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REVIEW ARTICLE

Pharmacological and Toxicological Properties of *Nigella sativa*

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The seeds of *Nigella sativa* Linn. (Ranunculaceae), commonly known as black seed or black cumin, are used in folk (herbal) medicine all over the world for the treatment and prevention of a number of diseases and conditions that include asthma, diarrhoea and dyslipidaemia. This article reviews the main reports of the pharmacological and toxicological properties of *N. sativa* and its constituents.

The seeds contain both fixed and essential oils, proteins, alkaloids and saponin. Much of the biological activity of the seeds has been shown to be due to thymoquinone, the major component of the essential oil, but which is also present in the fixed oil.

The pharmacological actions of the crude extracts of the seeds (and some of its active constituents, e.g. volatile oil and thymoquinone) that have been reported include protection against nephrotoxicity and hepatotoxicity induced by either disease or chemicals. The seeds/oil have antiinflammatory, analgesic, antipyretic, antimicrobial and antineoplastic activity. The oil decreases blood pressure and increases respiration. Treatment of rats with the seed extract for up to 12 weeks has been reported to induce changes in the haemogram that include an increase in both the packed cell volume (PCV) and haemoglobin (Hb), and a decrease in plasma concentrations of cholesterol, triglycerides and glucose.

The seeds are characterized by a very low degree of toxicity. Two cases of contact dermatitis in two individuals have been reported following topical use. Administration of either the seed extract or its oil has been shown not to induce significant adverse effects on liver or kidney functions.

It would appear that the beneficial effects of the use of the seeds and thymoquinone might be related to their cytoprotective and antioxidant actions, and to their effect on some mediators of inflammation.

Keywords: Nigella sativa; thymoquinone; antiinflammatory; antineoplastic.

INTRODUCTION

Nigella sativa Linn. (family Ranunculaceae), commonly known as black seed or black cumin, is an annual plant that has been traditionally used in the Indian subcontinent (Nadkarni, 1976), Arabian countries (Sayed, 1980) and Europe (Lautenbacher, 1997) for culinary and medicinal purposes as a natural remedy for a number of illnesses and conditions that include asthma, hypertension, diabetes, inflammation, cough, bronchitis, headache, eczema, fever, dizziness and influenza. The seeds or its oil are used as a carminative, diuretic, lactagogue and vermifuge. They are also used in food as a spice and a condiment.

Traditionally, there is a common Islamic belief that the 'black seed', as it is commonly known in Arabic, is a panacea (universal healer) that is a remedy for all ailments, but cannot prevent ageing or death. In the bible, *N. sativa* is also identified as 'curative black cumin', and is also described as the *Melanthion* of Hippocrates and Dioscorides and as the *Gith* of Pliny (Worthen *et al.*, 1998). Many of the claimed folk medicinal uses of this plant have been scientifically tested. The following is a brief overview of the available literature on the main phytochemical, pharmacological and toxicological properties of this plant.

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CONSTITUENTS

N. sativa seeds contain 36%–38% fixed oils, proteins, alkaloids, saponin and 0.4%–2.5% essential oil (Lautenbucher, 1997). The fixed oil is composed mainly of unsaturated fatty acids, including the unusual C20:2 arachidic and eicosadienoic acids (Houghton *et al.*, 1995). The essential oil was analysed by Burits and Bucar (2000) using GC-MS. Many components were characterized, but the major ones were thymoquinone (Fig. 1.1) (**1**) (27.8%–57.0%), *p*-cymene (7.1%–15.5%), carvacrol (5.8%–11.6%), t-anethole (0.25%–2.3%), 4-terpineol (2.0%–6.6%) and longifoline (1.0%–8.0%). Thymoquinone readily dimerizes to form dithymoquinone (El-Dakhakhny, 1963). Four alkaloids have been reported as constituents of *N. sativa* seeds. Two, nigellicine (Fig. 1.2) (**2**) (Atta-ur-Rahman *et al.*, 1985b) and

