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AN OVERVIEW OF THERAPEUTIC POTENTIAL OF THYMOQUINONE

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ABSTRACT: Herbal medication has attracted much attention in recent years and is being used as an alternative to chemical medicines. Some evidence supports the positive effects of medicinal plants in the prevention and treatment of different types of diseases. Thymoquinone (TQ) is the most abundant component of *Nigella sativa* seeds, and most of the properties of *Nigella sativa* are attributed primarily to TQ. It belongs to a class of naturally presenting phenols, chemically known as 2-isopropyl-5-methyl benzo-1, 4-quinone ($C_{10}H_{12}O_2$), is a dark yellow crystalline monoterpene diketone, abundantly found in the seeds of *Nigella sativa*. Besides *Nigella sativa*, TQ is an active ingredient of several plants as *Juniperus*, *Monarda*, *Coridothymus*, *Agastache*, *Satureja*. It has been reported to possess various beneficial therapeutic effects including anti-oxidant, anti-inflammatory, anti-microbial, anti-diabetic, hepato-protective and cardioprotective effects. It is significant to say that TQ may be effective as a powerful contender of natural origin with therapeutic potential against an array of maladies.

INTRODUCTION: Thymoquinone (TQ) is a major bioactive constituent mainly found in *Nigella sativa* [1]. *Nigella sativa*, belonging to Ranunculaceae family is commonly known as black cumin, Kalonji or kalajeera [2]. It is an annual herbaceous plant, native to south and southwest Asia. Seeds of *Nigella sativa* have been used for thousands of years as a spice and food preservative to a variety of food products as bread, yogurt, pickles, sauces, salads, *etc*. [3] Furthermore, *Nigella sativa* seeds are reported to possess anti-histaminic, antihypertensive, antimicrobial, anti-tumor, insect repellent and lactogogous effects [4, 5].

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Nigella sativa seeds contain several bioactive compounds that include thymoquinone (TQ), dithymoquinone (DTQ), thymohydroquinone (THQ), thymol (THY), tocopherols, trans-retinol, and selenium *etc*. TQ is the most abundant phenolic compound, and this functional ingredient is predominantly present in fixed and essential oils of *Nigella* seeds [6].

Besides Ranunculaceae, this compound has been confirmed its presence in several genera of the Cupressaceae and Lamiaceae family [7]. The traces of TQ were also reported in *Nigella arvensis* [8]. It was first extracted by El-Dakhakhny using thin layer chromatography on silica gel [9]. Illustration of *Nigella sativa* plant, its flower, seeds and the chemical structure of TQ are presented in **Fig. 1**. TQ holds anti-oxidant, analgesic, anti-convulsant, and anti-cancer effects. It has also been shown to protect against liver, kidney and heart damage in several animal studies.

TQ is an important agent of natural origin and has generated interest in the field of scientific research for its therapeutic effect. The present review presents an overview of its therapeutic potential in a disease condition.

Chemistry of Thymoquinone: TQ is a monoterpene diketone, chemically known as 2-isopropyl-5-methyl benzo-1, 4-quinone. It is a dark yellow crystalline substance with a boiling point and melting point of 230–232 °C and 44-45 °C, respectively. Its molecular weight is 164.204 g/mol, and Log *P* value is 2.20. Due to low molecular weight (less than 500 g/mol) and Log *P* (less than five) value, it can penetrate the blood-brain barrier. Thus, it might be suitable for clinical trials [10, 11]. The most significant properties are summarized in **Table 1**. [12]

FIG. 1: (A) *NIGELLA SATIVA* PLANT (B) ITS FLOWER AND SEEDS (C) CHEMICAL STRUCTURE OF ACTIVE COMPOUND OF SEEDS, THYMOQUINONE

TABLE 1: THE RELEVANT PROPERTIES OF THYMOQUINONE

IUPAC Name	2-isopropyl-5-methyl benzo-1, 4-quinone
Molecular formula	$C_{10}H_{12}O_2$
Molar Mass	164.20g mol^{-1}
Appearance	Crystalline and dark yellow
CAS number	490-91-5
Pub Chem CID	10281

Structurally, it is as similar to coenzyme Q, which is an important antioxidant of the electron transport system [13]. By oxidation of THY with H_2O_2, TQ can be readily synthesized in gram amounts [14]. Moreover, according to one hypothesis based on chemical composition, the controlled heating causes oxidation of THY and converts it into THQ. The heating process leads to a further oxidative process that converts THQ into TQ, resulting in the accumulation of larger amounts of TQ.

