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Potential of Thibbun Nabawi Habbatusauda (*Nigella sativa*); Review of the Active Pharmacological Timoquinone

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ABSTRACT

Habbatusauda or Black Seed or Black Cumin (Nigella sativa) has been widely mentioned in various Islamic studies, including its potential as a "cure for all diseases except death. The hadith can be interpreted as improving immunity and enhancing memory (physical and cognitive aspects). Scientifically, the high content of thymoquinone and DHA in Black Seed plays a major role as an immunomodulator and brain nutrition. Black Seed contains both hydrophilic and lipophilic compounds. Amino acids, proteins, carbohydrates, essential oils, fixed oils, sterols, alkaloids, saponins and crude fiber, and minerals, thymoquinone, p-cymene, longifoline thujene, carvacrol, cubebene, pinene, limonene, pinene, sabinene are the ingredients. Timoquinone is present at a concentration of 3.5-8.7 mg/g in oil. Black Seed Oil is also high in DHA (3%). The content of the active compound Timoquinone is most responsible for its wide range of effects.

KEYWORDS: *Habbatusauda, Nigella sativa, Thibbun Nabawi*

INTRODUCTION

Black Seed (Nigella sativa) belongs to the Ranunculaceae family and is an annual herbaceous plant that grows in many parts of southern Europe and parts of Asia, including Syria, Turkey, Saudi Arabia, Pakistan and India. It can grow up to 30 cm and produces pale blue flowers. The fruit consists of a follicle that contains the seed, the most useful part of the plant. Nigella sativa (NS) seeds, which have a sharp bitter taste, are used in confectionery and liquor (Shuid, 2012)

So far, several chemical compounds have been extracted and identified from different Nigella species. N. sativa contains protein, fat, ash, fiber, free nitrogen extract, iron, copper, zinc, phosphorus, calcium, thiamin, niacin and folic acid per kg. In addition, studies have shown the presence of different active ingredients in N. sativa seeds, including thymoquinone, thymol, limonene, carvacrol, p-cymene, alpha-pinene, 4-terpineol, longifolene, and t-anethole benzene (Kooti, 2016) . The use of Black Seed in various traditional herbal systems is known for a variety of ailments including respiratory tract disorders, for pain such as chronic headaches and backaches, diabetes, paralysis, infections, inflammation, hypertension, and related gastrointestinal tract (Yimer, 2019).

Effects on the body's defense system have also been widely reported, including its

Figure 1. Plants, flowers, seeds, and Black Seed oil

synergistic effect with curcumin on the immune response against viruses (Umar, 2016), acting as a balancing factor on Th1/Th2 lymphocytes, as a chemopreventive, and as an immunomodulator (Akrom, 2019). In addition, the effects on the nervous system that have been reported include reducing nerve injury, treating nervous system diseases such as memory disorders, epilepsy, neurotoxicity, and pain (Keshavarzi, 2019). Rizky, Firmansyah, & Darmalaksana (2021) have used mentakhrij and sharah habbatussauda as medicine. The Prophet SAW said he told us Abu Salamah Yahya bin Khalaf told us Abu 'Ashim from Uthman bin Abdul Malik he said; I heard Salim bin Abdullah tell his father that the Messenger of Allah 'alaihi wasallam said: "You should use this al-Habbah as-Sauda (black cumin). Verily, he contains the antidote for every disease except death" (H.R Ibn Majah No. 3439). The hadith is interpreted as a recommendation to consume Black Seed. Chemical constituents such as timoquinone make up 30-48% of the total compounds that have an immunomodulatory effect and many other benefits can be interpreted as a cure for all diseases except death.

Hajiri, Abdillah, & Zulfikar (2020) studied the effects of Thibbun Nabawi Black Seed. Nigella sativa or Black Cumin or Black Cumin or Black Seed is one of the herbal medicines that is part of the Prophet's medicine which is still used routinely (Mushodiq, 2017). Based on the results of previous research, it was concluded that the most important bioactive substance was thymoquinone. Black Seed is included in Prophetic Medicine (Thibbun Nabawi) which describes 61 types of plants and shrubs as prevention and treatment of various types of diseases Black Seed is believed to be an herbal medicine and can be used as a food product, has been used for centuries widely throughout the world. The compounds in Black Seed have been studied for a long time

by the most famous doctor and philosopher in the Islamic world, namely Ibn Sina because of the many benefits in it.

