The preventive and curative role of Nigella sativa in poisoning cases.

Said Said Elshama*

Department of Forensic Medicine and Clinical Toxicology, College of Medicine, Suez Canal, University, Ismailia City, Egypt, College of Medicine, Taif University, Taif, Saudi Arabia

Abstract

Nigella sativa **was used in folk medicine as a promising medicinal plant from many years ago. Therapeutic efficacy of Nigella sativa is attributed to thymoquinone that has cytoprotective action. Thymoquinone is a potent antioxidant effect *via* the oxidizing agents reduction and antioxidant molecules induction. A lot of studies proved that *Nigella sativa* has an effective preventive and curative outcome in many intoxicated cases. Most of these studies showed that *Nigella sativa* has the ability to prevent or cure the serious toxic manifestations of common drugs including some chemotherapeutic drugs, antibiotics, and analgesics besides some chemicals such as insecticides, organic solvents, and toxic elements.**

Keywords: *Nigella sativa,* antioxidant, prevention, curative

Accepted on August 26, 2018

Introduction

Folk or alternative medicine that is based on herbal plants was used a traditional treatment in many diseases for centuries in the different areas of the world especially the developing countries. Until now, it is still used in rural areas wherein 80% of the Asian and African population utilize it in primary health care. So, many studies were conducted on these medicinal plants to investigate its efficacy and safety [1]. *Nigella sativa* is a marvel medicinal plant because of its wide potent therapeutic effects which were guaranteed historical and religious. *Nigella sativa* is called black seed among Muslim people wherein it was mentioned in the prophetic medicine as a promising medicinal plant [2].

Nigella sativa is one of Ranunculaceae family which grows spontaneously in the several areas of the world. This plant contains a lot of tiny dark black seeds that are used in cheese, bread, and pastry as a known spice and flavoring additive. However, it was also used in traditional medicine as a remedy for many illnesses owing to the reported therapeutic effects. The black seeds contain more than 100 bioactive molecules such as the different types of vitamins (A, B, C) and minerals (calcium, potassium, zinc, iron) besides the saturated and unsaturated fatty acids [3]. According to many studies, the seeds of *Nigella sativa* and its oil have a broad range of curative effects wherein it is considered anti-hypertensive, anti-diabetic, anti-inflammatory, diuretic, analgesic, antibacterial, antiviral, anthelmintic, immunomodulator, anti-tumor and antioxidant [4].

The health benefits of *Nigella sativa* have been due to its active ingredients that are concentrated in fixed and essential oil. This oil is rich source of bioactive phytochemicals that represents 85% of the total compounds such as thymoquinone and tocopherols [5]. *Nigella sativa* oil supplementation in the food products is utilized to promote the human health against common disorders such as hyperglycemia and hypercholesterolemia. The nutritional value of *Nigella sativa* oil is attributed to its ability to preserve the food from the degradation during processing and storage. *Nigella sativa* oil diminishes the microbial growth and delays the oxidation of oxidizable materials such as lipids [6].

Therapeutic efficacy of *Nigella sativa* is attributed to its essential constituent that is called thymoquinone and its derivatives which are cytoprotective agents through its potent antioxidant effect via the reduction of oxidizing agents and the induction of the cellular antioxidant molecules [7]. From this a point of view, more attention have been paid to the use of *Nigella sativa* as a preventive and curative agent in the poisoning cases wherein the toxic manifestations of drugs and chemical intoxications are attributed to the oxidative stress process that produces the reactive oxygen species leading to a damage in the different cellular components and a lipid peroxidation in the various organs such as kidney, liver, and brain [8,9].

In the last years, a lot of studies were conducted on *Nigella sativa* using its health benefits for addressing many medical problems. So, this article endeavors to concentrate on the preventive and therapeutic role of *Nigella sativa* in the poisoning cases based on the available published researches.

Nigella sativa and Drug Intoxication

In the previous years, a lot of studies were carried out to investigate the efficacy of *Nigella sativa* in addressing the toxic manifestations that are emerging due to the use of some common medications. Cyclophosphamide is considered one of these medications that cause a known significant toxicity in the clinical field wherein induce significant alterations in the liver and renal functions, a decrease in hemoglobin concentration, an increases in the blood sugar level associated with an increase in the levels of triglyceride, cholesterol and low-density lipoprotein.

Alenzi and his colleagues [10] studied the preventive role of *Nigella sativa* in modulating the toxicity of cyclophosphamide wherein they proved the ability of *Nigella sativa* as an antioxidant to overcome the overall toxicity of cyclophosphamide that is resulted from the overproduction of reactive oxygen spices and the associated oxidative stress.

