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# The Protective Role of Thymoquinone against Drugs Toxicity: A Review

**Mohsen G. Alrashedi[1*]**

[1]*Sulaymi Hospital, Ministry of Health, Hail City, Kingdom of Saudi Arabia.*

***Author's contribution***

*The sole author designed, analyzed, interpreted and prepared the manuscript.*

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## ABSTRACT

Any drug can have side effect at a certain dose which limits its use. On the other hand, evidence support the role of herbal medicines in the prevention and cure of several diseases. Thymoquinone (TQ) is a bioactive component found in the volatile oil of *Nigella sativa* "black seed". Studies have demonstrated the therapeutic and protective activity of TQ against drug toxicities on various body systems which have been attempted to be reviewed in this article.

*Keywords: Thymoquinone; Nigella sativa; black seeds; drug toxicity; nephrotoxicity; hepatotoxicity; cardiotoxicity; ototoxicity.*

## 1. INTRODUCTION

A normal therapeutic dose of any drug used for the treatment of a disease imposes certain unintentional and harmful side effects which result in a limit to its long-term usage. One of the approaches to protect against the harmful effects of the drug is the use of natural products. Herbs have been used as traditional medicine for human health since ancient times**.** Among the promising medicinal herbs is black seeds also called as *Nigella sativa* (NS). Being an effective medicinal herb whose seeds and oil have been commonly used as a traditional remedy for the treatment of a variety of diseases for more than hundreds of years, its use as a medicine has significant religious importance as well [1]. Thymoquinone (TQ), the most abundant

**Corresponding author: E-mail: Abu_geza@hotmail.com, rashedi.drk@gmail.com;*

constituent of NS, is a bioactive component of the volatile oil of black seeds and has been reported to possess many therapeutic effects.The present review aimed to critically evaluate the studies regarding the protective effect of *NS* and its active ingredient (TQ) in drug toxicity, an area that has not been studied completely in literature till date.

An exhaustive literature review was done on the articles available in the databases such as PubMed, Scopus, Science Direct, Google Scholar and other published manuscripts related to studies of the protective effect of *Nigella sativa* and its active ingredient TQ on drug toxicity. The effort was made to include all possible available articles in the literature that used *Nigella sativa* or TQ for attenuation of drug imposed side effects.

## 2. *Nigella sativa*

*Nigella sativa* (NS) is a medicinal herb commonly called as Black Seed in English and habba-tu sawda in Arabic which grows as a wild plant in Asia, North Africa and southern Europe [2]. It has been used as a natural remedy for many diseases including hypertension, diabetes, asthma, bronchitis, cough, eczema, headache, influenza and dizziness for over hundreds of years, [3,4,5]. The use of this plant dates back to primitive times as can also be understood by its significant use during the Islamic period of Prophets, thus making it religiously significant [1].

## 3. CHEMICAL COMPOSITIONS AND TOXICITY

Extensive research was done to identify the components of the *NS* that revealed its seeds to include ingredients such as proteins,fixed oil, saponin, alkaloid and essential oil. The essential oil of NS has two components; fixed and volatile. The fixed oil (32-40 %) includes : unsaturated fatty acids which contains eicosadienoic , arachidonic, linolenic , linoleic, oleic, palmitic, almitoleic , myristic acid ,stearic and as well as cycloeucalenol, beta-sitosterol ,cycloartenol, sterol glucosides and sterol esters [6,7] The volatile oil (0.4-0.45 %) includes saturated fatty acids which contains : Thymoquinone (TQ), thymohydroquinone (THQ), nigellone which is the only constituents of the carbonyl fraction of the oil, thymol, dithymoquinone, α and β-pinene ,carvacrol, d-citronellol ,d-limonene, *p*-cymene, t-anethole ,4-terpineol,carvacrol and longifoline. [6,8] NS has two forms of alkaloids: pyrazol alkaloid which includes: nigellicine and nigellidine and isoquinoline alkaloid which includes: nigellicimine n-oxide , nigellicimine, The nutritional constituents of black seeds are vitamins, mineral elements , carbohydrates, proteins and fats [6,8]. Safety of *Nigella sativa* was documented in the literature, for example, powdered seed when given at high doses (28 g/kg) orally to rabbits did not induce any toxic effects [9]. Also, administration of the seed extract did not produce a significant change in kidney or liver functions [3,8].

## 4. THYMOQUINONE (TQ)

TQ (2-Isoprop l- 5-methyl benzo - 1, 4-quinone) (Fig. 1) is an active ingredient of *NS*. TQ was first isolated and identified in1963 from the essential oil of the *Nigella sativa* [5,10].

