Saudi Journal of Biological Sciences (2016) **23**, 542–553

King Saud University

Saudi Journal of Biological Sciences

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Panacea seed "Nigella": A review focusing on regenerative effects for gastric ailments

Shahida A. Khan [a,1], Aziz M. Khan [a,1], Sajjad Karim [b,1], Mohammad Amjad Kamal [a], Ghazi A. Damanhouri [a], Zeenat Mirza [a,*]

[a] *King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia*
[b] *Center of Excellence in Genomic Medicine Research, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Saudi Arabia*

Received 26 August 2014; revised 1 October 2014; accepted 2 October 2014
Available online 13 October 2014

KEYWORDS

Gastric ulcer;
Gastropathies;
Gastro-protective;
Nigella sativa;
Medicinal plant

Abstract *Nigella sativa* (NS) or black cumin is a dark, thin, and crescent-shaped, seeded shrub belonging to the Ranunculaceae family commonly growing on Mediterranean coasts in Saudi Arabia, northern Africa and Asia. They have amazing curative and therapeutic features that make them one of the most popular, safe, non-detrimental, and cytoprotective medicinal plant that can be used for prevention and treatment of many complicated diseases. Originally, *N. sativa* was used to treat migraines and allergy, and researches have shown its effectiveness in destroying cancer cells as well. The gastro protective effect of NS oil and its constituents has also been reported earlier; however, the complete perception on etiology and pathogenesis of gastric ulcer is not yet clear. Herein, we attempt to unveil some of the potential mechanisms exhibited by NS in preventing problems related to gastric ulcers. Gastric ailments like ulcers and tumors are the most common disorders of the gastro-intestinal tract in the present day life of the industrialized world. Gastric

Abbreviations: NS, *Nigella sativa*; TQ, thymoquinone; PGs, prostaglandins; NSAIDs, non-steroidal anti-inflammatory drugs; PUFAs, polyunsaturated fatty acids; ROS, reactive oxygen species; GI, gastrointestinal; NF-κB, nuclear transcription factor kappa B; GSH, glutathione; LOX, lipoxygenase; COX, cyclooxygenase; 5-FU, 5-flourouracil.

* Corresponding author at: King Fahd Medical Research Center, King Abdulaziz University, Post Box No 80216, Jeddah 21589, Saudi Arabia. Tel.: +966 6401000x72074, mobile: +966 553017824; fax: +966 6952076.
E-mail addresses: zmirza1@kau.edu.sa, zeenat_mirza@rediffmail.com (Z. Mirza).

[1] Equal contribution and sharing first authorship.

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.sjbs.2014.10.001

ulcer being a multifaceted problem exhibits complex etiology and is the fourth most common cause of cancer mortality. Drug interactions and toxicity are the main hindrances in chemotherapy. The existing merits and demerits of modern-day drugs make us turn toward the plant kingdom which may provide a valuable resource of novel potent natural compounds for pharmaceuticals or alternately, as dietary supplements. In this context, the revered phytotherapeutic *N. sativa* comes as a promising savior in today's times. This review aims to summarize, both the functional and disease-related effects in the area of gastroenterology.

1. Introduction

Nigella sativa (NS), a medicinal and nutritional plant, became the focus of interest among modern day researchers from Chemistry, Biology, Agriculture, Pharmacology and Medical Sciences since 1970s. However, the Ayurvedic, Unani and Herbal Medicine practitioners were extensively using NS since hundreds of years for ailments ranging from a simple headache to disorders like diabetes, hypertension, gastrointestinal problems, menstruation and lactation (Al-Rowais, 2002; Salem, 2005).

NS, a member of Ranunculaceae family growing on the Mediterranean coasts, is a short 8–12 inch high annual herb, with pinnate segmented leaves. The blue and white flowers are solitary, self pollinating and form a fruit capsule consisting of trigonal seeds. Presently, these seeds due to its pepper oregano like taste are generally used as a seasoning in cuisines world over. Additionally they have significant medicinal benefits, making it one of the most cherished medicinal spices (Fallah Huseini et al., 2011). Arabs considered it as 'Habbatul Barakah' or the blessed seed (Al-Rowais, 2002). Metabolites of *N. sativa* seeds possess myriad of potent therapeutic features for the immune, cardiovascular, respiratory, gastric and endocrinal health (Ahmad et al., 2013; Gilani et al., 2001). The black cumin seeds contain more than 100 chemical compounds, a number of them are yet to be characterized. The phyto-components of NS seeds include nigellone, thymoquinone, phytosterols, fatty acids, vitamins, and minerals (Boseila and Messalam, 2011). The composition and yield of its essential oils differ depending upon geographical conditions as well as the varied hydrodistillation methods employed for oil extraction. Primary components of the essential oil are monoterpenes (87.7%) like *p*-cymene, carvacrol, α-thujene, γ-terpinene, α-pinene and β-pinene and its oxygenated derivatives (9.9%), rest being sesquiterpenes and derivatives (Wajs et al., 2008).

Gastric ulcer, one of the most prevalent ailments, is due to an imbalance between the aggressive and defensive mechanisms (Alkofahi and Atta, 1999). The gastric mucosa is constantly exposed to harmful agents such as drugs, pepsin, gastric acid, bile acids, microbial antigens like *Helicobacter pylori* (*H. pylori*), Epstein Barr virus and food ingredients (Peskar and Maricic, 1998). These causative factors have been associated with the pathogenesis of gastric ulcerations by means of pronounced gastric acidity, increased inflammatory markers and cell proliferation along with reduced gastric motility and gastric blood flow (Toma et al., 2005). Gastric irritants like ethanol are also known to induce contraction of the fundic strip circular muscles in rats, causing musculo-compression. Such a stress at the mucosal fold crests progresses toward ulceration and necrotic effects (Abdulla et al., 2010). Treatment of peptic ulcers either counteracts aggressive factors like pepsin, acid, active oxidants, leukotrienes, platelet aggravating factor, endothelins, bile and exogenous factors including non-steroidal anti-inflammatory drugs (NSAIDs) or stimulates the mucosal defenses like normal blood circulation and production of mucus, prostaglandins (PGs), nitric oxide and bicarbonate (Borrelli and Izzo, 2000). An imbalance of harmful and protective factors leads to gastric ulcers. Stress is a prime factor in the pathogenesis of gastric ulcers, wherein neutrophil infiltration (Abdallah et al., 2009), pepsin (Kotani et al., 2007), secretion of gastric acid (Tanaka et al., 2002) and formation of lipid peroxidation products, nitric oxide and redox imbalance (El-Abhar et al., 2003) are the main parameters implicated. The gastric lesions produced are healed by antioxidants (Yoshikawa et al., 1991, 1989), proton pump inhibitors and drugs lowering gastric secretion (Kitano et al., 2006). Treating peptic ulcer involves relief from pain and acidity, ulcer healing and recurrence prevention. Currently, no economically feasible treatment meeting all these goals exists. Many over the counter drugs, claiming to give relief are introduced overnight and then also hurriedly withdrawn on findings of serious side effects. Under these circumstances a tried and tested remedy over centuries can be far more safely relied upon. Hence, majority of the people around the globe rely on natural remedies. Spices such as NS, oregano, black pepper, fennel, clove, cinnamon, fenugreek, turmeric, and ginger contain potential anti-oxidative phytoconstituents (Adhikari et al., 2007). Herbs like galanga, pepper, cloves, turmeric, and cardamom have been favorably researched for their anti-ulcer effects (Al-Mofleh et al., 2006; Al-Moflehi et al., 2005; Al-Yahya et al., 1990; Al Mofleh et al., 2008; Alhaider et al., 2005a,b; Rafatullah et al., 1995, 1990).

Due to limitation of scientific investigation and resource dependency, socio-economic factors, religious faith, and ancestral experience, locally available spices and herbal medicine were considered as a central part of traditional complementary medicine. However, effective practice and result oriented usage over a long period of time have established the efficacy of many cheap and easily available specific flora for the treatment of various ailments. Spices contain anticancer potential in addition to their anti-ulcerogenic activity which is likely due to the anti oxidative action of their different phytoconstituents (Mothana et al., 2009; Shan et al., 2005). The antioxidant and scavenging ability of reactive oxygen species (ROS) intercedes gastro-protection.

This review aims to elaborate our present pharmacological and toxicological knowledge of the actions of this plant in specific context to gastric ulcers. We hope to produce a clinical appraisal and evaluation of its efficacy in the treatment of gastric ailments, due to the different properties exhibited by

the seeds and oil. The review systematically analyzes and documents the complementary scientific knowledge for later generations who may have not known the benefits of the long standing usage and practice of natural remedies. It also corrects the misunderstanding of such people who are misled by the pharmaceutical trade and medicine in declining the usage of NS on account of lack of scientific validation in gastric pathophysiology.

2. Chemical constituents of *N. sativa*

NS oil is dark yellowish in color containing thymoquinone, carvone, D-limonene, melanthin, tannins, *p*-cymene, α-pinene, thymol, dithymoquinone, thymohydroquinone and alkaloids (nigelline-*N*-oxide, nigellone, and nigellimine). The oil content of NS seeds ranges from 0.1% to 1.5%, depending on extraction method and distillation duration. A high quantity of unsaturated fatty acids (74.4–82.5%), comprising arachidonic, eicosadienoic, oleic, linoleic and linolenic acid and a lesser extent of saturated fatty acids (14.9–17.3%) were noted in its oil as well (Al-Jassir, 1992; Boseila and Messalam, 2011). The constituents of the black seed, nigellone, thymoquinone and numerous unsaturated fatty acid esters with terpene alcohols, make it an immune system booster. However, toxic property of melanthin in large doses and paralytic effect of nigelline have been alerted to be used in moderation.