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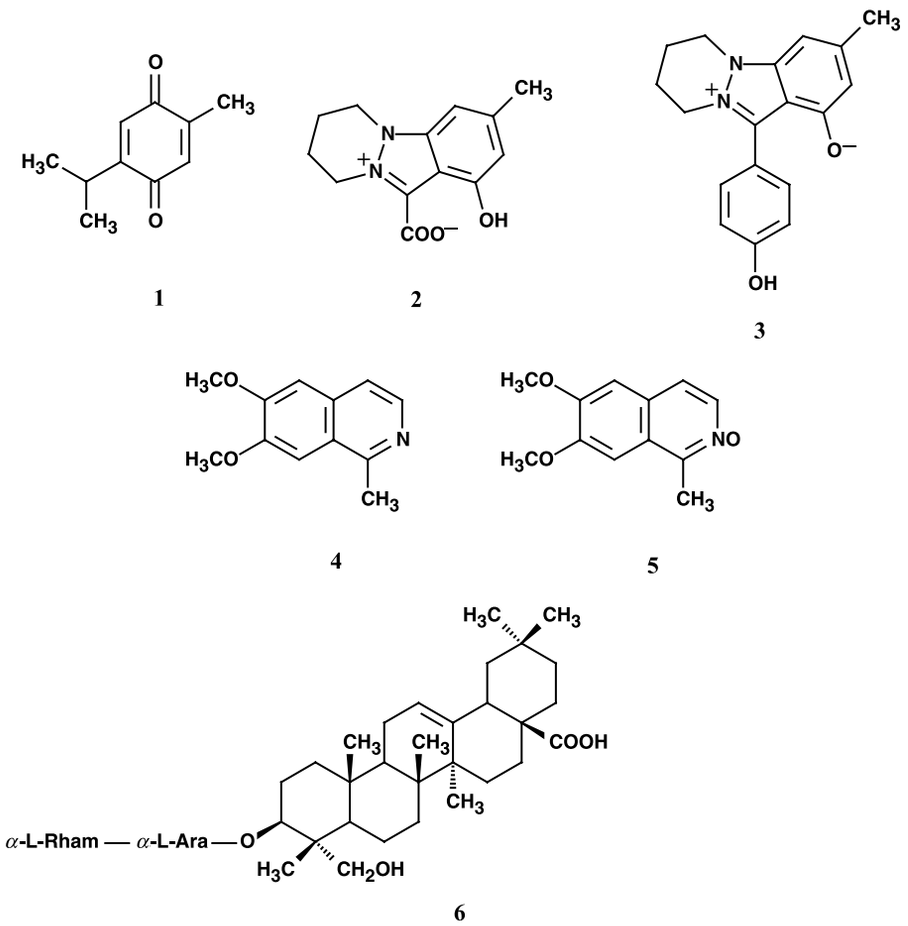

Figure 1. Chemical structures of some major constituents of *Nigella sativa* seeds.

nigellidine (Fig. 1.3) (**3**) (Atta-ur-Rahman *et al*., 1995) have an indazole nucleus, whereas nigellimine (Fig. 1.4) (**4**) (Atta-ur-Rahman *et al*., 1992) and its N-oxide (Fig. 1.5) (**5**) (Atta-ur-Rahman *et al*., 1985a) are isoquinolines.

Recently, a monodesmosidic triterpene saponin, α-hederin (Fig. 1.6) (6), was isolated from *N. sativa* seeds. This compound had been found previously in *Hedera helix* leaves (Swamy and Benny, 2001). Much earlier, the aglycone of α-hederin had been ascribed the name melanthigenin, but this compound was shown to be identical to hederagenin by Zahira and Gabra (1943).

PHARMACOLOGICAL PROPERTIES

Many studies have been conducted, particularly during the past two decades, on the effect of *N. sativa* seed extract or its active compound(s) (thymoquinone) on various body systems *in vivo* or *in vitro*. The following is a selection of some of these studies.

