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Review Article

PHARMACOLOGICAL REVIEW OF NIGELLA SATIVA AND ITS THERAPUTIC USE FOR TREATMENT OF GASTROINTESTINAL DISORDER

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ABSTRACT

Currently, considerable populations around the world have gastro-intestinal disorders. Acid reflux and gastric ulcers are typical GIT disorders that can have induce negative impact on person's health. An effective rational solution has not yet been introduced to offer the maximum possible therapeutical relieve. The conventional medications currently available in the market have high risks and serious side effects. Therefore, alternative medicines may exclusively be utilized -for the ailments of various chronic gastrointestinal disorders because of its natural source and minimum side effects. Numerous medicinal effects associated with *Nigella sativa* (*N. sativa*) and its components i.e., dithymoquinone, thymol and carvacrol have been reported. Additionally this plant has variety of therapeutical usage, including anti-oxidant, antibacterial, anti-inflammatory, anti-cancer, and immunomodulatory. It also has therapeutic properties, such as resolving bronchial asthma, jaundice, hydrophobia, paralysis, conjunctivitis, piles, skin diseases, anorexia, headache and GIT disorders. Thus, we aimed this study to review and summarizes the effects of *N. sativa* and its components with a focus on GIT disorders

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INTRODUCTION

Esophageal, stomach, small intestine, colon, rectum, liver, gallbladder and pancreas disorders include gastro-intestinal tract (GIT) disorders. Symptoms of GIT disorders include such as pain, heartburn, indigestion, gas, nausea, vomiting, coughing, constipation, and diarrhea. These are the most commonly encountered motility disorders and transfer in clinical practice and the general public. These GIT diseases are 10-20 % prevalent in western countries. GIT disease are chronic illnesses that impair quality of life and require long-term care [1]. Commonly used medicines have side effects that include osteoporosis, intestinal flora changes, kidney stones, anemia, and an elevated risk of stomach carcinoma. In recent decades, the emphasis was focused on using natural source medicines to treat different diseases due to less or no the side effects.

Herbal medicines are commonly used to treat many illnesses as the primary medicines in traditional system of medicines such as Unani and Ayurveda. *Nigella sativa* (N. sativa) is an important drug used in this system of medicine [2, 3]. In developing countries, almost 80 % of the population depends on herbal medicine in primary medical therapy [4]. Medicinal plants are the source of enormous drugs, and many important drugs were derived directly or indirectly from plants or from molecules of plant origin.

The annual plant of *Nigella sativa*, occurring in southern Europe, North Africa and southwest Asia, is a flowering plant of the *Trichosanaceae* family. Seeds contain oil, protein, carbohydrates, fiber, saponin and water. *Nigella sativa* contains water. *Nigella sativa* oil contains much of linoleic acid, oleic and palmitic acid, stearic acid, myristic acid, and estrogen. The seeds produces a high amount of oil from *Nigella sativa*, consisting of acid and glycol [5].

Based on its normal use in folk medicine for different diseases, scientists have researched its implications on asthma, hypertension, diabetes and inflammation [6-9]. This plant is well known for its anti-oxidants, analgesic, and anti-schistosomiasis, anti-fungal, anti-bacterial, antispasmodics, and neuroprotective effects [10-15]. In addition, it showed healing potential in gastrointestinal disturbances [16]. There have been comprehensive studies over thirty years in order to recognize and understand the processes of natural substances of plant origin. N. sativa extract can enhance antioxidant activity (i.e. Catalase, glutathione peroxidase and S-transferase glutathione) and function as a free radical scavenger [17]. As anti-cancer drugs have been shown to be effective in modulating molecular target activity (such as p53, p73, PTEN, STAT3, PPAR-g). In the process of modulating Th1/Th2 lymphocytes response and enhancing the immune response mediated by T-cells and NK cells, it also suppressed inflammatory mediators, leukotrienes, prostaglandins and B-cells [18].

Described the worldwide usage in different nations and countries

Gastrointestinal effects

Anti-cancer effect

A preventive impact on HCT-116 human colon cancer cells was assessed for Thymoquinone (TQ), the significant component of *Nigella sativa*. The findings show that TQ is an efficient drug for colon cancer cells and contributes to apoptosis through a mechanism that is p53 dependent [19]. A separate study showed that TQ did not have any effect on cancer cells of HEp-2 [20].

