Article

Review Article

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The Efficacy of *Eucalyptus globulus* Essential Oil in the Management of Pain

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Abstract

Eucalyptus globulus (Myrtaceae family) is the only recognized medicinal species of the *Eucalyptus* genus, by Commission E, and its leaves are used to extract essential oil with minimum content of 60% 1,8-cineole content. Eucalyptus essential oil is traditionally used to treat rheumatoid arthritis, muscle joint pains, and inflammation. The purpose of this review is

to evaluate the effectiveness of *Eucalyptus globulus* essential oil in the management of pain and inflammation. The analgesic and anti-inflammatory effects of eucalyptus essential oil were confirmed in some pharmacological and clinical studies of pain. Eucalyptus essential oil reduced the pain and inflammation, which is antagonized by naloxone, suggesting the participation of μ-opioid receptors in its analgesic effects. The analgesic effects of eucalyptus essential oil are related to its 1,8-cineole content as its main component, which inhibits the production or synthesis of pro-inflammatory cytokines, by attenuation of TREM pathway surface receptor (TREM-1) and MKP-1 phosphatase. Eucalyptus essential oil and 1,8-cineole are the activators of hTRPM8, the antagonist of hTRPA1, and the inhibitor of the P2X3 receptor, which reduces pain and inflammation. The role of other components in eucalyptus essential oil in pain is confirmed. Eucalyptus essential oil or 1,8-cineole can be used as an alternative treatment in topical pain preparation, but it is better to be evaluated in well-designed clinical trials of pain and inflammation.

Keywords

1,8-cineole, eucalyptus essential oil, inflammation, naloxone, pain.

INTRODUCTION

Eucalyptus sp. belong to the Myrtaceae family has more than 700 species of flowering plants, which are native to tropical regions of the world [1]. *Corymbia*, *Eucalyptus*, *Arillastrum, Stockwellia, Angophora*, *Allosyncarpia* and *Eucalyptopsis* are seven genera in eucalyptus group [2]. *The Eucalyptus* genus has important plants in different industries. *Eucalyptus* sp. is a good source of essential oils and are used in forestry or the pulp industry and are used to control wind erosion.

Among different species of *Eucalyptus*, *Eucalyptus globulus* is the only official medicinal species, which is approved by Commission E for treatment of different diseases [3]. *Eucalyptus globulus* is an evergreen flowering tree with height of 45-100 m (98-180 ft) tall, which its leaves are used to extract the eucalyptus essential oil (0.8-2.0% w/w dry weight). The juvenile whitish waxy leaves are on the lower surface of glossy green, lance-shaped adult leaves. Therefore, these leaves are used to extract the essential oils during the year. The best season for harvest of leaves to extract the high yield of essential oils is summer [4].

The pale yellow color-eucalyptus essential oil with strong earthy camphoraceous aroma is rich in a terpenoid oxide, 1,8-cineole (Eucalyptol) (about 60% of total oil composition) [5]. 1,8-

Cineole (> 70%), d-limonene (2-15%), α-pinene (1-10%) were the major constituents of the *E. globulus* essential oil from the leaves and twigs according to ISO standard 770:2002. *p*-cymene (1-isopropyl-4-methylbenzene), γ-terpinene, α-phellandrene, myrcene, α-terpineol, β-pinene, 4-terpinenol, terpinolene, α-terpinene, 4-hydroxy-4-methylpentan-2-one were detected in *E. globulus* essential oil in content of higher than 0.1% [6].

Eucalyptus essential oil is added to feed and water for drinking in chicken for fattening, laying hens, turkey for fattening, piglet, pig for fattening, sow lactating, veal calf (milk replacer), cattle for fattening, dairy cow, sheep/goat, horse, rabbit, salmon, dogs, cats , and ornamental fish (160-400 mg/kg) [7].

Eucalyptus species traditionally have been used for the treatment of different ailments. Eucalyptus essential oil is used traditionally for treatment of neuropathic pain [8], headache [9], viral infections [10], respiratory tract diseases [11], rheumatoid arthritis [12], and boosting the immunity system against viral infections (measles, flu, cold, chickenpox) [13]. Brazilians have used eucalyptus essential oil as an anti-inflammatory, analgesic, and antipyretic agent [14]. *E. globulus* essential oil was traditionally used as a bath additive to decrease muscle pain, which is attributable to the analgesic effects of eucalyptus essential oil [15]. Topical eucalyptus essential oil ointments have been used for thousands of years in treatment of wounds in traditional Aboriginal medicine, Aborigines made a topical poultice containing the leaves to relieve the joint pain and treatment of wounds, and infections [16].

