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Review Article

Neuropharmacological effects of *Ocimum basilicum* and its constituents

Farzaneh Shakeri[1], Mahmoud Hosseini[2,3]*, Ahmad Ghorbani[4]

1. Natural Products and Medicinal Plants Research Center, North Khorasan University of Medical Sciences, Bojnurd, Iran
2. Division of Neurocognitive Sciences, Psychiatry and Behavioral Sciences Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
3. Neurogenic Inflammation Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
4. Pharmacological Research Center of Medicinal Plants, Mashhad University of Medical Sciences, Mashhad, Iran

Abstract

Introduction: Various pharmacological effects of *Ocimum basilicum* (*O. basilicum*) have been investigated including: antioxidant, antibacterial, anti-ulcerogenic, cardiac stimulant, hypoglycemic, hypolipidemic, hepatoprotective, anti-inflammatory, anticancer and immunomodulatory properties. It has also the beneficial effects in nervous system disorders, reproductive disorders and respiratory diseases. In this article the neuropharmacological effects of *O. basilicum* and its constituents is reviewed.

Methods: The data was gathered by searching: PubMed, Science Direct, Scopus and Google Scholar using the following key words: Basil, *O. basilicum*, neuropharmacological, neurotoxicity, neurodegeneration, memory, learning, epilepsy, pain, anticonvulsant, antianxiety, anxiety, depression and anti-depressant.

Results: This review indicates that *O. basilicum* and its constituents have various properties including anti-depression, anti-anxiety, anti-analgesic, anti-nociceptive and memory enhancer which are probably due to its antioxidant property of *O. basilicum*.

Conclusion: It seems that *O. basilicum* and its constituents could be of therapeutic values in nervous system diseases.

Keywords:
O. basilicum;
Seizure;
Depression;
Anxiolytic;
Analgesic

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***Correspondence to:**
M. Hosseini

Tel: +98-5138828565
Fax: +98-5138828564

Email:
Hosseinim@mums.ac.ir

Introduction

Ocimum basilicum (*O. basilicum*) or basil is an aromatic annual and perennial herb which is a member of Lamiaceae family (Blank et al., 2012). It is called basil, common basil or sweet basil (English), babui tulsi (Hindi and Bengali), badrooj, hebak or rihan (Arabic), nasabo or sabje (Gujrati), jangli tulsi (Urdu) and tohrakhurasani and okimon (Persian and Unani) (Bilal et al., 2012). *O. basilicum* could be raised to 0.6 to 0.9m high, with simple, opposite and green leaves. The flowers are small, white/purple in color and commonly removed to enhance the yield of leaves (Duke, 1985). The basil seed is a tiny black, ellipsoid seed that is used for eating are the seeds from the sweet basil plant, *O. basilicum* (Fig. 1).

O. basilicum is used in Ayurveda and in traditional Chinese medicine for a variety of conditions and disorders including antispasmodic, aromatic, carminative, digestive, galactagogue, stomachic, tonic agents, heart and blood, local anesthetic, snake

Fig.1. Whole plant, flower and seeds of *O. basilicum* (Hanif et al., 2011).

bites, skin infections, parasiticide, antiseptic, blood dysentery, hematuria, inflammation and congestion of kidney (Duke and Ayensu, 1985; Pullaiah, 2006). The seeds of the plant are used in traditional for treatment of colic ulcer, dyspepsia and diarrhea (Simon et al., 1999). *O. basilicum* used in traditional Iranian medicine to treat fevers, throat congestions and stomachache (Omidbeigi, 2000) and as a well-known source of flavoring principles (Javanmardi et al., 2002).

Various pharmacological effects of this plant such as analgesic (Choudhury Golak et al., 2010), anti-inflammatory (Eftekhar et al., 2019), anti-microbial (Adigüzel et al., 2005), antioxidant (Eftekhar et al., 2019), anti-ulcerogenic (Akhtar and Munir, 1989), chemomodulatory (Dasgupta et al., 2004), hepatoprotective (Marzouk, 2009), anti-asthmatic (Eftekhar et al., 2019), immunomodulatory (Dashputre and Naikwade, 2010), hypoglycaemic and hypolipidaemic (Zeggwagh et al., 2007) have been reported. It should be noted that its safety in animal and human models has been confirmed (Katalinic et al., 2006). Rosmarinic acid (RA) is a naturally occurring phenolic compound which is found in several plants of the Lamiaceae family such as *Ocimum basilicum*, *Rosmarinus officinalis*, *Origanum vulgare*, *Melissa officinalis* and *Salvia officinalis* (Shekarchi et al., 2012). Different therapeutic effects have been described for RA such as anti-asthmatic (Shakeri et al., 2019), anti-bacterial (Ekambaram et al., 2016), anti-inflammatory (Shakeri et al., 2019), analgesic activities (Gamaro et al., 2011) and immunomodulatory actions (Shakeri et al., 2019). RA is a prominent anti-anxiety agent by acting as a GABA transaminase inhibitor, it also inhibits the expression of indoleamine 2,3-dioxygenase through its cyclooxygenase-inhibiting properties in murine dendritic cells (Lee et al., 2007; Awad et al., 2009).