Hepatoprotective effect

In rats, the protective effect on the reperfusion injury/liver ischemia was studied by *Nigella sativa* (0.2 ml/kg; intraperitoneal: intraperitoneal). Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), and lactate dehydrogenase (LDH), total anti-oxidant potential (TAC), catalase (CAT), total oxidation state (TOS), Oxidation Stress Index (OSI), and myeloperoxidase (MPO) were evaluated. The result shows that *Nigella sativa* can be an effective anti-oxidant and have possible anti-ischemia / reperfusion effect on the liver [21].

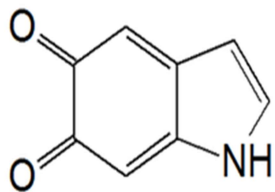
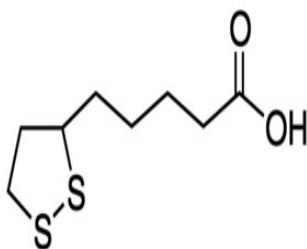
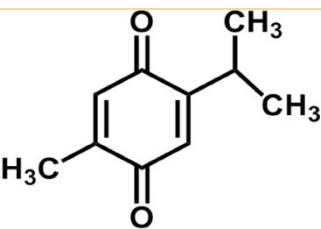
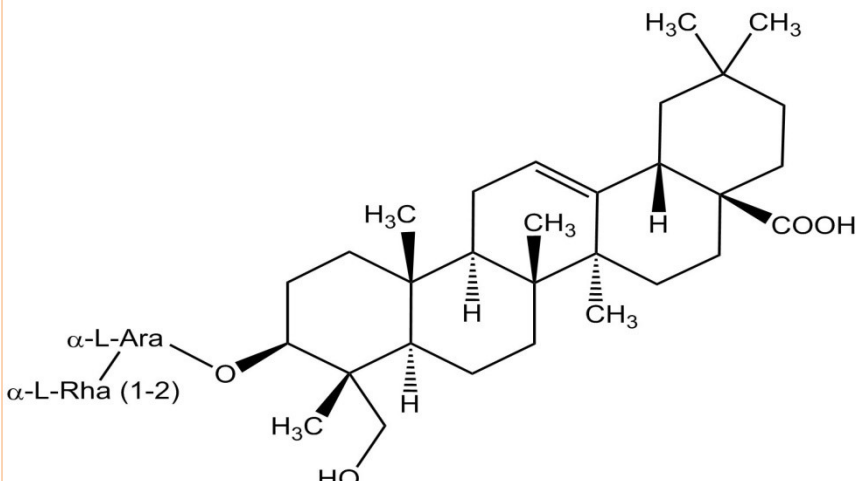
Melanin	
α -lipoic acid	
Thymoquinone	 Thymoquinone
α -hederin	

Figure 1: Structure of some important chemical component of *Nigella sativa*.

Table 1. Scientific classification

Kingdom:	<u>Plantae</u>
Clade:	<u>Tracheophytes</u>
Clade:	<u>Angiosperms</u>
Clade:	<u>Eudicots</u>
Order:	<u>Ranunculales</u>
Family:	<u>Ranunculaceae</u>
Genus:	<u>Nigella</u>
Species:	<i>N. sativa</i>

