Journal of Ethnopharmacology 265 (2021) 113326

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jethpharm

Review of aromatherapy essential oils and their mechanism of action against migraines

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ARTICLE INFO

Keywords:
Plant essential oils
Anti-migraine
Monomer composition
Possible mechanism

ABSTRACT

Ethnopharmacological relevance: Migraines have become a major threat to human health, as they significantly affect human health and quality of life due to a high prevalence rate, attack rate and pain intensity. Aromatherapy, with its comfortable and pleasant natural characteristics and rapid and efficient characteristics, is widely favored by patients in the folk. Chinese folk also have the application history and related records of aromatic plants in the treatment of migraine.

Aim of the study: This study was conducted to review the pathogenesis of migraine, the application of plant essential oils in the treatment of migraine, and further explore the material basis and mechanism of action of plant essential oils against migraine.

Materials and methods: Search the electronic literature of essential oils with anti-migraine effect in Google Scholar, PubMed and China National Knowledge Infrastructure, and further search the research situation of the monomer components of essential oils in migraine, inflammation, pain and other aspects.

Results: studies show that there are 10 types of plant essential oils that could relieve migraine symptoms, and that 16 monomers may play a role in migraine treatment by effectively inhibiting neurogenic inflammation, hyperalgesia and balancing vasorelaxation.

Conclusion: Aromatic plant essential oils can relieve migraine effectively, these findings can be used as an important part of the development of anti-migraine drugs.

1. Introduction

Migraine is a type of primary neurovascular dysfunction disease, that is characterized by unilateral or bilateral pulsatile pain, and is accompanied by photophobia, phonophobia, nausea, vomiting and other symptoms IHS. Studies have shown that several mental, environmental and genetics can influence or induce a migraine (Kunkler et al., 2018; Sirri et al., 2018). The increasingly high-intensity, stressful working and living environment in China has led to an increase in the prevalence rate of migraines, reaching 9.3% in 2012 (Sirri et al., 2018). Patients with migraine experience many social, physical and psychological problems, which seriously affect their quality of life. Currently, the treatment of migraine primarily includes drug therapy, acupuncture therapy, massage therapy and aromatherapy. The complex pathogenesis of a migraine leads to limitations in a patient's response to drugs, and specific side effects and contraindications have further limited the choice of available drugs to treat this condition (Markus et al., 2016; Negro and Martelletti (2019)) (Table 1). Therefore, patients with migraine have explored alternative treatments such as aromatherapy for alleviation of their symptoms. Aromatherapy is a comfortable and pleasant all-natural therapy that produces a fast and efficient effect against migraine

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https://doi.org/10.1016/j.jep.2020.113326
Received 26 May 2020; Received in revised form 23 July 2020; Accepted 25 August 2020
Available online 30 August 2020
0378-8741/

Abbreviations

CNKI	China National Knowledge Infrastructure
CGRP	Calcitonin gene-related peptide
SP	Substance P
VIP	Vasoactive intestinal peptide
5-HT	5-hydroxytryptamine
ADP	Adenosine diphosphate
5-HIAA	5-hydroxyindoleacetic acid
NO	Nitric oxide
PGs	Prostaglandins
ET	Endothelin
PKC	Protein kinase C
GPCRs	G-protein coupled receptors
COX-2	cyclooxygenase-2
AC	Adenylate cyclase
cAMP	Cyclic adenosine monophosphate
CaM	calmodulin
MLCK	Myosin light chain kinase
ATP	Adenosine triphosphate
NOS	Nitric oxide synthase
L-Arg	L-arginine
eNOS	Endothelial nitric oxide synthase
nNOS	Neural nitric oxide synthase
iNOS	Inducible nitric oxide synthase
cNOS	Constitutive nitric oxide synthase
sGC	Soluble guanylyl cyclase
GTP	Guanosine 5′- triphosphate
cGMP	Cyclic guanosine monophosphate
PKG	Protein kinase G
NKA	Neurokinin A
TNF-α	Tumor necrosis factor-α
IL-1β	Interleukin-1β
IL-6	Interleukin-6
PGE2	Prostaglandin E2
MAPK	Mitogen-activated protein kinase
NF-κB	Nuclear factor-kappa B
JNK	c-Jun amino-terminal kinase
PGF2	Prostaglandin F2
PGI_2	Prostaglandin I2
VCAM-1	Vascular cell adhesion molecule-1
ICAM-1	Intercellular adhesion molecule-1
CA	cutaneous allodynia
TRP	Transient receptor potential
SG	Substantia gelatinosa
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazole propionate
NMDA	N-methyl-D-aspartate
CSD	Cortical spreading depression
IM	Inflammatory mediator
BO	Borneol
AITC	Allyl isothiocyanate
SNL	Spinal nerve ligation
CIN	1,8-Cineole
LPS	Lipopolysaccharides
HO-1	Heme oxygenase-1
LA	Linalyl acetate
ACh	Acetylcholine
MTN	L-menthone
UCMS	Unpredictable chronic mild stress
NE	Norepinephrine
SNI	Spared nerve injury
PHE	Phenylephrine
EAE	Experimental autoimmune encephalomyelitis
LIG	Ligustilide
VDCC	Voltage-dependent calcium channel
ROCC	Receptor-operated calcium channel
BCP	β-caryophyllene
CB2	Cannabinoid receptor type 2
NP	Neuropathic pain
MPP^+	1-methyl-4-phenylpyridinium
AN	Anethole
DADs	Diallyl disulfide
ROS	Reactive oxygen species
DATS	Diallyl trisulfide
BK	Bradykinin
HIS	Histamine
CT	Citronellol

symptoms. Its application has been evidenced in traditional Chinese medicine, as well as the records of aromatic plants in the treatment of migraine. Traditional Chinese Medicine Aromatherapy is a monograph that introduces the related efficacy of aromatic plants and their application in various diseases. it is also a university textbook that details the usage of aromatic plants in the treatment of migraine (Table 2). In this study, the data were selected using the following terms: "*essential oils*", "*volatile oils*", "*terpenes*" and "*migraine*" as well as the names of experimental models of migraine in animals such as "*nitroglycerin*", "*reserpine*", "*neurogenic imflammation*", "*electrophotoluminescence*", "*chemical stimulation*" and "*Mechanical stimulation*". The search was conducted in the scientific databases including Google Scholar, PubMed and China National Knowledge Infrastructure (CNKI), and 10 types of plant essential oils were found to be used in migraine treatment (Table 3). In this review the key substances and mechanisms involved in the action of plant essential oils against migraine are explored in order to provide a theoretical basis for aromatherapy in the treatment of migraine and to provide a reference for the development of novel anti-migraine essential oils and products.

2. Understanding migraines and their relation to modern medicine

Migraine is the second largest cause of disability in the world according to the 2016 Global Burden of Disease study Global 2016. Based on the migraine characteristics, they are primarily divided into migraine without aura and migraine with aura. The diagnostic criteria for migraine without aura is unilateral pulsatile headache lasting 4–72 h that may be aggravated by physical activity or head movement and accompanied by photophobia, phonophobia, nausea, vomiting and other symptoms. Migraine with aura refers to the appearance of aura symptoms hours or days before onset, which manifest as recurring unilateral reversible sight, sensation, or other central nervous system symptoms, followed by migraine symptoms (Anon., 2018b) IHS. Although the exact pathogenesis of migraine has not yet been elucidated, several potential mechanisms of action that have been suggested by researchers include 1) Intracranial vasoconstriction of the meninges causes local ischemia, followed by intracranial and extracranial vasodilation; 2) Perivascular nerves release calcitonin gene-related peptide (CGRP), substance P (SP) and vasoactive intestinal peptide (VIP) to induce a neurogenic inflammatory response; 3) Nociceptive stimuli are uploaded to the pain center step by step along with the pain conduction system, causing the pain center to be sensitized. These studies have also

gradually refined people's understanding of the pathogenesis of migraine.

3. Pathogenesis of a migraine

3.1. Migraine and abnormal vasomotor function

3.1.1. 5-Hydroxytryptamine (5-HT)

The neurotransmitter 5-HT is considered to be closely related to migraines as it affects the vasomotor functions. Currently, the receptor subtypes involved in migraine vasoconstriction are the 5-HT1B/D, 5-HT2B, and 5-HT7 receptors, these receptors could cause migraines by regulating dural vasodilation (Pei et al., 2016; Sokolov et al., 2011). A study of the relationship between platelet aggregation and 5-HT release has found that increased vascular shear stress, reversible vasoconstriction, or other cardiovascular abnormalities led to platelet activation and aggregation. activated platelets could release platelet-dense granules and other contents. Furthermore, platelet dense granules have been shown to release 5-HT and adenosine diphosphate (ADP), high concentrations of 5-HT cause vasoconstriction, leading to premonitory neurological symptoms. Moreover, 5-HT is metabolized to 5-hydroxyindoleacetic acid (5-HIAA) that is excreted in the urine, which decreases

Table 1
Advantages and disadvantages of conventional medicine and essential oil for anti-migraine.

