IJBPAS, November, 2022, 11(11): 5306-5314

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

1, 8-CINEOLE: A REVIEW

KAUR P[1], KAUR K[2], JOSHI G[3], MAAN M[4] AND BHANDARI DD[3*]

1: School of Pharmaceutical Sciences, RIMT University, Mandi Gobindgarh

2: School of Pharmacy, Desh Bhagat University, Mandi Gobindgarh, Punjab

3: University Institute of Pharma Sciences, Chandigarh University, Mohali, Punjab, India

4: Faculty of Pharmaceutical Sciences, LBS College of Pharmacy, Jaipur

***Corresponding Author: Dr. Divya Dhawal Bhandari: E Mail: divya.pharma@cumail.in**

Received 28th Dec. 2021; Revised 26th Jan. 2022; Accepted 27th Feb. 2022; Available online 1st Nov. 2022

https://doi.org/10.31032/IJBPAS/2022/11.11.6577

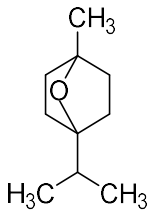
ABSTRACT

Eucalyptol, potentially known as 1,8-cineole is an active ingredient of a number of plant species which is mainly responsible for providing aromatic character to plants. 1,8-cineole can be found among more than 20 plant species and possess a number of biological activities which includes anticancer potential, analgesic action, anti-inflammatory and antimicrobial properties, helps in a number of neurodegenerative disorders, reduces cardiac hypertrophy, induces bronchodilator effect, effective as anti-anxiety agent and also possess lipid lowering potential. 1,8-cineole possess great pharmacological potential but much more is required to explore in this direction. This review focus on some of the plant species containing 1,8-cineole as an active ingredient and also the various pharmacological activities being reported till date. More research is needed in this field to explore various other unseen potential of 1,8-cineole by exploring various species of plants containing eucalyptol as an active ingredient.

Keywords: 1,8-Cineole, Analgesic, Cardio protective, Neurodegenerative, Inflammation

INTRODUCTION

Eucalyptol or 1,8-Cineole, an achiral aromatic component of various plants, such as Salvia and Eucalyptus leaves, rhizospher e volatile in Arabidopsis, allelopathic agent from Salvia and Artemisia, and has folivore preventive activity **[1]**. It is a colorless liquid with camphor like odor and spicy cooling taste.



1,8-Cineole

1,8-cineole, a natural monoterpene, is a main component of essential oils of plants specially isolated from Eucalyptus globulus oil. As isolated one, it is showing a number of therapeutic benefits specially for respiratory tract as mucolytic and anti-spasmolytic with proven clinical efficancy **[2]**. Eucalyptol, a naturally produced cyclic ether is an ingredient of mouthwash and cough suppressant of various brands. It initiates anti-inflammatory cytokine inhibition thus helps in controlling airway mucus hypersecretion and asthma. It is also effective to treat non purulent rhino sinusitis. Topical applications of eucalyptol reduce pain as well as inflammation and also kills leukemia cells in vitro. It also has a role as a flavouring agent **[3]**.