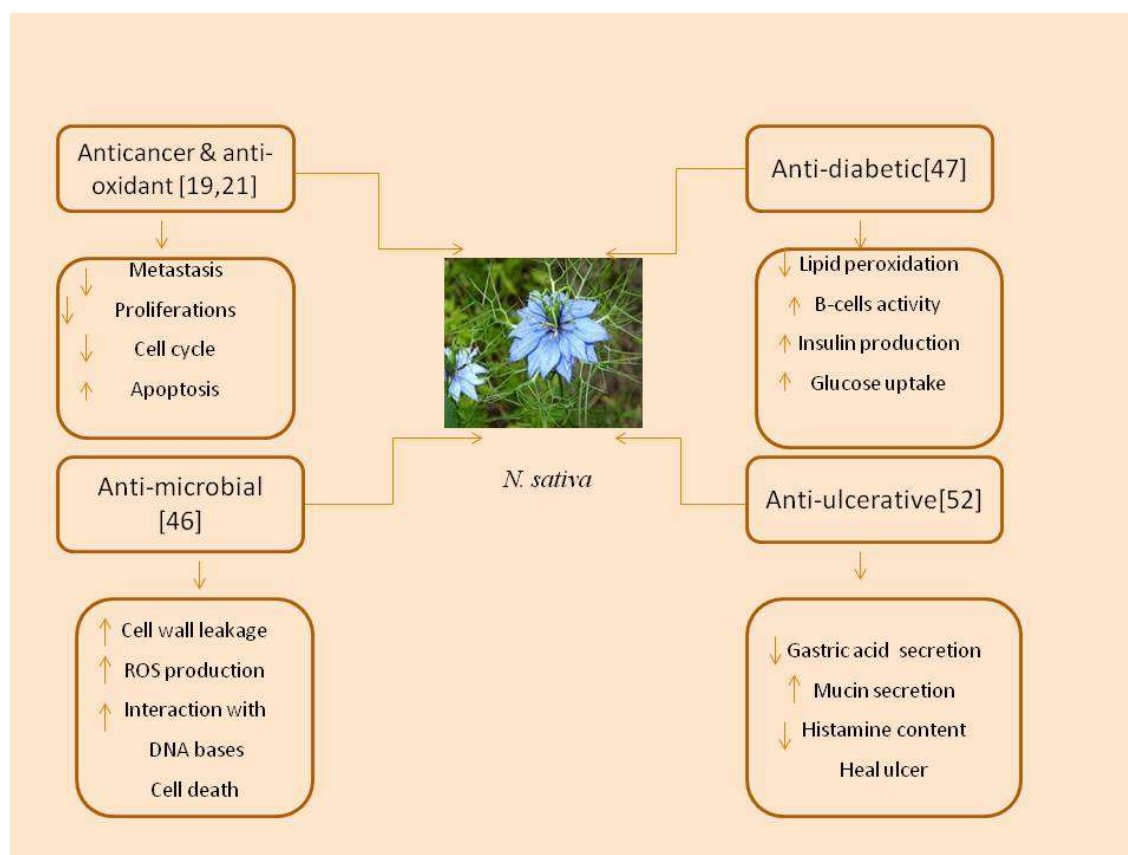


Figure 2: Important pharmacological activities of *Nigella sativa* against gastrointestinal disorders
 Redesign properly in more scientific manner

N. sativa (0.2 ml/kg, i.p.) influence on cholestatically damaging rats was investigated in another study. The authors have found that *Nigella sativa* influences cholestatic hepatic wounds in rats in terms of prevention. This protective effect may also be responsible for decreased neutrophil infiltration and oxidative stress [22]. Moreover, the protective action on hepatotoxicity induced by lead acetate in male rats by *Nigella sativa*

seeds (5% of packaging weight) is reported. *N. sativa* seeds caused significant elevation in AST, improved biochemical and histopathological profiles and reduced damage areas [23].

The protective effects of *N. sativa* oil (0.2 mL/kg, i.p.) and *Urtica dioica* oil (2 mL/kg, i.p.) on carbon tetrachloride (CCl₄)-induced liver toxicity were studied in rats. Findings showed that *N. sativa* and *U. dioica* reduced lipid peroxidation and liver enzymes, and enhanced antioxidant defense system activity in CCl₄-treated rats [15]. In the rats, CYP 3A1 and N-1 spermidine acetyltransferase/spermine were evaluated for effects of TQ (10 mg/kg orally) in renal ischemia/reperfusion of the expressed genes of liver and kidney dysfunction. TQ prevents ischemia and reperfusion damage by anti-oxidants and can reduce the expression of the CYP3A1 and SSAT genes [24], according to this report.

The protective effect from TQ was tested in isolated rat liver cells on the toxicity of tert-butyl hydroperoxide. Pretreatment with 1 mM TQ of liver cells reduced the leakage of cyto-enzymes, ALT and AST [25]. A one-dose oral TQ in the Swiss male albino mouse (100 mg/kg) can provide protection due to the anti-oxidant effects of the TQ on CCl₄-mediated hepatotoxicity [26].

Another research investigated the protective effect of TQ on aflatoxin B₁-induced liver toxicity in a mouse (4.5, 9 and 18 mg/kg intraperitoneal injection). The results of the analysis showed that TQ decreased the AST, ALT, ALP and Malondialdehyde (MDA) levels significantly. Increased resistance against oxidation burst and reduced lipid peroxidation can mediate this protective effect [27].

