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Black Cumin (Nigella sativa L.): A Review on Effect and Scientific Developments in Animal and Human Ailments

Research Article

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Abstract

This review aimed to strength the effect of black cumin to remedies of different diseases. The seed of Nigella sativa has been used around the world for centuries to treat various animal and human ailments. So far, numerous studies demonstrated the seed of Nigella sativa and its main active constituent, thymoquinone, to be medicinally very effective against various illnesses including different chronic illness: neurological and mental illness, cardiovascular disorders, cancer, diabetes, inflammatory conditions, and infertility as well as various infectious diseases due to bacterial, fungal, parasitic, and viral infections. The strong antioxidant property of this valued seed has recently gained increasing attention with regard to its potential role as dietary supplement with minimal side effects.

Keywords: Black Cumin; Pharmacological; Phytochemicals; Folk Remedies; And Toxicological Properties.

Introduction

The seed of Nigella sativa has been used around the world for centuries to treat various animal and human ailments. Recently, the usage of phyto-medicine has been amplified dramatically for numerous ailments because of not only their easy accessibility and low cost but also the belief that natural remedies have fewer harmful effects as compared to synthetic medicines [1].

The development of new products from natural sources is also encouraged because it is estimated that, of the 300,000 herbal species that exist globally, only 15% have been explored for their pharmacological potential [2]. Among several medicinal plants, Nigella sativa L. (Ranunculaceae) has been considered one of the most treasured nutrient-rich herbs in history around the world and numerous scientific studies are in progress to validate the traditionally claimed uses of small seed of the is species [3, 4]. The maximal nutritional value of black cumin can be linked to the presence of substantial amount of vegetable protein, fiber and minerals, and vitamins.

The phytochemical analyses of N. sativa displayed the presence of over hundreds of phyto-constituents which include mainly alkaloids, saponins, sterols, and essential oil but the composition of many of these have not been chemically recognized nor have been biologically verified. The N. sativa seed contain 26-34% fixed oil of which the major fatty acids are linoleic acid (64.6%) and palmitic acid (20.4%). The seed oil is comprised of 0.4%-2.5% essential oil [5, 6].

Amongst different active constituents reported so far, thymoquin one found as major component to the essential oil is the most bioactive compound and exhibits wide ranging therapeutic benefits [7]. The nutritional composition reported from different sources revealed 20-85% of protein,38.20% of fat, 7-94%of fiber, and 31.94%of total carbohydrates. Among various amino acids identified glutamate, arginine, and aspartate while cysteine and methionine were the major and minor amino acids, respectively. Black cumin seeds also contain significant levels of iron, copper, zinc, phosphorus, calcium, thiamin, niacin, pyridoxine, and folic acid [3, 4]. In this review, the alternative health value has been highlighted including authentication studies of Nigella sativa.

Methods

Black cumin or Nigella sativa has been broadly studied for years, studies have reported that it possesses a number of medicinal properties, Toxicological, physicochemical, and pharmacological

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actions. The relevant literatures with respective subtopics, have used Scopus Google Scholar, PubMed, grey literatures and Science Directs using different searching terms such as "Black cumin" or "Black seed" and respective disease conditions.

Physico-chemical properties and chemical composition of Nigella sativa oil

Nigella sativa oil was typically obtained by non-polar solvent extraction and cold-press procedure. The oil contents in most Nigella seeds studied were typically 30-40%, depending on environmental conditions such as water-stress, saline conditions, and temperatures [8, 9] the oil contents of Nigella seeds obtained from Morocco using hexane extraction and cold press-extraction yielded 37% and 27%, respectively. Some physico-chemical parameters were also affected by techniques used for oil extraction [10]. Also compared the yields of NSO obtained by three different extracts. The highest yield was observed using Soxhlet (37.33 ± 0.15%), using petroleum ether as a solvent, over Modified Bligh–Dyer with a yield of 33.24 ± 0.59% and hexane extraction with a yield of 31.76 ± 0.64% [11].

