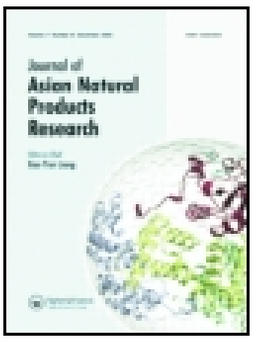

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1,8-Cineole: a review of source, biological activities, and application

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ABSTRACT

1,8-Cineole (also known as eucalyptol) is mostly extracted from the essential oils of plants, which showed extensively pharmacological properties including anti-inflammatory and antioxidant mainly via the regulation on NF-κB and Nrf2, and was used for the treatment of respiratory diseases and cardiovascular, *etc*. Although various administration routes have been used in the application of 1.8-cineole, few formulations have been developed to improve its stability and bioavailability. This review retrospects the researches on the source, biological activities, mechanisms, and application of 1,8-cineole since 2000, which provides a view for the further studies on the application and formulations of 1,8-cineole.

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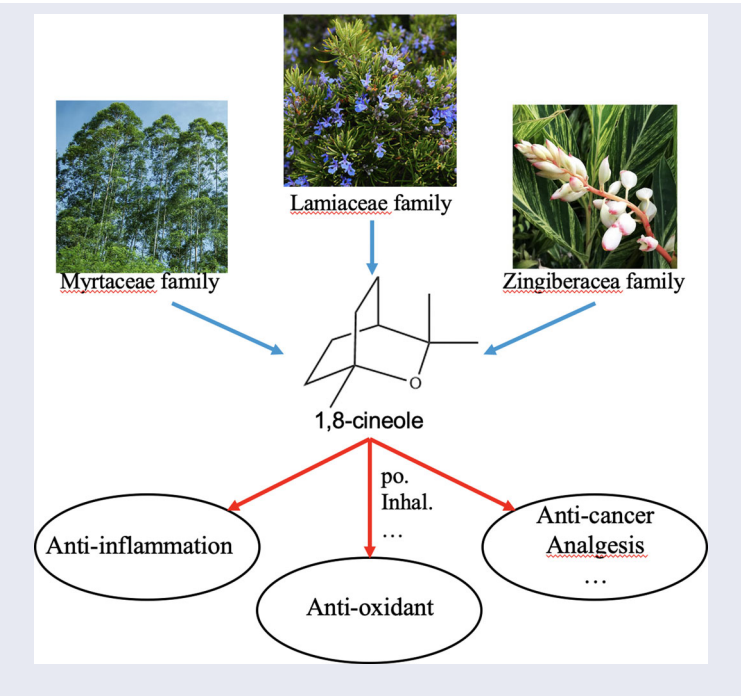
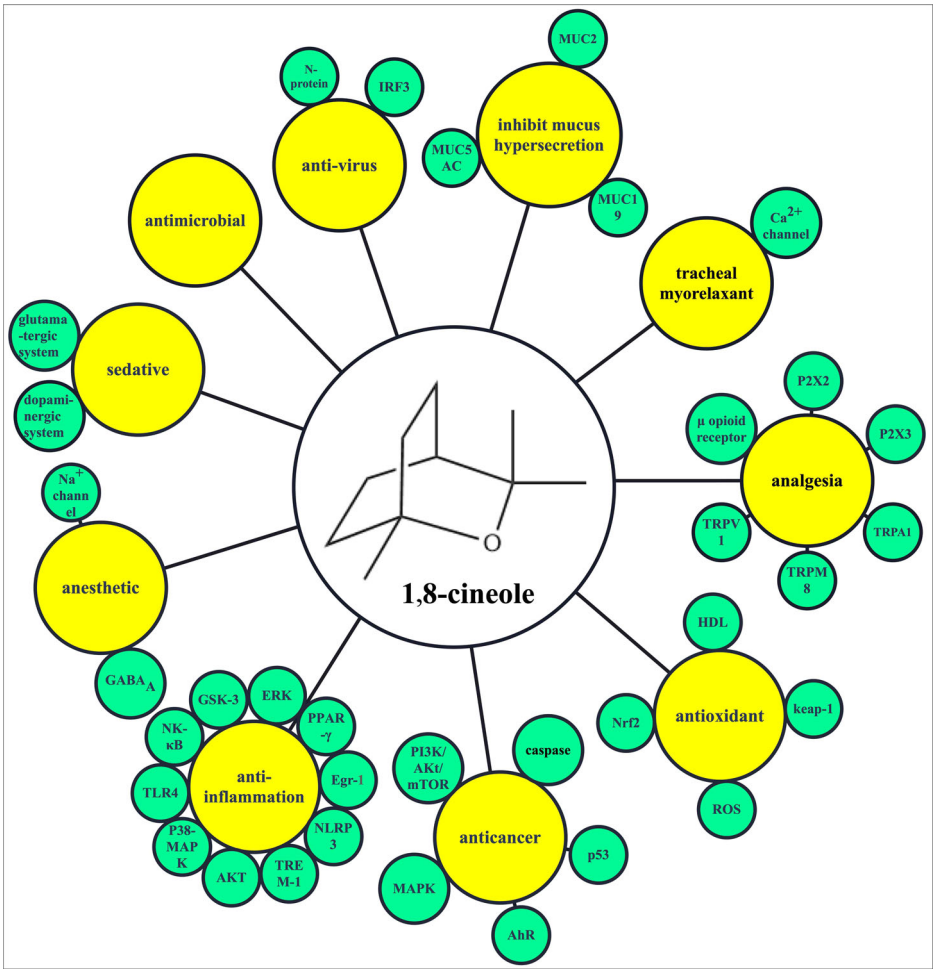