PHARMACOLOGICAL EFFECT OF HABBATUSAUDA

Immunomodulator

The immune system is a set of interconnected cells, tissues, organs, and soluble mediators, constantly evolving to provide protection against organisms from foreign attacks that threaten the integrity of the organism. One of the main functions of the immune system is its ability to distinguish between own cells and foreign molecules (Catanzaro, 2018).

The immune response is divided into innate and adaptive immunity which includes different and specific functions in the immune defense response. The natural immune system provides rapid but incomplete protection against foreign substances and has no long-term memory. The natural and adaptive immune systems work in tandem with each other. The innate immune system recognizes infection and "reminds" the adaptive immune system through antigen presentation, which occurs due to the presence of MHC proteins. Natural immune cells also release other chemical signals, to fully activate the adaptive system. In particular, B and T lymphocytes regulate and stop the immune response after the exposure is overcome, so that an exaggerated immune system response can be avoided.

Currently, there is a wealth of epidemiological data providing information about the increase in immune system diseases leading to the development of a particular class of molecules, known as immunomodulators, which are capable of enhancing or suppressing the immune response in immune system-mediated diseases. Immunomodulators are natural or synthetic substances that help in the regulation or normalization of the body's immune system. An imbalanced immune system can be corrected by immunomodulators. Research by Hanieh Shaterzadeh-Yazdi, et al. (2018) on the immunomodulatory and anti-inflammatory effects of timoquinone reported that TQ has important anti-inflammatory properties that prevent the biosynthesis of mediators in inflammatory and asthmatic processes such as 5-LO, COX, PGD2 and LTs. TQ also reduces LPS-induced proinflammatory cytokines such as interleukins and TNF-. In addition, TQ suggests an immunomodulatory role in cellular and humoral immunity. This study also found that TQ increased the toxicity of imidacloprid through reduced oxidative stress and increased chemokinesis, chemotaxis, phagocytic activity, antibody levels and immunoglobulin hemagglutination as well as by reducing serum MDA levels and liver enzymes (Shaterzadeh-Yazdi, 2018).

Research by Hina Aslam, et al (2018), on the immunomodulatory effect of timoquinone in atopic dermatitis showed the potential to

improve atopic dermatitis by significantly reducing inflammatory cell infiltration in the blood ($p < 0.001$) and increasing the dermatitis score ($p < 0.001$). Significant reductions in ear thickness ($p < 0.001$) and IgE levels ($p < 0.001$) were also observed. TQ and tacrolimus also significantly attenuated the mRNA expression levels of IL-4, IL-5 and IFN-γ ($p < 0.001$). Overall, the results showed that oral and topical application of thymoquinone exerted an immunomodulatory effect in animal models of atopic dermatitis (Aslam, 2018).

Research by Muhammad Fakhar-e-Alam Kulyar, et al. (2020), on the potential effect of Nigella sativa in strengthening the immune system: Hopes for slowing the COVID-19 pandemic, reported that Timoquinone suppresses mRNA expression that downregulates interferon genes and other inflammatory responses. Similarly, -hederin suppresses the expression of miRNA-126 which consequently interferes with the IL-13 secretory pathway (Kulyar, 2020).

Antioxidant

Oxidative stress and elevated levels of free radicals are one of the main markers associated with several progressive pathological conditions, including neurological disorders, cancer, aging, and endocrine diseases. (Lupoli, 2018). To date, medicinal plant therapies have become increasingly important in choice as natural antioxidants. Among various natural medicinal plants, Nigella sativa has been reported to have effective antioxidant activity in both in vivo and in vitro studies (N. Ozdemir, 2018). Concomitant use of Allium sativum and N. sativa seeds in thirty postmenopausal women after two months of consumption revealed a significant reduction in plasma malondialdehyde (MDA) levels with increased erythrocyte glutathione peroxidase (GSH-Px) and superoxide dismutase activity. Separate administration of N. sativa and nano-sized clinoptilolite in Wistar rats also showed significant improvement in antioxidant parameters compared to the concurrent use of both extracts and diabetes group (H. Omidi, 2017). A randomized controlled clinical trial in fifty volunteer obese subjects also showed that N. sativa seed oil together with a lower calorie diet significantly reduced superoxide dismutase (SOD) levels and body weight compared to the placebo group in an eight-week trial (N. Namazi, 2015).