Eucalyptus essential oil was evaluated for treatment of respiratory infections, rhinosinusitis, bronchitis, asthma and chronic obstructive pulmonary disease (COPD), SARS-CoV-2 [17], gastrointestinal disorders [18], dental plaque [19], pain management [20], cancer [21], and diabetes mellitus [22] in modern investigations.

Topical application of eucalyptus essential oil as a bath additive for one week is used for the symptomatic relief of localized muscle pain [23]. Soaking the eucalyptus leaves in coconut oil or sesame oil is useful for muscle joint pain and back pain [24].

Despite different prescriptions for the use of eucalyptus essential oil in treatment of pain, there is no review article on the efficacy and safety of *E. globulus* essential oil in treatment of pain, and its mechanism of action or identifying the components responsible for its analgesic effects. So, according to the topical application of eucalyptus essential oil in the treatment of pain, the aim of this review was to the efficacy and safety of eucalyptus essential oil in the management of different pains and its mechanism of action.

MATERIALS AND METHODS

An online literature search in scientific resources (Google Scholar, PubMed, Springer, Science Direct, Magiran), books, thesis, etc., was done by the keywords of *Eucalyptus globulus*, 1,8-cineole, *Eucalyptol* plus pain, inflammation, mechanism of actions, and safety during the years of 1987-2024. All 60 articles including in vitro, animal and clinical studies were selected and the information from articles was reviewed, categorized and then discussed. There was no inclusion or exclusion criteria to select the articles. All related articles were useful to prepare this manuscript.

RESULTS

1. *E. globulus* essential oil and pain

1) The efficacy of eucalyptus essential oil in pain management

Animal studies confirmed the efficacy of eucalyptus essential oil in pain and inflammation animal model studies (Table 1). The analgesic and anti-inflammatory effects of intraperitoneal administration eucalyptus essential oil (0.1, 10, and 100 mg/kg) were confirmed in acetic acid-induced writhes in mice and hot plate thermal stimulation in rats. Eucalyptus essential oil significantly reduced the number of acetic acid-induced writhes in mice. The analgesic effect of eucalyptus essential oil was not dose dependent on acetic acid-induced writhes, eucalyptus essential oil (10 and 100 mg/kg each) significantly prolonged the reaction time in the hot plate test in a dose dependent manner. Eucalyptus essential oil inhibited the carrageenan or histamine-induced paw edema in rats, which is confirmed by inhibition of neutrophil migration into rat peritoneal cavities in rat animal models [15].

Table 1 Eucalyptus oil and pain in animal studies

Route of administration	Dose	Test	Animal	Results	Ref
Intraperitoneal	0.1, 10, and 100 mg/kg oil	Acetic acid-induced writhes Hot plate	Rats	Analgesic effects Anti-	[15]

Route of administration	Dose	Test	Animal	Results	Ref
		thermal stimulation Carrageenan or histamine-induced paw edema		inflammatory effects	
Inhalation	0.1, 10, and 100 mg/kg oil	Acetic acid-induced writhes Hot plate thermal stimulation Carrageenan or histamine-induced paw edema	Rats	Analgesic effects Anti-inflammatory effects	[15]
Transdermal	(100 mg/kg) oil nanoparticles	Hot plate test	Rats	Analgesic effects	[25]
Inhalation	3% dissolved in almond oil (n = 25) Almond oil (n = 27)	VAS pain score (0-10), blood pressure and heart rate, C-Reactive Protein (CRP)	Patients with total knee replacement		[26]

Intraperitoneal injection of eucalyptus essential oil (45 mg/kg) inhibited the pain in the second phases of pain in formalin-induced inflammatory pain in hind-paw of rats (91%) same as morphine (86%), eucalyptus essential oil did not reduce the licking during the first phase of pain, while morphine as positive control reduced the licking time in the first phase of test by 45%. The inhalation of eucalyptus essential oil inhibited pain in the first and second phase of the formalin test and longer inhalation of eucalyptus essential oil increased its analgesic effects. There was no analgesic effect for eucalyptus essential oil on somatic pain, while it had a central analgesic effect on inflammatory pain. Intraperitoneal injection of eucalyptus essential oil showed an anti-nociceptive effect during the writhing test as indomethacin [14].

