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Review Article

Efficacy and Safety of Immunomodulatory Therapy Activity of Nigellia Sativa Seeds Oil Extract for Corona Virus COVID-19 Patients

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ABSTRACT

Nigella sativa L. (NS) seeds, known as black seed, is a traditional herbal medicine used in various diseases including, antimicrobial, immunomodulatory, gastro and hepatoprotictive , bronchodialator. This review aimed to assess the studies supporting the medicinal use of NS in covid-19 patients and to highlight future research priorities. Various medical databases were searched for the effects of NS and its active secondary metabolites in Anti-inflammatory and analgesic properties asthma inflammation and outcomes. There were several preclinical studies describing multiple effects of NS in animal or cellular models immunological disorder including eczema, bronchodilation, anti-histaminic, anti-inflammatory, anti-leukotrienes and immunomodulatory effects. Furthermore, clinical studies showed improvements in different cytokines outcomes and laboratory parameters. In conclusion, NS could be therapeutically beneficial in control cytokine storm. Associate with COVID-19 infection which is accompanied by an aggressive inflammatory response with the release of a large amount of pro-inflammatory cytokines, but the evidence remains scanty and is often based on poorly characterized preparations. Accordingly, well-designed large clinical studies using chemically well characterized NS preparation are required.

INTRODUCTION

Nigella sativa is a commonly used herb which belongs to Ranunculaceae family that goes back to ancient time when the seeds and oil are used traditionally for variable purposes, It is described by prophet Mohammed (PBUH) as the black seed that having a curative powers, the holy bible mentioned it as the curative black cumin and Hippocrates and Discroides identified it as the Melanthion(1,2).NS contains many active constituents, such as thymoquinone (TQ), alkaloids,saponins, flavonoids, proteins and many others(1). Among these components Quinones thymoquinone and dithymoquinone are the most abundant and important one(1,2).

Thymoquinone (TQ) has been investigated for its anti-inflammatory, antioxidant and anticancer properties, It was also demonstrated an anti allergic action on patients with allergic diseases (including atopic eczema, asthma and allergic rhinitis) thus it could be used as prophylactic against allergic diseases(3).

METHODS

A literature search for scientific studies published in electronic databases (PubMed, Research Gate, Semantic Scholar and Google Scholar)

was done using the terms Nigella sativa, Black seed, Thymoquinone and their pharmacological effects on cytokines and immune system . Studies were searched for electronically between the years 1995 and 2020.

RESULTS

Safety Measures for use of NS

Amira E Elfouly et al. evaluated the safety of crushed nigella sativa (NS) in dyslipidaemic patients, it reported that an intervention of 1gm of NS seeds for 6 months showed decreased level of serum creatinine compared to the control group (p=0.037). (4)Several studies have demonstrated the acute and chronic lethal effects of NS seeds, oil and TQ effect on rats and

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mice concluded that there are no toxic effect were reported, LD50 values of the NS oil were reported to be 26 mg/kg when used orally and 1.9 mg/kg for intraperitoneal administration. Moreover hepatic enzymes Levels and histopathological modifications were not recognized in rats treated with oral dose of 2 ml/kg of NS for 12 months duration (5).

There are limited reports on the use of NS during pregnancy, however some studies reported that the use of phytovagex pessery of NS in experiment's rats in the first half of pregnancy evaluated that NS has no overall effect on the pregnancy duration, delivery, early pup growth, and external malformations. Also, its does not convinced any cytotoxic effects on the ovarian cells. (6)

Thymoquinone Therapeutic uses

N.sativa has been extensively investigated for its therapeutic and biological effects, and has showen a wide range of therapeutic activities such as diuretic, antidiabetic, antihypertensive, analgesic, anti-inflammatory, antimicrobial, immunomodulatory, gastro and hepatoprotictive , bronchodialator and many others. TQ has different beneficial properties, focus on the outcomes of the antimicrobials,TQ works on the gram negative and gram positive bacteria , helminths , parasites , fungi and viruses with wide range of efficacies depend on target organisms(7)

The most Important Pharmacological Activities of NS are listed below

A-Antimicrobial Effects

Antibacterial activity of NS oil and seeds was studied and results shown to have antibacterial effect against species of Staphylococcus and Staphylococcus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa and a pathogenic yeast Candida albicans and many other fungi. NS showed antibacterial synergism with many antibiotics .(7,8)

N. sativa has been detected to increase helper and cytotoxic T cells as well as natural killer cell activity . In addition to improving immunity NS has some inhibitory activity on proteases of human immune deficiency virus(7)

Ethanolic extract of NS has a marked antiviral effect in embryonated chicken egg by decreasing both viral load and mortality. A study concluded that NS and its derived compounds have been seen to carry out antiviral effect against many human and animal viruses.(2)

B-Anti-Inflammatory and Analgesic Properties

The anti-inflammatory and anti nociceptive effects of TQ , promoting the common perception of N.S as a potent anti-inflammatory and analgesic agent, have been recently studied. mechanism(s) other than the action on the opioid receptors are codidered to be involved in the analgesic effect of N.Sativa. TQ anti-inflammatory effect is linked to its attributable inhibition of cytokines (interleukins IL-6 and IL1) and many transcriptional factors in addition to induction of apoptosis(9)

Further immune action of TQ will be discussed below...

