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Antimicrobial and Anticancer Activity of *Nigella sativa oil* –A Review

[1,2]Al-Khalaf M.I and [1,3]Kholoud S. Ramadan

[1]Department of Biochemistry, Faculty of Girls Science, King Abdulaziz University, Jeddah, Saudi Arabia.
[2]Department of Chemistry, College of Sciences, qassim University- Buraidah, Saudi Arabia.
[3]Biochemistry Department, Faculty of Science, Ain Shams University, Cairo, Egypt.

Abstract: *Nigella sativa (N. sativa)* is an annual herb of the *Ranunculaceae* family, which grows in countries bordering the Mediterranean Sea, Pakistan and India. Acute and chronic toxicity studies have recently confirmed the safety of *N. sativa* oil and its most abundant active component, thymoquinone, particularly when given orally. The extracts of *N.sativa* seeds have been used by patients to suppress coughs, disintegrate renal calculi, retard the carcinogenic process, treat abdominal pain, diarrhea, flatulence and polio, and exert choler tic and uricosuric activities, anti-inflammatory and antioxidant effects. The present work is aimed at summarizing the extremely valuable work done by various investigators on the effects of N. sativa seed, antimicrobial and antiparasitic activity of Nigella sativa oil. We hope this review will help interested researchers to conduct further clinical studies to evaluate the antimicrobial, anticancer activities of *N. sativa*, its active constituents and their derivatives.

Key words: *Nigella sativa*; Thymoquinone; Alpha-Hederin; Antimicrobial; Mechanism; Derivatives.

INTRODUCTION

Herbal medicines have long been viewed as a source of curative remedy based on religious and cultural traditions (Ghazanfer, 1994). *Nigella sativa (N. sativa)* is an annual herb of the *Ranunculaceae* family, which grows in countries bordering the Mediterranean Sea, Pakistan and India. This widely distributed plant is native to Arab countries and other parts of the Mediterranean region (Atta, 2003). For thousands of years, this plant has been used in many Asian, Middle Eastern and Far Eastern Countries as a spice and food preservative as well as a protective and health remedy in traditional folk medicine for the treatment of numerous disorders. The seed of this plant is commonly known as black seed and is referred to by the prophet Mohammed as having healing powers. The seeds are commonly eaten alone or in combination with honey and in many food preparations. The oil prepared by compressing the seeds of *N.sativa* is used for cooking. Black seed is also identified as the curative black cumin in the Holy Bible, and is described as the Melanthion of Hippocrates and Discroides and as the Gith of Pliny. Other names for the seed include black caraway seed, Habbatu Sawda and Habatul Baraka ‘‘the Blessed Seed’’. An authentic saying of the Prophet Muhammad (Peace Be upon Him) about black seed is also quoted in AlBukhari (AlBukhari, 1976).

Abu Huraira (Allah be pleased from him) narrated that Allah’s Apostle (peace be upon him) said “Use the black seed, which is a healing for all diseases except ‘As-Sam” and As-Sam is Death (Al-Bukhari, 1976). *N.sativa* plant is one of the most extensively studied, both phytochemically and pharmacologically. The extracts of *N.sativa* seeds have been used by patients to suppress coughs, disintegrate renal calculi (Hashem and El-Kiey, 1982), retard the carcinogenic process, treat abdominal pain, diarrhea, flatulence and polio, exert choleretic and uricosuric activities, anti-inflammatory and antioxidant effects (Mansour *et al*.,2002).

Besides, the essential oil was shown to have anthelminthic, antinematodal, antischistosomal, antimicrobial and antiviral effects. The latter pharmacological properties appear to be involved in the beneficial effects of *N. sativa* oil on headache, flatulence, blood homeostasis abnormalities, rheumatism and related inflammatory diseases. Moreover, the seeds are believed to have carminative, stimulatory and diaphoretic properties and are used in the treatment of bronchial asthma and eczema (Salem and Hossain, 2000).

Description:

Nigella sativa is an annual flowering plant, native to south and southwest Asia. It grows to 20–30cm (7.9–12 in) tall, with finely divided, linear (but not thread-like) leaves. The flowers are delicate, and usually colored pale blue and white, with 5-10 petals (Fig 1). The fruit is a large and inflated capsule composed of 3-7 united follicles, each containing numerous seeds. The seed is used as a spice (Nadkarni, 1976).