3. *N. sativa*: a potential medicinal candidate for various ailments

NS is one of the most promising curative herbs with a lot of folklore, and traditional therapeutic applications worldwide and more so in the Arab world (Al-Rowais, 2002) (Fig. 1). It has been known to retard the progression of many chronic diseases (Ragheb et al., 2009). NS seeds and oil extract have been known to be positively implicated in allergy, diabetes, cardiovascular problems like hypertension and hyperlipidemia, gastro-intestinal problems, inflammatory and oxidative damage processes. Its antihistaminic, antioxidative and immunomodulator properties cover a wide range of degenerative health problems (Fallah Huseini et al., 2011) apart from few recent reports of its anti-viral properties against HIV and Hepatitis C (Barakat et al., 2013; Onifade et al., 2013). Low toxicity and antioxidant properties of NS leading to free radical quenching make it a potential candidate drug for inflammatory as well as stress related disorders (Bylka, 2009; Hasani-Ranjbar et al., 2009). The natural antioxidant potential of this seed is evident by the phenols, phospholipids, phytosterols and tocopherols present in them. Radical scavenging activity of the oil fractions toward stable galvinoxyl and 1,1-diphenyl-2-picrylhydrazyl radical showed that the phospholipids possess greater free radical scavenging activity as compared to glycolipids and neutral lipids (Ramadan et al., 2003). NS is an extremely potential herbal source for the development of pharmaceutical products and drugs against a number of pathological conditions relating to oxidative damage. Though thymoquinone is the main bioactive compound of NS, other compounds like alkaloids, phytosterols, flavonoids, carotene, and saponins do contribute their bit toward the immense benefits this seed possesses.

Mechanisms involved in the damage and repair of the gastro-intestinal tract could help to develop new therapeutic approaches to the problems envisaged. Experiments conducted by Sabikhi et al. suggest that oils rich in α-linolenic acid and γ-linolenic acid exhibit both antisecretory and anti-ulcerogenic properties (Sabikhi and Sathish Kumar, 2012). Gastric lesions seem to be reduced and gastric microcirculation increased, showing that the bioactivity of NS stretches from its antioxidant property to being anti-ulcerative and cytoprotective (Zayachkivska et al., 2004). Cancer cell development, growth and proliferation are important aspects in carcinogenesis. Cell cycle regulatory protein expression, and/or activity seem to be affected by NS leading to apoptosis, and DNA damage (Gali-Muhtasib et al., 2004).

Effective healing, protection and repair of gastric damage with the use of NS probably are due to its antioxidant, antihistaminic and antiperoxidative actions (Kanter et al., 2006) (see Table 1). We have listed numerous pharmacological properties of NS applicable to various diseases; however this article will focus on its potential effects on gastric acidity, and properties of its ingredients as anti-microbial, anti-inflammatory, antioxidant, anti-histaminic, immunopharmacological and immunomodulatory aspects in gastric ulcers/cancer.

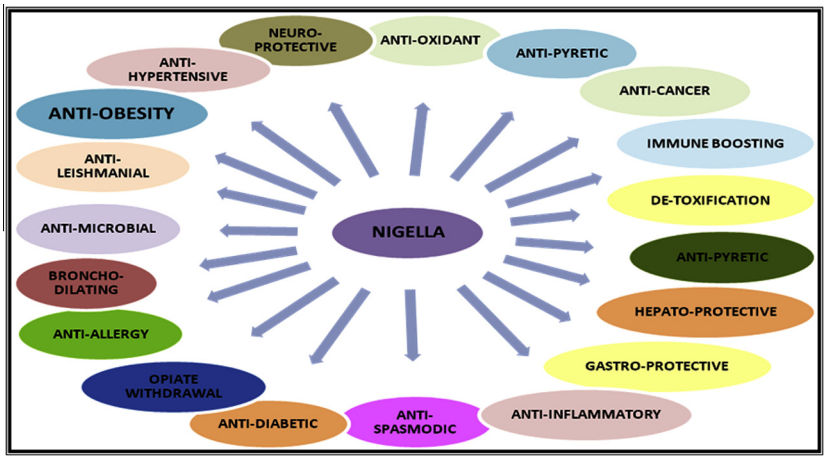

Figure 1 Medicinal importance and potential applications of *Nigella sativa*.

Table 1 Protective effects of the active constituents of Nigella on gastric pathophysiology.

Active constituent	References	Proposed mechanism of action
Thymoquinone (30–48%)	Ahmad et al. (2013)	Cytoprotection, hydroxyl radical scavenging activity, inhibition of LPO, anti-inflammatory, immune boosting, digestive and carminative
Carvacrol, carvone, D-limonene, melanthin, tannins, *p*-cymene, α-pinene, thymol, dithymoquinone and thymohydroquinone	Ahmad et al. (2013)	Hydroxyl radical scavenging activity
Alkaloids: nigelline-*N*-oxide, nigellone, nigellimine	Ahmad et al. (2013)	Anti-histamine
Saponin, triterpene-alpha-hederin	Ahmad et al. (2013)	Anticancer and anti-leishmanial property
Total fat (28.5%)	Ahmad et al. (2013) and	Anti-inflammatory, immune boosting, skin moisture balancer
Fatty acids: saturated (30%)-myristic acid, palmitic acid, stearic acid	Ramadan and Morsel (2002)	
Unsaturated (70%)-oleic (20–24%), linoleic acid (50 – 60%), linolenic acid (0.83–2.38%), eicosadienoic acid (3%), arachidonic acid, dihomolinoleic acid (10%)		
Flavonoids	Badary et al. (2003) and Merfort et al. (1997)	Superoxide anion scavenging activity
Phenols, vanillic acid (0.143%)	Shan et al. (2005)	Antioxidant and antimutagenic activity
Phytosterols (1.9–2.8%): α-sitosterol (44–54% of total sterols), stigmasterol (6.57–20.92% of total sterols)	Ahmad et al. (2013), Heese-Peck et al. (2002) and Matthaus and Özcan (2011)	Yeast endocytosis
α, β and γ-tocopherols (0.009–0.027%)	Matthaus and Özcan (2011)	Antioxidant, immune boosting
Vitamins: carotene, vitamin B1, vitamin B2, vitamin B3, folic acid	Ahmad et al. (2013)	Free radical scavenger and primary antioxidant, immune boosting
Minerals: calcium, iron, copper, zinc, and phosphorous (1.79–3.4%)	Bassim Atta (2003)	Chelating action, inhibition of free radical generations by stabilization of transition metals, thereby reducing free radical damage

3.1. Effect of N. sativa on gastric acidity

Gastric acidity is an important indicative factor for gastro-intestinal damage. Experiments show that the volume of gastric acid produced determines the permeability of the gastric-mucosal wall which triggers and accelerates the development of ulcers (Money et al., 1986). Inhibition of acid production by NS may well maintain the permeability of the gastric mucosal membrane and help reduce the formation of gastric ulcers. Lowering of gastric acidity by NS and increase in the gastric mucosal content act as a potential defensive factor against the gastric damage and ulceration (Swarnakar et al., 2005). Reduced gastric surfaces exhibiting ulcerations, suppression of edema and infiltration of leucocytes on the sub-mucosal layer have been observed in the NS treated group as compared to the controls. Pre-treatments with NS have shown to exhibit a preventive action against gastro-intestinal damage and ulcerogenic acceleration. Also neutralization of the acid content in the stomach may well be reasoned enough for speeding up the healing of gastric ulcers (Abdel-Sater, 2009).

NS exhibits a gastroprotective effect, which might be because of reduced concentration of acid secretion. The curative action of thymoquinone on acute gastric damage induced by ethanol in rats has been shown in studies done by Arslan et al. (Arslan et al., 2005). Recent results of *in vitro* experiments done by Ahmet and colleagues show that dose of 2 mg/100 ml DMSO and 5 mg/100 ml DMSO of NS aqueous extracts decreases histamine stimulated gastric acid secretion. A 5 mg/100 ml DMSO of NS aqueous extract also lessened bethanechol stimulated gastric acid secretion, but none of the NS doses seemed to affect pentagastrin-induced acid secretion. Antisecretory studies with NS show noteworthy reduction in acidity, pepsin content as well as ulcer index (Topal and Celebi, 2011). Up regulation of gastric mucosal secretion is also observed after NS administration. Gastric mucosal production which is one of the defensive factors against gastric ulcer formation is increased by NS (Mahmood et al., 2011; Wasman et al., 2010), thus making NS a strong anti-ulcerous compound.

3.2. Anti-microbial effects of N. sativa on gastric ulcers

NS seed extract has been shown to possess anti-microbial activity against *Staphylococcus aureus, Escherichia coli, Proteus vulgaris,* and *Candida albicans*. Its essential oils act more against gram-positive bacteria than the gram-negative ones. NS essential oil has a higher antibacterial activity compared to tetracycline, cefuroxime, and ciprofloxacin and stronger antifungal properties in contrast to clotrimazole (Haloci et al., 2012). The use of natural therapeutic products will probably not bring forth resistance in microorganisms as compared to the common menace of antibiotic resistance.