The transdermal use of eucalyptus essential oil in the form of micellar nanoparticles (100 mg/kg) demonstrated the analgesic effects in pain animal model of rat. There were prolonged rat's pain responses towards the thermal stimulus in the hot plate test for eucalyptus oil's nanoparticles compared to normal saline (negative control) [25].

The results of animal studies were confirmed by only one clinical study (Table 2). The results of the analgesic effects of eucalyptus essential oil were evaluated in patients with total knee replacement, who were treated with inhalation of dissolved eucalyptus essential oil in almond oil (n = 25), or almond oil (n = 27). Patients with diagnosed osteoarthritis, who replaced total knee, participated in double blind control study. Pain medications were used by all patients, the patients had no complications (antidepressant therapy, hormone, or aroma therapy), or inflammatory diseases after surgery. The pain score according to visual analog scale (VAS) was higher than 4. Eucalyptus oil (3% dissolved in almond oil) was placed onto a gauze pad (4 × 2 inch), between the nose and philtrum for 30 minutes on 3 consecutive days, for the first third day after surgery in experimental group. The control group received the almond oil as treatment same as experimental group. VAS pain score (0-10), blood pressure and heart rate, C-Reactive Protein (CRP) was measured in patients in each day of oil inhalation, before and after treatment.

Table 2 Eucalyptus oil and pain in clinical study

Route of administration	Dose	Test	Animal	Results	Ref
Inhalation	3% dissolved in almond oil (n = 25) Almond oil (n = 27)	VAS pain score (0-10), blood pressure and heart rate, C-Reactive Protein (CRP)	Patients with total knee replacement		[26]

Gas chromatography–mass spectrometry (GC-MASS) analysis of eucalyptus essential oil showed the presence of 1,8-cienol (61.46%), limonene (13.68%), ρ-cymene (8.55%), γ-terpinene (5.87%), and α-pinene (4.95%) as major components.

There was no significant difference between the two groups in regards of demographic and disease-associated characteristics. Fifty-two participants with mean age of 68.2 years (range, 43-85 years), average body mass index 26.4 ± 3.1 kg/m^2, were participated in the study, while the majority was female. The mean durations of osteoarthritis were 8.5 ± 5.7 years and 6.0 ± 5.2 years, in experimental and control groups, respectively. The similar VAS pain score, blood pressure (systolic and diastolic), heart rate, CRP, and WBC count were between two groups at the baseline and before treatment.

There was a significant difference between the VAS pain scores for patients in the eucalyptus essential oil group and the control group ($P < 0.001$). Eucalyptus essential oil inhalation

significantly reduced the pain and inflammatory responses in patients, without any effect on heart rate and serum CRP concentrations in comparison with the control group. Systolic blood pressure and diastolic blood pressure were lower in the eucalyptus essential oil group than in the control group [26].

The results of pharmacological and clinical studies suggest that eucalyptus essential oil can be effective in the treatment of inflammatory pains.