In this review article, we summarized and discussed neuropharmacological effects of *O. basilicum* and its constituents including anti-convulsant, anti-anxiety, anti-depressant, anti-nociceptive and analgesic

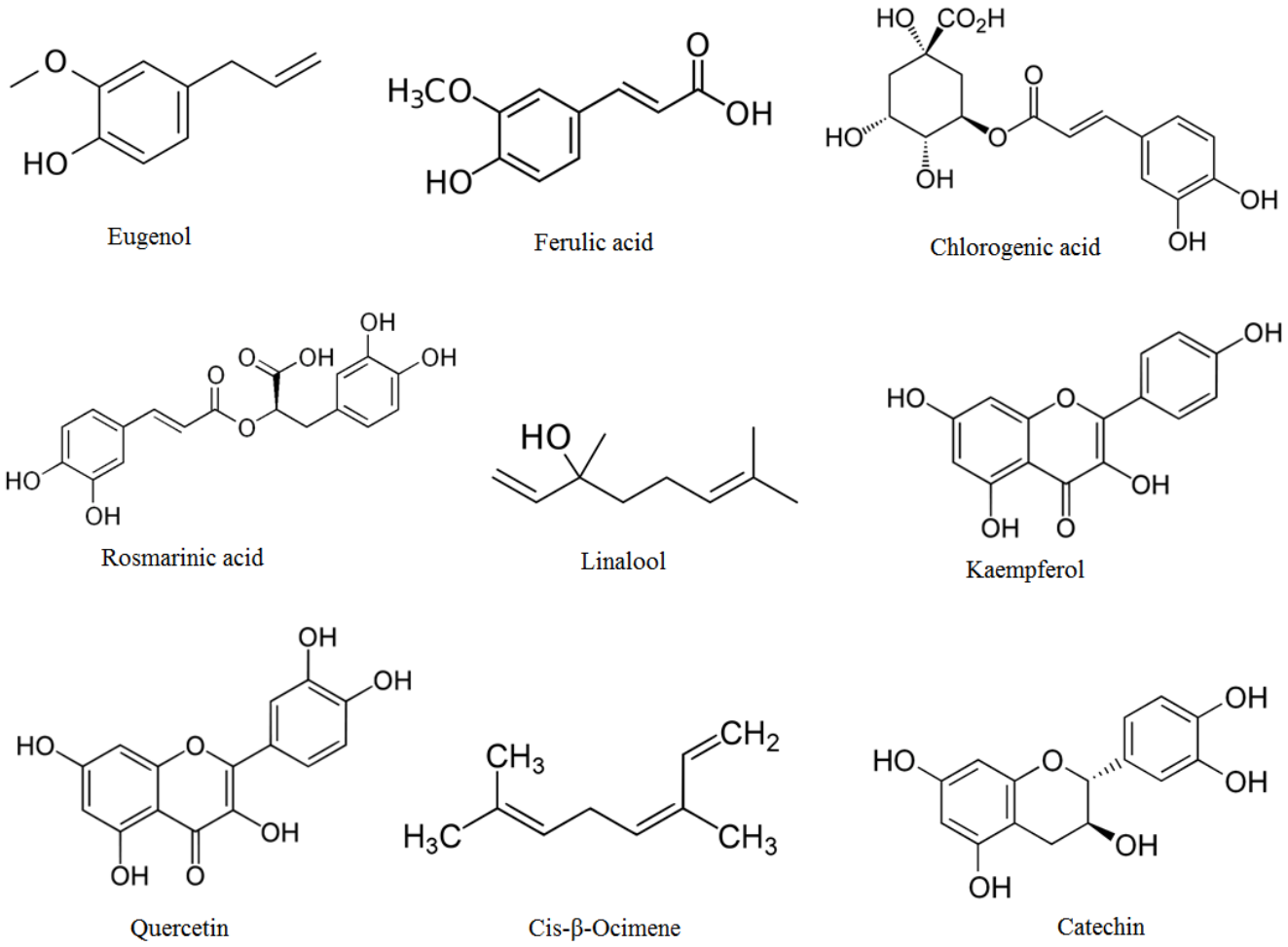

Fig.2. Chemical structure of some bioactive compounds of *O. basilicum*.

properties. Also, effects of *O. basilicum* on the memory and learning and its protective action against neurotoxicity and neurodegeneration are reviewed.