Corresponding Author: Kholoud S. Ramadan, Department of Biochemistry, Faculty of Girls Science, King Abdulaziz University, Jeddah, Saudi Arabia.
E-mail: ramadankholoud@yahoo.com, Tel: 0551291289

Fig. 1: *Nigella sativa* plant and seeds.

Chemical Constituents and Active Principles in N. sativa Seeds:

Millions of people in the Mediterranean region and on the Indian subcontinent use the oil from the seed of *N. sativa* daily as a natural protective and curative remedy. The seeds are very rich and diverse in chemical composition. They contain amino acids, proteins, carbohydrates, fixed and volatile oils (Khan, 1999). Many of the pharmacological activities mentioned above have been attributed to quinine constituents in the seed. Thymoquinone (TQ) (Figure 2) is the main active constituent of the volatile oil of the black seed. They also other studies have shown thymoquinone is the main active constituent of the volatile oil extracted from *N. sativa* (El Gazzar *et al*., 2006). In addition, El-Dakhakhny *et al*., 2002, determined that the 'nigellone' isolated earlier was a dimer of TQ, which was later named dithymoquinone (TQ2) (Figure 2). The latter compound was shown to be formed via photodimerization of TQ as a consequence of exposure to sunlight during separation and extraction of the quinones from the seed. The molecular and therapeutic potential of thymoquinone in cancer have also been reviewed (Banerjee *et al*., 2010a), but it does not include studies on the anticancer activities of N. sativa seed, its oil, various extracts and other active compounds, such as alpha-hederin.

The chemical composition of the black seed of *N.sativa* was found to contain a fixed oil (30%) and a volatile oil (average 0.5%,maximum 1.5%). The volatile oil was found to contain 54% TQ and many monoterpenes such as p-cymene and a-pinene,TQ2 and THQ. In recent years, the seeds of *N.sativa* have been subjected to a range of photochemical investigations (Ali *et al*., 2012). They have been shown to contain more than 30%(w/w) of a fixed oil with 85% of total unsaturated fatty acid. The seeds also contain alkaloids of unknown pharmacological actions, such as Nigellicine, nigellidine, nigellimine-N-oxide, thymoquinone, dithymoquinone, thymohydroquinone, nigellone, thmol, carvacrol, oxy-coumarin, 6-methoxycoumarin and 7-hydroxy coumarin, alpha-hedrin, steryl-glucoside as well as rich amounts of flavonoids, tannins, essential fatty acids, essential amino acids, ascorbic acid, iron and calcium. Saponins and crude fiber as well as minerals such as calcium, iron, sodium and potassium. Other constituents of the volatile oil include thymol (TOH) (Figure 2) .In conclusion, *N. sativa* seeds contain fixed oils and volatile oils, which are rich sources of quinines, unsaturated fatty acids, amino acids and proteins and contain traces of alkaloids and terpenoids. Most of the studies on the biological effects of *N.sativa* have dealt with its crude extracts in different solvents; however , some studies used its active principles. Among the components isolated from the volatile oil of *N.sativa*,TQ has been shown to be the principal active ingredient (Bourgou *et al*., 2008)

The presence of TQ, TQ2 and TOH in *N.sativa* seed was confirmed using thin layer chromatography (TLC) and normal phase high-performance liquid chromatography (HPLC) methods (Aboul-Enein and Abou Basha,1995). The content of TQ in *N.sativa* seed oil samples, obtained from different origins, was measured by gas chromatography (GC) analysis and found to be in the range of 0.13–0.17% w/v of the oil (Houghton *et al*.,1995). The seeds are also rich in proteins; when whole *N.sativa* seeds were fractionated using SDS-PAGE, they were found to contain a number of protein bands ranging from 10 to 94 kDa molecular mass (Haq *et al*., 1999). An HPLC method for quantifying the putative pharmacologically active constituents (TQ, TQ2, THQ and TOH) in the oil of *N.sativa* seed was recently described by Ghosheh *et al*., 1999. In this procedure, the four compounds mentioned were separated and quantified in commercial *N.sativa* seed oil with good resolution, reproducibility and sensitivity. Both heat and light are known to affect the levels of the constituents in the oil. Since various storage and manufacturing conditions are expected to make a difference in the amounts of the quinone constituents of the oil , the analytical HPLC method described by (Ghosheh etal.,1999) can be used to quantify the levels of the above constituents in the oil and seed extracts of *N.sativa* under different manufacturing conditions. The protocol is also useful as a quality control method for the determination of pharmacologically active quinones in *N.sativa* seed oil. Using TLC, the oil of black seed was found to contain TQ and the terpenoid components carvacrol, t-anethole and 4-terpineol (Burits and Bucar, 2000).