Classification	Drugs		Advantages	Disadvantages	References
Conventional Drugs	Nonsteroidal Antiinflamma-tory Drugs (NSAIDS)	Ibuprofen, Aspirin, Naproxen, Diclofenac, etc	It is suitable for the treatment and prevention of acute migraine	1) it can cause gastrointestinal reaction, liver injury and granulocytopenia; 2) long-term use has the risk of gastrointestinal bleeding; 3) there are many contraindications	(Biglione et al., 2020; Vécsei et al., 2015; Anon., 2016)
	Triptans	Sumatriptan, Zolmitriptan, Naratriptan, Rizatriptan, etc	It can specifically treat migraine, and it is effective at any time of headache	1) It can cause fatigue, nausea, headache, dizziness, drowsiness, bone pain, chest pain, weakness, dry mouth, vomiting, sensory abnormalities, gastrointestinal reactions, mental disorders, nervous system diseases, etc.; 2) myocardial infarction, arrhythmia and stroke can be caused in severe cases; 3) there are many contraindications	
	Ergotamine	Ergotamine tartrate, Dihydroergotamine, Ergotamine Caffeine, etc	It has the advantages of long drug half-life and low recurrence rate of headache, and is suitable for patients with long duration of attack	1) It can cause nausea, vomiting, dizziness, drowsiness, chest pain, anxiety, paresthesia, mental depression and ergotamine poisoning; 2) a very small amount of ergotamine can quickly lead to drug overdose headache; 3) there are many contraindications	
	Antiepileptic	Valproic acid, Topiramate, Gabapentin, etc	It is effective for paroxysmal and chronic migraine, and may be effective for drug overdose headache	1) It causes nausea, drowsiness, tremor, alopecia, weight change, liver dysfunction, ataxia, cognitive and language disorders; 2) there are many contraindications	
	Calcitonin gene-related peptide receptor antagonist	Telcagepant (MK0974), etc	It can restore dilated meningeal arteries to normal and reduce migraine symptoms, and the process does not lead to vasoconstriction. Some patients who are ineffective or intolerant to trotans may have a good response to gepant drugs	It causes nausea, vomiting, dizziness, drowsiness, dry mouth, fatigue and weakness, abnormal sensation, chest tightness and discomfort, etc.	
	Calcium antagonist	Flunarizine, etc	Prophylactic treatment of migraine is effective and generally well tolerated.	1) Common adverse reactions such as drowsiness and weight gain, rarely depression and extrapyramidal symptoms. 2) there are more contraindications	
	β-Blocker	Metoprolol, Propranolol, Bisoprolol, etc	The effect is clear in the preventive treatment of migraine	1) Common adverse reactions, such as bradycardia, hypotension, drowsiness, weakness, decreased exercise tolerance, were common, and insomnia, nightmares, impotence, depression, hypoglycemia and other symptoms were rare; 2) there are more contraindications	
	Antidepressant	Amitriptyline, etc	It is especially suitable for patients with tension headache or depression	1) It can cause dry mouth, drowsiness, weight gain and other adverse reactions; 2) there are more contraindications	
Essential oil	–	Chamomile essential oil, Angelicae Dahuricae Radix essential oil, Chuanxiong Rhizoma essential oil, etc	It belongs to the pure natural therapy that makes the patients comfortable and pleasant, and the effect is obvious. Some essential oils can relieve photophobia, nausea, vomiting and other symptoms at the same time. It also can strengthen the body's immunity and balance the body's function.	1) Some essential oils have different effects on different types of migraine; 2) Different concentrations of essential oil have different effects, so it is necessary to control the concentration of essential oil	(Niazi et al., 2017; Chen et al., 2015; Du et al., 2007)

Table 2
Aromatic plants with anti-migraine effect and their usage.

Treatment	★Prescription	Usage
Application method	Aconiti Radix (**Aconitum carmichaeli Debeaux**), 6g; Kusnezoff monkshood root (**Aconitum kusnezoffii Rchb.**), 6g; Menthae Haplocalycis Herba (**Mentha canadensis L.**), 6g; Asari Radix Et Rhizoma (**Asarum sieboldii Miq.**), 1g; Gypsum Fibrosum (*Gypsum*), 12g; Piperis Fructus (**Piper longum L.**), 1g	Grind the powder together, mix the liquor into paste and apply it to the temple
	Carthami Flos (**Carthamus tinctorius L.**), 10g; Olibanum (**Boswellia sacra Flück.**), 10g; Myrrha (**Commiphora myrrha (T.Nees) Engl.**), 10g	Grind it into fine powder, mix it with aged vinegar into paste, mix with a little borneol and stick it to both temples
Nose-plugging therapy	Angelicae Dahuricae Radix (**Angelica dahurica (Hoffm.) Benth. & Hook.f. ex Franch. & Sav.**); Chuanxiong Rhizoma (**Conioselinum anthriscoides 'Chuanxiong'**); Asari Radix Et Rhizoma (**Asarum sieboldii Miq.**); Cimicifugae Rhizoma (**Actaea heracleifolia (Kom.) J. Compton**); Borneolum Syntheticum (*Blumea balsamifera.* DC.); Menthae Haplocalycis Herba (**Mentha canadensis L.**) (Equal amount)	Grind it into fine powder, bottle it and set aside, dip a little disinfectant cotton ball in powder when used, and plug your nostrils
	3 Flos Caryophylli (**Syzygium aromaticum (L.) Merr. & L.M. Perry**); 7 Pedicellus melo (*Cucumis melo* L.); 7 Phaseolus calcaratus Roxb (**Vigna umbellata (Thunb.) Ohwi & H. Ohashi**); Borneolum Syntheticum (*Blumea balsamifera* DC.), 0.2g; Moschus (**Abelmoschus moschatus Medik.**), 0.1g	Grind it into fine powder, put proper amount into the nostril
Olfactory method	Iperis Fructus (**Piper longum L.**), 30g; 7 Semen Sojae Atricolor (*Glycine max* (L.) Merr.); Zingiberis Rhizoma Recens (**Zingiber officinale Roscoe**), 120g; 7 Jujubae Fructus (**Ziziphus jujuba Mill.**) (enucleation); 7 Bulbus Allii Fistulosi (*Allium jistulosum* L.)	Iperis Fructus and Semen Sojae Atricolor; Zingiberis Rhizoma Recens are ground into fines, smashed and evenly mashed with other drugs, wrapped with gauze and smelled

★The prescription is from the migraine treatment section of a university textbook traditional Chinese Medicine Aromatherapy, and the key drug is aromatic plants.

the plasma 5-HT concentration. In addition, low concentrations of 5-HT have been shown to stimulate perivascular pain fibers, local release of nitric oxide (NO), prostaglandins (PGs) and neuropeptides, which cause vasodilation, leading to a migraine attack (Borgdorff and Tangelder (2012); Ma (2018)) (as shown in Fig. 1).

3.1.2. Endothelin (ET)

ET is a type of vasoactive peptide with strong vasoconstrictive effects. Three types of ET are actively expressed: ET-1, ET-2 and ET-3. Experimental data studies suggest a role of ET-1 in the complex pathophysiology of migraine (Iljazi et al., 2018). ET-1 possesses two specific receptors, ET (A) and ET (B). ET (A) receptors are distributed in vascular smooth muscle cells and lead to vasoconstriction, while ET (B) receptors are expressed in vascular endothelial cells and regulate vasodilation (Mazzuca et al., 2013). Increases in plasma ET levels in the early stages of migraine attacks activate protein kinase C (PKC) and result in PKC-mediated Rab11A phosphorylation at serine 177. Furthermore, the

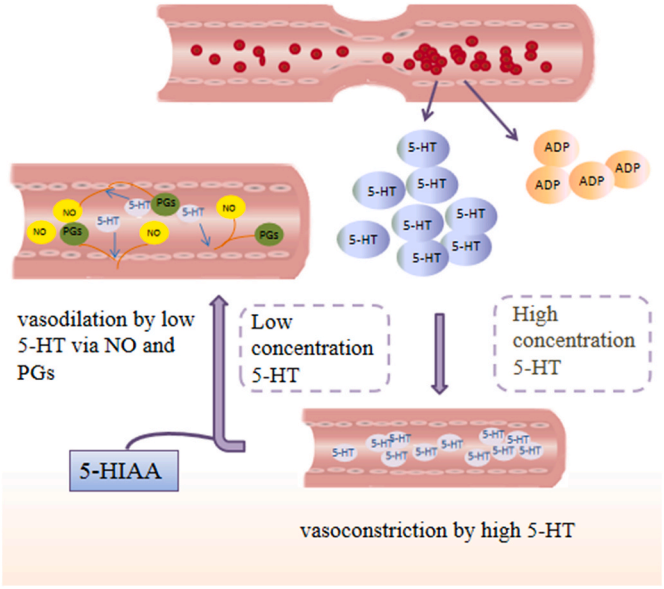

Fig. 1. Schematic view of the pathophysiological mechanism of migraine induced by 5-HT in two stages. Activated platelets can release substances such as platelet dense granules, which can release 5-HT and ADP, high concentration of 5-hydroxytryptamine cause vasoconstriction. Then, 5-hydroxytryptamine is metabolized into 5-HIAA and excreted through urine, thus reducing the concentration of 5-HT in plasma. Low concentration of 5-HT can stimulate pain fibers around blood vessels and release NO, PGs and neuropeptides locally, leading to vasodilation and migraine attacks.