Materials and methods

Method of literature search

An online literature search was performed in the databases Medline, Pubmed, Science Direct, Scopus and Google Scholar from 1950 to March 2018 to identify studies about neuropharmacological effects of *O. basilicum* and its constituents. The keywords used for the search were Basil, *O. basilicum*, neuropharmacological, neurotoxicity, neurodegeneration, memory, learning, epilepsy, pain, anti-convulsant, anti-anxiety, anxiety, depression and anti-depressant. A total of 75 articles were identified by authors, the search results were checked and 63 eligible articles were included in this review. The references of all relevant articles were checked for cross-references to find as many studies as possible.

Bioactive compounds of *O. basilicum*

O. basilicum chemical compositions and their amount are depending on geographical conditions including environmental and physiological factors as well as method of extraction. For example, an essential oil obtained from Iranian *O. basilicum* was consisted of Borneol, β-ocimene, caryophyllen oxide and fenchone (Farhang et al., 2014). Methyl cinnamate, linalool, tau-cadinol, α-bergamotene, γ-muurolene, sulfone-methyl styryl and methyl chavicol were reported for *O. basilicum* essential oil from Bangladesh, and in Northeast India the major constituents were found to be camphor, limonene, and β-selinene (Joshi, 2014). Aroma compounds of *O. basilicum* such as 1,8-cineole, bergamotene, eugenol, linalool, methyl chavicol, methyl cinnamate used in a wide variety of products such as cosmetics and natural flavors (Loughrin and Kasperbauer, 2001). *O. basilicum* produces a range of polyphenolic compounds including rosmarinic acid, p-hydroxy benzoic acid, ferulic acid, gallic acid, p-coumaric acid,

Table 1. Chemical composition of *O. basilicum* essential oils, polyphenolic and aroma compounds (Loughrin and Kasperbauer, 2001; Achel et al., 2011).

Essential oils	Polyphenolic	Aroma
α-Pinene	Rosmarinic acid	1 ,8-cineole
Camphene	p-hydroxy benzoic acid	Eugenol
β-Pinene	Ferulic acid	Linalool
β-Myrcene	Gallic acid	Methyl chavicol
1,8-Cineol	p-coumaric acid	Methyl cinnamate
Trans-β Ocimene	Benzoic acid	1 ,8-cineole
γ-Terpin	Kaempferol	Bergamotene
Linalool	Catechin	α-humulene
Camphor	Quercetin	α-bergamotene
Myrtenol	Chlorogenic acid	α-terpineol
α-Cubebene	Caffeic acid	Caryophyllene
Eugenol	Cinnamic acid	Limonene
Methyl cinnamate	Ellagic acid	α-pinene
Iso-Caryophyllene	Rutin	β-pinene
α-Caryophyllene	Miricetol	Myrcene
Azulene	Fisetin	Camphene
α-Farnesene	Quercitrin	Tepinen-4-o
Germacrene B	Sinapic acid	Bornyl acetate
Germacrene D	Apigenin	2-carene

benzoic acid, kaempferol, catechin, quercetin, chlorogenic acid, caffeic acid, cinnamic acid and ellagic acid (Fig. 2) (MHM et al., 2015).

The chemical composition of *O. basilicum* also changed by the four seasons. The amount of the oil in the *O. basilicum* samples collected in winter and summer are found 0.8% with 68.9% oxygenated monoterpenes and 0.5% with 24.3% sesquiterpene hydrocarbons respectively (Hussain et al., 2008). The nutritional and mineral compositions of *O. basilicum* including protein, crude fiber, ash, nitrogen-free extractives, carbohydrate, saponin, oxalate, flavonoid, polyphenols, β-carotene, niacin, thiamine, phosphorus, calcium, magnesium, potassium, sodium and zinc (Table 1) (Achel et al., 2011).