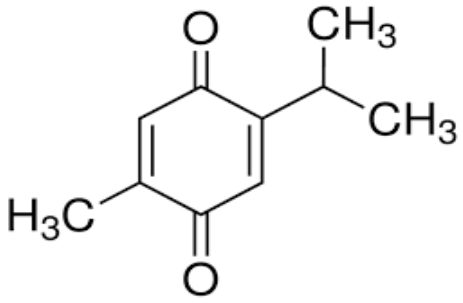


**Fig. 1. Chemical structure of Thymoquinone [10]**

## 5. THE PHARMACOLOGICAL ACTIVITY OF THYMOQUINONE

A number of studies reported that TQ has several pharmacological activities such as anti-inflammatory, antioxidant activity, chemoprotective] [11], antifungal, antiviral and even antibacterial activity against both gram-negative and gram-positive bacteria [12], hypoglycemic with antidiabetic effect [13], hypolipidemic effects [14], hepatoprotective and nephroprotective effects [15] including immunomodulatory properties, anti-histaminic and gastroprotective effect as well as pulmonary protective effect [3].

## 6. PROTECTIVE ACTIVITY OF THYMOQUINONE AGAINST DRUG-INDUCED TOXICITY

Toxicity of drug is a major side effect in some medications which attributes to the failed response of drugs in some cases. Extensive

researches are done to identify new and potential methods which may attenuate drug's toxicity without compromising the therapeutic potential of the drug. One of the approaches to protect against drugs induced toxicity is treatment by TQ. It has been demonstrated that TQ can ameliorate and protect against various drugs induced toxicity. Several studies on the protective effect of TQ against drug-induced toxicity suggests a potential complementary role of TQ to improve the quality of life in patients.

## 7. ROLE OF TQ IN DRUG-INDUCED NEPHROTOXICITY

Many studies documented that TQ has nephroprotective effects against various pathogenic conditions therefore much research was done against the effect of TQ in drug-induced nephrotoxicity. TQ was found to improve the kidney lesions which resulted from various toxic substances. TQ administration prevented gentamicin-induced renal failure by augmenting adenosine triphosphate (ATP) production and improving mitochondrial function. It reversed the increase in creatinine (Cr), Blood urea nitrogen (BUN), thiobarbituric acid reactive substances (TBARS) concentration induced by gentamicin and it also attenuated the nephrotoxicity indexes and degenerative change [16,17]. It was also reported to have a protective effect against vancomycin-induced nephrotoxicity. In the vancomycin group, the level of Cr, BUN and, malondialdehyde (MDA) were increased, TQ administration noticeably reversed these changes [18]. TQ usage in cyclosporine A (CsA) induced nephrotoxicity produced a small but non-significant decrease in serum Cr, and a significant decrease in Cystatin C. Histological assessments showed that co-administration of TQ with CsA prevented the major structural changes at both glomerular and tubular sides of rat's kidneys [19]. TQ supplemented with ifosfamide attenuated the severity of nephrotoxicity induced by ifosfamide. It drastically ameliorated ifosfamide-induced elevated Cr, BUN. Further, via the anti-oxidant mechanisms, it prevented lipid peroxide accumulation and renal glutathione (GSH) depletion [20]. Also, TQ had positive therapeutic effects on Doxorubicin;(DOX)-induced nephropathy. TQ supplementation was found to have markedly reduced kidney damage with reversing the high levels of Cr, BUN, urinary albumin and also lowered total cholesterol, total triglycerides and lipid peroxidation [21]. Furthermore, TQ was effective in acetaminophen-induced nephrotoxicity in rats, TQ reversed the elevated levels of Cr and BUN levels and alleviate tissue damage of kidney [22]. All the above data suggest that TQ can be used as a protective agent in drugs induced nephrotoxicity.

## 8. DRUGS-INDUCED HEPATOTOXICITY

Several studies demonstrated the hepatoprotective effect of NS and its active ingredient. TQ can neutralise the negative effects of many substances which may damage the liver tissue. Treating liver with TQ resulted in significant protection against liver injury of acetaminophen via the upregulation of antioxidant systems. TQ administration with acetaminophen reversed the elevated levels of aspartate aminotransferase (AST), serum Alanine aminotransferase (ALT), superoxide dismutase (SOD) activity, oxidised glutathione (GSSG) and the serum and MDA levels. Moreover, histopathological analysis of TQ + acetaminophen group resulted in significantly lower liver injury scores as compared to acetaminophen group [23]. A study was done by Nagi et al., showed that TQ supplementation (2 mg/kg/day) reduced acetaminophen-induced hepatotoxicity and resulted increasing the total nitrite/nitrate, lipid peroxide, ALT, with a decrease in mitochondrial energy ATP and GSH. This protective effect is possible via an increase in resistance to nitrosative and oxidative stress and ability to enhance mitochondrial energy ATP productions as well as glutathione S transferase (GST) [24]. TQ also has a positive effect against cyclophosphamide (CP) induced liver dysfunction by significantly reducing the levels of ALT and aspartate transaminase (AST). TQ visibly inhibited the increase in serum activity of the evaluated enzymes. TQ also protect against Tamoxifen (TAM) induced hepatic injury includes GSH depletion and lipid peroxidation (LPO) accumulation. Consistently, TQ normalised the activity of SOD, inhibited the rise in TNF-α and ameliorated the histopathological changes [25]. Moreover, it also reduced CP-induced haemorrhage, inflammation and injury in liver tissues [26]. TQ supplementations also reduced CP-induced hepatotoxicity through up-regulation of antioxidants mechanism [27]. TQ had a protective effect against anti-tuberculosis drugs induced hepatotoxicity by reducing the increase in the level of hepatic ALT, alkaline phosphatase (ALP) and AST enzymes as well as repair of liver tissue injury. Furthermore, it is a promising substance for maintaining normal liver function in