SOURCES OF 1, 8-CINEOLE

S. No.	Plant/ Family	Plant Part	Percentage	Native Place	References
1.	*Artemisia annua* L./ Asteraceae	Flowering Tops	Up to 51.6	China	4
2.	*Eucalyptus viminalis*/ Myrtaceae	Leaves	57.757	South-eastern Australia	5
3.	*Salvia rosmarinus* Spenn. from Ionian Coast/ Lamiaceae	Aerial Parts	16.28±2.11	Ionian Coast, Greece	6
4.	*Salvia rosmarinus* Spenn. from Tyrrhenian Coast / Lamiaceae	Aerial Parts	21.89±2.32	Tyrrhenian Coast,Itlay	6
5.	*Mentha longifolia*/ Lamiaceae	Essential oil	5.6-10.8	Europe excluding Britain and Ireland	7
6.	*Alpinia japonica*/ Zingiberaceae	Flower	10.5	Asia, Australia	8
7.	*Alpinia japonica*/ Zingiberaceae	Fruit	69.4	Asia, Australia	8
8.	*Alpinia japonica*/ Zingiberaceae	Leaves	30.6	Asia, Australia	8
9.	*Alpinia japonica*/ Zingiberaceae	Stem	8.7	Asia, Australia	8
10.	*Alpinia japonica*/ Zingiberaceae	Rhizome	12.7	Asia, Australia	8
11.	*Elettaria cardamomum*/ Zingiberaceae	Rhizome	22.2	Southern India	8
12.	*Elettaria cardamomum*/ Zingiberaceae	Root	10.0	Southern India	8
13.	*Elettaria cardamomum*/ Zingiberaceae	Leaves	6.5	Southern India	8
14.	*Eucalyptus kochii*/ Myrtaceae	Leaves	97.32	Western Australia	9
15.	*Eucalyptus loxophleba*/ Myrtaceae	Leaves	66.93	Western Australia	9
16.	*Eucalyptus globules*/ Myrtaceae	Leaves	77.02	Australia	9
17.	*Callistemon citrinus*/ Myrtaceae	Leaves	61.2-83.2	New South Wales, Victoria and Southern Queensland	10

18.	***Callistemon viminalis*/ Myrtaceae**	**Leaves**	**61.2-83.2**	**East – coast of Australia**	**10**
19.	***Croton rhamnifolioides*/ Euphorbiaceae**	**Leaves**	**41.33**	**Mexico**	**11**
20.	***Thymus capitellatus*/ Lamiaceae**	**Aerial Part**	**58.6**	**Southwest Portugal**	**12**
21.	***Eucalyptus cinerea*/ Myrtaceae**	**Fresh Leaves**	**74.98**	**South-eastern Australia**	**13**
22.	***Eucalyptus cinerea*/ Myrtaceae**	**Dried Leaves**	**85.32**	**South-eastern Australia**	**13**
23.	***Eucalyptus cinerea*/ Myrtaceae**	**Flowers**	**78.76**	**South-eastern Australia**	**13**
24.	***Eucalyptus cinerea*/ Myrtaceae**	**Fruits**	**80.97**	**South-eastern Australia**	**13**
25.	***Lavandula stoechas* L./ Lamiaceae**	**Essential Oil**	**61.36**	**France, Spain**	**14**

THERAPEUTIC APPLICATIONS OF 1,8-CINEOLE (Fig 1)

1. **Cancer:** 1, 8-Cineole found to have significant effect on human colon cancer cell lines HCT116 and RKO by WST-8 (2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium monosodium salt) and 5-bromo-2'-deoxyuridine (BrdU) assays. The cytoxicity of 1,8-Cineole was investigated by lactate dehydrogenase (LDH) activity assay and terminal deoxy-nucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) staining method. 1, 8-cineole causes the inactivation of survivin and Akt and activation of p38. These molecules cleave PARP (Poly adenosine diphosphate-ribose polymerase) and caspase-3 and causes apoptosis. Thus, it can be used in the treatment of colorectal cancer **[15]**.
2. **Respiratory Disorders:** 1, 8-Cineole decreases tumor necrosis factor-alpha (TNF-α), interleukin-1-beta (IL-1b), leukotriene B4 (LTB4) and thromboxane B2. It also decreases the production of mucus and also shows bronchodilatory effect. Hence it can be used in the treatment of respiratory diseases like asthma, chronic obstructive pulmonary disease (COPD), pulmonary tuberculosis, whooping cough (Pertussis), Viral or bacterial respiratory diseases, etc. **[16, 17]**.
3. **Pancreatitis:** Pancreatitis is an inflammatory condition of pancreas in which oxidative stress, NF-κB signaling and pro- inflammatory mediators play an important role. 1, 8- Cineole successfully reduces the level of pancreatic edema, NF-κB expression, myeloperoxidase,

malondialdehyde and also the proinflammatory cytokines (TNF-α, IL-1β, and IL-6). Therefore, 1, 8-Cineole can be used in acute pancretitis via anti-inflammatory mechanism **[18]**.