GC-MS analysis of the essential oil obtained from six different samples of *N.sativa* seeds and from a commercial fixed oil showed that the qualitative composition of the volatile compounds was almost identical. Differences were mainly restricted to the quantitative composition (Burits and Bucar, 2000).

N. sativa seeds are rich sources of protein. Proximate analysis of the seeds showed a composition of 20.85% protein, 38.20% fat, 4.64% moisture, 4.37% ash, 7.94% crude fibre and 31.94% total carbohydrate. No trace of

lead, cadmium and arsenic were found in the seeds. The predominant elements present were potassium, phosphorus, sodium and iron while zinc, calcium, magnesium, manganese and copper were found at lower levels (Al-Jassir, 1992). The seeds may potentially be an important nutritional source as the content of essential amino acids contributes to about 30% of the total protein content while about 84% of the fatty acids are composed of unsaturated fatty acids, predominantly linoleic and oleic acids. Oil extracts of the seeds also contain significant amounts of sterols. B-Sitosterol was the dominant sterol (69%); while campesterol and stigma sterol constitute 12% and 19%, respectively of the total sterols. The seed oil was found to be rich in polyphones (1,744 µg/g) and tocopherols (340 µg/g of total a-b- and g-isomers). *N.sativa* seeds contain 36%-38% fixed oils, proteins, alkaloids, saponins and 0.4%-2.5% essential oil (Hosseinzadeh and Parvardeh. 2004). The fixed oil is composed mainly of fatty acids, namely, linoleic(C18:2) , oleic (C18:1) and palmitic acids (C16:0) (table1) (Cheikh-Rouhou *et al*.,2007).

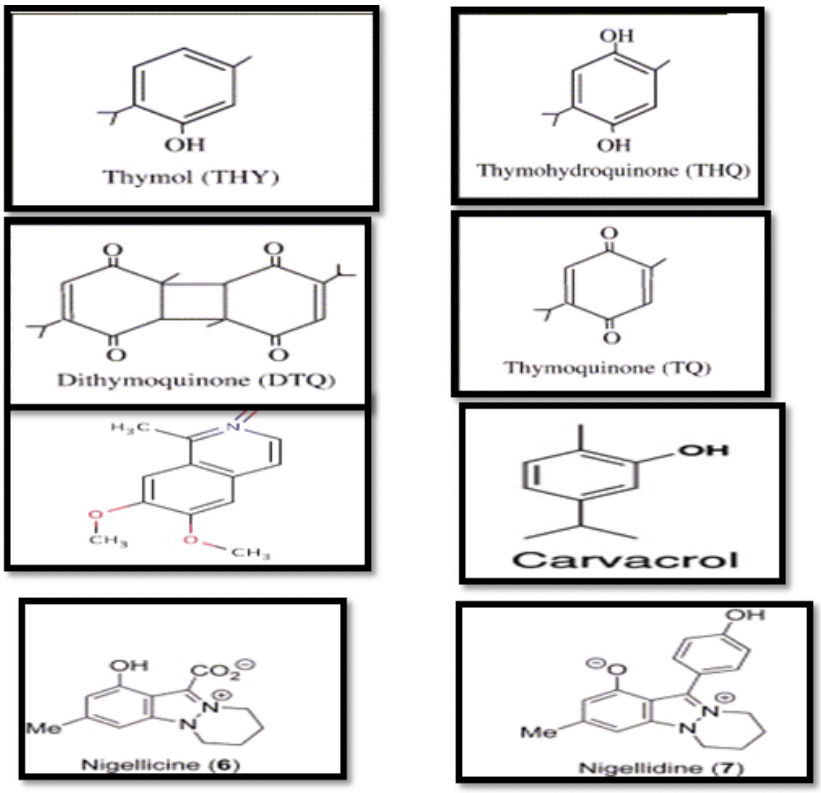


Fig. 1: The chemical Structure of the compound Present in Essential Oil From the Quinone Family.

Many components were characterized from the essential oil (table2). But the major ones were thymoquinone (27.8%-57.0%), ρ-cymene (7.1%-15.5%), carvacrol (5.8%-11.6%), tanethole (0.25%-2.3%), 4-terpineol (2.0%-6.6%) and longifoline (1.0%-8.0%) (Hosseinzadeh and Parvardeh, 2004).

