The therapeutic activity of thymoquinone derived from black seed (*Nigella sativa* L.)

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Abstract

Recently, natural products of herbal origin have acquired great importance in protecting against and curing many diseases as an alternative to chemical drugs that sometimes cause many side effects. In this study, we focused on thymoquinone (TQ), a natural product derived from black seed (*Nigella sativa* L.) that awards it its therapeutic activity. It has many therapeutic activities such as anti-inflammatory, anti-microbial, anti-oxidant, anti-histaminic, immunomodulatory and anti-tumor activity. Other therapeutic benefits were also encountered as gastroprotective, nephroprotective, neuroprotective and hepatoprotective activities. It has also cured diabetes, cardiovascular disorders, respiratory ailments, reproductive disorders and bone complications. Thymoquinone protects the body against diseases caused by oxidative stress as a phenolic derivative with a distinct antioxidant activity by scavenging the free radicals and reducing the oxidative stress. It also protects against the detrimental effects of nicotine on sperm count and sperm damage in rats. In this review, we introduced some potent therapeutic activities of thymoquinone and illustrated the most recent investigation reflecting its therapeutic effects. Recent investigations suggest that clinical trials must consider TQ as a novel drug.

Keywords: Thymoquinone, Nigella sativa, antioxidant, antidiabetic, therapy.

1- Introduction

Free natural products from plants, algae, or other biological systems or their nano or semi synthesized natural products have great therapeutic activity (Elsayed et al., 2021; Aljohani et al., 2023; Alhawiti et al., 2023, El Rabey and Almutairi, 2024). They successfully and

efficiently enhanced the treatment efficacy of many drugs via nanoparticles combination (Keshk et al., 2023; Almutairi et al., 2023; El Rabey et al., 2024).

Thymoquinone is a natural product constituting the abundant bulk of *Nigella sativa* seeds (black seed) that acquire it a potent therapeutic activity by protecting against many diseases and curing many others in the Middle East and North Africa (Al-Seeni et al, 2018; El Rabey et al., 2017; Albalawi and El Rabey, 2024). *Nigella sativa* is used in ethnomedicine to treat ailments and symptoms including, asthma, bronchitis, inflammation, eczema, fever, influenza, hypertension, cough, headache, dizziness, diabetes, kidney and liver dysfunctions, nervous disorders, rheumatism, cancer and related inflammatory diseases, gastrointestinal problems, and overall, for general well-being (Gali-Muhtasib et al., 2006; Singh et al., 2013; Darakhshan et al., 2015). In addition, *N. sativa* seeds (NS) contain diverse but well-characterized chemical components; they include both fixed and essential (volatile) oil, proteins and amino acids, vitamins, carbohydrates, crude fibers, organic acids, saponins, minerals and alkaloids, (Darakhshan et al., 2015).

Thymoquinone is a phenolic derivative as in Fig. 1.

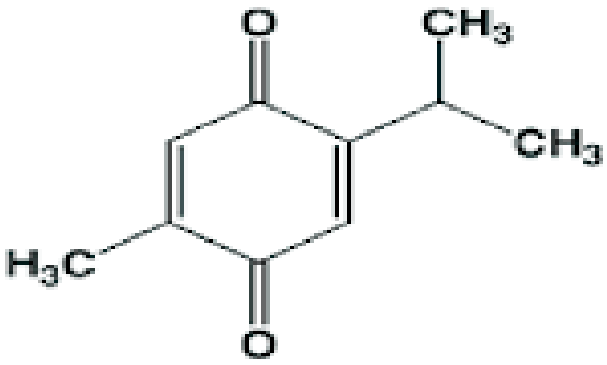

Fig. 1. Thymoquinone (TQ)

Thymoquinone plays an important role as a chemo-preventive and therapeutic agent in the treatment of various diseases and illnesses (Sarkar et al., 2021; Albalawi and El Rabey, 2024).

It was effective against many types of cancers as an anticancer drug (Asaduzzaman et al., 2017; Malik et al., 2021). It also showed an anti-inflammatory effect against neuro-inflammation (Malik et al., 2021; Abo Mansour et al., 2023). It also protected the liver of mice against hepatic injury induced by sodium fluoride (Daba and Abdel-Rahman, 1998; Malik et al., 2021). Thymoquinone has also a cardiac protective effect because of its antioxidant, hypocholesterolemic and anti-inflammatory activity (Kohandel et al., 2021; Rathod et al., 2022).