Based on the presence of light, the photoisomerization of TQ may cause an accumulation of its dimer, DTQ [13]. Besides this, during quinone separation and extraction from seeds, TQ photodimerization as a consequence of exposure to sunlight produces DTQ [15]. Conversions of different quinones by the chemical reaction are shown in **Fig. 2**.

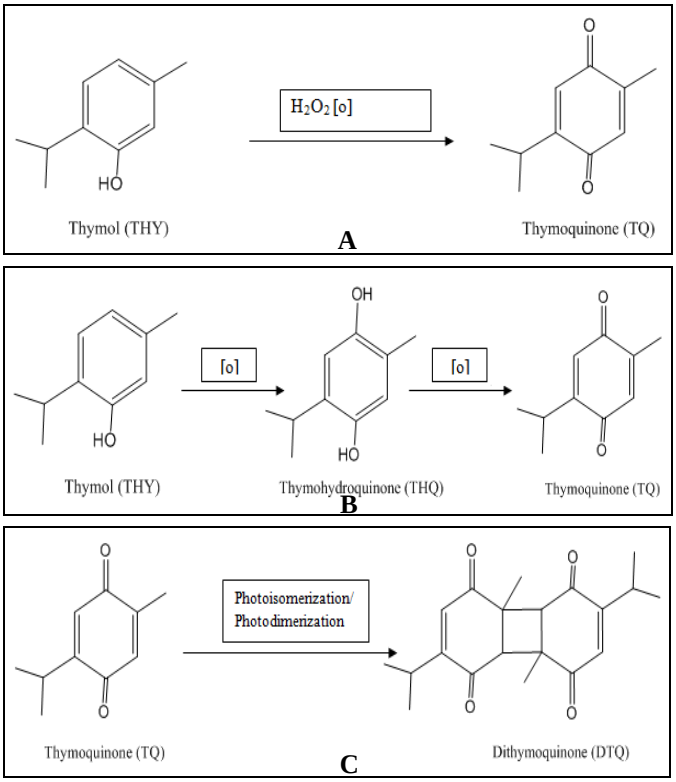

FIG. 2: (A) OXIDATIVE CONVERSION OF THYMOQUINONE FROM THYMOL. (B) HYPOTHESIZED MECHANISM OF TRANSITION BETWEEN QUINONES BY OXIDATION UNDER CONTROLLED HEAT. (C) CONVERSION OF DITHYMOQUINONE FROM THYMOQUINONE BY PHOTOISOMERIZATION OR PHOTODIMERIZATION REACTIONS

Pharmacological Potential of Thymol: Numerous *in-vitro* and *in-vivo* studies have been done to investigate the pharmacological potential of thymol.

Anti-Inflammatory Effects: Inflammation is one of the main causes of many diseases. Infection and oxidative stress activate the expression of inflammatory genes, which promoted a cascade of inflammatory mediators, including cytokines, eicosanoids, oxidants, and lytic enzymes. Therefore, the introduction of a preventive agent is promising for the treatment of inflammatory disorders. A number of studies showed TQ could suppress inflammatory mediators and oxidative stress markers [16]. Treatment with TQ inhibited the synthesis of 5-lipoxygenase and 5-hydroxyeicosatetraenoic acid production in calcium or ionophore-stimulated polymorphonuclear leukocytes in rats [17]. TQ inhibited eicosanoid generation by inhibiting 5-lipoxygenase and leukotriene C4 synthase in human blood cells [18]. TQ in the concentration of 0.16–16.4 mg/ml was effective for the inhibition of eicosanoid generation in human blood cells. It has been proved that TQ acts as a potent anti-inflammatory agent [19]. TQ exhibited a greater inhibitory effect in inflammatory cells of bronchoalveolar lavage (BAL) fluid and lung tissues. TQ also inhibited the expression of transforming growth factor-β1andmRNA levels of inducible nitric oxide synthase. These results suggested that TQ is more potent anti-inflammatory agents against asthma [19].