In the related context, Gore, et al. [11] showed that cyclophosphamide may induce hemorrhagic cystitis based on

an increase in the oxidative stress, the inflammatory cytokines, and associated with a suppression in the activity of nuclear factor related erythroid 2-related factor (Nrf2). Furthermore, Gore and his colleagues indicated that the repeated use of cyclophosphamide over a long period may lead to bladder cancer. So, the study of Gore, et al. demonstrated the preventive effect of thymoquinone (active constituent of *Nigella sativa*) against cyclophosphamide-induced hemorrhagic cystitis via a reduction in the oxidative stress, inhibiting of DNA damage and upregulation of Nrf2 expression.

In the same context, Suddek, eta al. [12] referred that thymoquinone can attenuate cyclophosphamide-induced pulmonary injury via the restoration of antioxidant enzymes levels besides a reduction in the secretion of pro-inflammatory cytokine and lipid peroxidation in the lung tissues. In addition to, thymoquinone significantly alleviated the pulmonary histopathological changes and improved the associated serum biomarkers, and then the inflammatory reactions.

Moreover, other researches were conducted on the beneficial effects of thymoquinone as an antioxidant and anti-inflammatory to modulate the toxic effect of another chemotherapeutic agent that is cisplatin. Al-Malki and Sayed, [13] suggested that thymoquinone can ameliorate all toxic effects of cisplatin on the liver wherein it improves the toxic hepatic histopathological changes, attenuates the activated NF-κB in the liver, increases the antioxidant enzymes activities including glutathione peroxidase and glutathione-S transferase in the hepatic tissues, and reduces the levels of malondialdehyde . In addition, the expression and concentrations of inflammatory tumor necrosis factor, nitric oxide synthetase, and interleukin were significantly reduced improving the energy metabolism, accelerating the injured organelles regeneration, and strengthening the endogenous antioxidant defense mechanism [14].

On another hand, other studies showed that thymoquinone may be a renoprotective agent against cisplatin-induced nephrotoxicity [15] wherein thymoquinone has an ability to prevent the onset and progression of nephrotoxicity via decreasing the lipid peroxidation and increasing the activity of antioxidant enzymes in the renal tissues [16]. Hosseinian and his colleagues [17] supported also the role of oxidative stress in the pathophysiology of cisplatin-induced nephrotoxicity and clarified the ability of *Nigella sativa* to recover the renal damage.

Likewise, Badary, et al. [18] demonstrated that the high antioxidant potential of thymoquinone can significantly modulate doxorubicin-induced hyperlipidemic nephropathy suppressing proteinuria and albuminuria wherein it is considered as an applicable protective agent for proteinuria and hyperlipidemia associated with nephrotic syndrome. Moreover, Alam, et al. [19] found that thymoquinone has a protective effect against doxorubicin-induced cardiotoxicity via accelerating the heart antioxidant defense mechanism and down-regulating the lipid peroxidation level towards the normality. Thus, thymoquinone may be utilized as a potential drug for toxic cardiomyopathy in accordance with Nagi and Mansour [20].

Furthermore, *Nigella sativa* may have cardioprotective effects according to the study of Ebru and his colleagues [21] who reported that its oil can lessen the cyclosporine A-induced cardiotoxicity owing to its antioxidant effect wherein the cardiac insult is a consequence of oxidative stress that is caused by the toxic effect of cyclosporine. In addition, *Nigella sativa* oil can abolish all toxic manifestations of cyclosporine on the heart decreasing the lipid peroxidation, improving the cellular protein oxidation, and normalizing the cardiac histopathological changes.

Over the past years, a number of researches were conducted on the protective role of *Nigella sativa* against paracetamol-induced hepatorenal damage that is manifested by a disturbance in the liver and renal function tests associated with the toxic hepatic and renal histopathological changes.

Hasan, et al. [22] confirmed the preventive role of *Nigella sativa* against paracetamol-induced hepatotoxicity and nephrotoxicity while Canayakin and his colleagues [23] showed the prophylactic role of *Nigella sativa* against paracetamol-induced nephrotoxicity wherein Hamza, et al. [24] and Adam, et al. [25] referred to hepatoprotective effects of *Nigella sativa* against acetaminophen-induced oxidative stress and hepatotoxicity. According to the results of these studies, the hepatoprotection role of *Nigella sativa* is attributed to the direct and indirect effects of thymoquinone wherein it is antioxidant besides enhancing the activity of other antioxidants such as glutathione, catalase, and superoxide dismutase boosting the body's antioxidant mechanism against the oxidative stress. On another hand, the nephroprotection role of *Nigella sativa* is due to enhancing the prostaglandin synthesis leading to an inadequate renal perfusion besides the detoxification of the free radicals via significant improving the activities of antioxidant enzymes promoting the antioxidant mechanism.