Black cumin in Folk Remedies

Nigella sativa has been widely used as a spice and flavoring agent in variety of food preparations such as in bread, yogurt, pickles, sauces, and salads. Seed of black cumin has long been used in traditional remedy in the Arabian countries, Far East Asia, Europe, and Africa [12].

Nigella sativa has also been described as the miraculous plant and considered by earliest herbal specialists as "The herb from heaven" [13]. The curative powers of the black seed as "Hold on to use this black seed, as it has a remedy for every illness except death" [14]. Avicenna, a well-knownphysicianof10th century famous for his book "The Canon of Medicine," has recommend use of Nigella seeds for enhancement of body's energy and also support during recovery from fatigue and dispiritedness.

Nigella sativa is also mentioned for its curative property in the Holy Bible and is also labelled as Melanthion by Hippocrates and Dioscorides [15, 16]. The medicinal use of black cumin seeds in various traditional herbal systems is known for a wide range of ailments which include different airway disorders, for pain such as chronic headache and back pain, diabetes, paralysis, infection, inflammation, hypertension, and digestive tract related problems administered in different kind of preparations. It has also been used topically where it is applied directly to the blisters, nasal abscesses, orchitis, eczema, and swollen joints [14]. Keeping in view of the numerous traditional medicinal uses of N. sativa seeds and its active component, thymoquinone, this valuable her can be explored as an effective folk medicine with multiple pharmacological actions.

Effects of Nigella sativa on Male Infertility

In fertility is the in capability of a copulate to attain offspring after 12 months of intercourse without contraception. It is more prevalent among men than women [17]. Sperm dysfunction is the main problem related with men infertility which accounts 60% of all reasons.

The structure, function, motility, and survival of sperm are deleteriously affected by oxidative stress that prominently leads to infertility. Hence, increasing spermatozoa counts, functionality, and sperm quality using antioxidants can improve fertility status [18, 19]. Evidence proves that some herbal medicines can reduce negative effects of oxidative stress by salvaging free radicals [20]. Among the various traditional plants, N. sativa was found to exhibit remarkable antioxidant effect [21]. Alcoholic extract of N. sativa indicated remarkable increment in the production of viable and motile sperm cells, enhanced epididymal sperm reservation, weight gaining of reproductive organs, blood testosterone density, gonadotropins content, amount of mature Leydig cells, and fertility indexes compared to the control group in male rats [22]. According to Mohammad et al., black cumin thought to trigger a rise in spermatogenesis hormones on pituitary gland, and an increase in the weight of reproductive organs. The study also reveals that N. sativa can affect oxidative phosphorylation enzymes and increases perm motility [22]. In addition, a randomized, double-blind, placebo-controlled clinical trial was conducted on 68 Iranian infertile men and half of them receive 2.5mL of black seed oil and the remaining received placebo twice daily for two months. The amount and the motility of sperm and the content of semen volume were raised significantly in black seed oil treated group compared with placebo group after two months of therapy [23]. This indicates that N. sativa can be a potential source for development of natural aphrodisiac agents.

Result

Nigella sativa oil obtained by two extraction methods (hexane extraction and cold press) have been compared in terms of Free fatty acids (as oleic %), Iodine value (g of I2/100 g), K232, K270, PV (MeqO2/kg), and Refractive index at 20°C. physicochemical properties of NSO extracted by three different methods (Soxhlet extraction using hexane, microwave extraction, and cold press) [24]. The values of corresponding these properties were compiled in Table 1.

