Eucalyptol and Its Role in Chronic Diseases

Geun Hee Seol and Ka Young Kim

Abstract Patients with chronic diseases such as cardiovascular diseases, chronic respiratory diseases, and neurological diseases have been shown to benefit from treatments such as aromatherapy in addition to medication. Most chronic diseases are caused by chronic inflammation and oxidative stress as well as harmful factors. Eucalyptol (1,8-cineole), a terpenoid oxide isolated from *Eucalyptus* species, is a promising compound for treating such conditions as it has been shown to have anti-inflammatory and antioxidant effects in various diseases, including respiratory disease, pancreatitis, colon damage, and cardiovascular and neurodegenerative diseases. Eucalyptol suppresses lipopolysaccharide (LPS)-induced proinflammatory cytokine production through the action of NF-κB, TNF-α, IL-1β, and IL-6 and the extracellular signal-regulated kinase (ERK) pathway, and reduces oxidative stress through the regulation of signaling pathways and radical scavenging. The effects of eucalyptol have been studied in several cell and animal models as well as in patients with chronic diseases. Furthermore, eucalyptol can pass the blood–brain barrier and hence can be used as a carrier to deliver drugs to the brain via a microemulsion system. In summary, the various biological activities of eucalyptol such as its anti-inflammatory and antioxidant properties, as well as its physicochemical characteristics, make this compound a potentially important drug for the treatment of chronic diseases.

Keywords Eucalyptol · Chronic disease · Anti-inflammatory · Antioxidant

G.H. Seol (✉)
Department of Basic Nursing Science, School of Nursing, Korea University, Seoul 02841, Republic of Korea
e-mail: ghseol@korea.ac.kr

K.Y. Kim
Department of Nursing Science, School of Nursing, Gachon University, Incheon 21936, Republic of Korea

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1 Introduction

Patient with chronic disease such as cardiovascular diseases, cancers, chronic respiratory diseases, diabetes, and mental illness needs to be constantly managed because the patient may be impacted by various factors including smoking, lack of physical activity, and poor eating habits [5]. Furthermore, the prevalence of chronic diseases tends to increase with age. Chronic diseases may result from various causes including chronic inflammation and oxidative stress [4, 16]. Chronic inflammation is regarded as one of the main causes of cancers, diabetes, cardiovascular diseases, autoimmune diseases, and other age-related diseases [16]. Moreover, it facilitates neoplastic transformation through inflammatory processes, including injury, repair, resolution, and oxidative stress [6]. Age-related diseases and cardiovascular diseases are characterized by inflammatory pathogenesis and oxidative stress [3, 7, 25].

Alternative medicines such as aromatherapy with aromatic plant oils including essential oils and plant materials may be helpful in the continuous care and management of patients with chronic disease. Natural plant-derived components have been widely used in a wide variety of diseases including chronic disease [8]. Eucalyptol, which has anti-inflammatory and antioxidant activities, has been used to treat lung inflammation and respiratory diseases including bronchitis, sinusitis, bronchial asthma, and chronic obstructive pulmonary disease (COPD) [11, 12, 17, 33, 34]. Furthermore, eucalyptol showed neuroprotective effects in an ischemic stroke model [20] and anti-inflammatory effects in neurodegenerative diseases such as Alzheimer's disease as well as significantly reducing preoperative anxiety in patients undergoing surgery [18].

This review describes the role of eucalyptol in chronic diseases through its regulation of cell signaling pathways and biological activities in animal models and humans.

2 Physicochemical Properties of Eucalyptol

Eucalyptol, also known as 1,8-cineole, is a terpenoid oxide isolated from Eucalyptus species such as *Eucalyptus globules* Labill. and *Eucalyptus tereticornis* Sm. Eucalyptol is derived from the leaf oil of these plants, which contains various volatile organic components [1]. Terpenes such as eucalyptol are lipophilic molecules that disturb intracellular lipids and increase drug penetration [21]. A lipid-based microemulsion system of eucalyptol has been utilized for transdermal drug delivery. Eucalyptol is metabolized to 2-exo-hydroxy-1,8-cineole by rat and human liver microsomal P450 enzymes and eliminated in the urine [22]. Moreover, eucalyptol can easily pass through the blood–brain barrier and may have direct action on receptors and enzymes in the brain [24].