1. Introduction

The natural plant resource is one of the most important sources for potential drug discovery. A compound extracted from a certain part of the plant may exhibit significant pharmacological properties, which might be a promising candidate in clinic. Chinese traditional and herbal medicines have been considered as a treasure trove of new drugs discovery. From 1949 to 2009, about 80 new drugs had been developed directly or indirectly from medicinal plants [1]. Fructus *Alpiniae zerumbet* is a *Miao* folk herbal medicine, which has been widely used to treat diseases among Miao people in Guizhou province of China. 1,8-Cineole is one of the main bioactive components in the essential oil of Fructus *Alpiniae zerumbet*, which possesses great medicinal value [2].

As a kind of saturated monoterpene, 1.8-cineole was mostly extracted from the essential oils of plants, including *Eucalyptus* [3], *Salvia lavandulifolia* Vahl. [4], and *Melaleuca quinquenervia* (Cav.) S.T. Blake [5]. It has been demonstrated that *Eucalyptus* essential oil contains the highest content of 1,8-cineole. Owing to its pleasant aroma and taste, 1,8-cineole is frequently added in flavored, cosmetic, or fragrance products such as bath additives, mouthwashes, insect repellants. The pharmacological properties of 1,8-cineole and related mechanisms are shown in Scheme 1, in which anti-inflammation and anti-oxidation are the dominant pharmacological properties. Through regulating on nuclear factor-kappa B (NF-κB) and nuclear factor erythroid-2-related factor 2 (Nrf2) pathways, 1,8-cineole inhibits the production of inflammatory cytokines and reactive oxygen species (ROS), respectively [6,7]. Therefore, 1,8-cineole has the ability to treat cardiovascular illness, digestive sickness, Alzheimer's disease



Scheme 1. The pharmacological action of 1,8-cineole and its related mechanism.

(AD), and respiratory ailment. In the treatment of bronchitis [8], asthma [9], and chronic obstructive pulmonary disease (COPD) [10], 1,8-cineole has entered clinical trials. Although 1,8-cineole has impressive preclinical profile in pharmacology researches, poor stability restricts its further clinical application. The development of suitable formulations is highly in need for further application *in vivo*. In order to present the research progress on 1,8-cineole in the past two decades from one aspect and provide enlightenments for the following studies, we summarized the researches on 1,8-cineole in terms of the sources, biological activities, mechanisms, and applications.

2. Source of 1,8-cineole

2.1. Myrtaceae

The genus *Eucalyptus* belongs to the Myrtaceae family and comprises about 900 species [11]. *Eucalyptus* extracts are important ingredients in perfumery, pharmaceuticals,

nutraceuticals, and furniture. Extensive researches have shown that the medicinal value of the essential oil of *Eucalyptus* depends largely on 1,8-cineole that accounts for a large proportion [11,12]. The essential oil of *Eucalyptus kochill* subsp. *Borealis* contains about 97.32% 1,8-cineole, which is considered to be the plant with the highest content of 1,8-cineole [13]. Except for *Eucalyptus*, the essential oil from other plants in the Myrtaceae family also contains 1,8-cineole. *Callistemon* has been reported to contain 1,8-cineole in the leaf, flower, and stem [14], especially in the essential oil of *Callistemon viminalis* leaves possessing 83.2% of 1,8-cineole [15]. *Melaleuca* originated from Australia contained about 86% of 1,8-cineole in the essential oil *of Melaleuca armillaris* [16]. The essential oils from other plants in Myrtaceae family contain relatively low percentage of 1,8-cineole. As well known, the content of substances in plants is closely related to the climate, geographical factors, and harvesting season [17]. However, the extraction efficiency (EE) depends on the solvents and extraction technologies. The polarity of extracting solvent influences the chemical composition of *Eucalyptus*. The content of 1,8-cineole in weak polar solvent extracts was 13% higher than that of strong polar and non-polar solvent extracts [18]. Hassine found that essential oil of *Eucalyptus gilii* extracted with hexane provided the highest EE of 1,8-cineole [19]. A number of extractive techniques such as steam distillation, organic solvent extraction, and hydro-distillation have been widely used in the extraction of the essential oil form plants. Hydro-distillation showed optimal EE in terms of 1,8-cineole from the plants in Myrtaceae family [20].