Thymoquinone showed also a potent anti-inflammatory efficacy in heart disorders, respiratory diseases, neuroinflammation, diabetes, and arthritis (Kohandel et al., 2021; Kanaç et al., 2022). The antioxidant activity is a great property of the reduced form of thymoquinone through the high radical-scavenging activity more than the oxidized form (Malik et al., 2021; Isaev et al., 2023). The hypoglycemic activity of thymoquinone is another important characteristic that can regulate insulin resistance and diminish oxidative damage (Bule et al., 2020).

Thymoquinone also showed antipathogenic effects against various pathogenic microbial strains, including bacteria, viruses, parasites and fungi (Chaieb et al., 2011; Malik et al., 2021, Al-Khalifa et al., 2021). In addition, it revealed an antitoxic activity as a protective antioxidant agent against toxicities induced by numerous drugs (Albalawi and El Rabey, 2024). Furthermore, thymoquinone protects against nicotine-affected sperm in rats (Rosli et al., 2019).

Recently, the therapeutic activity of thymoquinone was enhanced by coating it with nanoparticles alone or in combination with other natural products or therapeutic agents (Ullah et al., 2017). *In vitro* and *in vivo* studies showed that the therapeutic activity of thymoquinone is owing to its potent activity by acting on various mechanisms, pathways, receptors and genes Malik et al., 2021).

In this review, we collected most therapeutic activities of thymoquinone both in its free form or nanoparticles in combination with other natural products or therapeutics.

2- The antioxidant activity of thymoquinone

The reduced form of thymoquinone revealed antioxidant activity through the high radical-scavenging activity more than the oxidized form (Malik et al., 2021. also increases nitrate concentrations and constitutive nitric oxide synthase activity while decreasing Inducible nitric oxide synthase (iNOS) activity, which is beneficial in treating endothelial (Isaev et al., 2023). Thymoquinone also acted as an effective natural potent antioxidant with strong hydroxyl radical scavenging properties that enhance the stability of edible oils as an alternative to synthetic antioxidants (Erdoğan, 2022; Khither et al., 2018). It was able to decrease oxidative stress thymoquinonehas revealed a potent superoxide scavenging activity (Sakib et al., 2023). In addition, Thymoquinone scavenging capacity against free radicals was increased in a human normal lung fibroblast by dual encapsulation in palmitoyl-chitosan nanoparticles **(**Othman et al.**,** 2023).

3- The antidiabetic activity of thymoquinone

Thymoquinone regulated insulin resistance and diminished oxidative damage resulting from protease inhibitors (Bule et al., 2020). The green synthesis of silver nanoparticles for the methanolic extract of thymoquinone containing *Nigella sativa* methanolic protected against the diabetic neuropathy of diabetic patients (Alkhalaf et al., 2020). Thymoquinone could activate the imidazoline receptor and increase glucagon-like peptide-1 secretion in diabetic rats (Lee et al., 2023).

In addition, by using the molecular docking approach in a rat trial, thymoquinone decreased the diabetes-induced hepatic damage by regulation of apoptosis, oxidative/nitrosative stress, and inflammatory cascade (Hafez et al., 2024).

4- The antitumor activity of thymoquinone

Thymoquinone showed anticancer activity for different types of cancers that may lead to the development of new thymoquinone-derived therapies to replace the current treatments such

as chemotherapy, radiotherapy and surgery but have several side effects (Asaduzzaman et al., 2017; Malik et al., 2021). Thymoquinone is a crucial agent in the prevention and progression of Triple-Negative Breast Cancer Prevention and Progression through the Modulation of the Tumor Microenvironment (Adinew et al., 2022). When mixed with propolis, thymoquinone improved its therapeutic and nutritive value and increased the antioxidant and anticancer properties of propolis (AlDreiniet al., 2023). Besides its antioxidant, anti-inflammatory, cytotoxic, hepatoprotective, antiparasitic antifungal, antiprotozoal, and other encountered therapeutic values, thymoquinone showed a potent anticancer making it a potent treatment for different types of cancers (Sowunmi and Kaka, 2023). The nanoformulations of Poly Lactic-co-Glycolic Acid (PLGA) loaded thymoquinone when combined with chitosan nanoparticles (PLGA-CS-TQ-NPs) increased its effectiveness against triple-negative breast cancer (TNBC) (Gao et al., 2023).