TQ has also demonstrated a protective effect on lipopolysaccharide-induced endotoxemia because of its anti-inflammatory, anti-apoptotic and anti-oxidant impact [28]. The protective effect of TQ (10 mg/kg orally) has been shown to enhance anti-oxidant conditions and minimize biochemical changes in rat sodium fluoride liver toxicity and oxidative stress. The TQ suppresses the rise in lipid peroxidation (OLP), increases stabilization of cell membrane integrity and causes reduction of liver enzyme leaks [29]. TQ (50 mg/kg body weight) has also been shown to considerably inhibit depletion and normalize Superoxide Dismutase (SOD) activity of tamoxifen-induced hepatic glutathione [30]. TQ (0.5, 1 and 2 mg/kg/day, oral) combated against acetaminophen-induced hepatotoxicity and decreased acetaminophen-induced hepatotoxicity in a dose-dependent manner as evidenced by reduction in serum ALT activities. Hepatoprotective effect of TQ was probably mediated by increased resistance to oxidative and nitrosative stress and improved mitochondrial energy production [31].

In a clinical study, the effects of ethanolic extracts of *N. sativa*, *Zingiber officinale* (*Z. officinale*) and their mixture were evaluated in patients with hepatitis C virus (HCV) infection. Patients were divided into five groups: I) Healthy subjects, II) HCV control; III) HCV patients receiving a capsule containing 500 mg *N. sativa* extract twice daily; IV) HCV patients receiving a capsule containing 500 mg *Z. officinale* extract twice daily and V) HCV patients receiving a capsule containing 500 mg *Z. officinale* and 500 mg *N. sativa* extracts twice daily. The results showed that ethanolic extracts of *N. sativa* and *Z. officinale* had a significant effect in HCV patients as shown by a decrease in viral load and restoration of liver functions [32].

Add the pictures of plant at different stage, location and process.

Anti-bacterial and anti-schistosomiasis effects

The effect of *N. sativa* seed (0%, 1%, 2% and 3% of diet) on performance, intestinal *Escherichia coli* (*E. coli*) colonization and jejunal morphology in laying hens was evaluated. The results showed that ileal *E. coli* numeration reduced with 1% *N. sativa*. However, the best intestinal health indices were obtained following administration of 2% *N. sativa* [32].

In rats, the TQ (10 mg/kg, i.p.) effect of bacterial translocation and mechanical intestinal obstruction inflammation was investigated. Results demonstrated that TQ decreased inflammatory cytokines, oxidative damage, bacterial transport and improved function of the intestinal barrier in bowel-impaired rats [33].

A clinical trial was carried out in patients with non-ulcer dyspepsia comparing the effects of clarithromycin, amoxicillin and omeprazole on the effects of helicobacter pylori (*H. pylori*). Patients were divided randomly into four groups: I) triple therapy; II) 1 g / day *N. sativa*+ omeprazole 40 mg; III) 2 g *Nigella sativa* + 40 mg omeprazole daily and IV) 3 g *Nigella sativa* daily + 40 mg omeprazole for four weeks. The findings suggest the best therapeutic effect on *Helicobacter pylori* activity for 2 g *Nigella sativa* + 40 mg omeprazole every day [34].

A garlic aqueous solution (125 mg kg⁻¹, i.p) and *Nigella sativa* (0.2 mg kg⁻¹, i.p) have been investigated for anti-oxidant and anti-schistosomiasis effects in normal mice and mice infected with *Schistosoma mansoni* (*S. mansoni*). Hematological parameters and levels of MDA, GSH, LDH, AST, and ALT were assessed in the liver. The results revealed that garlic extract and *N. sativa* oil reversed most of the hematological and biochemical changes and markedly improved the antioxidant capacity of treated infected mice as compared to untreated infected mice [35].

The schistosomicidal effect of *N. sativa* seed against *S. mansoni* miracidia, cercariae, and adult worms was evaluated. Findings showed that *N. sativa* seed had a strong biocidal effect against all stages of the parasite life and showed inhibitory effect on egg-laying in adult female worms. The results also indicated that *N. sativa* seed induced oxidative stress against adult worms which was determined by reduction in the activities of antioxidant enzymes [14].

Anti-inflammatory and anti-oxidant effects

In adult male rats, *Nigella sativa* oil (0.88 g / kg PO) has been evaluated for its effect on gastric secretion and ethanol-induced ulcers. The results show a rise in gastric mucin, free acid and glutathione content, and a reduction in gastric histamine. *Nigella sativa* oil was found to resist ethanol ulcers [36].

