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A Review of Medicinal Uses and Pharmacological Activities of *Nigella sativa*

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Abstract: *Nigella sativa* seeds (Kalonji) have been widely used in traditional medicine as diuretic, antihypertensive liver tonic, digestive, antidiarrheal, appetite stimulant, emmenagogue, analgesic, anthelmintic, antibacterial and useful in skin disorders. Consequently, Kalonji has been extensively studied for its biological activities and has been shown to be antidiabetic, anticancer and immunomodulator, analgesic, antimicrobial, anti-inflammatory, spasmolytic, bronchodilator, hepatoprotective, antihypertensive, renal protective and antioxidant properties.

Key words: *Nigella sativa,* Thymoquinone, Hypoglycemic, Antihypertensive, Antioxidant

INTRODUCTION

The seeds of *Nigella sativa* plant have been used to promote health and fight disease for centuries especially in the Middle East and Southeast Asia. In South Asia, it is called Kalonji, its Arabic name is Habat-ul-Sauda and its English name is Black cumin[1]. The plant is widely grown in different parts of the world and is an annual herb cultivated in India and Pakistan. As an oriental spice, *Nigella sativa* has long been used as a natural medicine for the treatment of many acute as well as chronic conditions. This plant has been a great focus of research for centuries and has several traditional uses and consequently has been extensively studied for its chemical constituents and biological activities.

Traditional uses: *Nigella sativa* is widely used natural remedy and the seeds are extensively used as spice, carminative, condiment and aromatic. Traditionally, they have been used as diuretic, diaphoretic, stomachic, liver tonic and digestive. As a confection with other ingredients, they are used in diarrhea, indigestion, dyspepsia and sour belching; they also remove foul breath and watering from the mouth. The seeds of *Nigella sativa* are given with butter-milk to cure obstinate hiccups and are also useful in loss of appetite, vomiting, dropsy and puerperal diseases. They are used as emmenagogue and galactagogue and as abortifacient in large doses. In different combinations, the seeds of *Nigella sativa* have been used in obesity and dyspnoea. They have antibilious property and are administered internally in intermittent fevers[1]. The herb has been regarded as a valuable remedy in hepatic and digestive disorders as well as stimulant in a variety of conditions ascribed to "cold humours". Constant inhalation of fried seeds relieves cold and catarrh. They have also been used in chronic headache and migraine[2]. The decoction of the seeds with some sweet oil forms a useful application in skin diseases. They have been useful in mercury poisoning, sores and leprosy[3]. Brayed in water, its application removes swellings from hands and feet. *Nigella sativa* is also used externally in leucoderma, alopecia, eczema, freckles and pimples[2]. The seeds of *N. sativa* have also been used as anthelmintic and antibacterial[4].

Phytochemistry: In view of its wide range of medicinal uses, the plant has under gone extensive phytochemical studies and a variety of compounds isolated. The seeds of *Nigella sativa* contain a yellowish volatile oil (0.5-1.6%), a fixed oil (35.6-41.6%), proteins (22.7%), aminoacids; e.g. albumin, globulin, lysine, leucine, isoleucine, valine[5], glycine, alanine, phenylalanine, arginine, asparagine, cystine, glutamic acid, aspartic acid, isoleucine, proline, serine, threonine, tryptophan and tyrosine[6], reducing sugars, mucilage, alkaloids, organic acids, tannins, resins, toxic glucoside, metarbin, bitter principles, glycosidal saponins, melanthin resembling helleborin, melanthigenin, ash, moisture and arabic acid. The seeds have also been found to contain fats, crude fiber, minerals e.g. Fe, Na, Cu, Zn, P, Ca and vitamins like ascorbic acid, thiamine, niacin, pyridoxine and folic acid, thus also possessing nutritional value[7]. *Nigella sativa* seeds yield esters of fatty acids; e.g. palmitic acid, oleic acid, linoleic acid and dehydrostearic acid, higher terpenoids, aliphatic alcohols and α-β-unsaturated hydroxy ketones. Free sterols, steryl esters, steryl

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glucosides and acylated steryl glucosides were isolated from the seed oil[8]. A novel alkaloid, nigellicine, an isoquinoline alkaloid, nigellimine and an indazole alkaloid, nigellidine, were also isolated from the seeds of *Nigella sativa*[9-11]. The seeds also contain lipase, phytosterols and β-sitosterol[6].

The active constituents of the seeds include the volatile oil consisting of carvone, an unsaturated ketone, terpene or d-limonene also called carvene, α-pinene and p-cymene[4]. The crystalline active principle, nigellone, is the only constituent of the carbonyl fraction of the oil. Pharmacologically active constituents of volatile oil are thymoquinone, dithymoquinone, thymohydroquinone and thymol[12]. Water stress influences the yield and composition of essential oil. The content of thymoquinone was highest (57.78%) when water was withheld for 12 days[13].

In a recent study, *Nigella sativa* seed oil was extracted with two different solvents; n-Hexane and a mixture of Chloroform/Methanol, the latter was found to contain higher amounts of total lipids. Major fatty acids were linoleic acid, palmitic acid, oleic acid and stearic acid and major phospholipids as phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and phosphatidylinositol. Phosphtidylglycerol, lysophosphatidylethanolamine and lysophosphatidylcholine were isolated in smaller quantities[14].

Pharmacological activities: The popularity of the plant was highly enhanced by the ideological belief in the herb as a cure for multiple diseases. In fact, this plant has occupied special place for its wide range of medicinal value in the Islamic civilizations. Due to the sayings of the Holy prophet, Mohammed (peace be upon him) that the plant is full of medicinal value[15], it gained immense popularity. Consequently, Kalonji has been extensively studied particularly in the Islamic world, which justifies its broad traditional therapeutic value.

Hypoglycemic effects: In view of the folkloric use of plant mixture extracts for treatment of diabetes in the Middle East, Al-Awadi and Gumaa[16] studied a plant mixture (*Nigella sativa*, Myrrh, Gum olybanum and Gum asafoetida) for its blood glucose lowering effect in rats and found it effective. Further studies on the plant mixture containing *N. sativa,* revealed that the blood glucose lowering effect was due to the inhibition of hepatic gluconeogenesis and the plant extract mixture may prove to be a useful therapeutic agent in the treatment of non-insulin dependent diabetes mellitus[17]. An aqueous decoction of a plant mixture containing *Nigella sativa* was found to lower the blood glucose level significantly after oral administration[18]. The intraperitoneal administration of volatile oil of *N. sativa* seeds produced a significant hypoglycemic effect in normal and alloxan-induced diabetic rabbits[19]. The hypoglycemic effect of *N. sativa* in combination with other herbs has also been demonstrated in a study on alloxan-induced diabetic rats[20]. In a more recent study, the seed extract when given orally decreased the elevated glucose levels in alloxan-induced diabetic rabbits after 2 months of treatment[21].