In general, due to the large number of plants in genus *Eucalyptus* and the relatively high content of 1,8-cineole in the essential oil of leaves, the genus *Eucalyptus* is regarded as the major natural source of 1,8-cineole in Myrtaceae family. Hydro-distillation has been most commonly used for the extraction of 1,8-cineole in *Eucalyptus* species. With the renovation on cultivation and extraction techniques, the maximum content of 1,8-cineole in *Eucalyptus* oil might be increased in the future.

2.2. Lamiaceae

The Lamiaceae (Labiatae) family, including approximately 7200 species in 237 genera, is mainly distributed in Mediterranean and Central Asia [21]. *Thymus mastichina* subspecies *mastichina* is the plant with the most abundant 1,8-cineole in the Lamiaceae family, possessing up to 67.4% of 1,8-cineole in the essential oil from the aerial parts [22], which might account for its potential antifungal activity. *Rosmarinus officinalis* L., an evergreen shrub of the genus Rosemary, is mainly observed in Spain, former Yugoslavia, Bulgaria, and Tunisia, which is used for inflammation-related diseases. The content of 1,8-cineole in *Rosmarinus officinalis* essential oil is up to 62.4% [23], and the leaves oil contains the higher content of 1,8-cineole than the stems and flower oil, especially in fructifying stages [24]. Because of the geographic origins, environmental conditions, and development stages, the content of 1,8-cineole collected from rosemary leaf is totally different, which was supported by the study by Gurbuz [25] and Bajalan et al. [26]. The genus *Hyptis*, including 775 species, is one of the most abundant genera of the Lamiaceae family, which are mainly spread in tropical America [27]. There are several literatures reporting that 1,8-cineole is derived from the essential oils of *Hyptis suaveolens* L. Poit [28], *Hyptis fruticose* Pohl

(ex Benth) [29], *Hyptis spicigera* (Lam.) [30], *Hyptis martiusii* Benth [31], in which *Hyptis suaveolens* contains the highest content of 1,8-cineole [32]. Although it was found in the essential oils of other plants in the Lamiaceae family as well as *Lavandula dentate* and *Salvia officinalis* [33], relative low content was detected. According to the published data, steam distillation is more suitable for the extraction of 1,8-cineole from plants in the Lamiaceae family compared with hydro-distillation. Boutekedjiret et al. found that the EE of 1,8-cineole by the steam distillation was almost 20% higher than that of hydro-distillation [34]. Nevertheless, hydro-distillation is still the main method in the extraction of 1,8-cineole due to the low cost and organic solvent-free. Unlike *Eucalyptus*, there is no widely recognized extraction method of 1,8-cineole from the plants in Lamiaceae family and the optimal extraction technology requires further researches.

2.3. Zingiberaceae

Alpiniae zerumbet (Pers.) B. L. Burtt. et R. M. Sm belongs to the genus *Alpinia* of the Zingiberacea family, which is the largest product of "Southern Medicine" in Guizhou province of China. The essential oil of *Alpiniae zerumbet* has been used for insect repellent and anti-inflammation. 1,8-Cineole is the major component in the essential oils from fructus (27.17%) [35] and leaves (43.5%) of *Alpinia zerumbet* [36], which showed higher content in winter than in summer [37]. The essential oil of other plants in the generus *Alpinia*, such as *Alpinia speciose* K. Schum [38], *Alpinia katsumadai* Hayata [39], and *Alpinia calcarata* K. Schum [40], contains 1,8-cineole as well. Among them, the essential oil from rhizomes of *Alpinia galangal* (L.) contains 61.9% of 1,8-cineole, which is the highest in the genus *Alpinia* [41]. Nevertheless, Jirovetz et al. found the highest content of 1,8-cineole in the stem essential oil, compared with that in the essential oils from the leaves, rhizomes, and roots [42]. Besides, 1,8-cineole was detected in the essential oil from other species in the Zingiberacea family, like *Amomum tsaoko* Crevost et Lemarie (*Amomum* genus) [43], *Siphonochilus aethiopicus* (Schweinf.) B. L. Burtt (*Siphonochilus* genus) [44], and *Hedychium coronarium* J. Koenig (*Hedychium* genus) [45]. With regard to the extraction techniques, headspace solid-phase microextraction (HS-SPME) has been used in addition to the steam distillation and hydro-distillation [36]. HS-SPME is a relatively new technique for the extraction of essential oil [46]. Because HS-SPME is more sensitive than traditional extraction methods, more compounds were extracted and identified by HS-SPME. However, special equipments required in the HS-SPME limit the wide application in large-scale extraction.