C-Pulmonary and Anti-Asthmatic Effect of the N.Sativa

Asthma is a chronic inflammatory disorder involving a variety of inflammatory mediators and reaction. Years ago, N. sativa have been used under the name 'nigellone' for the bronchial asthma for both children and adults, many scientists have worked to investigate the exact mechanism of action behind this antiallergic effect, Chakravarty, M.D., conducted a study which proved that N.S inhibits protein kinase C (a substance that trigger histamine release) it also inhibits calcium reaptake be the mast cell which results in histamine inhibition(10).

Most of the aspects of the pathogenesis of asthma have been related to an underlying chronic inflammatory process that is based on a balance between pro-inflammatory and anti-inflammatory mediators. The balance is tipped between increased and decresed levels of cytokines,Ayad Mohammed Salem. et al demonstrated that N. sativa as well as thymoqiunone augment the release of IFN-γ and suppress IL-4 production which improves some measures of inflammation and pulmonary function.(11)

Moreover, N. sativa has anti-cancer, gastroprotective, nephroprotective , Hepatoprotective and Miscellaneous nutraceutical effects.(9,10)

D-Immune Mechanism of Thymoquinone

Thymoquinone (TQ) , the active component in Nigella sativa (black seed) (12,13) has a beneficial effect on human body; many studies reported it's effect acts as an anticancer, antimicrobial and anti-inflammatory substance(14-18).In addition, scientist found an important role for Thymoquinone in immune system and T-cell during in-vitro study on mice and resulted in increasing transgenic CD8+(19). Also it has different effect on cellular immunity, humoral immunity, TH cell and NK cell.

Effects of TQ on Cellular Immunity

A lot of studies investigated the action of Thymoquinone on cellular immunity. In 2007, El Gazzar established in vitro study on lipopolysaccharide (LPS) activated RBL-2H3 cells (rat mast cell) to find the effect on IL-5, IL-13,IL-10 and Th2 cytokine, and he found that TQ decreased the level of IL-5 and IL-13 by and it has no effect on IL-10(20).also, it has role on transcription factor by stopping the action of globin transcription factor (GATA) transcription factor which play an important role with activator protein 1 (AP-1), and nuclear factor of activated T cells (NF-AT) in the transcription of IL-5 and IL-13, and this study show no effect for TQ on AP-1 and NF-AT (20).

Xuan with his team studied cytokines release on LPS-induced dendritic cell by adding thymoquinone (1-20 μM) in dependent dose manner and they found inhibition in releasing IL-10, IL-12 and TNF-α, at the same time, it activated caspase 3 and caspase 8 and binding of annexin V(21). Also, a study on diabeteic rats which have a high level of IL-1b, IL-6, and TNF- α and low level in IL-2 showed that a 20 mg/kg of TQ lead to increase in the level of IL-2, IL-1b, IL-6, and TNF- α(22). in addition, the level of apoptotic peripheral T cells and thymocytes was lower in

diabetic rats treated with TQ compared to diabetic rats with no intervention (22).

The anti-cancerous effect of TQ showed an inhibition in the growth of medulloblastoma and hepatocellular carcinoma cells (23,24). It suppressed the IL-8 and NF-κB in tumor cell leading to decrease the number of hepatocellular carcinoma cell and medulloblastoma cells (23,24) Also, it increase the apoptosis by increasing the level of the executioner caspase-3 and caspase-7 (24).

Regarding inflammation and cytokines, TQ act as anti-inflammatory by reducing pro-inflammatory cytokines and it lead to decrease IL-1β in Osteoarthritis Chondrocytes (25). Also, a 1or 2 mg/kg from TQ for 2 hours in mouse suffering from sepsis lead to decrease in death and level of IL-1, IL-2, IL-6, IL-10 and TNF- α (26), and in activated microglia cells the level of IL-2, IL-4, IL-6, IL-10, and IL-17a decreased by Thymoquinone (27)

Many factor lead to increase the level of inflammatory cytokines such as inflammation, Gamma radiation and arthritis (28-30), Gamma irradiation cause increase in the level of cytokine in male rats but when we added TQ, it restored IL-6 and TNF- α to the normal level(30), The same effect was documented in inflammation of testicular tissue by decreasing TNF- α, IL-1b, IL-6 (29), and reduced TLR2, TLR4, IL-1, NFκB and TNF-α in rheumatoid arthritis(28)

Effects of TQ on Humoral Immunity

Only study reported the effect of TQ on humoral immunity in rats which were given imidacloprid insecticide, and they found that TQ enhanced immunoglobulin level of IgG and agglutination of anti-bodies, and this finding showed a beneficial role for TQ on humoral immunity (31).

COVID and TQ

Since the emergence of COVID-19 in Wuhan city on December 2019(32), the world is facing a huge problem from the pandemic which resulted in infecting millions of people with COVID-19 and more than 460,000 deaths around the world(33)

Several studies reported the immunological profile for COVID-19 patients, and they found that the levels of (IL-2R), IL-6, IL-10, and (TNF-α) were elevated in patients with severe disease compared with less severe patients (34). Also, they found that deceased patients with diabetes have a significant increase in the level of IL-2 receptor, IL-6 and CRP compared with survived patients (35), another study confirmed that interleukin-6 and C-reactive protein predict the severity of COVID-19 (36). TQ showed an anti-inflammatory effect by reducing Interleukin level and CRP and it can show a good result by decreasing the mortality and improving the severity in patients with covid-19, future studies should focus on the effect of TQ on hospitalized patients to study its effect on the outcome.

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