Table 3
Descriptive table of main chinese herbal medicines mentioned in this paper.

Plant family	English Name	Plant Name	Local Chinese Name	Parts used	References
Lamiacae	Lavender	Lavandula angustifolia Mill.	Xun-yi-cao	Dried flower heads; Aerial foliage	Sasannejad et al. (2012)
Lamiacae	Peppermint	Mentha × piperita L.	Bo-he	flowering aerial parts; leaves	de Groot and Schmidt (2016)
Umbelliferae	Angelicae Dahuricae Radix	Angelica dahurica (Hoffm.) Benth. & Hook.f. ex Franch. & Sav.	Bai-zhi	Root	Sun et al. (2017)
Umbelliferae	Chuanxiong Rhizoma	*Ligusticum chuanxiong* Hort.	Chuan-xiong	Rhizome	Zhang et al. (2012)
Compositae	Chamomile	Matricaria chamomilla L.	Yang-gan-ju	Flower	Zargaran et al. (2018)
Magnoliaceae	Anise	Illicium verum Hook.f.	Hui-xiang	Fruit	Mosaffa-Jahromi et al. (2016)
Liliaceae	Garlic	Allium sativum L.	Da-suan	Bulb	Liang et al. (2007)
Lamiacae	Basil	Ocimum basilicum L.	Luo-le	Aerial part	Ahmadifard et al. (2020)
Rosaceae	Rose	Rosa × damascena Herrm.	Mei-gui	Petal	Niazi et al. (2017)
Vitaceae	Grape seed	Vitis vinifera L.	Pu-tao-zi	Seed	Du et al. (2007)

Rab11A and surface transport of Rab11A-dependent β1 subunits are inhibited, which decrease the surface β1 subunit level and result in transient BK inhibition and vasoconstriction, leading to migraine development (Iljazi et al., 2018; Zhai et al., 2017). Studies have shown that ET-1 can be activated by cyclooxygenase-2 (COX-2), which leads to vasoconstriction (Munakata et al., 2016).

3.1.3. CGRP

CGRP is a vasoactive neuropeptide composed of 37 amino acids that regulates immunity and inflammation by relaxing the blood vessels. A study found that the cerebrospinal fluid and serum CGRP levels in patients with migraines were significantly higher than those in healthy subjects (van Dongen et al., 2017). CGRP activates specific G-protein-coupled receptors (GPCRs) and activates adenylate cyclase (AC). Furthermore, CGRP increases the concentration of intracellular cyclic adenosine monophosphate (cAMP) and activates the cyclic adenosine monophosphate signaling pathway. This neuropeptide then blocks the flow of calcium into the cell. A low concentration of intracellular calcium leads to the inactivation of the calmodulin (CaM)-dependent myosin light chain kinase (MLCK), which hinders the activation of actin adenosine triphosphate (ATP) enzyme and leads to vasodilation (Egea and Dickerson (2012); Wang (2012)) (Fig. 2). The CGRP level can be regulated by NR2B-mediated NR2B tyrosine phosphorylation (Liang (2014)).

3.1.4. NO

The synthesis of NO, an endothelial relaxing factor, is catalyzed by NO synthase (NOS) oxidizing a nitrogen atom in the guanidine group at the end of L-arginine (L-Arg). There are three subtypes of NOS endothelial (eNOS), neural (nNOS), and inducible (iNOS) (Pradhan et al., 2018). eNOS and nNOS are collectively referred to as constitutive nitric oxide synthase (cNOS), and their expression requires mediation by calcium ions, while iNOS is considered calcium-independent (Moncada and Higgs (2006)). The synthesis of NO is catalyzed by cNOS, which produces neurotoxic effects that stimulate the trigeminal neurovascular reflex and causes cerebral vasodilation, resulting in migraine symptoms (Rathnasiri Bandara, 2013). The mechanism of action may be attributable to NO spreading to the adjacent target cells via a biofilm or body fluids, and then binding to the heme site of the soluble guanylyl cyclase (sGC). The sGC converts guanosine 5′-triphosphate (GTP) into a cyclic guanosine monophosphate (cGMP) signal molecule, which increases the level of cGMP (Pradhan et al., 2018). cGMP stimulates dependent protein kinase G (PKG) and cell membrane calcium pumps to phosphorylate calcium-sensitive potassium channels, which in turn activate potassium channels to cause potassium outflow, resulting in smooth muscle relaxation and vasodilation (Olesen, 2008) (as shown in Fig. 3).

3.2. Migraine and neurogenic inflammation

The trigeminal neurovascular theory states that aseptic neurogenic inflammation is a key link to the pathogenesis of migraine. Following activation of the trigeminal neurovascular system in the dura mater, CGRP, SP, neurokinin A (NKA), and other vasoactive peptides are released, triggering the release of inflammatory cytokines, which results in sterile neurogenic inflammation that promotes migraine attacks (Burgos-Vega et al., 2015; Malhotra, 2016). In previous clinical studies,

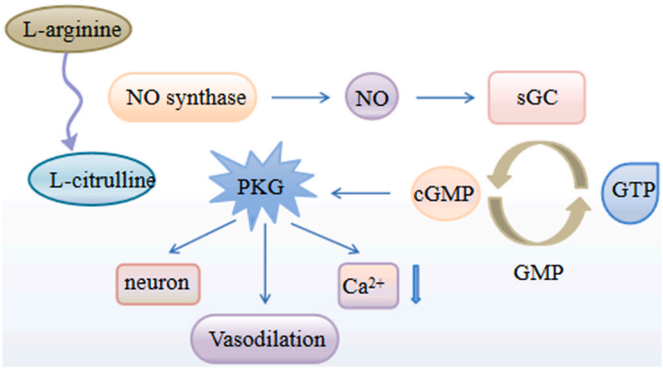

Fig. 3. Schematic view of possible mechanism of vasodilation induced by NO. NOS oxidizes L-arginine to catalyze the synthesis of NO, NO binds to the heme site of sGC to convert GTP into cyclic cGMPsignal molecule, which increases the level of cGMP, CGMP stimulates PKG, resulting in smooth muscle relaxation and vascular relaxation.

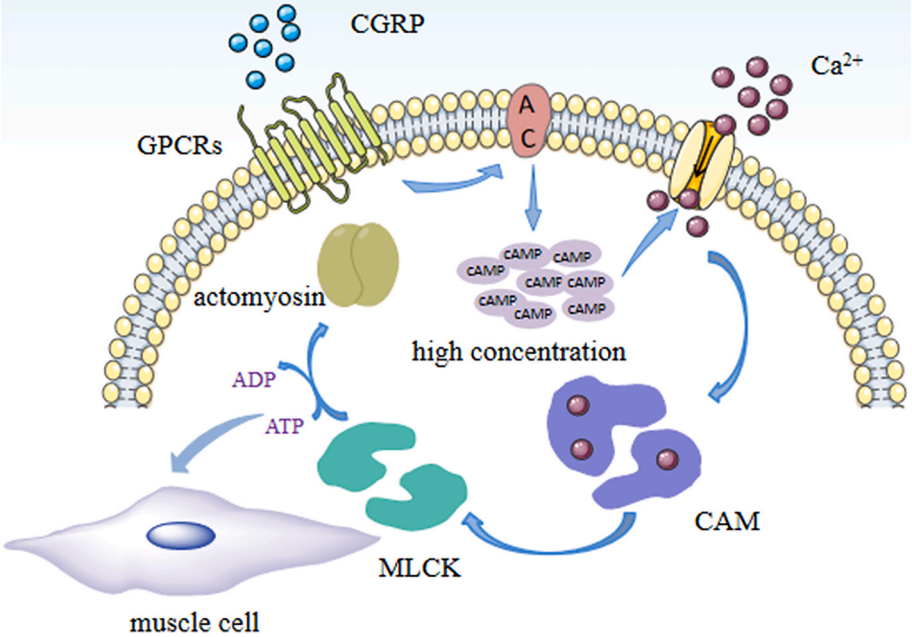

Fig. 2. Schematic view of the relationship between CGRP and vasodilation. When CGRP is activated, it can act on GPCRs, and then activate AC, to increase the concentration of intracellular cAMP, and then break the flow of calcium ions into the cells. low concentrations of intracellular calcium ions lead to the inactivation of CaM-dependent MLCK, which hinders the activation of actin ATP enzyme and leads to vasodilation.

the levels of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) in patients with migraine were higher than those in healthy subjects (Martami et al., 2018; Yücel et al., 2016). Furthermore, the levels of plasma COX-2 and prostaglandin E2 (PGE2) in some patients were significantly higher than those in healthy subjects (Antonova et al., 2013; Li et al., 2017). Studies have also shown that the mitogen-activated protein kinase (MAPK) and the nuclear factor-kappa B (NF-κB) pathways play an important role in the neurogenic inflammation of migraines (Antonova et al., 2013).