The anti-inflammatory effect of TQ was observed in allergic encephalomyelitis. TQ (1mg/kg, injected into the tail vein) increased the levels of glutathione and reduced perivascular inflammation and encephalomyelitis symptoms in rats [20]. TQ (15mg/kg) treatment showed 90 percent preventive and 50 percent curative effects in chronic relapsing multiple sclerosis [21].

Anti-Tumor Effects: There are many studies are available which support the antitumor effect of TQ in both *in-vitro* and *in-vivo* studies [22]. The inhibitory effect of TQ (10–200 µM) was shown on the growth of colon cancer cell. The apoptotic effects of TQ could be modulated by Bcl-2protein by an increase in the mRNA expression of p53 [23]. Also, TQ in the dose of 20, 40 and 80 µmol/l showed anti-tumor and anti-angiogenic effects in the human osteosarcoma cell line (SaOS-2) through suppressing NF-κB, its regulated molecules and blocking the human umbilical vein endothelial cell tube formation [24]. TQ is an anti-neoplastic drug that decreased cell survival in a dose-dependent manner. This effect was more significantly in p53-null MG63 cells (IC (50) = 17 µM) than in p53-mutant MNNG/HOS cell (IC_{50} =38 µM) [25].

Moreover, TQ (IC_{50} = 10.67 ± 0.12 and 9.33 ± 0.19 µg/ml) exhibited cytotoxic effects in several cancer cell lines. TQ was more potent than cisplatin in eliminating cervical squamous carcinoma (SiHa) cells *via* apoptosis with down-regulation of Bcl-2 protein [26].

TABLE 2: ANTI-TUMOR EFFECT OF THYMOQUINONE

Compound	Study Models	Effects	References
Thymoquinone	HCT-116 human colon cancer cells	Apoptotic effects of TQ on HCT-116 (by ↑ Bcl-2 protein and mRNA expression of p53)	23
Thymoquinone	Human osteosarcoma cell line (SaOS-2)	Apoptotic effect (↓tumor angiogenesis and tumor growth through suppressing NF-κB)	24
Thymoquinone	Human umbilical vein endothelial cell	Apoptotic effect (↓tumor angiogenesis and tumor growth through suppressing NF-κB)	24
Thymoquinone	Human osteosarcoma cell lines	p53-independent apoptosis in human osteosarcoma cells	25
Thymoquinone	Human cervical squamous carcinoma cells	Cytotoxic effect (elevation of p53 and downregulation of the anti-apoptotic Bcl-2 protein)	26

Anti-Microbial Effects: The anti-bacterial activity of TQ and its biofilm inhibitory effect on 11 human pathogenic microscopic organisms were explored. TQ (0-512 µg/ml) demonstrated a noteworthy enemy of the bacterial movement against the vast majority of the microscopic organisms tested (MIC values ranged from 8-32 µg/ml), particularly Gram-positive microorganisms (*Staphylococcus epidermidis* CIP and 106510 *Staphylococcus aureus* ATCC 25923). The cell oxidative movement was affected by TQ, which avoided cell attachment to the surface of the glass slide [27].

Effects on Metabolic Disorders: Several studies have been exhibited anti-hyperlipidemic and anti-diabetic activities of TQ and its effect on other metabolic disorders. Several possible mechanisms have been proposed for justifying these effects. It was demonstrated that TQ might reduce the expression of gluconeogenic enzymes *viz*., glucose-6-phosphatase, fructose 1, 6 bi-phosphatase and hepatic glucose production [28, 29]. TQ could enhance the uptake of low-density lipoprotein-cholesterol (LDL-C) by upregulation of LDL-C hepatic receptors [30].

