Thymoquinone: Possible role in Treatment of Neurological Diseases

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Abstract

Background: Nigella sativa (N. Sativa), well recognized as black cumin has been utilized as a medicinal plant that has a strong traditional background. The seeds of N. sativa contain fixed oil, essential oil, proteins, alkaloids and saponins. A good number of biologically active molecules are also present, such as thymoquinone (TQ), flavonoids, α-hederin, alkaloids, antioxidants and fatty acids which are good for a healthy well-being. Numerous laboratory research and clinical studies have established that TQ exhibited a role in cancer management through the activation and inactivation of molecular cascades. It exhibits killing of cancer cells through activation of tumour-suppressor gene, inhibition of angiogenesis and inhibition of transcription factor as well as enzymes linked to cancer development and progression. The implications of TQ as an antitumor agent were studied based on breast carcinoma and it was confirmed that it is an anti-proliferative agent. Thymoquinone (TQ) possesses anticonvulsant, antianxiety, antidepressant, and antipsychotic properties. It could be utilized to treat drug misuse or dependence, and those with memory and cognitive impairment. TQ protects brain cells from oxidative stress, which is especially pronounced in memory-related regions. TQ exhibits antineurotoxin characteristics, implying its role in preventing neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease. TQ's antioxidant and anti-inflammatory properties protect brain cells from damage and inflammation. Glutamate can trigger cell death by causing mitochondrial malfunction and the formation of reactive oxygen species (ROS). Reduction in ROS production can explain TQ effects in neuroinflammation.

Keywords: Thymoquinone, Neurological Diseases

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1. Introduction

Nigella sativa (N. Sativa), well recognized as black cumin has been utilized as a medicinal plant that has a strong traditional background. The seeds of N. sativa contain fixed oil, essential oil, proteins, alkaloids and saponins. A good number of biologically active molecules are also present, such as thymoquinone (TQ), flavonoids, α-hederin, alkaloids, antioxidants and fatty acids which are good for a healthy well-being **(1).**

N.sativa has many of therapeutic actions, such as anti-inflammatory, anticancer, antidiabetic, antimicrobial, antiepileptic, antioxidant, hepatoprotective activities and many others. It possesses a good potential to be used as a drug against neurodegenerative disorders and brain damage which adversely affect memory and learning **(2).**

(2-Isopropyl-5-methylbenzo-1,4-quinone) or commonly called as thymoquinone (TQ) is the most principal component of the essential oil obtained from N. sativa seeds and has been intensively investigated. It makes up 30–48% of the total compounds present in N. sativa seeds. TQ possesses numerous therapeutic and

pharmacological properties. Thymoquinone has been shown to exert anti-inflammatory, antidiabetic,antimicrobial,analgesic,immunomodulatory, spasmolytic, hepatoprotective, renal-protective, gastroprotective, bronchodilatory, antioxidant and antineoplastic effects **(3).**

Numerous laboratory research and clinical studies have established that TQ exhibited a role in cancer management through the activation and inactivation of molecular cascades. It exhibits killing of cancer cells through activation of tumour-suppressor gene, inhibition of angiogenesis and inhibition of transcription factor as well as enzymes linked to cancer development and progression. The implications of TQ as an antitumour agent were studied based on breast carcinoma and it was confirmed that it is an anti-proliferative agent **(4).**

In addition to the above mentioned well-recognized activities, its anti-inflammatory and antioxidant properties are well recognized now. TQ acts as an antioxidant or pro-oxidant at various concentrations. However, the pro-oxidant or antioxidant potential of TQ depends on the situation where it is present as it can be reduced to semiquinone (one reduction) or thymohydroquinone (two reductions). Thymohydroquinone acts as an antioxidant while semiquinone has been reported as pro-oxidant generating ROS **(5).**

Thymoquinone has been shown to act as potent antioxidant by scavenging anion and reactive oxidative species (ROS). It can antagonize the adverse effects resulting from elevated ROS levels in various disorders. Antioxidant property is considered one of the vital properties of TQ. Mitochondrial electron transport chain has a significant potential in the antioxidant property of TQ. It converts TQ from the oxidized form which has a very low antioxidant activity to the reduced form; thymohydroquinone which possesses high radical-scavenging capability.TQ can also decrease the toxic effects of anticancer drugs and ameliorate multiple organ toxicity in oxidative stress models **(6).**