In addition, methanol extract and essential oil fractionated from N. sativa seeds in atherogenic suspension of fed mice have been reported to effectively replenish plasma total antioxidant power by eighty-eight percent against free radicals (R. M. Mostafa, 2013; Beg, 2016) . Similarly, administration of N. sativa oil and thymoquinone significantly ameliorated cisplatin-induced changes in carbohydrate biotransformation and enzymatic and nonenzymatic antioxidant defense systems in gastric mucosa (F. Shahid,

2018). Therefore, the marked antioxidant activity of N. sativa and thymoquinone may be potential new antioxidant agents and be used as essential nutrients for life for health promotion and disease prevention.

Antihypertensive

Many antihypertensive agents have been used clinically to control hypertension and to relieve associated comorbid conditions. However, the effectiveness of these agents is only in 40-60% of hypertensive patients and generally a combination of two or more blood-lowering agents from diverse antihypertensive classes is required to achieve the desired results (O. K. Vasant, 2012). This ultimately increases the likelihood of unwanted effects and also increases the cost of therapy. A number of herbal products such as N. sativa seeds have been used and claimed to have positive effects on high blood pressure. According to a nonrandomized controlled trial, 57 patients who were allocated to receive 2 g of black cumin daily supplementation for one year showed marked reductions in systolic, diastolic, and mean arterial blood pressure, heart rate, TC, LDL-c, fraction TC/ HDL-c, and LDLc/HDL-c while serum HDL-c was suggestively increased compared to the corresponding baseline values and the control group (A. Badar, 2017). Although a tendency to decrease blood pressure was observed after administration of N. sativa, one randomized controlled clinical trial failed to demonstrate a significant reduction in blood pressure in elderly patients with hypertension (A. Rizka, 2017). In addition, N. sativa was used to determine the blood pressure-lowering potential and possible mechanisms of N. sativa in rat models, and it was found that the N. sativa seed oil and nicardipine treatment group showed substantial reductions in blood pressure. Blood pressure lowering effects were associated with decreased cardiac lipid peroxidation products and inhibition of angiotensin converting enzyme activity in both groups but plasma nitric oxide levels were significantly increased in the group receiving N. sativa oil compared to placebo and the group receiving nicardipine (K. Jaarin, 2015).

Black cumin and its active component, thymoquinone, show reduced oxidative stress through calcium channel blockade and increased urine output activity which may have been associated with lowering blood pressure (X. F. Leong, 2013). Based on most reports, various preparations of N. sativa demonstrated sustained reduction of blood pressure in animal models and clinical studies could therefore be explored as a promising basis of natural antihypertensive drugs.

Neuroprotective

Neurological disorders such as depression are among the most common illnesses globally. This is mainly influenced by neurotransmitter hypoactivity, mainly due to inadequate serotonin activity (T. Perveen,

2014). Stress is a major triggering aspect in the initiation of depression and this premise continues to be supported by numerous clinical observations. Studies in experimental animals have shown that excessive stress conditions result in neurochemical modification and behavioral decline (M. A. Wilson, 2015). A large number of medicinal plants and isolated compounds have been known to have therapeutic benefits and potential. Among the promising medicinal plants, Nigella sativa is a valuable herb with a rich historical and religious basis for treating depression and many other neurological disorders.

Intragastric supplementation of TQ (20 mg/mL) in aluminum trichloride and D-galactose-induced neurotoxicity in rats showed significant improvement of cognition, SOD, and total antioxidant capacity while reducing acetylcholinesterase activity. It also demonstrated decreased MDA, nitric oxide levels, and tumor necrosis factor-derived immunoreactivity and neurotrophic amplification.

factors and levels of Bcl-2 (Y. S. Abulfadl, 2018). While the effect of repeated administration of N. sativa in rats shows that there is an increase in learning and memory status (M. Hosseini, 2015). In addition, flavonoids isolated from Nigella sativa have been shown to modulate critical neural signaling pathways involved in memory processes and tend to influence synaptic plasticity and potentiation mechanisms (M. K. A. Sahak, 2016)

Antiosteoporosis

The main bone disease is osteoporosis, which is a systemic bone disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with consequent increased bone fragility and susceptibility to fracture. According to the World Health Organization (WHO), osteoporosis is defined as bone mineral density that is 2.5 standard deviations or more below the average value for healthy young women. In osteoporosis, bone loss occurs mainly in the trabecular region when the balance of bone remodeling leads to bone resorption. Bone loss is associated with changes in bone biochemical markers such as decreased levels of osteocalcin, a marker of bone formation and increased cross-linking of C-telopeptide, a marker of bone resorption. The diagnosis of osteoporosis is made using a dual emission X-ray absorptiometry (DEXA) machine, but more sophisticated three-dimensional micro-computational tomography (microCT) opens the way for better diagnosis (Shuid, 2012).