Anti-convulsant effects

The anti-epileptic effect of hydroethanolic extract of *O. basilicum* on female Balb/C mice was evaluated in pentylenetetrazole (PTZ)-induced epilepsy model as follows: I) control (0.5ml normal saline, intraperitoneal administration: ip); II) diazepam (2mg/kg, ip); III, IV, V and VI) *O. basilicum* extract (100, 250, 300 and 350mg/kg, ip). The results showed that *O. basilicum* extract at the dose at 250mg/kg could be recommended as the best dose compared with diazepam probably because of the enhancement cerebral GABA content (Modaresi and Pouriyanzadeh, 2013; Modaresi et al., 2014). The effect of *O. basilicum* essential oil (100, 200 and 400mg/kg, ip) on seizure induced by PTZ, picrotoxin and strychnine on male albino mice showed that *O. basilicum* at the doses of 200 and 400mg/kg significantly elevated the latency time and reduced the percentage of convulsion and lethality on PTZ and picrotoxin-induced convulsion, but did not effect on strychnine model (Oliveira et al., 2009).

In a comparative study, the anti-epileptic effects of *O. basilicum* and *Fumaria schleicheri* (*F. schleicheri*) aqueous extract (100mg/kg, intragastric administration: ig) on maximal electroshock (MES) test (duration of 0.2s, frequency of 50Hz and current

Table 2: Summary of studies reporting anti-convulsant effects of *O. basilicum*. PTZ: pentylenetetrazole; ig: intragastric administration; ip: intraperitoneal administration.

Plant preparation	Experimental model	Dose	Effect	Reference
Hydroethanolic extract	PTZ-induced epilepsy in female mice	(100, 250, 300, 350 mg/kg, ip)	Delayed the onset of seizures Reduced the duration of myoclonic seizures	(Modaresi and Pouriyanzadeh, 2013)
Hydroethanolic extract	PTZ-induced epilepsy in female mice	(100, 250, 300, 350 mg/kg, ip)	Reduced the frequency of epilepsy, and mortality rate	(Modaresi et al., 2014)
Essential oil	PTZ, picrotoxin and strychnine-induced epilepsy in male mice	(100, 200, 400 mg/kg, ip)	Elevated the latency time Reduced the percentage of convulsion and lethality on PTZ and picrotoxin-induced convulsion	(Oliveira et al., 2009)
Aqueous extract	PTZ-induced epilepsy in male mice	(100 mg/kg, ig)	Reduced the duration of convulsions, time of recovery and lethality level	(Tsyvunin and Shtrygol, 2015)
Essential oil	PTZ, picrotoxin and strychnine-induced epilepsy in male/female mice	(0.2, 0.4, 0.8, 1.2 mg/kg, ip)	Elevated the latency time for the onset of clonic seizures Reduced the percentage of convulsion and lethality	(Ismail, 2006)
Hydroethanolic extract	PTZ-induced epilepsy in male mice	(25, 50,100 mg/kg, ip)	Delayed the onset of clonic and generalized tonic-clonic seizures Improved oxidative damage of brain tissue	(Khodabakhshi et al., 2017)

Table 3: The effects of *O. basilicum* on neurotoxicity and neurodegeneration. GSH: glutathione; ig: intragastric administration; MDA: malondialdehyde; SOD: superoxide dismutase.

Plant preparation	Experimental model	Dose	Effect	Reference
Methanolic extract	Neuronal toxicity induced by EMF in the male rat	(0.5 g/kg, ig)	Increased the levels of SOD, GSH peroxidase, and catalase activity Reduced MDA level.	(Khaki, 2016)
Essential oil and linalool	In the trauma sciatic nerve of male rats	(0.01 to 1.0 mg/ml)	Reduced the excitability of peripheral nervous system	(Medeiros Venancio et al., 2016)
Ethyl acetate extract	Neuronal damage induced by global cerebral ischemia and reperfusion in male mice	(100,200 mg/kg, orally)	Reduced the cerebral infarct size, MDA Improve GSH content, short-term memory, and motor coordination	(Bora et al., 2011)

of 50mA) and PTZ-induced epilepsy model in male albino mice were investigated. Findings exhibited that both of extracts reduced the duration of convulsions, time of recovery and lethality level in MES condition, but in PTZ model *F. schleicheri* extract was effective in preventing convulsions. The possible mechanism for these effects could be due to biologically active substances as flavonoids, alkaloids, as well as terpenes and volatile components of essential oils (Tsyvunin and Shtrygol, 2015). Anti-epileptic effects of *O. basilicum* essential oil (0.2, 0.4, 0.8 and 1.2mg/kg, ip) on seizure induced by pentylenetetrazol, picrotoxin and strychnine on albino mice of either sex were also evaluated. *O. basilicum*

significantly elevated the latency time for the onset of clonic seizures and reduced the percentage of convulsion and lethality in a dose-dependent manner on PTZ and picrotoxin-induced epilepsy model, but in strychnine model, two higher doses of *O. basilicum* significantly delayed the onset and reduced the percentage of convulsion and lethality. The possible mechanism for anti-convulsant effects of *O. basilicum* could be associated to the presence of terpenes such as linalool, 1,8-cineole and eugenol (Ismail, 2006). The effect of *O. basilicum* hydroethanolic extract (25, 50 and 100mg/kg, ip) on convulsions induced by PTZ showed that pretreatment with *O. basilicum* delayed the onset of clonic and generalized tonic-clonic seizures and improved the oxidative damage of brain tissue in mice (Khodabakhshi et al., 2017). The anti-convulsant effects of *O. basilicum* were summarized in Table 2.