Discussion

Toxicological Properties

The acute oral toxicity of active constituents of black cumin seed, thymoquinone, lethal dose 50 value has been reported to be 2.4g per kg of body weight of Swiss albino mice, whereas the instant behavioral alteration at two and three g per kg of body weight of the composite was hypo activity and trouble in breathing, while late toxicities comprising a substantial lessening in the virtual organ weight and glutathione distribution of the hepatic, renal, and cardiovascular system have been reported [25]. Daily administration of aqueous extract of N. sativa to mice for six weeks led to death of one mouse after 2 weeks of treatment with 6.4g/kg of administration of aqueous extract. On the other hand, 2 and 3 mice experienced death at 3rd and 5th weeks while they received 21g/kg and 60g/kg of the extract, respectively. Otherwise, no other deaths were recorded for the application of other doses used [26].

In addition, the sub-chronic toxicity study in mice treated with 30, 60, and 90mg/kg/day of thymoquinone for 90 days resulted in no mortality or signs of toxicity but substantial decrement of

fasting plasma glucose and also showed no change in toxicological significance in body organs and histological investigation [25]. The toxicity of the fixed oil of black cumin in mice and rats was also examined and the lethal dose 50 values were found to be 28.8ml/kg and 2.06ml/kg when given by oral and intra peritoneal routes, respectively.

Chronic toxicity was also studied in rats treated daily with an oral dose of 2ml/kg for 12 weeks' black cumin oil, while alteration sin vital liver enzyme levels and histopathological modifications (heart, liver, kidneys, and pancreas) were not detected [27]. The min or and/or negligible toxicological effects and wider therapeutic margin of N. sativa and its active constituents, thymoquinone, as evident by various scientific studies support its safe use for the long-term traditional food and medicinal purposes.

Phytochemicals (High-Value Bioactive Compounds) in the Seed of Black cumin

Several bioactive compounds from the seed of N. sativa have been reported in the literature; among those the most important bioactive ones are thymoquinones. Other main phytochemicals reported from different varieties of N. sativa include sterols and saponins, phenolic compounds, alkaloids, novel lipid constituents and fatty acids, and volatile oils of varying composition [28].

The essential oil composition (0.4-0.45%) reported in various studies represented about forty different compounds, amongst the abundantly constituents identified are trans-anethole, p-cymene limonene, carvone, α-thujene, thymoquinone, thymo-hydroquinone, dithymo- quinone, carvacrol, and β-Pinene with various concentration [29-31].

The quantity of most important bioactive constituent, thymoquinone, present in the volatile oil isolated by different extraction methods from the seeds of N. sativa varied over a wide range: using SC-CO 2 (1.06, 4.07mg/g) [32] and by Soxhlet extraction (2940.43mg/kg) [33] and (8.8mg/g) oil [34]. The seed oil fatty acid composition (32-40%) has been reported by various authors to contain mainly, linoleic, linolenic, oleic, palmitoleic, palmitic acids together with arachidonic, eicosa-dienoic, stearic, and myristic acid [31, 32, 35]. A new dienolate and two known monoesters along with novel lipids have been isolated from the un saponified extract of the seed, namely methylnonadeca-15,17-dienoate, pentyl hexadec-12-enoate, and pentyl pentadec-11-enoate [36]. Phytosterols are important part of human diet and are gaining greater interest due to their nutraceutical and medicinal benefits in lowering low density lipoprotein and total cholesterol level [37]. Phytosterols are also important as characteristic compounds for assessing the quality of vegetable oils and food labeling. The total sterols content of black cumin seed oils as estimated by different researchers was found to be between 18 and 42% of the un saponified matter.

The major sterols identified were β-sitosterol, campe-sterol, stigmasterol, and 5-avenasterol [35, 38]. Tocopherols exhibited attractive scavenging potentials of free radicals which are believed to terminate lipids peroxidation [39]. The total tocopherol contents of black seed oil reported in varied quantities from diverse sources ranged from 9.15 to 27.92mg/100g. Among the foremost tocopherols recognized in black cumin seeds, α- and γ-tocopherol and β-tocotrienol are well recognized [35].