Table 1: Fatty acid composition of the fixed oil of Nigella sativa (David *et al*, 2007).

Fatty acid	RT	Percentage
Lauric acid	4.68	0.6
Myristic acid (C14:0)	5.91	0.5
Palmitic acid (C16:0 Stearic acid	7.48	12.5
(C18:0) Oleic acid (C18:1)	9.37	3.4
Linoleic acid (C18:2) (omega-6)	9.79	23.4
Linolenic acid (18:3n-3) (omega-3)	10.52	55.6
Eicosadienoic acid	11.95	0.4
	12.71	3.1
Total fatty acids		99.5

Table 2: Chemical composition of the volatile constituents of Nigella sativa.

Compound	RI	Percentage
n-Nonane	901	1.7
3-Methyl nonane	931	0.3
1,3,5-Trimethyl benzene	969	0.5
n-Decane	1001	0.4
1-Methyl-3-propyl benzene	1052	0.5
1-Ethyl-2,3-dimethylbenzene	1087	0.2
n-Tetradecane	1400	0.2
n-Hexadecane	1600	0.2
Nonterpenoid hydrocarbones		4.0
α-Thujene		2.4
α-Pinene	928	1.2
Sabinene	935	1.4
B-pinne	975	1.3
Myrcen	979	0.4
α-Phellandrene	992	0.6
p-Cymene	1007	14.8
Limonene	1026	4.3
γ-Terpinene	1030	0.5
	1059	
Monoterpenoid hydrocarbons		26.9
Fenchone		1.1
Dihydrocarvone	1097	0.3
Carvone	1206	4.0
Thymoquinone	1245	0.6
Monoterpenoid ketones	1251	6.0
		0.7
Terpinen-4-ol		0.4
p-Cymene-8-ol	1179	1.6
Carvacrol	1186	
Monoterpenoid alcohols	1302	2.7
		0.3
α-Longipinene	1353	0.7
Longifolene	1408	1.0
Sesquiterpenoid hydrocarbons		
		1.9
Estragole	1200	1.7
Anisaldehyde	1255	38.3
trans-Anethole	1289	1.4
Myristicin	1523	1.8
Dill apiole	1627	1.0
Apiole	1684	46.1
Phenyl propanoid compounds		
Total compounds		86.7%

Physiological Effects of N. sativa and its Component TQ:

The oil extract of black seed has been shown to exert effects on various systems including the respiratory, cardiovascular, gastric and uterine and smooth muscle. The effects of intravenous administration of volatile oil and of TQ were investigated on the respiratory system of the guinea pig. The latter compounds were found to increase the intratracheal pressure in the dose range of 4–32 ml/kg and 1.6–6.4mg/kg, respectively. Although *N.sativa* oil (NSO) significantly increased the discovery and new trends respiratory rate of guinea pigs, TQ was without any effect. The effects of NSO were significantly antagonized by treatment of the animals with antihistamines such as atropine and reserpine, suggesting that the oil-induced respiratory effects were mediated via the release of histamine and indirect activation of muscarinic and cholinergic mechanisms. This also suggested that the removal of TQ from black seed oil might provide a potential centrally acting respiratory stimulant (El-Tahir *et al*., 1993a). This same group demonstrated that the intravenous administration of NSO (4–32 ml/kg) or TQ (0.2–1.6mg/kg) to rats decreased the arterial blood pressure and the heart rate in a dose-dependent manner (El Tahir *et al*., 1993b) suggesting that the oil may possess antihypertensive effects. The cardiovascular depressant effects of the oil were significantly antagonized by atropine and cyproheptadine, suggesting that these effects were mediated mainly centrally via indirect and direct mechanisms that involved both 5-hydroxy tryptaminergic and muscarinic mechanisms (Hamdy and Taha, 2009).