Antioxidant effect

It has been shown that both the fixed oil of *N. sativa*, as well as thymoquinone (the main compound of the essential oil), inhibit non-enzymatic lipid peroxidation in liposomes (Houghton *et al.*, 1995). Using thin-layer chromatography (TLC), it has also been shown that compounds isolated from *N. sativa* (including thymoquinone, carvacol, t-anethole and 4-terpineol) have appreciable free radical scavenging properties (Burtis and Bucar, 2000). These compounds were found in a series of other *in vitro* tests to have variable antioxidant, but no prooxidant properties. The different compounds in the oil were found to act in a synergistic manner (i.e. more than the mere summation of the actions of the individual compounds). This stresses the importance of using the whole oil (or the crude extract) of the seeds in pharmacological studies. This property has been noted before with a number of spices (Beckstrom-Sternberg and Duke, 1994). Although the antioxidant property of *N. sativa* is multifactorial, it does not seem to involve iron-complexing activity (Burtis and Bucar, 2000).

Generation of free radicals may be, at least partially, the basis of many human diseases and conditions. Therefore, the antioxidant action of *N. sativa* may explain its claimed usefulness in folk medicine. This antioxidant property would explain its action against CCl_4 hepatotoxicity (Nagi *et al.*, 1999), liver fibrosis and cirrhosis (Türkdogan *et al.*, 2000), and hepatic damage induced by *Schistosoma mansoni* infection (Mahmoud *et al.*, 2002) (see section on antihepatotoxicity).

Antiinflammatory and analgesic actions

Khanna *et al.* (1993), using three antinociceptive tests in rats and mice (hot plate test, tail-pinched test, acetic acid-induced writhing), concluded that the fixed oil of the seeds is endowed with strong antinociceptive

actions, and that these actions were due to an opioid principle in the oil, as they were antagonized by naloxone. Further, these authors have shown that the oil has significant CNS depressing properties. These results were confirmed by Abdel-Fattah (2000) who used four different models of analgesia (hot plate test, tail-pinched test, acetic acid-induced writhing and formalin-induced pain). The oil and/or thymoquinone were given either orally (p.o.) or by injection, either intraperitoneally (i.p.) or intracerebroventrically (i.c.v.). The mechanism of the analgesia was examined by the use of the general opioid antagonist naloxone, and a number of mu, kappa and delta receptor antagonists. These experiments suggested that *N. sativa* oil and thymoquinone produce antinociceptive effects through indirect activation of the superspinal mu_1 and kappa receptors. To test the popular claim that *N. sativa* is useful in inflammatory conditions in humans, the aqueous extract of *N. sativa* seeds was tested for its antiinflammatory, analgesic and antipyretic action in mice (Al-Ghamdi, 2001). Using carrageenan-induced paw oedema as a model of inflammation, and the hot plate reaction time as a model of nociception, the extract was found to possess significant antiinflammatory and analgesic action, but it failed to induce yeast-induced pyrexia. This finding lends some credence to the folk medicinal use of the plant as an antiinflammatory and analgesic substance, and also confirms previous reports on the antinociceptive (Abdel-Fattah *et al.*, 2000) and antiinflammatory (Mutabagani and El-Mahdi, 1997) effects of *N. sativa* oil and its major component, thymoquinone, in mice.

The possible mechanism by which *N. sativa* exerts its antiinflammatory action has been studied. Thymoquinone has been shown to be a potent inhibitor of eicosanoid generation, namely thromboxane B_2 and leucotrienes B_4, by inhibiting both cyclooxygenase and lipooxygenase, respectively (Houghton *et al.*, 1995). Interestingly, it was found that the fixed oil of *N. sativa* had both antioxidant (see above) and anti-eicosanoid effects greater than thymoquinone, which is its active constituent (Houghton *et al.*, 1995).