Otherwise, Omar [26] pay more attention to the neuroprotective role of *Nigella sativa* and proved that administration of its oil can protect the cortical neurons and myelinated axons against tramadol-induced toxic changes wherein it alleviates ultrastructural apoptotic changes in the motor cerebral cortex. On another hand, Elkhateeb, et al. [27] indicated to the hepatoprotective and nephroprotective roles of Linn oil of *Nigella sativa* on hepatotoxicity and nephrotoxicity of tramadol.

Elshama, et al. [28] also proved that *Nigella sativa* can modulate the toxic testicular manifestations of the colchicine repeated use via normalization the plasma testosterone level, reducing the number of abnormal-shaped sperms, improving the sperm motility and liveability. In another context, Ali [29] and Rehman, et al. [30] showed the ability of *Nigella sativa* to ameliorate the renal toxic effects of gentamicin normalizing the renal biochemical parameters and the renal morphological changes.

Every day and with the scientific research development, the utilizing field of *Nigella sativa* in the treatment of poisoning cases is expanded to overcome the toxic side effects of other new therapeutic agents such as hypervitaminosis, oxytetracycline, isoproterenol, sodium valproate, and isoniazid.

According to Al-Suhaimi [31] *Nigella sativa* oil has a considerable hepatoprotective effect against hypervitaminosis A and a humoral immune response to vitamin A intoxication

wherein it is an effective inducer of IgG and IgM in the serum with the high doses of vitamin A.

In the related context, Abdel-Daim and Ghazy [32] indicated to the hepatoprotective and renoprotective effect of *Nigella sativa* oil against oxytetracycline - induced hepatotoxicity and nephrotoxicity while Hassan, et al. [33] demonstrated the cardioprotective effect of *Nigella sativa* against isoproterenol-induced myocardial infarction via restoring the normal levels of cardiac biomarkers as well as antioxidant markers associated with modulation the cardiac histopathological changes.

Furthermore, Wahba [34] suggested that *Nigella sativa* may also protect the testicular tissues against the toxic effect of sodium valproate. In accordance with the results of the previous studies, the study of Hassan, et al. [35] referred also to the protective role of *Nigella sativa* in the hepatotoxicity of another drug that is one of the antituberculous drugs (isoniazid).

Table 1 shows a summary of the ameliorative effect of *Nigella sativa* on the above-mentioned drugs intoxication related to the affected organ or system.

Nigella sativa and Chemical Intoxication

In another context, a number of researches focused on the protective role of *Nigella sativa* against chemicals intoxication and conducted to the fruitful results in this field. Nagi and Almakki [36] showed that *Nigella sativa* is a promising prophylactic agent against chemical toxicity and carcinogenesis via enhancing the activities of glutathione transferase and quinone reductase. El Gendy, et al. [37] reported that *Nigella sativa* corrects the toxic biochemical disturbance which is induced by nitrosamine precursors administration wherein it ameliorates the levels of oxidative stress markers such as reduced glutathione, nitric oxide and the cancer-related genes such as bcl2, p53, and HER-2/neu.

Table 1. *Ameliorative effect of Nigella sativa against different drugs intoxication.*

Drug	Affected Organ or System	Reference
Cyclophosphamide	Hemorrhagic cystitis Pulmonary injury	Alenzi, et al. [10] Gore, et al., [11] Suddek, et al., [12]
Cisplatin	Hepatotoxicity Nephrotoxicity	Al-Malki and Sayed [13] Hosseinian, et al. [17]
Doxorubicin	Hyperlipidemic nephropathy Cardiotoxicity Toxic cardiomyopathy	Badary, et al. [18] Alam, et al. [19] Nagi and Mansour [20]
Cyclosporine A	Cardiotoxicity	Ebru, et al. [21]
Paracetamol	Hepatotoxicity Nephrotoxicity	Hasan, et al. [22] Canayakin, et al. [23] Hamza, et al., [24] Adam, et al., [25]
Tramadol	Neurotoxicity Hepatotoxicity Nephrotoxicity	Omar [26] Elkhateeb, et al. [27]
Colchicine	Testicular toxicity	Elshama, et al. [28]
Gentamicin	Nephrotoxicity	Ali. [29] Rehman, et al. [30]
Hypervitaminosis A	Hepatotoxicity	Al-Suhaimi [31]
Oxytetracycline	Hepatotoxicity Nephrotoxicity	Abdel-Daim and Ghazy [32]
Isoproterenol	Cardiotoxicity	Hassan, et al. [33]
Sodium Valproate	Testicular toxicity	Wahba [34]
Isoniazid	Hepatotoxicity	Hassan, et al. [35]

Furthermore, Ahmad and Alkreathy [38] proved that the ameliorative effect of *Nigella sativa* against thioacetamide-induced hepatorenal toxicity wherein thioacetamide is classified as a potent centrilobular hepatotoxic agent and carcinogen of class 2B. Noteworthy, acute and chronic thioacetamide exposure leads to hepatic toxicity via interfering DNA, RNA, protein synthesis, and gamma-glutamyl transpeptidase activity by its bioactive metabolites.