Protective effects of *O. basilicum* on neurotoxicity and neurodegeneration

Epilepsy has been reported to be accompanied with neuronal injury and brain damage which has been attributed to oxidative stress (Choopankareh et al., 2015; Karami et al., 2015; Anaeigoudari et al., 2016; Seghatoleslam et al., 2016; Ebrahimzadeh-Bideskan et al., 2018). The effect of *O. basilicum* methanolic extract (0.5g/kg, ig) on neuronal toxicity induced by an electromagnetic field (EMF, 50Hz for 8 weeks) has been reported. EMF-lesioned rats showed a reduction in the levels of superoxide dismutase (SOD), glutathione peroxidase (GSH) and catalase activity and an enhancement in the malondialdehyde (MDA) level. Treatment with extract significantly improved oxidative damage in brain tissues of the male rat (Khaki, 2016). In another study, the effects of *O. basilicum* essential oil and linalool at the range dose of 0.01 to 1.0mg/ml in the compound action potential of rat sciatic nerve were investigated. Both of them *O. basilicum* essential oil and linalool markedly reduced the excitability of peripheral nervous system in a same way and potency and the effects of *O. basilicum* essential oil on excitability could be associated to the presence of linalool (Medeiros Venancio et al., 2016). In a global cerebral ischemia and reperfusion model, oral administration of *O. basilicum* ethyl acetate extract (100 and 200mg/kg) could reduce cerebral infarct size, lipid peroxidation (LPO) and improve GSH content, short-term memory and motor coordination in albino mice of either sex (Bora et al., 2011). The effects of *O. basilicum* on neurotoxicity and neurodegeneration were summarized in Table 3.

Anti-anxiety and anti-depressant effects

The anti-depressant effect of *O. basilicum* essential oil has been carried out by behavioral test including forced swim test, elevated plus-maze and the open field test, biochemical and histopathological features on male Swiss albino mice subjected to chronic unpredictable mild stress (CUMS). Animals were divided into 4 groups including: I) control; II) CUMS; III) CUMS+ fluoxetine (20mg/kg, ig) and IV) CUMS+ *O. basilicum* essential oil (2.5ml/unit, inhalation administration: ih). Findings showed that *O. basilicum* reduced the depressive-like behavior, the corticosterone level, hippocampal neuron atrophy and apoptosis induced by CUMS and enhanced the thickness and the surface area of the DG granular and CA3 pyramidal cell layer, the number of the astrocytes and new nerve cells, GFAP-positive cells as well as BDNF and GR immunoexpression in the hippocampus. The possible mechanism for anti-depressant effects of *O. basilicum* could be associated to the presence of phenolic, flavonoid and tannin contents (Ali et al., 2017; Ayuob et al., 2017; Ayuob et al., 2018). The anti-depressant effect of different extract of *O. basilicum* on albino wistar rats of either sex was also evaluated in eleven animal groups as follows: I) control (1ml/100g normal saline, orally); II) fluoxetine (20mg/kg, ip); III, IV, V) water extract (100, 200 and 400mg/kg, orally); VI, VII, VIII) ethanol extract (100, 200 and 400mg/kg, orally) and IX, X, XI) petroleum ether extract (100, 200 and 400mg/kg, orally). The results showed that petroleum ether extract of *O. basilicum* at the doses at 200 and 400mg/kg significantly ameliorated the depressive status in a dose-dependent manner, although the differences in petroleum ether extract at the dose at 100mg/kg, water and ethanol extracts were not significant compared to control group (Brar et al., 2015). In a model of EMF exposure (50Hz for 8 weeks) in Albino male Wistar rats, it was shown that oral administration of *O. basilicum* (1.5g/kg, ig) increased swimming and reduced immobility scores in forced swimming test. The results also suggested that the possible mechanism of this effect due to antioxidative property and free radical scavenging