Anticarcinogenic and mutagenic activity

Several workers have investigated the possible antitumour activity of some crude and purified components of *N. sativa*. For example, Salomi *et al.* (1992) have shown that a crude methanol extract of the seeds of this plant exhibited a strong cytotoxic action on Erlich ascites carcinoma, Dalton's ascites lymphoma and sarcoma 180 cells, while exerting minimal cytotoxicity to normal lymphocytes. The same authors confirmed the cytotoxic property of the seeds *in vivo* by inhibiting the growth of Erlich ascites carcinoma in mice receiving 2 mg of the extract/mouse/day for 10 days (Salomi *et al.*, 1992). It has also been shown that exposure to the volatile oil of *N. sativa* altered the cellular expression of specific polypeptides in Jukart T lymphoma cells, suggesting that changes in polypeptide expression might play a role in the biological activities attributed to *N. sativa* (Hailat *et al.*, 1995). *N. sativa* seeds or compounds isolated therefrom have been shown to prevent cancer and/or to reduce the cytotoxicity of standard antineoplastic drugs. For example, it has been shown that topical application of *T. sativa* extract inhibited the two-stage initiation-promotion of skin cancer by dimethylbenzo[a] anthracene-croton oil in mice (Salomi *et al.*, 1991). These authors noted that intraperitoneal injections of the same *N. sativa* extract reduced by about 67% the incidence of soft tissue sarcomas seen after 30 days of subcutaneous 20-methylcholanthrene (MCA) injections. In another study, Nair *et al.* (1991) showed that treatment with a crude ethanol extract significantly reduced cisplatin-induced mice. It was also noted that *N. sativa* extract, given to rats 30 min before cisplatin, protected against the nephrotoxicity of the antineoplastic drug (El Daly, 1998). The mode of protective action of the extract is not certain, but it was ascribed to a possible decrease in the development of nephrotoxicity or to an enhancement of the excretion of cisplatin. Thymoquinone (the main constituent of *N. sativa* oil) when given in the drinking water (5 mg/kg/day) for 5 days before and 5 days concomitantly with ifosfamide (IFO) has been shown to attenuate significantly the renal toxicity of IFO (Fanconi syndrome) and to enhance its antitumour activity in mice (Badary, 1999). The antioxidant action of thymoquinone has been suggested as the mechanism by which the nephrotoxicity of IFO is mitigated, and this is reminiscent of the reported protective action of thymoquinone on cisplatin nephrotoxicity in mice and rats (Badary *et al.*, 1997). These workers have also shown that thymoquinone enhances the antitumour activity of cisplatin.

Worthen *et al.* (1998) have tested *in vitro* a crude gum, a fixed oil and two purified components of the seed [thymoquinone (TQ) and dithymoquinone (DIM)] for their cytotoxicity to several parental and multi-drug resistant (MDR) human tumour cell lines. The gum and the oil (up to 1% w/v) were devoid of cytotoxicity, while both TQ and DIM were both cytotoxic to all of the cell lines. Both the parental cell lines and their corresponding MDR variants (that were resistant to several standard antineoplastic drugs) were equally sensitive to TQ and DIM. The action of the latter components as cytotoxic agents was found not to be related to generation of free radicals. Strong *in vitro* cytotoxic action of the ethyl acetate fraction of *N. sativa* seed extract against different classes of cancer cell lines has been reported (Swamy and Tan, 2000).

The *in vivo* and *in vitro* inhibitory effects of thymoquinone against 20-methylcholanthrene (MC)-induced fibrosarcoma (Badary and Gamal, 2001) and against benzo(a)pyrene-induced forestomach carcinogenesis (Badary *et al.*, 1999) were reported in mice. The incidence and multiplicity of the fibrosarcoma was significantly inhibited by about 43% and 34%, respectively, and the forestomach cancer by 70% and 67%, respectively, when thymoquinone was administered (0.01% in the drinking water) 1 week before and after MC treatment. The onset of fibrosarcoma and incidence of mortality were both delayed by the treatment. It has also been shown that thymoquinone was effective in inhibiting the survival of the fibrosarcoma *in vitro*. The bases of these effects are not certain, but were ascribed to interference with DNA synthesis coupled with enhancement of the detoxification process and/or to a beneficial effect on the oxidant status, as they were accompanied by restoration of the concentrations of reduced glutathione (GSH) and lipid peroxides and the activities of some enzymes.