Osteoporosis patients were found to be under oxidative stress because their lipid peroxidation level was increased and antioxidant enzymes were reduced (Sontakke, 2002). Most risk factors for osteoporosis are associated with oxidative stress such as hypertension (Cappuccio, 1999), diabetes

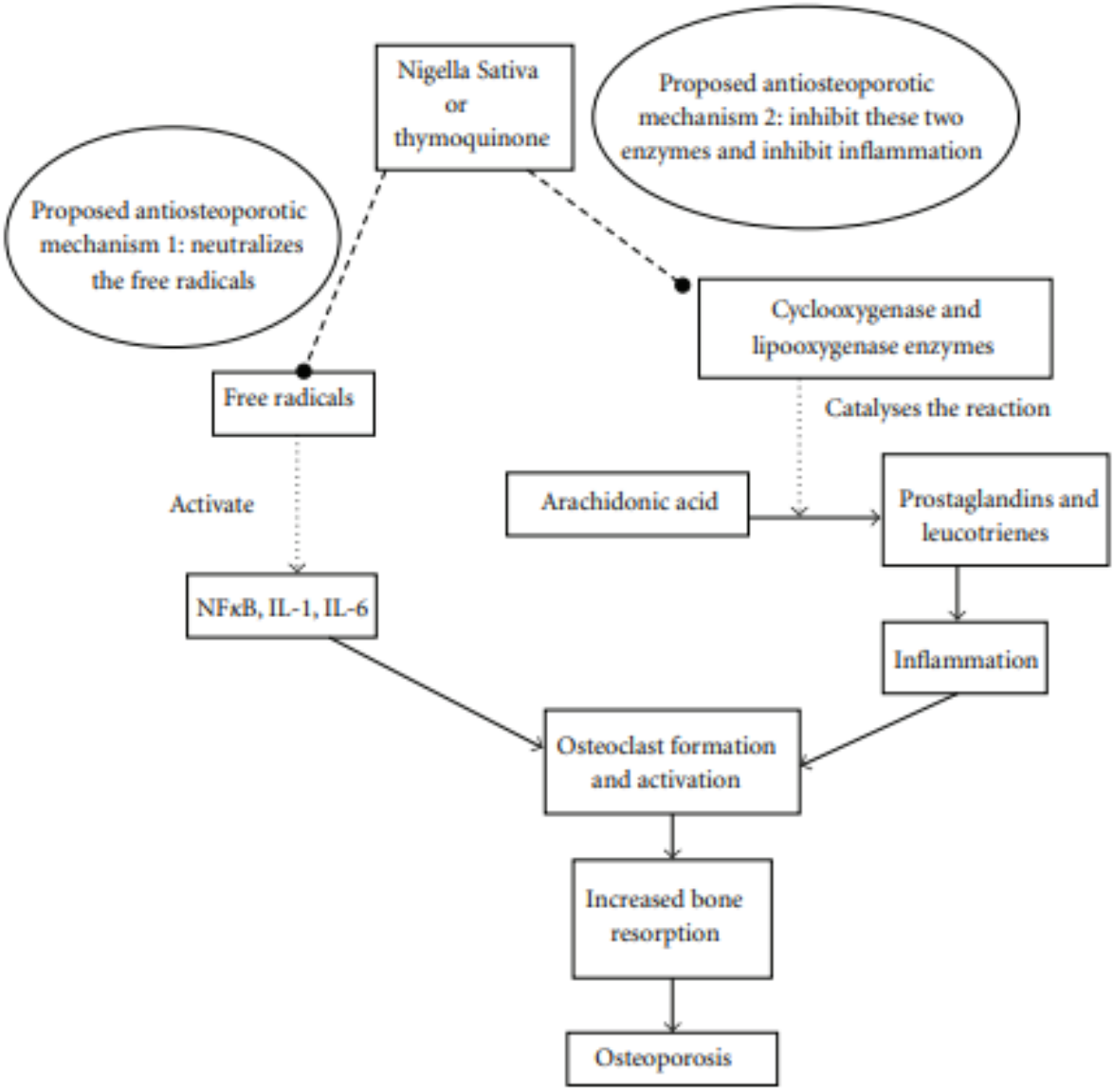

Figure 2. Two pathways that can lead to osteoporosis, namely, activation of osteoclastic bone resorption activity by radicals and by inflammation. Inhibition of these two pathways by Nigella sativa or Thymoquinone, their active components, may explain the mechanisms involved in osteoporosis prevention (Shuid, 2012).

