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Beneficial Effects of Eucalyptol in the Pathophysiological Changes of the Respiratory System: A Proposal for Alternative Pharmacological Therapy for Individuals with COPD

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Authors' contributions

This work was carried out in collaboration between all authors. Authors FLG, GRS and IFMGN wrote the first draft of the manuscript and managed the literature searches. Author DSS reviewed and edited the manuscript. Author FSAC supervised the study. All authors read and approved the final manuscript.

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ABSTRACT

It is estimated that there will be an increase in the incidence of chronic obstructive pulmonary disease (COPD) in the coming decades. Thus, the pharmacological attributes of products of plant origin should be considered as an important economic and scientific strategy in the investigation of therapeutic alternatives, since their experimental validations are indispensable to substantiate the reliability of these products in the treatment of chronic diseases. Like biologically active compounds,

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Eucalyptol, also known as 1,8- cineole, is the major constituent of the leaf oil of eucalyptus species, such as *Eucalyptus globulus* and *Eucalyptus tereticornis*. It is a terpenoid oxide, free of steroid-like side effects. This study is based on a review of the specialised literature with purpose to discuss the biological effects of Eucalyptol in the respiratory system and its interaction with some of the most promising targets in the treatment of COPD, such as: receivers and membrane channels, oxidative stress, transcription and expression of cytokines, cell adhesion molecules and neutrophil chemotaxis, proteases and remodeling.

Keywords: Anti-inflammatory; biological activity; COPD; eucalyptol; herbal medicine; respiratory system; 1,8- cineole.

1. INTRODUCTION

Individuals with chronic physiologic dysfunctions such as cancer, diabetes, cardiovascular disease, asthma and chronic obstructive pulmonary disease (COPD) are often affected by a number of factors including irregular physical activity, poor eating habits, smoking, and environmental pollutants [1].

Although it is preventable and treatable, COPD is still the fourth leading cause of death in the world, and it is estimated that there will be an increase in its incidence in the coming decades due to population ageing and continuous exposure to its risk factors [2]. In parallel, the study of the pharmacological attributes of plant origin products used for medicinal purposes should be recognised as an important economic and scientific strategy in the investigation of therapeutic alternatives, since their experimental validations are indispensable to base the reliability of these products. With this motivation, components derived from plant species have been widely used in a wide variety of diseases, including chronic diseases [3].

Like biologically active compounds, Eucalyptol, also known as 1,8- cineole, is a major constituent of the leaf oil of eucalyptus species, such as *Eucalyptus globulus* Labill and *Eucalyptus tereticornis* SM. It is classified as a terpenoid oxide, compound responsible for fragrance and pleasant taste, endowed with an immense variety of structures and biological activities, free of steroid-like side effects. Thus, systemic therapy with Eucalyptol seems to be favourable in relation to its lipophilicity related to the terpene group, and its excretion predominant by exhalation [4-6].

Such characteristics of this compound attribute approval of Eucalyptol by the US Food and Drug Administration (USFDA) for consumption as a food additive and license as a medicinal product (SoledumTM capsules, Cassella-med, Cologne, Germany) in Germany [7]. In view of the above, this review aims to describe the cell signalling pathways and biological activities of Eucalyptol in the respiratory system, to provide scientific support on its efficacy as an alternative therapy for the treatment of COPD.

This study is based on the reviews of the specialised literatures, in which references were collected from books and scientific articles selected from electronic databases such as Scielo, Medline, Pubmed and ScienceDirect. The inclusion criteria for the studies found were the therapeutic approaches in COPD, the biological activity of Eucalyptol on the respiratory system, as well as the cellular signalling pathways of this constituent. We excluded studies that reported aspects with an emphasis in another discussion that the focus was not related to the respiratory system or pharmacological properties of Eucalyptol.

2. GLOBAL INITIATIVE PROJECT ON COPD

It is estimated that there will be an increase in the incidence of COPD in the coming decades. Since 2001, the global strategy for the diagnosis, management, and prevention of COPD has been a valuable resource for professional health promoters. Thus, the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) project strives to improve prevention and care in COPD worldwide. Its specific topics address diagnosis, management of exacerbations in Asthma and COPD, and means of treating the disease when in its stable stage [2].

Despite current and future needs, the scientific committee of the GOLD project, in its catalogue of scientific papers suggested for reading and deepening, explains the need for discussion, elucidation and new research on the pathophysiological factors involved in COPD, such as: immune system, membrane specific

receptors, gene transcription factors, cytokines, chemokines, proteases, antiproteases [8-14] and aggravating and/or causative agents of the disease, which cause dysfunction in the airways and pulmonary parenchyma, such as exposure to cigarette smoke and environmental pollutants [15-18].

