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Clinical Applications of Nigella Sativa: A Review Article

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ABSTRACT: Black seed herb (Nigella sativa L.) is considered a nutraceutical herb, well-known among health-conscious individuals due to its wide range of benefits that attract curiosity not only from discerning individuals who value their health but also from scientific and pharmaceutical industries. It stands among those herbs which have been recently scrutinized for their anti-oxidative and anti-inflammatory abilities. The seeds of N. sativa have been attributed several pharmaceutical and biological properties. It has also been found to promote anti-cancer activity, neuroprotective effects, treating infertility, pulmonary protective activity, enhancing renal and hepatic functions, protection of digestive system, antihypertensive actions, metabolic acceleration, antidiabetic, anti-hyperlipidemic, increasing cell survival and immunomodulatory effects.

1. INTRODUCTION

The use of medicinal herbs to treat diseases has a long history in traditional folk medicine practices— spanning centuries and diverse cultures. In addition, medicinal herbs find their place in herbal medicine preparation due to the belief that they are safer than modern pharmaceuticals. A significant number of plant species are still not well investigated for their potential medicinal characteristics, mode of action, assessment of efficacy — thus researchers turn their focus towards medicinal plant species. In the myriad world of medicinal plants, one herb from the Family Ranunculaceae known as black cumin catches attention due to its religious and historical importance. Recent literature reveals its wide range of pharmacological actions which resonates back to its miraculous standing within various cultural context (Hannan et al., 2021).

Black cumin, or black seeds (scientifically: Nigella sativa L.), is known for its culinary uses which have historical significance in traditional medicine. The cultivation of black cumin is widespread in regions across Pakistan, India, Saudi Arabia, Turkey, Albania, Syria, Greece, Iran and Egypt— including many countries in Asia (Southwest and subcontinent Indian), northern Africa and the eastern Mediterranean. The use of N. sativa seeds in traditional medicine finds basis in a multitude of medicinal properties such as hepatoprotective and nephroprotective and gastroprotective — along with antidiabetic and cardioprotective antimicrobial and antihypertensive neuroprotective anticancer immunomodulatory anti-inflammatory antioxidant capabilities that they possess (Yimer et al., 2019).

The adoption of herbal remedies as alternative therapy is becoming widespread and popular all over the globe. Medicines can either be plant-derived or synthesized naturally remedies. Scientific research has identified the pharmacological benefits of Nigella sativa seed, oil and bioactive components like thymoquinone and alpha-hederine extracted from it; these compounds exhibit significant pharmacological effects both in test tube and living organisms models against many diseases due to their wide spectra activity. It has also been noted that utilization of Black Seed is relatively safe (Ahmad et al., 2013).

ACTIVE GRADIENTS

Black Seed (Nigella sativa) composition has been the subject of numerous research studies. Among the ingredients found in Nigella sativa seeds are essential oils, saponins, alkaloids, carbohydrates, proteins, oils. The fixed oil [non-volatile] is found to be present at a rate of (31.9–40.0%) and it contains unsaturated fatty acids which include glucosides sterol and esters, sterols— cycloartenol and cycloeucalenol beta-sitosterol as well as acid myristic and stearic palmitic oleic linoleic eicosadienoic arachidonic (Clarrett & Hachem, 2018 ; Maret-Ouda et al., 2020).

Black Seed contains a variety of alkaloids. In terms of nutritional composition, Black Seed consists of vitamins, carbohydrates, minerals, fats, and proteins— in addition to saponin and alpha hederine which are absent in lemons and citronellol (as should be the case with differing types of vitamins and minerals like Cu and P, Zn, K, Ca and Fe (Hosseinzadeh et al., 2005).

One of the sterols found in significant amounts in black cumin oil is β-sitosterol (44–54%). Another major sterol present in this oil is stigmasterol, which makes up 16.6–20.9% of the total sterols. It is not advisable to use larger quantities of Black Seed or oil as it does not intensify the action; for each disease, the maximum daily dose should not exceed three teaspoons per day (Cheikh-Rouhou et al., 2019).