mellitus (Christensen, 1999), and smoking (Hackshaw, 1997). Exposure to oxidative stress will result in a reduction in bone mineral density. Since it is clear that oxidative stress can cause osteoporosis, antioxidants may play a role in protecting bones against the damaging effects of free radicals.

Based on the findings, it is known that the most significant property of timoquinone, namely the active compound Nigella Sstiva, is its antioxidant activity. It has been reported that thymoquinone's free radical scavenging ability is as effective as superoxide dismutase. It is most effective in scavenging superoxide, a reactive oxygen species that plays an important role in osteoclast activation.

Antimicrobial

A large number of scientific articles referring to the antibacterial activity of Black Seed have been published in the journals PubMed/Medline, Science Direct, Scopus and Google Scholar and many other publishers. In summary, the oil extracted from Nigella sativa showed a significant antibacterial effect against multidrug-resistant Staphylococcus aureus isolated from an injured diabetic patient from Southeastern Nigeria (Emeka, 2015). Nigella sativa oil showed effective antibacterial activity against a large number of methicillin-resistant and coagulase-negative Staphylococcus aureus, the safety of the oil was checked, and there was no cytotoxic effect on gingival fibroblast proliferation (Ugur, 2016). Black cumin oil is recommended for use as an antimicrobial agent in food production to prevent spoilage. Based on the results showed that this oil at a concentration of 2.0% was able to inhibit the growth of twenty-four pathogenic bacteria, spoilage and lactic acid (Arici, 2005). The ethanolic and n-hexane extracts of black cumin recorded remarkable dose-dependent antibacterial effects against different gram-positive and gram-negative strains, namely Bacillus cereus, Bacillus subtilis, Escherichia coli, Staphylococcus epidermidis, Klebsiella pneumonia and Salmonella typhmurium. However, no antibacterial activity was detected against Pseudomonas aeruginosa and Enterobacter aerogens (KhanAR, 2016). Black cumin seeds show antibacterial activity against Salmonella typhi (Utami, 2016).

Anti-inflammatory and Analgesic

Inflammation has a key role in various medical conditions such as cystic fibrosis, rheumatoid arthritis, osteoarthritis, asthma, allergies, and cancer, all of which are associated with acute and/or chronic pain. Existing anti-inflammatory agents usually consist of a class of drugs that produce severe side effects such as gastric ulcers, bone marrow depression, water and salt retention, due to long-term use (B. K. Das, 2014). Herbal remedies including black cumin may be a potential source of new biologic compounds that are safer and with fewer side effects. Black cumin essential oil and timoquinone at various doses provided dose-dependent anti-inflammatory activity against carrageenan-induced hind paw edema in rats comparable to indomethacin (Padwa, 2017). The essential oil of N. sativa seeds also showed a substantial pain-relieving effect in acetic acid-induced writhing, formalin, and tail fick tests (A. Zakaria, 2018). As Al-Ghamdi said, black cumin water extract also has an anti-inflammatory effect. in carrageenan-induced leg edema comparable to acetyl salicylic acid at appropriate doses but failed to exhibit antipyretic activity against yeast-induced fever (Al-Ghamdi, 2001).

In addition, black cumin alcohol extract showed a more potent pain-relieving effect in

rats than diclofenac sodium (Qureshi, 2010). Additional studies have also shown that Nigella sativa essential oil has important activity as a painkiller induced by acetic acid, formalin, and tail fick tests. It was also revealed that this extract might significantly increase swimming ability and anoxia tolerance time (Kuldeep, 2011). The anti-inflammatory effect of thymoquinone may be related to the inhibition of the oxidative products of arachidonic acid formation, such as thromboxane B2 and leukotrienes by blocking both cyclooxygenase and lipoxygenase enzymes (Tornhamre, 2004).