NSO has also been shown to increase bile secretion in dogs and uric acid in rats as well as protect guinea pigs against histamine-induced bronchospasm (El-Dakhakhany *et al*., 2002). The fatty and petroleum extracts shortened bleeding time and inhibited fibrinolytic activity in rabbits. In a recent study, the crude extract of *N.sativa* seeds was found to exhibit spasmolytic and bronchodilator activities mediated possibly through calcium channel blockade and this activity was concentrated in the organic fraction of the extract (Gilani *et al*., 2001). Traditionally *N.sativa* plant has been in use in many Middle Eastern countries as a natural remedy for diabetes. Significant reduction in blood glucose and cholesterol levels in humans following the use of the plant

was reported. The oil of this plant has a great potential in the treatment of diabetic animals because of its combined hypoglycemic (Zaoui *et al*., 2002) and immunopotentiating properties (Haq *et al*., 1999). A plant extract mixture comprising *N.sativa*, myrrh, gum Olibanum, gum asafetida and aloe was found to lower blood glucose in streptozotocin diabetic rats. In an attempt to elucidate the mechanism of this antidiabetic action, the rate of gluconeogenesis in isolated hepatocytes as well as the activity of pyruvate carboxylase and phosphoenol pyruvate carboxykinase in rat liver homogenates was examined. It was found that the plant extracts significantly decreased hepatic gluconeogenesis, suggesting that it may prove to be a useful therapeutic agent in the treatment of non-insulin-dependent diabetes mellitus.

Similar insulin tropic effects of NSO were recently observed in streptozotocin plus nicotinamide-induced diabetes mellitus in hamsters (a model of type 2 diabetes) orally fed with the oil (Fararh *et al*., 2002). In this study, positive immune reactivity for the presence of insulin was observed in the pancreases from oil-treated vs. non-treated hamsters using immune histochemical staining, suggesting that the hypoglycemic effect of NSO resulted, partly, from a stimulatory effect on beta cell function with consequent increase in serum insulin level. The ability of NSO to lower blood glucose concentrations was later confirmed in streptozotocin diabetic rats following 2, 4 or 6weeks of treatment (El-Dakhakhny *et al*., 2002). In addition, the effects of NSO, nigellone and TQ were studied on insulin secretion of isolated rat pancreatic islets. The blood glucose-lowering effect of NSO was not paralleled by a stimulation of insulin release. The data indicated that the hypoglycemic effect of NSO might be mediated by extrapancreatic actions, to be elucidated, rather than by stimulated insulin release (El-Dakhakhny *et al*., 2002). The medicinal potential of black seed (*Nigella sativa*) 137 in many Arab countries *N. sativa* and its derived products are consumed abusively for traditional treatment of blood homeostasis abnormalities and as a treatment for dyslipidemia (Zaoui *et al*., 2002). Several studies support the use of NSO extract for the treatment of thrombosis and dyslipidemia (Zaoui *et al*., 2002). The purified components (2-methoxypropyl-5-methyl- 1, 4-benzenediol, thymol and carvacrol) obtained from the methanol-soluble portion of NSO showed inhibitory effects on arachidonic acid-induced platelet aggregation and blood coagulation.

Interestingly, some aromatic compounds present in the extract were found to be more potent than aspirin, which is well known as a remedy for thrombosis (Enomoto *et al*., 2001). In addition, an aqueous suspension of *N. sativa* seeds was found to decrease the serum total lipids and body weight in Psammomys obesus sand rat. Analogous results, accompanied by decreases in serum lipid levels have also been observed in rats chronically treated with *N. sativa* fixed oil (Zaoui *et al*., 2002). Animals were treated daily with an oral dose of 1 ml/kg body weight of the *N.sativa* seed fixed oil for 12 weeks. The serum cholesterol, triglycerides and the count of leukocytes and platelets decreased significantly by15.5%, 22%, 35% and 32%, respectively, compared to the control values. Haematocrit and hemoglobin levels increased significantly by 6.4% and 17.4%, respectively (Zaoui *et al*., 2002), suggesting that the oil influences blood homeostasis. *N.sativa* is also used in Arab folk medicine as a diuretic and hypertensive plant. In an attempt to experimentally support the above traditional uses of the plant, a study was conducted on the diuretic and hypertensive effects of the dichloromethane extract of *N.sativa* seeds in the spontaneously hypertensive rat.

An oral dose of either *N.sativa* extract (0.6mL/kg/day) or furosemide (5mg/kg/day) significantly increased diuresis by 16% and 30%, respectively, after 15 days of treatment. The urinary excretions of Cl^-, Na+, K+ and urea were also increased after 15 days of treatment. In the same rat study, a comparison between *N.sativa* and nifedipine found mean arterial pressure to be decreased by 22% and 18% in the *N.sativa* and nifedipine-treated rats, respectively, suggesting that *N.sativa* extract may play a role in decreasing blood pressure. Evidence indicates that NSO has a protective role against gastric ulcers (El-Dakhakhny *et al*., 2002).

