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A Systematic Review on Multimodal Effects of Thymoquinone

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ABSTRACT:- Thymoquinone (TQ) is a purely standard biological active component of Nigella sativa widely known as black cumin, Kalonji seeds or kalajeera belongs to Ranunculaceae family. TQ has favourable affect in viral infection especially in COVID-19 (SARS Covid-2) by inhibiting virus entry to the cell and its increases endosomal P^H that results in inhibition of virions release and destroys virions by oxidizing lipophilic evelope. Thymoquinone could move effectively cross the plasma membrane of infected cells due to its hydrophobicity than Chloroquine and Hydroxychloroquine. Thymoquinone acts as neuroprotective by inhibiting the generation of free radicals, increasing antioxidant enzymes and inhibiting activation of microglia in neuronal cells. Thymoquinone decreased plasma glucose level and increased serum insulin level in DM. TQ prevented tumor angiogenesis and tumor growth therefore a potential drug for cancer therapy. TQ has potential effect as anticonvulsion which effects on epilepsy by lowering cell membrane electrical excitability and improving synaptic inhibition mediated by GABA. Thus TQ posses Neuroprotective, tumor protective, anticonvulsant, antiviral and anticancer effect. TQ have powerful anti-oxidant and free radical scavenging activity. It is safe upto 100mg/kg.

KEYWORDS : Thymoquinone, Nigella Sativa, Covid-19, SARS Covid-2, Antiviral, Anticancer, Antidiabetic,Neuroprotective,Anticonvulsant

I. INTRODUCTION

Thymoquinone (TQ) is a significant bioactive constituent essentially found in Nigella sativa. Nigella sativa commonly called as black cumin, kalonji or kalajeera, that belongs to the Ranunculaceae family.[1] Nigella sativa L is an yearly herbaceous plant cultivated and naturalized in Europe , North Africa and native to South West Asia.[2] The plant develops to a most extreme tallness of around 40-70cm and has finely separated foliage and light blue and white flowers. Plenty small caraway-type black seeds are produced from the fruit capsules (length: 2.5 to 3.5 mm and width: 1.5 to 2mm).[3]

Nigella sativa has been used in numerous varieties of herbal medicine to cure many illnesses, including asthma, high blood pressure, diabetes, inflammation, cough, bronchitis, fatigue, eczema, fever, dizziness.[2] There are various bioactive compounds in Nigella sativa plants, including thymoquinone (TQ), dithymoquinone (DTQ), thymohydroquinone (THQ), thymol (THY), tocopherols, trans-retinol, selenium, etc. TQ is the most excessive phenolic compound, and this functional ingredient is mainly found in fixed and essential oils of Nigella seeds.[1]

II. ISOLATION OF THYMOQUINONE

Thymoquinone was first obtained using the thin layer chromatography on a silica gel by El-Dakhakhny. TQ is an chief agent of natural origin and it has created interest for its therapeutic impact in the field of scientific research.[1]

III. DOSAGE FORM OF THYMOQUINONE

Various toxicological experiments have showed that oral administration of 10 to 100 mg/kg of TQ dose does not have any toxic or lethal effects in mice. The maximal tolerated dosage of TQ was found to be 22.5 mg/kg in male rats and 15 mg/kg in female rats when injected with IP, Also the dose was 250 mg/kg after oral administration in both male and female rats.[4]

IV. SCIENTIFIC RESEARCHES AND PHARMACOLOGICAL POTENTIALS

Anti-convulsants, anti-virals, anti-microbials, anti-cancer, anti-histamines, anti-diabetic, anti-inflammatory, and anti-oxidants were the main pharmacological activities that are carried out by Thymoquinone.[5]

V. ANTI-VIRAL EFFECTS

Thymoquinone (TQ), a bioactive constituent largely unknown to many experts in Western countries, to the attention of the science and medical community, which is focused on helping people afflicted with the virus by

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(a) By inhibiting its replication,
(b) By suppressing it,
(c) By its anti-inflammatory effect and
(d) By immunomodulatory effects

- maybe acting synergistically or even like a prophylactic solution to prevent SARSCoV-2 infection. However, the systemic bioavailability of the TQ is poor mainly due to its hydrophobicity. There are nanocarriers targeting the lungs and the TQ has also been used successfully for nanomedicines targeting multiple organs other than the lungs.[6]

