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Antidepressant and anti-nociceptive effects of *Nigella sativa* and its main constituent, thymoquinone: A literature review

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ABSTRACT

Medicinal plants and their ingredients have beneficial effects on human health. *Nigella sativa* is a herbal plant with multiple biological and pharmacological activities. Previous studies demonstrated the anti-inflammatory and antioxidant properties of *Nigella sativa* and its main constituent thymoquinone significantly contributes to the antidepressant and anti-nociception effects of this plant. It has been reported that thymoquinone may achieve its antidepressant effect by preventing the elimination of brain neurotransmitters affecting depression such as serotonin. The role of brain-derived neurotrophic factors in the antidepressant effects of thymoquinone has also been documented. Additionally, thymoquinone can attenuate pain by upregulation of intracellular signaling pathways related to nitric oxide and K^+_{ATP} channels. The present review summarizes the antidepressant and anti-nociceptive activity of *Nigella sativa* and its main constituent thymoquinone by searching literature on electronic databases such as PubMed, Web of Science, Scopus, and Google Scholar from the beginning of 2010 until the end of August 2022.

KEYWORDS: *Nigella sativa*; Thymoquinone; Antidepressant; Anti-nociceptive; Depression; Anti-inflammatory; Sickness behaviors; Pain

1. Introduction

In recent years, the focus on traditional medicine and use of natural products derived from medicinal plants has increased[1]. Public interest in use of herbal medicines is due to their lower side effects and availability than modern drugs[2]. Therefore, in research centers, a large number of scientific studies are conducted to discover the effective substances of medicinal plants and their therapeutic properties[3,4].

Nigella sativa (*N. sativa*), black cumin or black seed, is an annual flowering plant belonging to Ranunculaceae family. This herbaceous plant grows in different regions of Asia, Africa, and Europe, and possesses threadlike leaves and delicate flowers. The colors of flowers can be white, yellow, pale blue, and pink. The fruit of *N. sativa* is a large and inflated capsule made of three to seven united follicles containing black seeds which are utilized as a spice[2,5].

Because of various biological and pharmacological activities, *N. sativa* is known as a miracle herb[6]. Its biological activities include anti-inflammatory[7], antioxidant[8] antimicrobial[9], anti-apoptotic[10], anti-mutagenic[11] and anti-cancer[12] activities. *N. sativa* has been known to be a good remedy for alleviation of chronic obstructive pulmonary diseases[13], cough[14], fever[15], diarrhea[16], and eczema[17]. It is also traditionally employed to cure increased level of blood glucose[18], high blood pressure[19], allergic reactions[20], and stomach ache[2]. Thymoquinone (TQ) presented in the extract of *N. sativa* contributes to the majority of these effects. This review will summarize the reported activities of this plant and its main constituent TQ on depression and pain.

2. Method

Scientific evidence cited in this review was collected from electronic databases such as PubMed, Web of Science, Scopus, and Google Scholar from the beginning of 2010 until the end of August 2022 using keywords such as "*Nigella sativa*" or "thymoquinone" and "antidepressant", "sickness behaviors", "anti-nociceptive" and

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"pain" (Figure 1). Human and animal studies were checked.

3. Chemical compounds of *N. sativa*

Biochemical analyses proved the presence of various types of chemical compounds in *N. sativa*. An important group of these compounds is volatile phytochemicals in the essential oil of *N. sativa* including TQ, thymol, dithymoquinone, carvacrol, 4-terpineol, *p*-cymene, α-pinene, β-pinene and *t*-anethole[21]. Among these compounds, TQ has different pharmacological properties. Other chemicals found in *N. sativa* extract are alkaloids such as nigellicimine, nigellicimine-*N*-oxide, nigellicine, and nigellidine. In addition, the essential oil of *N. sativa* contained proteins, saturated and unsaturated free fatty acids, vitamins, and minerals[22].

4. *N. sativa* and traditional medicine

In traditional medicine, *N. sativa* has been demonstrated to have considerable therapeutic effects on different kinds of ailments and disturbances. In this section, some of the applications of *N. sativa* and its active ingredient TQ in traditional medicine will be mentioned.