Diseases like peptic ulcer, gastric cancer and chronic gastritis are ascribed to *H. pylori*. Though antimicrobial agents could successfully remove *H. pylori* infection it could also lead to regression of disorders associated with *H. pylori*. *H. pylori* is increasingly turning antibiotic resistant, making it necessary to research out novel effective agents. NS possesses *in vitro* anti-helicobacter activity comparable to triple therapy (Salem et al., 2010). The antibacterial activity of the phenolic component of NS oil was first reported by Toppozada in 1965 (Toppozada

et al., 1965). NS also produces synergistic and additive effects with several antibiotics *in vitro*. Diethyl-ether extract of NS inhibits both gram-positive and gram-negative bacteria, as well as pathogenic yeast (Hanafy and Hatem, 1991) and has a promising effect on multi-drug resistant organisms (Morsi, 2000). In an *in vitro* experiment, NS extract produced a 100% growth inhibition of all the *H. pylori* strains that were tested within 60 min (O'Mahony et al., 2005). It is therefore likely that a combination of NS with antibiotics will reduce the possibility of emergence of resistant *H. pylori* colonies thereby improving the antibiotic efficacy.

3.3. Anti-inflammatory properties

Interventions in pathways of inflammation have been known to possibly delay cancer development and progression thereby improving patient life quality. Compounds like PGs and leukotrienes (LT) are well known as inflammatory mediators (Brzozowski et al., 2005; Christie and Henderson, 2002). NS is known to possess approximately 78.4% total unsaturated fatty acids namely linoleic acid (52.6%), alpha-linolenic acid (0.83–2.38%), oleic acid (23.5%) and cis-11, 14-eicosadienoic acid (1.2–3.1%) (Ali et al., 2012; Nickavar et al., 2003). Dietary lipids enriched with omega-3 fatty acids, a derivative of polyunsaturated fatty acids (PUFAs), are known to possess anti-inflammatory properties and increase membrane permeability of the mucosal barrier (Grant et al., 1988). Earlier researches have also shown the association of PUFAs with gastric and duodenal ulcers as well as *H. pylori* growth (Frieri et al., 1995). Release of PUFAs from the injured mucous cell membrane has been shown to competitively inhibit the pro-inflammatory cytokines and tumor necrosis factor α (Ciacci et al., 1993). Oral doses of PUFAs have been shown to exhibit bacteriostatic effects on *H. pylori*, though higher doses could prove bactericidal (Knapp and Melly, 1986; Thompson et al., 1990; Thompson and Spiller, 1995). Dosage and time period of supplementation of PUFAs could be instrumental in exhibiting its activity. Thus the presence of PUFAs and TQ in NS oils makes it a powerful anti-inflammatory compound by inhibiting the synthesis of inflammatory cytokines (Mori and Beilin, 2004; Wallace, 2005) namely leukotrienes and thromboxanes by inhibiting the lipoxygenase (LOX) and cyclooxygenase (COX) activities (Houghton et al., 1995). The inflammatory LOX cascade plays a vital role in the gastric ulcers induced by irritants such as alcohol (Lange et al., 1985). Production of 5-hydroxy-eicosatetraenaoic and 5-LOX that are important for the cancer cell viability is inhibited by NS (El-Dakhakhny et al., 2002). Therefore, inhibition of 5-LOX enzyme could well be an approach toward apoptosis (Hoque et al., 2005). Reduced production of leukotrienes by TQ increases its potential in making NS an important candidate in anti-inflammation (Padhye et al., 2008).

Restitution of the gastro-intestinal lining has been found to be influenced by PUFAs (Ruthig and Meckling-Gill, 1999, 2002). The fixed oil exhibits anti-inflammatory properties greater than a NS active TQ constituent illustrating that synergetic property and effects of other phytochemicals, also have a significant role in the anti-inflammatory cascade. TQ was found to significantly inhibit production of interleukins IL-5 and IL-13 mRNA expression but not IL-10 production in various studies (El Gazzar, 2007; El Gazzar et al., 2007). The nuclear transcription factor kappa B (NF-κB) is now being looked upon as an important mediator of inflammation. Suppression or alteration in the NF-κB dimers, signals the onset of a pathological condition. Activation of the redox sensitive NF-κB, stimulates the expression of different enzymes, cytokines and intermediary compounds related to the inflammatory cascade (Sayed and Morcos, 2007). Therefore the proper activation and expression of NF-κB decide the pathological condition of a particular disease. Apart from other diseases, NF-κB pathway is also elemental in inflammatory bowel disease and other inflammatory conditions of the gastro-intestinal system (Aggarwal et al., 2011). TQ also has been shown to down regulate NF-κB dependant antiapoptotic genes, NF-κB and the bcl2 family (Rajkapoor et al., 2002). NS exhibiting potent anti-inflammatory properties could well inhibit NF-κB thereby reducing the chronic inflammation and prevents or delays the onset of chronic health problems (Aggarwal et al., 2011; Sethi et al., 2008).

3.4. Anti-oxidative properties of N. sativa

Oxidative stress is a key factor in gastric ulcer pathogenesis, and antioxidants offer gastric mucosal protection against different agents causing necrosis (Pathak et al., 2005; Trivedi and Rawal, 2001). NSAID's, bile acids and alcohol reduce the protective barrier and increase the hydrogen ion H^+ back diffusion and thereby augments susceptibility to ulcers (Al Mofleh, 2010). Several epidemiological studies show a direct correlation of increased antioxidant intakes with decreased risk of cancer (Borek, 2004). NS is a powerhouse of antioxidants and contains compounds aiding the inhibition of gastric secretion. The antioxidant properties in NS not only depend on the composition of phenolic compounds in the seed variety, but also other conditions of growth and processing (Skrovankova et al., 2012). The plant extract of NS exhibits gastro protective activities by strengthening the mucosal barrier and withstanding endogenous as well as exogenous ulcerogenic agents probably due to its antioxidant activity (Meral et al., 2001). Flavonoids present in NS (Merfort et al., 1997) may be responsible for the antiulcerative effects (Zayachkivska et al., 2004, 2005), and thereby offer gastroprotection (La Casa et al., 2000). Flavonoids in NS stimulate the gastric mucus and help strengthen the mucosal immune defense system by scavenging superoxide and hydroxyl free radicals (Badary et al., 2003; Kruk et al., 2000; Mansour et al., 2002). Various components in the oil or seed extract have been found to act synergistically thereby increasing their antioxidant capacity as well as usage in the pharmaceutical industry (Ali and Blunden, 2003).

Antioxidant status in plasma along with the cellular structure and function of membrane is restored by effectively reducing the concentrations of plasma lipid peroxidation markers like malondialdehyde, conjugated diene, and lipid hydroperoxide, thus making thymoquinone (TQ) a potent food additive against free radical damage. TQ has been shown to inhibit carcinogenesis by decreasing lipid peroxidation and increasing the cellular antioxidant capacity (Badary et al., 2007).

Non-enzymatic inhibition of lipid peroxidation has been observed with TQ as well as the whole oil (Houghton et al., 1995). Kanter and colleagues studied the gastro-protective effect of NS oil in chemically induced gastric ulcers in rats (Kanter et al., 2003, 2005). 1 ml/kg dose of volatile *NS* oil

given to rats one hour prior to the induction of gastric ulcers with ethanol considerably protected the animals. Also significant elevation in the gastric glutathione (GSH), superoxidase dismutase and the glutathione-S-transferase activities along with major reductions in alcohol-induced lipid peroxidation in the gastric mucosal cells was observed. Supplementation studies with NS, resulted in an increase in the antioxidant GSH levels thereby accelerating the gastric healing process (Shen, 1979). Even reduced dosages of raw NS at 0.25 g/kg showed considerable improvement in the ulcer healing. Depletion of GSH, a very potent antioxidant and component for gastric mucosal protection results in the mucosal damage. NS oil in low concentrations has been shown to suppress the formation of lipid peroxide and lactate dehydrogenase and increase the availability of superoxide dismutase and GSH, simultaneously decreasing lipid peroxidation and free radical generation (Houghton et al., 1995; Mansour, 2000; Wada et al., 1995, 1997). NS has a vital function in electron transfer and oxygen activation with TQ having the potential to be used in free radical related disorders. TQ can effectively quench superoxide anion radical ($O^{\bullet -2}$) and hydroxyl radical ($HO^{\bullet}$) (Kruk et al., 2000). Moreover total antioxidant enzyme levels can be normalized by modulating the levels of glutathione reductase, reduced GSH, glutathione-S-transferase, glutathione peroxidase, superoxide dismutase, catalase, and erythrocyte membrane-linked ATPases (Ahmad and Beg, 2013). These gastro-protective effects of NS are observed in the raw state, but not when the seed or oil is boiled due to possible alterations in the chemical composition (Bastaki et al., 2011).

Non-enzymatic reactions of GSH with reduced forms of NADPH and NADH result in the rapid formation of glutathionyl-dihydro-thymoquinone and a slower formation of dihydro-thymoquinone (DHTQ). The combination of these two renders them as free radical scavengers possibly more powerful than TQ itself (Khalife and Lupidi, 2007). Total antioxidant activity of these reduced compounds against 2,2/-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) and 2,2-diphenyl-1-picrylhydrazyl (DPPH) showed scavenging effect of glutathionyl-dihydrothymoquinone quite similar to DHTQ. TQ on its own exhibited a slightly lesser scavenging potential (Padhye et al., 2008).

In vitro studies showed DPPH radical inhibition and ferric reducing capacity values to be 95.89% and 3.33 mmol/L Trolox, respectively with NS when compared to a few other essential oils like thyme, fennel and lavender (Viuda-Martos et al., 2011). The metabolite dihydrothymoquinone formed from TQ is also responsible for the various beneficial effects of NS (Mansour et al., 2002). Histological studies corroborate the beneficial effects by showing that TQ pretreated groups in the dose of 20 mg/kg helped maintain an intact cellular structure.