activity of *O. basilicum* (Abdoly et al., 2012). Another study showed that *Ocimum sanctum* L. (*O. sanctum*) and *O. basilicum* essential oils (200ul, ih) have anxiolytic and anti-depressant effects in Alzheimer's disease induced by β-amyloid (400pmol, icv). According to the study basil essential oils increased time spent, the number of entries and crossing in the open arms in elevated plus-maze (Gradinariu et al., 2015). The investigation of anxiolytic effect of the hydroethanolic extract of *O. basilicum* (25, 50 and 100mg/kg, orally) has been carried out by elevated plus maze model and the results exhibited that *O. basilicum* caused a concentration-dependent increase in the percentage of animal entries and time spent in open arms but did not effect on total distance traveled by animals and the number of entries in the closed arms (Nemati et al., 2015). The hydroethanolic extract of *O. basilicum* (50, 100 and 200mg/kg, ip) prevented depressive-like behavior in rats sensitized by ovalbumin (Neamati et al., 2016). The protective effect of a hydroethanolic extract of *O. basilicum* on CUMS-induced depression in male Albino rats was evaluated. Rats were divided randomly into five groups: control, CUMS, CUMS+imipramine (30mg/kg, orally), CUMS+*O. basilicum* (250mg/kg, orally) and CUMS+*O. basilicum* (500mg/kg, orally). Findings showed that *O. basilicum* extract reduced immobility time in forced swimming test and LPO level and increased levels of glutathione reduced (GR), ascorbic acid, SOD, catalase and glutathione peroxidase in the brain tissue. The possible mechanism of *O. basilicum* anti-depressant effects is through the antioxidative activity of phenolic compounds such as flavonoids, phenolic acids and phenolic diterpenes (Muneefa et al., 2017). The anxiolytic effect of the hydroethanolic extract of *O. basilicum* (25, 50, 100, 200, 400 and 600mg/kg, ip) in male mice has been demonstrated by elevation plus-maze test. The results of this study showed that all extract of *O. basilicum* significantly increased the percentage of time of permanence and the entrances in the open arms (Arzi, 2015). The results of another study suggested that the essential oil (200mg/kg, ip) and hydroethanolic extract of *O. basilicum* (100, 150 and 200mg/kg, ip) have anxiolytic and sedative effects through enhancement of time spent in open arm and reduction of motor activity in male mice, and possible pathway was through phenol and terpenoid components of *O. basilicum* (Rabbani et al., 2015). The anti-anxiety effect of *O. basilicum* hydroethanolic extract (100mg/ml, orally) has been demonstrated by an open field and elevated plus maze models in male mice (Zahra et al., 2015). The sedative effect of the hydroethanolic extract of *O. basilicum* (10 and 30mg/kg, orally) was evaluated in male Albino Wister rats by pentobarbitone (35mg/kg, ip) sleeping time test and open field test. It was demonstrated that *O. basilicum* extract decreases movement activity (numbers of the square which crossed and escape jumping) but increases sleeping time (Al-Ghurabi, 2014). In pentobarbital-induced sleep model, former treatment with *O. basilicum* hydroethanolic extract (25, 50 and 100 mg/kg, ip), ethyl acetate (50mg/kg, ip), n-butanol (50mg/kg, ip) and water fractions (50mg/kg, ip) could enhance sleep duration, although the sleep latency in ethyl acetate and water fractions were not significant compared to control group (Askari et al., 2016). The sedative and anesthetic effect of *O. basilicum* essential oil (10, 25, 50, 100, 200, 400 and 600µl/l) in Nile tilapia juveniles indicated that the effective doses for sedation and anesthesia were 10/25 and 400µl/l, respectively (Netto et al., 2017). The anti-anxiety and anti-depressant effects of *O. basilicum* were summarized in Table 4.

Anti-nociceptive and analgesic effects

The evaluation of anti-nociceptive effect of rosmarinic acid (10 and 30 mg/kg, orally) is a naturally occurring phenolic compound is obtained from the plant *O. basilicum* has been carried out by the tail flick method, formalin test and tactile allodynia in male Wistar rats and the results exhibited rosmarinic acid elevated tail-flick latency, paw withdrawal threshold and reduced licking time during both formalin test phases (Hasanein and Mohammad Zaheri, 2014). The oral administration of hydroethanolic extract of *O. basilicum* (10 and 30mg/kg) in male Albino Wister rats caused significant analgesic effect on nociceptive response initiated by formalin test at early and late phase, although this analgesic effect was less than that produced by diclofenac (0.71mg/kg, orally) at late phase (Al-Ghurabi, 2014). The effects of *O.basilicum* essential oil (OEO, 25mg/kg, po) and *O.basilicum* essential oil+β-cyclodextrin (OEO+ß-CD, 25, 50 or 100mg/kg, po) on an animal model for fibromyalgia were investigated in male mice. The results indicated that both OEO and OEO+ß-CD complexes caused a pronounced inhibitory effect on the nociceptive