In a study by Abd-Elkareem *et al*., *N. sativa* seeds showed the renoprotective effect against monosodium glutamate-induced nephrotoxicity *via* ameliorating the oxidative stress status and increasing the level of antioxidant agents such as superoxide dismutase (SOD) and glutathione[23]. In a similar study, it was proved that the hepatoprotective effect of *N. sativa* in a rat model of monosodium glutamate-caused hepatotoxicity was attributed to its antioxidant and anti-apoptotic properties[24]. Based on the research carried out by Liang *et al*., TQ derived from *N. sativa* also protected the human skin keratinocytes from ultraviolet irradiation-induced injuries by suppressing inflammatory reactions and neutralization of free radicals[25]. It has been documented that a novel polyherbal formulation containing TQ dose-dependently improved the hepatorenal dysfunction caused by CCl_4[26]. The role of *N. sativa* in the treatment of cardiovascular diseases[27], type 2 diabetes mellitus[28], rheumatoid arthritis[29], and asthma[30] has also been documented. In an animal model of lipopolysaccharide (LPS)-induced memory impairment, hydro-alcoholic extract of *N. sativa* corrected the performance of rats in Morris water maze and passive avoidance tests by ameliorating the brain inflammation and oxidative stress[31]. Asiaei *et al*. also showed that *N. sativa* could exert a neuroprotective effect on hypothyroidism-induced injuries in the hippocampal tissue of juvenile rats[32]. Additionally, TQ has been recognized to have a potent ability in reversing the detrimental effects of propylthiouracil on cognitive activities and brain oxidative damage in juvenile rats[33]. In patients with Hashimoto's thyroiditis, *N. sativa* attenuated the severity of disease, decremented the level of thyroid stimulating hormone, anti-thyroid peroxidase antibodies, and vascular endothelial growth factor-1 and increased the serum concentration of triiodothyronine[34]. Previous studies also reported the antimicrobial properties of *N. sativa* extract. For example, in a study conducted by Tiji *et al*., the antifungal and antibacterial effect of *N. sativa* extracts against *Candida albicans*, *Staphylococcus aureus*, *Bacillus cereus*, and *Escherichia coli* was confirmed. They reported

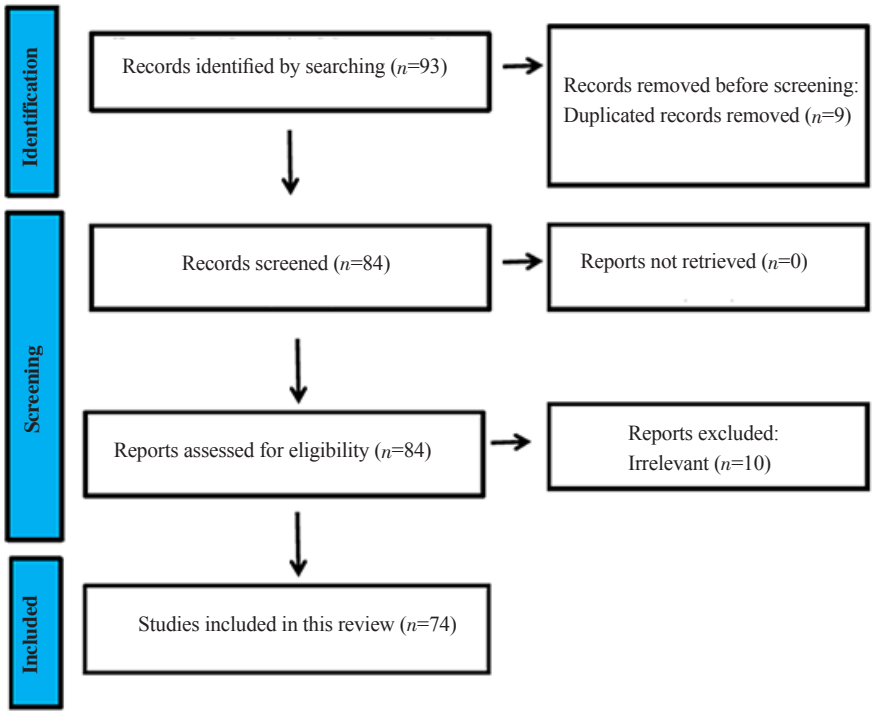

Figure 1. Flowchart of literature screening.

that TQ, beta-cymene, alpha-thujene, origanene, cysteine, gallic acid, and apigenin compounds play main roles in the antimicrobial effects of *N. sativa*[35]. Furthermore, *N. sativa* and its constituents showed useful effects against infections resulting from coronavirus disease 2019 (COVID-19)[36]. TQ has also been recognized to have anti-microsporidial effect against *Encephalitozoon intestinalis in vitro*[37].