2.4. Artificial syntheses

Although 1,8-cineole is widely found in the essential oils of *Eucalyptus* and other plants, there are still problems in the industrialized extraction and separation of 1.8-cineole including the acquisition of plants with sufficient essential oil and high cost for separation. Therefore, artificial synthetic methods of 1,8-cineole were developed. Wu et al. [35] reported that the Keggin-structured phosphotungstic acid was used as

the solid acid catalyst for the isomerization of α-terpineol to 1,8-cineole, and the yield was up to 35%. Another way for 1,8-cineole synthesis used heteropoly acid $H_3PW_{12}O_{40}$ as a catalyst in homogeneous and heterogeneous systems, which exerted yield of 25% and 35%, respectively [47]. Because stereoselective step is inevitable in the chemical syntheses of 1,8-cineole, low yield and higher cost are still the problems. The development of the microbial metabolic engineering and the synthetic biology provides another way for chemical compound syntheses. The researchers found the biosyntheses, an effective method for artificial syntheses of 1,8-cineole with yield up to 98% [48], in which 1,8-cineole synthase was important [49].

This section has provided a brief summary for the sources of 1,8-cineole, which was divided into natural resources extraction and artificial syntheses ways. Among the natural plants, the content of 1,8-cineole is highest in the leaves of *Eucalyptus* and the commonly used extraction methods for 1,8-cineole involved hydro-distillation and steam distillation. Some new technologies have emerged as well. For example, the maximum EE of 1,8-cineole from Cardamom (*Elettaria cardamomum*) seeds was obtained by supercritical carbon dioxide [50], which is a promising extraction method for wide application. Moreover, the content of 1,8-cineole from natural sources is susceptible to the planting location, the environment, the harvesting time, and other factors. Compared with extraction from natural products, the biosyntheses methods developed for 1,8-cineole are of great importance for large-scale production.

3. Biological activities and mechanisms of 1,8-cineole

Essential oils containing 1,8-cineole have been used as folk medicines for decades. Moreover, several studies have revealed that 1,8-cineole, as an active compound, plays an important role in the treatment of respiratory diseases, cancers, digestive disorders, dysphoria, AD, cardiovascular illnesses, and bacilli.

3.1. Respiratory diseases

1,8-cineole has therapeutic effects on many respiratory diseases, such as influenza [51], bronchitis [8], rhinosinusitis [52], pneumonia [53], asthma [54] and COPD [10], and entered in clinical trials in some cases [8–10,54]. As an adjuvant for asthma and COPD, 1,8-cineole improved the patients' lung function, respiratory status, and the quality of life [9,10]. In combination with guideline medications such as budesonide and/or formoterol, 1,8-cineole improved the efficacy of glucocorticoid in the treatment of COPD and asthma [55]. Moreover, 1,8-cineole presented cross-protection against influenza virus combined with vaccine [56] or oseltamivir [51] to prolong survival time, reduce weight loss, mortality, and lung damage in animals. Besides, 1,8-cineole alone effectively attenuated airway [57] and lung injury [58], resisted infectious virus [59], and relaxed airway muscles [60]. The pharmacological effects of 1,8-cineole in the treatment of respiratory diseases were mainly attributed to the anti-inflammation [61], muscle relaxation [62], and mucus hypersecretion inhibition effects [63], resulting in the down-regulation of inflammation cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) [64]. To date, a number of