Table 4. Summary of studies reporting anti-anxiety and anti-depressant effects of *O. basilicum.* GSH: glutathione; ig: intragastric administration; ip: intraperitoneal administration; ih: inhalation administration; SOD: superoxide dismutase

Plant preparation	Experimental model	Dose	Effect	Reference
Essential oil	Chronic unpredictable mild stress in male mice	(2.5 ml/unit, ih)	Reduced depressive-like behavior, the corticosterone level, hippocampal neuron atrophy and apoptosis	(Ali et al., 2017; Ayuob et al., 2017; Ayuob et al., 2018)
Water, ethanol, petroleum ether extract	Male/female rats	(100, 200, 400 mg/kg, orally)	Ameliorated the depressive status	(Brar et al., 2015)
Methanolic extract	Electromagnetic field exposure in male rats	(1.5 g/kg, ig)	Increased swimming Reduced immobility scores in a forced swimming test	(Abdoly et al., 2012)
Essential oil	Alzheimer's disease induced by a β-amyloid male in rat	(200 ul, ih)	Increased time spent, the number of entries and crossing in the open arms in elevated plus-maze	(Gradinariu et al., 2015)
Hydroethanolic extract	Male rats	(25, 50, 100 mg/kg, orally)	Increased the percentage of animal entries and time spent in open arms	(Nemati et al., 2015)
Hydroethanolic extract	Depressive-like behavior in rats sensitized by ovalbumin in the male rat	(50, 100, 200 mg/kg, ip)	Reduced the immobility Increased the swimming and climbing times	(Neamati et al., 2016)
Hydroethanolic extract	Chronic unpredictable mild stress in male mice	(250, 500 mg/kg, orally)	Reduced immobility time in forced swimming test and LPO level Increased levels of reduced GSH, ascorbic acid, SOD, catalase and GSH peroxidase in the brain tissue	(Muneefa et al., 2017)
Hydroethanolic extract	Male mice	(25, 50, 100, 200, 400, 600 mg/kg, ip)	Increased the percentage of time of permanence and the entrances in the open arms	(Arzi eta l., 2015)
Essential oil, hydroethanolic extract	Male mice	(200 mg/kg, ip) (100, 150, 200 mg/kg, ip)	Enhancement of time spent in open arm Reduction of motor activity	(Rabbani et al., 2015)
Hydroethanolic extract	Male mice	(100 mg/ml, orally)	Improved latency transfer and exploratory behavior in the open field and elevated plus maze	(Zahra et al., 2015)
Hydroethanolic extract	Pentobarbitone induced sleeping in male rat	(10, 30 mg/kg, orally)	Decreases movement activity (numbers of the square which crossed and escape jumping) Increases sleeping time	(Al-Ghurabi, 2014)
Hydroethanolic extract Ethyl acetate, n-butanol, water extract	Pentobarbital-induced sleep model in mice	(25, 50, 100 mg/kg, ip) (50 mg/kg, ip)	Enhance sleep duration	(Askari et al., 2016)
Essential oil	Nile tilapia juveniles	(10, 25, 50, 100, 200, 400 and 600 µl/l)	The sedative and anesthetic effect	(Netto et al., 2017)

behavior in mechanical hyperalgesia induced by acid saline. Immunofluorescence assays for Fos protein exhibited that OEO and OEO+ß-CD at 100mg/kg dose significantly activated neurons at periaqueductal grey, nucleus raphe magnus and locus coeruleus. Findings also demonstrated that OEO complexed with ß-CD was more effective than OEO. The possible mechanism of anti-hyperalgesic and anti-nociceptive effects of OEO could be related to linalool with its ability to modulate the muscarinic, opioid, dopaminergic, adrenergic and glutamatergic systems, as well as due to the interaction between glutamate

Table 5: Summary of studies reporting anti-nociceptive and analgesic effects of *O. basilicum.* ip: intraperitoneal administration; MPO: myeloperoxidase