Antidiabetic

Despite advances in the management of diabetes mellitus, exploration of innovative agents continues as existing synthetic agents have many limitations (R. Daryabeygi-Khotbehsara, 2017). Administration of black cumin for one month in streptozotocin-induced diabetic rats showed a significant reduction of fasting plasma glucose, serum MDA, interleukin-6, and immunoglobulin A, G, and M while a substantial increase of endogenous antioxidant enzymes; SOD, Glutathione-S-transferase, and catalase expression were observed. Pancreatic histology in the N. sativa treatment group also showed increased pancreatic cell degeneration, inflammation, and congestion compared to diabetes controls (H. A. El Rabey, 2017). The combination administration of N. sativa and Cinnamomum cassia (NSCCe) extracts in STZ-induced diabetic rats also showed significantly stable serum glucose concentrations, lipid profiles, and renal function parameters compared to diabetic controls. A significant effect was observed in animals receiving the combined extract and metformin on these parameters. Substantial reversal of histopathological pancreatic cell injury was also observed in animals receiving NSCce extract concomitantly (G. Kaur, 2018). Marked antidiabetic activity of three months of N. sativa supplementation (2 g/day) together with oral antidiabetic agents in type 2 DM patients has also been reported. In this study, the group receiving N. sativa showed significant reductions in fasting plasma glucose, hemoglobin A1c, and TBARBs, while significant increases in total antioxidant capacity, SOD, and glutathione levels were reported (H. Kaatabi A. O., 2015).

Subsequently, an experimental randomized controlled trial of 99 diabetic patients received a placebo and two treatment groups received oral black seed oil. Administration of 1.5 and 3 mL/day of black cumin oil for 20 days showed a significant decrease in glycated hemoglobin A1c and random blood sugar levels (P. N. R. Rachman, 2017). The effect of N. sativa seeds on glycemic control of patients with type-2 diabetes (DM-2) was also used as an adjunct treatment added to oral hypoglycemic agents. N. sativa at a dose of 2g/day also led to a substantial decrease in fasting plasma glucose and glycated

hemoglobin (HbA1c) without major changes in body weight (A. Bamosa, 2015). N. sativa (NSO) oil at 2 mL/kg was also shown to decrease fasting plasma glucose and increase insulin levels in diabetic rats compared to controls. Diabetic mice that received NSO showed substantial improvement in lipid profile and increased expression of pancreatic and hepatic antioxidant enzymes also added to the histologic picture and glycogen content in addition to an increase in the mean pancreatic islet area than the diabetic group (Abdelrazek, 2018). Different doses of N. sativa seeds (1, 2, and 3 g/day) in patients with DM-2 were also evaluated. Administration of 1 g/day increased high-density lipoprotein cholesterol (HDL-c) levels after 3 months, while 2 and 3 g/day N. sativa seeds significantly reduced serum total cholesterol (TC) and triglyceride (TG) and lipoprotein cholesterol levels. low density (LDL-c) and increased plasma HDL-c (H. Kaatabi A. O., 2012). Referring to the research of modern scholars on the possible effects of medicinal herbs in diabetes management, a recent meta-analysis of the antidiabetic effects of N. sativa also demonstrated the maintenance of glucose homeostasis and serum lipid profiles in diabetic human subjects (R. Daryabeygi-Khotbehsara, 2017) . In general, the possible antidiabetic mechanism of N. sativa might be mediated through modulation of oxidative status (either through upregulation of endogenous antioxidants or reduction of oxidative species), attenuation of inflammation, improvement of lipid profile, increase of good cholesterol (HDL-c), while reducing bad cholesterol (LDL-c). c, TC, and TG) and body weight.

Antifungal

N. sativa essential oil of different origins has been reported to have moderate inhibitory action against pathogenic strains of yeast, dermatophytes and non-dermatophytic flamentous fungi along with aflatoxin-producing fungi. The action of N. sativa targets the cell wall, plasma membrane, and membrane organelles, especially in the nucleus and mitochondria as evident in the morphology of this toxigenic fungus (Shokri, 2016). In addition, different extracts of black cumin and TQ showed strong fungicidal activity against dermatophyte strains including Trichophyton mentagrophytes and Microsporum gypseum which were superior to fuconazole, but inferior to ketoconazole (Mahmoudvand, 2014). Tymoquinone also inhibited the growth of Aspergillus niger and Fusarium solani comparable to Amphotericin-B (S. H. Aljabre, 2015) and was effective against C. albicans, C. tropicalis, and C. krusei (A. Piras, 2013).