the course of long-term treatment with anti-tuberculosis medications [28]. Also, supplementation of TQ attenuated thioacetamide (TAA) induced hepatic fibrosis. This effect showed that the use of TQ reversed the hepatic tissue injury as compare to TAA alone group, which is characterised with accumulation of extracellular matrix (ECM) proteins and less inflammatory infiltration. Furthermore, TQ reduced the TAA-induced hepatic fibrosis significantly, which is associated with decrease in protein and messenger ribonucleic acid (mRNA) expression of collagen-I, tissue inhibitor of metalloproteinase-1 (TIMP-1) and α-smooth muscle actin (α-SMA). Moreover, TQ remarkably downregulated the expression of toll-like receptor 4 (TLR4) and reduced pro-inflammatory cytokine levels. It significantly inhibited phosphorylation of phosphatidylinositol 3-kinase (PI3K) and enhanced adenosine monophosphate-activated protein kinase (AMPK) and liver kinase B (LKB) phosphorylation [29]. Hepatoprotection property of TQ is known to be due to its antioxidant and anti-inflammatory effects which have been demonstrated both *in vivo* and *in vitro*. Also, TQ may reduce oxidative stress via direct anti-oxidant activity and induction of endogenous anti-oxidant enzymes leading to the protection against hepatotoxicity. TQ effectively enhanced the hepatic and plasma antioxidant capacity and increased the expression of SOD, catalase (CAT), glutathione peroxidase (GSH-Px) genes of liver antioxidant [30]. These studies confirm the hepatoprotective effects of TQ against liver toxicity induced by various medications.

## 9. DRUG-INDUCED CARDIOTOXICITY

Cardiovascular disease remains one of the most leading cause of death worldwide. Some drugs have side effects causing cardiotoxicity which limits its use in long-term treatment. Supplementation of herbal remedies such as TQ can be used as therapeutic options in cardiovascular complications. Cisplatin is very effective in different types of cancer along with cardiotoxicity as one of its side effects. But the use of TQ with cisplatin can protect against cardiac injury by administrations of TQ (40 mg/kg/day) for 5 days before using cisplatin. Utilisation of TQ significantly exhibited increased expression of antiapoptotic protein B-cell lymphoma 2 (Bcl-2). Moreover, histological improvement in heart tissue is observed by lower congestion and pycnotic nuclei as compared to Cisplatin group [31]. The drug DOX exhibited a broad spectrum of anticancer property along with cardiotoxicity as the main side effect of the drug. TQ treatment showed that it can protect against DOX-induced cardiac injury without compromising its therapeutic activity. TQ in a dose of 8 mg/kg/day, administered with drinking water starting from five days prior to DOX injection and continued throughout the experiment. The result was supported by significantly reduced serum lactate dehydrogenase (LDH) and elevated levels of creatine kinase, as well as histopathological improvement in heart tissue. TQ acted as the scavenger for superoxide radical and inhibitor of lipid peroxidation in DOX-induced heart injury in rats [32,33]. Cyclophosphamide (CP) resulted in a significantly increased in LDH, Cr, serum creatine kinase, BUN, triglycerides, tumour necrosis factor-alpha (TNF- a) and cholesterol. In the cardiac tissues, it also significantly increased the total nitrite/nitrate and TBARS along with significant reduction in GSH, GSH-Px, CAT and ATP levels. Interestingly, after the use of TQ, it resulted in a reversal of all these biochemical changes to their original control values [34]. The hyperhomocysteinemia (HHcy) seems to be associated with a high risk of cerebral, peripheral, coronary and vascular disease; and the HHcy pathogenesis is well known to be related to the free radical formation. Oral treatment with TQ with a dose of 100 mg/kg, protected against methionine-induced HHcy [35]. TQ was also effective in protecting against hypertension which is induced by N-nitro-l-arginine methyl ester (l-NAME)-, perhaps by anti-oxidant activity as well as TQ reduced the elevated creatinine level, increased GSH levels, and inhibited superoxide radicals' productions [36]. These data indicate the role of TQ as a promising agent if properly used in protection against drugs induced cardiovascular complication.