Anti-Diabetic Effects: Diabetes is a metabolic disorder that consists of elevation in serum glucose levels and develops a deficiency, sensitivity or both of insulin caused by destruction or inactivity of β-cells. Diabetes is usually associated with several chronic complications such as cardiovascular diseases, neuropathy and nephropathy [31, 32]. Scientific validation of traditional medicinal plant remedies for diabetes may lead to the development of alternative drugs. More than 1200 plant species reported having been used to treat diabetes and its related complications, including *Nigella sativa* [33]. The anti-diabetic effect of TQ has been shown in the STZ-induced diabetic rats. TQ reduced the activation of the COX-2 enzyme in the pancreatic β-cells. Supplementation of diabetic rats with TQ also decreased the MDA levels and increased the Superoxide Dismutase (SOD) levels in the pancreatic tissue [34]. It was also showed that treatment with TQ (20 mg/kg body weight) of diabetic mice during pregnancy and lactation periods protected their offspring from diabetes and its related complications *via* decreasing blood glucose levels, plasma pro-inflammatory cytokines (IL-1β, IL-6 and TNF-a), free radicals, lipids and restoring the number of circulating lymphocytes, T-cell proliferation and aberrant AKT phosphorylation [35].

TQ (50 mg/kg, body weight) reduced blood glucose levels in diabetic hamster during pregnancy by inhibiting the synthesis of gluconeogenic enzymes [36]. In another study, TQ (80 mg/kg, body weight) decreased plasma glucose levels and increased insulin levels by enhancing glucose utilization and decreasing hepatic glucose production. TQ has been shown to suppress the activity of glucose-6-phosphatase and fructose-1, 6-bisphosphatase enzymes [37]. TQ ameliorated the increased levels of lipid peroxidation and decreased the level of vitamin C, vitamin E, catalase, glutathione-S-transferase, glutathione peroxidase, and reduced glutathione content. These findings exhibited that TQ has the ameliorating effects on β-cell action via its antioxidant potential [37].

Gastro-Protective Effects: Ample evidence exists for supporting the protective effect of TQ on gastrointestinal tract. TQ showed a protecting effect against gastric lesions, which may be due to its potent anti-oxidant property. TQ corrected ischemia/ reperfusion (I/R)-induced gastric dysfunction and stomach ulcer in rats. It increased the levels of glutathione and superoxide dismutase activity and reduced malonaldehyde levels and myeloperoxidase activity [38]. TQ possessed protecting action against liver enzyme leakage and lipid peroxidation. It showed anti-oxidant, membrane stabilizing and free radical scavenging action [39, 40]. The gastroprotective mechanisms of TQ resulted from inhibiting acid secretion, proton pump (H^+/K^+-ATPase), neutrophil infiltration, through enhancing mucin secretion and nitric oxide (NO) production [41]. Pretreatment with TQ (10 mg/kg body weight for 3 days) in rats was able to give complete protection against acetic acid-induced colitis, however, thymoquinone in a dose of 5 mg/kg body weight produced partial protection. These results showed a protective effect of thymoquinone against experimentally-induced colitis which may be partly due to an antioxidant action [42]. The anti-histaminic effect is an essential defensive mechanism against gastric injury [43] and TQ showed potent anti-histaminic effect [42]. Altogether, these studies confirm the gastro-protective effect of TQ in an animal model which makes it possible to use as a natural drug against gastrointestinal defects in human.

Cardio-Protective Effect: Cardiovascular diseases are increasing rapidly worldwide. The alteration in lipid profiles, diabetes and hypertension, are the major risk factors for the development of cardiovascular diseases [44]. Atherosclerosis is the main cause of coronary artery disease identified by a complex process of thickening and narrowing of the arterial walls caused by the accumulation of lipids, primarily oxidized cholesterol, in the intimal or inner layer in combination with connective

tissue and calcification creating an atheromatous (fibrofatty) plaque [45]. Atherosclerotic plaque is composed of lipids, cholesterol, oxidized-low density lipoprotein (Ox-LDL), calcium and fibrin that cause hardening and narrowing of the arteries [45]. Hypercholesterolemia is the main cause of the initiation and progress of atherosclerosis [46]. Inflammatory cells such as vascular endothelial cells and polymorphonuclear leukocytes are activated in hypercholesterolemia and cause increased production of free radicals [47]. Several studies have been shown that natural antioxidant components such as TQ ameliorated oxidative stress-induced atherosclerosis [48]. Other studies also observed that TQ (20 mg/kg body weight) decreased the oxidative stress markers, lipid profiles and prevented the progression of plaque formation in hypercholesterolemic animals [49].