The hydrophobic aspect of TQ leads to the avoidance of early immobilisation of the compound during its transport to the target organs. TQ could more effectively cross the plasma membrane of the infected cells due to its hydrophobicity and smaller size compared to Chloroquine (CQ) and Hydroxychloroquine (HCQ). On the path to infected cells, SARS-CoV-2 can be killed by TQ before joining the cells simply by binding to and oxidizing the lipophilic envelope of the virus, in line with the hydrophobic design of the molecule. Thus, the antiviral effect of CQ and HCQ in endosomes is virtually limited to P^H modulation. Whereas the drug delivery could be prepared for hydrophobic TQ in one-stage process but the Immobilization of the polar CQ in the hydrophobic nanoparticles is very less trivial.[7]

Despite in orderly to exploit the full synergistic capacity of TQ clinically, it would be important to create a effective biodegradable nanocarriers for delivery of the drug to the site of SARS-CoV-2 infection, for example- to the lungs. A considerable amount of work on the TQ encapsulation has already been completed.[4] Thus these studies showed that thymoquinone may have potential drug for the treatment and prophylaxis of SARS-CoV-2 infected patients.[6]

A modern study showed that TQ could function against the SARSCoV-2 as an antiviral. since it as revealed that in silico, TQ could have inhibitory actions against its viral protease. This very fascinating finding prompted the study of the documented roles of TQ in controlling proteins that are involved both in COVID-19 and pathogenesis of cancer. First, it decreases the chance of entry into cells of SARS-CoV-2. Second, in the COVID-19-infected cancer patients, TQ helps to enhance the deleterious effects of Cytokine release syndrome, thus it protects against a multiple organ damage. Thus it summarize it as a typical molecular targets and the effects of TQ that are helpful in both the cancer and COVID-19 patients. Overall, TQ is a promising option that could win the battle against COVID-19 and Cancer.[8]

VI. NEUROPROTECTIVE EFFECTS

The most prevalent movement condition in the population is Parkinson's disease, which is marked by deteriorating motor disorders such as resting tremor, muscle rigidity, trouble performing voluntary movements, and postural dysfunction. Neuronal dysfunction in patients with Parkinson Disease is also due to mitochondrial dysfunction and elevated oxidative stress.[9] A studies have showed that 1) TQ's ability for guarding dopaminergic neurons from MPP+ and rotenone cytotoxicity in cell culture.[10]

2) TQ could minimise neuronal harm and loss by counteracting oxidative stress, probably by regulating the antioxidant defence system and inhibiting the generation of free radicals.[11]

3) TQ has also been reported to decrease peroxidation levels, increase the activity of enzymatic and non-enzymatic antioxidants in the brain tissue of rats.[12]

Neuroinflammation is the main factor implicated in the pathogenesis of neurodegenerative disorders. The main factor involved in the ignition and development of the neuroinflammation is the activation of microglia by responding to stimuli such as infection and traumatic brain injury (TBI).[13] Therefore inhibition of microglia activation is effective for neuronal cell survival. Thus the studies showed that thymoquinone has lowered the release and levels of TNF-α, IL-6, IL-1β, and prostaglandin E2 (PGE2) messenger RNA (mRNA) in rat microglia cells exposed to lipopolysaccharides (LPS; 100 ng/ml).[14]

Another study was performed to assess the neuroprotective effects of thymoquinone due to its strong free radical scavenging action against superoxide anions such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase, it has been found to elicit powerful antioxidant activity.[5]

VII. ANTI-CONVULSANT EFFECTS

Epilepsy is a very common disorder which affects 0.5-1% of the population[15]. It is suspected that existing antiepileptic medications (AEDs) function primarily by: a) lowering cell membrane electrical excitability, and b) improving synaptic inhibition mediated by GABA.[16]

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Simultaneous firing of frontal neurons is characterised by epileptic seizures. The clinical use of anti-epileptic medications has been focused on reducing the activity of Na+, K+, or Ca2+ flux in neurons, inhibiting neurotransmission of glutamate (Glu), or encouraging γ-aminobutyric acid (GABA) activity in the Cl-channel.[17] Studies have shown that thymoquinone exerts its anticonvulsant effects by mechanism of action in the central nervous system by stimulating the opioid receptors.[18]
Another study showed that a favourable impact of thymoquinone in rats with a penicillin-induced epilepsy. Multiple doses of TQ (10, 50, and 100 mg/kg, IP) were used and their effects were compared with other groups providing a vehicle (dimethylsulfoxide), sham, or control. Thus the findings showed that TQ extended lag time and decreased epileptic seizure frequency and power relative to the vehicle-receiving group.[19]