Black cumin alkaloids can be classified based on their alkaloidal skeletons. The first type includes indazole or pyrazole alkaloidal compounds such as nigellicine and nigellidine; the second form is isoquinoline alkaloids, which consist of nigellicimine-N-oxide and nigellicimine. Furthermore, alkaloid nigelamines A1–A5 are also identified from black cumin that fall under the diterpene family group— these are reported to have potent lipid metabolism-promoting activity (Akram Khan & Afzal, 2016).

Tocopherols refer to key natural antioxidants that exert an effect in free radical scavenging activity as well as inhibiting lipid peroxidation in living cells' membranes. The four isomers of tocopherols are delta (δ), gamma (γ), beta (β), and alpha (α) — distinguished by the position of the methyl group on the chromanol ring. Some extraction methods may alter the composition of these tocopherol isomers. Variations in black cumin's tocopherol isomer composition can be attributed to differences in cultivation areas, maturity periods, and storage conditions within which they are kept (Kiralan et al., 2014).

The terpenes and terpenoids family make up the major chemical group of black cumin — which includes TQ and its derivatives like longifolene sesquiterpene, p-cymene, dithymoquinone, THQ, t-anethol, thymol, α-pinene, 4-terpineol, carvacrol. This diversity in the pharmacological properties of black cumin primarily owes itself to the quinine components' presence; among which TQ is most prevalent (Hannan et al., 2021).

Black seeds, on the other hand, boast a total of 19 polyphenols. Let's take a closer look at these: apigenin, kaempferol, luteolin, patuletin, quercetin, quercitrin, fisetin, myricetin. The list goes on. Among these bioactive compounds, quercetin and kaempferol reign supreme in black cumin— with levels reaching 105.6 ± 0.12 and 12.2 ± 0.04 μg per gram of dry weight respectively. Why is this important? The answer is that , kaempferol is an antioxidant polyphenol that fights off oxidative cell damage while quercetin acts as your shield against a myriad of diseases such as bone disorders cardiac disorders or even lung cancer. (Dabeek & Marra, 2019).

CLINICAL APPLICATIONS

Pregnancy and lactation

Black seed is advised for consumption while breastfeeding but not recommended during pregnancy. This is due to the presence of keratin protein in black seed, which gets converted into Vitamin A— an essential nutrient that pregnant women can consume. The nutritious elements in Black Seed are vital for both the mother and child during the growth phase; its immune system boosting properties serve as a natural way to enhance disease resistance, ensuring safety for both mother and child. Moreover, research indicates that Black Seed also helps in increasing milk supply (Ferizi et al., 2023).

LOWERING OXYGEN FREE RADICALS

There have been numerous reports on the antioxidant efficacy of black seeds in both in-vivo and in-vitro studies. Black cumin is considered a rich source of natural antioxidants that can reduce the level of reactive oxygen species (ROS). It achieves this by upregulating important antioxidant enzymes like Superoxide Dismutase (SOD) and Catalase (CAT) as well as molecules such as Glutathione (GSH), as shown by several research findings. A study revealed a significant increase in Total Antioxidant Capacity (TAC) levels and decrease in Malondialdehyde (MDA) production among rabbits supplemented with black cumin seeds. Another study on Wister rats given Nigella sativa oil showed notable reductions in ROS and Nitric Oxide production within the amygdala, thus mitigating chlorpyrifos-induced oxidative stress without hampering memory-related behaviors; the data are not found to be shown for MDA and TAC indices (De Giorgi et al., 2006; Imam et al., 2018; El-Gindy et al., 2020).