In another context, *Nigella sativa* has an ability to counteract the toxic effect of gamma radiation on the jejunal mucosa attenuating the toxic morphological changes [39]. It is also a promising radioprotective agent against hemopoietic, immunosuppressive, and oxidative effects of gamma irradiation toxicity [40].

In addition, *Nagilla sativa* has a protective effect against the toxicity of another inorganic chemical compound that is sodium nitrite; it is a commonly used color fixative and preservative. Thymoquinone is able to restore the normal balance between pro and anti-inflammatory cytokines and protect the renal tissue form extrinsic and intrinsic apoptosis that is attributed to the toxicity of sodium nitrite [41]. Mansour, et al. [42] also demonstrated the protective effect of the volatile oil of *Nigella sativa* against carbon tetrachloride -induced hepatic damage as an efficient antioxidant in accordance with Krishnan and Muthukrishnan [43].

In the previous years, the large number of studies was carried out for the use of the protective effect of *Nigella sativa* in amelioration the hepatotoxicity of other toxic agents such as ethanol. Alsaif [44] and Develi, et al. [45] indicated that *Nigella sativa* is an effective agent in protecting the oxidative stress-induced hepatotoxicity in accordance with Hosseini, et al. [46] who confirmed also the protective effect of thymoquinone against ethanol-induced hepatotoxicity and nephrotoxicity together. El-Dakhakhny, et al. [47] conclude that *Nigella sativa* exerts a gastroprotective effect against ethanol-induced ulcer via a significant increase in the glutathione level, mucin content, and the free acidity associated with a significant decrease in the gastric mucosal histamine content.

Toluene is one of the aromatic hydrocarbons wherein it is used as a major solvent in numerous household products and occupational locations. Toluene Inhalation is one of the most popular forms of inhalant abuse wherein chronic toluene exposure is one of the most serious chemical toxicities. So, the toxic effects of chronic toluene exposure have been investigated extensively by the researchers to find a solution protecting the body systems such as the central nervous system and lung against its serious impact.

In the last years, more attention was paid towards this problem by Kanter who conducted some studies on chronic toluene exposure and its effects on CNS, lung, and testis by using *Nigella sativa* and the derived thymoquinone as a protective agent to ameliorate its toxic manifestations. Kanter showed that *Nigella sativa* can improve neurodegeneration in hippocampus that is caused by chronic toluene exposure [48]. In another research, Kanter proved that *Nigella sativa* is able to modulate the pulmonary toxicity of toluene via inhibiting the inflammatory pulmonary responses, alveolar edema and exudate, interstitial

fibrosis and necrosis besides a significant reduction in the activity of apoptosis, inducible nitric oxide synthase, and an increase in the pulmonary expression of surfactant protein D [49]. In the third research of Kanter, *Nigella sativa* demonstrated an excellent efficacy in preventing the toluene-induced testicular toxicity and re-establishing the spermatogenesis via a significant reduction in the endothelial nitric oxide synthase and a rise in the expression of proliferating cell nuclear antigen in the testicular tissues [50].

Aluminum is another chemical toxic element and has serious hazards on human health; its oral exposure leads to hepatotoxicity, nephrotoxicity and hematological changes. Many studies used *Nigella sativa* to minimize the hazards of aluminum. These studies indicated to the protective effect of *Nigella sativa* against aluminum toxicity wherein co-administration of black seed with aluminum showed marked improvement in the hepatic and renal biochemical parameters [51,52] as well as alleviating the histopathological findings and hematological disorders [53].

In the different types of researches, the ameliorative action of *Nigella sativa* against the toxicity of other elements was proved. Parveen and Shadabig [54] indicated to its protective effect against iron-induced chromosomal aberrations in the bone marrow cells while Farrag, et al. [55] showed its preventive role against lead-induced hepatorenal toxicity. In the related context, Mohammed, et al. [56] referred also to the ability of *Nigella sativa* to attenuate cadmium-induced nephrotoxicity and neurotoxicity based on the biochemical and histological studies.

Recently, the poisoning cases of the widely used environmental chemicals such as the pesticides and insecticides become one of the most toxicological problems that face physicians in the clinical field. So, many researchers focused on their researches to find an efficient new substitute to treat or prevent the insecticides toxicity. Thus, *Nigella sativa* was used in many of these various studies as a new preventive agent in insecticides intoxication cases.