Steroidal glycosides of new and known structures have been isolated from N. sativa seeds which include 3-O-[β-Dxylopyranosyl-(1→2)-α-L-rhamnopyranosyl-(1→2)-βDglucopyranosyl-11-methoxy-16,23-dihydroxy-28-methylolean-12-enoate, stigma-5,22-dien-3-β-D glucopyranoside [40], and 3-O-[β-D-xylopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→4)-β-D-glucopranosyl]-11-methoxy-16-hydroxy17-acetoxy hederagenin [41].

Moreover, alkaloids of diverse types have been isolated from the seeds of black cumin, which include novel Dolabellane-type diterpene alkaloids: nigellaminesA1, A2, B1, and B2 and nigella mines A3, A4, A5, and C [42, 43] possessing lipid metabolizing property, and indazole class of alkaloids: nigellidine, nigellicine [44, 45], andnigellidine-4-O-sulfite [46].

Pharmacological Activities of Nigella sativa

Nigella sativa has been broadly studied in the last few decades and studies have reported that it possesses a number of medicinal properties and pharmacological actions.

Antioxidant Activity: Oxidative stress and an intensification in the levels of free radicals are amongst the foremost central markers associated with several progressive pathological conditions, including neurological disorder, cancer, aging, and endocrine illness [47]. To date, there has been a growing importance in the therapeutic option of medicinal plants as natural antioxidants. Among the various naturally occurring medicinal plants, N. sativa has been reported for its effective antioxidant activities of in-vivo and in-vitro studies [48].

The concomitant usage of Allium sativum and N. sativa seed in thirty postmenopausal women after two months of consumption revealed a significant reduction in plasma malondialdehyde levels within creased activity in erythrocyte glutathione peroxidase and superoxide dismutase [49]. Likewise, the fixed and essential oil of black cumin seed revealed a significant increment of Glutathione S-transferase, glutathione reductase and glutathione peroxidase against oxidative stress brought by potassium bromate in rats' model [50]. The separate administration of N. sativa and nano-sized clinoptilolite to Wistar rats also showed significant improvement on antioxidant parameters than concomitant uses of both extracts and diabetic groups [51].

A randomized controlled clinical trial in fifty volunteer obese subjects also demonstrated that N. sativa seed oil along with a less caloric diet significantly diminished the superoxide dismutase level and body weight as compared to the placebo group in eight weeks' trial [52].

Moreover, the methanolic extract and essential oil fractioned from N. sativa seed in atherogenic suspension nourished rats has been reported effectively replenished the plasma total antioxidant power by eighty-eight percent against free radicals [53]. Similarly, the oil of N. sativa and thymoquinone administration markedly ameliorated cisplatin-induced alteration on carbohydrate biotransformation and enzymatic and nonenzymatic antioxidant defense system in the gastric mucosa [54]. Hence, the marked antioxidant activity of N. sativa and thymoquinone might be a potential newer antioxidant agent and used as essential nutrients for life for health promotion and diseases prevention.

Antidiabetic Activity: Even with the advancement in the management of diabetes mellitus, exploration for innovative agents continues since the existing synthetic agents have numerous limitations [55]. The administration of black cumin seed for one month to streptozotocin-induced diabetic rats displayed a significant reduction of fasting plasma glucose, serum malondialdehyde, interleukin-6, and immunoglobulin A, G, and M while substantial increment of endogenous antioxidant enzymes; superoxide dismutase, Glutathione-S-transferase, and catalase expression were noticed.

The histology of pancreas in N. sativa treated group also revealed an improvement in the pancreatic β-cells degeneration, exhibited the maintenance of glucose homeostasis and serum lipid profiles in diabetic human subjects [55, 56]. Generally, the possible anti diabetic mechanisms of N. sativa might be mediated via modulation of oxidative status (either through up regulation of endogenous antioxidants or reduction of oxidative species) [57, 58], attenuation of inflammation [57], improvement of lipid profiles, increased good cholesterol (HDL-c), while reducing bad cholesterols (LDL-c, TC, and TG) and bodyweight [55, 59, 56].