Thymoquinone acts by induction of cytoprotective enzymes resulting in cells' protection against oxidative stress induced cellular damage. Several studies have reported that TQ upregulates mRNA expression and activation of antioxidant cytoprotectiveenzymesincluding, catalase (CAT) , superoxideismutase (SOD), glutathione reductase (GR),glutathione-S-transferase (GST) and glutathione peroxidase (GPx), whose functions are scavenging hydrogen peroxide and superoxide radicals and preventing lipid peroxidation .The antioxidant potential of TQ was confirmed against pesticides , heavy metals, aflatoxins and carcinogens induced oxidative damage **(7).**

Several studies also suggest that TQ acts as a pro-oxidant and has been reported to potentially induce apoptosis in cancer cells, generate ROS, and downregulate pro-survival genes, making conformational changes in pro-apoptotic genes and therefore, loss of mitochondrial membrane potential leading to the induction of caspase-3, caspase-9 and polyadenosine 5'-diphosphate ribose polymerase cleavage and caspase dependent apoptosis **(8).**

These beneficial effects of thymoquinone support the use of this natural compound as a drug with a wide range of medical applications. It is systemically well-tolerated with a large safety profile and has the potential to reduce oxidative stress and systemic toxicity as the dose increases. Its less toxic effects, availability, and lower price versus synthetic substances make it as excellent and simple selection in the treatment of several nervous lesions **(9).**

Effect of Thymoquinone on Neurological Diseases

Alzheimer's Disease

AD is the most common neurodegenerative disorder manifested by reduced memory and other cognitive functions. The symptoms begin in the temporal and frontal lobes of the brain. AD usually affects patients above 60 years of age but sometimes those who are significantly younger. The primary mechanism for neural damage in AD is activating glial cells caused by the inflammation and releasing the proinflammatory cytokines in the hippocampus that can suppress memory and learning ACh is

the principal neurotransmitter, and its declined release and subsequent hydroxylation with AChE and butyrylcholinesterase (BChE) decrease ACh rapidly, resulting in learning deficits. Pathophysiology of AD is related to the poisoned consequence of beta-amyloid (A_), a dysfunctional amyloid precursor protein leading to the accumulation of amyloid plaques in the brain, resulting in damage to the signaling activity of the nerves. TQ ameliorates and prevents A_-induced neurotoxicity and mitochondrial membrane depolarization by inhibiting ROS formation and reducing oxidative stress by antioxidant properties. TQ improves synaptic vesicle recycling and inhibits A_ 1–42 aggregation.

pretreatment with TQ can inhibit apoptosis and free radicals' production, causing cell regeneration. In this regard, in vitro studies of anti-Alzheimer impacts of TQ demonstrate that TQ acting on signal pathways that TNF-a mediates leads to the inhibition of oxidation of Beta-amyloid (Ab). These happen through downregulation and upregulation effects on nitric oxide (NO) and glutathione (GSH) **(10).**

Parkinson's Disease

PD is a multi-centric neurodegenerative disease distinguished by degeneration of the dopaminergic system in the pars compacta, the portion of the substantia nigra. The pathophysiology of PD is mainly related to oxidative stress and inflammation. The major manifestations of PD are bradykinesia, rigidity, numbness, limpness, and resting tremors, and are reduced with dopamine replacement therapies. Excessive and continuous muscle contraction causes the rigidity that characterizes resistance to movement. Furthermore, the progression of the disease may lead specifically to dyskinesia. Other symptoms in the advanced stage of PD such as dementia, depression, autonomic failure, and sleep abnormality are also evident. Previous clinical therapy of patients includes observing several factors such as signs and symptoms, disease stage, age, and level of functional disability. Some medicinal herbs such as Nigella sativa improve PD symptoms and prevent the deterioration of motor symptoms. Rotenone, an insecticide and pesticide, can cause movement failure or Parkinson's symptoms such as incoordination, muscle tremor, or rigidity. Cotreatment of rotenone and TQ prevented PD symptoms induced by rotenone. **(11).**