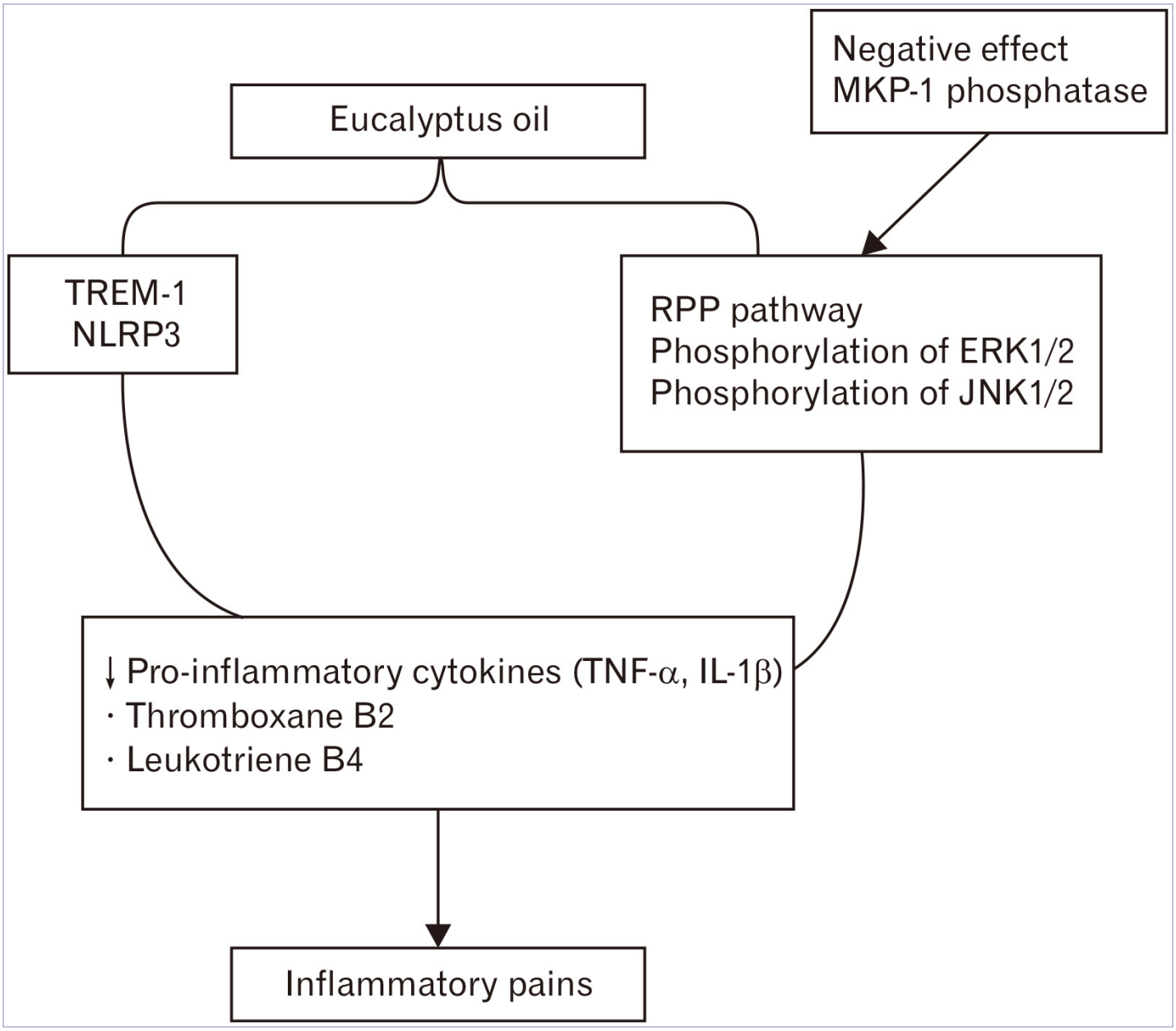
2) The mechanism of action of eucalyptus essential oil in pain and inflammation

The anti-inflammatory, and analgesic effects of eucalyptus essential oil are attributed to the downregulation of pro-inflammatory cytokines (IL-4 and TNF-α) [27,28]. Eucalyptus essential oil decreased the level of TNF-α, IL-6, iNOS, COX-2, NO activity, and NF-κB in LPS-induced inflammation [29] and LPS-activated RAW264.7 [30]. Eucalyptus essential oil reduced the secretion of IL-8 in the T24 human uroepithelial cell line (TNFα- induced bladder pain syndrome (BPS)/interstitial cystitis (IC)) [31]. The results are consistent with another study which confirms that eucalyptus essential oil inhibits the production/synthesis of TNF-α, IL-1β, thromboxane B2, leukotriene B4 in lipopolysaccharide (LPS)-and IL-1β stimulated human monocytes [32].