Another study was designed to investigate the possible insulinotropic properties of *Nigella sativa* oil in Streptozotocin plus Nicotinamide-induced diabetes mellitus in hamsters. After four weeks of treatment with *N. sativa* oil, significant decrease in blood glucose level together with significant increase in serum albumin level were observed. The results showed that the hypoglycemic effect of *N.igella sativa* oil was, at least partly, because of a stimulatory effect on beta cell function with consequent increase in serum insulin level and possess insulinotropic properties in type II like model[22].

In another study, the hypoglycemic effect of *Nigella sativa* was supposed to be mediated by extrapancreatic actions rather than by stimulated insulin release[23]. The effect of seed oil on blood glucose concentrations was studied in Streptozotocin-induced diabetic rats. The effect of seed oil and other constituents such as nigellone and thymoquinone were studied on insulin secretions of isolated rat pancreatic islets in the presence of 3, 5.6 or 11.1 mM glucose. Oil significantly lowered the blood glucose concentrations in diabetic rats after 2, 4 and 6 weeks, which was, however, not paralleled by a stimulation of insulin release in the presence of oil, nigellone or thymoquinone; thus indicating the extrapancreatic actions to be responsible for hypoglycemic effects of *Nigella sativa* oil.

A recent clinical study on human volunteers showed that 1 g of *N. sativa* seeds twice daily caused a decrease in blood glucose level after 2 weeks of oral treatment[24].

Effects on immune system and cancer: *Nigella sativa* seeds and its oil have been traditionally used as a tonic to promote health and prevent diseases. They were reported to exhibit immunopotentiating[25], immunomodulating and interferon-like activities. The ethanolic extract was found to inhibit cancer cells and endothelial cells progression *in vitro*[26,27].

The protective effect of Nigella grains as nutraceuticals was studied on the oxidative stress and carcinogenesis induced by methylnitrosourea in Sprague Dawley rats and it was found to produce about 80%

protection against methylnitrosourea-induced oxidative stress, inflammatory response and carcinogenesis[28].

The alcoholic extract also showed the cytotoxic activity and was found to cure oral cancers[29]. In a study, a crude gum, a fixed oil and two purified components of Nigella seed, thymoquinone and dithymoquinone were assayed *in-vitro* for their cytotoxicity for several parental and multi drug resistant human tumor cell lines. Although as much as 1% w/v of the gum or oil was devoid of cytotoxicity, both thymoquinone and dithymoquinone were found to be cytotoxic for several types of human tumor cells[30]. The proteins of *Nigella sativa* fractionated by ion-exchange chromatography were also found to possess immunomodulatory effect. The effect of these proteins on the production of cytokines was further evaluated by using specific enzyme-linked immunosorbant assay (ELISA). The results, however, showed that the fractionated *Nigella sativa* was less effective when compared with whole Nigella proteins[31].

Topical application of the seed extract inhibited skin carcinogenesis in mice and intraperitoneal administration (100 mg Kg^{-1} body weight) delayed the onset of papilloma formation[32].

The active principle of *Nigella sativa* seeds containing certain fatty acids was studied for anti-tumor activities against Ehrlich ascites carcinoma, Dalton's lymphoma ascites and Sarcoma-180 cells *in vitro* and *in vivo*. The active principle showed complete inhibition in *in vivo* and 50% cytotoxicity in *in vitro* studies[33].

In mice bearing Ehrlich ascites carcinoma xenograft, thymoquinone (from volatile oil) significantly enhanced the anti-tumor effect of ifosfamide (analogue of cyclophosphamide). There was also less weight loss and lower mortality rate compared to ifosfamide single therapy, thus thymoquinone was found to improve the therapeutic efficacy of ifosfamide by both decreasing ifosfamide-induced nephrotoxicity and improving its anti-tumor activity[34]. In another study, thymoquinone inhibited the benzopyrene-induced forestomach carcinogenesis in mice. The possible modes of action were discussed to be through its antioxidant and anti-inflammatory activities coupled with enhancement of detoxification process[35].

Thymoquinone-induced cytotoxicity was investigated in a study using canine osteosarcoma, its cisplatin-resistant variant, human breast adenocarcinoma, human ovarian adenocarcinoma and Madin-Darby canine (MDCK) cell lines. Thymoquinone-induced cytotoxicity was determined using a proliferation assay (MTT assay) and apoptosis assays. Effects on the cell cycle were determined using flow cytometry and thymoquinone was found to produce cell cycle arrest[36].

In another study, the aqueous and alcoholic extracts of *Nigella sativa* alone or in combination with H_2O_2 as an oxidative stressor, were found to be effective *in-vitro* in inactivating MCF-7 breast cancer cells[37].

The fresh aqueous extract augmented Natural Killer Cells (62.3%) in developing cytotoxicity against YAC *in vitro*. Fresh aqueous extracts appeared to be more potent than old dried extracts or ethanolic extracts[38]. Aqueous extract of *Nigella sativa* seeds was also found to significantly augment the splenic natural killer cells in generating cytotoxicity in mice against YAC tumor targets[39].

In a study using murine Cytomegalovirus as a model, intraperitoneal administration of oil substantially decreased the viral load in liver and spleen. There was an increase in interferon-γ, macrophages and CD4+ T cells and decrease in both number and function of NK cells. On day 10, the virus titer was undetectable in the spleen and liver of infected mice, while positive in controls[40].

A fraction of the ethanolic extract of *Nigella sativa* seeds was studied in mice against intraperitoneally implanted murine P388 leukemia and subcutaneously implanted Lewis lung carcinoma cells. The life span of treated mice increased by 153% as compared to dimethyl sulphoxide-treated control mice. α- Hederin, a triterpene saponin isolated from this fraction produced significant tumor inhibition rates; while, the underlying mechanism(s) of antitumor activity of α-Hederin remained to be established[41].

In a recent study, the stimulating effect of α-hederin on the release of nitric oxide and upregulation of inducible nitric oxide synthase gene expression in mouse macrophages were examined. Thus showing a mechanism responsible for its biological effects including its antitumor activities[42].

In another study, the anti-tumor effect of thymoquinone was investigated both *in-vivo* and *in-vitro* in male Swiss albino rats on fibrosarcoma induced by 20-methylcholanthrene and it was found to inhibit tumor incidence and tumor burden significantly. The possible modes of action were discussed as its antioxidant activity and interference with DNA synthesis coupled with enhancement of detoxification processes[43].

Effects on the nervous nervous system: *Nigella sativa* seeds revealed promising narcotic analgesic activity mediated possibly through opioid receptors[44]. The oil from the seeds exhibited CNS depressant and potent analgesic effects. It was also found to potentiate pentobarbitone-induced sleeping time[45].

Aqueous extract in mice revealed an analgesic effect, which peaked after 2 hours and sustained for 4 h[46]. The

oral administration of oil dose- dependently suppressed dose-dependently the nociceptive response in the hot-plate test, tail-pinch test, acetic acid-induced writhing test and in the early phase of formalin test.