## 10. DRUG-INDUCED RESPIRATORY PROBLEMS

NS and TQ have known the therapeutic effect on respiratory diseases such as asthma including allergic rhinitis and atopic eczema, dyspnea and pulmonary fibrosis. It neutralises the negative results of various substances induced pulmonary injury [37-39]. The role of TQ in Bleomycin-induced pulmonary fibrosis was investigated. Bleomycin significantly increased the levels of lactate dehydrogenase ( LDH), total protein, total leucocytic count, and mucin and supplementation with TQ reduced these effects significantly. As a marker of oxidative stress, bleomycin

significantly elevated the amount of nitric oxide (NO) and lipid peroxides along with a visible reduction in antioxidant activity of the enzyme of SOD and glutathione transferase. Treatment with TQ reversed these markers to their original normal values. It also counteracted inflammatory cell infiltration and emphysema in air alveoli. It also counteracted cells activation of lymphoid hyperplastic which surrounds the bronchioles. It further activated nuclear factor kappa-B (NF-B) overexpression of lung tissue induced by bleomycin. The fibrosis marker was evaluated by measuring the hydroxyproline content, which was significantly increased with the bleomycin treatment alone and drastically decreased with concurrent treatment with TQ. Moreover, the histopathological studies also confirmed that the TQ has an antifibrotic effect [40]. In another study, TQ showed a protective effect against Cyclophosphamide (CP) induced pulmonary injury. A single CP injection in lung homogenates markedly changed the levels of many biomarkers. Also, a significant increase in lipid peroxides concentration in the lung was observed in parallel with the reduction in the level of GSH. The CP increased the level of LDH, total protein, and TNF-α. Treatment with TQ for one week before and after CP injection ameliorated the alterations in serum and lung biomarkers significantly related with less lipid peroxidation, inflammatory reactions and restoration of antioxidants. Furthermore, the secretion of TNF-α, pro-inflammatory cytokine in rat serum was attenuated with TQ administration. In addition, TQ attenuated the CP-induced histopathological alterations in lung tissue effectively [41]. Therefore, the above findings suggest that TQ contains a potential antifibrotic effect. Also, its antioxidant activity which maybe via NF-κB inhibition indicates that TQ has a protective effect against drugs induced pulmonary damage.

## 11. TQ AND DRUGS INDU GASTRITIS

TQ showed healing potential in gastrointestinal disorders. It possesses protecting activity against the stomach lesions which may be related with the protection of gastric mucosal redox state [42]. The effects of oral administration of oil of NS (0.88 g/kg) on the ethanol-induced ulcer and gastric secretion were studied in the rat model. The final results concluded that NS can increase the content of stomach mucin, GSH level and free acidity and can reduce the gastric mucosal histamine content. Also, the study data showed that NS can have a protective effect on ethanol-induced gastric ulcer [43]. Further, in the male albino rats, the study was done to investigate the protective effect of TQ (10 mg/kg, orally) and NS oil (10 mL/kg, orally) against acute alcohol-induced gastric mucosal disturbance. The result demonstrated that TQ and NS decreased the ulcer index and MDA level and also improved the healing of stomach injury and GST, SOD and GSH levels [44].

The anti-secretory and gastroprotective property of NS powder (1.0, 1.5 and 2.0 g/kg, orally), aqueous and ethanolic extracts of NS powder (2.0 g/kg, orally) and NS ethanol-ethyl acetate fraction (2.0 g/kg, orally) were studied against indomethacin-induced gastric injury in a dose-dependent manner. Ethanolic extract significantly decreased a volume of stomach secretions, acid output pH and ulcer index. Whereas aqueous extract reduced stomach acid output [45]. In another study, the gastroprotective of TQ and sulforaphane (SF) against acetylsalicylic acid (ASA)-induced gastric injury were investigated, SF and TQ decreased gastric ulcer indices, total oxidant status, apoptosis, asymmetric dimethylarginine, inducible nitric oxide synthase and nuclear factor kappa-light-chain-enhancer of activated B cells TNF- α levels. Both tested compounds increased GSH-Px activity, SOD activity, total antioxidant status, nitric oxide, total thiol levels, endothelial nitric oxide synthase. Also, the results suggest that pre-treatment with TQ may decrease the ASA-induced gastric injury via anti-inflammatory, antiapoptotic and antioxidant effects [46]. In another study with rats, the gastroprotective property of NS oil (10 ml/kg) against piroxicam-induced gastric ulcer was studied using light electronic microscopy. The results showed that NS improved the mucosal structure that received piroxicam and increased mucus secretion in the rats [47].

TQ exhibited novel gastric protection mechanisms via inhibition of proton pump, secretion of acid and neutrophil infiltration while enhancing secretion of mucin, and nitric oxide production [48]. These studies confirm that TQ may be employed as a useful therapeutic agent to prevent the gastrointestinal side effects that limit the use of several drugs.