Antivirus

N. sativa seed oil was found to suppress viral load in a murine model: cytomegalovirus-infected mice to undetectable levels in the liver and spleen in 10-day intraperitoneal administration. This

may be due to an increase in the number and function of CD4+ve T cells and an increase in the production of interferon- (INF-) gamma (F. Forouzanfar, 2014). Interestingly, patients (30) with hepatitis C virus (HCV) infection, who were not eligible for IFN-α/ribavirin therapy showed a significant increase in HCV RNA (16.67% became seronegative and 50% showed a significant decrease) and laboratory-proven parameters such as total protein, red blood cell, and platelet counts, decreased fasting blood glucose, and postprandial glucose in diabetic and nondiabetic HCV patients and reduced lower limb edema after they were administered with black cumin seed oil (E. M. F. Barakat, 2013).

According to a case report conducted by Onifade et al., after treatment with 10 mL of Black Seed twice a day for 6 months, a 46-year-old HIV-positive patient was shown to be fully cured and seroreverted (A. Onifade, 2013). In addition, a 27-year-old HIV-infected woman was diagnosed during antenatal care; he is not eligible for antiretroviral therapy; the herbal therapist initiated it with a mixture of black cumin and honey (10 mL) three times a day for a year. Re-serologic assessment for HIV infection was negative with an undetectable viral load. This woman was also blessed with 3 children (2007, 2010, and 2012) all of whom were breastfed and none of the children were infected with HIV and their CD4 count was not less than 750 cells/μL (A. A. Onifade, 2015). Currently HIV/AIDS is a serious global threat and in this regard, N. sativa could be a promising natural therapy to cure this chronic infectious disease, after validating its full therapeutic efficacy with further investigation.

Antiparasitic

Nigella sativa seeds have shown schistosomicidal properties against Schistosoma mansoni (in vitro), through a strong biocidal effect against all stages of the parasite and an inhibitory effect on adult female egg-laying worms (M. A. Assi, 2016) (M. E. Abd El-Hack, 2016). N. sativa seed ointment significantly contracts and inhibits the inflammatory reaction to cutaneous leishmaniasis experimentally produced in rats by subcutaneous inoculation of Leishmania major at the axial base of the tail (A. F. Bafgh, 2011). N. sativa extract at a dose of 1.25 g/kg significantly reduced Plasmodium yoelii infection in rats by 94%; However, the effect of chloroquine was only 86% compared to the untreated group. In addition, the methanolic extract of N. sativa resulted in higher parasite clearance and recovery of biochemical indicators altered by P. yoelii infection from chloroquine (V. O. Okeola, 2011). Therefore N. sativa as an antiparasitic agent in the future will have a very important role as input after further examination of its curative, prophylactic and chemopreventive activities, especially in the era of the emergence of antimalarial drug resistance.

Effect on male infertility

Sperm dysfunction is a major problem associated with male infertility accounting for 60% of all cases. Sperm structure, function, motility, and viability are strongly influenced by oxidative stress which predisposes to infertility. Therefore, increasing sperm count, functionality, and sperm quality by using antioxidants can improve fertility status (R. J. Aitken, 2014) (C. Wright, 2014). The available evidence reveals that some herbal medicines can reduce the negative effects of oxidative stress by scavenging free radicals (F. M. Awah, 2012). Among various traditional plants, N. sativa was found to exhibit remarkable antioxidant effects (S. S. Ashraf, 2011).

Alcoholic extract of N. sativa showed a remarkable increase in the production of viable and motile sperm cells, increased epididymal sperm reservation, reproductive organ weight gain, blood testosterone density, gonadotropin content, mature Leydig cell count, and fertility index compared to the control group in male rats (R. Parandin, 2012). According to Mohammad et al., black cumin is thought to trigger an increase in the hormone spermatogenesis in the pituitary gland, and an increase in the weight of the reproductive organs. This study also revealed that N. sativa can affect oxidative phosphorylation enzymes and increase sperm motility (R. Parandin, 2012). In addition, a randomized, double-blind, placebo-controlled clinical trial was conducted on 68 infertile Iranian men and half of them received 2.5 mL of black seed oil and the rest received a placebo twice daily for two months. Sperm count and motility and semen volume content increased significantly in the black seed oil treatment group compared to the placebo group after two months of therapy (M. Kolahdooz, 2014). This indicates that N. sativa can be a potential source for the development of natural aphrodisiac agents.