VIII. ANTI-DIABETIC EFFECTS

Diabetes is a chronic metabolic disorder consisting of serum glucose progression and the production of insulin deficiency triggered by b-cell injury. Serious complications, particularly cardiovascular diseases, can be associated with diabetes.[20-22] ROS plays an important role in the progression of various diseases such as diabetes mellitus. The participation of ROS in diabetes pathophysiology is manifested by changes in the production of lipid peroxides, antioxidant enzymes, oxidative stress formation, auto-oxidation of glucose, glycosylation of non-enzymatic proteins and ultimately impaired metabolism of glutathione.[23-25] Free radicals induce ROS overgeneration, which initiates multiple pathways associated with inflammatory signalling cascades, leading to inflammation.[26] Activation of pro-inflammatory genes can promote local cell inflammation that can deteriorate local cells and eventually cause type 2 diabetes and apoptosis of β-cells.[27,28] A Scientific study shows that TQ reduces the activation of the enzyme COX-2 in β-cells. Treatment with thymoquinone were also resulted in a decrease in MDA (Malondialdehyde) levels and an increase in SOD (Superoxide Dismutase) levels in the pancreatic tissue of diabetic rats.[29] By decreasing ROS and thus protecting the β-cell from damage, TQ has anti-diabetic properties.[30-32]

IX. ANTI-CANCER EFFECTS

Transformation of a normal cell to a cancer cell is a multi-step process, involving the gene instability, irregular of gene expression, angiogenesis, metastases and immune evasion.[33] A studies have showed that the treatment of tumor-bearing mice with 10mg/kg of thymoquinone demonstrated a substantial ($P<0.05$) potential to decrease a tumor development with a percentage of difference in tumour size (−1.25%) relative to the untreated mice (+209.82%). A greater decrease in tumour development was found in tumor-bearing mice treated with 141mg/kg of CB 1954 with a percentage shift in tumour size about (−10.34%). The largest reduction of tumour size was recorded for mice treated with a combination of TQ and CB 1954 with a decrease in tumour size about (−21.58%).[34]

In another study thymoquinone was examined against benzo-pyrene mediated forestomach tumour in female Swiss albino mice. Thymoquinone (0.01 per cent of drinking water) given one week before and after treatment with benzo-pyrene has been shown to decrease the frequency and multiplicity of Benzo-pyrene-induced forestomach tumours.[35] Thymoquinone (0.01 per cent of drinking water) administered one week before, after and after 20-methylcholanthrene treatment greatly inhibited the occurrence of fibrosarcoma tumours and the burden of tumours in male Swiss albino mice.[36]

Thymoquinone also blocked tumour angiogenesis in the mouse model of human prostate cancer xenograft (PC3) and suppressed human prostate tumour development at low dosage with almost no chemotoxic side effects. In comparison, endothelial cells have been found to be more susceptible to tymoquinone-induced cell apoptosis, cell proliferation and suppression of migration compared to PC3 cancer cells. Thymoquinone inhibited the vascular endothelial growth factor and mediated the extracellular signal by regulating the kinase activation but it did not inhibited the vascular endothelial growth factor of receptor-2 activation. It also hindered cell proliferation and blocked the activation of AKT and extracellular signal mediated kinase. Overall, these findings showed that thymoquinone prevented tumour angiogenesis and tumor growth and will therefore a potential drug for cancer therapy.[37]

CONCLUSION

This review enumerate the biological properties of thymoqinone and its therapeutic potential against several diseases including SARS Covid-2, Diabetic milletus, Neurodegenerative illness, convulsion/Epilepsy, cancer. This review

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concluded that thymoquinone has the favourable effect in viral infections especially in Covid-19 by inhibiting the viral entry to the cell by increasing the endosomal P^H & inhibiting the virus infection. Thymoquinone also been used successfully for nanomedicines targeting multiple organs other than lungs. Thymoquinone acts as neuroprotective by inhibiting the activation of microglia in the neuronal cells and by inhibiting the generation of free radicals. Thymoquinone has the anticonvulsant or antiepileptic effects by lowering cell membrane electrical excitability and improving synaptic inhibition mediated by GABA. In Diabetes mellitus, Thymoquinone significantly decreases the ROS generation and inhibits the inflammation of β-cell damage. Thymoquinone prevented tumor angiogenesis and tumor growth therefore a potential drug for cancer therapy. The overall review shows that thymoquinone has multimodal effects which acts as antiviral, antidiabetic, anticancer and anticonvulsion/antiepileptic and neuroprotective activity.

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