4. **Inflammation:** 1, 8-Cineole efficiently reduces paw edema induced by carrageenan as well as dextran. It also reduces vascular permeability [protein extravasation] and edema induced by histamine and arachidonic acid. It successfully reduced acute and chronic phase of inflammation, hence can be used as new anti-inflammatory agent **[19]**. 1, 8- Cineole has also shown its inhibiting potential on acetic acid-induced peritoneal capillary permeability and the chemical nociception induced by formalin and acetic acid **[20]**.
5. **Hyperlipidemia:** 1, 8-Cineole has shown inhibitory activity on cupric ion-mediated oxidation of lipoproteins and simultaneously increased removal of ferric ion from high-density lipoprotein. The study including hypercholesterolemia induced in zebrafish using cholesterol-feeding treatment showed that 1, 8-Cineole lowers the lipid level and possess anti-inflammatory activity. Serum amyloid A, interleukin-6 levels and lipid accumulation were also decreased in the liver **[21]**.
6. **Analgesia:** Some scientists reported that 1, 8-Cineole inhibits the production of prostaglandins and cytokines by stimulated monocytes. Therefore, it can be used as analgesic agent **[20, 27]**. It inhibits Transient Receptor Potential Cation channel subfamily A1 (TRPA1) currents activated by allyl isothiocyanate and menthol and also activates Transient Receptor Potential Cation channel subfamily M8 (TRPM8) receptors. For analgesic effect, TRPA1 and TRPM8 receptors play an important role as TRPM8 receptor is a thermo-sensitive receptor that detects cool temperatures whereas TRPA1 is a sensor of noxious cold **[22]**.
7. **Microbial Growth:** 1, 8-Cineole posses antimicrobial activity and also increases the effect of other antiseptics. With chlorhexidine, cineole shows the synergistic effect against many micro-organisms such as *Staphylococcus aureus*, *Klebsiella pneumonia, Candida albicans*, *Enterococcus faecalis* and *Escherichia coli* **[23]**.
8. **Cardiac hypertrophy:** 1, 8-Cineole reduces the cardiac

hypertrophy in heart failure. It also improves cardiomyocyte viability and decreases cytoplasmic vacuole formation, myofibre loss, fibrosis and apoptosis caused by endoplasmic reticulum stress by inhibiting the miR-206-3p/SERP1 pathway **[24]**.