MAPK subfamily c-Jun amino-terminal kinase (JNK) and p38 MAPK-mediated signaling pathways are activated by various stressors, such as pro-inflammatory cytokines and inflammatory mediators (Kim and Choi (2010); Ryuno et al., 2017). Following activation, JNK binds to the N-terminal active region of the c-Jun and phosphorylates at serine 63 and serine 73, which enhances transcriptional activity and promotes the expression of transcription factors such as c-jun and c-fos, resulting in neuronal death (Xin, 2010) (Fig. 4a). The activation of the JNK pathway upregulates the expression of COX-2, resulting in increased levels of pro-inflammatory factors such as PGE2, prostaglandin F2 (PGF2), and prostaglandin I2 (PGI2), leading to the development of pain (K. Li et al., 2015; Wang et al., 2007) (Fig. 4b).

Under normal physiological conditions, NF-κB phosphorylation is inactive, and the NF-κB phosphorylation site is blocked by IκB. However, following inflammatory injury, IKK kinase degrades IκB so that the nuclear localization signal of p50 is exposed, and p65 is then quickly transferred to the nucleus. P65 can recognize specific DNA sequences and bind to the κB sites on some inflammatory factor gene promoters or enhancers, thereby initiating gene transcription and inducing excessive expression of multiple cytokines that trigger inflammation (Reuter et al., 2002) (Fig. 4c). Inflammatory cytokines such as TNF-α, IL-1β, IL-6, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1) and inflammatory related enzymes such as iNOS and COX-2 are induced by NF-κB (Lin et al., 2019).

3.3. Migraine and central pain sensitization

Pain hypersensitivity is a typical manifestation of central sensitization. Studies have shown that 50%–80% of patients with migraine experience abnormal skin pain. Patients with migraine with cutaneous allodynia (CA) exhibit a longer course of disease, more severe pain, and common concomitant symptoms such as nausea and phonophobia (Güven et al., 2013). It is currently believed that the central sensitization of patients with migraine is caused by the primary neurons in the trigeminal neurovascular system (Noseda and Burstein, 2013). The transient receptor potential (TRP) channel family of proteins distributed on the trigeminal ganglion can convert cold, thermal, chemical, and mechanical stimulation into inward currents to participate in impulse conduction, and once the TRP channel is activated, it can increase the concentration of calcium and sodium ions in cells (Ramsey et al., 2006), and then increase the spontaneous release of l-glutamate into the spinal dorsal horn lamina II (substantia gelatinosa; SG) neurons (Kumamoto and Fujita, 2016). Glutamate acts on α-amino-3--hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors and N-methyl-D-aspartate (NMDA) receptors, which further increases the calcium influx, Glutamate also enhances the effect of these receptors, and depolarizes the postsynaptic membrane, which produces an excitatory postsynaptic potential, thereby forming and maintaining a sensitized state (Latremoliere and Woolf, 2009). CA usually manifests as a painful sensation to non-noxious stimuli such as cold, heat, and pressure (Si-Jie et al., 2013) might be an externally sensitive manifestation caused by central sensitization of the migraine conduction pathway. In addition to neurons, microglia have been confirmed to be involved in the central sensitization process of migraines (He et al., 2019; Long et al., 2020); however, the specific mechanism involved has not yet been elucidated.

4. Study of the anti-migraine activity of essential oils

From a database search using the keywords "*essential oils*", "*volatile*

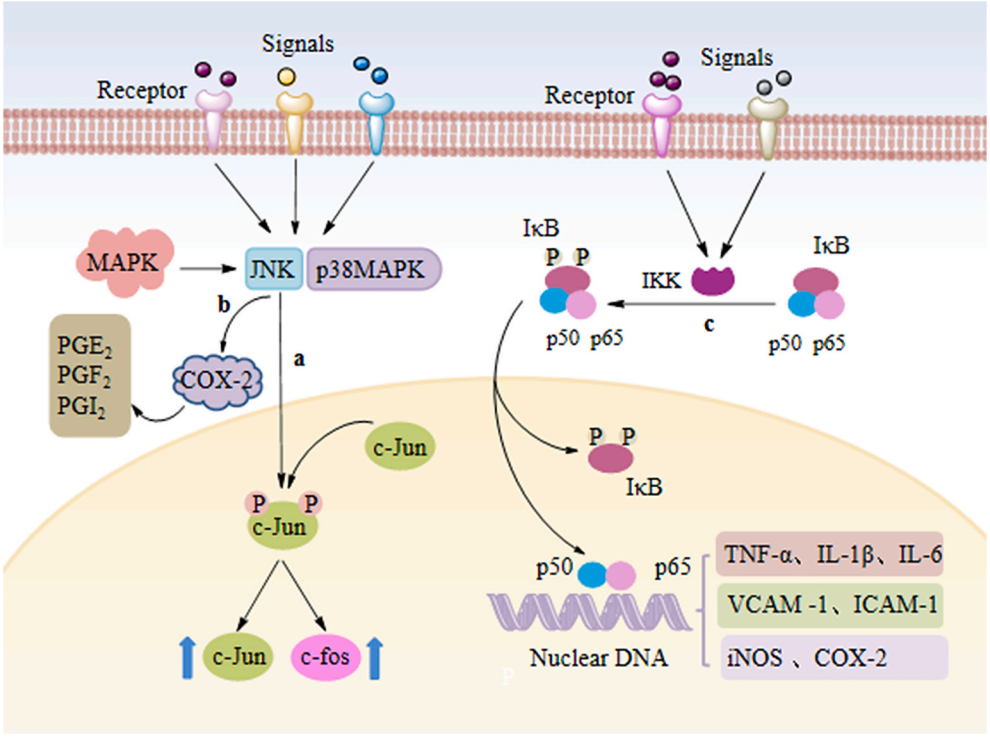

Fig. 4. The role of MAPK and NF-κB pathway in migraine neurogenic inflammation. a. When JNK was activated, it combined with the amino terminal active region of c-jun to phosphorylate c-Jun. b. JNK pathway activation upregulated COX-2 expression. c. Phosphorylation of NF-κB induces inflammatory process.

oils", "*terpenes*" and "*migraine*" as well as the names of experimental models of migraine in animals such as "*nitroglycerin*", "*reserpine*", "*neurogenic imflammation*", "*electrophotoluminescence*", "*chemical stimulation*" and "*Mechanical stimulation*", 9 types of single plant essential oils (extracted from one plant) that could relieve migraine headaches were found, including lavender, peppermint, Angelicae Dahuricae Radix, Chuanxiong Rhizoma, chamomile, anise, garlic, rose, and basil essential oils. A mixed essential oil (a mixture of several plant essential oils) (lavender essential oil:grape seed essential oil:base oil = 3:2:10) was also identified. The primary components, experimental types,

Table 4
Analysis of the anti-migraine activity of plant essential oils.

Name Of Essential Oil	Main Component	Experimental Type	Administration Method	Anti-migraine Activity	References
Lavender essential oil	Linalool (33.25%); Linalyl acetate (35.35%); Camphor (17.77%); Borneol (4.26%); 1,8-cineol (8.1%)	Animal Experiment; Clinical Trials	Inhalation administration (Rats: Inhale 1%, 10%, 100% concentration of lavender essential oil in a relatively airtight space; Patients: Smear 2–3 drops on the upper lip)	1%, 10%,100% concentration of essential oils significantly reduces the number of head scratches in migraine rats; All migraine sufferers had their migraine symptoms completely or partially relieved within the first 2 h of use of essential oils, nausea, vomiting, photophobia, voice fear, and olfactory disturbance improved	(Sasannejad et al., 2012; Chen et al., 2015)
peppermint essential oil	Menthol (23.0%–47.9%); Menthone (10.6%–38.5%); Limonene (0.3%–18.5%); 1,8-cineol (0.3%–9.9%); Menthyl Acetate (0.5%–7.7%); neo-Menthol (0.2%–7.4%); α-Pinene (0.2%–6.5%)	Clinical Trials	Inhalation administration (2 drops of 1.5% essential oil in the nostril)	The symptoms of the patients were relieved after administration of 5min, and the intensity and frequency of headache decreased compared with those before treatment.	(de Groot and Schmidt, 2016; Rafieian-Kopaei et al., 2019)
Angelicae Dahuricae Radix essential oil	Dodecyl alcohol (13.71%); Elemene (7.54%); Hexadecanoic acid, ethyl ester (7.32%); α-Pinene (6.25%); 1-Pentadecanol (6.08%); Linoleic acid ethyl ester (3.92%)	Animal Experiment	Intragastric administration(Pure essential oil)	140mg/kg, 70mg/kg, 35mg/kg essential oil can significantly reduce the serum NO level in rats; 140mg/kg and 70mg/kg can significantly reduce NO level in brain tissue, CGRP level in plasma and increase ET level	Sun et al. (2017)
Chuanxiong Rhizoma essential oil	Ligustilide (58%); Butylidenephthalide (5.29%); Sabinene (6.08%)	Animal Experiment; Clinical Trials	Intragastric administration (Rapeseed oil diluted to 18.0, 36.0, 54.0 μl/ml). Oral administration of 3 capsules	The essential oils of 90.0 μl/kg and 135.0 μl/kg significantly inhibited the expression of c-fos; 45.0 μl/kg and 135.0 μl/kg can significantly reduce plasma CGRP levels and increase 5-HT and ET levels; 45.0 μl/k and 90.0 μl/kg significantly increased plasma ET levels. 2 h following administration of the medicine, the migraine symptoms of the patients with an acute attack were relieved.	(Peng et al., 2009;Li, 2012
Chamomile essential oil	Chamazulene (9.75%); β-Caryophyllene (6.86%); Bisabolone oxide A (57.37%); Bisabolol oxide A (14.29%); Methyl ester 5,8,11-heptadecatriynoic acid (5.08%)	Clinical Trials	2 ml of the drug was applied by rubbing topically into the temporal and forehead areas, and beyond the ears (5.5% essential oil gel)	The symptoms of pain, nausea, vomiting, photophobia, and phonophobia in migraine patients were significantly alleviated after 30min.	Zargaran et al. (2018)
Anise essential oil	Anethole (E−) (89.342%); Limonene (1.25%); Carvone (3.9%); Himachalene (γ-)	Clinical Trials	Smear on the temporal and forehead areas (7% essential oil cream)	The frequency of migraine attacks decreased from 3.45 (±1.89) times/week to 1.89 (±1.94), and the average duration decreased from 17.38 (±29.22) h to 5.18 (±7.72).	Mosavat et al. (2019)
Garlic essential oil	Diallyldisulfide; Diallyl trisulfide; Diallyl sulfide	Animal Experiment	Intraperitoneal injection (1ml/L essential oil)	After 60 min of administration of essential oils, the dose (1, 10, 100, 500 μl/L) dependently reduced potassium chloride-induced inhibition of rat cortical spreading.	Marschollek et al. (2017)
Basil essential oil	1,8-cineol (3%); Terpinene(γ-) (1.5%); Linalool (1.5%); Estragole (93%); Eugenol (1%)	Clinical Trials	Smear administration in frontal and temporal lobes (2%, 4%, 6% essential oils)	The pain intensity and attack frequency of patients decreased with the passage of time of the study.	Ahmadifard et al. (2020)
Rose (Rosa damascena Mill.) oil	Citronellol (3.48%); Geraniol (1.23%)	Clinical Trials	Smear on the temporal and forehead areas (filtrate 2 ml obtained from the mixed soaking of fresh flower petals and 20% (W/W) sesame oil)	Relieved the pain intensity of patients with hot migraine syndrome (red eyes, photophobia, spicy taste, and facial heat during headaches).	Niazi et al. (2017)
Mixed essential oil	No report	Clinical Trials	Pushed to the face, forehead, and back neck (lavender essential oil: grape seed essential oil: base oil = 3: 2: 10)	Most patients' symptoms disappear within 20 days, and there is no recurrence within 1 year; some patients have prolonged the onset cycle, and the pain level is significantly reduced compared with before	(Du et al., 2007)