Systemic administration of the main constituent of *N. sativa* seeds, thymoquinone, attenuated the nociceptive response in both early and late phases of formalin test. Results from using different opioid receptor antagonists suggested that both the seed oil and thymoquinone produced antinociceptive effects through activation of supraspinal μ_1 and κ- opioid receptor subtypes[47].

In another investigation, the aqueous and methanolic extracts of *N.igella sativa* seeds produced an alteration in the general behaviour patterns, significant reduction of spontaneous motility, reduction in normal body temperature and significant analgesic action against hot plate and pressure tests, suggesting the CNS depressant action[48].

In a more recent study, thymoquinone was found to inhibit the oxidative stress leading to improvement in animals having Experimental Allergic Encephalomyelitis, an autoimmune demyelinating disease of the central nervous system. Thus, suggesting the role of thymoquinone in the treatment of Multiple Sclerosis[49].

Effects against microbials: The plant extract and its constituents have been extensively studied for its their antimicrobial effect against a wide range of bacterial, fungal and parasitic organisms. The methanolic extract of *N. sativa* seeds was found to exhibit anti-plaque action by potently inhibiting *Streptococcus mutans*, thus also preventing dental caries[50]. Alcoholic extracts of the seeds showed antibacterial activity against *Micrococcus pyogenes var. aureus*[4]. It was also found to possess antibacterial activity against *Shigella dysenteriae, S. sonnei, S. boydii*, *Vibrio cholerae* and *Escherichia coli*[51]. The ether extracts showed *in vitro* antimicrobial activity against Gram-positive bacteria; e.g. *Staphylococcus aureus*, Gram-negative bacteria; e.g. *Pseudomonas aeruginosa* and *Escherichia coli*[52]. In another study, it was found to exhibit antibacterial activity especially against Bacillus pumilus, B. subtilis, Streptococcus mutans, Staphylococcus lutea, Staph. aureus and *Pseudomonas aeruginosa*[53].

The essential oil from the seeds of *N. sativa* in pure state and at various dilutions was screened *in vitro* against some microbes and helminths and it was found to exhibit promising activity against *Shigella flexneri*[54]. It also showed anthelmintic activity against hook worms and nodular worms[55]. The ethanolic extract was found to possess anticestodal effect in children[56]. The essential oil showed *in vitro* antifungal activity against *Aspergillus species* and *Curvularia lunata*[57] as well as against pathogenic yeast *Candida albicans*[58]. In our recent study, we found that the aqueous extract of the seeds possess potent *in-vivo* antifungal activity against Candidiasis in mice[59].

The protective effect of *N. sativa* seed extract and its main constituent, thymoquinone, was studied on mouse cells infected with schistosomiasis. Bone marrow cells and spleen cells were used *in vivo* and *in vitro* respectively to evaluate the protective effects of these compounds against chromosomal aberrations induced as a result of schistosomiasis[60].

Effects against inflammation: Traditionally, the fixed oil expressed from seeds of *Nigella sativa* is of great use in skin eruptions, paralysis, hemiplegia, back pain, rheumatism and related inflammatory diseases on external application. The crude fixed oil of *Nigella sativa* and thymoquinone both have been found to inhibit the eicosanoid generation and membrane lipid peroxidation, through the inhibition of cyclooxygenase and 5-lipoxygenase pathways of arachidonate metabolism, thus responsible for the anti-inflammatory activity[61].

The aqueous extract was investigated for anti-inflammatory, analgesic and antipyretic activities in animal models. The anti-inflammatory effect was demonstrated by its inhibitory effect on carrageenan induced-paw edema[46] and analgesic effect by significant increase in hot plate reaction time in mice. However, it showed no effect on yeast-induced pyrexia[62].

The essential oil of *Nigella sativa* seeds and its active principle thymoquinone, were found to possess dose-dependent anti-inflammatory activities and inhibited edema and granuloma formation[63].

In a recent study, *Nigella sativa* oil, nigellone (Polythymoquinone) and derived thymoquinone were studied to evaluate their effect on the formation of 5-lipoxygenase (5-LO) products from polymorphonuclear leukocytes (PMNL). They were found to produce concentration dependent inhibition of 5-LO products and 5-hydroxy eicosa-tetraenoic acid (5-HETE) production, probably due to an antioxidant action, thus showing in part their role in ameliorating inflammatory diseases[64].

A more recent study in our laboratory on the aqueous extract of *Nigella sativa* showed that its aqueous extract inhibits the production of nitric oxide, a pro-inflammatory mediator and thus anti-inflammatory action might be mediated partly through this mechanism[65] and thymoquinone, its main constituent has also been shown to exhibit similar effect in rat macrophages[66].

Effects on the gastrointestinal system: The seeds of *Nigella sativa* have been traditionally used in a wide

range of gastrointestinal disorders[1]. The aqueous extract of the seeds was reported to exhibit anti-ulcer activity by decreasing the volume of acid in gastric juice in acetylsalicylic acid (ASA)-treated rats[67] . In a study, the effect of alcoholic extract of *N. sativa* was investigated in rats to evaluate the antiulcer activity by using two models, i.e. pyloric ligation and aspirin-induced gastric ulcer. The volume of gastric acid secretion, free acidity, total acidity and ulcer index were significantly reduced[68].

Administration of *N. sativa* oil in rats produced a significant increase in mucin content and glutathione level and a significant decrease in mucosal histamine content in the stomach, leading to significant protection against ethanol-induced ulcer in rats[23]. In a more recent study, *N. sativa* oil and thymoquinone were found to possess gastroprotective effect against gastric lesions, which may be related to the conservation of the gastric mucosal redox state[69].

In a study, the aqueous seed extract of *N. sativa* caused mild to moderate dose-dependent relaxation effects, increased the sensitivity of the ileum to acetylcholine and interacted with serotonin in a dose-dependent manner[70].

The volatile oil and ethanolic extract of *N. sativa* inhibited spontaneous movements of the rabbit jejunum as well as agonist-induced contractions and the spasmolytic effect involved calcium channel blockade[71]. The aqueous-methanolic extract of Nigella seeds also showed spasmolytic effect mediated through calcium antagonist effect thus providing scientific basis for its traditional use in diarrhoea[72].

In another study, the hepatoprotective effect of Nigella oil was shown in some models of liver toxicity. In *Schistosoma mansoni* infected mice, the oil succeeded partially to correct the previous changes in L-alanine aminotransferase (ALT), Gamma glutamyl transferase (GGT) and Alkaline phosphatase (AP) activity as well as the Albumin content in serum. *Nigella sativa* oil was suggested to play a role against the alterations caused by *Schistosoma mansoni* infection, an effect which may be induced partly by improving the immunological host system and to some extent with its antioxidant effect[73].