## 12. DRUG-INDUCED OTOTOXICITY

Certain therapeutic medications have toxic effects on vestibular functions and hearing which is known as drug-induced ototoxicity. This type of toxicity has a significant impact on health

because it can resist most of the medical therapies [49]. The protective effect of TQ (40 mg/kg/orally) against amikacin induced ototoxicity was investigated. The distortion product otoacoustic emission (DPOAE) values showed significant reduction and auditory brainstem response (ABR) thresholds showed an increase in its values of the amikacin group on $7^{th}$ and $15^{th}$ day, as compared to the amikacin+TQ group. Whereas the ABR thresholds of the amikacin group significantly elevated on $7^{th}$ and $15^{th}$ day as compared to their initial values, but there was no significant difference between the values of initial and $7^{th}$ and $15^{th}$ day of ABR thresholds in the amikacin+TQ group. The total oxidative stress index and oxidant status values in the amikacin+TQ group were much less than the amikacin group while the total antioxidant status values of the amikacin+TQ group were much higher than the amikacin group. This study showed that the amikacin-induced ototoxic effect may be eliminated with the concurrent use of TQ [50]. It also protected against gentamicin-induced ototoxicity. The threshold's value of ABR was maintained in the gentamicin+TQ group when compared to the gentamicin group alone. The TUNEL-positive cells were fewer and caspase-3 and caspase-9 expressions were found to be weaker in the outer and inner hair cells of the organ of Corti in the gentamicin+TQ group when compared to gentamicin alone. Therefore, the cochlear histo-morphological conclusion was supportive of the auditory findings, and it was concluded that the ototoxicity induced by gentamicin can be prevented with the use of TQ [51]. The TQ potential for a protective effect against cisplatin-induced ototoxicity was studied and the results showed that ABR thresholds and DPOAE responses were preserved in the TQ+cisplatin treated group when they were compared with only cisplatin group [52]. Therefore, according to the above data, drugs induced ototoxicity can be prevented by TQ administration.

Some important activities of TQ on the toxicity of drug are summarized in Table 1 which include nephrotoxicity, hepatoxicity, cardiotoxicity, lung injury, gastritis, ototoxicity.

**Table 1. The activity of TQ on drug toxicity**

| Drug toxicity | Experimental/test system | Activity | Refs |
|---|---|---|---|
| **Nephrotoxicity** | **Gentamicin (GM) induced renal toxicity** | TQ completely reversed the increased BUN, Cr, TNF-α, TBARS and NO; and the decreased the GSH, GPx, CAT and ATP to control values. Further, a histopathological study of kidney tissues confirmed that TQ prevents GM-induced degenerative changes in kidney tissues. | [16 -17] |
| | **Vancomycin(VCM)-induced nephrotoxicity in rats** | TQ administration significantly ameliorated the increased levels of serum BUN, Cr and kidney tissue MDA in VCM group and the decreased activities of SOD and GSH-Px in kidney tissue | [18] |
| | **Cyclosporine induced nephrotoxicty** | Administration of TQ significantly reversed the increased Cystatin C and alteration of kidney parenchyma | [19] |
| | **Nephrotoxicity induced by acetaminophen** | TQ significantly reduced the BUN, Cr levels. The NO activity and tissue MDA levels were also reduced significantly. Also, TQ ameliorated the tissue damage scores | [22] |
| | **Cyclophosphamide-(CP)induced hepatotoxicity** | TQ significantly reduced the levels of AST, ALT and serum bilirubin. It also protected the activity of SOD and CAT in CP-injected mice. Also, TQ reduced the CP-induced inflammation and hemorrhage in liver tissues. | [25] |
| | **Acetaminophen-induced** | TQ reverse the acetaminophen-induced | |

| Drug toxicity | Experimental/test system | Activity | Refs |
|---|---|---|---|
| | **hepatotoxicity** | increase in ALT, total nitrate/nitrite, lipid peroxide level and a decrease in GSH and ATP level. | [24] |
| **Hepatotoxicity** | **liver damage induced by Tamoxifen (TAM)** | TQ visibly inhibited the increase in serum activity of the evaluated enzymes. It also prevented TAM-induced hepatic GSH depletion and lipid peroxidation (LPO) accumulation. Consistently, TQ normalised the activity of SOD, inhibited the rise in TNF-α and ameliorated the histopathological changes. | [25] |
| | **Doxorubicin-induced cardiotoxicity** | TQ significantly reduce in LDH and creatine kinase elevated levels and further supplemented by histopathological examination of cardiac tissue. | [32-33] |
| **Cardiotoxicity** | **Cisplatin-induced cardiac injury** | TQ group exhibited a significant increase in expression of antiapoptotic protein Bcl-2. It exhibited counteraction against the histopathological changes associated with cisplatin administration | [31] |
| | **Cyclophosphamide (CP)-induced cardiotoxicity** | TQ completely reverse all the biochemical changes induced by CP to their control values. From this study, the suggested mechanism of TQ, its ability to decrease oxidative and nitrosative stress as well as its ability to improve the mitochondrial function and energy production was determined. | [34] |
| **Lung injury** | **Lung injury induced by bleomycin** | TQ significantly reduced the increased levels of lactate dehydrogenase, total protein, total leucocytic count, and mucin. TQ also counteracted inflammatory cell infiltration, emphysema in air alveoli. Also, the fibrosis marker hydroxyproline content was significantly decreased by concurrent TQ. | [40] |
| | **Cyclophosphamide (cp)-induced pulmonary injury** | TQ significantly alleviate the changes in lung and serum biomarkers related to inflammatory reactions, with less LPO and restoration of antioxidants. Moreover, TQ reduced the secretion of the pro-inflammatory cytokine, TNF-α in serum. Also, TQ effectively alleviated CP-induced histopathological alterations in lung tissue. | [41] |
| **Gastritis** | **Indomethacin-induced gastric ulcer** | TQ attenuate the indomethacin-induced alterations in gastric juice volume, acid-output, pH and ulcer index | [45] |
| | **Acetylsalicylic acid-induced gastric ulcer** | TQ reduced gastric ulcer indices, apoptosis, dimethylarginine, total oxidant status, asymmetric, and tumour necrosis factor-alpha levels, nuclear factor kappa-light-chain-enhancer of activated B cells, | [46] |