administration methods, and anti-migraine activities of the above essential oils are described in Table 4.

4.1. Analysis of anti-migraine plant essential oil application methods

Plant essential oils possess strong volatility and permeability. Clinical applications of aromatherapy include massage, inhalation, bathing, and wet application. However, most pure plant essential oils (except lavender, tea tree, and chamomile) are irritating and cannot come into direct contact with the skin or mucous membranes. In the clinical trials of the effects of plant essential oils against migraine in Table 4, the essential oils are primarily inhaled or smeared on the temple and forehead. During application, the lavender essential oil was directly applied, peppermint essential oil was diluted to a 1.5% concentration, chamomile essential oil was prepared in 5.5% essential oil gel, chuanxiong rhizoma essential oil was prepared in soft capsules, anise essential oil was converted into 7% essential oil cream, basil essential oil was diluted to 2%, 4%, and 6% concentrations, rose essential oil was extracted with 20% (W/W) sesame oil, and mixed essential oil was diluted using a base oil. In animal experiments, inhalation, intragastric administration, and intraperitoneal injection were the primary modes of administration. The lavender essential oil was inhaled at concentrations of 1%, 10%, and 100%, Angelicae Dahuricae Radix was administered intragastrically with pure essential oils of 35, 70, and 140 mg/kg, and Chuanxiong Rhizoma essential oil was diluted with rapeseed oil to a concentration of 18.0, 36.0, and 54.0 μL/mL. Garlic essential oil was diluted to a concentration of 1mL/L via intraperitoneal injection. Because animals do not understand these treatments, smear administration causes stress and discomfort, which leads to grasping, smearing, and other behaviors that result in errors in the experimental results. Thus, the smear administration was not experimented further.

4.2. Analysis of the anti-migraine mechanism of the plant essential oils

Among the 10 anti-migraine essential oils identified, plant essential oils such as lavender essential oil, peppermint essential oil, chamomile essential oil, anise essential oil, basil essential oil, rose essential oil, and mixed essential oils were associated with relieving the migraine intensity and reducing the attack frequency. Some of these oils can reduce photophobia, phonophobia, nausea, vomiting, and other symptoms; however, the specific mechanisms involved requires further study. Angelicae Dahuricae Radix oil and Chuanxiong Rhizoma essential oil were shown to reduce the levels of NO and CGRP in rats and reduce the expression of ET, 5-HT, and c-fos. Therefore, these two oils might alleviate migraine by balancing abnormal vasomotion and inhibiting inflammation. Garlic essential oil was shown to reduce the amplitude of cortical spreading depression (CSD) in the cerebral cortex in a dose-dependent manner (1–500 μL/L). CSD is a slow-spreading depolarized wave in brain neurons and glial cells that activates the trigeminal neurovascular system and triggers a neuroinflammatory cascade, Furthermore, activates the NF- κB pathway of astrocytes (Yang et al.,). The above research indicated that garlic essential oil might relieve migraine

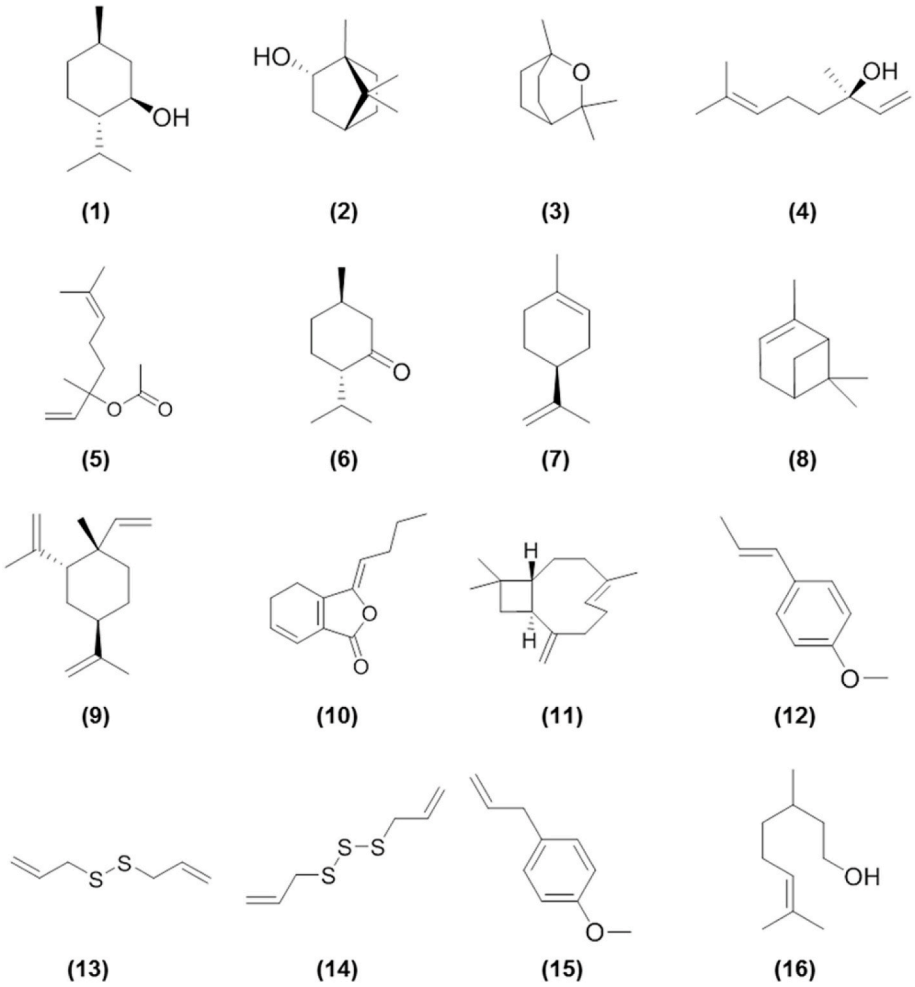

Fig. 5. Related chemical structures that may have anti migraine effects.(1) L-menthol; (2) D-borneol; (3) 1,8-cineole; (4) L-linalool; (5) Linalyl acetate; (6) L-menthone; (7) Limonene; (8) α-pinene; (9) β-elemene; (10) (Z)-ligustilide; (11) β-caryophyllene; (12) Anethole; (13) Diallyl disulfide; (14) Diallyl trisulfide; (15) Estragole; (16) Citronellol.

by inhibiting neurogenic inflammation and central sensitization.