Clinical condition of methionine induced hyper-homocysteinemia was corrected by oral feeding of NS oil or TQ which protects by enhancing the antioxidant status and ameliorating the triglycerides, lipid peroxide and cholesterol concentration in plasma. Most recently, the antioxidant properties of the methanolic crude extract of NS seed cake were also investigated and some of the phenolic compounds such as syringic, hydroxybenzoic and *p*-coumaric acids were identified with significant antioxidant properties under *in vitro* systems (Shrivastava et al., 2011).

3.5. Anti-histaminic/anti allergic properties of *N. sativa*

Histamine is released by basophils and mast cells, producing allergic reactions associated with bronchial asthma, urticaria and food allergy. Increased numbers of mast cells are associated with gastric mucosal damage induced by the use of NSAIDs (Rioux and Wallace, 1996). The use of *NS* seeds and its active ingredients has a considerable effect on the histamine mediated inflammatory and gastric diseases. A low concentration of nigellone effectively inhibits histamine release from mast cells. Kanter et al. have shown that volatile oil therapy of NS and more so its constituent TQ, significantly reduced mast cell number and the gastric ulcerated lesions in ethanol-treated rats (Kanter et al., 2006). Myeloperoxidase activities and histamine levels were found to be amplified in ethanol treated rats, and NS or TQ treatment reversed this condition suggesting that NS could partly shield gastric mucosal lining from acute alcohol-induced damage. This gastroprotection can be attributed to their antioxidant, antihistaminic and anti-peroxidative effects. Stimulation process of gastric secretion through histamine is suppressed with NS. This was supported by the experiments with *NS* oil exhibiting an increase in concentrations of mucin and glutathione transferase with a simultaneous decline in the mucosal histamine concentrations (El-Dakhakhny et al., 2000).

Low concentration of nigellone effectively inhibits the histamine release from the mast cells, indicating an anti-asthmatic role. TQ dimer isolated from NS's volatile oil, 'Nigellone' suppressed symptoms when given orally to bronchial asthma patients with effective results without any toxicity (el-Dakhakhny, 1965). Administration of *N. sativa* oil to patients with allergic problems, like allergic rhinitis, atopic eczema, and bronchial asthma decreased the immunoglobulin E, and eosinophil count (Kalus et al., 2003), indicating NS oil effectiveness as adjuvant for treating allergic maladies. The anti-allergic feature of NS seed constituents is due to their anti-histaminic effects and this notion is duly supported by *in vitro* studies too. In another study on guinea pig by Boskabady and colleagues NS aqueous extract displays anti-histaminic and relaxant properties (Boskabady et al., 2004). The inhibitory outcome of nigellone on histamine release from rat peritoneal mast cells was shown to be mediated by diminishing intracellular calcium by the inhibition of protein kinase C, a substance known to prompt histamine release as a result of stimulation by various secretagogues and antigen sensitized cells (Chakravarty, 1993; Gilani et al., 2001). Moreover, TQ causes a concentration-dependent decrease in the tension of the guinea pig isolated tracheal smooth muscle precontracted by carbachol (Al-Majed et al., 2001). TQ totally eliminated the pressor effects of histamine and serotonin, suggesting inhibition effects mediated by lipoxygenase products of arachidonic acid production and possibly by non-selective blocking of the serotonin and histamine receptors. In ethanol induced gastric ulcer model a significant increase in mucosal histamine content was seen, but in rats pretreated with NS oil before ulcer induction it caused a considerable decline in gastric mucosal histamine content (El-Dakhakhny et al., 2000). Contrasting to the observed relaxant effect of TQ, a different study compared stimulative effect of TQ with the NS volatile oil on respiratory system of the urethane-anaesthetized guinea pig. The intratracheal pressure and the respiratory rate increased

by the intravenous administration of the NS oil in a dose-dependent manner mediated by histamine release with direct association of histaminergic mechanisms and indirect activation of muscarinic cholinergic methods (el Tahir et al., 1993). Alternatively, TQ administration significantly raises the intratracheal pressure without changes in the respiratory pace. Hence, it appears that special ingredients of NS oil possess diverse impacts on histamine release. The NS active ingredient nigellone acts as calcium channel blocker(s), explaining the complimentary therapeutic usage of NS toward asthma, diarrhea and hypertension.

Although Marozzi and colleagues reported a TQ-induced histamine enhancement in gastric ulcers induction, yet oral administration of TQ prior to alcohol intake protected the animals against alcohol-induced ulcers by approximately 38%. These antioxidant mechanisms involved an increase in the superoxide dismutase activity and reactive oxygen radical's inhibition (Marozzi et al., 1970; Tanaka et al., 2002). TQ thus exhibited a slightly lesser potential effect than that of the whole volatile oil (Kanter et al., 2003, 2005). TQ helps in retaining the NO content thereby suppressing histamine release and reducing gastric acid output (Marozzi et al., 1970). Peptic activity appears to be inhibited by the suppression of histamine release, propelling a decrease in the formation of pepsin from pepsinogens (Kanter et al., 2006). This acid influx is regulated by cGMP (Kato et al., 2009) and/or release of somatostatin from cells (Arebi et al., 2002).

3.6. Immunopharmacological and immunomodulatory functions of *N. sativa*

The gastric mucosal cells are protected by the gastric mucosal wall that prevents their exposure to exogenous and endogenous irritants and toxins (Zayachkivska et al., 2005). Insults to this layer precipitate in the development and progression of different gastric disorders like gastric ulcers, cancers and gastritis. Different flavonoids and antioxidants of plant origin possess the potential to contribute protection to the gastric system and hasten up the healing process. Anti-inflammatory properties of these compounds render help by downregulation of the cytokine cascade in the GI system (Alarcon de la Lastra et al., 1995). Suppression of cytokines promotes the presence of beneficial growth factors which support tissue repair and aid healing. These growth factors exhibit oxidant scavenging properties and also promote antioxidant activities required for repair of oxidative stress insults to the gastric mucosal lining (Liu et al., 2002; Pastrana-Bonilla et al., 2003). In addition growth factors are bestowed with anti carcinogenic and anti-nucleolytic, cytochrome P450 2F1 inhibitory activities (Bagchi et al., 2002; Kyogoku et al., 1979). Like many other herbs viz; Quercus, Swertia herb (Niiho et al., 2006), Chinese herbal drug "Baishouwu" (Shan et al., 2006), *Phyllanthus niruri* (Abdulla et al., 2010), several studies have shown NS also as gastroprotective. A two gram dose was found almost as effective as the traditional triple therapy in eradication of *H. pylori* in earlier researches (Salem et al., 2010).

The oil and seed ingredients particularly TQ, display prospective usage in traditional medicine and show valuable immunomodulatory properties by boosting the natural killer cell and T cell - mediated immune responses (Salem, 2005). Also the active ingredients illustrated anti-tumor and antimicrobial properties toward different cancers and microbes. The knowledge of potent immunomodulatory effects of TQ compels us to investigate TQ effects on the antigen presenting cells, and on the Th-1 and Th-2 (helper T-cells) mediated inflammatory immune diseases.

TQ exhibits gastroprotective mechanisms through neutrophil infiltration, acid secretion and proton pump inhibition. It also enhances nitric oxide production and mucin secretion (Magdy et al., 2012). Decreases in acid level mediated by TQ are due to normalization of proton pump activity, thereby inducing a decreased secretion of acid from the parietal cells. 20–50 μM concentration of TQ did not produce advanced glycation end products implicated in chronic disorders and exhibited toxic effects to platelet lactate dehydrogenase and plasma thiols thereby increasing its potential in various food applications (Losso et al., 2011).

Cell apoptosis and cell growth inhibitory properties of TQ have made this a potential molecule against various tumors. *In vitro* experiments show that TQ assumes an essential role in the sensitization, inhibition and augmentation of gastric tumor cells to apoptosis induced by 5-flourouracil (5-FU). This cell inhibition depends on dosage of TQ as well as incubation time. Western immunoblotting technique assessing protein expression levels revealed a lowered expression of bcl-2, increased expression of bax protein, enhanced caspase-3 and caspase-9 activity and efflux of cytochrome C into the cytosol. Therapeutic effects show that incubation with TQ prior to adding 5-FU or addition in conjunction could lead to the anti tumor effects of TQ. *In vivo* antitumor effects on xenograft mice using the terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL) assay showed that TQ in combination with 5-FU showed a comparatively larger number of apoptotic bodies as compared to the controls. Thus TQ triggers the apoptotic body formation and inhibits cell viability (Lei et al., 2012).

3.7. Toxicity studies of *N. sativa*

NS has been associated relatively with very low toxicity. A history of NS usage as food and medicine reports rare adverse effects following administration of the seeds within recommended dosages. Contact dermatitis in a couple of cases following extensive use of high doses for longer periods of topical use has been reported. As such no significant harmful side effects on any major organs and their functions has been observed and reported in earlier studies. Studies conducted on various aspects promote its safe usage in many inflammatory conditions with low incidence of side effects. Doses as high as 50–100 mg/kg have been shown to lower the GSH concentration drastically; resulting in lowered GSH content and a high mortality rate seen 24 h after reperfusion (El-Abhar et al., 2003). Smaller doses are therefore advisable for treatment purposes. Oral administration of the oil or seed formulation does not have any adverse effect on liver or kidney functions. Laboratory animal studies for acute chronic conditions have reported that NS, its oil and TQ, are also safe when given orally (Al-Ali et al., 2008; Badary et al., 1998; Mansour et al., 2001).