5. Anti-depressant effects of *N. sativa* and TQ

Depression is a mental disorder that is characterized by confusion[38], sadness[39], anxiety[40], and lack of interest and motivation[41]. Epidemiologic studies show that a large number of people suffer from depression and it has become a human health problem[42]. Genetic and environmental factors such as stress are considered the main causes of the development of depression[43]. Depression may affect the structure and function of different areas of the brain. It has been indicated that depression can lead to hippocampus and prefrontal cortex atrophy[44]. In addition, previous studies show that synaptic plasticity impairment in some brain areas including the hippocampus can play a key role in the pathogenesis of depression[45]. Neurotrophic factors are endogenous soluble proteins regulating neuronal plasticity[46]. One of the most well-known neurotrophic factors is brain-derived neurotrophic factor (BDNF). It has been illustrated that stress inhibits the generation of BDNF in the hippocampus[47]. Treatment by medicinal plants can mitigate the complications of depression by affecting BDNF production[48]. In a clinical trial, researchers evaluated the effect of the capsules containing 1 000 mg of *N. sativa* oil extract on male depressed patients. The results demonstrated that *N. sativa* extracts resulted in a remarkable reduction in depression score, anxiety, and stress and significantly enhanced the serum level of BDNF[49]. It has been also reported that a significant number of dialysis patients suffer from different degrees of depression and suicide is prevalent among them[50]. In a double-blind, randomized controlled trial, the effect of *N. sativa* oil supplementation on hemodialysis-induced depression was checked. In this research, treatment with two soft gels of *N. sativa* attenuated the symptoms of depression in patients[51].

Sickness behaviors are behavioral complexes that may be induced by infections, immune system disturbances, and overproduction of pro-inflammatory cytokines[52]. There are noticeable similarities between sickness behaviors and depression. Anorexia, weight loss, sleepiness, fatigue, malaise, anxiety, and cognitive deficits are considered common points between sickness behaviors and depression[53]. In animal studies, sickness behaviors were assessed by behavioral techniques including open field, elevated plus maze, and forced swimming tests[54]. It has been documented that acute administration of 100, 200, and 400 mg/kg of ethanolic extract of *N. sativa* exhibited marked anti-anxiety and antidepressant effects in the open field, elevated plus maze, and forced swimming tests[55]. Microbial toxins can disturb immune system function and induce anxiety and depression-like behaviors. LPS is a potent bacterial endotoxin that stimulates the production of pro-inflammatory cytokines and consequently induces sickness behaviors[56]. In an animal study, pretreatment with hydro-alcoholic extract of *N. sativa* (100, 200, and 400 mg/kg) could improve LPS-induced sickness behaviors in rats, which was attributed to anti-inflammatory and antioxidant effects of *N. sativa*[57].

Increasing evidence reveals that toxic heavy metals can induce depression-like behaviors[58]. Mercury is a toxic heavy metal that can hazard the stomach, kidneys, and cardiovascular system[59]. The effects of *N. sativa* oil (2 mL/kg/day) against mercuric chloride-induced anxiety and depression were evaluated in Wistar rats. In this study, administration of mercuric chloride for three weeks induced anxiety and depression-like behaviors in rats. Treatment with 2 mL/kg of *N. sativa* oil for four weeks reversed the harmful effects of mercuric chloride on behavioral functions of rats, as evidenced by increasing the number of line crossing, time spent in open arm, and swimming time in the forced swimming test. The improvement in behavioral performance was linked to antioxidant effect of *N. sativa* oil[60].