More recently, Kumara and Huat (2001) isolated a principle from the seeds of *N. sativa*, termed alpha-hederin, that has strong *in vivo* antitumour activity in mice implanted with Lewis lung sarcoma and murine P388 leukaemia.

Using karyotyping, *N. sativa* seed extract and thymoquinone have recently been shown to protect mouse bone marrow and spleen cells infected with schistosomiasis from chromosomal aberrations (Aboul-Ela, 2002). Probably this is the first and only report that suggests, both *in vivo* and *in vitro*, that *N. sativa* and its main constituent are endowed with antimutagenic properties.

Antihepato and nephrotoxic action

In some countries *N. sativa* seeds are sold to treat conditions that include liver diseases [(Boulos, 1983, cited by Daba and Abdel-Rahman (1998)]. Using isolated rat hepatocytes, Daba and Abdel-Rahman (1998) investigated the protective action of thymoquinone isolated from *N. sativa* against the hepatotoxicity of tert-butyl hydroperoxide (TBHP). Thymoquinone showed protective actions against TBHP. The hepatoprotection of thymoquinone was compared with that of silybin, a known hepatoprotective agent. On the whole, thymoquinone was as effective as silybin in protecting certain aspects of hepatic function. The mechanism of the hepatoprotective action of thymoquinone is not certain, but may be related to the preservation of intracellular glutathione (the depletion of which by oxidative stress is known to increase the susceptibility of cells to irreversible injury). It was also suggested that the mechanism of action may be related to the inhibitory action of thymoquinone to the generation of thromboxane B_2, as the latter substance is known to be implicated in the mechanism of hepatocyte plasma membrane bleb formation (dissociation of the membrane lipid bilayer from the underlying cytoskeleton).

It has also been shown that pretreatment of rats with *N. sativa* oil for 4 weeks was effective in protecting against carbon tetrachloride and D-galactosamine-induced hepatic damage (El-Dakhakhny *et al.*, 2000b). The protection against the former hepatotoxicity was partial, while that of the latter was complete. No ill effects on liver function were observed when the oil was given orally at a dose of 800 mg/kg/day for 4 weeks. The oil was also found to reduce significantly serum total cholesterol, low-density lipoproteins and triglycerides and reduce high-density lipoproteins. In rabbits, experimental liver cirrhosis and fibrosis (induced by carbon tetrachloride) was shown to be prevented by the prior administration of *N. sativa.* The seed extract improved the histological picture and the indices of oxidative status of the liver (Turkdogan *et al.*, 2000). In mice, thymoquinone (8 mg/kg/day for 5 days before and 1 day after carbon tetrachloride was administered with the drinking water) was also found to protect against the biochemical and histological markers of liver damage (Al-Gharably *et al.*, 1997). The protection was suggested to be related to the ability of thymoquinone to inhibit lipid peroxidation.

More recently, it has been shown that *N. sativa* oil was effective in reversing the alterations seen in some of the biochemical constituents in the serum of mice infected with *Schistosoma mansoni* (Mahmoud *et al.*, 2002). These constituents are considered reliable indicators of liver function. These results are in line with others that suggest an ameliorative effect on liver function of both *N. sativa* and compounds extracted therefrom.

Administration of *N. sativa* seed extract (50 mg/kg) 30 min before the administration of the nephrotoxic drug cisplatin was effective in ameliorating the biochemical and physiological indices of nephrotoxicity (El Daly, 1998). This was in confirmation of an earlier report (Badary *et al.*, 1997) that thymoquinone attenuates the nephrotoxicity of cisplatin and enhances its antitumour activity (see above). The reason for the protective action is not certain, but may be related to the antioxidant action of the extract, and the fact that the nephrotoxic drug may induce its effect via generation of free radicals.

Respiratory and immunological actions

It has been reported that intravenous administration of the volatile oil of *N. sativa* dose-dependently increases the respiratory rate and intratracheal pressure of guinea-pigs (El-Tahir *et al.*, 1993a). However, thymoquinone increased the intratracheal pressure without significantly affecting respiratory rate. Based on the effects of certain antagonists, the actions of the volatile oil were ascribed to histaminergic and muscarinic mechanisms. These authors suggested that *N. sativa* volatile oil might be a potentially useful respiratory stimulant if thymoquinone were removed from it. This experimental work in guinea-pigs supports the folkloric use of the plant in asthmatic patients.