Thymoquinone was found to be hepatoprotective against ter-butyl-hydroperoxide- induced hepatotoxicity[74] and protecting liver also against carbon tetrachloride-induced hepatotoxicity in mice via its antioxidant mechanism[75]. Thymoquinone, given to mice 5 days before and during the carbon tetrachloride treatment, ameliorated hepatotoxicity. This was evidenced by: (1) a significant reduction in elevated levels of serum enzymes (alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase), (2) a significant decrease in the hepatic malondialdehyde content (represents hepatic lipid peroxidation) and (3) a significant increase in the total sulfhydryl content (decrease in sulfhydryl group signifies hepatotoxicity) 24 h after carbon tetrachloride administration[76]. More recently, it has been shown in our laboratory that thymol, one of the constituents of Nigella seeds, also exhibits hepatoprotective effect in rodents[77].

Another study showed the possible effects of thymoquinone on acetic acid-induced colitis in rats. The smaller dose of thymoquinone (5 mg Kg^{-1}) produced partial protection; whereas, higher dose (10 mg Kg^{-1}) was found to give complete protection even significantly higher than sulfasalazine. The possible mechanism of the protective effects might be partly due to an antioxidant action[78].

Effects on genito-urinary system: The seeds of *Nigella sativa* were found to significantly reduce the cisplatin (a cytotoxic drug)-induced nephrotoxicity, blood urea nitrogen (BUN) and serum creatinine levels as well as cisplatin-induced serum total lipids increases[79].

In another study, *N.igella sativa* extract, when given orally, was found to be a potent chemopreventive agent causing the suppression of Potassium bromate (a potent nephrotoxic agent), $KBrO_3$-mediated renal oxidative stress, toxicity and tumor promotion response in rats[80].

The ethanolic extract of *Nigella sativa* seeds showed antifertility effect in male rats that is probably due to its inherent estrogenic nature[81]. In another study, the hexane extract of the seeds showed significant contraceptive activity in rats[82]. The volatile oil of *Nigella sativa* also inhibited the spontaneous movements of rat and guinea-pig uterine smooth muscle and also the contractions induced by oxytocin, showing its antioxytocic potential[83]. In a more recent study, *N. sativa* in combination with *Abroma augusta* (Ulatkambal) in 1:2 ratio, was found to induce oestrus in buffaloes and two out of six buffaloes conceived[84].

Thymoquinone, the main constituent of volatile oil of Nigella seeds, was found to possess high antioxidant potential and was found to be applicable as a protective agent for doxorubicin-induced nephropathy, proteinuria, albuminuria and hyperlipidemia associated with nephrotic syndrome[85]. In a recent study, the protective effects of *N. sativa* oil on methotrexate-induced toxicity were studied in albino rats[86].

Effects on the respiratory system: Powdered seeds in suitable vehicles have been traditionally used to alleviate respiratory disorders; e.g. asthma, bronchospasm and chest congestion[2]. Nigellone, an active ingredient of *Nigella sativa*, was shown to be an effective prophylactic

agent in asthma and bronchitis with higher efficacy in children than in adults.

Nigellone, an active ingredient of *Nigella sativa*, was found to inhibit effectively the histamine release from the mast cells[87], thus showing the basis for its traditional use in asthma. In a recent study, the antianaphylactic effect of a polyherbal formulation containing *N. sativa* on the rat mesenteric mast cells was studied. The antianaphylactic activity was supposed to be possibly due to the membrane stabilizing potential, suppression of antibody production and inhibition of antigen induced histamine release[88]. We recently showed that the bronchodilatory effect of the crude extract of *N. sativa* seeds[72] was shown to be mediated possibly through calcium channel blockade.

In another study, the effects of the volatile oil and thymoquinone were investigated and compared on the respiratory system of the urethane-anesthetized guinea-pigs. Intravenous administration of volatile oil induced dose-dependent increases in the respiratory rate and the intratracheal pressure, whereas, thymoquinone induced significant increases in the intratracheal pressure without any effect in the respiratory rate. The results suggested that volatile oil-induced respiratory effects were mediated via release of histamine with direct involvement of histaminergic mechanisms and the indirect activation of muscarinic cholinergic mechanisms[90]. These conflicting reports warrant further studies before a definite conclusion is drawn.

Effects on the cardiovascular system: The essential oil from the seeds of *Nigella sativa* exhibited a depressant action on the frog heart and a relaxant effect on isolated smooth muscles of rat. The unsaponifiable matter of the fixed oil showed a marked depressant effect on heart and produced bradycardia[57]. The volatile oil from the seeds and its constituent thymoquinone, induced the cardiovascular depressant effects, which were mediated mainly centrally via indirect and direct mechanisms and involved both 5-hydroxytryptaminergic and muscarinic mechanisms[91].

In another study, the crude extract of *N. sativa* was found to significantly lower blood pressure in spontaneously hypertensive rats similar to that of nifedipine[92]. Recently, it was observed that the active ingredients of Nigella seeds, such as thymol[89] lower blood pressure through blockade of calcium channels. These studies showed that the plant contains multiple chemicals with antihypertensive effect acting at multiple sites.

Nigella sativa seed treatment was also found to lower the levels of serum cholesterol[93]. In another study supporting the traditional use of *N. sativa* as a treatment of dyslipidemia and hyperglycemia, the effects of the fixed oil of Nigella seeds in rats were investigated by monitoring blood homeostasis and body weight as well as toxicity. The serum cholesterol, triglycerides and glucose levels and the count of leukocytes and platelets decreased while hematocrit and hemoglobin levels increased significantly[94].

Recently, the effect of *N. sativa* crushed seeds and total oil were studied on serum levels of glucose, cholesterol, triglycerides, creatine kinase, prolactin, red blood cells, white blood cells, platelets, haemoglobin and some liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma glutamyltransferase (γ-GT) in healthy female volunteers. Both crushed seeds and total oil decreased glucose, prolactins, triglycerides and cholesterol level. Crushed seeds produced a significant increase in RBCs, WBCs and hemoglobin levels, while total oils increased hemoglobin levels. Only the total oil produced a significant increase in ALT and AST. Both total oil and crushed seeds showed a significant increase in γ-GT and ALP[95].

The extract of *Nigella sativa* seeds was found to produce protection against cisplatin-induced falls in hemoglobin levels and leukocyte counts[96]. In a recent study, Bamosa *et al.*[97] studied the effect of thymoquinone on the blood levels of cholesterol, triglycerides, HDL and LDL in albino rats. After 4 days of intraperitoneal treatment, the hypocholesterolemic as well as a reducing effect on triglycerides, HDL and LDL was commenced[97].

In another study, the methanol soluble portion of black cumin oil, showed inhibitory effects on arachidonic acid- induced platelet aggregation and blood coagulation. Methanol soluble part was purified to isolate a new compound 2-(2-methoxypropyl)-5-methyl-1,1,4-benenediol and two known compounds, thymol and carvacrol, having very strong inhibitory activity[98].