Eucalyptol has been reported to have antimicrobial, anti-inflammatory, antioxidant, analgesic, and spasmolytic effects in various diseases including colds, influenza, other respiratory infections, rhinitis, and sinusitis [28]. Eucalyptol acted as a strong inhibitor of proinflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β and showed an analgesic effect in an inflammatory model [28]. Eucalyptol significantly increased the beat frequency of nasal cilia in mucus membranes and had bronchodilation effects [33]. In addition, it decreased exacerbation in asthma, sinusitis, and COPD symptoms by inhibiting cytokine-induced airway mucus hypersecretion [28]. It exhibits antioxidant activity by radical scavenging [30] and reduces Ca^{2+} influx via calcium channels in cardiac muscle [31].

3 Eucalyptol Modulation of Cell Signaling Pathways

Chronic diseases are closely associated with chronic inflammation and oxidative stress [4, 16]. The pathological features of chronic inflammation include the production of inflammatory cytokines and tissue damage [16]. Oxidative stress disturbs the normal functions of lipids, proteins, and DNA and is therefore toxic to cells and tissues. Free radicals cause mutations and damage DNA in cancer and age-related diseases. Oxidative stress regulates signaling pathways that induce the production of proinflammatory cytokines and chemokines [16, 26].

Lipopolysaccharide (LPS) plays an important role in inflammatory processes by activating the NF-κB and MAPK signaling pathways [10]. Eucalyptol was shown to inhibit LPS-induced cytokine production by human lymphocytes and monocytes [28] and to reduce LPS-induced NF-κB activity and to increase IκBα protein levels in the human astrocyte U373 and HeLa cell lines [8]. In a BALB/C mouse model, eucalyptol reduced the number of inflammatory cells, expression of matrix metalloproteinase-9 (MMP-9), and production of cytokines including TNF-α and IL-6 as well as nitric oxide and NF-κB [17]. Moreover, early growth response factor-1 (Egr-1) mediates LPS-induced tissue factor and TNF-α gene expression in human monocytic cells [9]. Eucalyptol inhibited LPS-stimulated expression of Egr-1 through the extracellular signal-regulated kinase (ERK) pathway in human monocyte THP-1 cells, without affecting NF-κB expression [35]. Eucalyptol injection improved cerulein-induced acute pancreatitis and significantly reduced the histological damage induced by cerulein, including pancreatic edema, as well as the expression of NF-κB, myeloperoxidase (MPOs), malondialdehyde (MDA), and proinflammatory cytokines, including TNF-α, IL-1β, and IL-6 [20]. Moreover, eucalyptol exerted an anti-inflammatory effect by regulating NF-κB and MAPK in LPS-induced inflammatory models.

In addition to the above effects, studies in rat neurons and glia found that eucalyptol reduced oxygen glucose deprivation/reoxygenation (OGD/R)-induced ischemic injury by decreasing oxidative stress [27]. In a cell model of Alzheimer's disease, pretreatment of PC12 cells with eucalyptol reduced mitochondrial

membrane potential and the levels of ROS, NO, COX-2, NF-κB, and the proinflammatory cytokines TNF-α, IL-β, and IL-6 induced by $A\beta_{25-35}$ [15].

4 Role of Eucalyptol in Chronic Diseases

Eucalyptol was shown to have effects in various inflammatory diseases including respiratory diseases, pancreatitis, and cardiovascular and neurodegenerative disease as well as reducing colon damage [11, 15, 20, 23, 29, 34]. In particular, it is reported that eucalyptol has been studied in animal and human model-related chronic disease (Table 1). Eucalyptol is used in inflammatory airway diseases as a mucolytic agent. Eucalyptol treatment significantly reduced dyspnea and enhanced lung function and quality of life relative to placebo in patients with stable COPD [33]. Eucalyptol treatment also resulted in improvements in patients with asthma, a disease characterized by a chronic inflammatory process, by enhancing lung function and general health [32]. Moreover, eucalyptol has been used to treat chronic bronchitis, sinusitis, and rhinitis.

The protective effects of eucalyptol in neurodegenerative diseases may be due to its anti-inflammatory activities [15]. Eucalyptol also showed antihypertensive effects by increasing nitrite levels and reducing MDA activity [23]. Eucalyptol was also reported to reduce heart rate through a parasympathetic mechanism and to induce hypotension by vasorelaxation in cardiovascular diseases [19].