Hepatoprotector

The liver is a major metabolic organ and is responsible for many important functions in the body. If the liver becomes sick or injured, the next threat to the body's metabolic system can be life-threatening. Many previous researchers have shown that antioxidants prevent hepatotoxicity by inhibiting lipid peroxidation, ROS formation, and also by suppressing the activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) (Yen, 2007) (Mostafa, 2015). (Park, 2012). In vitro and in vivo findings suggest that N. sativa seed extract has a protective effect against paracetamol-induced hepatotoxicity and metabolic disorders by increasing antioxidant activity and suppressing lipid peroxidation and ROS formation (Adam, 2016). In another study, it was found that degeneration of hepatocytes, distribution and density of fibers around the central vein and portal space were observed in the carboplatin group compared with the

control group and NSO, hepatocyte cords were preserved integrity, partial degeneration of hepatocytes and decreased distribution of collagen fibers around the central vein. noted in the N. sativa (NSO)-carboplatin oil group as compared to the carboplatin group. Apoptosis was lower in the NSO-carboplatin group compared to the carboplatin group, but no statistically significant difference was found between the two groups (Erisgin, 2019).

Brain nutrition

Nutrition can substantially affect the development and health of brain structure and function. Nutrition provides the right building blocks for the brain to make and maintain connections, which are critical for improving cognitive function and academic performance. Brain function is highly dependent on adequate nutrition, and short-term variations in the amount and composition of nutrient intake in healthy individuals affect measures of cognitive function. The brain is a fatty tissue with a higher proportion of lipids than proteins. Brain lipids, including phospholipids, sphingolipids, and cholesterol, are known to play an important role in the structure and function of cell membranes. Phospholipids in the mammalian brain, including phosphatidylcholine, phosphatidyl-ethanolamine, phosphatidylethanolamine plasmalogen, phosphatidylserine (PS) and phosphoinositides have polyunsaturated fatty acids (PUFAs). Each of the PUFA phospholipids has a specific profile. For example, fatty acids in PS consist of high levels of palmitic acid and docosahexaenoic acid (DHA), while fatty acids in PI have high levels of stearic acid and arachidonic acid (AA). (Sun, 2017). PUFAs are generally considered to have beneficial health effects on the body. Phosphatidylserine is a major class of acidic phospholipids which accounts for 13-15% of phospholipids in the human cerebral cortex. PS plays an important role in nerve function. PS also affects the neuroprotective properties of nitric oxide synthase, a key enzyme in oxidative function in the brain. Deficiency of DHA in the brain can lead to deficiencies in memory function (Sun, 2017).

Seeds of Black Seed are known to contain linoleic acid, oleic acid, and palmitic acid which are components that form DHA. Research by Saeed Samarghandian, et al (2018), on a review of the Possible Therapeutic Effects of Nigella sativa and Thymoquinone on Neurodegenerative Diseases, reported that N. sativa and TQ have protective effects against neurodegenerative diseases, including; Alzheimer's, depression, encephalomyelitis, epilepsy, ischemia, Parkinson's, and traumatic brain injury have been studied using cell lines and experimental animal models (Samarghandian, 2018).

Research by N. K. Isaev1, et al. (2020), regarding Thymoquinone as a potential neuroprotector in acute and chronic brain

disease pathology, reported that the neuroprotective effects of thymoquinone are mediated through inhibition of lipid peroxidation, downregulation of proinflammatory cytokines, major protective potential of mitochondrial membranes, and prevention of apoptosis through inhibition of caspases 3, 8, and 9 Thymoquine-based mitochondrial-targeted antioxidants accumulate in mitochondria and exhibit neuroprotection. (Isaev, 2020). Research by Marco Cascella, et al. (2018), on Dissecting the Potential Role of Nigella sativa and Its Compound Timoquinone in the Prevention and Development of Alzheimer's Disease, reported that NS or TQ may represent an effective strategy against AD due to the balance of oxidative processes and binding of specific intracellular targets. The overall effect is mainly related to the prevention of hippocampal pyramidal cell loss and the improvement of cognitive function (Cascella, 2018).

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