studies have demonstrated that the anti-inflammatory effect of 1,8-cineole might associate with an important nuclear transcription factor – NF-κB. On the one hand, 1,8-cineole inhibited IκBα degradation, thereby suppressing NF-κB p65 translocation and attenuating the expression level of pro-inflammatory NF-κB target genes [65]. On the other hand, 1,8-cineole attenuated activation of NF-κB p65 subunit, resulting in reduced inflammatory cells, cytokines secretion, and oxidative stress [66]. Moreover, the upstream signals of NF-κB was also suppressed by 1,8-cineole, such as the toll-like receptor 4 (TLR4) [67], the extracellular signal-regulated kinase (ERK) [68], and the dephosphorylation of glycogen synthase kinase 3 (GSK-3) [69]. The p38 mitogen-activated protein kinase (MAPK), protein kinase B (Akt), trigger receptors expressed on myeloid cells-1 (TREM-1), and Nod-like receptors 3 (NLRP3) inflammasome [70,71] are the other signaling pathways which can be activated by 1,8-cineole to inhibit the secretion of inflammatory cytokines. The synthesis and nuclear internalization of early growth response factor-1 (Egr-1) is also restricted by 1,8-cineole [72]. The mechanism of 1,8-cineole as a tracheal myorelaxant may be closely related with the blockage of L-type voltage-gated calcium channels [73]. Rhinosinusitis and bacteria-induced mucus hypersecretion generally linked to mucin expression was suppressed by 1,8-cineole [63,74]. Besides, virus-induced respiratory diseases were treated by 1,8-cineole by inhibiting the N-protein [59] and potentiating the interferon regulatory factor (IRF3) [75].

The accumulated evidence suggests that 1.8-cineole is a potential drug for the treatment of respiratory diseases and the therapeutic effects in the clinical trials have been proved on asthma [9], COPD [10], and rhinosinusitis [52]. Most researches on the therapeutic mechanisms of 1,8-cineole are focused on its capability to alleviate inflammation in respiratory diseases through multiple signaling pathways, resulted in the amelioration of pathophysiological features in chronic airway diseases including pulmonary vascular changes and abnormal mucus production.

3.2. Anticancer activities

Over the past few years, researchers have shown great interests in searching anticancer agents from natural plants. According to published literatures, 1,8-cineole was verified as a potential anticancer agent against leukemia [76], skin [77], oral [78], colon [79], breast [80], liver [81], and ovarian [82] cancer both *in vitro* and *in vivo*. The anticancer activities are mainly due to the activation of cancer cell apoptosis via tumor suppressor protein p53 signaling pathway. 1,8-Cineole was verified to effectively induce apoptosis and G2/M phase arrest of skin carcinoma cells by upregulating the expression of p53 protein, meanwhile showed almost no effect on the normal keratinocyte [77]. Moreover, 1,8-cineole delayed skin cancer incidence and reduced tumor nodules by suppressing the expression of the aryl hydrocarbon receptor (AhR) [83]. In the treatment of human oral epidermoid carcinoma cells, 1,8-cineole induced apoptosis via not only mitochondrial stress, but also caspase-dependent pathway and MAPK-mediated pathway [78]. Besides, 1,8-cineole can induce apoptosis via activation of p38 MAPK and Akt as well, resulting in cleaved caspase-3 and poly ADP-ribose polymerase (PARP) in human colorectal cancer [79]. Recently, Rodenak-

kladniew et al. demonstrated that 1,8-cineole could regulate Adenosine 5′-monophosphate-activated protein kinase (AMPK), Akt/mammalian target of rapamycin (mTOR), and MAPK pathway to promote G0/G1 arrest and senescence of hepatocellular carcinoma cells [81]. However, 1,8-cineole only has the protection effect on ultraviolet light-induced skin cancer. Taken together, the anticancer activities of 1,8-cineole have been verified *in vitro* mainly though MAPK and phosphatidylinositol 3 kinase (PI3K)/AKt/mTOR signaling pathways.

3.3. Digestive diseases

1,8-Cineole also has therapeutic effects on colonic damage [84], acute pancreatitis [85], non-alcoholic steatohepatitis [86], diarrhea [87], and gastric [88] or liver injury [89]. Of note, oral administration of 1,8-cineole inhibited castor oil-induced diarrhea through its antispasmodic and antisecretory activities [87]. However, Rocha Caldas et al. [90] proposed that the gastroprotective effect of 1,8-cineole was not attributed to the antisecretory activity, as the basal gastric acid secretion decreased without reduction on total acidity. Three mechanisms might be involved in the gastroprotective effect of 1,8-cineole: the healing property to promote regeneration of the gastric cells, the cytoprotective effect to increase gastric mucus, and the antioxidant activity to reduce myeloperoxidase (MPO) activity. The antioxidant and anti-inflammatory effects of 1,8-cineole in the treatment of trinitrobenzene sulfonic acid-induced colitis and cerulean-induced acute pancreatitis were indicated by the reduced levels of MPO and pro-inflammatory cytokines [84]. Furthermore, the antioxidant capacity of 1,8-cineole may be attributed to its ability of binding with Keap1 that stimulates the activation and translocation to the nuclear of Nrf2, resulting in the increased level of antioxidant enzymes such as superoxide dismutase (SOD) and catalase. So far, the mechanisms of treatment on digestive diseases by 1.8-cineole are mainly limited to the antioxidant effects, and further studies on the anti-inflammatory activity are associated with NF-κB [85]. Besides, 1,8-cineole improved the fibrosis progression and the liver cirrhosis by activating the PI3K-AKt signaling pathway for the treatment of non-alcoholic steatohepatitis [86]. Although 1,8-cineole has been verified to protect the organs involved in the digestive system from inflammatory mediators and oxidative stress, it has not been approved for clinical trials yet.