5 Biological Activities of Eucalyptol in Animal Models

The anti-inflammatory and antihypertensive effects of eucalyptol have been studied in several animal models. Eucalyptol inhalation suppressed the inflammatory process in airways of ovalbumin-challenged guinea pigs [2]. Eucalyptol also showed anti-inflammatory effects in bronchoalveolar fluid of mice with LPS-induced lung inflammation [17] and suppressed acute pulmonary inflammation by reducing the levels of TNF-α, IL-1β, NF-κB p65, and toll-like receptor 4 (TLR4) in mice [34]. Eucalyptol improved cerulein-induced acute pancreatitis through an anti-inflammatory mechanism and antioxidative activity in mice [20] and reduced colonic damage in rats with acute trinitrobenzene sulfonic acid (TNBS)-induced colitis [29].

Moreover, eucalyptol was found to lower blood pressure through the regulation of NO and lipid peroxidation in a rat model of hypertension induced by chronic exposure to nicotine [23]. Eucalyptol was also reported to relax bronchial and vascular smooth muscle by reducing isometric contractions in rat ventricular papillary muscle [31].

Table 1 Summary of the effects of eucalyptol in chronic diseases

Related chronic disease	Model/methods	Measurement parameter	Results	Reference
Asthma	32 patients with steroid-dependent bronchial asthma in a double-blind, placebo-controlled trial	Lung function using ATS guideline	Eucalyptol treatment maintained lung function four times longer despite administering lower dosages of prednisolone	[12]
	Administered as eucalyptol 200 mg t.i.d. or placebo capsules at 3, 6, 9, 12 weeks as outpatients	Mini-Wright peak-flow meter to measure PEFR (peak expiratory flow rate)	Reductions in daily prednisolone dosage of 36 % with active treatment versus a decrease of only 7 % in the placebo group were tolerated	
	Glucocorticosteroid dose reduced by 2.5 mg every 3 weeks	Scores for frequency of dyspnea	Eucalyptol treatment did not tolerate any reduction in glucocorticosteroid dosage showed steroid-saving effects in asthma	
COPD	242 patients with stable COPD in double-blind trial Eucalyptol 200 mg 3 times as concomitant therapy for 6 months	Frequency, duration, severity, and symptoms of exacerbations	The number ($p = 0.0016$), degree ($p = 0.0031$), and severity ($p = 0.0025$) of exacerbations by Wei-Lachin test procedure were statistically significant in eucalyptol. Eucalyptol decreased the frequency, severity, and duration of exacerbations in lung function	[33]
		Lung function, respiratory symptoms, and quality of life	Eucalyptol increased the forced vital capacity (FVC) by 62 ml (2.7 %) compared with placebo of a reduction of 25 ml (1.1 %)	
		Spirometric measurements: before the beginning of the study to determine the reversibility of the airflow limitation, determination of forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and vital capacity (VC) at commencement and after 3 and 6 months	The improvement of SGRQ total symptoms score was statistically significant in the eucalyptol group ($p = 0.0224$)	
		Symptom score for dyspnea, weekly frequency of dyspnea, general condition, and cough	The increase in FEV1, improvement of dyspnea, and total SGRQ score were statistically significant by the Wei-Lachin test procedure for multiple criteria ($p = 0.0024$)	

(continued)

Table 1 (continued)