In Pakistan, Gilani *et al.* (2001) studied the effects of a crude extract of *N. sativa* seeds on isolated rabbit jejunum and guinea-pig tracheal preparations. The extract was found to cause a dose-dependent relaxation of spontaneous contractions in the rabbit jejunum, and inhibition of KCl-induced contractions. These actions were similar to those produced by verapamil, a calcium-channel antagonist. In the tracheal preparation, the extract antagonized the contractions induced by histamine, carbachol and KCl. The spasmolytic and bronchodilator actions observed were suggested to be mediated via calcium channels. The above pharmacological activities of the petroleum ether fraction of the extract were about 10 times higher than those of the crude extract.

In an experiment carried out on rat peritoneal mast cells *in vitro*, it has been shown that nigellone, a carbonyl polymer of thymoquinone isolated from *N. sativa* seeds, was highly effective in inhibiting histamine release (Chakravarty, 1993). This was in confirmation of an earlier report that suggested that thymoquinone and thymohydroquinone possess significant antihistaminic effects (Marozzi *et al.*, 1970). El-Kadi and Kandil (1987) were probably the first to show that *N. sativa* seeds have immuno-potentiating properties in human T cells *in vitro*. This was confirmed by Haq *et al.* (1995), who showed that *N. sativa* seeds activate T-lymphocytes to secrete the interleukin, IL-3, and increased IL-1β production indicating a stimulatory effect on macrophages either through a direct effect or via IL-1β. In further experiments the same authors purified the proteins in the whole *N. sativa* seeds, and showed that some proteins have suppressive and others stimulatory properties in lymphocyte cultures (Haq *et al.*, 1999). The proteins were also effective in the production of cytokines (e.g. IL-1β). These results were somewhat

different from those of Swamy and Tan (2000) who reported that, using mouse spleenocytes, *N. sativa* extract, *per se*, has no immunomodulatory activity. In the presence of optimal doses of mitogen, however, there was a significant potentiation of the immune response, the mechanism of which is unclear (Swamy and Tan, 2000).

Antidiabetic action

The effect of *N. sativa* on some of the complications of experimental (alloxan-induced) diabetes mellitus in rabbits has been investigated by a number of workers (e.g. Al-Hader *et al*., 1993; El-Zawahrawy and Al-Zahraa, 1998; Meral *et al.*, 2001). Al-Hader *et al.* (1993) reported that intraperitoneal administration of the volatile oil of *N. sativa* seeds (50 mg/kg) significantly reduced (by about 15%–23%) the fasting blood glucose concentration in normo- and hyperglycaemic rabbits, 4–6 h after administration. Insulin concentration was unaffected by the treatments, possibly indicating that the hypoglycaemic effect was mediated by an (as yet unidentified) mechanism that does not involve insulin.

El-Zawahrawy and Al-Zahraa (1998) suggested that treatment with the extract was effective in restoring the structural integrity of the pancreas in diabetic rats.

Meral *et al.* (2001) investigated, in diabetic rabbits, the influence of the plant extract on lipid peroxides and glutathione, ceruloplasmin and glucose, as well as the histology of the liver and pancreas. The results indicated that treatment with the extract for 2 months significantly reduced the elevated concentration of glucose and lipid peroxides, and decreased that of glutathione and ceruloplasmin, and ameliorated the biochemical and histological signs of liver damage. It was postulated that the basis of the beneficial effect of *N. sativa* in diabetes might be its antioxidant property (see antioxidant actions above). These results are in contrast to earlier reports from Kuwait, which seems to suggest that *N. sativa* seeds were without effect in streptozotocin-induced diabetes in rats (Al-Awadi and Gumaa, 1987). It has been reported, though, that a mixture of five plants (including *N. sativa*) is commonly used by Kuwaiti diabetics to aid in the control of hyperglycaemia. The plant mixture was experimentally found to improve glucose tolerance in both streptozotocin diabetic and normal rats (Al-Awadi and Gumaa, 1987; Al-Awadi *et al.*, 1991).