Antihypertensive Activity: Numerous antihypertensive agents have been clinically used to control hypertension and to relieve associated comorbid conditions. However, the effectivenessofthe-seagentsisonly in 40-60%ofhypertensive patients and commonly combination of two or more blood lowering agents from diverse antihypertensive classes is required to attain the desired outcomes [60]. This eventually increases the likelihoods of untoward effects and also raises the cost of therapy. A number of herbal products such as the seed of N. sativa have been used and claimed to have positive effects against elevated blood pressure.

According to a nonrandomized controlled trial, 57 patients who were allocated to receive 2g daily supplementations of black cumin for one year displayed a noticeable reduction in systolic, diastolic, and mean arterial BP, heart rate, TC, LDL-c, the fractions of TC/HDL-c, and LDLc/HDL-c while serum HDL-c was suggestively raised compared with the corresponding baseline values and the control group [61].

Although a trend towards reduction in BP was observed after N. sativa administration, one randomized controlled clinical trial failed to show a significant reduction of BP in elderly patients with hypertension [62]. This might be because of the sample size, dosage (300mg BID for 4 weeks) of the N. sativa used in this study, the severity of hypertension, and study population used. For instance, previous clinical studies conducted on mild hypertensive patients with the dosage of 200mg BID for 4 weeks and 500mg BID for 6 weeks, respectively, showed a significant reduction of SPB [63, 64].

In addition, it has been employed to determine the blood pressure lowering potential and possible mechanisms of N. sativa in rats' model, and it was found that the seed oil and nicardipine received groups revealed substantial reduction in blood pressure. The blood pressure diminishing effect was related with a reduction in cardiac lipid peroxidation product and inhibitory activity of angiotensin converting enzyme in both groups but plasma nitric oxide level significantly increased in N. sativa oil received group than the placebo and nicardipine received groups [65]. Black cumin and its active component, thymoquinone, exhibited a reduction in oxidative stress via calcium channel blockade and increasing urine output activity which might have been linked to reduction in blood pressure [66]. Based on majority of these reports, various preparation of N. sativa showed a sustainable reduction of the BP in animal models and clinical studies hence can be explored as a promising basis of natural antihypertensive drugs.

Neuro protective Effects: Neurological disorder such as depression is amongst the most prevailing illnesses globally. It is principally affected by the hypo activity of neurotransmitters, particularly owing to inadequate activity of serotonin [67]. Stress is the chief triggering aspect in the initiation of depression and this premise is steadily supported by various clinical observations. Studies in experimental animals displayed that overwhelming stress conditions produce neurochemical modifications and behavioral deficits [68].

A large number of medicinal herbs and their isolated compounds have been revealed to have medicinal benefits and therapeutic potential. Among the promising medicinal plants, black cumin is a worthwhile herb with a rich historical and religious basis to manage depression and many other neurological disorders. The intra gastric supplementation of thymoquinone(20mg/mL) in aluminum trichloride and D-galactose induced neurotoxicity in rats showed a meaningful improvement of cognition, superoxide dismutase, and total antioxidant capacity while reducing acetyl cholinesterase activities.

It also exhibited a reduction in malondialdehyde, nitric oxide levels, and tumor necrosis factor-α immune re activity and amplified brain derived neurotrophic factor and Bcl-2 levels [69]. While the effects of repeated administration of N. sativa in rats indicated that, there was an improvement in learning and recall status [70]. In addition, flavonoids isolated from black cumin have been shown to modulate critical neuronal signaling paths involved in the processes of memory and are likely to affects synaptic plasticity and long-standing potentiating mechanisms [71]. Based on the wide-ranging neuro pharmacological effects, black cumin seed, its oil, and the active principle thymoquinone can be explored as a promising natural remedy for improvement of numerous neurological disorders.