| Drug toxicity | Experimental/test system | Activity | Refs |
|---|---|---|---|
| | | and inducible nitric oxide synthase expressions | |
| | **Piroxicam-Induced Gastric Mucosal Damage** | TQ protected the structure of the mucosa nearly similar to control as well as the percentage of total length of the damaged mucosa was significantly decreased | [47] |
| **Ototoxicity** | **Amikacin-induced ototoxicity** | ABR thresholds were preserved by concurrent use of TQ as well as TQ significantly decreased the total oxidant status and oxidative stress index values. Total antioxidant status values were significantly increased by concurrent use of TQ. | [48] |
| | **Gentamicin ototoxicity** | ABR thresholds were preserved by concurrent use of TQ when compared with the group receiving gentamicin alone as well as by using of TQ there were fewer TUNEL-positive cells and caspase-3 and caspase-9 expressions were weaker in the inner and outer hairy cells of the organ of Corti | [51] |
| | **Cisplatin-induced ototoxicity** | The DPOAE responses and ABR thresholds were preserved by concurrent use of TQ | [52] |

## 13. CONCLUSION

Despite the therapeutic benefits of drugs, they have side effects that limit their long-term use. One of the approaches to protect against drugs induced side effects is treatment by medicinal herbs. *NS* (Ranunculaceae family), have been used for hundreds of years as a medicinal remedy for several diseases. TQ is an active ingredient of NS that is well known to possess a wide variety of pharmacological activity. In the present article, the protective effect of TQ against drug toxicities is separately reviewed for the first time as per our knowledge. In many animal model experiments, clear documentation of the protective effect of TQ has been exhibited against drug-induced nephrotoxicity, hepatoxicity, cardiotoxicity, respiratory problems, gastritis and ototoxicity. Therefore, TQ may be considered as a promising agent to be employed as adjuvants with drugs for protection against drugs induced toxicity. However, further basic and clinical studies are required to confirm these results which should be beneficial without compromising the main therapeutic effect of drugs.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Author has declared that no competing interests exist.

## REFERENCES

1. Islam Web. Black Seed (*Nigella sativa*) a cure for every disease. 2010. Accessed 26 October 2016. Availabile:https://www.islamweb.net/en/article/157049/black-seed-nigella-sativa-a-cure-for-every-disease.
2. Khan MA. Chemical composition and medicinal properties of *Nigella sativa* Linn. Inflammopharmacology. 1999;7:15-35.
3. Salem ML. Immunomodulatory and therapeutic properties of the *Nigella sativa* L. Seed. Int Immunopharmaco. 2005;5:1749-70.
4. Ali B, Blunden G. Pharmacological and toxicological properties of *Nigella sativa*. Phytotherapy Research: An international journal devoted to pharmacological and toxicological evaluation of natural product derivatives. 2003;7:299-305.