Anticancer Effects of N. sativa:

The active principles in NSO have been found to exert antineoplastic effects both in vitro and in vivo using various models of carcinogenesis. Black seed preparations (TQ and TQ2) have been demonstrated to have significant antineoplastic activity against various tumor cells in vitro figure (2) (Jafri *et al*., 2010). The active principles of N.sativa showed 50% cytotoxicity against Ehrlich ascites carcinoma, Dalton's lymphoma ascites and Sarcoma-180 cells at a concentration of 1.5,3 and 1.5 mg, respectively, with little activity against lymphocytes (El-Najjar *et al*., 2010). In vitro cytotoxicity was also demonstrated against human pancreatic adenocarcinoma, uterine sarcoma and leukemic cell lines. The growth inhibitory activity was found to be related to the extract's ability to inhibit DNA synthesis as measured by the incorporation of tritiated thymidine into cells. These findings were later confirmed by (Worthen *et al*.1998) who assayed the in vitro cytotoxicity of a crude gum, a fixed oil and two purified components of *N.sativa* seed, TQ and TQ2, on several parental and multidrug resistant human tumor cell lines. Although as much as 1% w/v of the gum or oil was devoid of cytotoxicity, both TQ and TQ2 were cytotoxic for all of the tested cell lines(IC50: 78 to 393 mM). Interestingly, the multidrug resistant cell variants that are over 10-fold more resistant to the standard antineoplastic agents doxorubicin and etoposide were sensitive to TQ and TQ2 The ethyl acetate fraction of *N.sativa* seeds (identified as CC-5) was later found to exhibit significant growth inhibition on a variety of cancer cell lines without inhibiting the growth of normal human endothelial cells (Swamy and Tan, 2000). The ED50 values of the

extract showed increased sensitivity towards Hep G2, LL/2 and Molt4 cell lines compared with SW620 and J82 cell lines. Badary and Gamal El-Din, 2001 also showed that TQ inhibited the survival of fibrosarcoma cells with IC50 of 15 mM by inhibiting the incorporation of 3H thymidine into cells. The cellular mechanism of antineoplastic activity of TQ was only recently investigated (Shoieb *et al*., 2003). In this study, the cellular mechanisms of TQ-induced cytotoxicity in parental and cisplatin-resistant osteosarcoma human breast adenocarcinoma, human ovarian adenocarcinoma and Madin–Darby canine cell lines have been examined. The cisplatin-resistant cells were the most sensitive to TQ treatment, while the canine cell lines were the least sensitive. A dose of 25 mM of TQ induced apoptosis of osteosarcoma cells 6 h after treatment. This dose also decreased the number of cells in S-phase and increased cells in G1-phase, indicating cell cycle arrest at G1. These results suggest that TQ induces cell cycle arrest and apoptosis in cancer cells. Interestingly, non-cancerous cells are relatively resistant to the apoptotic effects of TQ (Shoieb *et al*., 2003).

The effect of CC-5 (ethyl acetate fraction of NSO) was evaluated for its in vivo antitumor activity against intraperitoneally implanted murine P388 leukemia and subcutaneously implanted Lewis lung carcinoma cells in BDF1 mice (Kumara and Huat, 2001). At doses of 200 and 400 mg/kg b.w., the fraction prolonged the life span of these mice by 153% compared to DMSO-treated control mice. The antitumor activity of a 21-day treatment of CC-5 against subcutaneously implanted LL/2 was tested and found to produce a 60–70% tumor inhibition rate. Atriterpene saponin was isolated from the CC-5 fraction and identified to be a-hederin. This compound was found to exert more potent anticancer effects compared to the commonly used anticancer drug, cyclophosphamide. When a-hederin was given i.p. at doses of 5 and 10 mg/kg b.w. to mice with formed tumors, it produced significant dose-dependent tumor inhibition rate values of 50% and 71%, respectively, on day 15, compared to 42% on day 15 in the cyclophosphamide (CP)-treated group. The underlying mechanism (s) of antitumor activity of a-hederin is not defined yet (Kumara and Huat, 2001). The protective effect of Nigella grains on carcinogenesis induced by methylnitrosourea in Sprague Dawley rats was investigated. When given orally (0.2 g ground Nigella grains) alone or with honey, a 6-month treatment reduced MNU-induced inflammatory reaction in lung and skin and MNU-induced colon adenocarcinomas by 80% (Mabrouk *et al*., 2002). There was an associated elevation of malondialdehyde and nitric oxide in sera obtained from methylnitrosourea-treated animals, which was lowered by ingestion of *N.sativa* grains. Interestingly, combined oral treatment of honey and *N.sativa* grains protected 100% against methylnitrosourea-induced oxidative stress, carcinogenesis and abolished the nitric oxide and malondialdehyde elevations shown in sera of animals that did not receive these nutrients (Mabrouk *et al*., 2002).