Plant preparation	Experimental model	Dose	Effect	Reference
Rosmarinic acid	Male rats	(10, 30 mg/kg, oral)	Elevated tail-flick latency, paw withdrawal threshold Reduced licking time during both formalin test phases	(Hasanein and Mohammad Zaheri, 2014)
Hydroethanolic extract	Male rats	(10, 30 mg/kg, orally)	Analgesic effect on nociceptive response initiated by formalin test at early and late phase	(Al-Ghurabi, 2014)
Essential oil Essential oil+β-Cyclodextrin	Animal model for fibromyalgia in male mice	(25 mg/kg, p.o.) (25, 50 or 100 mg/kg, oral)	Inhibitory effect on the nociceptive behavior in mechanical hyperalgesia induced by acid saline	(Nascimento et al., 2014)
Essential oil	Male mice	(50, 100, 150 mg/kg, ip)	Suppressed the nociceptive response in the formalin test	(Min et al., 2009)
Ethanol extract	Carrageenan-induced paw inflammation in male rats	(2.5, 5, 10 mg/kg, ip)	Anti-inflammatory effect in the carrageenan test Decreased MPO activity and spongy-like appearance in epidermis and oedematasis in the dermis	(Rameshrad et al., 2015)
Essential oil and linalool	Orofacial nociception induced by formalin, glutamate, and capsaicin in male mice	(50, 100, 200 mg/kg, ip)	Reduced face rubbing behavior	(Venâncio et al., 2011)

Table 6: The effects of *O. basilicum* on memory and learning. ip: intraperitoneal administration

Plant preparation	Experimental model	Dose	Effect	Reference
Volatile oils Linalool 1,8-cineol, Eugenol Camphor	Learning and memory deficits induced by scopolamine in male mice	(100, 200, 400 mg/kg, ip) (90 mg/kg, ip) (30 mg/kg, ip) (70 mg/kg, ip) (100 mg/kg, ip)	Increased latency time in passive avoidance test Decreased acetylcholinesterase activity in brain tissue	(Tadros et al., 2014)
Hydroethanolic extract	Male mice	(100, 200, 400, 800 mg/kg, ip)	Increased step-down latency in passive avoidance task and retrieval of memory	(Sarahroodi et al., 2012)

and GABA systems (Nascimento et al., 2014). The systemic administration of OEO (50, 100 and 150mg/kg, ip) suppressed the nociceptive response in the formalin test (Min et al., 2009). In another study, *O.basilicum* ethanol extract (2.5, 5 and 10mg/kg, ip) exerted a significant anti-inflammatory effect in the carrageenan test. The extract also decreased myeloperoxidase activity and spongy-like appearance in epidermis and oedematasis in the dermis which could be due to the presence phenolic and flavonoid content in the plant (Rameshrad et al., 2015). The effects of *O. basilicum* essential oil and linalool (50, 100 and 200mg/kg, ip) on orofacial nociception induced by formalin, glutamate and capsaicin in male mice were evaluated. Results showed that all concentrations of linalool and two higher concentrations of *O. basilicum* essential oil significantly reduced face rubbing behavior in early and late phases of formalin test, although in glutamate and capsaicin models, only two higher concentrations of *O. basilicum* essential oil and linalool suppressed nociceptive behavior (Venâncio

et al., 2011). The anti-nociceptive and analgesic effects of *O. basilicum* were summarized in Table 5.

Effects on memory and learning

The effects of *O.basilicum* and *Ocimum africanum* (*O. africanum*) volatile oils (100, 200 and 400mg/kg, ip) and their terpenoids including linalool (90mg/kg, ip), 1,8-cineol (30mg/kg, ip), eugenol (70mg/kg, ip) and camphor (100mg/kg, ip) on learning and memory deficits induced by scopolamine were investigated in male albino mice. Findings showed that the high concentration of *O.basilicum*, medium concentration of *O. africanum*, 1,8-cineol, eugenol, and camphor significantly increased latency time in passive avoidance test but decreased acetylcholinesterase activity in brain tissue (Tadros et al., 2014). The investigation of retention and retrieval of memory of the hydroethanolic extract of *O. basilicum* (100, 200, 400 and 800mg/kg, ip) has been carried out by passive avoidance test, and the results exhibited that *O. basilicum* at the dose at 400mg/kg could be recommended as the best dose because of the presence of terpenoids, flavonoids, tannins and scavenge reactive oxygen species property (Sarahroodi et al., 2012). The effects of *O. basilicum* on memory and learning were summarized in Table 6.

Conclusion

Herbal compounds are good candidates for finding new therapies for neurological disorders. Several pharmacological studies on animal models displayed that *O. basilicum* and its bioactive components possess beneficial effects on nervous system particularly anti-convulsive, anti-nociceptive and anti-anxiety activities. The exact mechanisms by which *O. basilicum* modulate the function of the nervous system needs to be clarified by further studies. Many phytochemicals in *O. basilicum* including flavonoids, alkaloids and terpenes may be responsible for the neuropharmacological effects of this plant. The number of clinical trials that supporting these effects of *O. basilicum* on is currently insufficient and further well-designed clinical studies should be performed in this field.

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Conflict of interest

The authors have no conflict of interests to declare.

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