5- The hepatoprotective activity of thymoquinone

Thymoquinone administration protected the liver of mice against hepatic injury induced by sodium fluoride in combination therapy with N-acetylcysteine, as both drugs can downregulate various inflammatory pathways that include cyclooxygenase-2 (COX-2), nuclear factor kappa B (NF-κβ) and signal transducer and activator of transcription 3 (STAT-3) (Daba and Abdel-Rahman, 1998; Malik et al., 2021; (Sowunmi and Kaka, 2023). Thymoquinone showed hepatoprotective, anti-inflammatory, antioxidant, cytotoxic and anti-cancer activity that support it as a promising future drug (Khader and Eckl, 2014).

6- The cardioprotective activity of thymoquinone

Owing to its antioxidant and anti-inflammatory activity, thymoquinone improves the cardioprotective activity in β-receptor stimulated myocardial Infarcted rats (Rathod et al., 2022) by lowering Hypercholesterolemia which is a well-established risk factor for cardiotoxicity (El Rabey et al. 2017; Al-Seeni et al., 2018). Thymoquinone has a potent utility as a potential drug for cardiomyopathy. Blood serum markers; aspartate aminotransferase (AST), Alanine aminotransferase (ALT), creatine kinase myocardial band (CK-MB) and lactate dehydrogenase (LDH)) and the oxidative stress markers

(lactoperoxidase, LPO), GSH, catalase (CAT), superoxide dismutase (SOD), and glutathione *S*-transferases (GST)) that are enhanced during doxorubicin-induced cardio-cytotoxicity are ameliorated by thymoquinone (Kohandel et al., 2021; Rathod et al., 2022).

7- Anti-inflammatory activity of thymoquinone

Its anti-inflammatory efficacy in heart disorders, respiratory diseases, neuroinflammation, diabetes, and arthritis was approved (Malik et al., 2021; Kohandel et al., 2021). In addition, Thymoquinone alleviates inflammation in cerulein-induced acute pancreatitis (Kanaç et al., 2022). Thymoquinone was elected to be an anti-inflammatory agent in treating the secondary infections caused by COVID-19 owing to its antioxidant, broad-spectrum antimicrobial, and anti-inflammatory effects, (Dahmash et al., 2022).

8- The neuroprotective activity of thymoquinone

Thymoquinone suppresses arsenate neurotoxicity and suppresses the nervous system oxidative stress through its antioxidant activity (Kassab and El-Hennamy, 2017). It also remediates sodium nitrite-induced brain alteration through attenuation of oxidative stress, blocks elevated levels of pro-inflammatory cytokines, retrieves the reduced concentration of glutathione, reduces the apoptosis markers and restores cytochrome c oxidase activity, in rats' brain tissues (Hamdan et al., 2019). Thymoquinone has also an anti-inflammatory effect against neuro-inflammation that gives it potent protection against several neurological disorders such as epilepsy, Parkinsonism, Alzheimer's disease anxiety, encephalomyelitis and depression by activating the innate immune system to protect the central nervous system (Farkhondeh et al., 2018; Malik et al., 2021; Abo Mansour et al., 2023).

9- The antitoxic activity of thymoquinone

Thymoquinone also has a protective antioxidant agent against toxicities induced by numerous drugs (Albalawi and El Rabey, 2024). Black seed exerts many antioxidant and antitoxic activities against the toxicity of tartrazine (Al-Seeni et al., 2018), protects against CCl4-induced hepatotoxicity (Al-Seeni et al., 2016) and also protects against STZ-induced

diabetes in rats (El Rabey et al., 2017). The antioxidant and anxiolytic properties of thymoquinone attenuated the arsenic-associated anxiogenic changes and expressed positive shifts in cytokine levels and the hippocampal oxidative stress with decreased DNA fragmentation which suggest that it might alleviate depressive outcomes and anxiety of arsenic intoxication (Kassab and El-Hennamy, 2017; Firdauset al., 2018). In addition, thymoquinone containing *Nigella sativa* oils alleviates cytotoxicity and hepatotoxicity (Sowunmi and Kaka (2023).

10- The antimicrobial activity and food preservation

Thymoquinone showed antipathogenic effects against various pathogenic microbial strains, including bacteria, viruses, parasites and fungi (Chaieb et al., 2011; Malik et al., 2021, Al-Khalifa et al., 2021). Furthermore, the eugenol combination of thymoquinone increased its antioxidant and antimicrobial activity, improving the food industry by increasing shelf life (Yousefizade et al., 2022). In addition, thymoquinone has an antibacterial and therapeutic protective activity against prostatic tissue injury in bacterial prostatitis (Inci et al. (2013). Furthermore, adding thymoquinone to vegetable-edible oils awarded them chemical stability and lowers peroxide value because of its oxidation protection efficiency instead of synthetic antioxidants and improves their stabilization (Erdoğan, 2022; Mizuno and Fukuhara, 2022).

