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Review Article

Nigella Sativa Loaded Nanoparticles: A Promising Alternative Treatment For Murine Schistosomiasis Mansonai

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Abstract:

Human schistosomiasis is considered as one of the most important parasitic diseases, endemic in 78 countries, including tropical and subtropical regions and infecting about 250 million individuals worldwide. To date, the treatment of schistosomiasis depends mainly on the anti-parasitic drug, praziquantel; which was found to be not fully effective and its excessive usage resulted in the development of resistant strains of Schistosoma mansonai. Lately, the therapeutic potential of natural products and medicinal plants, which are frequently considered to be less toxic and free of side effects in treating certain diseases, has been widely recognized. According to a prophetic hadith, Muslims believe that Nigella sativa is the remedy for all diseases except death. Its essential oil is considered one of the promising alternative drugs for the treatment of Schistosma mansonai with potent antischistosomal effects. Nanoparticles can be used as drug carriers to modulate pharmacokinetics, boost bioavailability and target release with limited harmful effects. Nigella sativa can be incorporated into nanoparticles and is considered as a new delivery system and a suitable carrier with high physical stability. Different studies showed that it can be used as efficient drug delivery vehicle in treating Schistosoma mansonai. This article aims to highlight the therapeutic effect of Nigella sativa loaded nanoparticles on murine schistosomiasis mansonai.

Keywords: Nigella sativa, Nanoparticles, Schistosoma mansonai.

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Introduction:

Schistosomiasis is the second most important parasitic disease affecting human, next to malaria with a great socioeconomic impact.[(1)] It causes great morbidity and mortality, mainly across Africa and in the developing countries.[(2)] It requires snail intermediate host where the asexual reproduction occurs to produce cercariae, which infect the mammalian hosts by penetration of skin and mucus membranes upon exposure to the contaminated water. In mammalian hosts, the sexual reproduction occurs to produce eggs, which pass to the external environment with excreta.[(3)] In severe cases, Schistosoma mansonai leads to the development of periportal fibrosis (PPF), which leads to portal hypertension with opening of the collateral circulation and esophageal varices, and often accompanying ascites.[(4)]

For diagnosing Schistosoma mansonai, examination of stool samples for the presence of eggs, is one often used technique for species identification and for documenting infection intensity.[(5)] Serological and immunological tests may be helpful in demonstrating exposure to infection and the need for a thorough evaluation, treatment, and follow-up for individuals residing in non-endemic or low-transmission places.[(6)]

Treatment of Schistosoma mansonai:

Praziquantel is the standard treatment for Schistosoma mansonai and Oxamniquine, a highly discarded alternative, also appears to be effective.[(7)] Praziquantel works through affecting the permeability of cell membrane leading to the contraction of schistosome by increasing influx of calcium (Ca^{2+}),[(8)] this leads to tetany of the musculature of the tegument.[(9)] Praziquantel also causes vacuolation and blebbing of tegumental and subtegumental structures of the adult worms but not the juveniles.[(8)], so increases the exposure of the parasite antigens at the surface of schistosome, .[(10)] which in turn leads to parasite recognition and clearance by the host immune system .[(11)] The major drawback of praziquantel is that it is ineffective against sexually immature juveniles in the 2–4 weeks following infection. [(12)] Also drug resistance has been documented globally due to the overuse of praziquantel, parasite mutations, poor treatment compliance, and co-infection with other strains of parasites, and overall parasitic load.[(13)] Therefore; there is a need for new treatment strategies to overcome the back draws and limitations of praziquental.

Nigella sativa:

Black cumin, or Nigella sativa, was referred to as "The herb from heaven" by ancient herbalists. It is also known as a miracle herb or Haba al-Barakah (blessed seeds). The Prophet Mohammad (PBUH) also stated, “This black cumin is healing for all diseases except death”, and it was mentioned in the Holy Bible for its curative properties. Hippocrates and Dioscorides named black cumin as ‘Melanthion’ (little black seed). [(14)]

The seeds of N. sativa contain a wide range of components, including proteins, alkaloids, fixed and volatile oils, and saponins. Its oil content is about 30–40%, of which >98% is fixed and 0.1–2% is essential oil. Saturated and unsaturated fatty acids, as well as species of triacylglycerol, are the main components of the oil and might differ according to the seed's origin and the extraction technique employed. Tocopherols, phytosterols, and essential oils are among the less abundant components .[(15)] Thymoquinone (TQ), a key component of the essential oil, is the most bioactive component among the various active ingredients that has been reported so far and offers a wide variety of therapeutic effects. [(16)]

N. sativa has numerous pharmacological actions which include immunomodulatory, antibacterial, anticancer, antioxidant, and wound healing properties. Additionally, it possesses antiparasitic activities as antinematodal and anticestodal capabilities in addition to activities against some protozoal infections as toxoplasmosis and Trichomonas vaginalis .[(17)] Its essential oil is considered one of the promising plant-based alternative medications with potent antischistosomal properties.[(18)]

Nigella sativa in treating Schistosoma mansonai:

Nigella sativa extracts contain antioxidants which found to inhibit both the host's antioxidant enzymes and the enzymes hexokinase and glucose-6-phosph-

ate, which are involved in the metabolism of glucose. This increases oxidative stress, which in turn make the parasite more liable to be damaged by host immune response. Antioxidants induce the separation of males and females, which decreases or even prevents the release or production of eggs, the primary factor in the development of inflammatory granulomas in target organs and the spread of schistosomiasis. Antioxidants have demonstrated possible schistosomicidal efficacy against both mature and immature S. mansonai developmental stages, both in vitro and in vivo, counteracting one of the main disadvantages of PZQ. Antioxidants also have the ability to restore liver functions and inhibit thiososomal activity causing considerable changes in many cytokines. Cytokines, in turn not only exhibit antischistosomal activity but also promote enhanced host immunity and induce the restoration of organ target functions. [9]

An in vitro study was conducted to evaluate the schistosomicidal activity of Nigella sativa seeds against adult worms, cercariae, and miracidia of Schistosoma mansonai. The outcomes demonstrated both a strong biocidal effect against all stages of the parasite and an inhibiting effect on the adult female worms' ability to produce eggs.[19] An in vivo study was conducted on mice infected with S. mansonai after administering several doses of the plant extract. The results indicated the presence of calcifications, damage to the worm eggs in the liver and spleen, and a reduction in granuloma size in the treated mice .[20] Additionally, early Nigella sativa oil (NSO) administration in S. mansonai-infected mice protects against the oxidative processes generated by schistosomiasis, as shown by Soliman et al. (2003), in which hematological results, revealed that NSO considerably reduced the total leukocyte count while significantly increasing PCV, RBCs, and Hb content. Morphometric and histopathological findings of the liver demonstrated a modification in the pathological profile of schistosomiasis by decreasing the degree of histopathological alterations and suppressing hepatic granuloma. [21]

Ali et al. (2016) observed a significant reduction in the total worm burden and the total number of eggs deposited by S. mansoni females in the livers of mice treated with Nigella sativa oil. Scanning electron microscopy studies revealed that the worms' tegmental surface, oral, and ventral suckers also had significant alterations; some of the tubercles were swollen and torn out, also the tubercles lost their spines. The tegmental surface was injured and the suckers were swollen and became enlarged and edematous [15]. Also in a study conducted by Abououf et al. testing the possible prophylactic and therapeutic effects of Nigella sativa oil in treating S. mansonai, the results indicated that the oil may have some bioactivity against adult stages and may be able to improve hepatic pathology. [22]

Nanoparticles:

Nanoparticles (NPs) are materials with a size range of 1 to 100 nm. Based on their characteristics, forms, or sizes, they can be divided into several classes. NPs' large surface area and nanoscale size give them exceptional physical and chemical characteristics .[23] Nanomedicine has drawn a lot of attention in recent years with a potential for its use in biomedical applications, such as disease prevention, diagnosis, and therapy due to its distinct physiochemical and physiological characteristics .[24] Also biodegradability, biocompatibility, storage stability, and ease of surface modification of nanoparticles have made them ideal carriers for a wide range of medications. [25]

Drug delivery systems (DDS) employing nanotechnology have been used to treat a number of parasitic diseases, including leishmaniasis, toxoplasmosis, trypanosomiasis, and malaria .[26] Experimentally in murine cutaneous leishmaniasis, polymeric nanoparticles have been used to deliver chalcone or amphotericin B intracellularly. [27] Metal nanoparticles (NPs), chitosan (CS), and liposomes are conjugated with a variety of drugs, including as praziquantel, chloroquine, amphotericin B, rifampicin, and albendazole, to treat schistosomiasis, malaria, visceral leishmaniasis (VL), and visceral larva migrans.[28]

In Schistosoma mansonai, it was found that solid lipid nanoparticles coated with celecoxib effectively inhibited the various developmental stages of S. mansonai infection. [29] When used for the treatment of murine schistosomiasis mansonai, resveratrol loaded on niosomes exhibited anti-fibrotic and antiparasitic properties .[30] Additionally, oleic acid-loaded polymeric nanocapsules have shown signif-

icance in vitro activity against S. mansonai and were thought to be an effective new therapeutic alternative .[31] It was discovered that PZQ loaded solid lipid nanoparticles improved PZQ's pharmacological and safety properties on S. mansonai in vitro .[28]

Nigella sativa loaded nanoparticles in treating Schistosoma mansonai:

By augmenting the effects of praziquantel and lowering resistance to it, Nigella sativa loaded chitosan nanoparticles (NSLCN) emerged as a novel promising candidate medication against S. mansonai in vitro,[18] and in vivo .[32] The effects of thymoquinone loaded with chitosan nanoparticles (TQ/ChNPs) on S. mansonai free larval stages (miracidia and cercariae) found also to be promising. TQ/ChNPs exhibited greater cercaricidal and miracidicidal action compared to TQ alone. The percentages of infection and cercarial production/infected treated snail were significantly reduced by Nigella sativa and thymoquinone loaded with chitosan nanoparticles (TQ/ChNPs). [33] Additionally, Kishik et al. effectively used NSLCN preparation against the adult stage of S. mansonai in vitro.[18] Thymoquinone loaded with chitosan nanoparticle (TQ/ChNP) demonstrated potential bioactivity against adult stages of S. mansonai as well as potentiality to improve hepatic pathology. [34]

Conclusion:

Nanoparticles can act as drug carriers that have the capacity to control pharmacokinetics, boost bioavailability, and target release while having negligible harmful effects. The incorporation of Nigella sativa into nanoparticles as a new delivery system revealed them as suitable carriers in the pharmaceutical fields with high physical stability and may act as a new, safe, and effective alternative for the treatment of Schistosoma mansonai.

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