Effect on cardiovascular system and blood

El-Tahir *et al.* (1993b) investigated the actions of the volatile oil of *N. sativa* and its active constituent thymoquinone on the arterial blood pressure and heart of anaesthetized rats. Both agents, when injected intravenously, dose-dependently decreased arterial blood pressure and heart rate. These effects were antagonized by cyprohepatidine (a serotonin and histamine (H_1) receptor antagonist), atropine (a cholinergic (M) receptor antagonist), hexamethonium (a ganglionic nicotinic (N) receptor antagonist), reserpine (an adrenergic depleting agent) and by spinal pithing. It was concluded that cardiovascular actions of these agents are multifactorial, and are mediated mainly centrally via direct and indirect mechanisms that involve (among others) tryptaminergic and cholinergic mechanisms. It was suggested that the oil could be utilized as a centrally acting antihypertensive drug. These results lend credence to the folkloric use of the oil as an antihypertensive agent.

The methanol soluble portion of *N. sativa* oil showed inhibitory effects on arachidonic acid (AA) induced-platelet aggregation and blood coagulation (Enomoto *et al.*, 2001). Several compounds that have an anti-coagulation effect were isolated from the oil, and these were found to be more potent than aspirin, which is a known therapeutic agent for thrombosis.

Workers in Morocco have found that the dichloromethane extract of *N. sativa* seeds is endowed with strong diuretic and antihypertensive actions in spontaneously hypertensive rats (Zaoui *et al.*, 2000). The diuretic effect of the extract (0.6 mL/kg) was increased by about 16% in comparison with frusemide (5 mg/kg), which increased diuresis by 30%. Diuresis was accompanied by an increase in the excretion of chloride, sodium, potassium and urea. *N. sativa* decreased hypertension by 22%, when compared with that of the calcium channel blocker nifedipine (0.5 mg/kg), which caused an 18% decrease in arterial blood pressure. The authors suggested that the diuretic action of *N. sativa* might be, at least partially, responsible for its antihypertensive action. A central action has been suggested as the mechanism for the antihypertensive action (see El-Tahir *et al.*, 1993b above).

More recently, Zaoui (2002a) reported that the oral treatment of rats with the fixed oil of *N. sativa* (1 mL/kg/day/12 weeks) decreased serum cholesterol, triglyceride and glucose levels, and leucocyte and platelet counts by about 15–35%, compared to control values.

The Hb and PCV levels were significantly increased by 6–17%, respectively. These results indicate a possible beneficial effect of the oil in hyperglycaemia and hyperlipidema, and probably as an adjunct to the treatment of certain types of anaemia.

Antiulcer action

A single report in rats has suggested that the aqueous extract of *N. sativa* seeds was effective in reducing the ulcer index (induced by aspirin) by about 36% (Akhtar *et al.*, 1996). The treatment reduced the peptic activity and acid production, but did not change mucin activity. These results seem to suggest that the folkloric use of the plant to treat peptic ulcer may not be founded. However, more recently El-Dakhakhny *et al.* (2000a) obtained opposite results and reported that administration of *N. sativa* oil (0.88 g/kg/day) for 2 weeks increased gastric mucin and glutathione content, reduced histamine content, but did not affect the free acidity and peptic activity of the gastric juice. The above report is in line with earlier ones that have suggested a cytoprotective action of *N. sativa* oil (El-Kadi *et al.*, 1987), and lends some credence to the folkloric use of the oil as an antiulcer agent. However, further work on the action of the oil and extract of the seeds on experimental gastric and duodenal ulcer is warranted.