11- The immunomodulatory activity of thymoquinone

Thymoquinone acts as an inhibitor of proinflammatory pathways by inhibiting TNF-α, interleukin (IL)-1β, monocyte chemo-attractant protein-1 (MCP-1), and COX-2, ultimately reducing the NF-κB activation in pancreatic ductal adenocarcinoma cells, indicating its role (Chehl et al., 2009). It also suppressed IL-8 expression and NF-κB signaling in childhood malignant brain tumor medulloblastoma which leads to the induction of intrinsic and extrinsic apoptosis (Ashour et al., 2016).

Thymoquinone-nanoparticles were applied as chemotherapeutic combinations without any toxicity (Upadhyay et al., 2019**;** Alkhalaf et al., 2020). It has also therapeutic protection against intestinal because of its immunomodulating, free radical scavenging, and antioxidant effects (Parlar and Arslan, 2020).

12- Fertility ameliorative activity of thymoquinone

Thymoquinone ameliorated nicotine-induced sperm count, sperm damage and testosterone levels in Nicotine-Treated Sprague Dawley Rats Rosli et al., 2019). In a dose-dependent manner, thymoquinone positively affects bleomycin-induced toxicity of the testis in mice models (Nezhad et al., 2021). On the other hand, treatment with *N. sativa* containing thymoquinone ameliorates the reproductive parameters and sex hormones in both genders, improves semen fluid in men the sperm parameters, and graph follicle count, Leydig cell count, level of sex hormones (testosterone in men and progesterone in women) and corpus luteum (Darand.et al., 2019).

13- The therapeutical advantages of thymoquinone nanoparticles formulations

The nanoformulations of thymoquinone revealed a promising nutraceutical value for human health (Alkhalaf et al., 2019). Thymoquinone and Its Nano-formulations may be safely applied to treat lung disorders (Al-Gabri et al., 2021). The nanoformulations of thymoquinone were also efficiently used as an adjuvant therapy to protect against nephrotoxicity in cisplatin cancer treatment without affecting its antitumor efficacy (Harkaeh et al., 2022). When nanoformulations of Poly Lactic-co-Glycolic Acid (PLGA) loaded thymoquinone are coated with chitosan nanoparticles (PLGA-CS-TQ-NPs), its effectiveness against Triple-negative breast cancer (TNBC) (Gao et al., 2023). Furthermore, when **c**urcumin was formulated with thymoquinone the drug loading and dissolution rate were increased as an anti-cancer and anti-inflammatory therapy (Alwadei et al., 2019).

Conclusion

Thymoquinone-the main constituent of *Nigella sativa* seeds- showed several therapeutic activities due to its potent antioxidant activity that was acquired by its phenolic composition. It showed *in vitro* and *in vivo* anti-oxidant and anti-inflammatory effects that protect against

all increased oxidative stress-caused diseases such as diabetes, hypercholesterolemia, atherosclerosis, Parkinson's disease hypertension, Alzheimer's disease, hepatic diseases, and epilepsy by reducing oxidative stress through direct anti-oxidant effect as well as induction of endogenous anti-oxidant enzymes leading to the prevention of these diseases. Administration of thymoquinone increased the activities of catalase, glutathione-s-reductase, superoxide dismutase, quinone reductase and glutathione transferase and so reduced the increased oxidative stress. These antioxidant properties make it a therapy against chemical carcinogenesis and toxicity caused by increased oxidative stress and consequently protect against all the above-mentioned increased oxidative stress correlated diseases. Recent research activities showed that providing thymoquinone nanoparticles is more efficient than the natural free thymoquinone. For this approved clinical therapeutic activity of thymoquinone, it is suggested to be part of the future therapy of numerous diseases.

List of abbreviations

ALT: Alanine aminotransferase

AST: aspartate aminotransferase

CAT: catalase
CK-MB: creatine kinase myocardial band
COX-2: cyclooxygenase-2

DHTQ: dihydroxy thymoquinone

GST: glutathione *S*-transferases
iNOS: Inducible nitric oxide synthase

LPO: lactoperoxidase

NF-κβ: nuclear factor kappa B

NPs: Nanoparticles

PLGA: Poly Lactic-co-Glycolic Acid

SOD: superoxide dismutase

STAT-3: signal transducer and activator of transcription 3

TNBC: Triple-negative breast cancer

TQ: Thymoquinone

Conflict of interest

The authors declare no conflict of interest.

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