Suleman, et al. [57] indicated to the ability of the *Nigella sativa* oil in amelioration the hepatotoxicity induced via an exposure to the bifenthrin while Ince, et al. [58] reported that thymoquinone can attenuate the toxicity from the use of pyrethroid wherein it can prevent cypermethrin-induced oxidative stress and toxicity.

Propoxur is another widely used carbamate insecticide that has neurotoxic effects inducing lipid and protein peroxidation, a decrease in acetylcholine esterase activity in the brain associated with a decrease in the levels antioxidant activities and non-enzymatic antioxidant. Mohamadin, et al. [59] conclude that *Nigella sativa* significantly reduces propoxur induced toxicity and oxidative stress in the brain via a free radicals scavenging mechanism.

In the related context, Pourgholamhossein, et al. [60] showed that thymoquinone can alleviate the lung fibrosis induced by paraquat herbicide through the oxidative stress inhibition and pro-fibrotic genes down-regulation wherein paraquat is considered one of the highly toxic pesticides which cause a serious toxicity among humans. Furthermore, another study confirmed the protective role of *Nigella sativa* oil against chlorpyrifos that also is one of the most commonly used insecticides in the world. This study demonstrated that the concurrent administration of *Nigella sativa* oil and chlorpyrifos can reverse all manifestations of the reproductive toxicity wherein it improves the testosterone level, semen picture, antioxidant enzymes activities, and the testicular histopathological changes [61].

Finally, the protective effect of *Nigella sativa* extended to overcome the toxic effects of other chemical agents such as tartrazine that is widely used as an additive in the foods and drugs improving its taste. Al-Seenia, et al. [62] concluded that *Nigella sativa* can protect against tartrazine toxicity improving the kidney and liver functions, and other toxic manifestations on the testis and stomach. *Nigella sativa* can also normalize the total protein, total cholesterol, triglycerides, low and high-density lipoproteins, antioxidants activities and the lipid peroxidation in the different body tissues.

Table 2 shows a summary of the ameliorative effect of *Nigella sativa* on the above-mentioned toxic agents effects related to the affected organ or system.

Conclusion

Nigella sativa is one of the medicinal plants that have marvel protective and therapeutic effects in a lot of the intoxicated cases. A number of studies revealed that *Nigella sativa* is a potent antioxidant agent and has an outstanding efficacy in preventing or treating the toxic manifestations of some common

Table 2. *Ameliorative effect of Nigella sativa against different toxic agents effects.*

Toxic agent	Affected Organ or System	Reference
Nitrosamine	Hepatotoxicity	El Gendy, et al. [37]
Thioacetamide	Hepatotoxicity Nephrotoxicity	Alkreathy [38]
Gamma Radiation	Jejunal affection Hemototoxicity Immunotoxicity	Orhon, et al. [39] Assayed [40]
Sodium Nitrite	Nephrotoxicity	Elsherbiny, et al. [41]
Carbon Tetrachloride	Hepatotoxicity	Mansour, et al. [42] Krishnan and Muthukrishnan [43]
Ethanol	Hepatotoxicity Nephrotoxicity Toxic gastric ulcer	Alsaif [44] Develi, et al. [45] Hosseini, et al. [46] El-Dakhakhny, et al. [47]
Toluene	CNS Affection Pulmonary toxicity Testicular toxicity	Kanter [48] Kanter [49] Kanter [50]
Aluminum	Nephrotoxicity Hepatotoxicity Hematotoxicity	Mahdy and Farrag [51] Mohammed. [52] Mohamed and Awad [53]
Iron	Chromosomal Aberrations	Parveen and Shadabig [54]
Lead	Hepatotoxicity Nephrotoxicity	Farrag, et al. [55]
Cadmium	Nephrotoxicity Neurotoxicity	Mohammed, et al. [56]
Bifenthrin	Hepatotoxicity	Suleman, et al. [57]
Pyrethroid	Oxidative toxicity	Ince, et al. [58]
Propoxur	Neurotoxicity	Mohamadin, et al. [59]
Paraquat	Lung fibrosis	Pourgholamhossein, et al. [60]
Chlorpyrifos	Reproductive toxicity	Mosbah, et al. [61]
Tartrazine	Hepatotoxicity Nephrotoxicity Testicular toxicity	Al-Seenia, et al. [62]

drugs and chemicals based on its oxidative stress mechanism inducing toxicity.

Recommendation

Further human researches should be conducted in the future to investigate the preventive and curative efficacy of *Nigella sativa* in the various intoxication cases.

Conflict of Interest Statement:

There is no conflict of interest.