Antioxidant activity: The seed oil and its main active constituent, thymoquinone, are reported to inhibit peroxidation in ox brain phospholipid liposomes[61]. Similarly, thymoquinone was shown to exhibit protective effect against ter-butyl-hydro-peroxide induced hepatotoxicity[74] and also hepatoprotective effect against carbon tetrachloride induced toxicity in mice[75], rats[23] and rabbits. Furthermore, thymoquinone was found to exhibit renal protective effect in rats through its antioxidant action[34,85].

The essential oil of *Nigella sativa* seeds was tested for a possible antioxidant activity. The essential oil,

thymoquinone and other components; carvacrol, anethole and 4-terpineol demonstrated respectable radical scavenging property[99]. The free radical scavenging effects of thymol, thymoquinone and dithymoquinone were studied on the reactions generating reactive oxygen species such as superoxide anion radical (O_2^-), hydroxyl radical (HO) and singlet oxygen ($1O_2$) using the chemiluminescence and spectrophotometric methods[100].

The hepatoprotective effects of Nigella oil[73] and thymoquinone[75,76,101] were found via the antioxidant mechanism. Similarly, the protective effect of thymoquinone against doxorubicin-induced nephropathy[85] and that against doxorubicin-induced cardiotoxicity[102,103] was also found to be due to its antioxidant activity.

In some other studies, the modulating effect of thymoquinone on benzopyrene-induced forestomach tumors in mice[35] and its antitumor effect on 20-methylcholanthrene-induced fibrosarcoma tumorigenesis[43] were found to be partly through its antioxidant effect. The possible mechanism of the protective effect of thymoquinone against acetic acid-induced colitis in rats was also supposed to be partly its antioxidant action[78].

Toxicity studies: No acute toxic effects were observed after oral administration of a high dose as 25 g Kg^{-1}; however, toxic symptoms were observed after i.p. administration of 25 g Kg^{-1}[104]. In another study, the toxicity of the fixed oil of *Nigella sativa* seeds in mice and rats was investigated through the determination of LD_{50} values and examination of possible biochemical, hematological and histopathological changes. The low toxicity of *N. sativa* fixed oil, evidenced by high LD_{50} values, key hepatic enzyme stability and organ integrity suggested a wide margin of safety for therapeutic doses of fixed oil of the Nigella seeds[94].

Nigella sativa has significant effects on multiple biological systems. Both ethanolic and aqueous extracts as well as the volatile oil have been proven to possess beneficial effects. This points out the fact that *N. sativa* contains both active proteins and lipid soluble elements, thus proving the multiple mechanisms of action behind this phytotherapeutic agent. Most of the pharmacological activities are attributed to the presence of thymoquinone as an active component. Lately *N. sativa* has become an important topic for research world wide, but more studies need to be conducted to find new possible activities of this versatile phytotherapeutic agent as well as clinical trials to prove the therapeutic efficiency of the plant.

REFERENCES

1. Nadkarni, A.K., 1976. Indian Materia Medica. Popular Prakashan Pvt. Ltd., Bombay, India.
2. Usmanghani, K., A. Saeed and M.T. Alam, 1997. Indusyunic Medicine: Traditional Medicine of Herbal, Animal and Mineral Origin in Pakistan. B.C.C. and T. Press, University of Karachi, Pakistan.
3. Evans, W.C., 1996. Pharmacognosy. 14th Edition, WB Saunders Company Ltd., London, UK.
4. Kapoor, L.D., 1990. Handbook of Ayurvedic Medicinal Plants. CRC Press, Inc., Boca Raton, Florida, USA.
5. Al-Gaby, A.M., 1998. Amino acid composition and biological effects of supplementing broad bean and corn proteins with *Nigella sativa* (Black cumin) cake protein. Nahrung, 42: 290-294.
6. Duke, J.A., 1992. Handbook of Phytochemical Constituents of GRAS Herbs and other Economic Plants. CRC Press, Inc., Florida, USA.
7. Takruri, H.R.H. and M.A.F. Dameh, 1998. Study of the nutritional value of black cumin seeds (*Nigella sativa*). J. Sci. Food and Agric., 76: 404-410.
8. Menounos, P., K. Staphylakis and D. Gegiou, 1986. The sterols of *Nigella sativa* seed oil. Phytochemistry, 25: 761-763.
9. Atta-ur-Rahman, S. Malik and K. Zaman, 1992. Nigellimine: A new isoquinoline alkaloid from the seeds of *Nigella sativa*. J. Natural Products, 55: 676-678.
10. Atta-ur-Rahman, S. Malik, S.S. Hasan, M.I. Chaudhary, C.Z. Ni and J. Clardy, 1995. Nigellidine-A new indazole alkaloid from the seeds of *Nigella sativa*. Tetrahedron Lett., 36: 1993-1996.
11. Atta-ur-Rahman, S. Malik, C.H. He and J. Clardy, 1985. Isolation and structure determination of nigellicine, a novel alkaloid from the seeds of *Nigella sativa*. Tetrahedron Lett., 26: 2759-2762.
12. Ghosheh, O.A., A.A. Houdi and P.A. Crooks, 1999. High Performance liquid chromatography analysis of the pharmacologically active quinines and related compounds in the oil of the black seed (*Nigella sativa*). J. Pharm. Biomed. Ana., 19: 757-762.
13. Mozaffari, F. S., M. Ghorbanli, A. Babai and M.F. Sepehr, 2000. The effect of water stress on the seed oil of *Nigella sativa* L. J. Essential Oil Res., 12: 36-38.
14. Ramadan, M.F. and J.T. Morsel, 2002. Characterization of Phospholipid Composition of Black cumin (*Nigella sativa*) seed oil. Nahrung, 46: 240-244.