TQ derived from *N. sativa* is well known for its antioxidant and anti-inflammatory properties[61]. Besides free radicals scavenging effect, TQ possesses the antimicrobial[62], anti-toxicity[63], anti-diabetic[64], antihypertensive[65] and hepatoprotective[66] properties. One of the limitations of use of TQ in scientific studies is low solubility and bioavailability. To overcome this problem, a formulation of TQ solid lipid nanoparticles (TQSLN) is used[67]. Serotonin (5-HT) is a monoamine neurotransmitter with antidepressant effects which is synthesized from amino acid tryptophan (TRP)[68]. In addition, TRP can be metabolized through the kynurenine (KYN) pathway[69]. Indoleamine-2,3-dioxygenase (IDO) as the first enzyme of this pathway is activated by inflammatory mediators such as interferon-gamma (IFN-γ). Therefore, the activity of IDO is associated with the decrement of 5HT level and the enhancement of KYN concentration[70]. KYN pathway has also been exhibited to have a key role in depression[69]. Alam *et al*. investigated the antidepressant effect of TQSLN (20 mg/kg, *p.o.*) in a rat model of chronic forced-swim stress. In this study, the antidepressant effect of TQSLN was associated with decreased concentration of tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6 and increased levels of BDNF in the hippocampus tissue of rats. The results of the study also demonstrated that treatment with TQSLN reversed the increased activity of IDO in stressed rats. Reduction of IDO activity was determined by a reduced ratio of hippocampal KYN/TRP and an increased ratio of 5HT/TRP[71]. Based on the results of another study, TQSLN alleviated depressive behavioral conditions in LPS-exposed rats. TQSLN significantly decreased the immobility time in the tail suspension test. In the forced swimming test, TQSLN lessened the immobility time and increased swimming time and climbing time in rats. The improvement of behavior performance was associated with a significant increase in BDNF and 5HT/TRP ratio and a considerable reduction in KYN/TRP ratio and the expression of TNF-α, IL-6, and NF-κB in hippocampus tissue of rats treated by TQSLN[72].

It has also been documented that some antihypertensive drugs such as reserpine are depressogenic[73]. In another study, Samad *et al*. showed that 10 and 20 mg/kg of TQ improved reserpine-stimulated anxiety and depression in mice by reducing inflammation and oxidative damage of the hippocampus[74].

Diabetes mellitus is a metabolic disorder that threatens the health of a large number of people throughout the world[5]. There is a two-way relationship between diabetes mellitus and depression[75]. In an animal study, TQ (10 and 20 mg/kg) could mitigate depression in type 2 diabetic rats by decreasing the level of IL-1β and TNF-α and oxidative stress[76].

Concanavalin A (Con A) is a plant mitogen belonging to legume lectin family which strongly stimulates the immune system[77]. This chemical compound has also been reported to trigger sickness behaviors in rodents[78]. Nazir *et al*. reported that TQ (10 mg/kg) could protect the mice against Con A-caused anxiety and depression *via* the anti-inflammatory activity[79]. In addition, the anxiolytic effect of TQ (2.5 and 5 mg/kg/day) against arsenic-caused hippocampal damage in rats was examined. Firdaus *et al*. revealed that pretreatment with 5 mg/kg of TQ improved the behavior performance in behavior tests, enhanced glutathione and SOD activity and mitigated the levels of lipid peroxidation (LPO), TNF-α and IFN-γ in hippocampus tissue of rats[80]. Table 1 exhibits the antidepressant effects of *N. sativa* and TQ.

6. Anti–nociceptive effects of *N. sativa* and TQ

Besides unpleasant feelings, pain is a sensory modality providing human survival. Few people in the world do not complain of pain[81]. Nociceptors are free nerve endings that detect different types of noxious stimuli. Two types of nerve fibers send pain impulses to the brain: (1) C fibers and (2) Aδ fibers. C fibers are small in diameter and unmyelinated. They send the nerve impulses

Table 1. Antidepressant effects of *Nigella sativa* and its main constituent thymoquinone.