A greater understanding of the inflammatory mechanisms involved in COPD, achieved in the last decades, has resulted in the identification of several processes and goals for the development of new anti-inflammatory treatments [19]. The following topics bring a sequential approach to the action of pathophysiological mediators parallel to the regulation of these exerted by Eucalyptol.

3. PHARMACOLOGICAL STUDIES

3.1 Receivers and Membrane Channels

Hypersecretion of mucus, one of the causes of airflow limitation in COPD, is due to the increase in the number of goblet cells and submucosal glands, both due to chronic irritation in the airways by noxious agents. In this situation, many mediators stimulate mucus hypersecretion exerting their effects through the activation of the epidermal growth factor receptor (EGFR), whose ligands, such as transforming growth factor alpha (TGF-α), are produced by neutrophils and macrophages [20-23].

Analyses were performed on bronchial biopsy specimens obtained from asthmatic individuals and patients with COPD. Results showed a positive correlation between EGFR and mucin MUC5AC expression [24,25], as EGFR acts as a transcription factor that plays a regulatory role in the expression of many genes important for inflammation [26,27]. Zhou and collaborators [28] performed a study to elucidate the anti-inflammatory mechanisms in monocytes obtained from asthmatic subjects incubated with Eucalyptol thirty minutes before being stimulated with lipopolysaccharides (LPS). In this work, it was observed that Eucalyptol in a concentration-dependent manner (1, 10, and 100 mg/L, 30 min) was able to inhibit EGFR synthesis, providing an evidence of the role of 1,8- cineole in the control of inflammation and limitation to airway flow.

In a study conducted by Nascimento and collaborators [29], 1,8- cineole reduced the tracheobronchial resistance *in vivo* after bronchospasm was induced by the challenge to carbachol. A similar effect was seen when compared to the response obtained with fenoterol, a drug used in asthmatic crises and exacerbation of COPD. In addition, it also directly relaxed in vitro the airway smooth muscle previously contracted with the induction of carbachol, a high concentration of potassium and histamine. Inhibition of phasic contractions suggests that Eucalyptol has an antagonistic action on the transmembrane influx of calcium or its intracellular action as a second messenger.

Bastos and collaborators [30], in a model of airway hyper reactivity with subsequent treatment with a single dose of Eucalyptol (1 mg/mL) administered by inhalation, significantly developed lower tracheal ring contractions when compared to the untreated group. Specifically, we observed Eucalyptol's preferential action on voltage-operated calcium channels (VOCCs).

In accordance with such myorelaxant properties, Soares and collaborators [31] have shown that 1,8- cineol could induce a negative inotropic effect on rat heart tissues, while it blocked the influx of Ca^{2+} through the VOCCs located in the sarcolemma of cardiac myocytes. Therefore, the relaxation induced by Eucalyptol in the muscle tissue of the trachea and bronchus in the murine model may be related to its negative interference in the influx of calcium through the cell membrane.

Although it is still a question of transmembrane proteins, it is important to note that a signalling pathway associated with Toll-like 4 standard recognition receptors (TLR4), such as the activation of p38 mitogen-activated protein kinase (MAPK p38), play a critical role in inflammation allergic reaction [32]. Continuous inhalation of irritants, such as cigarette smoke, fossil fuel gases and environmental particles, activate TLR4 [33,34]. This mechanism leads to the propagation of an innate immune response, with activation of airway epithelial cells and secretion of mucus [35].

Zhao and collaborators [36], investigated the expression of these receptors in mice with LPS-induced lung inflammation after treatment with Eucalyptol. In this study, a single oral dose of Eucalyptol (100 mg/kg) was found to decrease TLR4 expression when compared to the non-constituent group and the positive control group treated with prednisone, a substance used in anti-inflammatory drugs. Later, , the effects of Eucalyptol in a model of solution-induced asthma

composed of dust mites at home were investigated by Lee and collaborators [37], where TLR4 suppression and mitogen-activated protein kinase p38 (MAPK p38) in mice was treated with Eucalyptol (10 mg/mL), via nebulization, before each exposure to the aggressive agent.

3.2 Oxidative Stress

The redox imbalance is also an important mechanism of conduction in the pathophysiology of chronic diseases and a crucial target for therapies in COPD [38], because reactive oxygen species (ROS) activate nuclear factor kappa B (NF-κB) and MAPK p38, thus leading to a further intensification of inflammatory genes and inhibition of the activity of endogenous antiproteases. This suggests that antioxidants may be very useful in the treatment of COPD by reducing the inflammatory process, as well as repairing and reversing resistance to corticosteroids [19].