References

1. World Health Organization (WHO), "Traditional medicine", Fact sheet 134. Geneva: WHO, 2008.
2. Islam MT, Guha B, Hosen S, et al. Nigellalogy: A review on Nigella Sativa. MOJ Bioequiv 2017; 3:167-81.
3. Gharby S, Harhar H, Guillaume D, et al. Chemical investigation of Nigella sativa L seed oil produced in Morocco. J Saudi Soc Agric Sci 2015; 14:172-7.
4. Ahmad A, Husain A, Mujeeb M, et al. A review on therapeutic potential on Nigella sativa: A miracle herb. Asian Pac J Trop Biomed 2013; 3:337-52.
5. Cheikh-Rouhoua S, Besbesa S, Lognayb G, et al. Sterol composition of black cumin (Nigella sativa L.) and Aleppo pine (Pinus halepensisMill.) seed oils. J Food Comp Anal 2008; 21:162-8.
6. Ramadan MF. Nutritional value and applications of Nigella ativa essential oil: a mini review. Journal of Essential Oil Research 2015; 27:271-5.
7. Amin B, Hosseinzadeh H. Black Cumin (*Nigella sativa*) and its Active Constituent, Thymoquinone: An Overview on the Analgesic and Anti-inflammatory Effects. Planta Med 2016; 82:8-16.
8. Sahebkar A, Beccuti G, Simental-Mendía LE, et al. *Nigella sativa* (black seed) effects on plasma lipid concentrations in humans: A systematic review and meta-analysis of randomized placebo-controlled trials. Pharmacol Res 2016; 106:37-50.
9. Ali BH, Blunden G. Pharmacological and toxicological properties of *Nigella sativa*. Phytother Res 2003; 17:299-305.
10. Alenzi FQ, El-bolkiny YE, Salem ML. Protective effects of *Nigella sativa* oil and thymoquinone against toxicity induced by the anticancer drug cyclophosphamide. British journal of biomedical science 2010; 67:20-7.
11. Gore PR, Prajapati CP, Mahajan UB, et al. Protective Effect of Thymoquinone against Cyclophosphamide-Induced Hemorrhagic Cystitis through Inhibiting DNA Damage and Upregulation of Nrf2 Expression. Int J Biol Sci 2016; 12:944-53.
12. Suddek GM, Ashry NA, Gameil NM. Thymoquinone attenuates cyclophosphamide-induced pulmonary injury in rats. Inflammopharmacol 2013; 21:427-35.
13. Al-Malki AL, Sayed AAR. Thymoquinone attenuates cisplatin-induced hepatotoxicity via nuclear factor kappa-β. BMC Complement Altern Med 2014; 14:282-90.
14. Farooqui Z, Afsar M, Rizwan S, et al. Oral administration of *Nigella sativa* oil ameliorates the effect of cisplatin on membrane enzymes, carbohydrate metabolism and oxidative damage in rat liver. Toxicol Rep 2016; 3:328-35.
15. Cascella M, Palma G, Barbieri A, et al. Role of *Nigella sativa* and Its Constituent Thymoquinone on Chemotherapy-Induced Nephrotoxicity: Evidences from Experimental Animal Studies. Nutrients 2017; 9:625.
16. Ulu R, Dogukan A, Tuzcu M, et al. Regulation of renal organic anion and cation transporters by thymoquinone in cisplatin induced kidney injury. Food Chem Toxicol 2012; 50:1675-9.
17. Hosseinian S, Hadjzadeh MA, Roshan NM, et al. Renoprotective Effect of *Nigella sativa* against Cisplatin-induced Nephrotoxicity and Oxidative Stress in Rat. Saudi J Kidney Dis Transpl 2018; 29:19-29.
18. Badary OA, Abdel-Naim AB, Abdel-Wahab MH, et al. The influence of thymoquinone on doxorubicin-induced hyperlipidemic nephropathy in rats. Toxicology 2000; 143:219-26.
19. Alam MF, Khan G, Safhi MM, et al. Thymoquinone Ameliorates Doxorubicin-Induced Cardiotoxicity in Swiss Albino Mice by Modulating Oxidative Damage and Cellular Inflammation. Cardiol Res Pract 2018.
20. Nagi MN, Mansour MA. Protective effect of thymoquinone against doxorubicin-induced cardiotoxicity in rats: a possible mechanism of protection. Pharmacol Res 2000; 41:283-9.
21. Ebru U, Burak U, Yusuf S, et al. Cardioprotective Effects of *Nigella sativa* Oil on Cyclosporine A-Induced Cardiotoxicity in Rats. Basic & Clinical Pharmacology & Toxicology 2008; 103:574-80.
22. Hasan MN, Khan RA, Nasiruddin M, et al. Protective effect of *Nigella sativa* against paracetamol induced hepatic and renal damages. International Journal of Basic & Clinical Pharmacology 2015; 4:503-9.
23. Canayakin D, Bayir Y, Baygutalp K, et al. Paracetamol-induced nephrotoxicity and oxidative stress in rats: the protective role of *Nigella sativa*. Pharm Biol 2016; 54:2082-91.
24. Hamza RZ, Al-Harbi MS. Amelioration of paracetamol hepatotoxicity and oxidative stress on mice liver with silymarin and *Nigella sativa* extract supplements. Asian Pac J Trop Biomed 2015; 5:521-31.
25. Adam GO, Rahman MM, Lee SJ, et al. Hepatoprotective effects of *Nigella sativa* seed extract against acetaminophen-induced oxidative stress. Asian Pac J Trop Med 2016; 9:221-7.
26. Omar NM. *Nigella sativa* oil alleviates ultrastructural alterations induced by tramadol in rat motor cerebral cortex.