5. Darakhshan S, Pour AB, Colagar AH, Sisakhtnezhad S. Thymoquinone and its therapeutic potentials. Pharmacological Research. 2015;95:138-158.
6. Tembhurne SV, Feroz S, Sakarkar DM. A review on therapeutic potential of *Nigella sativa* (kalonji) seeds. J Med Plants Res. 2014;8.
7. Forouzanfar F, Bazzaz BSF, Hosseinzadeh H. Black cumin (*Nigella sativa*) and its constituent (thymoquinone): A review on antimicrobial effects. Iranian Journal of Basic Medical Sciences. 2014;917:12-929.
8. Ahmad A, Husain A, Mujeeb M, Khan SA, Najmi AK, Siddique NA, et al. A review on therapeutic potential of *Nigella sativa*: A miracle herb. Asian Pac J Trop Biomed. 2013;35:337-352.
9. Zaoui A, Cherrah Y, Mahassini N. Alaoui K. Acute and chronic toxicity of *Nigella sativa* fixed oil. Phytomedicine. 2002;9:69-74.
10. Paarakh PM. *Nigella sativa* Linn.–A comprehensive review. Indian J Nat Prod Resour. 2010;1:409-29.
11. Woo CC, Kumar AP, Sethi G, Tan KHB. Thymoquinone: Potential cure for inflammatory disorders and cancer. Biochem Pharmacol. 2012;83:443-451.
12. Taha M, Azeiz A, Saudi W. Antifungal effect of thymol, thymoquinone and thymohydroquinone against yeasts, dermatophytes and non-dermatophyte molds isolated from skin and nails fungal infections. Egyptian Journal of Biochemistry & Molecular Biology. 2010;28:109-126.
13. Sangi SMA, Sulaiman MI, El-Wahab MFA, Ahmedani EI, Ali SS. Antihyperglycemic effect of thymoquinone and oleuropein, on streptozotocin-induced diabetes mellitus in experimental animals. Pharmacogn Mag. 2015;11:S251.
14. Bamosa AO, Ali BA, Al-Hawsawi ZA. The effect of thymoquinone on blood lipids in rats. Indian J Physiol Pharmacol. 2002;46:195-201.
15. Ali B, Blunden G. Pharmacological and toxicological properties of *Nigella sativa*. Phytotherapy Research. 2003;7:299-305.
16. Sayed-Ahmed MM, Nagi MN. Thymoquinone supplementation prevents the development of gentamicin-induced acute renal toxicity in rats. Clin Exp Pharmacol Physiol. 2007;34:399-405.
17. Mahmoud AM, Ahmed OM, Galaly SR. Thymoquinone and curcumin attenuate gentamicin-induced renal oxidative stress, inflammation and apoptosis in rats. EXCLI J. 2014;13:98.
18. F Basarslan, N Yilmaz, S Ates, T Ozgur, M Tutanc, Motor VK, et al. Effects of thymoquinone on vancomycin-induced nephrotoxicity in rats, Hum Exp Toxicol. 2012;31:726–733.
19. Alrashedi MG, Ali AS, Ali SS, Khan LM. Impact of thymoquinone on cyclosporine a pharmacokinetics and toxicity in rodents. J Pharm Pharmacol. 2018;70(10):1332-1339.
20. Cascella M, Palma G, Barbieri A, Bimonte S, Amruthraj NJ, Muzio MR. Role of *Nigella sativa* and its constituent thymoquinone on chemotherapy-induced nephrotoxicity: Evidences from experimental animal studies. Nutrients. 2017;9:625.
21. Badary OA, Abdel-Naim AB, Abdel-Wahab MH, Hamada FM. The influence of thymoquinone on doxorubicin-induced hyperlipidemic nephropathyin rats. Toxicology. 2000;143:219–226.
22. Aycan İÖ, Tokgöz O, Tüfek A, Alabalık U, Evliyaoğlu O, Turgut H, et al. The use of thymoquinone in nephrotoxicity related to acetaminophen. Int J Surg. 2015;13:33-37.
23. Aycan İÖ, TüfekA, Tokgöz O, Evliyaoğlu O, Fırat U, Kavak GÖ. Thymoquinone treatment against acetaminophen-induced hepatotoxicity in rats. Int J Surg. 2014;12:213-218.
24. Nagi MN, Almakki HA, Sayed-Ahmed MM, Al-Bekairi AM. Thymoquinone supplementation reverses acetaminophen-induced oxidative stress, nitric oxide production and energy decline in mice liver. Food Chem Toxicol. 2010;48:2361-2365.
25. Suddek GM. Protective role of thymoquinone against liver damage induced by tamoxifen in female rats. Can J Physiol Pharmacol. 2014;92:640-644.
26. Laskar AA, Khan MA, Rahmani AH, Fatima S, Younus H. Thymoquinone, an active constituent of *Nigella sativa* seeds, binds with bilirubin and protects mice from hyperbilirubinemia and cyclophosphamide-induced hepatotoxicity. Biochimie. 2016;127:205-213.
27. Alenzi FQ, El-Bolkiny S, Yel ML, Salem. Protective effects of *Nigella sativa* oil and thymoquinone against toxicity induced by

the anticancer drug cyclophosphamide. Br J Biomed Sci. 2010;6720–28.