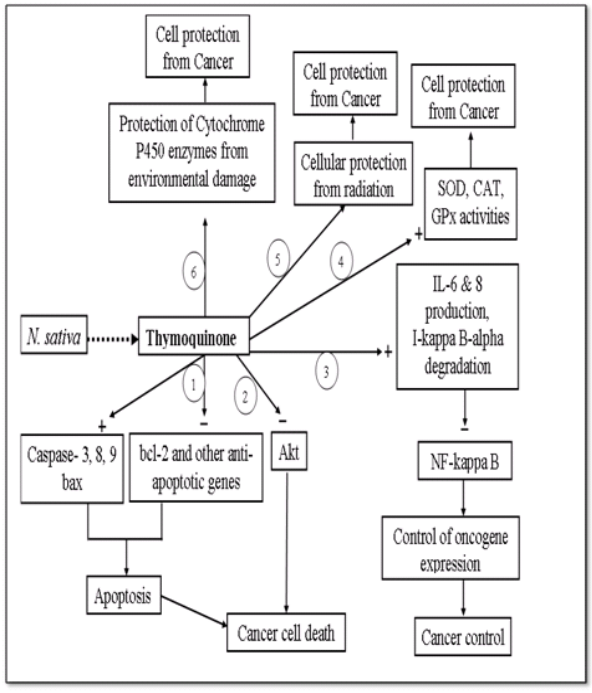


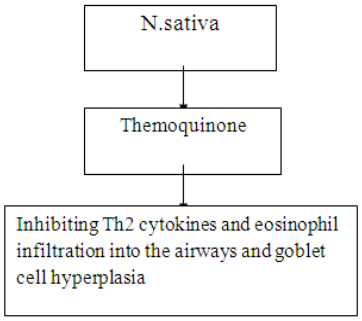
Fig. 2: Possible mechanisms of Thymoqunone (EL-Mahdy *et al*., 2005).

Antiinflammatory Effects of N. sativa:

N.sativa and its derived products have been traditionally used as a treatment for rheumatism, liver diseases and related inflammatory disorders. The effect of black seed on the immune system has been investigated by

several researchers (Al-Ghamdi, 2001). All studies have shown that the oil and its most abundant component, TQ, inhibit many inflammatory mediators, and, thus, may be useful in ameliorating inflammatory and autoimmune conditions.

In rat models of acute lung injury or acute respiratory distress syndrome, thymoquinone (6 mg/kg, administered intraperitoneally) was able to improve lung oxygenation while its coadministration with steroids (thymoquinone 6 mg/kg plus methylprednisolone 10 mg/kg, intraperitoneally) protected lung tissue from the hazardous effects of intratracheal instillation of human gastric juice (pH 1.2) (El Mezayen *et al*.,2006). The anti-inflammatory effects of thymoquinone was supported by its ability to attenuate allergic airway inflammation by inhibiting Th2 cytokines and eosinophil infiltration into the airways and goblet cell hyperplasia (Boskabady *et al*., 2004).



Attenuation of airway inflammation occurred concomitant to inhibition of COX-2 (cyclogenase) protein expression and prostaglandin D2production in a mouse model of allergic airway inflammation induced with ovalbumin (Boskabady *et al*., 2004). Aqueous and macerated extracts of *N.sativa* produced relaxant, anticholinergics (functional antagonism) and antihistaminic effects on guinea pig tracheal chains (Gilani *et al*., 2004). The relaxant effect of the extracts, however, was probably not associated with the calcium channel blocking effect of the herb as the extracts did not inhibit KCl-induced contraction of tracheal chains (Gilani *et al*., 2004).