The protective effects on the stomach from *Nigella sativa* (2.5 ml/kg orally) and TQ (5, 20, 50 and 100 mg/kg orally) were investigated in another study. It was tested in human Wistar rats for the ischemia/reperfusion injury of the gastric mucosa. Results demonstrate the reduction in LDH, LPO, GSH and SOD in *Nigella sativa* oil and TQ groups at 5 and 20 mg/kg respectively. *Nigella sativa* oil and TQ were found to protect gastric wounds [37].

The effects of *N. sativa* oil (10 mL/kg body weight, orally) and TQ (10 mg/kg body weight, orally) against acute alcohol-induced gastric mucosal injury were investigated in male albino rats. The findings showed that *N. sativa* oil caused a reduction in ulcer index and MDA level and promoted healing of gastric injury and SOD, GSH and GST levels. Likewise, TQ has a protective activity on gastric lesions but less than that of *N. sativa* [38].

Another research has also applied optical and scanning microscopy to examine the damage in piroxicam mediated gastric mucosa in adult male albino rats to determine the *Nigella sativa* oil's safety effect (10 ml/kg body weight). *Nigella sativa* oil has been shown to restore the structure of the mucosa and increase the secretion of the mucus in piroxicam treated rats [39].

The protective effect of *N. sativa* oil (10 ml/kg body weight) on stress-induced gastric ulcer in hypothyroid rats was studied. Animals were randomly divided into six groups: I) Control; II) Surgically thyroidectomized

group; III) Acute cold restraint stressed group; IV) Surgically thyroidectomized and stressed group; V) N. sativa oil group and VI) Surgically thyroidectomized and stressed receiving N. sativa oil group. Findings indicated a reduction in thyroid hormone level and an increase in stress-induced gastritis which can be inhibited by N. sativa oil [40].

In one study, the effects of TQ (10 and 20mg/kg), omeprazole (10 and 20mg/kg) or co-administration of TQ (10mg/kg) and omeprazole (10mg/kg) on gastric mucosal ischemia/reperfusion injury induced by pyloric ligation (30 min), ischemia (30 min)/reperfusion (120 min) were investigated in rats. The results revealed that TQ had gastroprotective effects which were mediated by inhibiting proton pump, acid secretion and neutrophil infiltration, and increasing mucin secretion, and nitric oxide production [41].

The effects of N. sativa (500mg/kg, oral) and TQ (10mg/kg, orally) on ethanol-induced gastric mucosal injury in rats were studied. N. sativa significantly decreased the number of mast cells, the area of gastrointestinal erosions, histamine levels, and myeloperoxidase activity. The TQ impact, on the other hand, was less prominent than with N. sativa. N. sativa's gastroprotective effects may be related to its anti-oxidant, per-oxidative, and anti-histaminergic properties, according to the results of this study. [42].

TQ (5 and 10 mg/kg) and sulfasalazine (500 mg/kg) as anti-colitis drugs were tested in rats for their effects on acetic acid-induced colitis. Results showed that TQ protects against colitis better than sulfasalazine, and this may be due to its antioxidant properties.[43]. The effect of TQ (100 mg/kg, orally) on chronic pancreatitis induced by high fat diet and ethanol was studied in rats. Findings revealed that TQ has a protective effect on pancreatitis via reducing the secretion of amylase and lipase from pancreas, inflammatory cytokine and lipid peroxidation [44].

CONCLUSION

N. sativa and its primary component TQ demonstrated promising potential in animal models for gastrointestinal diseases such as cancer, hepatitis toxicity, ischemia/reperfusion and dyspepsia. They include anti-cancer, anti-bacterial, anti-schistosomiasis, protective for the stomach disorders, anti-inflammatory and antioxidant activities. The use of N. sativa might aid to prevent and treat the inflammatory, oxidative, and harmful damage caused by various food-borne toxins, microorganisms and allergens. The herbs and their ingredients are often preventive and calming for various gastrointestinal disorders, as shown by clinical studies. N. sativa thus has a precautionary and therapeutic impact on gastrointestinal diseases. However, further clinical and experimental studies are required for the clinical and molecular basis of N. sativa usage and to understand its pharmacological basis completely.

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