15. Ghaznavi, K., 1996. Tibbe Nabvi aur Jadeed Science. Al-Faisal Publishers, Lahore, Pakistan, pp: 246-254.
16. Al-Awadi, F.M. and K.A. Gumaa, 1987. Studies on the activity of individual plants of an antidiabetic plant mixture. Acta. Diabetol. Let., 24: 37-41.
17. Al-Awadi, F., H. Fatima and U. Shamte, 1991. The effect of a plant mixture extract on liver gluconeogenesis in Streptozotocin-induced diabetic rats. Diabetes. Res., 18: 163-168.
18. Akhtar, M.S. and M.U. Shah, 1993. Elemental constituents of antidiabetic screening of a folkloric medicinal plant prescription. International Journal of Toxicology, Occupational and Environmental Health, 2: 46.
19. Al-Hader, A., M. Aqel and Z. Hasan, 1993. Hypoglycemic effects of the volatile oil of *Nigella sativa*. International J. Pharmacognosy, 31: 96-100.
21. Meral, I., Z. Yener, T. Kahraman and N. Mert, 2001. Effect of *Nigella sativa* on glucose concentration, lipid peroxidation, anti-oxidant defense system and liver damage in experimentally-induced diabetic rabbits. J. Vet. Med. A. Physiol. Pathol. Clin. Med., 48: 593-599.
22. Fararh, K.M., Y. Atoji, Y. Shimizu and T. Takewaki, 2002. Insulinotropic properties of *Nigella sativa* oil in Streptozotocin plus Nicotinamide diabetic hamsters. Res. Vet. Sci., 73: 279-282.
23. El-Dakhakhny, M., M. Barakat, M. El-Halim and S.M. Aly, 2000. Effects of *Nigella sativa* oil on gastric secretion and ethanol-induced ulcer in rats. J. Ethnopharmacol., 72: 299-304.
24. Bamosa, A.O., B.A. Ali and S.A. Sowayan, 1997. Effect of oral ingestion of *Nigella sativa* seeds on some blood parameters. Saudi Pharmaceutical J., 5: 126-129.
25. Hailat, N., Z. Bataineh, S. Lafi, E. Raweily, M. Aqel, M. Al-Katib and S. Hanash, 1995. Effect of *Nigella sativa* volatile oil on Jurkal T cell leukemia polypeptides. International J. Pharmacognosy, 33: 16-20.
26. Medenica, R., J. Janssens, A. Tarasenko, G. Lazovic, W. Corbitt, D. Powell and D. Jocic, 1997. Anti-angiogenic activity of *Nigella sativa* plant extract in cancer therapy. Proc. Annu. Meet. Am. Assoc. Cancer. Res., 38: A1377.
27. Swamy, S.M.K. and B.K.H. Tan, 2000. Cytotoxic and immunopotentiating effects of ethanolic extract of *Nigella sativa* seeds. J. Ethnopharmacol., 70: 1-7.
28. Mabrouk, G.M., S.S. Moselhy, S.F. Zohny, E.M. Ali, T.E. Helal, A.A. Amin and A.A. Khalifa, 2002. Inhibition of Methylnitrosourea (MNU)-induced oxidative stress and carcinogenesis by orally administered bee honey and Nigella grains in Sprague Dawley rats. J. Exp. Clin. Cancer. Res., 21: 341-346.
29. Salomi, M., J.K.R. Panikar, M. Kesvan, S. Donata and K. Rajagopalan, 1989. Anticancer activity of *Nigella sativa*. Ancient Science of Life, 8: 262-266.
30. Worthen, D.R., O.A. Ghosheh and P.A. Crooks, 1998. The *in vitro* anti-tumor activity of some crude and purified components of blackseed, *Nigella sativa*. Anticancer Res., 18: 1527-1532.
31. Haq, A., P.I. Lobo, M. Al-Tufail, N.R. Rama and S.T. Al-Sedairy, 1999. Immunomodulatory effect of *Nigella sativa* proteins fractionated by ion-exchange chromatography. International J. Immunopharmacol., 21: 283-295.
32. Salomi, M.J., S.C. Nair and K.R. Panikkar, 1991. Inhibitory effects of *Nigella sativa* and saffron (*Crocus sativus*) on chemical carcinogenesis in mice. Nutr. Cancer, 16: 67-72.
33. Salomi, N.J., S.C. Nair, K.K. Jayawardhanan, C.D. Varghese and K.R. Panikkar, 1992. Antitumour principles from *Nigella sativa* seeds. Cancer Lett., 63: 41-46.
34. Badary, O.A., 1999. Thymoquinonoe attenuates ifosfamide-induced Fanconi syndrome in rats and enhances its anti-tumor activity in mice. J. Ethnopharmacol., 67: 135-142.
35. Badary, O.A., O.A. Al-Shabanah, M.N. Nagi, A.C. Al-Rikabi and M.M. Elmazar, 1999. Inhibition of benzopyrene-induced forestomach carcinogenesis in mice by thymoquinone. European J. Cancer Prevention, 8: 435-440.
36. Shoieb, A.M., M. Elgayyar, P.S. Dudrick, K.L. Bell and P.K. Tithof, 2003. *In vitro* inhibition of growth and induction of apoptosis in cancer cell lines by thymoquinone. Int. J. Oncol., 22: 107-113.
37. Farah, I.O. and R.A. Begum, 2003. Effect of *Nigella sativa* and oxidative stress on the survival pattern of MCF-7 breast cancer cells. Biomed. Sci. Instrum., 39: 359-364.
38. Abuharfeil, N.M., A. Maraqa and S.V. Kleist, 2000. Augmentation of natural killer cell activity *in vitro* against tumor cells by wild plants from Jordan. J. Ethnopharmacol., 71: 55-63.
39. Abuharfeil, N.M., Maher Salim and S.V. Kleist, 2001. Augmentation of natural killer cell activity *in vivo* against tumor cells by some wild plants from Jordan. Phytotherpay Research, 15: 109-113.