The production of reactive oxygen species (ROS) caused by smoking is linked to the protease/antiprotease imbalance that contributes to the development of COPD [39,40]. Kennedy-Feitosa and collaborators [41], analysed the efficacy of Eucalyptol against acute lung inflammation caused by cigarette smoke (CF), in which mice were exposed to CF and treated with Eucalyptol (10 mg/mL) via inhalation 15 minutes a day, for 5 days. In this protocol, it was observed that the group treated with Eucalyptol, when compared to the group exposed to smoke and untreated, was able to reduce ROS levels, confirmed by the reduction of the enzymatic activities of catalase (CAT) and superoxide dismutase (SOD). In parallel, the compound reduced oxidative damage through lipid peroxidation, evidenced by reduced levels of malondialdehyde (MDA).

3.3 Transcription and Expression of Cytokines

Both MAPK p38 and oxidative stress induce the activation of NF-κB by promoting the transcription of pro-inflammatory cytokines [42-45], resulting in its translocation to the nucleus, adhesion to DNA and effectuation of genetic transcription. The pathway of activation of this factor is associated with the transcription of genes involved in the inflammatory process, such as cytokines, chemokines and adhesion molecules [46].

In a model of acute lung injury (IPA) induced by LPS, BALB / C, mice were subjected to single dose pre-treatment via intraperitoneal injection with 400 mg/kg Eucalyptol, where it caused a reduction in NF-κB expression and, consequently, cytokines and proteinases [47]. Similar results in NF-kB suppression, compared to Eucalyptol treatment, were also observed in the IPA model caused by cigarette smoke [41] and pneumonia model caused by influenza virus infection (IFV), where BALB / C mice received oral treatment at 120 mg/kg, two days prior to the viral exposure [48]. In addition, Greiner and collaborators [49], suggested a novel mode of NF-kB blockade through inhibition of nuclear translocation by the nuclear factor kappa B alpha inhibitor (IκBα) and increased levels in response to treatment with Eucalyptol after stimulation with LPS.

As mentioned above, epithelial cell and macrophage-activated NF-kB regulate the secretion of many cytokines and chemokines in both asthma and COPD, and these inflammatory mediators play a potential role in the initiation and perpetuation of airway mucus hypersecretion in consequence to inflammatory stimuli [45,50,51].

Under these conditions, cytokines are secreted by the resident tissue cells, and also culminate in the recruitment of leukocytes. Specifically, tumor necrosis factor alpha (TNF-α), interleukin 1b (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8) and interleukin-17 (IL-17) are documented for their important roles in this process and are present in high concentrations in bronchial, lung and sputum biopsy samples of patients with COPD [52-55]. Eucalyptol has been shown to be able to reduce the number of macrophages, as well as the expression of TNF-α, IL-1β, IL-6 and IL-17, is responsible for the initiation and propagation of inflammation [4,30,36,41,47,48,56].

Another property pertinent to the interaction with these mediators, related to the biological activities of Eucalyptol, relates to an increased expression of interleukin 10 (IL-10) [30,36,48] and cytokine that play an anti-inflammatory role in the innate and adaptive response of the immune system, with significantly lower expression in sputum samples from patients with asthma and COPD [57].

3.4 Cell Adhesion Molecules and Neutrophil Chemotaxis

Some of these cytokines, such as TNF-α factor, IL-1β, stimulate endothelial cells to express intercellular adhesion molecule (ICAM) -1 and

vascular cell adhesion molecule (VCAM) -1 in bronchial vessels and alveoli, culminating in leukocyte migration to the site of infection [58,59]. In parallel, leukotrienes, a class of eicosanoids present at high levels in asthma and COPD [60], are also capable of inducing the adhesion and activation of leukocytes in the endothelium [61,62]. In contrast to the stimulation of monocytes from asthmatic individuals, Juergens and collaborators [63], observed significant inhibition of cytokines, tramboxane B2 and leukotriene B4 (LTB4) after three days of Eucalyptol therapy with daily doses of 600 mg (3 x 200 mg /day).

Li and collaborators [48], analysed the expression of cell adhesion molecules on the cell surface of mice in response to Influenza virus infection, where positive regulation of ICAM-1 and VCAM-1 was observed, and a significant reduction in the expression of these molecules in the group receiving oral Eucalyptol (120 mg/kg) before and after inoculation of the virus. The results observed in the Eucalyptol treated group, such as suppression of proinflammatory cytokines, transcription factors and adhesion molecules were similar to the positive control group treated with Oseltamivir, the antiviral substance commonly used against influenza virus.

Chemokines, such as IL-8, exert their function by coupling to the G protein of the receptor expressed in inflammatory cells, regulating their transit towards the pulmonary interstitium [64]. The level of IL-8 is related to the absolute number of neutrophils in induced sputum in individuals with COPD, in addition to being increased in patients with α1- antiprotease deficiency [44,65,66].