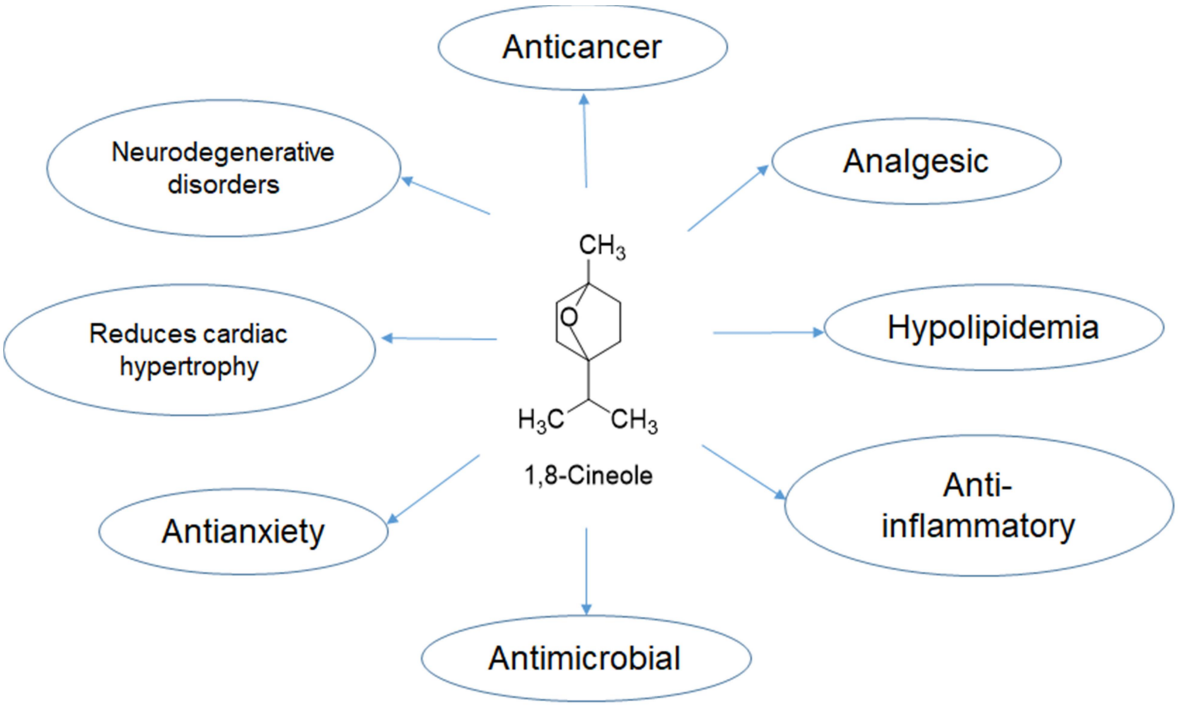


Figure 1: Therapeutic applications of 1,8-Cineole

9. **Anxiety**: 1, 8- Cineole acts on $GABA_A$ and benzodiazepines receptors and work as $GABA_A$ receptor antagonist. It possess anxiolytic effect and also reduces depression like behavior **[25]**. It also proved that aromatherapy / inhalation of 1, 8-Cineole ameliorates anxiety in patients **[26]**.
10. **Neurodegeneration:** 1, 8- Cineole has been found effective in the treatment of neurodegenerative disorders pertaining to its anti-inflammatory potential. It reduces the level of pro-inflammatory cytokines TNF-alpha, IL-beta and IL-6 and also reduces the NF-KB, NOS-2 and COX-2 expression **[28]**. The early stages of alzheimers disease can be treated using 1, 8-cineole due to its anticholinesterases activity **[29]**.

CONCLUSION

Evidences are there to support the analgesic and anti-inflammatory activity of 1,8-cineole which might be due to stimulation of TRP cation channels cool temperature-detecting transient receptor and also thermosensitive which further inhibits sensor of noxious cold i.e. the human

transient receptor potential cation channel, subfamily A, member 1 (TRPA1) **[30]**. 1,8-cineole is also reported to prevent skin cancer induced by UV-B radiations by targeting the aryl hydrocarbon receptor **[31]**. These findings suggest the 5HT-3 receptor inhibitory potential for eucalyptol and also their binding being confined to a small area opens the platform for 1,8-cineole as novel allosteric modulators **[32]**. More research is needed in this field to explore various other unseen potential of 1,8-cineole by exploring various species of plants containing eucalyptol as an active ingredient.

ACKNOWLEDGMENT

Authors would like to thank Chandigarh University and RIMT university for providing necessary facilities to access e-resources.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

REFERENCES

[1] Edward M. Davis, 1.15 - Advances in the Enzymology of Monoterpene Cyclization Reactions, Editor(s): Hung-Wen (Ben) Liu, Lew Mander, Comprehensive Natural Products II, Elsevier, 2010, Pages 585-608, ISBN 9780080453828.

[2] Juergens RU, Anti-inflammatory properties of the monoterpene 1.8-cineole: current evidence for co-medication in inflammatory airway diseases. Drug Research. 2014 Dec;64(12):638-646.

[3] **https://pubchem.ncbi.nlm.nih.gov/compound/Eucalyptol**

[4] Bilia AR, Santomauro F, Sacco C, Bergonzi MC, Donato R. Essential oil of *Artemisia annua* L.: an extraordinary component with numerous antimicrobial properties. Evidence-based complementary and alternative medicine. 2014 Apr 1; 2014.

[5] Maghsoodlou MT, Kazemipoor N, Valizadeh J, Seifi MF, Rahneshan N. Essential oil composition of *Eucalyptus microtheca* and *Eucalyptus viminalis*. Avicenna journal of phytomedicine. 2015 Nov; 5[6]:540.