Related chronic disease	Model/methods	Measurement parameter	Results	Reference
Airway inflammatory disease	Male guinea pigs that were sensitized by means of three intraperitoneal injections of ovalbumin (OVA, 10 mg/kg) every other day	Inflammatory parameters such as mucociliary clearance, tracheal responsiveness to carbachol, cytokine levels (TNF-α, IL-1β, IL-10), and myeloperoxidase activity on bronchoalveolar lavage fluid (BALF)	Eucalyptol inhalation before OVA administration reduced tracheal contractions than inhaled eucalyptol before administration of saline	[2]
			Proinflammatory cytokine levels including TNF-α and IL-1β were decreased in BALF of eucalyptol group	
			Eucalyptol treatment reduced the increase in myeloperoxidase (MPO) activity	
			In OVA-challenged guinea pigs, the number of inflammatory cells was smaller in BALF of eucalyptol-treated guinea pigs than in BALF that did not treat eucalyptol	
			Pretreatment with eucalyptol completely abrogated the OVA-induced increase in TNF- α and IL-1 levels after antigen challenge	
	OVA-sensitized conscious guinea pigs inhaled a single dose of eucalyptol for 15 min		Eucalyptol inhibited the decrease of the mucociliary clearance in antigen-induced changes	
Asthma	247 asthmatic patients that receive the concomitant therapy with eucalyptol	Lung function, asthma symptoms, and quality of life: nocturnal asthma scores, diagnosis-related quality of life by Asthma Quality of Life Questionnaire (AQLQ), forced vital capacity (FVC) and vital capacity (VC), symptom scores for dyspnea frequency and intensity during rest and after exercise, coughing and propensity to cough, scores for quantity of secretion	Lung function, symptoms of asthma, cough, hypersecretion, and Asthma Quality of Life Questionnaire (AQLQ) were improved by concomitant therapy with eucalyptol	[32]
			After 6 months of eucalyptol treatment, Wei-Lachin test procedures including forced expiratory volume in 1 s (FEV1), asthma symptoms, and AQLQ were significant as $p = 0.0398$, $p = 0.0325$, and 0.0475, respectively	

(continued)

Table 1 (continued)

Related chronic disease	Model/methods	Measurement parameter	Results	Reference
			In lung function, the difference between the mean increase of FVC and the increase of peak-flow rate was significant in the eucalyptol compared to the placebo group ($p = 0.0226$, $p = 0.0197$)	
			The perceived difference was significant for dyspnea at rest ($p = 0.0198$) and dyspnea during exercise ($p = 0.0446$)	
			At 6 months, the mean improvement of quality of life according to AQLQ was significant ($p = 0.0475$)	
	Administered as eucalyptol 200 mg 3 times for 6 months in a double-blind, placebo-controlled trial		The differences of hypersecretion ($p = 0.0015$) and coughing ($p = 0.0007$) at multiple endpoints were significantly in the eucalyptol group	
Cardiovascular disease	The hypertension model using male Sprague–Dawley rats induced chronically by 0.8 mg/kg nicotine for 21 days, followed by 3 mg/kg nicotine the next day	Systolic blood pressure, plasma nitrite concentration, and plasma corticosterone concentration were measured by a tail-cuff transducer, nitrite assay, and enzyme immunoassay, respectively	Eucalyptol decreased the nicotine-induced increase in systolic blood pressure ($p = 0.011$)	[23]
			Eucalyptol (0.1 mg/kg) effectively inhibited the increase in SBP induced by nicotine	
	Eucalyptol was injected intraperitoneally at 0.01, 0.1, and 1 mg/kg		Eucalyptol reduced the concentration of plasma nitrite ($p = 0.03$) and plasma corticosterone ($p = 0.05$) that was increased in nicotinic rat model	

6 Biological Activities of Eucalyptol in Humans

Eucalyptol has been reported to have anti-inflammatory and analgesic effects in clinical studies. Eucalyptol treatment of patients with asthma significantly increased lung function and overall health condition and reduced dyspnea [32]. Systemic therapy with eucalyptol for 12 weeks had anti-inflammatory effects in patients with steroid-dependent bronchial asthma [12]. Moreover, eucalyptol decreased the discomforts of non-purulent rhinosinusitis in acute rhinosinusitis patients [14], and showed anti-inflammatory effects in various chronic respiratory diseases in a clinical study.

Eucalyptol has been found to have analgesic and antianxiety effects in humans. Inhalation of eucalyptus oil, which is mainly composed of eucalyptol, effectively reduced pain and blood pressure in patients who underwent total knee replacement [13]. A randomized clinical trial found that inhalation of eucalyptol significantly reduced anxiety in patients before selective nerve root block (SNRB) [18].

7 Conclusions

Eucalyptol exerts anti-inflammatory and antioxidative effects by regulating the NF-κB and MAPK signaling pathways in several diseases, including chronic diseases. These beneficial effects of eucalyptol have been observed in clinical studies and in several animal models. Eucalyptol, which has lipophilic properties and exerts various actions on receptors and enzymes, may be a potentially important drug in the treatment of chronic diseases.

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