Antimicrobial actions

A number of reports have been published on the actions of *N. sativa* extracts or its oil on different bacterial

isolates. The extract and the oil have been reported to have a broad spectrum of activity against a number of microbes. For example, *in vitro* antibacterial effects of the essential oil showed pronounced activity even in 1:100 dilutions against several organisms that included *Staphylococcus albus*, *Escherichia coli*, *Salmonella typhi*, *Shigella niger* and *Vibrio cholera* (Agrawal *et al.*, 1979). Generally speaking the oil was more effective against Gram-positive than Gram-negative organisms. The oil was also found to have excellent antifungal activity, particularly against *Aspergillus* species (Agrawal *et al.*, 1979). Among others, El-Kamali *et al.* (1998), using the plate diffusion method, confirmed the above report and showed that the essential oil of *N. sativa* was effective against Gram-positive (*Staphylococcus aureus*, *Bacillus subtilis*) and Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*). The antibacterial effect was maximal when *Bacillus subtilis* was used.

It has been shown that both the crude alkaloid extract and the water extract of the seeds were effective against a variety of organisms (isolated from human patients suffering from septic arthritis), even those that were resistant to antibiotics (Morsi, 2000). It was noted that Gram-negative were affected more than Gram-positive isolates and that, like some antimicrobial agents, the extracts exerted more antibacterial action at lower than higher concentrations. Physico-chemical factors (for example, solubility and diffusion) may account for this.

N. sativa oil, given intraperitoneally, has been shown to exhibit a potent action against murine cytomegalovirus infection in mice. The action was suggested to be related to the potentiating action of the oil on innate immunity (Salem and Hossain, 2000).

Antiparasitic actions

N. sativa oil has been shown to possess anticestodal and antinematodal properties comparable to those of piperazine (Agrawal *et al.*, 1979). In a recent study, Mahmoud *et al.* (2002) showed that *N. sativa* oil (2.5 and 5.0 mL/kg, orally for 2 weeks) was effective in reducing the number of *Schistosoma mansoni* worms in the liver and decreased the total number of ova deposited in both the liver and the intestine. Furthermore, it increased the number of dead ova in the intestinal wall and markedly reduced the granuloma diameters. Administration of *N. sativa* oil concomitantly with praziquantel lowered further the number of dead ova than was observed when praziquantel was given alone, indicating that the plant oil potentiates the action of praziquantel.

TOXICOLOGICAL PROPERTIES

The seed extract and its constituents appear to have a low level of toxicity. The administration of *N. sativa* seed extract (50 mg/kg) intraperitoneally to rats for 5 days did not significantly affect the activities of several enzymes and metabolites indicative of hepatic and renal function (El Daly, 1998). Oral administration of the seed oil at doses up to 10 mL/kg in rats and mice did not cause any mortality or overt toxicity during the observation period of 48 h (Khanna *et al.*, 1993). This was recently confirmed when it was shown that oral administration of the fixed oil of *N. sativa* at a dose of 10 mL/kg, for up to 12 weeks did not cause any mortality or significant alteration of the key hepatic enzymes in rats (Zaoui *et al.*, 2002b). The LD_{50} value of thymoquinone was found to be 2.4 g/kg (range 1.52–3.77) (Badary *et al.*, 1998). Acute administration of high doses (2 g/kg or more) caused hypoactivity and difficulty in respiration. Biochemically, these high doses depleted GSH concentrations in liver, kidney and heart, and damaged liver and kidney, as evidenced by significant increases in plasma metabolites and enzymes (Badary *et al.*, 1998). Inclusion of thymoquinone in the drinking water of mice at concentrations of up to 0.03% for 90 days resulted in no sign of toxicity, except for a significant decrease in fasting plasma glucose concentration ((Badary *et al.*, 1998).

Two case reports of allergic contact dermatitis were reported for two persons who suffered maculopapular eczema after topically using pure oil of *N. sativa*. Paradoxically, the oil was marketed to help in 'disorders of skin dysfunction, inflammation, acne and eczema'. Previously, cases of contact dermatitis have been reported with the use of essential oils present in cosmetics and perfumes. These cases were treatable with topical corticosteroids (Steinmann *et al.*, 1997; Zedlitz *et al.*, 2002).

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