[6] Leporini M, Bonesi M, Loizzo MR, Passalacqua NG, Tundis R. The essential oil of *Salvia rosmarinus Spenn*. from Italy as a source of health-promoting compounds: Chemical profile and antioxidant and cholinesterase inhibitory activity. Plants. 2020 Jun;9[6]:798.

[7] Mikaili P, Mojaverrostami S, Moloudizargari M, Aghajanshakeri S. Pharmacological and therapeutic effects of *Mentha Longifolia* L. and its main constituent, menthol. Ancient science of life. 2013 Oct;33[2]:131.

[8] Asakawa Y, Ludwiczuk A, Sakurai K, Tomiyama K, Kawakami Y, Yaguchi Y. Comparative study on volatile compounds of *Alpinia japonica* and

Elettaria cardamomum. Journal of oleo science. 2017;66[8]:871-6.

[9] Aldoghaim FS, Flematti GR, Hammer KA. Antimicrobial activity of several cineole-rich Western Australian Eucalyptus essential oils. Microorganisms. 2018 Dec;6[4]:122.

[10] Oyedeji OO, Lawal O, Shode F, Oyedeji A. Chemical composition and antibacterial activity of the essential oils of *Callistemon citrinus* and *Callistemon viminalis* from South Africa. Molecules. 2009 Jun;14[6]:1990-8.

[11] Martins AO, Rodrigues LB, Cesário FR, de Oliveira MR, Tintino CD, e Castro FF, Alcantara IS, Fernandes MN, de Albuquerque TR, da Silva MS, de Sousa Araujo AA. Anti-edematogenic and anti-inflammatory activity of the essential oil from Croton rhamnifolioides leaves and its major constituent 1, 8-cineole [eucalyptol]. Biomedicine & Pharmacotherapy. 2017 Dec 1; 96:384-95.

[12] Machado M, Dinis AM, Santos-Rosa M, Alves V, Salgueiro L, Cavaleiro C, Sousa MC. Activity of *Thymus capitellatus* volatile extract, 1, 8-cineole and borneol against Leishmania species. Veterinary parasitology. 2014 Feb 24;200[1-2]:39-49.

[13] Silva SM, Abe SY, Murakami FS, Frensch G, Marques FA, Nakashima T. Essential oils from different plant parts of *Eucalyptus cinerea* F. Muell. ex Benth.[Myrtaceae] as a source of 1, 8-cineole and their bioactivities. Pharmaceuticals. 2011 Dec;4[12]:1535-50.

[14] Boukhatem MN, Sudha T, Darwish NH, Chader H, Belkadi A, Rajabi M, Houche A, Benkebailli F, Oudjida F, Mousa SA. A new eucalyptol-rich lavender [*Lavandula stoechas* L.] essential oil: Emerging potential for therapy against inflammation and cancer. Molecules. 2020 Jan;25[16]:3671.

[15] Murata S, Shiragami R, Kosugi C, Tezuka T, Yamazaki M, Hirano A, Yoshimura Y, Suzuki M, Shuto K, Ohkohchi N, Koda K. Antitumor effect of 1, 8-cineole against colon cancer. Oncology reports. 2013 Dec 1;30[6]:2647-52.

[16] Galan DM, Ezeudu NE, Garcia J, Geronimo CA, Berry NM, Malcolm BJ. Eucalyptol [1, 8-cineole]: an underutilized ally in respiratory disorders?. Journal of Essential Oil Research. 2020 Mar 3;32[2]:103-10.

[17] Juergens LJ, Worth H, Juergens UR. New perspectives for mucolytic, anti-inflammatory and adjunctive therapy with 1, 8-cineole in COPD and asthma: review on the new therapeutic approach. Advances in therapy. 2020 May;37[5]:1737-53.

[18] Lima PR, de Melo TS, Carvalho KM, de Oliveira ÍB, Arruda BR, de Castro Brito GA, Rao VS, Santos FA. 1, 8-

cineole [eucalyptol] ameliorates cerulein-induced acute pancreatitis via modulation of cytokines, oxidative stress and NF-κB activity in mice. Life Sciences. 2013 Jul 10;92[24-26]:1195-201.