3.4. Sedative, anesthetic, and analgesia effect

The essential oil extracted from *Lantana camara* leaves was used for sedation by inhalation and 1,8-cineole as the major component in the essential oil was identified as the bioactive ingredient with sedative effect [91]. It was further proved in a clinical trial that inhalation of 1,8-cineole before operations effectively reduced preoperative anxiety and pain of patients [92]. The sedative mechanisms of 1,8-cineole may be related with the suppression on the central nervous system by modulating glutamatergic and dopaminergic systems [93]. Many studies focused on the mechanisms of anesthesia involved the blockage of the Na^+ channels of the superior cervical ganglion neurons [94] or sciatic nerve excitability [95] and the regulation on the γ-Aminobutyric acid type A ($GABA_A$) receptor complexes via benzodiazepine-binding site [96].

The studies on the analgesia effect of 1,8-cineole suggest that it mainly suppresses peripheral pain, like acute orofacial [97], oedema [98], and tail-flick and hot-plate test [99]. The mechanism is generally related to the transient receptor potential (TRP) channels. Transient receptor potential A1 (TRPA1) as one of TRP channels is a receptor for pain or irritation that can be activated by a wide variety of compounds, whereas transient receptor potential melastatin 8 (TRPM8) is activated to relieve pain and correlated temperature and inflammation processes. 1,8-Cineole as an agonist of TRPM8 could not only activate TRPM8 but also inhibit TRPA1 to achieve analgesic effect [100]. Therefore, 1,8-cineole could diminish leukocyte infiltration, myeloperoxidase activity, and the levels of inflammatory cytokines via TRP channels [101]. It was also suggested that 1,8-cineole can play the role of an antagonist for the μ-opioid receptor [99] or transient receptor potential vanilloid 1 (TRPV1) channel [97]. In addition to peripheral pain, 1,8-cineole was verified to inhibit neuropathic pain through regulating the transcription and translation of purine 2X (P2X) receptor [102]. 1,8-Cineole restrained the transmission of pain signals and alleviated the symptoms of neuropathic pain. In summary, the sedation, analgesia, and anesthetic effects of 1,8-cineole mainly acted through cation ion channels such as Na^+ channel, TRP channel, and P2X receptor, which are totally different from other biological activities of 1,8-cineole.

3.5. Alzheimer's disease

AD is an irreversible and progressive brain disease generally in the elderly people. Extracellular amyloid beta (Aβ) plaques deposition and intracellular neurofibrillary tangles are the main features of AD. Increasing evidence indicated that deposition of Aβ induced the inflammation [103]. It was verified to be ameliorated by 1,8-cineole on $A\beta_{25-35}$ in pheochromocytoma cells [104] and the anti-inflammatory mechanism might be related to NF-κB [105]. Given that oxidative stress is one of the pathogenesis of AD, the antioxidant effect of 1,8-cineole might also contribute to the treatment. After pretreatment with 1,8-cineole, the balance of oxidant/antioxidant was maintained by Nrf2-activated ROS scavenging effects [106]. The treatment of the early stage of AD by 1,8-cineole is mainly through inhibiting the acetylcholinesterase (AChE) with unclear mechanism [107]. However, studies have shown that 1,8-cineole-rich extract of plants was more effective than pure 1,8-cineole in the prevention of AD [108]. It might be attributed to the multiple components in the natural extract that achieve synergistic effects.

Based on the previous researches, 1,8-cineole is a promising drug to prevent and treat AD through the anti-inflammatory, antioxidant, and anti-AChE effects. However, the studies are limited in the *in vitro* studies. How to ensure the sufficient delivery of 1,8-cineole to the brain via overcoming the blood–brain barrier is the limiting step in the treatment of AD.