Anti-Inflammatory and Analgesic Effects: Inflammation has a key role in various medical conditions such as cystic fibrosis, rheumatoid arthritis, osteoarthritis, asthma, allergies, and cancer which all are associated with acute and/or chronic pain. The existing anti-inflammatory agents commonly comprise classes of drugs that produce severe adverse effects such as gastric ulcer, bone marrow depression, water, and salt retention, resulting from the extended use [72]. Medicinal herbs including black cumin might be a potential source of novel biological compounds that are safer and with fewer side effects.

The volatile oil of black cumin and thymoquinone at various doses revealed a dose-reliant anti in flammatory activity against carrageen an-induced hind paw edema in rats' parallel to indomethacin [73]. The volatile oil of N. sativa seed also displayed a substantial pain-relieving effect in acetic acid-induced writhing, formalin, and tail flick tests [74]. As stated by Al-Ghamdi, the water extract of black cumin also retained anti-inflammatory effects in carrageenan-induced paw edema comparable to acetyl salicylic acid at corresponding doses but failed to display antipyretic activ-

ity against yeast-induced pyrexia [75].

Furthermore, the alcoholic extract of black cumin exhibited a noteworthy pain-relieving effect in mice as compared to diclofenac sodium [76]. Additional study also showed that essential oil of black cumin has notable activity as a painkiller in acetic acid-induced writing, formalin, and tail flick tests. It was also revealed that this extract might elevate a significant swimming and anoxia tolerance time [77].

The anti-inflammatory action of thymoquinone might be related to inhibition of the oxidative product of arachidonic acid formation, such as thromboxane B2 and leukotriene by blocking both cyclooxygenase and lipoxygenase enzymes [78, 79]. In addition, the action of black cumin seed on tracheal sensitivity and pulmonary inflammation of guinea pigs, which were exposed to breathe Sulphur mustard together with black cumin, displayed expressively lower magnitude compared to that of only Sulphur mustard exposed group [80]. The bronchial relaxation effects of the boiled extract of N. sativa in contrast with theophylline were assessed in asthmatic patients and it was found that black cumin extract caused substantial rises in entirely measured respiratory function tests and the starting time of bronchodilator action of the extract was comparable to that of theophylline [81].

The various extracts, oil, and active constituent (α-hederin) of N. sativa also show edanim provident of tracheal responsiveness and significant anti-inflammatory activity via decreasing the release of histamine and leukotrienes while increasing the PGE2 from them as cells and perfused lungs in anima model of allergic asthma [82-85]. This anti-asthmatic effect is further substantiated by different clinical studies, and majority of them reported that different N. sativa preparations showed an improvement of clinical symptoms and pulmonary function as well as various asthma biomarkers [81, 86-89]. These preclinical and clinical studies evidenced the potential anti-asthmatic effects of N. sativa but further investigations are required to assure its efficacy.

The efficacy of black cumin oil in patients with rheumatoid arthritis was also evaluated and data from 40 female patients diagnosed with RA who took N. sativa oil capsules (500mg) twice daily exhibited improvement in disease activity score compared to placebo ($P<0.05$). Correspondingly, a noticeable improvement was displayed in number of inflamed joints, incidence of morning stiffness, and disease activity after the consumption of black cumin [90].

Chronic inflammation has been implicated in various chronic illnesses [(cancer, cardiovascular disorders, diabetes, Alzheimer's disease, epilepsy, amyotrophic lateral sclerosis, rheumatoid arthritis, and asthma) that involve progressive and irreversible damage to the cell and/or neurons] as well as in many infectious conditions [91, 92]. Therefore, the crucial role of anti-inflammatory actions of different N. sativa preparations and thymoquinone might be the possible sources for the development to fa new gene ratio no fa nti-inflammatory agent to treat these wider anging conditions.

Antimicrobial Activity: Antimicrobials have been the bases of clinical medicine since the second half of the 20th century and have saved prominent number of people from serious microbial infections. Nevertheless, in the late 20th century and the earliest 21st century it has perceived the advent and widespread of antimicrobial resistance in pathogenic microorganisms throughout the globe [93, 94].