Antioxidant Effects of N. sativa:

The antioxidant activity of N.sativa oil extracted using supercritical CO_2 as the solvent was dependent on thymoquinone and carvacrol but was only 0.14 of the activity of a-tocopherol (Thippeswamy *et al*., 2005). The antioxidant potency of a methanolic extract of *N.sativa* was found to be higher than the aqueous extract in soybean lipoxygenase and rat liver microsomal lipid peroxidation assays, and also in the DPPH assay. The phenolic content in both the methanolic and aqueous extracts was about 4.1 mg/g (Al-Saleh *et al*., 2006). Antioxidants present in *N.sativa* seeds include selenium, DL-a- and DL-g-tocopherol, all-trans retinol, thymoquinone and thymol with mean concentrations of 0.17,9.02,5.42,0.27, 2224.5 and 169.4 mg/kg fresh weight, respectively (Al-Saleh *et al*.,2006). *N.sativa* and thymoquinone partly protected rat gastric mucosa from acute ethanol-induced gastric mucosal damage, with the gastroprotection mediated by their antiperoxidative, antioxidant and antihistaminic effects (Kanter *et al*, .2006). Supplementation of the diet of rats fed oxidised corn oil with *N.sativa* led to an improvement in the overall antioxidant capacity as evidenced by a marked reduction in red blood cell hemolysis and plasma AST/ALT activities and a reduction in the formation of thiobarbituric acid reactive substances, indices of peroxiddative damag. The antioxidant effects are attributed to thymoquinone, a main constituent of the volatile oil of *N.sativa* (Al-Saleh *et al*, .2006).

Hepatoprotective Effects of N. sativa:

In an attempt to evaluate the hepatoprotective effects of TQ studied its ability to protect against oxidative stress caused by tert-butyl hydroperoxide in isolated rat hepatocytes and compared it to the effects of the known hepatoprotective agent silybin. The toxicity of tert-butyl hydroperoxide was manifested by the loss of cell viability and the progressive depletion of intracellular glutathione and leakage of cytosolic enzymes, alanine transaminase and aspartic transaminase in isolated rat hepatocytes treated with this compound (Ahmed *et al*., 2010). Preincubation of cells with 1mM of either TQ or silybin resulted in protection against tert-butyl hydroperoxide-induced toxicity as evidenced by decreased leakage of alanine transaminase and aspartic transaminase and increased cell viability. Silybin was slightly more potent in preventing loss of cell viability and enzyme leakage, but both compounds prevented tert-butyl hydroperoxide-induced depletion of glutathione to the same extent (Farrag *et al*., 2007).

It was shown that *N.sativa* seeds given orally every day for 2 months decreased the lipid peroxidation, increased the antioxidant defense system and prevented the lipid peroxidation-induced liver damage in experimentally induced diabetic rabbits (Uz *et al*., 2008) , suggesting that the seed may be used in diabetic patients to prevent lipid peroxidation.

Antimicrobial and Antiparasitic Effects of N. sativa Oil:

Several investigations have been directed towards N. sativa antibacterial properties (Suresh *et al*., 2010). The preliminary assessment of the in vitro antimicrobial effects of different germinating stages of N. sativa extracts revealed some basic outcomes in the present study. First, the methanol extracts of N. sativa showed good inhibitory effect against Gram-positive and Gram-negative clinical bacterial strains during germination phases as compared to seed extract, the extracts showed highest activity from 5th day to 11th day of germination (Islam *et al*., 2013).

The ethanolic extract of *N.sativa* was shown to have outstanding in vitro antibacterial activity against methicillin resistant and sensitive strains of Staphylococcus aureus (Dadgar *et al*., 2006). Salmonella thyphimurium was non-sensitive to the range of concentrations of the extract used in the study (25-400 µg/disc). The extract showed antibacterial synergism with streptomycin and gentamycin. In vivo studies showed that the diethyl ether extract successfully eradicated localized infections of S.aureus in mice (Nair *et al*., 2005). *N.sativa* oil may potentially be useful for inhibition of Listeria monocytogenes in food as it showed strong antibacterial activity against 20 strains of the bacteria with the oil producing inhibition zones that were significantly larger than that of gentamicin (Nair *et al*., 2005).

Conclusions:

The use of ethnobotanical drugs among Asians as complementary medicine is prevalent and is also gaining increasing popularity in the West. More than 25% of currently used drugs are derived directly from plants; while the other 25% are chemically altered natural products. Evidence indicates that *N.sativa* seeds have a potential medicinal value and are relatively safe to consume. Future research should focus on the mechanisms by which *N.sativa* seeds exert their medicinal effects. With the increased understanding of its mechanism of bioactivity, the incorporation of this medicinal herb as complementary medicine into mainstream medical science can be achieved in the future.

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