3.6. Cardiovascular diseases

The effects of 1,8-cineole on cardiovascular diseases, including hypertension [109], ischaemic stroke [110], and atherosclerosis [111], might be contributed to the effects

of reduction of blood pressure [109], relaxation of blood vessels [2], enhancement on reverse cholesterol transport [112], resistance of cortical cell damage [110], amelioration of vascular endothelium injury [113], and depression of myocardial contractility [114]. The mechanisms for the treatment of cardiovascular diseases are mainly antioxidant and anti-inflammation. 1,8-Cineole was considered as a ROS scavenger and an enhancer of SOD activity in cerebral ischemic injury model [110]. Moreover, 1,8-cineole protected high-density lipoprotein (HDL) from oxidative damage with antiatherogenic function [115] and enhanced the HDL function, thereby strengthening reverse cholesterol transport [112]. 1,8-Cineole suppressed phosphorylation of NF-κB p65 and prevented translocation of NF-κB from the cytoplasm into the nucleus, leading to the reduced inflammatory cytokines secretion and down-regulated nitric oxide (NO) overexpression, which resulted in amelioration of endothelial cell injury [111]. The peroxisome proliferator-activated receptor γ (PPAR-γ), an upstream signal of NF-κB, was also reported to be one of the targets of 1,8-cineole to regulate NF-κB indirectly [113].

Taken together, these studies support the notion that 1,8-cineole may be a feasible agent in the treatment of cardiovascular diseases, especially for the treatment of atherosclerosis. The significant therapeutic effect of 1,8-cineole on atherosclerosis can be clarified from anti-inflammatory and antioxidant effect. In addition, 1,8-cineole can also decrease blood pressure by regulating the balance of NO or the cardiac systolic function, which provides a theoretical basis for 1,8-cineole in the treatment of atherosclerosis with hypertension.

3.7. Bactericide

Previous literature has demonstrated that 1,8-cineole as a bactericide has relatively strong antimicrobial effects against many pathogens and spoilage organisms, such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Bacillus subtilis* [116,117]. L-asparaginase is a antibacterial target of 1,8-cineole [118]. But the antimicrobial activity of single 1,8-cineole is not as good as essential oils due to the synergistic effects of compounds [117,119]. The enhanced antimicrobial activities were also obtained when 1,8-cineole and chemical antibacterial agents were used together, such as mupirocin [120] and chlorhexidine digluconate [121]. In some cases, both antimicrobial and anti-inflammatory effects of 1,8-cineole are exerted. In the treatment of bacterial vaginosis, vulvovaginal candidiasis, and acne, 1,8-cineole resisted *Gardnerella vaginalis*, *Candida albicans*, and *Propionibacterium acnes*, respectively, and inhibited inflammation through NF-κB pathway [122]. To date, the antimicrobial mechanisms of 1,8-cineole are still not very clear. However, the synergistic effect of 1,8-cineole with common antimicrobial drugs is generally observed in antimicrobial experiments, indicating the role of 1,8-cineole as an promising adjuvant against bacteria.

In view of all that has been mentioned above, 1,8-cineole is a potential therapeutic agent for AD, cancers, respiratory diseases, digestive disorders, cardiovascular illnesses, dysphoria, and bacilli. Anti-inflammation and antioxidant effects are the most important mechanisms in the treatments. 1,8-Cineole was reported to achieve anti-inflammatory effect mainly via regulating NF-κB pathways in the treatment of

respiratory disorders, AD, and other diseases. Because of the strong ROS scavenging capacity, it was used in the treatment of cardiovascular illnesses and digestive diseases. In addition, 1,8-cineole was applied in the treatment of gout arthritis [123] and children with IgA nephropathy [124] as well.

4. Application of 1,8-cineole

In the clinical trials, 1,8-cineole was applied via capsules and directly sniff [92]. In addition, several other formulations have been developed, including tablets, microemulsion, inhalation, injection, and nasal drops. However, 1,8-cineole with camphor smell and a cool herbal taste possesses high volatility and poor water solubility, which restricts the absorption of 1,8-cineole after oral administration. The same problems also encountered in the pulmonary and intranasal administration. Therefore, safe and effective formulations of 1,8-cineole are highly in need.

4.1. Oral administration

Oral administration is the principal application of 1,8-cineole. Soft capsules is commonly used formulation of 1,8-cineole in clinical trials for the treatment of acute bronchitis, asthma, COPD and sinusitis [8–10,52,54,124], which might reduce the volatilization, dissociation, and exudation of 1,8-cineole. Recently, the novel drug delivery systems, involving self-microemulsion (SME) and cyclodextrin inclusion compound, have been developed for 1,8-cineole to promote the oral administration [125,126].