40. Salem, M.L. and M.S. Hossain, 2000. Protective effect of black seed oil from *Nigella sativa* against murine cytomegalovirus infection. International J. Immunopharmacol., 22: 729-740.
41. Kumara, S.S. and T.K. Huat, 2001. Extraction, Isolation and characterisation of anti-tumor principle, α- hederin, from seeds of *Nigella sativa*. Planta Medica, 67: 29-32.
42. Jeong, H.G. and C.Y. Choi, 2002. Expression of inducible nitric oxide synthase by α-hederin in macrophages. Planta Medica, 68: 392-396.
43. Badary, O.A. and A.M. Gamal-el-Din, 2001. Inhibitory effects of thymoquinone against 20-methylcholanthrene-induced fibrosarcoma tumorigenesis. Cancer Detect. Prev., 25: 362-368.
44. Vohora, S.B. and P.C. Dandiya, 1992. Herbal analgesic drugs. Fitoterapia, 63: 195-207.
45. Khanna, T., F.A. Zaidi and P.C. Dandiya, 1993. CNS and analgesic studies on *Nigella sativa*. Fitoterapia, 64: 407-410.
46. Khan, M.T.H., Shaila Jabbar, M.S.K. Choudhuri and M.A. Ghafur, 1999. Analgesic and anti-inflammatory activity of *Nigella sativa* Linn. Hamdard Medicus, 42: 22-29.
47. Abdel-Fattah, A.F.M., K. Matsumoto and H. Watanabe, 2000. Antinociceptive effects of *Nigella sativa* oil and its major component, thymoquinone, in mice. European J. Pharmacol., 400: 89-97.
48. Al-Naggar, T.B., M.P. Gomez-Serranillos, M.E. Carretero and A.M. Villar, 2003. Neuropharmacological activity of *Nigella sativa* extracts. J. Ethnopharmacol., 88: 63-68.
49. Mohamed, A., A. Shoker, F. Bendjelloul, A. Mare, M. Alzrigh, H. Benghuzzi and T. Desin, 2003. Improvement of Experimental Allergic Encephalomyelitis (EAE) by thymoquinone, an oxidative stress inhibitor. Biomed. Sci. Instrum., 39: 440-445.
50. Namba, T., M. Tsunezuka, K. Saito, N. Kakiuchi, M. Hattori, D.M.R.B. Dissanayake and U. Pilapitiya, 1985. Studies on dental caries prevention by traditional medicines, screening of Ayuruedic medicines for anti-plaque action. Shoyakugaku Zasshi, 39: 146-153.
51. Ferdous, A.J., S.N. Islam, M. Ahsan, C.M. Hasan and Z.U. Ahmad, 1992. *In vitro* antibacterial activity of the volatile oil of *Nigella sativa* seeds against multiple drug-resistant isolates of Shigella species and isolates of *Vibrio cholerae* and *Escherichia coli*. Phytotherpy Res., 6: 137-140.
52. Sokmen, A., B.M. Jones and M. Erturk, 1999. The *in vitro* antibacterial activity of Turkish medicinal plants. J. Ethnopharmacol., 67: 79-86.
53. El-Kamali, H.H., A.H. Ahmad, A.S. Mohammad, A.A.M. Yahia, I. El-Tayeb and A.A. Ali, 1998. Antibacterial properties of essential oils from *Nigella sativa* seeds etc. Fitoterapia, 69: 77-78.
54. Chowdhury, A.K.A., A. Islam, A. Rashid and A. Ferdous, 1998. Therapeutic potential of the volatile oil of *Nigella sativa* seeds in monkey model with experimental shigellosis. Phytotherapy Res., 12: 361-363.
55. Agarwal, R., M.D. Kharya and R. Shrivastava, 1979. Antimicrobial and anthelmintic activities of the essential oil of *Nigella sativa*. Indian J. Experimental Biol., 17: 1264-1265.
56. Akhtar, M.S. and S. Riffat, 1991. Field trial of *Saussurea lappa* roots against nematocides and *Nigella sativa* seeds against cestodes in children. J. Pak. Med. Association, 41: 185-187.
57. Agarwal, R., M.D. Kharya and R. Shrivastava, 1979a. Pharmacological studies of essential oil and unsaponifiable matter of seeds of *Nigella sativa*. Indian J. Pharmacological Sci., 41: 248, Abst. C 17.
58. Hanafy, M.S. and M.E. Hatem, 1991. Studies on the antimicrobial activity of *Nigella sativa* seed (Black cumin). J. Ethnopharmacol., 34: 275-278.
59. Khan, M.A., M.K. Ashfaq, H.S. Zuberi, M.S. Mahmood and A.H. Gilani, 2003. The *in vivo* antifungal activity of the aqueous extract from *Nigella sativa* seeds. Phytotherapy Res., 17: 183-186.
60. Aboul-Ela and I. Ezzat, 2002. Cytogenetic studies on *Nigella sativa* seeds extract and thymoquinone on mouse cells infected with schistosomiasis using karyotyping. Mutat. Res., 516: 11-17.
61. Houghton, P.J., R. Zarka, B. De-las-Heras and J.R. Hoult, 1995. Fixed oil of *Nigella sativa* and derived thymoquinone inhibit eicosanoid generation in leukocytes and membrane lipid peroxidation. Planta Medica, 61: 33-36.
62. Al-Ghamdi, M.S., 2001. The anti-inflammatory, analgesic and antipyretic activity of *Nigella sativa*. J. Ethnopharmacol., 76: 45-48.
63. Mutabagani, A. and S.A.M. El-Mehdy, 1997. A study of the anti-inflammatory activity of *Nigella sativa* and thymoquinone in rats. Saudi Pharmaceutical J., 5: 110-113.
64. El-Dakhakhny, M., N. Mady, N. Lembert and H.P. Ammon, 2002. The hypoglycemic effect of *Nigella sativa* oil is mediated by extrapancreatic actions. Planta Medica Medica, 68: 465-466.