LOWERING BLOOD PRESSURE

There have been many investigations into the properties of N. sativa seed, all of which point to its significant antihypertensive effects. In an animal model induced with angiotensin II to raise hypertension levels, it was found that black cumin seed may work towards normalizing high blood pressure by counteracting the cardiovascular actions of angiotensin II— demonstrating promise as a potential antihypertensive agent. In 2017, Hussain et al. conducted a study involving 163 mild-moderate male and female patients between the ages of 20 and 65 who displayed high blood pressure as well as high lipid profile markers; their findings revealed that virgin oil from N. sativa significantly reduces both hyperlipidemia and hypertension (Enayatfard et al., 2018).

Further research has been conducted in a similar vein: clinical trials involving mild hypertensive patients who were administered black seed oil twice daily for 4 to 6 weeks. The studies showed a notable decrease in blood pressure (Dehkordi & Kamkhah, 2008; Qidwai et al., 2009). However, not all findings align towards a positive outcome— an example being a randomized controlled clinical trial that did not observe any statistically significant lowering in blood pressure among geriatric patients with high blood pressure (Rizka et al., 2017 .

REDUCTION OF BLOOD GLUCOSE LEVEL

The antidiabetic effects of black seeds are commonly acknowledged. It has been documented that the intake of black cumin seed over a period of one month by streptozotocin-induced diabetic rats resulted in notable decrease of fasting plasma glucose. The histopathology of pancreas in N. sativa treated group also exhibited an enhancement in the pancreatic β-cells degeneration, inflammation, and congestion as compared to diabetic control. The structural changes observed depict a positive response to the treatment with Nigella sativa in diabetic condition (El Rabey et al., 2017). Antidiabetic effects have been reported when N. sativa is supplemented for three months at a dosage of 2g daily along with oral antidiabetic agents in type 2 DM patients. The group that received N. sativa showed a significant reduction in fasting plasma glucose, hemoglobin A1c, and TBARBs levels; they also noted a significant increase in the total antioxidant capacity plus SOD and glutathione levels (Kaatabi et al., 2015). Furthermore, black cumin extracts have demonstrated positive effects on disease progression in both alloxan and streptozotocin-induced diabetic rodents through a mechanism that involves reducing oxidative stress. This is achieved by upregulating the activity of antioxidant enzymes (Widodo et al., 2016).

The potential antidiabetic actions of N. sativa usually involve addressing oxidative stress through controlling the body's oxidation levels (either boosting natural antioxidants or limiting oxidative components), fighting inflammation, optimizing lipid profiles— by elevating HDL cholesterol while reducing LDL cholesterol and triglycerides— all which help to manage weight (Kaur et al., 2018).

REDUCTION OF INFLAMMATION

Promising as they may be, most studies demonstrating the anti-inflammatory properties of black cumin and TQ have been conducted on animals. Yet it remains that such activities are pivotal pharmacological properties of the plant. Black cumin's anti-inflammatory potential in human disease conditions should be an area of focus for future research. A low-grade inflammation in pre-adipocytes showed reduction of interleukin-6 levels when exposed to fresh black seeds oil; conversely, IL-1β levels were reduced with stored oil. In rats with inflammatory edema, treatment with black seeds oil resulted in improvement of pro-inflammatory cytokines; similarly, topical application of balm stick containing black seeds oil helped mitigate acute and sub-acute inflammation effectively. These are significant findings warranting further exploration to better understand the scope of anti-inflammatory capabilities that can be harnessed from these natural sources (Attia et al., 2016; Bordoni et al., 2019).

Results from a study performed by Umar et al. (2012) revealed that the use of black seeds has antioxidant properties and is effective in treating arthritis in rats through collagen induced arthritis (CIA). The study showed that the use of black seeds helped to lower the levels of inflammatory cytokines and oxidative stress, while increasing the levels of anti-inflammatory cytokine. Similarly, another study looked into the effectiveness of black cumin oil on patients with rheumatoid arthritis (RA). The study involved 40 female patients with RA who took N. sativa oil capsules (500 mg) twice daily; results showed a positive change in disease activity score upon intake of the oil in comparison to a placebo group ($P < 0.05$). Moreover, improvements were also noted in the number of inflamed joints and morning stiffness after consumption of black cumin (Gheita & Kenawy, 2012).