4. Discussion and conclusion

NS is a very prized plant used in folk medicine, affording protection against many ailments, one of them being gastro protection. Plant origin bioactive substances and their

functions help us in deciphering mechanisms of different GI tract injury-related diseases and open up new vistas in treatments. NS is a complex food additive with numerous components, some of which are contributory toward its anti-oxidant, anti-inflammatory, antimicrobial, cytoprotective and immunotherapeutic potential. Mediators of inflammation and oxidative stress seem to be targeted by this indigenous bioactive factor rich seed. The drive of today's health conscious man toward reducing risk of a particular disease has become the prime approach toward identifying foods with these enriched bioactive components and enhanced nutritional value. Polyphenols, flavonoids, bio-functional proteins and lipids along with many phytochemicals exhibiting various benefits, make NS a very potent functional food additive for gastro protection. Also its characteristic ability to exhibit the various benefits in aqueous, alcoholic as well as oil extracts makes it the supplemental food of choice for future therapeutics. Knowledge of their specific functions, mode of multiple and synergetic action, cascade in the cell metabolism would improve our utilization of functional food additives through scientific evidence.

Ulcer indices appear to be considerably reduced following pretreatment with NS exhibiting its preventing medicinal effects (Kanter et al., 2005). Changes in composition of fatty acids both *in vivo* and *in vitro* could alter membrane bound receptors, enzyme action and various mechanisms of transport involved. The antioxidant potential of NS is quite comparable to Trolox, a recognized antioxidant standard compound rendering it very beneficial in antioxidant therapy.

Mechanisms by which TQ protects the gastric system may be a combination of proton pump inhibition and retention of anti-oxidative enzymes. Proton pump inhibition by TQ appears to be a new property ascribed to it, which is instrumental in decreasing acid and pepsin production, and reducing neutrophil infiltration. Also TQ reduces the oxidative insults to the gastric system by increasing the enzyme antioxidant levels. Combination therapy utilizing the properties and benefits of NS as well as available drugs can make future therapeutics more acceptable to the common man (Magdy et al., 2012). Components of NS or their derivatives could well be utilized in different appropriate combinations for chemotherapy. NS rich in PUFAs has shown in conjunction with other unique chemical components, significant gastro protective benefits over centuries. This entails its re-look and re-emergence in leaps and bounds for the nutraceutical industry. NS can play a novel and significant role in the present restricted and skewed pharmaceutical health approach. Invariably, NS seed, its oil and extracts and its active ingredients, particularly TQ and α-hederin, possess remarkable *in vitro* and *in vivo* healing activities against different types of cancers; unfortunately in theoretical applications not yet in practice.

5. Future perspectives

Mechanism of NS action at the molecular level needs to be explored to understand the cellular, anti-inflammatory and immuno-modulatory effects. Damage limiting ability of NO released by NSAID's to the GI tract, makes NS a good candidate for combination therapy. Specific inhibitory effects with the different active components would clarify the unknown anti-inflammatory pathways by the way of modulation of COX1 or COX 2 enzymes. The role of 15-R-Lipoxin A4 and its analogs in gastro protection could have immense therapeutic value. Immuno-modulatory effects of shifts from the Th-1 pro-inflammatory type to the Th-2 anti-inflammatory type could well be investigated. Cytoprotection creating innate cell immunity and behavior of CD4 and CD8 T cells would pave learning of specific and non-specific inhibitory effects. Mechanism by which the gastric mucosa protects the GI tract against exogenous damage using proton pump inhibitors and specific cellular and molecular targets of the active components of NS should be identified as different diseases exhibit differently mediated pathways. Few studies show that platelets regulating proteinase activated receptors which in turn aid in releasing the protective growth factors for gastroprotection, may help in deciphering the mechanism of action. Nutritional strategies including food additives and combinations rich in omega-3 fats should therefore be promoted for an enhanced production of anti-inflammatory PG (Cleland et al., 1988). Drug designing studies similar to capsaicin, may elucidate role of NS-sensitive afferent nerves in gastro protection and promote ulcer healing. This reverse pharmacological approach by scientifically revalidating the ancient and neglected medical experience can reshape our outlook toward this invaluable but neglected herbal medicine. We hope this review article would offer a source of information to researchers in the field of gastric cancer and NS to plan and conduct their experiments as future studies on this subject are warranted.

Conflict of interest

The authors confirm that there is no conflict of interest for the information presented in this review.

Acknowledgements

Authors gratefully acknowledge the research facility provided by the King Fahd Medical Research Center (KFMRC) and Center of Excellence in Genomic Medicine Research (CEGMR), King Abdulaziz University (KAU), Jeddah, Saudi Arabia.

References

Abdallah, D.M., El-Abhar, H.S., Abdel-Aziz, D.H., 2009. TEMPOL, a membrane-permeable radical scavenger, attenuates gastric mucosal damage induced by ischemia/reperfusion: a key role for superoxide anion. Eur. J. Pharmacol. 603 (1–3), 93–97.

Abdel-Sater, K.A., 2009. Gastroprotective effects of *Nigella Sativa* oil on the formation of stress gastritis in hypothyroidal rats. Int. J. Physiol. Pathophysiol. Pharmacol. 1 (2), 143–149.

Abdulla, M., Ahmed, K.A.-A., Al-Bayaty, F.H., Masood, Y., 2010. Gastroprotective effect of *Phyllanthus niruri* leaf extract against ethanol-induced gastric mucosal injury in rats. Afr. J. Pharm. Pharmacol. 4 (5), 226–230.

Adhikari, S., Indira Priyadarsini, K., Mukherjee, T., 2007. Physico-chemical studies on the evaluation of the antioxidant activity of herbal extracts and active principles of some Indian medicinal plants. J. Clin. Biochem. Nutr. 40 (3), 174–183.

Aggarwal, B.B., Prasad, S., Reuter, S., Kannappan, R., Yadev, V.R., Park, B., Kim, J.H., Gupta, S.C., Phromnoi, K., Sundaram, C., Prasad, S., Chaturvedi, M.M., Sung, B., 2011. Identification of novel anti-inflammatory agents from Ayurvedic medicine for prevention of chronic diseases: "reverse pharmacology" and