J Microscopy Ultrastructure 2015; 4:76-84.

27. Elkhateeb A, El Khishin I, Megahed O, et al. Effect of *Nigella sativa* Linn oil on tramadol-induced hepato and nephrotoxicity in adult male albino rats. Toxicol Rep 2015; 2:512-51.
28. Elshama SS, Shehab GMG, El-Kenawy AE, et al. Role of *Nigella Sativa* Seeds on Modulation Testicular Toxicity of Colchicine Repeated Use in Adult Albino Rats. Life Science Journal 2013; 10:1629-39.
29. Ali BH. The effect of *Nigella sativa* oil on gentamicin nephrotoxicity in rats. Am J Chin Med 2004; 32:49-55.
30. Rehman K, Saleem U, Ahmed B, et al. Nephrocurative and nephroprotective effects of *Nigella sativa* oil in combination with vitamin C in gentamicin- induced renal toxicity. Indian Journal of Pharmaceutical Science & Research 2012; 2:25-32.
31. Al-Suhaimi EA. Hepatoprotective and immunological functions of *Nigella sativa* seed oil against hypervitaminosis A in adult male rats. Int J Vitam Nutr Res 2012; 82:288-97.
32. Abdel-Daim MM, Ghazy EW. Effects of *Nigella sativa* oil and ascorbic acid against oxytetracycline-induced hepatorenal toxicity in rabbits. Iran J Basic Med Sci 2015; 18:221-7.
33. Hassan MQ, Akhtar M, Ahmed S, et al. *Nigella sativa* protects against isoproterenol-induced myocardial infarction by alleviating oxidative stress biochemical alterations and histological damage. Asian Pac J Trop Biomed 2017; 7:294-9.
34. Wahba HMA. Protective effect of *Nigella Sativa*, linseed and celery oils against testicular toxicity induced by sodium valproate in male rats. Journal of American Science 2011; 7:687-93.
35. Hassan AS, Ahmed JH, Al-Haroon SS. A study of the effect of *Nigella sativa* (Black seeds) in isoniazid (INH)-induced hepatotoxicity in rabbits. Indian J Pharmacol 2012; 44:678-82.
36. Nagi MN, Almakki HA. Thymoquinone supplementation induces quinone reductase and glutathione transferase in mice liver: possible role in protection against chemical carcinogenesis and toxicity. Phytother Res 2009; 23:1295-8.
37. El Gendy S, Hessien M, Abdel Salam I, et al. Evaluation of the possible antioxidant effects of Soybean and *Nigella sativa* during experimental hepatocarcinogenesis by nitrosamine precursors. Turkish J Biochem 2007; 32:5-11.
38. Ahmad A, Alkreathy HM. Comparative biochemical and histopathological studies on the efficacy of metformin and *Nigella sativa* oil against thioacetamide-induced acute hepatorenal damage in rats", Biomedical Research 2018; 29:3106-16.
39. Orhon ZN, Uzal C, Kanter M, et al. Protective effects of *Nigella sativa* on gamma radiation-induced jejunal mucosal damage in rats. Pathol Res Pract 2016; 212:437-43.
40. Assayed ME. Radioprotective effects of black seed (*Nigella sativa*) oil against hemopoietic damage and immunosuppression in gamma-irradiated", Immunopharmacol Immunotoxicol 2010; 32:284-96.
41. Elsherbiny NM, Maysarah NM, El-Sherbiny M, et al. Renal protective effects of thymoquinone against sodium nitrite induced chronic toxicity in rats: impact on inflammation and apoptosis. Life Sci 2017; 180:1-8.
42. Mansour M, Ginawi O, El-Hadiyah T, et al. Effects of volatile oil constituents of *Nigella sativa* on induced hepatotoxicity in mice: evidence for antioxidant effects of thymoquinone. Res Commun Mol Path Pharmacol 2001; 110:239-52.
43. Krishnan N, Muthukrishnan S. Effect of *Nigella sativa* seed extract on carbon tetrachloride-induced hepatotoxicity in rats. Journal of Acute Medicine 2012; 2:107-13.
44. Alsaif MA. Effect of thymoquinone on ethanol induced hepatotoxicity in wistar rats. J Med Sci 2007; 7:1164-70.
45. Develi S, Evran B, Kalaz EB, et al. Protective effect of *Nigella sativa* oil against binge ethanol-induced oxidative stress and liver injury in rats. Chin J Nat Med 2014; 12:495-9.
46. Hosseini SM, Taghiabadi E, Abnous K, et al . Protective effect of thymoquinone, the active constituent of *Nigella sativa* fixed oil, against ethanol toxicity in rats. Iran J Basic Med Sci 2017; 20:927-39.
47. El-Dakhakhny M, Barakat M, El-Halim MA, et al. Effects of *Nigella sativa* oil on gastric secretion and ethanol-induced ulcer in rats. J Ethnopharmacol 2000; 72:299-304.
48. Kanter M. Nigella sativa and derived thymoquinone prevents hippocampal neurodegeneration after chronic toluene exposure in rats. Neurochem Res 2008; 33:579-88.
49. Kanter M. Thymoquinone attenuates lung injury induced by chronic toluene exposure in rats. Toxicol Ind Health 2011; 27:387-95.
50. Kanter M. Thymoquinone reestablishes spermatogenesis after testicular injury caused by chronic toluene exposure in rats. Toxicology and Industrial Health 2011; 27:155-66.
51. Mahdy KA, Farrag AR. Amelioration of aluminum toxicity with black seed supplement on rats. Toxilogoc. and Environmental Chemistry J 2009; 91:567-76.
52. Mohammed AK. Ameliorative effect of black seed (*Nigella sativa* L) on the toxicity of aluminum in rabbits. Iraqi J Vet Med 2010; 34:110-16.
53. Mohamed MA, Awad SM. Effect of *Nigella sativa* oil on some haematological values in aluminium- treated rats. Austral J Basic Appl Sci 2008; 2:1157-64.
54. Parveen N, Shadabig GG. Ameliorative action of *Nigella sativa* against iron induced chromosomal aberrations in rat bone marrow cells in vivo. International Journal of Pharma and Bio Sciences 2011; 2:470-7.
55. Farrag AR, Mahdy KA, Abdel Rahman GH, et al. Protective effect of *Nigella sativa* seeds against lead-