5. Study of the possible mechanism of action of the monomer components of the essential oils against migraine

Currently, Only three essential oils of Angelica dahurica, Chuanxiong Rhizoma and garlic were used to study the mechanism of anti-migraine, and the main chemical components of all essential oils except for the mixed essential oils list the main chemical components. To accurately determine the material basis and mechanism of action of the plant essential oils against migraine, the mechanism of action of the monomer components of these essential oils against migraine was searched. Overall, 16 monomer components that could cause an anti-migraine effect were found (Fig. 5). In addition to the direct evidence of menthol, the other 15 monomer components showed indirect evidence of anti-migraine effects. The following components were found: borneol, 1,8-cineole, linalool, linalyl acetate, menthone, limonene, α-pinene, elemene, ligustilide, β-caryophyllene, anethole, diallyl disulfide, diallyl trisulfide, estragole, and citronellol. Research has focused on the possible mechanism and the anti-migraine effect, anti-inflammation effect, pain relief effect, vasomotor balance, and inhibition of central pain sensitization (as shown in Table 5).

5.1. Menthol

In nature, menthol primarily exists in essential oils of plants such as Menthae Haplocalycis Herba (Jirovetz et al., 2009) and peppermint (de Groot and Schmidt, 2016) in the form of l-menthol. Menthol is a TRPM8 channel agonist (Behrendt et al., 2004). Ren et al. (2015) established a migraine mouse model via injection of an inflammatory mediator (IM) into the dura mater and then intervened with menthol, they found that menthol in the dura mater significantly reduced the duration of the nociceptive behavior in mice. However, the same dose of menthol failed to affect the TRPM8 gene-knockout mice, which indicated that menthol might cause an antinociceptive effect via activating the TRPM8 channels. Andersen et al. (2016) studied the effects of menthol on skin pain and hyperalgesia induced via local application of the TRPA1 agonist trans-cinnamic aldehyde. They revealed that menthol interacted with TRPA1 in a bimodal concentration-dependent manner and that TRPA1 channels were reversibly blocked at higher concentrations. Moreover, the intensity of spontaneous pain, neurogenic inflammation, primary mechanical hyperalgesia, secondary mechanical hyperalgesia, and thermal hyperalgesia in the participants were reduced following menthol treatment. Thus, menthol might have other mechanisms of action in addition to TRPM8 and pro-inflammatory mediators. Furthermore, menthol has been proven to be effective in the direct treatment of migraines. When 10% menthol solution was applied to the forehead and temporal lobe region of patients, significant relief from headaches, nausea, vomiting, photophobia, and other symptoms was achieved. Furthermore, 6% menthol gel could relieve migraine symptoms in patients experiencing an acute attack (Borhani Haghighi et al., 2010; St Cyr et al., 2015). Therefore, menthol might relieve migraines by interfering with central pain sensitization and neurogenic inflammation.

5.2. Borneol

D-borneol is a main commercial structure, which naturally exists in lavender oil (Sasannejad et al., 2012), Rhizoma Curcumae oil (Li et al., 2018), rosemary oil (Eissa et al., 2017), and Cinnamomum camphora oil (Chen et al., 2018).. TRPA1, a member of the TRP family, increases intracellular NO levels and calcium concentration following activation (Sun et al., 2014), which induces the neurons to release CGRP and SP, which participate in migraine development (Nassini et al., 2014; Wang et al., 2019). Takaishi et al. (2014) discovered that borneol (BO) inhibited human TRPA1 induced by allyl isothiocyanate (AITC) in a dose-dependent manner. Sherkheli et al. (2015) found that BO inhibited

Table 5
Possible anti-migraine mechanism of monomer components of plant essential oil.

Component	Distribution In Plants	Possible Anti-migraine Activity
L-menthol	Menthae Haplocalycis Herba (Mentha canadensis L.); Peppermint (Mentha × piperita L.)	Interfering with the central pain sensitization; Inhibiting neurogenic inflammation;
D-borneol	Lavender (Lavandula angustifolia Mill.); Rhizoma Curcumae (Curcuma longa L.); Rosemary (Salvia rosmarinus Spenn.); Cinnamomum camphora (Cinnamomum camphora (L.) J.Presl)	Relaxing the blood vessels; Inhibiting neurogenic inflammation; Inhibiting central allergic reactions;
1,8-cineole	Tea tree (Melaleuca alternifolia (Maiden & Betche) Cheel); cajuput (Melaleuca cajuputi Maton & Sm. ex R.Powell); Magnoliae flos (Magnolia biondii Pamp.); Ravensara (*Nepeta menthoides* Boiss. & Bohse.)	Dilating blood vessels; Inhibiting neurogenic inflammation; Inhibiting central sensitization;
L-linalool	ZanthoxyLi Pericarpium (Zanthoxylum schinifolium Siebold & Zucc.); Bergamot (Citrus × limon (L.) Osbeck); Lavender (Lavandula angustifolia Mill.); coriander (Coriandrum sativum L.)	Inhibiting neurogenic inflammation; Inhibiting central pain sensitization;
Linalyl acetate	Clary Sage (Salvia sclarea L.); Bergamot (Citrus × limon (L.) Osbeck); Lavender (Lavandula angustifolia Mill.)	Inhibiting neurogenic inflammation; Balancing the vasomotor abnormalities;
L-menthone	Menthae Haplocalycis Herba (Mentha canadensis L.); Peppermint (Mentha × piperita L.); Schizonepetae Herba (Nepeta tenuifolia Benth.)	Inhibiting neurogenic inflammation;
Limonene	Peppermint (Mentha × piperita L.); Foeniculi Fructus (Foeniculum vulgare Mill.); Lemon peel (Citrus × limon (L.) Osbeck)	Inhibiting hyperalgesia; Inhibiting neurogenic inflammation; Balancing the vasomotor abnormalities;
α-pinene	Houttuyniae herba (*Houttuynia cordata* Thunb.); Lavender (Lavandula angustifolia Mill.); Frankincense (*Boswellia serrata* Roxb.)	Inhibiting neurogenic inflammation;
β-elemene	Curcumae rhizome (Curcuma longa L.); Curcuma wenyujin (Curcuma aromatica Salisb.)	Inhibiting neurogenic inflammation;
(Z)-ligustilide	Chuanxiong Rhizoma (Conioselinum anthriscoides 'Chuanxiong'); Angelicae Sinensis Radix (Angelica sinensis (Oliv.) Diels).	Relaxing blood vessels; Inhibiting neurogenic inflammation; Inhibiting hyperalgesia;
β-caryophyllene	Lime mint (Mentha aquatica L.); Copaiba (Copaifera officinalis L.)	Inhibiting neurogenic inflammation; Balancing the vasomotor abnormalities;
Anethole	Anise (Illicium verum Hook.f.); Foeniculi Fructus (Forsythia suspensa (Thunb.) Vahl)	Inhibiting neurogenic inflammation;
Diallyl disulfide	Garlic (Allium sativum L.); Onion (Allium cepa L.)	Inhibiting neurogenic inflammation; Balancing the vasomotor abnormalities;
Diallyl trisulfide	Garlic (Allium sativum L.)	Inhibiting neurogenic inflammation;
Estragole	Croton zehntneri (Croton grewioides Baill.); Foeniculi Fructus (Forsythia suspensa (Thunb.) Vahl)	Inhibiting neurogenic inflammation; Balancing the vasomotor abnormalities;
Citronellol		

(*continued on next page*)

Table 5 (*continued*)

Component	Distribution In Plants	Possible Anti-migraine Activity
	Rose (*Rosa damascena* Mill.); Pelargonium (Pelargonium sidoides DC.)	Relaxing blood vessels; Inhibiting neurogenic inflammation; Inhibiting hyperalgesia;

the TRPA1-mediated calcium influx of the heterologous expression systems such as xenopus oocytes and trigeminal ganglion neurons in the low millimole range (IC50 = 0.3 mM). They also suggested that BO exert an antinociceptive effect by affecting the potential channel of the TRPA1 receptor. Previous studies found that oral or intrathecal administration of d-BO could reduce the neuropathic pain induced by spinal nerve ligation (SNL) in a dose-dependent manner (Jiang et al., 2015), and inhibit the expression of TNF-α, iNOS, IL-1β, and COX-2 in an ischemic stroke rat model (Liu et al., 2011; Wu et al., 2014). During SNL-induced chronic pain, increased levels of glutamate and cytokines, such as IL-1β and TNF-α in the spinal dorsal horn contribute to neuronal sensitization (Ji and Woolf, 2001). Thus, BO might relieve migraines by relaxing the blood vessels, inhibiting neurogenic inflammation and central allergic reactions.

5.3. 1,8-Cineole

1,8-Cineole (CIN) is present in more than 200 natural essential oils such as Tea tree (Li et al., 2020), cajuput (Hamoud et al., 2012), Magnoliae flos (Chen et al., 2020) and Ravensara (Kahkeshani et al., 2018). Takaishi et al. (2012) found that CIN induced an inward current in HEK293T cells expressing human TRPM8 and demonstrated dose-dependent inhibition of human TRPA1 activated by allyl isothiocyanate, mint, fulvic acid, or octanol, suggesting that CIN exhibits a similar effect as that of menthol. Pinto et al. (2009) induced contraction in an isolated rat aorta with phenylephrine, and subsequent exposure to a CIN (0.0000647–19.5 mM) solution that resulted in complete vasodilation. This reaction was significantly reduced in the endothelial exfoliation ring. Lahlou et al. (2002) found that CIN (0.006–2.6 mM) also inhibited KCl-induced contraction of an isolated rat thoracic aorta in a concentration-dependent manner. Another study observed the effects of CIN pretreatment on inflammation of differentiated PC12 cells induced by Ab. CIN successfully decreased the mitochondrial membrane potential, reactive oxygen species (ROS), and NO level in Ab-treated cells as well as the levels of TNF-α, IL-1β, IL-6 and the expression of NOS-2, COX-2 and NF-κB (Khan et al., 2014). Thus, CIN might interfere with migraine development by dilating blood vessels, inhibiting neurogenic inflammation and central sensitization.