Epilepsy

Epilepsy is one of the most heterogeneous neurological disorders caused by a simultaneous electrical release of neurons in the brain and is considered a biochemical phenomenon that is not completely understood. It is characterized by persistent neuronal activity and repeated spontaneous seizures. Epilepsy is considered an asymptomatic occurrence instead of a disease arising from traumatic brain injury and genetic factors. As a result of an increased escape of glutamate neurotransmitters, it leads to binding with glutamatergic neurons, giving rise to high liberation of calcium in the postsynaptic neuronal cells. Epilepsy has different categories that depend on age, type of seizures, deterioration of the condition, and therapy. TQ offers protection from glutamate-induced cellular toxicity in SH-SY5Y neurons. Glutamate has several toxic effects as it can cause loss of viability, the generation of ROS, dysfunction of the mitochondria that will lead to apoptosis through the decreased Bax/Bcl-2 ratio, and increased expression of caspase 9. TQ can also protect from the effects of glutamate by reducing ROS production by inhibiting mitochondria dysfunction, hence inhibiting apoptosis. **(12).**

Effect of Thymoquinone on Learning and Memory

Learning and memory are essential for developing the human brain, and impairment is a significant cause of dementia. It can occur by aging, brain injuries, or neurodegenerative disorders. Usually, impairment interferes with learning and memory function. The effects of TQ on memory and cognition are related to spatial memory. This includes the ability of the brain to recognize, store, and recover information. ACh, a neurotransmitter in CNS, plays an essential role in managing learning and memory. Memory diminishing could becaused when the release of

ACh decreases. AChE is an enzyme used for the degradation of ACh. Clinical studies establish that TQ inhibits AChE activity, which increases ACh, thereby preserving the effects by programming new memories. Another study reports that TQ prevents memory deficit induced by scopolamine in rats, as the study showed a decrease in the release of AChE activity in the cortex tissue and hippocampus. TQ has a similar effect to donepezil, an inhibitor of AChE known to have a favorable impact on reducing brain tumor necrosis factor-alpha (TNF-_) content and increasing glutathione brain contents. TQ has a valuable ability that protects the brain against cellular damage due to oxidative stress through free radical scavenging properties, which could help preserve memory loss. One study shows that prolonged use of TQ increases the consolidation and recall capability of information storing and spatial memory in diabetic animals **(13).**

Safety and Adverse Effects

The Nigella Sativa oil extracts appear to have a low toxicity level. The administration of 50 mg/kg of oil to the rats for five days did not show any meaningful hepatic and renal enzymes activity. When administrating doses up to 10 mL/kg in rats, there were no signs of toxicity during the 48 h of observation. This indication was also shown when oral administration for 12weeks reported the same result as the 48-h observation. Therewas not any change in mortality or haptic enzyme. Acute administration of 2 g/kg or more, considered an extremely high dose, could cause respiration problems. Clinically, high doses release an antioxidant known as glutathione in the heart, kidney, and liver. Administration concentrations of up to 0.03% for 90 days of TQ in mice's drinking water showed no toxicity. However, there was a significant decrease in the fasting plasma glucose concentration **(14,15).** Furthermore, a concentration of 1 mM instantly caused cytotoxicity, as exhibited by nuclear shrinkage and plasma membrane blebs. TQ lower concentrations such as 100 lM cause cell death within a few hours after receiving the treatment. TQ concentrations of 50 lM and 25 lM displayed acute cytotoxicity by high necrosis levels and nearly complete cell annihilation at the time of collecting within two days. Lower concentrations inducing necrosis were less toxic. Increasing the concentration of TQ up to 10 lM induces genotoxicity, a significant increase in the reoccurrence of chromosomal aberrations. Furthermore, it shows cystic- and genotoxic effects in a concentration-dependent manner. At 2.5 lM, the cytotoxic effect is proven by an excessive increase in necrotic cells. At 20 lM, an antiproliferative effect is supported by a significant decline of mitotic cells. **(14,15).**

Conclusions

TQ is the primary active crude extract of Nigella sativa seeds and shows many therapeutic benefits, lowers chance of toxicity, and presents minimized side effects. Researchers in different regions have studied the evolution of ancient uses of TQ to find an alternative remedy to the current treatments, and they work to minimize the side effects of the use of TQ.

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