65. Mahmood, M.S., A.H. Gilani, A. Khwaja, A. Rashid and M.K. Ashfaq, 2003. The *in vitro* effect of Aqueous extract of *Nigella sativa* seeds on Nitric Oxide Production. Phytotherapy Res., 17: 921-924.
66. El-Mahmoudy, A., H. Matsuyama, M.A. Borgan, Y. Shimizu, M.G. El-Sayed, N. Minamoto and T. Takewaki, 2002. Thymoquinone suppresses expression of inducible nitric oxide synthase in rat macrophages. Int. Immunopharmacol., 2: 1603-1611.
67. Akhtar, A.H., K.D. Ahmad, S.N. Gilani and A. Nazir, 1996. Antiulcer effect of aqueous extracts of *Nigella sativa* and *Pongamia pinnata* in rats. Fitoterapia, 67: 195-199.
68. Rajkapoor, B., R. Anandan and B. Jayakar, 2002. Anti-ulcer effect of *Nigella sativa* Linn. against gastric ulcers in rats. Current Science, 82: 177-185.
69. El-Abhar, H.S., D.M. Abdallah and S. Saleh, 2003. Gastroprotective activity of *Nigella sativa* oil and its constituent, thymoquinone, against gastric mucosal injury induced by ischaemia/reperfusion in rats. J. Ethnopharmacol., 84: 251-258.
70. Chakma, T.K., M.S.K. Choudhuri, Shaila Jabbar, M.T.H. Khan, Mahiuddin Alamgir, M.A. Gafur, Kabir Ahmed and B.K. Roy, 2001. Effect of some medicinal plants and plant parts used in Ayurvedic system of Medicine on isolated guinea-pig ileum preparations. Hamdard Medicus, 44: 70-3.
71. Aqel, M.B., 1993. Effect of Nigella sative seeds on intestinal smooth muscles. Int. J. Pharmacogn., 31: 55-60.
72. Gilani, A.H., N. Aziz, I.M. Khurram, K.S. Chaudhary and A. Iqbal, 2001. Bronchodilator, spasmolytic and calcium antagonist activities of *Nigella sativa* seeds (Kalonji): a traditional herbal product with multiple medicinal uses. J. Pak. Med. Assoc., 51: 115-120.
73. Mahmoud, M.R., H.S. El-Abhar and S. Saleh, 2002. The effect of *Nigella sativa* oil against the liver damage induced by *Schistosoma mansoni* infection in mice. Journal of Ethnopharmacology, 79: 1-11.
74. Daba, M.H. and M.S. Abdel-Rahman, 1998. Hepatoprotective activity of thymoquinone in isolated rat hepatocytes. Toxicol. Lett., 95: 23-29.
75. Nagi, M.N., K. Alam, O.A. Badary, O.A. Al-Shabanah, H.A. Al-Sawaf and A.M. Al-Bekairi, 1999. Thymoquinone protects against carbon tetrachloride hepatotoxicity in mice via an antioxidant mechanism. Biochem. Mol. Biol. Int., 47: 153-159.
76. Mansour, M.A., 2000. Protective effects of thymoquinone and desferrioxamine against hepatotoxicity of carbon tetrachloride in mice. Life Sci., 66: 2538-2591.
77. Janbaz, K.H., S.A. Saeed and A.H. Gilani, 2003. Hepatoprotective Effect of Thymol on Chemical-induced Hepatoprotectivity in Rodents. Pakistan J. Biol. Sci., 6: 448-451.
78. Mahgoub, A.A., 2003. Thymoquinone protects against experimental colitis in rats. Toxicol. Lett., 143: 133-143.
79. El-Daly, E.S., 1998. Protective effect of cysteine and vitamin E, *Crocus sativus* and *Nigella sativa* extracts on cisplatin-induced toxicity in rats. J. Pharm. Belg., 53: 87-93.
80. Khan, N., S. Sharma and S. Sultana, 2003. *Nigella sativa* (black cumin) ameliorates potassium bromate-induced early events of carcinogenesis: diminution of oxidative stress. Human and Experimental Toxicol., 22: 193-203.
81. Agarwal, C., A. Narula, D.K. Vyas and D. Jacob, 1990. Effect of seeds of "Kalaunji" (*Nigella sativa*) on fertility and sialic acid content of the reproductive organs of the male rat. Geobios, 17: 269-272.
82. Keshri, G., V. Lakshmi and M.M. Singhe, 1998. Postcoital contraceptive activity of some indigenous plants in rats. Contraception, 57: 357-360.
83. Aqel, M. and R. Shaheen, 1996. Effects of the volatile oil of *Nigella sativa* seeds on the uterine smooth muscle of rat and guinea pig. J. Ethnopharmacol., 52: 23-26.
84. Kabir, K.K., J.P. Varshney, C.V.S. Rawal, R.S. Srivastava and M.R. Ansari, 2001. Comparative efficacy of herbal preparations in the management of anoestrus in non-descript rural buffaloes. Indian J. Animal Reproduction, 22: 143-145.
85. Badary, O.A., A.B. Abdel-Naim, M.H. Abdel-Wahab and F.M. Hamada, 2000. The influence of thymoquinone on doxorubicin-induced hyperlipidemic nephropathy in rats. Toxicol., 143: 219-226.
86. Abul-Nasr, S.M., M.D.M. El-Shafey and M.M.H. Osfor, 2001. Amelioration by *Nigella sativa* (L.) of methotrexate-induced toxicity in male albino rats: a biochemical, haematological and histological study. Sceintia Agriculture Bohemica, 32: 123-160.
87. Chakravarty, N., 1993. Inhibition of histamine release from mast cells by nigellone. Ann-Allergy, 70: 237-242.
88. Padmalatha, K., B.V. Venkataraman and R. Roopa, 2002. Antianaphylactic effect of DLH-3041 (polyherbal formulation) on rat mesenteric mast cell degranulation. Indian J. Pharmacol., 34: 119-122.

89. Gilani, A.H., F. Shaheen and T. Shakir, 2001. Thymol lowers blood pressure through blockade of calcium channels. Fundamental and Clinical Pharmacology, 15: 8P163.
90. El-Tahir, K.E., M.M. Ashour and M.M. Al-Harbi, 1993a. The Respiratory actions of the volatile oil of the black seed (*Nigella sativa*) in guinea-pigs: elucidation of the mechanism(s) of action. General Pharmacol., 24: 1115-1122.
91. El-Tahir, K.E., M.M. Ashour and M.M. Al-Harbi, 1993. The Cardiovascular actions of the volatile oil of the black seed (*Nigella sativa*) in rats: elucidation of the mechanism of action. General Pharmacol., 24: 1123-1131.
92. Zaoui, A., Y. Cherrah, M.A. Lacaille-Dubois, A. Settaf, H. Amarouch and M. Hassar, 2000. Diuretic and hypotensive effects of *Nigella sativa* in the spontaneously hypertensive rat. Therapie, 55: 379-382.
93. Hassanin, N.I. and F.M. Hassan, 1996. A preliminary study on the effect of *Nigella sativa* seeds on hypoglycemia. Veterinary Medical J. Giza, 44: 699-708.
94. Zaoui, A., Y. Cherrah, N. Mahassine, K. Alaoui,H. Amarouch and M. Hassar, 2002. Acute and chronic toxicity of *Nigella sativa* fixed oil. Phytomedicine, 9: 69-74.
95. Ibraheim, Z.Z., 2002. Effect of *Nigella sativa* seeds and total oil on some blood parameters in female volunteers. Saudi Pharmaceitical J., 10: 54-59.
96. Nair, S.C., M.J. Salomi, B. Panikkar and K.R. Panikkar, 1991. Modulatory effects of *Crocus sativus* and *Nigella sativa* extracts on cisplatin-induced toxicity in mice. J. Ethnopharmacol., 31: 75-83.
97. Bamosa, A.O., B.A. Ali and Z.A. Al-Hawsawi, 2002. The effect of thymoquinone on blood lipids in rats. Indian J. Physiol. Pharmacol., 46: 195-201.
98. Enomoto, S., R. Asano, Y. Iwahori, T. Narui, Y. Okada, A.N. Singab and T. Okuyama, 2001. Hematologic studies on black cumin oil from the seeds of *Nigella sativa*. Biological and Pharmaceutical Bulletin, 24: 307-310.
99. Burits, M. and F. Bucar, 2000. Antioxidant activity of *Nigella sativa* essential oil. Phytotherapy Res., 14: 323-328.
100. Kruk, I., T. Michalska, K. Lichszteld, A. Kladna and H.Y. Aboul-Enein, 2000. The effect of thymol and its derivatives on reactions generating reactive oxygen species. Chemosphere, 41: 1059-1064.
101. Mansour, M.A., M.N. Nagi, A.S. El-Khatib and A.M. Al-Bekairi, 2002. Effects of thymoquinone on antioxidant enzyme activities, lipid peroxidation and DT- diaphorase in different tissues of mice: a possible mechanism of action. Cell Biochem. Funct., 20: 143-151.
102. Al-Shabanah, O.A., O.A. Badary, M.N. Nagi, N.M. Al-Gharably, A.C. Al-Rikabi and A.M. Al-Bakairi, 1998. Thymoquinone protects against doxorubicin-induced cardiotoxicity without compromising its antitumor activity. J. Exp. Clin. Cancer Res., 17: 193-198.
103. Nagi, M.N. and M.A. Mansour, 2000. Protective effect of thymoquinone against doxorubicin-induced cardiotoxicity in rats: a possible mechanism of protection. Pharmacol. Res., 41: 283-289.
104. El-Shabrawy, O.A. and S.A. Nada, 1996. Biological evaluation of multicomponent tea used as hypoglycemic in rats. Fitoterapia, 67: 99-102.