induced hepatorenal damage in male rats. Pak J Biol Sci 2007; 10:2809-16.

56. Mohammed ET, Hashem KS, Abdel Rheim MR. Biochemical study on the impact of *Nigella sativa* and virgin olive oils on cadmium-induced nephrotoxicity and neurotoxicity in rats. J Invest Biochem 2014; 3:70-7.
57. Suleman S, Javid I, Ikram S, et al. Amelioration by black seed (*Nigella sativa*) oil of hepato-histopathologies induced in mice by exposure to the tri-fluoridated pyrethroid insecticide bifenthrin. Research report Fluoride 2017; 50:276-86.
58. Ince S, Kucukkurt I, Demirel HH, et al. Thymoquinone attenuates cypermethrin induced oxidative stress in Swiss albino mice", Pestic Biochem Physiol 2012; 104:229-35.
59. Mohamadin AM, Sheikh B, Abd El-Aal AA, et al. Protective effects of *Nigella sativa* oil on propoxur induced toxicity and oxidative stress in rat brain regions. Pesticide Biochemistry and Physiology 2010; 98:128-34.
60. Pourgholamhossein F, Sharififar F, Rasooli R, et al. Thymoquinone effectively alleviates lung fibrosis induced by paraquat herbicide through down-regulation of pro-fibrotic genes and inhibition of oxidative stress. Environ Toxicol Pharmacol 2016; 45:340-5.
61. Mosbah R, Yousef MI, Maranghi F, et al. Protective role of *Nigella sativa* oil against reproductive toxicity, hormonal alterations, and oxidative damage induced by chlorpyrifos in male rats. Toxicology and Industrial Health 2014; pp:1-12.
62. Al-Seenia MN, El Rabeyb HA, Al-Hameda AM, et al. *Nigella sativa* oil protects against tartrazine toxicity in male rats. Toxicology Reports 2018; 5:146-55.

***Correspondence to:**

Said Said Elshama
Department of Forensic Medicine and Clinical Toxicology
College of Medicine
Suez Canal University
Ismailia City, Egypt
E-mail: saidelshama@yahoo.com