The ever-increasing terrorization of microbial infection sand anti-microbial resistant bacteria demands for a global struggle to discover for novel solutions that might be grounded on the natural products such as plants, which are selected on the basis of renowned ethno-medicinal use [95, 96]. Among the inspiring medicinal plants, black cumin is the one that displayed strong antibacterial, antifungal, antiviral, and antiparasitic actions.

A. Antibacterial Activity: Thymoquinone obtained from seeds of N. sativa revealed broader spectrum activities against multiple strains of gram-positive and gram-negative bacteria, including Bacillus, Listeria, Enterococcus, Micrococcus, Staphylococcus, Pseudomonas, Escherichia, Salmonella, Serovar, and Vibrio parahaemolyticus in addition to inhibiting bacterial biofilm formation [97].

The methyl alcoholic extract of the seed also displayed larger inhibition zone on gram-positive (S. pyogenes) as compared to gram-negative bacteria (P. aeruginosa, K. pneumoniae, and P. vulgaris) [98]. For different isolates of methicillin-resistant S. aureus, various concentrations of (100%,80%, 50%,40%,30%, and 20%) N. sativa oils displayed an expressively higher zone of inhibitions against all the tested bacterial strains [99].

Thymoquinone also revealed a significant bactericidal activity against gram positive cocci with MICs ranging from 8 to 32μg/mL and proved the minimum biofilm inhibition concentration at 22 and 60μg/mL for S. aureus and S. epidermidis, respectively [100]. Moreover, black seed (2g/day) owed clinically valuable anti-H. pylori effect comparable to triple therapy [101] and this can provide a scientific basis for the exploration of potential uses of this valued seed for the treatment of H. pylori-induced gas triculcers.

B. Antifungal Activity: The essential oil of N. sativa of different origins has been reported to possess moderate inhibitory action against pathogenic strains of yeasts, dermatophytes and non-dermato phytic filamentous fungi along with aflatoxin-producing fungi. The N. sativa treatment targeted the cell wall, plasma membrane, and membranous organelles, mainly in the nuclei and mitochondria as were evident in the morphology of these toxigenic fungi [102]. Moreover, different extracts of black cumin and thymoquinone exhibited powerful fungicidal activity against dermatophyte strains including Trichophyton menta grophytes and Microsporumgypseum superior to fluconazole, but lesser than that of ketoconazole [103].

Thymoquinone also arrested the growth of Aspergillus niger and Fusarium solani comparable to Amphotericin-B [104] and was effective against C. albicans, C. tropicalis, and C. krusei [105]. Similarly, as stated by Taha et al., the active constituent of black cumin such as thymoquinone, thymo-hydro quinone, and thymol revealed potent antifungal effect against several clinically isolated fungal strains including dermatophytes, molds, and yeasts [106]. As a potential candidate with multiple antimicrobial activities, N. sativa can also be explored as a natural preservative and food additive to protect foods from spoilage.

C. Antiviral Activity: N. sativa seed oil was found to suppress viral load in murine model: cytomegalovirus infected mice to undetectable level in the liver and spleen in 10 days' intra peritoneal administration. This was possibly due to the increase in number and function of CD4+ve T cells and increased production of interferon- gamma [107].

Interestingly, patients (30) with hepatitis C virus infection, who were not eligible for interferon-α/ribavirin therapy showed significant improvement in hepatitis C virus viral load (16.67% became seronegative and 50% showing significant decrement) and proved laboratory parameter like total protein, red blood cell, and platelet count, decreased fasting blood glucose, and postprandial glucose in both diabetic and nondiabetic hepatitis C virus patients and reduced lower-limb edema after they are managed with black cumin seed oil [108].