Both *in vitro* [4] and *in vivo* [37] experiments demonstrated the efficacy of Eucalyptol in the inhibition of IL-8, as well as the reduction in the number of leukocytes in bronchoalveolar lavage of mice induced to acute pulmonary inflammation [41].

3.5 Proteases and Remodeling

It is known that neutrophils are implicated in the release of inflammatory cytokines, lipid mediators and enzymes capable of promoting tissue injury [67]. Thus, constant inflammatory stimuli and a growing influx of these leukocytes into the pulmonary parenchyma cause a large release of proteases by these cells, such as matrix metalloproteinases (MMPs). Type 9 matrix metalloprotease (MMP-9) is thought to be the most promising target for drug development due to its predominance in the degrading potential of collagen fibres and elastin, causing pulmonary emphysema and stimulation of mucus hypersecretion, causing chronic bronchitis [19,68-71].

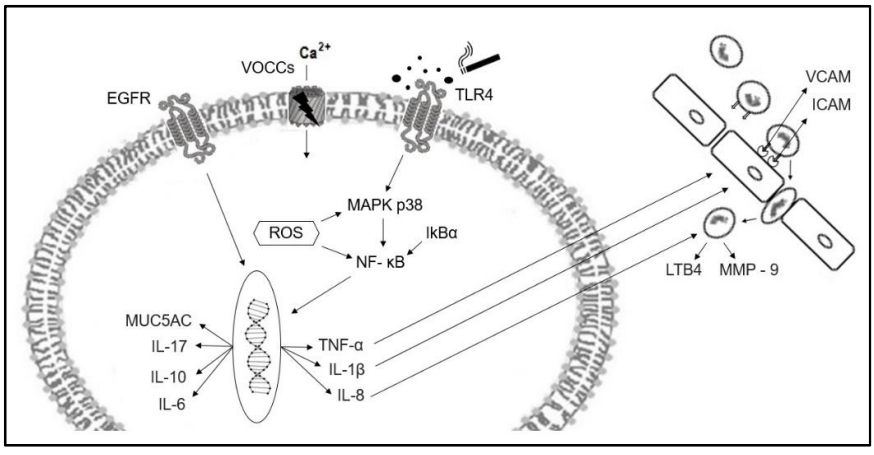

Fig. 1. Schematic diagram, developed from the information collected in the present study, with representation of biological components, which have functionality altered by inhaled irritants (cigarette smoke, air pollutants, indoor dust), capable of interacting with Eucalyptol, such as membrane proteins (EGFR, VOCCs and TLR4), proteins involved in the production of mucus (MUC5AC), elements (TNF-α, IL-1β, IL-6, IL-8, IL-10, IL-17), transcriptional protein activators (MAP38 p38 and ROS), transcriptional proteins (NF-kB), leukins (TNF-α, IL-1β, IL-6, IL-8, IL-10, IL-17), cell adhesion molecules (VCAM, ICAM), LTB4 and MMP-9

In a study conducted by Kim, Lee and Seol [47] it was observed that pre-treatment with Eucalyptol (400 mg/kg), injected intraperitoneally, significantly attenuated the expression of MMP-9 and prevented the histopathological changes caused by said proteolytic enzyme. These results were also similar to the positive control of the study, where dexamethasone was used because it is a drug that has potential anti-inflammatory effects.

Despite having properties that preserve the histoarchitecture of lung tissue, there is a lack in the literature of studies investigating the effects of Eucalyptol in the functional mechanics of the respiratory system. However, Worth et al. [72] conducted a randomised, placebo-controlled study of Eucalyptol (600 mg/kg/day, orally) over 6 months for patients with stable COPD using concomitant pharmacological therapy (β-agonists, anticholinergics and theophylline). In the spirometric protocols, improvement of forced expiratory volume in 1 second (FEV1), vital capacity (CV) and reduction of exacerbations of Eucalyptol-treated group disease in relation to placebo was observed in the spirometric protocols.

The literature review discussed in the present study shows that the biological activities of Eucalyptol when administered orally (100 to 600 mg/kg), intraperitoneal (400 mg/kg), or by inhalation (1 to 10 mg/mL), involve various stages and crucial molecules in the development of the acute and chronic inflammatory process in the respiratory system, as exemplified in Fig.1

4. CONCLUSION

The interaction of Eucalyptol in animal experimental models with pathophysiological mediators (oxidative stress, transcription molecules of cytokines, pro-inflammatory cells and proteases) identified in human respiratory system affections show a relevant alternative treatment option concomitant with the anti-inflammatory drugs in asthma and COPD.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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