Hepato-Protective Effect: In recent years, consideration has been attracted to various plants and plant-derived compounds for the treatment of liver infirmities. The defensive impact of TQ on liver injuries has been demonstrated by a few investigations. TQ could neutralize the negative impact of different harming agents on liver tissues. TQ has been shown to prevent non-enzymatic lipid peroxidation in liver homogenates and showed the protective action against CCl_4-induced toxicity through its anti-oxidant potential. Oral administration of TQ (100 mg/kg body weight), gave considerable protection against the treatment of carbon tetrachloride (CCl_4) hepatotoxicity [50]. TQ showed hepatoprotective activity against tert-butyl hydroperoxide (TBHP)- induced toxicity in isolated rat hepatocytes. It prevented the reduction of intracellular glutathione and maintained the integrity of the cell membrane, as well as decreasing the leakage of the alanine transaminase (ALT) and aspartic transaminase (AST). This protective role of TQ is comparable to the silybin, hepato-protective agent possessing anti-oxidant properties [39].

TQ supplementation efficiently reduced acetaminophen-induced oxidative stress, nitric oxide production and improved mitochondrial energy production [51]. TQ protected liver injury through various mechanisms, including inhibition of lipid peroxidation, increase in total thiol content and reduced glutathione level, radical scavenging, increasing the activity of quinine reductase, superoxide dismutase, catalase and glutathione transferase and inhibition of NF-κB activity [50].

Toxicological Studies: Increased interest in phytomedicine, brings health issues of safety and legal requirements. Numerous examinations were done to evaluate the toxicological properties of TQ *in-vitro* and *in-vivo* [52, 53] and just a set number of reports on the possible harmful impacts of TQ exist. In the pathological conditions where TQ has been appeared to be a most promising prophylactic agent, it additionally has been appeared to be enriched with a moderately low harmfulness [54, 55]. TQ is a very well tolerated drug in mice. It has been shown that TQ administered for 20 consecutive days has not induced death in Balbo/C rats or has not affected the average body weight, which is a very sensitive parameter for toxicity in the rodent [56]. Neurological function of TQ was not associated with any therapeutic changes in laboratory variables. TQ administered in the dose of 1 mg/kg body weight /day was mostly well tolerated [57]. There was no sign of toxicity except for the reduction in the amount of plasma glucose concentration in addition to TQ at concentrations up to 0.03% for 3 months in drinking water of rats [58]. The steady delivery of TQ for 30 days using Tri-Calcium Phosphate Lysine with 0.02 grams of TQ for adult male rats, showed very little or no side effect on reproductive organs [59].

CONCLUSION: In recent years, the focus on traditional uses of natural products, received much attention as they are believed to be safe for human use. They deserve scrutiny for phytochemical investigation, biological evaluation on experimental animal models, toxicity studies and investigation of the molecular mechanism of actions. This review enumerates the biological properties of TQ and reveals its therapeutic potential against many diseases including diabetes, cancer, cardiac, liver illnesses, and gastrointestinal defects. Available data are indicators of its use as a nutraceutical or prophylactic or adjuvant for long-lasting chronic oxidative stress and long-lasting diseases associated with inflammation. Molecular pharmacological data from many studies show that TQ modulates apoptotic, enzymatic, and cell signaling pathways, transcription factors, different receptors, and ion channels, modify to meet their

pharmacological effects. TQ acts as antidiabetic agent and improved hyperlipidemia through increasing antioxidant and decreasing lipid peroxidation. TQ showed protective properties against a cardiovascular disease which may be related to its anti-inflammatory and antioxidant activities. The present review reveals on all the aspects of the herbal compound and throws the attention to set the mind of the researchers to carry out the work for developing its various formulations, which can ultimately be beneficial for the human as well as animals. However, further research at the clinical and pre-clinical levels is necessary to determine the therapeutic potential of TQ in various diseases.

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