KILLING OF GERMS

Thymoquinone obtained from seeds of N. sativa exhibited more expanding spectrum effects against multiple strains of gram-negative and gram-positive bacteria, including Vibrio, Serovar, Salmonella, Escherichia, Pseudomonas, Staphylococcus, Micrococcus, Enterococcus, Listeria, and Bacillus in addition to inhibiting bacterial biofilm formation (Abdallah, 2017).

One clinical study demonstrated the efficacy of combining black seeds and honey (referred to as Dosin) in eliminating gastric H. pylori infection. The trial involved nineteen patients who had H. pylori infection but no previous history of gastrointestinal bleeding, gastric cancer, peptic ulcer. They were recommended to take one teaspoon of Dosin (consisting of 6g black seeds and 12g honey) three times daily after meals for two weeks. The findings that led to this conclusion were mainly based on a negative urea breath test (UBT) and a substantial reduction in total dyspepsia symptoms without any adverse effects: Dosin was thus viewed as a promising anti-H. pylori as well as anti-dyspeptic agent. (Hashem-Dabaghian and Agah, 2016).

In addition, black cumin extracts along with TQ were found to have potent antifungal effects against certain dermatophyte strains. This includes Microsporum gypseum and Trichophyton mentagrophytes which showed higher susceptibility to fluconazole but lower than that of hymoquinone. On the other hand, ketoconazole stopped the growth of Fusarium solani and Aspergillus niger at a level similar to Amphotericin-B (Mahmoudvand et al., 2014; Aljabre and Alakloby, 2015).

When it comes to parasites, Nigella sativa seeds have demonstrated activity against Schistosoma properties against *Schistosoma mansoni* (in vitro) — showing a potent biocidal action on all parasite stages and anti-egg-laying action by adult female worms. An ointment prepared from N. sativa seed was found to significantly reduce the size and inflammatory responses of cutaneous leishmaniasis in mice that were induced by an experimental inoculation of *Leishmania major* at the base of the tail (Bafghi et al., 2011; Abd El-Hack et al., 2016).

ENHANCEMENT OF NEURAL FUNCTIONS

Positive effects have been reported for black cumin and TQ against depression, anxiety, and schizophrenia according to Hannan et al. (2021). Black cumin and TQ have shown positive results in various animal epilepsy models by reducing convulsions and enhancing memory capabilities. Previous research demonstrated that oral intake of hydroalcoholic seed extract helps in controlling convulsions and improving memory performance by altering redox status— another study highlighted protection against seizure induced cognitive impairment through probiotic supplementation alongside black cumin (Vafaee et al., 2015).

Conversely, rats' repeated intake of N. sativa showed positive effects on their learning and memory capabilities. Moreover, flavonoids derived from black cumin have been identified to influence important neuronal signaling pathways that play a role in memory processes— thus potentially hampering synaptic plasticity along with long-term potentiation mechanisms (Sahak et al., 2016).

CONCLUSIONS

Black cumin, or black seeds (scientifically: Nigella sativa L.), is known for its culinary uses which have historical significance in traditional medicine. Among the ingredients found in Nigella sativa seeds are essential oils, saponins, alkaloids, carbohydrates, proteins, oils. It stands among those herbs which have been recently scrutinized for their anti-oxidative and anti-inflammatory abilities. The seeds of N. sativa have been attributed several pharmaceutical and biological properties. It has also been found to promote anti-cancer activity, neuroprotective effects, treating infertility, pulmonary protective activity, enhancing renal and hepatic functions, protection of digestive system, antihypertensive actions, metabolic acceleration, antidiabetic, anti-hyperlipidemic, increasing cell survival and immunomodulatory effects.

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