"bedside to bench" approach. Curr. Drug Targets 12 (11), 1595–1653.
Ahmad, A., Husain, A., Mujeeb, M., Khan, S.A., Najmi, A.K., Siddique, N.A., Damanhouri, Z.A., Anwar, F., Kishore, K., 2013. A review on therapeutic potential of *Nigella sativa*: a miracle herb. Asian Pac. J. Trop. Biomed. 3 (5), 337–352.
Ahmad, S., Beg, Z.H., 2013. Alleviation of plasma, erythrocyte and liver lipidemic-oxidative stress by thymoquinone and limonene in atherogenic suspension fed rats. J. Funct. Foods 5 (1), 251–259.
Al-Ali, A., Alkhawajah, A.A., Randhawa, M.A., Shaikh, N.A., 2008. Oral and intraperitoneal LD50 of thymoquinone, an active principle of *Nigella sativa*, in mice and rats. J. Ayub Med. Coll. Abbottabad 20 (2), 25–27.
Al-Jassir, M.S., 1992. Chemical composition and microflora of black cumin (*Nigella sativa* L.) seeds growing in Saudi Arabia. Food Chem. 45 (4), 239–242.
Al-Majed, A.A., Daba, M.H., Asiri, Y.A., Al-Shabanah, O.A., Mostafa, A.A., El-Kashef, H.A., 2001. Thymoquinone-induced relaxation of guinea-pig isolated trachea. Res. Commun. Mol. Pathol. Pharmacol. 110 (5–6), 333–345.
Al-Mofleh, I.A., Alhaider, A.A., Mossa, J.S., Al-Sohaibani, M.O., Rafatullah, S., Qureshi, S., 2006. Protection of gastric mucosal damage by *Coriandrum sativum* L. pretreatment in Wistar albino rats. Environ. Toxicol. Pharmacol. 22 (1), 64–69.
Al-Moflehi, A., Alhaider, A., Mossa, J., Al-sohaibani, M., Rafatullah, S., Qureshi, S., 2005. Inhibition of gastric mucosal damage by *Piper nigrum* (Black pepper) pretreatment in Wistar albino rats. Pharmacogn. Mag. 1 (2), 64–68.
Al-Rowais, N.A., 2002. Herbal medicine in the treatment of diabetes mellitus. Saudi Med. J. 23 (11), 1327–1331.
Al-Yahya, M.A., Rafatullah, S., Mossa, J.S., Ageel, A.M., Al-Said, M.S., Tariq, M., 1990. Gastric antisecretory, antiulcer and cytoprotective properties of ethanolic extract of *Alpinia galanga* willd in rats. Phytother. Res. 4 (3), 112–114.
Al Mofleh, I.A., 2010. Spices, herbal xenobiotics and the stomach: friends or foes? World J. Gastroenterol. 16 (22), 2710–2719.
Al Mofleh, I.A., Alhaider, A.A., Mossa, J.S., Al-Sohaibani, M.O., Al-Yahya, M.A., Rafatullah, S., Shaik, S.A., 2008. Gastroprotective effect of an aqueous suspension of black cumin *Nigella sativa* on necrotizing agents-induced gastric injury in experimental animals. Saudi J. Gastroenterol. 14 (3), 128–134.
Alarcon de la Lastra, A.C., Martin, M.J., Motilva, V., Jimenez, M., La Casa, C., Lopez, A., 1995. Gastroprotection induced by silymarin, the hepatoprotective principle of *Silybum marianum* in ischemia-reperfusion mucosal injury: role of neutrophils. Planta Med. 61 (2), 116–119.
Alhaider, A., Al-Mofleh, I., Mossa, J., Al-Sohaibani, M., Qureshi, S., Rafatullah, S., 2005a. Pharmacological studies on 'Clove' *Eugenia caryophyllata*. Pharmacogn. Mag. 1 (3), 1055–1059.
Alhaider, A.A., Al-Mofleh, I.A., Mossa, J.S., Al-Sohaibani, M.O., Qureshi, S., Rafatullah, S., 2005b. Pharmacological and safety evaluation studies on "Cardamom" *Elettaria cardamomum*: an important ingredient of Gahwa (Arabian coffee). Arab. J. Pharm. Sci. 3 (1), 47–58.
Ali, B.H., Blunden, G., 2003. Pharmacological and toxicological properties of *Nigella sativa*. Phytother. Res. 17 (4), 299–305.
Ali, M.A., Sayeed, M.A., Alam, M.S., Yeasmin, M.S., Khan, A.M., Muhamad, I.I., 2012. Characteristics of oils and nutrient contents of *Nigella sativa* Linn. and *Trigonella foenum-graecum* seeds. Bull. Chem. Soc. Ethiop. 26 (1).
Alkofahi, A., Atta, A.H., 1999. Pharmacological screening of the anti-ulcerogenic effects of some Jordanian medicinal plants in rats. J. Ethnopharmacol. 67 (3), 341–345.
Arebi, N., Healey, Z.V., Bliss, P.W., Ghatei, M., Van Noorden, S., Playford, R.J., Calam, J., 2002. Nitric oxide regulates the release of somatostatin from cultured gastric rabbit primary D-cells. Gastroenterology 123 (2), 566–576.
Arslan, S.O., Gelir, E., Armutcu, F., Coskun, O., Gurel, A., Sayan, H., Celik, I.L., 2005. The protective effect of thymoquinone on ethanol-induced acute gastric damage in the rat. Nutr. Res. (New York, NY) 25 (7), 673–680.
Badary, O.A., Abd-Ellah, M.F., El-Mahdy, M.A., Salama, S.A., Hamada, F.M., 2007. Anticlastogenic activity of thymoquinone against benzo(a)pyrene in mice. Food Chem. Toxicol. 45 (1), 88–92.
Badary, O.A., Al-Shabanah, O.A., Nagi, M.N., Al-Bekairi, A.M., Elmazar, M.M.A., 1998. Acute and subchronic toxicity of thymoquinone in mice. Drug Dev. Res. 44 (2–3), 56–61.
Badary, O.A., Taha, R.A., Gamal el-Din, A.M., Abdel-Wahab, M.H., 2003. Thymoquinone is a potent superoxide anion scavenger. Drug Chem. Toxicol. 26 (2), 87–98.
Bagchi, D., Ray, S.D., Bagchi, M., Preuss, H.G., Stohs, S.J., 2002. Mechanistic pathways of antioxidant cytoprotection by a novel IH636 grape seed proanthocyanidin extract. Indian J. Exp. Biol. 40 (6), 717–726.
Barakat, E.M., El Wakeel, L.M., Hagag, R.S., 2013. Effects of *Nigella sativa* on outcome of hepatitis C in Egypt. World J. Gastroenterol. 19 (16), 2529–2536.
Bassim Atta, M., 2003. Some characteristics of nigella (*Nigella sativa* L.) seed cultivated in Egypt and its lipid profile. Food Chem. 83 (1), 63–68.
Bastaki, S., Dhaheri, A., Jaberi, A., Marzouqi, A., 2011. Comparative effect of garlic (*Allium sativum*), onion (*Allium cepa*), and black seed (*Nigella sativa*) on gastric acid secretion and gastric ulcer. Res. Rep. Med. Chem. 1, 3–9.
Borek, C., 2004. Dietary antioxidants and human cancer. Integr. Cancer Ther. 3 (4), 333–341.
Borrelli, F., Izzo, A.A., 2000. The plant kingdom as a source of anti-ulcer remedies. Phytother. Res. 14 (8), 581–591.
Boseila, A.A., Messalam, A.A., 2011. Immunostimulant effect of different fractions of *Nigella sativa* L. seeds against Rabies vaccine. Nat. Sci. 9 (2), 7.
Boskabady, M.H., Shirmohammadi, B., Jandaghi, P., Kiani, S., 2004. Possible mechanism(s) for relaxant effect of aqueous and macerated extracts from *Nigella sativa* on tracheal chains of guinea pig. BMC Pharmacol. 4, 3.
Brzozowski, T., Konturek, P.C., Konturek, S.J., Brzozowska, I., Pawlik, T., 2005. Role of prostaglandins in gastroprotection and gastric adaptation. J. Physiol. Pharmacol. 56 (Suppl. 5), 33–55.
Bylka, W., 2009. *Nigella sativa* L.-active compounds, biological properties. Herba Pol. 55 (1), 109–125.
Chakravarty, N., 1993. Inhibition of histamine release from mast cells by nigellone. Ann. Allergy 70 (3), 237–242.
Christie, P.E., Henderson Jr., W.R., 2002. Lipid inflammatory mediators: leukotrienes, prostaglandins, platelet-activating factor. Clin. Allergy Immunol. 16, 233–254.
Ciacci, C., Lind, S.E., Podolsky, D.K., 1993. Transforming growth factor beta regulation of migration in wounded rat intestinal epithelial monolayers. Gastroenterology 105 (1), 93–101.
Cleland, L.G., French, J.K., Betts, W.H., Murphy, G.A., Elliott, M.J., 1988. Clinical and biochemical effects of dietary fish oil supplements in rheumatoid arthritis. J. Rheumatol. 15 (10), 1471–1475.
El-Abhar, H.S., Abdallah, D.M., Saleh, S., 2003. Gastroprotective activity of *Nigella sativa* oil and its constituent, thymoquinone, against gastric mucosal injury induced by ischaemia/reperfusion in rats. J. Ethnopharmacol. 84 (2–3), 251–258.
el-Dakhakhny, M., 1965. Studies on the Egyptian *Nigella sativa* L. IV. Some pharmacological properties of the seeds' active principle in comparison to its dihydro compound and its polymer. Arzneimittelforschung 15 (10), 1227–1229.
El-Dakhakhny, M., Barakat, M., El-Halim, M.A., Aly, S.M., 2000. Effects of *Nigella sativa* oil on gastric secretion and ethanol induced ulcer in rats. J. Ethnopharmacol. 72 (1–2), 299–304.
El-Dakhakhny, M., Madi, N.J., Lembert, N., Ammon, H.P., 2002. *Nigella sativa* oil, nigellone and derived thymoquinone inhibit