Pretreatment of LPS-induced murine lung alveolar macrophage (AM) cell line MH-S with eucalyptus essential oil significantly attenuates the TREM pathway surface receptor (TREM-1), the intracellular PRR receptor NLRP3 of the inflammasome, which is associated with a reduction in IL-1β secretion. Reduction in phosphorylation of the transcription factor NF-kB and p38 in the presence of eucalyptus essential oil and increase in phosphorylation of the other two MAP kinases, ERK1/2 and JNK1/2 in the PRR pathway reduce the pro-inflammatory mediators TNF-α, IL-1α and IL-1β, and NO. Down-regulation of MKP-1 phosphatase, a negative regulator of MAPKs by eucalyptus essential oil is responsible for the anti-inflammatory and analgesic effects of eucalyptus essential oil [33].

For screening the analgesic effects of eucalyptus essential oil, opioid antagonists were used. 5'-guanidinonaltrindole (k-opioid antagonist) and naltrindole (δ-opioid antagonist) had no antagonizing effects on the analgesic effect of eucalyptus essential oil, while naloxone as a non-selective μ-opioid antagonist with highest binding affinity for μ-opioid receptor antagonized the analgesic effects of eucalyptus essential oil. So, non-selective μ-opioid receptors are involved in the analgesic effects of eucalyptus essential oil [14]. Fig. 1 provided the mechanism of action for eucalyptus essential oil in its analgesic effects.

Figure 1. The mechanisms of action involved in analgesic effects of eucalyptus oil.



Due to high content of 1,8-cineole in eucalyptus oil, the analgesic effects of 1,8-cineole will be discussed in different sections of this review.

3) Safety of eucalyptus essential oil

E. globulus essential oil is authorized as a feed additive in the European Union according to Regulation (EC) No 1831/2003 but this oil has not been assessed as a food additive in the EU., and cannot be used as flavor in food, so, it should not be ingested. The lowest maximum safe concentration (mg/kg feed) of eucalyptus essential oil is 10 for cats, and 12 for chickens for fattening, other poultry for fattening or reared for laying/reproduction, ornamental birds and other avian species at the same physiological stage, while the highest maximum safe concentration (mg/kg feed) is 75 for ornamental fish and then 56 for dogs [7]. There is a

monograph in the European Pharmacopoeia 11.0 for eucalyptus essential oil (*Eucalypti aetheroleum*), which defined it as the essential oil obtained by steam distillation from fresh leaves or the fresh terminal branchlets of different *Eucalyptus* sp. (*E. globulus*, *E. polybractea* and *E. smithii*) and rich in 1,8-cineole [7].

E. globulus oil from different geographical origins will have different toxicological profiles due to their chemical compositions. 3-methyl 3-methylbutyrate, citronellol, isopulegol, 3-methylpent-3-en-2-one, linalool, α-terpineol, 4-terpinenol, 2,6-dimethyloct-7-en-2-ol, fenchyl alcohol, isoborneol, 4-hydroxy-4-methylpentan-2-one, linalool oxide, 1,8-cineole, limonene, 1-isopropyl-4-methylbenzene (p-cymene), terpinolene, α-phellandrene, 1-isopropenyl-4-methylbenzene, α-terpinene, γ-terpinene, d-limonene, β-pinene, α-pinene, myrcene, camphene, β-ocimene, 3,7-dimethyl-1,3,6- octatriene, β-phellandrene were assessed by EFSA as chemically defined flavorings [7]. *E. globulus* essential oil should be considered as skin and eye irritating, and as a dermal and respiratory sensitizer. The LD_{50} value for *E. globulus* essential oil is 353 ± 64 mg/kg [15]. Eucalyptus essential oil has a myorelaxant effect in promoting emotional stability in healthy subjects [34]. According to HMPC, the permitted traditional transdermal application of *E. globulus* essential oil is between 1.7-4 g/100 L for bath water in the treatment of muscle pain and inflammation [23].

