ is an important component of N. sativa has a potential influence on myocardial IRI since it decreases the infarct size and arrhythmia score, ventricular tachycardia and ventricular fibrillation (Oskouei et al., 2018).

It has been investigated that antioxidants decrease infarct rate, myocardial dysfunction and occurrence of MI (Goyal et al., 2010; Agrawal et al., 2014). The TQ administration (intraperitoneal 10 mg/kg) in anaesthetized rat was found effective in preserving myocardial IRI-induced lethal ventricular arrhythmias (Tappia et al., 2001; Tullio et al., 2013; Goncaand, Kurt, 2015).

Since ROS has potential significance in pathophysiology of MI (Rona, 1985; Ojha et al., 2012), and it has been investigated that post-ischemia ROS production and decrease in antioxidant task cause tissue dysfunction and ventricular arrhythmias (Moens et al., 2005), the TQ like several other herbal antioxidants IRI (Marczin et al., 2003; Ojha et al., 2008; Frank et al., 2012; Zhang et al., 2014) that has beneficial effects in MI has shown protective effect in myocardial IR damage in rat (Gonca E, Kurt, 2015), causes decrease in oxidative stress in MI in rat model with chronic treatment for maintaining the activity of antioxidant enzymes in isoproterenol-induced MI (El Tahir et al., 1993), reduces heart rate and arterial blood pressure (El Tahir et al., 1993) and shows cardiovascular activity in in vitro studies leading to control of arterial force and rate of constriction intercede via blocking voltage-gated calcium channels (Ghayur et al., 2012). However, there are reports documenting no efficacy of N. sativa found for normalizing the BP or the required outcomes in patients with CHD (Qidwai et al., 2009; Bin Sayeed et al., 2013; Kaatabi et al., 2015; Namazi et al., 2015; Hadi et al., 2016; Nikkhah-Bodaghi et al., 2019; Ardiana et al., 2020; Hadi et al., 2021; Rashidmayvan et al., 2022; Kavyani et al., 2023).

A randomized, double-blind trial was carried out to study the effect of oral NSS (1000 mg/day) that did not show any significant change in BP, FBS, and serum levels of lipids, alanine aminotransferase, and creatinine because of the small sample size. A larger study with adequate sample size was recommended (Qidwai et al., 2009). A randomized controlled trial did not show any significant change for the supplementation of N. sativa (500 mg twice daily) in the biochemical cardiac markers (TC, triglycerides and HDL-C, very low-density lipoprotein (VLDL), and low-density lipoprotein (LDL) cholesterol, creatine kinase- myocardial band (MB) and SBP and DBP during nine-week study duration (Bin Sayeed et al., 2013). After eight weeks of supplementation with N. sativa oil, no statistically significant differences were found in SBP and DBP (Rashidmayvan et al., 2022). No significant effect on the level of total antioxidant capacity (TAC) and MDA could be obtained after N. sativa supplementation (Ardiana et al., 2020). Supplementation of N. sativa did not show any significant change in the levels of MDA, TAC and glutathione peroxidase (GPx) (Kaatabi et al., 2015; Namazi et al., 2015; Hadi et al., 2016; Nikkhah-Bodaghi et al., 2019).

A randomized controlled clinical trial revealed that HDL-C and homeostatic model assessment for insulin resistance (HOMA-IR) did not change significantly after N. sativa supplementation (500 mg per day) for eight weeks. Hence, it was suggested to carry out further long-term trials to confirm the therapeutic efficacy/benefits of N. sativa (Hadi et al., 2021). Furthermore, a review study conducted to determine the effect of N. sativa supplementation on inflammatory and oxidative markers in adults quite associated with the development of coronary heart disease showed no significant decrease in the levels of interleukin 6 (IL-6) (Kavyani et al., 2023).

The above description reveals that most reports indicate the beneficial effects of N. sativa supplementation in CHD. However, though some other reports provide evidence of no change in cardiac markers, antioxidant activity, and inflammatory and oxidative markers, quite a few studies directly point out the absence of the beneficial effect of N. sativa supplementation. Considering these reports altogether, it is suggested that N. sativa supplementation is generally beneficial for patients with CHD, though it is also suggested for carrying out further studies

with long-duration N. sativa supplementation of higher dosages.

6. CONCLUSION AND RECOMMENDATION

Cardiovascular diseases are managed by a variety of synthetic therapeutic products. However, inefficacy, side effects and pharmacokinetic situations incline us to use and predict the effects of natural alternative therapies, including the use of Nigella sativa or black cumin, a medicinal plant with rich bioactive compounds and other traditional approaches (Pop et al., 2020). It is quite interesting to note that N. sativa and its components show effective pharmacological and antioxidant responses for all cardiovascular risk factors (Pop et al., 2020).

The mechanism of action of N. sativa has been proposed. It decreases the synthesis of cholesterol by hepatocytes decreases its adsorption from the small intestine (de Jong et al., 2003). It stimulates cholesterol secretion in bile (Bamosa et al., 2002). Whereas the antioxidant components of N. sativa can prevent non-enzymatic lipid peroxidation, an important factor involved in atherosclerosis (Kanter et al., 2005). N. sativa decreases the foam cell formation in the blood vessel wall accelerates the local inflammatory response resulting to atherosclerotic plaque formation (Shabana et al., 2013). TQ has been found to improve high cholesterol in the blood and prevent the formation of plaques by decreasing oxidative stress and lipid profile (Ragheb et al., 2008).

It is known that oxidative stress and inflammation are responsible for vascular damage common to hypertension, hyperlipidemia, diabetes, CHD and several other diseases. Controlling these pathologies is of fundamental requirement and importance as they can degenerate into CVDs, which are the main cause of death the world over. The present review provides interesting information that encourages the clinical use of N. sativa particularly for CHD and other cardiovascular diseases.

Medicinal plants are used as alternative treatment therapies in a variety of chronic disorders because of their lower cost and reduced side effects. Within this study, the potential anti-inflammatory and antioxidant effects of N. sativa in relation to different types of chronic conditions are planned to be investigated. Since both inflammation and oxidative stress are highly interconnected pathophysiological processes influencing themselves, the most recent methods in regard to the experimental settings have been employed. Literature indicates that the use of black cumin in its different forms (as seeds, oil, or different extracts) can be used successfully to treat various inflammatory disorders. It was revealed that because of its pharmacological activities like antioxidant, anti-inflammatory and pro-apoptotic, N. sativa can be a valuable product against cardiovascular and related diseases.

It is suggested that further studies with the supplementation of high dosages of N. sativa for a longer duration must be carried out. The N. sativa effect on coronary angiogenesis needs to be explored further as it might lead to a new promising preventive and therapeutic agent for ischemic heart disease. Previous studies indicate cardiac adaptation to long-term administration of NS. Further studies with long duration will hopefully help understand the beneficial effects of N. sativa in coronary heart disease and explore the underlying mechanisms explaining how various complications lead to CHD and how N. sativa reverts these changes back towards normality.

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