28. Jaswal A, Sinha N, Bhadauria M, Shrivastava S, Shukla S. Therapeutic potential of thymoquinone against anti-tuberculosis drugs induced liver damage. Environ Toxicol Pharmacol. 2013;36;779–786.
29. Bai T, Yang Y, Wu YL, Jiang, S, Lee JJ, Lian LH, et al. Thymoquinone alleviates thioacetamide-induced hepatic fibrosis and inflammation by activating LKB1–AMPK signaling pathway in mice. Int Immunopharmacol. 2014;19:351-357.
30. M Ismail, Al-Naqeep G, Chan KW. *Nigella sativa* thymoquinone-rich fraction greatly improves plasma antioxidant capacity and expression of antioxidant genes in hypercholesterolemic rats. Free Radic Biol Med. 2010;48;664–672.
31. Adali F, Gonul Y, Kocak A, Yuksel Y, Ozkececi G, Ozdemir C. Effects of thymoquinone against cisplatin-induced cardiac injury in rats. Acta Cir Bras. 2016;31:271-277.
32. Al-Shabanah OA, Badary OA, Nagi MN, Al-Gharably NM, Al-Rikabi AC, Al-Bekairi AM. Thymoquinone protects against doxorubicin-induced cardiotoxicity without compromising its antitumor activity. J Exp Clin Cancer Res. 1998;17:193–198.
33. Nagi MN, Mansour MA. Protective effect of thymoquinone against doxorubicin-induced cardiotoxicity in rats: a possible mechanism of protection, Pharmacol Res. 2000;41:283–289.
34. Nagi MN, Al-Shabanah OA, Hafez MM, Sayed-Ahmed MM. Thymoquinone supplementation attenuates cyclophos-phamide-induced cardiotoxicity in rats. J Biochem Mol Toxicol. 2011;25;135–142.
35. El-Saleh SC, Al-Sagair OA, Al-Khalaf MI. Thymoquinone and *Nigella sativa* oil protection against methionine-induced hyperhomocysteinemia in rats. Int J Cardiol. 2004;93:19–23.
36. Khattab MM, Nagi MN. Thymoquinone supplementation attenuates hypertension and renal damage in nitric oxide deficient hypertensive rats. Phytother Res. 2007;21: 410–414.
37. El Gazzar M, El Mezayen R, Marecki JC, Nicolls MR, Canastar A, Dre-skin SC. Anti-inflammatory effect of thymoquinone in a mouse model of allergic lung inflammation. Int Immunopharmacol. 2006;6:1135–1142.
38. Kalus U, Pruss A, Bystron J, Jurecka M, Smekalova A, Lichius JJ, et al. Effect of *Nigella sativa* (black seed) on subjective feeling in patients with allergic diseases. Phytother Res. 2003;17:1209–1214.
39. Ammar El SM, Gameil NM, Shawky NM, Nader MA. Comparative evaluation of anti-inflammatory properties of thymoquinone and curcumin using an asthmatic murine model. Int Immunopharmacol. 2011;11: 2232–2236
40. El-Khouly D, El-Balky WM, Awad AS , El-Mesallamy HO, El-Demerdash E. Thymoquinone blocks lung injury and fibrosis by attenuating bleomycin-induced oxidative stress and activation of nuclear factor Kappa-B in rats. Toxicology. 2012;302:106-113.
41. Suddek GM, Ashry NA, Gameil NM. Thymoquinone attenuates cyclophos-phamide-induced pulmonary injury in rats. Inflammopharmacology. 2013;21:427-435.
42. Al Mofleh IA, Alhaider AA, Mossa JS, Al-Sohaibani MO, Al-Yahya MA, Rafatullah S, et al. Gastroprotective effect of an aqueous suspension of black cumin *Nigella sativa* on necrotizing agents-induced gastric injury in experimental animals. Saudi Journal of Gastroenterology: Official Journal of the Saudi Gastroenterology Association. 2008;4:128.
43. El-Dakhakhny M, Barakat M, El-Halim MA, Aly S. Effects of *Nigella sativa* oil on gastric secretion and ethanol induced ulcer in rats. J Ethnopharmacol. 2000;72:299-304.
44. Kanter M, Demir H, Karakaya C, Ozbek H. Gastroprotective activity of *Nigella sativa* L. oil and its constituent, thymoquinone against acute alcohol-induced gastric mucosal injury in rats. World J Gastroenterol. 2005;11:6662.
45. Rifat-uz-Zaman MSA, Khan MS. Gastroprotective and anti-secretory effect of *Nigella sativa* seed and its extracts in indomethacin-treated rats. Pak J Biol Sci. 2004;7:995-1000.
46. Zeren S, Bayhan Z, Kocak FE, Kocak C, Akcılar R, Bayat Z, et al. Gastroprotective effects of sulforaphane and thymoquinone against acetylsalicylic acid–induced gastric ulcer in rats. J Surg Res. 2016;203:348-359.
47. Mohammed SS, Naim MM, Mahmoud SH. Possible protective effect of *Nigella sativa* oil against piroxicam-induced gastric mucosal damage in adult male albino rats

(light and scanning electron microscopic study). Egypt J Histo. 2010;33:127-139.
48. Magdy MA, Hanan EA, Nabila EM. Thymoquinone: Novel gastroprotective mechanisms. Eur J Pharmacol. 2012;697: 126-131.
49. Kasse CA, Hyppolito MA, Cruz OL, de Oliveira JA. Ototoxicity and otoprotection. Rev Bras Med. 2008;4:105–115.
50. Aksoy F, Dogan R, Ozturan O, Tugrul S, Veyseller B, Ozer OF, et al. An evaluation of the protective effects of thymoquinone on amikacin-induced ototoxicity in rats. Clin Exp Otorhinolaryngol. 2015;8:312.
51. Sagit M, Korkmaz F, Gürgen SG, Kaya M, Akcadag A. Ozcan I. The protective role of thymoquinone in the prevention of gentamicin ototoxicity. American Journal of Otolaryngology. 2014;35:603-609.
52. Sagit M, Korkmaz F, Akcadag A, Somdas MA. Protective effect of thymoquinone against cisplatin-induced ototoxicity. European Archives of Oto-Rhino-Laryngology. 2013;270:2231-2237.



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