2. 1,8-cineol and pain

1) The efficacy of 1,8-cineole in pain management

1,8-cineole, cineole, or eucalyptol is a monoterpene oxide component, which is present in *E. globulus* essential oil with content up to 80% [35]. 1,8-cineole is internally or externally used for the treatment of rheumatism, cough, bronchial asthma, antiseptic, and analgesic agents [35,36]. There are some products containing 1,8-cineole or eucalyptus essential oil, which are widely used as a topical remedy for alleviating pain [37]. Oral administration of 1,8-cineole (400 mg/kg) significantly reduced joint pain in zymosan-induced arthritis mice, which is related to the reduction of proinflammatory cytokines [38]. Oral administration of 1,8-cineole suppresses the expression of neuropathic pain-related receptors in the spinal cord and dorsal horn of rats with chronic constriction injury [39]. 1,8-cineole showed the anti-inflammatory and analgesic effects in a monosodium urate (MSU) induced mechanical allodynia and ankle edema in mouse animal model of gout arthritis by a reduction in the infiltrations of inflammatory cells, pro-inflammatory cytokines, and oxidative stress in ankle tissues and the inhibition of NLRP3 inflammasome activation and TRPV1 expression [40].

2) Mechanism of action of 1,8-cineol

It seems that the analgesic effects of 1,8-cineole are related to its anti-inflammatory and antioxidant effects. Oral 1,8-cineole significantly reduced COX-2, TNF-α, NF-κB, IL-17, IL-6, and IL-1β levels and increased IL-4 and IL-10 in Complete Freund's Adjuvant -induced arthritic rat model. 1,8-cineole had high binding interaction with IL-17, TNF-α, IL-4, IL-10, iNOS, NF-κB, 5-LOX, and COX-2. 1,8-cineole significantly increased the antioxidant enzymes such as superoxide dismutase (SOD), catalase and glutathione levels, which is associated with an improvement in the structure of the joints [41]. 1,8-cineole as ibuprofen reduced the inflammatory cytokines (IL-1β, TNF-α, and IL-6), myeloperoxidase (MPO) activity, leukocyte infiltration, and inflammatory cytokines (TNF-α, IL-1β, IFN-γ and IL-6) in complete Freund's adjuvant foot pad inflammation wild mice model, which is associated with attenuated edema and mechanical allodynia [42]. 1,8-cineole significantly decreased MPO enzyme activity, pro-inflammatory cytokine levels IL-6, IL-1β, TNF-α, and IL-17A, IFN-γ levels [43,44], the pro-inflammatory mediators COX-2 and inducible nitric oxide synthase (iNOS) [43]. 1,8-cineole increased the anti-inflammatory cytokine IL-10 [45].

1,8-cineole significantly reduced the paw edema, the wet and dry weights of granulation tissue, weaker than indomethacin in cotton pellet-induced granuloma [46].

1,8-cineole inhibited the activated hTRPA1 induced by several agonists with different activation mechanisms, but it activates hTRPM8 and hTRPV3, which suggests the analgesic and anti-inflammatory activity of 1,8-cineole is related to its TRPM8-activating and TRPA1-inhibiting abilities [47]. The anti-inflammatory effects of 1,8-cineole is abolished in two models of inflammation in TRPM8 channel deficient mice, so, 1,8-cineole is the more potent agonist of human TRPM8 channels and the lower dosage of 1,8-cineole may be sufficient to activate the human TRPM8 channels and suppress the inflammation [42]. TRPM8 channels-expressing peripheral neurons are involved in the activation of central inhibitory circuits [48]. Topical 1,8-cineole inhibited the activated mice and human TRPA1 channels by mustard oil, the noxious agonist, and suppresses pain [47,49].

1,8-cineole and its metabolite 2-hydroxy-1,8-cineole activate the TRPM8 channels in humans and mice. 2-hydroxy-1,8-cineole may prolong the anti-inflammatory and analgesic effects of 1,8-cineole [42].

1,8-cineole inhibits the P2X3 receptor in dorsal root ganglion by the inhibition of P2X2 receptor protein and mRNA over-expression in the spinal cord and dorsal horn of rats with chronic constriction injury [50]. The P2X receptor binds to ATP and opens the rapid ion flows (Ca^{+2}, Na^{+}, K^{+}) across the membrane as a nonselective cation channel [51]. P2X2/3 uses

primary sensory neurons to transmit nociception and algesia information [39]. The P2X2 receptor is expressed high in the dorsal horn of the spinal cord [52]. The selective antagonists of P2X2/3 and P2X3 receptors effectively reduce neuropathic pain [39].