According to a case report conducted by Oni fade et al., after treatment with 10mL of black seed twice daily for 6 months, a complete regaining and sero reversion of a 46-year-old HIV positive patient was evidenced [109]. In addition, a 27-year-old HIV infected woman was diagnosed during ante-natal care; she was note ligible for antiretroviral therapy; hence herbal therapist initiated her on black cumin and honey mixture (10mL) thrice daily for a year. The repeat serology assessments for HIV infection became negative with undetectable viral load.

The woman also got 3 children (2007, 2010, and 2012) that all were breastfed and none of the children infected with HIV and her repeat CD4 count was not less than 750 cells/μL [110]. Nowadays HIV/AIDS is a serious global threat and, in this regard, N. sativa can be a promising natural therapy to cure such a chronic infectious disease, after validating its full therapeutic efficacy by further investigations.

D. Antiparasitic Activity: Nigella sativa seeds have shown schistose medical properties against Schistosoma man soni (*in vitro*), through a strong biocidal effect against all stages of the parasite and an inhibitory effect on egg-laying of adult female worms [111, 112]. Anointment of N. sativa seed significantly contracted and inhibited the inflammatory reactions to cutaneous leishmani as is produced experimentally inmice by a subcutaneous inoculation of Leishmani a major at the abaxial base of the tail [113].

N. sativa extract at a dose of 1.25g/kg prominently lowered Plasmodium yoelii infection in mice by 94%; however, the effect of chloroquine was only 86% as compared to the untreated group. In addition, methanolic extract of N. sativa revealed higher parasite clearance and restoration of altered biochemical indicators by P. yoelii infection than chloroquine [114]. Thus, considering N. sativa for future anti parasitic agents will have a very important input after conduction of further investigation of its curative, prophylactic and chemo preventive activity particularly in the era of emerging anti-malarial drug resistance.

Anticancer Activity: Cancer is a bigger challenge in medical science as the incidence of this health disorder is rapidly growing across the world. This prompts the efforts to search some effective natural anticancer therapies alternative to currently employed chemotherapies with limited applications. As there are ten cancer hallmarks which are common to most tumors, thymoquinone, a major active component of N. sativa, plays great role in affecting all markers of cancer [115].

Future Prospects

Both animal and human studies also showed that black seed and thymoquinone have potential to treat male infertility and their antioxidant activities have recently gained greater attention due to their role as dietary supplements with minimal side effects.

Moreover, when combined with different conventional chemotherapeutic agents, they synergize the effects which may reduce the dosage of the concomitantly used medicines and optimizing efficacy versus toxicity and it might also overcome drug resistance problem. Therefore, having wider safety margins and praiseworthy efficacy against wider range of maladies, it would be a potential herbal remedy to be assessed under clinical trial for numerous conditions. Isolation of novel bioactive components from black cumin and its oil and studies of their therapeutic effects using specific clinical models are further recommended.

Conclusion

Traditional medicinal plants have received much attention due to several factors such as low cost, ease of access, and lower adverse effect profiles as compared to synthetic medicines. Besides, various medicinal floras and their products are used on the basis of religious and cultural traditions. Among various plants, black cumin has been used by diverse human cultures around the world to treat numerous ailments.

To date, a number of studies showed that black seed and its component including thymoquinone have revealed a remarkable natural therapy for treatment of a wide range of illnesses including chronic noninfectious (neurologic disorders, DM, hypertension, dyslipidemia, inflammatory disorders, cancer, etc.) and infectious disease (bacterial, fungal, viral, and parasitic infections).

In spite of limited studies conducted so far, the promising efficacy of N. sativa against HIV/AIDS can be explored as an alternative option for the treatment of this pandemic disease after substantiating its full therapeutic efficacy. Moreover, the strong antioxidant property of this valued seed has recently gained increasing attention with regard to its potential role as dietary supplement with minimal side effects.

Besides, when combined with different conventional chemotherapeutic agents, it synergizes their effects resulting in reducing the dosage of concomitantly seed drugs with optimized efficacy and least and/or no toxicity. A number of pharmaceutical and biological properties have been a scribed to seeds of N. sativa.

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