5.4. Linalool

Optical isomers of linalool exist in nature, l-linalool is primarily derived from ZanthoxyLi Pericarpium oil (Luo et al., 2012), bergamot oil (Russo et al., 2013), lavender oil (Sasannejad et al., 2012), and coriander oil (Aelenei et al., 2019). Batista et al. (2008) administered l-linalool to mice via intraperitoneal injection (10–200 mg/kg), oral administration (5–100 mg/kg), and intrathecal injection (0.1–3 μg/site), l-linalool inhibited glutamate-induced pain in a dose-dependent manner and alleviated the behavioral nociceptive response induced via spinal injection of the proinflammatory cytokines IL-1β and TNF-α (Batista et al., 2010). Li et al., 2015stimulated BV2 microglia with lipopolysaccharides (LPS) and detected inflammatory mediators. This result showed that linalool inhibited LPS-induced TNF-α, IL-1β, NO, and PGE2 production in a dose-dependent manner. Moreover, linalool inhibited LPS-induced NF-κB activation, Nrf2 nuclear translocation, and heme oxygenase-1 (HO-1) expression. Some scholars used SNL models to study the effects of l-linalool on mechanical and thermal sensitivity in nerve injuries in mice. They proved for the first time that l-linalool reduced the mechanical pain abnormality in the SNL model mice and that this ability to reduce mechanical pain was not achieved by mediating inflammatory processes (Berliocchi et al., 2009). Glutamate, microglia, and various inflammatory factors were closely associated with migraine onset. The above studies indicate that linalool participates in anti-migraine effects by inhibiting neurogenic inflammation and central pain sensitization.

5.5. Linalyl acetate

Linalyl acetate (LA) naturally exists in essential oils such as Clary Sage (Blasko et al., 2017), Bergamot (Russo et al., 2013), and lavender (Sasannejad et al., 2012). Aoe et al. (2017) found that LA could inhibit TNF-α-induced E-selectin, P-selectin, VCAM-1, and ICAM-1 mRNA expression in a mouse brain endothelial cell line. Furthermore, the inhibition of phosphorylated NF-κB p65 in the nucleus indicated that LA exerted anti-inflammatory effects by inhibiting the activation of NF-κB. Koto et al. (2006) found that LA induced dilation of rabbit carotid arteries. Arginine nitrate, an inhibitor of NOS, and 1H-[1,2,4] oxadiazolo [4,3-α] quinoxaline-1-one, an inhibitor of GC, could significantly attenuate this relaxation effect. Shin et al. (2018) also found that intraperitoneal injection of a low concentration of LA increased the isolated aortic vasodilation of stress induced by acetylcholine (ACh) in diabetic rats. Moreover, as the concentration increased, ACh-induced vasodilation almost returned to the control levels. This research showed that LA might elicit an anti-migraine effect by inhibiting neurogenic inflammation and balancing the vasomotor abnormalities.

5.6. Menthone

Menthone exhibits optical isomerization, and L-menthone (MTN) is widely found in essential oils such as Menthae Haplocalycis Herba (Jirovetz et al., 2009), peppermint (de Groot and Schmidt, 2016) and Schizonepetae Herba (He et al., 2013). Depression is the most common mental comorbidity associated with migraine, and a study has shown that the pathogenesis of the two might be correlated (Zhai et al., 2017). Xue et al. (2015) studied the effects of MTN on the levels of the inflammatory cytokines and neurotransmitters in depressed mice induced by chronic mild stress (UCMS). They found that MTN reversed the changes of norepinephrine (NE) and 5-HT concentration in the hippocampus induced by UCMS and inhibited the expression of IL-1β, IL-6, and TNF-α. Cheng et al. (2008) found that MTN also inhibited the production of IL-1β, IL-6, and TNF-α in HaCat cells induced by LPS and inhibited the activity of NF-κB in the HaCat cells in a dose-dependent manner. Their study also found that the inhibitory effect of MTN on IL-1β and TNF-α induced by LPS in HaCat cells was related to the inhibition of I-κB phosphorylation. Therefore, MTN might play an anti-migraine effect by reducing the inflammatory factors that lead to neurogenic inflammation.

5.7. Limonene

There are three categories of limonene: l-limonene, d-limonene, and racemate. It is widely found in essential oils such as Peppermint (de Groot and Schmidt, 2016), Foeniculi Fructus (Lee et al., 2012) and Lemon peel (Zhang et al., 2018). Researchers have shown that oral administration of d-limonene in rats or mice significantly inhibits mechanical hyperalgesia induced via selective spared nerve injury (SNI) and intrathecal injection of TNF-α and IL-1β (Cheng et al., 2008; Piccinelli et al., 2017). Kaimoto et al. (2016) found that intraperitoneal injection of low concentrations of limonene significantly inhibited the activation of TRPA1 induced by H_2O_2. Furthermore, local administration of limonene promoted extracellular calcium influx to activate TRPA1; thus, limonene had a bimodal effect on TRPA1, which could reduce hyperalgesia through systemic administration. Tang et al. (2019) found that d-limonene reversed the effect of corticosterone on PC12

cells, inhibited the nuclear translocation of NF- κB, and decreased the expression of iNOS, COX-2, IL-6, IL-1β and TNF- α. Moreover, d-limonene has been shown to inhibit LPS-induced increases in NO and PGE2 levels in RAW 264.7 macrophages and the expression of TNF-α, IL-1β, and IL-6 (Yoon et al., 2010). In addition, limonene has been shown to affect vasoconstriction during KCl-induced contraction of rat aortic rings as limonene causes significant concentration-dependent relaxation of the endothelium-intact aortic rings. However, endothelial denudation significantly reduced this relaxation. In phenylephrine (PHE)-induced contraction of aortic rings that contained endothelial cells, limonene induced contractions at lower concentrations and concentration-dependent relaxation at higher concentrations (Cardoso-Teixeira et al., 2018). Therefore, limonene might regulate migraines by inhibiting hyperalgesia, neurogenic inflammation, and vasomotor balance.

5.8. α-Pinene

α-Pinene exists in many plant essential oils, such as Houttuyniae herba oil (Deng et al. (2011), lavender oil (Sasannejad et al., 2012) and Frankincense oil (DeCarlo et al., 2019). Zhou et al. (2004) incubated human mononuclear cells THP-1 with α-pinene and then stimulated them with LPS. They found that α-pinene pretreatment reduced the NF-κB/p65 nucleus of the LPS-stimulated THP-1 cells in a dose-dependent manner and increased the levels of cytoplasmic IκBα protein. in a study of LPS-induced inflammation in mouse peritoneal macrophages, Kim et al. (2015) found that α-pinene significantly decreased the levels of IL-6, TNF-α, NO as well as the expression of iNOS and COX-2 induced by LPS. Further studies found that α-pinene inhibited the phosphorylation of ERK and JNK in macrophages and decreased the levels of soluble IKK, phosphorylated IκB and NF-κB. Other studies showed that α-pinene could block the phosphorylation of p38 and JNK in IEC-6 cells induced by aspirin and reduce NO and IL-6 levels in an ischemic hemisphere of ischemic stroke rats (Bouzenna et al., 2017; Khoshnazar et al., 2019). These findings suggest that α-pinene playes an anti-inflammatory role by inhibiting the MAPK and NF-κB pathways to regulate inflammatory factors, which might also be a mechanism affecting neurogenic inflammation.

5.9. Elemene

Elemene includes several isomers of α, γ, and δ-elemene, which are primarily found in Curcumae rhizome oil (Lu et al., 2017) and Curcuma wenyujin oil (Zhou et al., 2015). Zhang et al. (2011) found that intraperitoneal injection of β-elemene significantly delayed the development of experimental autoimmune encephalomyelitis (EAE) in C57 mice and significantly reduced the production of IL-17, IL-6, and IL-23. In a study of the effect of β-elemene in a rat spinal cord injury model, it was found that β-elemene decreased the secretion of inflammatory factors such as IL-6 and IL-1β (Wang, J. et al., 2018). Fang et al. (2018) found that β-elemene dose-dependently inhibited the expression of IL-6, TNF-α, IL-1β, and other proinflammatory mediators and iNOS, IL-10 produced by LPS-induced RAW 264.7 macrophages. Patra et al. (2016) further found that the anti-inflammatory effect of β-elemene might be achieved by inhibiting the p38MAPK, JNK, and NF-κB pathways. Thus, β-elemene might resist migraine damage by inhibiting neurogenic inflammation.