[19] Martins AO, Rodrigues LB, Cesário FR, de Oliveira MR, Tintino CD, e Castro FF, Alcantara IS, Fernandes MN, de Albuquerque TR, da Silva MS, de Sousa Araujo AA. Anti-edematogenic and anti-inflammatory activity of the essential oil from *Croton rhamnifolioides* leaves and its major constituent 1, 8-cineole [eucalyptol]. Biomedicine & Pharmacotherapy. 2017 Dec 1;96:384-95.

[20] Santos FA, Rao VS. Antiinflammatory and antinociceptive effects of 1, 8-cineole a terpenoid oxide present in many plant essential oils. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2000 Jun;14[4]:240-4.

[21] Cho KH. 1, 8-cineole protected human lipoproteins from modification by oxidation and glycation and exhibited serum lipid-lowering and anti-inflammatory activity in zebrafish. BMB reports. 2012;45[10]:565-70.

[22] Takaishi M, Fujita F, Uchida K, Yamamoto S, Sawada M, Hatai C, Shimizu M, Tominaga M. 1, 8-cineole, a TRPM8 agonist, is a novel natural antagonist of human TRPA1. Molecular pain. 2012 Nov 29;8:1744-8069.

[23] Şimşek M, Duman R. Investigation of effect of 1, 8-cineole on antimicrobial activity of chlorhexidine gluconate. Pharmacognosy research. 2017 Jul;9[3]:234.

[24] Wang Y, Zhen D, Fu D, Fu Y, Zhang X, Gong G, Wei C. 1, 8-cineole attenuates cardiac hypertrophy in heart failure by inhibiting the miR-206-3p/SERP1 pathway. Phytomedicine. 2021 Oct 1;91:153672.

[25] Kim KY, Seo HJ, Min SS, Park M, Seol GH. The effect of 1, 8-cineole inhalation on preoperative anxiety: A randomized clinical trial. Evidence-Based Complementary and Alternative Medicine. 2014 Jan 1;2014.

[26] Dougnon G, Ito M. Inhalation administration of the bicyclic ethers 1, 8-and 1, 4-cineole prevent anxiety and depressive-like behaviours in mice. Molecules. 2020 Jan;25[8]:1884.

[27] De Cassia da Silveira e SR; Andrade LN, De Sousa DP. A Review on Anti-Inflammatory Activity of Monoterpenes. *Molecules* **2013**, *18*, 1227-1254.

[28] Khan A, Vaibhav K, Javed H, Tabassum R, Ahmed ME, Khan MM, Khan MB, Shrivastava P, Islam F,

Siddiqui S, Safhi MM. 1,8-Cineole [Eucalyptol] Mitigates Inflammation in Amyloid Beta Toxicated PC12 Cells: Relevance to Alzheimer's Disease. Neurochem Res, 2014, 39, 344-352.

[29] D. Kaufmann, A.K. Dogra, and M. Wink. Myrtenal inhibits acetylcholinesterase, a known Alzheimer target. J. Pharm. Pharmacol, 2011, 63, 1368.

[30] Takaishi M, Fuzita F, Ujita K, Yamamoto S. 1,8-Cineole, a TRPM8 agonist, is a novel natural antagonist of human TRPA1. Molecular Pain, 2012, 8 (1): 86.

[31] Lee J, Ha SJ, Park J, Kim YH, Lee NH, Kim YE, Kim Y, Song KM, Jung SK. 1,8-cineole prevents UVB-induced skin carcinogenesis by targeting the aryl hydrocarbon receptor. Oncotarget. 2017 Nov 20;8(62):105995-106008. doi: 10.18632/oncotarget.22519. PMID: 29285309; PMCID: PMC5739696.

[32] Jarvis GE, Barbosa R, Thompson AJ. Noncompetitive Inhibition of 5-HT3 Receptors by Citral, Linalool, and Eucalyptol Revealed by Nonlinear Mixed-Effects Modeling. J Pharmacol Exp Ther. 2016 Mar;356(3):549-62. doi: 10.1124/jpet.115.230011. Epub 2015 Dec 15. PMID: 26669427; PMCID: PMC5378937.