The SME drug delivery system was developed for 1,8-cineole to improve the solubility, decrease the volatility, and cover the pungent odor. Jiang et al. [126] developed a SME drug delivery system for 1,8-cineole to treat cardiovascular diseases which consisted of 1,8-cineole, kolliphor HS 15, and ethanol at ratio of 9:7:14. With appropriate amount of water, the SME of 1,8-cineole was prepared. It was confirmed that SME increased the stability of 1,8-cineole to exert superior anti-inflammatory effect than free 1,8-cineole suspension, resulting in better protection effect on the blood vessels from inflammatory damage. Cyclodextrin inclusion compound is another choice to improve the absorption and reduce the irritation and side effects of 1,8-cineole. Hydroxypropyl-β-cyclodextrin (HP-β-CD) was complexed with 1,8-cineole to form inclusion compound, which is used to combat *Ectomyelois ceratoniae*. Compared with free 1,8-cineole, HP-β-CD/1,8-cineole inclusion complex was demonstrated with more effective insecticidal characteristics and long-term toxicity [125].

4.2. Pulmonary administration

For respiratory illnesses, 1,8-cineole showed profound therapeutic effects via oral administration in clinical trials. However, pulmonary administration is an optimal way for emergency rescue induced by the respiratory diseases, which avoids first-pass effects with reduced irritation, fast effects, and less side effects. It is suggested for the long-term treatment as well. Several studies applied pulmonary administration of 1,8-

cineole as aerosol for the treatment of COPD, allergic asthma of animal models [7,57,70]. Ultrasonic atomization is an effective way to nebulize 1,8-cineole for the mitigation of lung or airway injury. But, the uncertainty of actual dosage after ultrasonic atomization limits the clinical application. It is meaningful to develop an inhalation drug delivery for accurate lung administration.

4.3. Intranasal administration

Intranasal administration can also avoid first-pass effects and degradation of drugs in the gastrointestinal fluid. The nasal mucosa with rich blood vessels and high permeability is beneficial for systemic absorption. Li et al. developed a 1,8-cineole-adjuvanted influenza vaccine. After intranasal administration, longer survival time, milder inflammation, less weight loss, reduced mortality rate and lower lung index, and viral titers were showed compared with vaccine without 1,8-cineole [56]. In view of the therapeutic effect of 1,8-cineole on rhinitis, it may be feasible to develop nasal drops for the treatment of rhinitis.

Besides, 1,8-cineole was used as a skin penetration enhancer for chlorhexidine [127], huperzine A, and ligustrazine phosphate [128], which was attributed to the interactions with lipids in the stratum corneum [129].

Above all, this part showed the main administration routes and formulations of 1,8-cineole both in laboratory investigation stage and clinical trials. In order to achieve the optimal therapeutic effect of 1,8-cineole, different administration routes and formulations are adopted according to the characteristics of diseases. The oral administration of 1,8-cineole as solutions and soft capsules were used for the treatment of atherosclerosis, hypertension, AD. However, pulmonary and intranasal administrations of 1,8-cineole were applied in the treatment of asthma, COPD, anxious, peripheral pain. Nevertheless, the studies on the development of 1,8-cineole formulations, especially the novel drug delivery systems, are much less than the pharmacological studies.

5. Conclusion

This review provides a brief summary of the researches relating to the origins, pharmacological effects, and applications of 1,8-cineole. As a monoterpene, 1,8-cineole is abundant in the essential oils of eucalyptus and rosemary. A large number of studies have proven that 1,8-cineole possesses a wide range of pharmacological effects and mainly acts via anti-inflammatory and antioxidant mechanisms. It is demonstrated that 1,8-cineole alleviates the inflammatory responses and oxidative stress principally through NF-κB and Nrf2 signaling pathway, respectively. Besides, MAPK, Akt, and TRP channels were reported as the targets of 1,8-cineole as well. There are still several limitations in the study of 1,8-cineole. First, few studies have been reported on the development of 1,8-cineole formulations, which is highly in need for the further clinical application, notably the development of pulmonary drug delivery formulations for the treatment of respiratory diseases. Second, only two papers focused on the pharmacokinetics of 1,8-cineole *in vivo* [130]. The systemic and

comprehensive pharmacokinetics studies are necessary for 1,8-cineole to guide rational clinical use. Third, the studies on the toxicity of 1,8-cineole remain insufficient. Although 1,8-cineole has been reported to be involved in the regime for the treatment of nausea, heartburn, rash, and diarrhea, studies on the safety and side effects of 1,8-cineole for long-term medication in the treatment of chronic diseases are required.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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