5.10. Ligustilide

Ligustilide (LIG) primarily exists in essential oils of Chuanxiong Rhizoma (Peng et al., 2009) and Angelicae Sinensis Radix (Cui et al., 2006). LIG has been found to reduce the production of pro-inflammatory cytokines such as TNF-α and IL-1β in primary cultured microglia induced by LPS and inhibit the expression of COX2, iNO, and IL-6 (Wang et al., 2010; Zhu et al., 2014). Su et al. (2011) found that LIG could inhibit the phosphorylation of IκBα, the inhibitor of NF-κB, and inhibit the phosphorylation of p38 MAPK and the activation of ERK and JNK in a dose-dependent manner to reduce inflammatory reaction.. Two other studies also proved that (Z)-ligustilide exerted anti-inflammatory effects by regulating the NF-κB and MAPK signaling pathways (Chung et al., 2012; Han et al., 2018). Ligustilide also has a certain vasodilation ability, Cao et al. (2006) showed that (Z)-ligustilide vasodilation was not dependent on endothelial cells but led to a concentration-dependent inhibition of the extracellular calcium influx and release through a voltage-dependent calcium channel (VDCC) and receptor-operated calcium channel (ROCC). These findings indicate that ligustilide might produce an anti-migraine effect by relaxing blood vessels, inhibiting neurogenic inflammation and hyperalgesia.

5.11. β-caryophyllene

β-caryophyllene (BCP) is naturally found in Lime mint oil (Yang et al., 2015) and copaiba oil (Ames-Sibin et al., 2018). BCP is a cannabinoid receptor type 2 (CB2) agonist that has potential therapeutic effects on neuropathic pain and mood disorders (Aguilar-Ávila et al., 2019). Studies have shown that intraperitoneal injection of BCP reduces rotenone-induced expression of proinflammatory cytokines and inflammatory mediators such as COX-2 and iNOS in the midbrain region of rats (Ojha et al., 2016). Furthermore, BCP inhibited the production of H_2O_2, NO, and TNF-α in EAE mice cultured cells in vitro (Fontes et al., 2017). In addition, BCP significantly inhibited the activation of HO-1 and the Phosphorylation of JNK in SH-SY5Y cells treated with 1-methyl-4-phenylpyridinium (MPP^+) (Wang et al., 2018). Hu et al. (2017) discussed the effect of BCP on Aβ1-42-induced neuroinflammation and found that BCP reduced the production of NO and PGE2. These researchers also determined the expression of iNOS and COX-2 and secretion of proinflammatory cytokines in Aβ1-42 treated BV-2 microglia. Segat et al. (2017) found that BCP attenuated PTX-induced mechanical analgesia in a CB2-dependent manner and that prophylactic administration reduced p38 MAPK and NF-κB activation. BCP affected vasomotor function, reduced expression of the adhesion molecule VCAM-1 prior to atherosclerosis, restored the balance of vascular eNOS/iNOS expression, and caused the levels of NO to return to normal (Youssef et al., 2019). Thus, BCP might affect migraine by inhibiting neurogenic inflammation and balancing vasomotor abnormalities.

5.12. Anethole

Anethole (AN) is found in anise (Mosavat et al., 2019), Foeniculi Fructus (Yu et al., 2020), and other essential oils. Wang et al. (2018) studied the antinociceptive effect of AN on neuropathic pain induced by chronic constriction injury, the results showed that intragastric administration of AN significantly reduced hyperalgesia and allodynia, inhibited the activation of glial cells, downregulated the levels of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, and upregulated the levels of the anti-inflammatory cytokines IL-10. Chainy et al. (2000) studied the anti-inflammatory mechanism of AN and treated ML1a cells with TNF and AN. They found that AN blocked TNF-induced degradation and phosphorylation of IkB to inhibit NF-κB activity, as well as activation of the c-Jun kinase and MAPK kinase. These results suggest that AN might produce anti-migraine effects via the inhibition of neurogenic inflammation through the MAPK and NF- κB pathways.

5.13. Diallyl disulfide

Diallyl disulfide (DADS), also known as allicin, is an organic sulfur compound that is commonly found in garlic (Marschollek et al., 2017), onions (Cantrell et al., 2020), and other essential oils of the genus Allium. Scholars have assessed the anti-inflammatory effects of DADS in BV2 microglia induced by LPS and found that pretreatment with DADS before LPS administration significantly inhibited the excessive production of NO, PGE2, iNOS, and COX-2 in a dose-dependent manner and

downregulated the expression of pro-inflammatory cytokines such as IL-1β and TNF-α (Park et al., 2012; Xu et al., 2020). Chu et al. (2017) found that DADS also inhibited the expression of NO, PGE2, iNOS, and COX-2 in RAW 264.7 macrophages induced by LPS and found that DADS produced a vasodilation effect, which was achieved by upregulating PGI2 production and COX-2 expression and downregulating the production of ROS and angiotensin-converting enzyme in SVEC4-10 cells. Thus, DADS might exert anti-migraine effects by inhibiting the expression of inflammatory factors to resist neurogenic inflammation and balance vasomotor function.

5.14. Diallyl trisulfide

Diallyl trisulfide (DATS) is naturally found in garlic oil (Marschollek et al., 2017). Shin et al. (2013) found that DATS significantly reduces the production of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) and NO in RAW 264.7 macrophages induced by LPS. Lee et al. (2015) further found that DATS inhibits the expression of iNOS and COX-2 and the production of PGE2 in macrophages, and exerts anti-inflammatory effects by inhibiting the degradation of IκB and downregulating the DNA-binding activity of NF-κB and the nuclear translocation of NF-κB p65 induced by LPS. Another study by this team showed that DATS inhibited the secretion of NO and PGE2 in BV2 microglia induced by LPS and inhibited the nuclear translocation of NF-κB by disrupting the degradation and phosphorylation of IκB-α in the cytoplasm (Lee et al., 2018).You et al. (2013) found that DATS attenuated LPS-induced production of proinflammatory mediators and cytokines by inhibiting the NF-κB and MAPKs signaling pathways. Thus, DATS might relieve migraines by inhibiting neurogenic inflammation mediated by the NF-κB and MAPKs signaling pathway.

5.15. Estragole

Estragole is derived from Croton zehntneri (Cabral et al., 2014), Foeniculi Fructus (Lee et al., 2012), and other plant essential oils. Rodrigues et al. (2016) found that estragole might exert anti-inflammatory effects by altering the contents of SP, bradykinin (BK), histamine (HIS), 5-HT, and NO. This result was confirmed by Ponte et al. (2012). Furthermore, estragole inhibited inflammation caused by SP, BK, HIS, TNF, 5-HT, and the NO donor sodium nitroprusside. Soares et al. (2007) found that estragole further enhanced the contraction of endothelium-intact aortic rings induced by PE and tetraethylammonium at low concentrations by opening voltage-dependent calcium channels and induced pre-contraction aortic relaxation at high concentrations, leading to concentration-dependent relaxation in the aortic rings without endothelial cells. This suggested that estragole might produce an anti-migraine effect by inhibiting neurogenic inflammation and balancing vasomotor function.

5.16. Citronellol

Citronellol (CT) is an essential oil with three natural products l-citronellol, d-citronellol and racemate, and is mainly found in rose (Niazi et al., 2017) and Pelargonium (Tabari et al., 2017) essential oils. Su et al. (2010) found that l-citronellol significantly reduces the expression of NO, PGE2, iNOS, COX-2 protein, and mRNA in macrophages induced by LPS and reverses the cytoplasmic degradation of IκBα and the upregulation of NF-κB p65 in the nucleus. Kobayashi et al. (2016) compared the effects of l-citronellol and d-citronellol on mast cell degranulation; the results showed that l-citronellol inhibited mast cell degranulation more effectively than d-citronellol. l-citronellol inhibited the production of TNF-α induced by immunoglobulin E by affecting ERK phosphorylation. l-citronellol also exhibited a vasodilation effect. Bastos et al. (2010) showed that citronellol caused vasodilation by directly acting on the vascular smooth muscle. Thus, citronellol might exert an anti-migraine effect by relaxing blood vessels, inhibiting neurogenic inflammation and hyperalgesia.

6. Conclusion

The increasing prevalence of migraines in humans results in severe impacts on the quality of life of the affected individuals and their families. Therefore, it is essential to identify anti-migraine products that meet the health needs of these patients. Aromatic plant essential oils have demonstrated pain-relieving effects on migraines, as they inhibit neurogenic inflammation and pain sensitization, and some of these oils also affect vasomotor activity. However, additional research is required on this topic as only a few types of anti-migraine plant essential oils have been researched thus far, and the pharmacodynamic effects have been primarily evaluated by the patient's senses, and these results could be influenced by autonomy. Furthermore, the specific mechanism involved in the anti-migraine activity of these oils has not yet been elucidated. Therefore, the author recommends that further research into plant essential oils should be conducted with a focus on applicability for use in the development of novel anti-migraine drugs. Moreover, studies should compare the efficacy of single essential oils with that of mixed essential oils in these anti-migraine studies. This review serves as a valuable resource of information to encourage the development of future therapies for migraine.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Acknowledgements

This study is supported by grants from Innovative Research Team Project of Chinese Medicine Discipline in Chengdu University of Traditional Chinese Medicine (CXTD2018006), Jiangxi university of Traditional Chinese medicine 1050 youth talent project (202001), First-class discipline construction project of Jiangxi province (JXSYLXK-ZHYAO009) and Sichuan Provincial Administration of traditional Chinese medicine pepper special project (2018HJZX023).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jep.2020.113326.

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