Treatment	Type of study	Dose	Effects	Reference
Oil extract of *Nigella sativa*	Human	1 000 mg	Reduction in depression score, anxiety and stress, and enhancement of the serum level of BDNF	[49]
Soft gel of *Nigella sativa*	Human	1 g	Attenuation of symptoms of depression	[51]
Ethanolic extract of *Nigella sativa*	Rat	100, 200 and 400 mg/kg	Increase of the crossing number, traveled distance, and time spent in central zone in OF test, decrement of entry number and time spent in closed arms and increment of time spent in open arms in EPM test, enhancement of climbing time in FST	[55]
Hydro-alcoholic extract of *Nigella sativa*	Rat	100, 200 and 400 mg/kg	Improvement of LPS-induced sickness behaviors	[57]
Nigella sativa oil	Rat	2 mL/kg	Increase of the number of line crossing in OF test, time spent in open arm in EPM test, and swimming time in FST	[60]
Thymoquinone	Rat	20 mg/kg	Decrease of TNF-α and IL-6 concentration and KYN/TRP ratio, and increase of BDNF level and 5HT/TRP ratio in hippocampus tissue	[71]
Thymoquinone	Mouse	10 and 20 mg/kg	Improvement of reserpine-stimulated anxiety and depression *via* reducing inflammation and oxidative damage of the hippocampus	[74]
Thymoquinone	Rat	10 and 20 mg/kg	Mitigation of type 2 DM-induced depression by decreasing IL-1β, TNF-α, and oxidative stress	[76]
Thymoquinone	Mouse	10 mg/kg	Protection against Con A-caused anxiety and depression	[79]
Thymoquinone	Rat	2.5 and 5 mg/kg	Improvement of arsenic-caused anxiety-like behaviors by elevating the level of GSH and SOD activity and mitigating the content of LPO, TNF-α, and IFN-γ in hippocampus tissue	[80]

BDNF: brain-derived neurotrophic factor, OF: open field, EPM: elevated plus maze, FST: forced swimming test, LPS: lipopolysaccharide, KYN: kynurenine, TRP: tryptophan, 5HT: 5-hydroxytryptamine, DM: diabetes mellitus, IL-1β: interleukin-1β, TNF-α: tumor necrosis factor-alpha, Con A: concanavalin A, GSH: glutathione, SOD: superoxide dismutase, LPO: lipid peroxidation, IFN-γ: interferon-gamma.

Table 2. Anti-nociceptive effects of *Nigella sativa* and thymoquinone.

Treatment	Type of study	Dose	Effects	Reference
5% gel of *Nigella sativa*	Human	Twice a day	Reduction of the mean score of pain	[100]
Nigella sativa oil	Human	1 mL	Alleviation of knee pain	[101]
Panch phoron extract	Mouse	100, 300 and 500 mg/kg	Mitigation of pain and inflammation	[104]
Nigella sativa extract	Mouse	0.5 mL	Decrease in writhing number	[105]
Ethanolic extract of *Nigella sativa*	Mouse	50 mg/kg	Reduction of writhing number	[106]
Thymoquinone	Rat	1.25, 2.5, and 5 mg/kg	Alleviation of neuropathic pain and modulation of oxidative stress	[109]
Thymoquinone	Rat	20 and 40 μg/paw and 2, 4, and 8 μg/kg	Decrease of paw licking time in early and late phases of formalin test	[112]

slowly. Aδ fibers are large in diameter, myelinated, and conduct pain impulses faster[82,83]. Pain sensations can be irritated due to inflammation and tissue injuries[84]. Chemical substances such as potassium[85], bradykinin[86], histamine[87], serotonin[88], substance P[89] and prostaglandins[90] can stimulate nociceptors. Endogenous chemicals including enkephalins, endorphins, and dynorphin also relieve pain by binding to the opioid receptors[91]. In addition, some drugs[92] and natural compounds[93] have been reported to mitigate pain. Dysmenorrhea, also named painful cramps, begins one or two days before menstruation[94]. This pain can result in vomiting, fatigue, and nausea[95]. Drug and non-drug treatments are recommended as the main methods for relieving dysmenorrhea. Herbal medicines including curcumin[96], saffron[97], and thyme[98] have been employed for alleviating dysmenorrhea. In a randomized double-blind clinical trial, *N. sativa* oil exerted analgesic effects in female students suffering from primary dysmenorrhea[99]. In another study, a 5% gel of *N. sativa* was used for reducing the worst experimental pain in patients with breast cancer who were treated by radiotherapy. In this study, a visual analog scale evaluated the worst experimental pain and the findings indicated that the mean score of pain in patients exposed to 5% gel was significantly lower than those treated with a placebo[100]. Kooshki *et al*. also reported the soothing effect of *N. sativa* oil (1 mL every 8 h for 3 weeks) on osteoarthritis-induced knee pain in elderly men and women[101]. In a rat model of arthritis, oral administration of 1.82 mL/kg and 0.91 mL/kg of *N. sativa* oil also exerted anti-nociceptive and anti-inflammatory effects[102]. Panch phoron comprises five plant species containing *N. sativa*, *Foeniculum vulgare*, *Trigonella foenum-graecum* Linn, *Brassica nigra*, and *Cuminum cyminum*[103]. This mixture was used in traditional medicine and has different therapeutic effects. Gias *et al*. demonstrated the anti-nociceptive effect of panch phoron extracts (100, 300, and 500 mg/kg) in the writhing test. Based on the results, the extract dose-dependently attenuated pain and inflammation in mice[104]. In addition, Zakaria *et al*. investigated the analgesic effect of 0.5 mL of *N. sativa* extract in a mice model of acetic acid-caused writhing. Their findings revealed that the extract could significantly lower the number of writhing compared with the control group, the analgesic effect of which was comparable to that of aspirin[105]. It has also been reported that intraperitoneal administration of 50 mg/kg of ethanolic *N. sativa* seed extract reduced the number of writhing compared to the control group in experimentally stimulated pain in albino mice[106].