synthesis of 5-lipoxygenase products in polymorphonuclear leukocytes from rats. J. Ethnopharmacol. 81 (2), 161–164.
El Gazzar, M.A., 2007. Thymoquinone suppresses in vitro production of IL-5 and IL-13 by mast cells in response to lipopolysaccharide stimulation. Inflamm. Res. 56 (8), 345–351.
El Gazzar, M.A., El Mezayen, R., Nicolls, M.R., Dreskin, S.C., 2007. Thymoquinone attenuates proinflammatory responses in lipopolysaccharide-activated mast cells by modulating NF-kappaB nuclear transactivation. Biochim. Biophys. Acta 1770 (4), 556–564.
el Tahir, K.E., Ashour, M.M., al-Harbi, M.M., 1993. The respiratory effects of the volatile oil of the black seed (*Nigella sativa*) in guinea-pigs: elucidation of the mechanism(s) of action. Gen. Pharmacol. 24 (5), 1115–1122.
Fallah Huseini, H., Mohtashami, R., Sadeqi, Z., Saidi, Y., Fallah Huseini, A., 2011. A review on pharmacological effects of *Nigella sativa* l. Seeds. J. Med. Plants 10 (38), 1–1.
Frieri, G., De Petris, G., Aggio, A., Santarelli, D., Ligas, E., Rosoni, R., Caprilli, R., 1995. Gastric and duodenal juxtamucosal pH and *Helicobacter pylori*. Digestion 56 (2), 107–110.
Gali-Muhtasib, H., Diab-Assaf, M., Boltze, C., Al-Hmaira, J., Hartig, R., Roessner, A., Schneider-Stock, R., 2004. Thymoquinone extracted from black seed triggers apoptotic cell death in human colorectal cancer cells via a p53-dependent mechanism. Int. J. Oncol. 25 (4), 857–866.
Gilani, A.H., Aziz, N., Khurram, I.M., Chaudhary, K.S., Iqbal, A., 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 (3), 115–120.
Grant, H.W., Palmer, K.R., Kelly, R.W., Wilson, N.H., Misiewicz, J.J., 1988. Dietary linoleic acid, gastric acid, and prostaglandin secretion. Gastroenterology 94 (4), 955–959.
Haloci, E., Manfredini, S., Toska, V., Vertuani, S., Ziosi, P., Topi, I., Kolani, H., 2012. Antibacterial and antifungal activity assessment of *Nigella Sativa* essential oils. World Acad. Sci. Eng. Technol. 66, 2012.
Hanafy, M.S., Hatem, M.E., 1991. Studies on the antimicrobial activity of *Nigella sativa* seed (black cumin). J. Ethnopharmacol. 34 (2–3), 275–278.
Hasani-Ranjbar, S., Larijani, B., Abdollahi, M., 2009. A systematic review of the potential herbal sources of future drugs effective in oxidant-related diseases. Inflamm. Allergy Drug Targets 8 (1), 2–10.
Heese-Peck, A., Pichler, H., Zanolari, B., Watanabe, R., Daum, G., Riezman, H., 2002. Multiple functions of sterols in yeast endocytosis. Mol. Biol. Cell 13 (8), 2664–2680.
Hoque, A., Lippman, S.M., Wu, T.T., Xu, Y., Liang, Z.D., Swisher, S., Zhang, H., Cao, L., Ajani, J.A., Xu, X.C., 2005. Increased 5-lipoxygenase expression and induction of apoptosis by its inhibitors in esophageal cancer: a potential target for prevention. Carcinogenesis 26 (4), 785–791.
Houghton, P.J., Zarka, R., de las Heras, B., Hoult, J.R., 1995. Fixed oil of *Nigella sativa* and derived thymoquinone inhibit eicosanoid generation in leukocytes and membrane lipid peroxidation. Planta Med. 61 (1), 33–36.
Kalus, U., Pruss, A., Bystron, J., Jurecka, M., Smekalova, A., Lichius, J.J., Kiesewetter, H., 2003. Effect of *Nigella sativa* (black seed) on subjective feeling in patients with allergic diseases. Phytother. Res. 17 (10), 1209–1214.
Kanter, M., Coskun, O., Uysal, H., 2006. The antioxidative and antihistaminic effect of *Nigella sativa* and its major constituent, thymoquinone on ethanol-induced gastric mucosal damage. Arch. Toxicol. 80 (4), 217–224.
Kanter, M., Demir, H., Karakaya, C., Ozbek, H., 2005. Gastroprotective activity of *Nigella sativa* L. oil and its constituent, thymoquinone against acute alcohol-induced gastric mucosal injury in rats. World J. Gastroenterol. 11 (42), 6662–6666.
Kanter, M., Meral, I., Yener, Z., Ozbek, H., Demir, H., 2003. Partial regeneration/proliferation of the beta-cells in the islets of Langerhans by *Nigella sativa* L. in streptozotocin-induced diabetic rats. Tohoku J. Exp. Med. 201 (4), 213–219.
Kato, S., Ohkawa, F., Ito, Y., Amagase, K., Takeuchi, K., 2009. Role of endothelial nitric oxide synthase in aggravation of indomethacin-induced gastric damage in adjuvant arthritic rats. J. Physiol. Pharmacol. 60 (4), 147–155.
Khalife, K.H., Lupidi, G., 2007. Nonenzymatic reduction of thymoquinone in physiological conditions. Free Radical Res. 41 (2), 153–161.
Kitano, S., Yasuda, K., Shiraishi, N., 2006. Laparoscopic surgical resection for early gastric cancer. Eur. J. Gastroenterol. Hepatol. 18 (8), 855–861.
Knapp, H.R., Melly, M.A., 1986. Bactericidal effects of polyunsaturated fatty acids. J. Infect. Dis. 154 (1), 84–94.
Kotani, T., Murashima, Y., Kobata, A., Amagase, K., Takeuchi, K., 2007. Pathogenic importance of pepsin in ischemia/reperfusion-induced gastric injury. Life Sci. 80 (21), 1984–1992.
Kruk, I., Michalska, T., Lichszteld, K., Kladna, A., Aboul-Enein, H.Y., 2000. The effect of thymol and its derivatives on reactions generating reactive oxygen species. Chemosphere 41 (7), 1059–1064.
Kyogoku, K., Hatayama, K., Yokomori, S., Saziki, R., Nakane, S., Sasajima, M., Sawada, J., Ohzeki, M., Tanaka, I., 1979. Anti-ulcer effect of isoprenyl flavonoids. II. Synthesis and anti-ulcer activity of new chalcones related to sophoradin. Chem. Pharm. Bull. (Tokyo) 27 (12), 2943–2953.
La Casa, C., Villegas, I., Alarcon de la Lastra, C., Motilva, V., Martin Calero, M.J., 2000. Evidence for protective and antioxidant properties of rutin, a natural flavone, against ethanol induced gastric lesions. J. Ethnopharmacol. 71 (1–2), 45–53.
Lange, K., Peskar, B.A., Peskar, B.M., 1985. Deutsche Pharmakologische Gesellschaft Abstracts of the Joint Meeting of the Belgian, Dutch, and German Pharmacological and Toxicological Societies. Naunyn Schmiedebergs Arch. Pharmacol. 330 (1), R-27.
Lei, X., Liu, M., Yang, Z., Ji, M., Guo, X., Dong, W., 2012. Thymoquinone prevents and ameliorates dextran sulfate sodium-induced colitis in mice. Dig. Dis. Sci. 57 (9), 2296–2303.
Liu, C.F., Lin, C.C., Lin, M.H., Lin, Y.S., Lin, S.C., 2002. Cytoprotection by propolis ethanol extract of acute absolute ethanol-induced gastric mucosal lesions. Am. J. Chin. Med. 30 (2–3), 245–254.
Losso, J.N., Bawadi, H.A., Chintalapati, M., 2011. Inhibition of the formation of advanced glycation end products by thymoquinone. Food Chem. 128 (1), 55–61.
Magdy, M.A., Hanan el, A., Nabila el, M., 2012. Thymoquinone: novel gastroprotective mechanisms. Eur. J. Pharmacol. 697 (1–3), 126–131.
Mahmood, A., Fouad, A., Noor, S., Wasman, S., Saba, F., 2011. Anti-ulcerogenic effects of *Nigella sativa* in ethanol-induced gastric injuries in rats. J. Med. Plants Res/ 5 (23), 5577–5583.
Mansour, M.A., 2000. Protective effects of thymoquinone and desferrioxamine against hepatotoxicity of carbon tetrachloride in mice. Life Sci. 66 (26), 2583–2591.
Mansour, M.A., Ginawi, O.T., El-Hadiyah, T., El-Khatib, A.S., Al-Shabanah, O.A., Al-Sawaf, H.A., 2001. Effects of volatile oil constituents of *Nigella sativa* on carbon tetrachloride-induced hepatotoxicity in mice: evidence for antioxidant effects of thymoquinone. Res. Commun. Mol. Pathol. Pharmacol. 110 (3–4), 239–251.
Mansour, M.A., Nagi, M.N., El-Khatib, A.S., Al-Bekairi, A.M., 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 (2), 143–151.
Marozzi Jr., F.J., Kocialski, A.B., Malone, M.H., 1970. Studies on the antihistaminic effects of thymoquinone, thymohydroquinone and quercetin. Arzneimittelforschung 20 (10), 1574–1577.

Matthaus, B., Özcan, M.M., 2011. Fatty acids, tocopherol, and sterol contents of some *Nigella* species seed oil. Czech J. Food Sci. 29 (2), 145–150.

Meral, I., Yener, Z., Kahraman, T., Mert, N., 2001. Effect of *Nigella sativa* on glucose concentration, lipid peroxidation, anti-oxidant defence system and liver damage in experimentally-induced diabetic rabbits. J. Vet. Med. Ser. A 48 (10), 593–599.

Merfort, I., Wray, V., Barakat, H., Hussein, S., Nawwar, M., Willuhn, G., 1997. Flavonoid triglycerides from seeds of *Nigella sativa*. Phytochemistry 46, 359–363.

Money, S.R., Cheron, R.G., Jaffe, B.M., Zinner, M.J., 1986. The effects of thyroid hormones on the formation of stress ulcers in the rat. J. Surg. Res. 40 (2), 176–180.

Mori, T.A., Beilin, L.J., 2004. Omega-3 fatty acids and inflammation. Curr. Atheroscler. Rep. 6 (6), 461–467.

Morsi, N.M., 2000. Antimicrobial effect of crude extracts of *Nigella sativa* on multiple antibiotics-resistant bacteria. Acta Microbiol. Pol. 49 (1), 63–74.

Mothana, R.A., Gruenert, R., Bednarski, P.J., Lindequist, U., 2009. Evaluation of the in vitro anticancer, antimicrobial and antioxidant activities of some Yemeni plants used in folk medicine. Pharmazie 64 (4), 260–268.

Nickavar, B., Mojab, F., Javidnia, K., Amoli, M.A., 2003. Chemical composition of the fixed and volatile oils of *Nigella sativa* L. from Iran. Z. Naturforsch. C 58 (9–10), 629–631.

Niiho, Y., Yamazaki, T., Nakajima, Y., Yamamoto, T., Ando, H., Hirai, Y., Toriizuka, K., Ida, Y., 2006. Gastroprotective effects of bitter principles isolated from Gentian root and Swertia herb on experimentally-induced gastric lesions in rats. J. Nat. Med. 60 (1), 82–88.

O'Mahony, R., Al-Khtheeri, H., Weerasekera, D., Fernando, N., Vaira, D., Holton, J., Basset, C., 2005. Bactericidal and anti-adhesive properties of culinary and medicinal plants against *Helicobacter pylori*. World J. Gastroenterol. 11 (47), 7499–7507.

Onifade, A.A., Jewell, A.P., Adedeji, W.A., 2013. *Nigella sativa* concoction induced sustained seroreversion in HIV patient. Afr. J. Tradit. Complement. Altern. Med. 10 (5), 332–335.

Padhye, S., Banerjee, S., Ahmad, A., Mohammad, R., Sarkar, F.H., 2008. From here to eternity – the secret of Pharaohs: therapeutic potential of black cumin seeds and beyond. Cancer Ther. 6 (b), 495–510.

Pastrana-Bonilla, E., Akoh, C.C., Sellappan, S., Krewer, G., 2003. Phenolic content and antioxidant capacity of muscadine grapes. J. Agric. Food Chem. 51 (18), 5497–5503.

Pathak, S.K., Sharma, R.A., Steward, W.P., Mellon, J.K., Griffiths, T.R., Gescher, A.J., 2005. Oxidative stress and cyclooxygenase activity in prostate carcinogenesis: targets for chemopreventive strategies. Eur. J. Cancer 41 (1), 61–70.

Peskar, B.M., Maricic, N., 1998. Role of prostaglandins in gastroprotection. Dig. Dis. Sci. 43 (9 Suppl.), 23S–29S.