Despite the involvement of non-selective μ-opioid receptors in the analgesic effects of eucalyptus essential oil [14], the participation of μ-opioid receptors in the analgesic effects of 1,8-cineole in the presence of naloxone was failed [52], which implied on the role of other components in eucalyptus essential oil in its mechanism of action.

Some studies identified the responsible compounds in eucalyptus essential oil as analgesic and anti-inflammatory effects. Cis-sabinol, globulol, α-eudesmol, β-eudesmol, and γ-eudesmol showed analgesic and anti-inflammatory effects, they bind to COX-2, and β-eudesmol has higher affinity to TNFα than that of TNF-α-IN-1. α-eudesmol had maximum affinity to interleukin 1β convertase [15]. Although these components are responsible for the analgesic effects of eucalyptus essential oil, 1,8-cineole as the main component of eucalyptus essential oil has been widely used for its natural analgesic effects [15].

3) Safety of 1,8-cineole

1,8-cineole is derived from eucalyptus, rosemary, and camphor laurel essential oils. A high concentration of 1,8-cineole is found in *E. nicholii* essential oil (up to 90%) [53]. 1,8-cineole is clinically used for its mucolytic and spasmolytic effects on asthma and chronic obstructive pulmonary disease (COPD) [37,54]. The oral acute and subacute toxicity LD_{50} values of 1,8-cineole in rats are 2,480 mg/kg [55], and 600 mg/kg [56] body weight, There are no chronic or genotoxic effects attributed to 1,8-cineole [56]. Single oral high dose of 1,8-cineole in mice had the LD_{50} value 3,849 mg/kg in acute toxic test [57] similar to accidental intoxications of eucalyptus essential oil [58]. Lesions of granular and vacuolar degeneration and vascular congestion in the liver and kidneys are caused by 1,8-cineole at a concentration of 192.45 mg/kg/day in sub-acute toxicity, while 1,8-cineole at concentrations of 21.38 and 64.15 mg/kg/day have no or mild damages on liver and kidney [57]. 1,8-cineole up to 600 mg/day is well tolerated [59], but it is metabolized in mice quite rapidly with an initial half-life of 6 min [60].

DISCUSSION AND CONCLUSION

The yellow eucalyptus essential oil rich in 1,8-cineol (up to 80%) from *E. globulus* leaf is the only officially clinically approved *Eucalyptus* sp. and eucalyptus essential oil is traditionally used for the treatment of muscle-joint pain from many years ago, the fresh eucalyptus leaf, which is soaked in some vegetable oil as ointment or its use as bath water implied on its traditional healers for management of pain. The pharmacological and clinical studies confirmed the efficacy of eucalyptus essential oil in inflammatory pains. Although there are different components responsible for the analgesic and anti-inflammatory effects of eucalyptus essential oil, most studies are focused on 1,8-cineole or eucalyptol as the major component of eucalyptus essential oil with analgesic and anti-inflammatory effects. Although there are some small differences in the mechanism of action of the analgesic effects of 1,8-cineole, and eucalyptus essential oil, the analgesic effects of eucalyptus essential oil are related to its antioxidant and anti-inflammatory effects. The involvement of some receptors, inhibition of pro-inflammatory cytokines, and activation of antioxidant enzymes are involved in the suppression of pain. Eucalyptus oil is used as a topical ointment or as inhalation and its oral use is not recommended. The use of each ingredient of eucalyptus essential oil is evaluated by EFSA as flavoring agent, but the use of eucalyptus essential oil is not permitted as flavor yet. Although the mechanism of action for analgesic effects of eucalyptus essential oil has been well identified, there is only one clinical trial on the efficacy of inhaled eucalyptus essential oil on pain in patients with knee replacement, and some different animal models of pain. There are some commercial products containing eucalyptus essential oil for management of pain in the world markets, but these formulations are usually in combination with some other essential oils. It seems that preparing a topical ointment with main ingredient of standard eucalyptus oil (min 70% 1,8-cineol) to evaluate its efficacy and safety in a large double blind clinical study with patients suffering from pains in comparison with placebo or current treatments is recommended. The stability tests should be done on this topical ointment to confirm its stability during the study.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHORS' CONTRIBUTIONS

MM is the author of this manuscript, who prepared, read and submitted the manuscript. ZM helps to finalize the manuscript. The author read and approved the final manuscript.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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