Neuropathic pain is a chronic annoying condition that is excited by damage to neuronal fibers in the peripheral and central nervous system. It can be associated with hyperalgesia caused by noxious stimuli or may be evoked by non-painful stimuli (allodynia)[107]. Due to the lack of proper effect of available drugs on neuropathic pain, recent studies are conducted to discover natural remedies attenuating this chronic condition. According to current scientific evidence, oxidative stress has a high contribution to induction of neuropathic pain[108]. Amin *et al*. examined the effect of TQ (1.25, 2.5, and 5 mg/kg) on pain irritated by chronic constriction injury in the sciatic nerve of rats. The results confirmed the improving effect of TQ on neuropathic pain by enhancing the antioxidant ability[109].

The role of signaling pathways related to nitric oxide (NO) in modulation of pain perception has been confirmed in many studies. It has been demonstrated that the activation of *L*-arginine, NO, 3',5'-cyclic guanosine monophosphate (cGMP) and potassium (K^+) channels (*L*-arginine/NO/cGMP/K_{ATP}) pathway can result in the mitigation of pain[110,111]. In an experimental research, the effect of peripheral (10, 20, and 40 μg/paw) and central (2, 4, and 8 μg/kg) administration of TQ on formalin-induced pain in rats was evaluated. Ipsilateral peripheral injection of 20 and 40 μg TQ into the paw of rats and intracerebroventricular (ICV) administration of TQ remarkably decreased the paw licking time in the early and late phases of the formalin test. In this study, intraperitoneal injection of 100 μg/paw of *L*-NG-nitroarginine methyl ester (*L*-NAME), a nitric oxide synthase inhibitor, reversed the anti-nociceptive effect of 20 μg/paw of TQ in the late phase of the formalin test. ICV injection of 1 μg/kg of *L*-NAME also attenuated the effect of 8 μg/kg of TQ in both phases of the formalin test. To determine the role of cGMP in the anti-nociceptive effect of TQ, methylene blue as a guanylyl cyclase inhibitor was employed. It could antagonize the positive effect of TQ (20 μg/paw, *i.p.* and 8 μg/kg, ICV) on formalin-induced pain. The blocker of the voltage-gated K^+_{ATP} channel, glibenclamide, was also used for checking the role of K^+ ions in the anti-nociceptive effects of TQ. The results illustrated that glibenclamide could diminish the peripheral and central anti-nociceptive effect of TQ[112]. Table 2 summarizes the anti-nociceptive effects of *N. sativa* and TQ.

7. Conclusion

The clinical and experimental evidence exhibts that *N. sativa* exerts alleviative effects on depression symtoms and pain. In addition, TQ as a main effective ingredient of *N. sativa* has good therapeutic effects on sickness behaviors and pain. Antidepressant and analgesic effects of *N. sativa* and TQ can be arrtibuted to their antioxidant and anti-iflammatory properties. One of underlying mechanisms of antidepressant effects of TQ is enhancement of brain level of serotonin and upregulation of BDNF. Upregulation of *L*-arginine/NO/cGMP/K_{ATP} channel pathway also involves in the anti-nociceptive effect of TQ. Although the results of many studies confirm antidepressant and anti-nociceptive effects of *N. sativa* and TQ, complementary studies in this field are required to further elucidate the mechanisms of their anti-nociceptive action.

Conflict of interest statement

The author declares that there is no conflict of interest.

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