Rafatullah, S., Galal, A., Al-Yahya, M., Al-Said, M., 1995. Gastric and duodenal antiulcer and cytoprotective effects of *Aframomum melegueta* in rats. Pharm. Biol. 33 (4), 311–316.

Rafatullah, S., Tariq, M., Al-Yahya, M.A., Mossa, J.S., Ageel, A.M., 1990. Evaluation of turmeric (*Curcuma longa*) for gastric and duodenal antiulcer activity in rats. J. Ethnopharmacol. 29 (1), 25–34.

Ragheb, A., Attia, A., Eldin, W.S., Elbarbry, F., Gazarin, S., Shoker, A., 2009. The protective effect of thymoquinone, an anti-oxidant and anti-inflammatory agent, against renal injury: a review. Saudi J. Kidney Dis. Transpl. 20 (5), 741–752.

Rajkapoor, B., Anandan, R., Jayakar, B., 2002. Anti-ulcer effect of *Nigella sativa* Linn. against gastric ulcers in rats. Curr. Sci. 82 (2), 177–179.

Ramadan, M.F., Kroh, L.W., Morsel, J.T., 2003. Radical scavenging activity of black cumin (*Nigella sativa* L.), coriander (*Coriandrum sativum* L.), and niger (*Guizotia abyssinica* Cass.) crude seed oils and oil fractions. J. Agric. Food Chem. 51 (24), 6961–6969.

Ramadan, M.F., Morsel, J.T., 2002. Characterization of phospholipid composition of black cumin (*Nigella sativa* L.) seed oil. Nahrung 46 (4), 240–244.

Rioux, K.P., Wallace, J.L., 1996. Mast cells do not contribute to nonsteroidal anti-inflammatory drug-induced gastric mucosal injury in rodents. Aliment. Pharmacol. Ther. 10 (2), 173–180.

Ruthig, D.J., Meckling-Gill, K.A., 1999. Both (n-3) and (n-6) fatty acids stimulate wound healing in the rat intestinal epithelial cell line, IEC-6. J. Nutr. 129 (10), 1791–1798.

Ruthig, D.J., Meckling-Gill, K.A., 2002. N-3 and n-6 fatty acids stimulate restitution by independent mechanisms in the IEC-6 model of intestinal wound healing. J. Nutr. Biochem. 13 (1), 27–35.

Sabikhi, L., Sathish Kumar, M.H., 2012. Fatty acid profile of unconventional oilseeds. Adv. Food Nutr. Res. 67, 141–184.

Salem, E.M., Yar, T., Bamosa, A.O., Al-Quorain, A., Yasawy, M.I., Alsulaiman, R.M., Randhawa, M.A., 2010. Comparative study of *Nigella sativa* and triple therapy in eradication of *Helicobacter pylori* in patients with non-ulcer dyspepsia. Saudi J. Gastroenterol. 16 (3), 207–214.

Salem, M.L., 2005. Immunomodulatory and therapeutic properties of the *Nigella sativa* L. seed. Int. Immunopharmacol. 5 (13–14), 1749–1770.

Sayed, A.A., Morcos, M., 2007. Thymoquinone decreases AGE-induced NF-kappaB activation in proximal tubular epithelial cells. Phytother. Res. 21 (9), 898–899.

Sethi, G., Ahn, K.S., Aggarwal, B.B., 2008. Targeting nuclear factor-kappa B activation pathway by thymoquinone: role in suppression of antiapoptotic gene products and enhancement of apoptosis. Mol. Cancer Res. 6 (6), 1059–1070.

Shan, B., Cai, Y.Z., Sun, M., Corke, H., 2005. Antioxidant capacity of 26 spice extracts and characterization of their phenolic constituents. J. Agric. Food Chem. 53 (20), 7749–7759.

Shan, L., Liu, R.H., Shen, Y.H., Zhang, W.D., Zhang, C., Wu, D.Z., Min, L., Su, J., Xu, X.K., 2006. Gastroprotective effect of a traditional Chinese herbal drug "Baishouwu" on experimental gastric lesions in rats. J. Ethnopharmacol. 107 (3), 389–394.

Shen, T.Y., 1979. Some medicinal chemical aspects of prostaglandin synthesis inhibitors. Agents Actions (Suppl. (6)), 177–184.

Shrivastava, R., Agrawal, R., Parveen, Z., 2011. A review on therapeutic applications of *Nigella sativa*. J. Chem. Chem. Sci. 1 (4), 241–248.

Skrovankova, S., Misurcova, L., Machu, L., 2012. Antioxidant activity and protecting health effects of common medicinal plants. Adv. Food Nutr. Res. 67, 75–139.

Swarnakar, S., Ganguly, K., Kundu, P., Banerjee, A., Maity, P., Sharma, A.V., 2005. Curcumin regulates expression and activity of matrix metalloproteinases 9 and 2 during prevention and healing of indomethacin-induced gastric ulcer. J. Biol. Chem. 280 (10), 9409–9415.

Tanaka, S., Hamada, K., Yamada, N., Sugita, Y., Tonai, S., Hunyady, B., Palkovits, M., Falus, A., Watanabe, T., Okabe, S., Ohtsu, H., Ichikawa, A., Nagy, A., 2002. Gastric acid secretion in L-histidine decarboxylase-deficient mice. Gastroenterology 122 (1), 145–155.

Thompson, L., Edwards, R., Greenwood, D., Spiller, R., 1990. Inhibitory effect of long-chain fatty-acids (lcfas) on colonic bacteria. Gut (British med journal publ group british med assoc house, Tavistock square, London, England wc1h 9jr).

Thompson, L., Spiller, R.C., 1995. Impact of polyunsaturated fatty acids on human colonic bacterial metabolism: an in vitro and in vivo study. Br. J. Nutr. 74 (5), 733–741.

Toma, W., Hiruma-Lima, C.A., Guerrero, R.O., Brito, A.R., 2005. Preliminary studies of *Mammea americana* L. (Guttiferae) bark/latex extract point to an effective antiulcer effect on gastric ulcer models in mice. Phytomedicine 12 (5), 345–350.

Topal, A., Celebi, F., 2011. Effects of *Nigella sativa* aqueous extracts on gastric acid secretion in isolated rat stomach. Kafkas Univ. Vet. Fak. Derg. 17 (4).

Toppozada, H.H., Mazloum, H.A., el-Dakhakhny, M., 1965. The antibacterial properties of the *Nigella sativa* l. seeds. Active principle with some clinical applications. J. Egypt. Med. Assoc. 48 (Suppl), 187–202.

Trivedi, N.P., Rawal, U.M., 2001. Hepatoprotective and antioxidant property of *Andrographis paniculata* (Nees) in BHC induced liver damage in mice. Indian J. Exp. Biol. 39 (1), 41–46.

Viuda-Martos, M., Mohamady, M.A., Fernández-López, J., Abd ElRazik, K.A., Omer, E.A., Pérez-Alvarez, J.A., Sendra, E., 2011. In vitro antioxidant and antibacterial activities of essentials oils obtained from Egyptian aromatic plants. Food Control 22 (11), 1715–1722.

Wada, K., Kamisaki, Y., Kitano, M., Kishimoto, Y., Nakamoto, K., Itoh, T., 1997. Effects of sucralfate on acute gastric mucosal injury and gastric ulcer induced by ischemia-reperfusion in rats. Pharmacology 54 (2), 57–63.

Wada, K., Kamisaki, Y., Kitano, M., Nakamoto, K., Itoh, T., 1995. Protective effect of cystathionine on acute gastric mucosal injury induced by ischemia-reperfusion in rats. Eur. J. Pharmacol. 294 (2–3), 377–382.

Wajs, A., Bonikowski, R., Kalemba, D., 2008. Composition of essential oil from seeds of *Nigella sativa* L. cultivated in Poland. Flavour Fragrance J. 23 (2), 126–132.

Wallace, J.L., 2005. Recent advances in gastric ulcer therapeutics. Curr. Opin. Pharmacol. 5 (6), 573–577.

Wasman, S., Mahmood, A., Salehhuddin, H., Zahra, A., Salmah, I., 2010. Cytoprotective activities of *Polygonum minus* aqueous leaf extract on ethanol-induced gastric ulcer in rats. J. Med. Plant Res. 4 (24), 2658–2665.

Yoshikawa, T., Naito, Y., Tanigawa, T., Yoneta, T., Yasuda, M., Ueda, S., Oyamada, H., Kondo, M., 1991. Effect of zinc-carnosine chelate compound (Z-103), a novel antioxidant, on acute gastric mucosal injury induced by ischemia-reperfusion in rats. Free Radical Res. Commun. 14 (4), 289–296.

Yoshikawa, T., Ueda, S., Naito, Y., Takahashi, S., Oyamada, H., Morita, Y., Yoneta, T., Kondo, M., 1989. Role of oxygen-derived free radicals in gastric mucosal injury induced by ischemia or ischemia-reperfusion in rats. Free Radical Res. 7 (3–6), 285–291.

Zayachkivska, O.S., Konturek, S.J., Drozdowicz, D., Brzozowski, T., Gzhegotsky, M.R., 2004. Influence of plant-originated gastroprotective and antiulcer substances on gastric mucosal repair. Fiziol. Zh. 50 (6), 118–127.

Zayachkivska, O.S., Konturek, S.J., Drozdowicz, D., Konturek, P.C., Brzozowski, T., Ghegotsky, M.R., 2005. Gastroprotective effects of flavonoids in plant extracts. J. Physiol. Pharmacol. 56 (Suppl. 1), 219–231.