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File: ■ Eucalyptus (*Eucalyptus globulus*, Myrtaceae)
■ Cough
■ Systematic Review/Meta-analysis

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RE: A Systematic Review on the Efficacy and Safety of Eucalyptus for Relieving Cough

Her L, Kanjanasilp J, Chaiyakunapruk N, Sawangjit R. Efficacy and safety of *Eucalyptus* for relieving cough: A systematic review and meta-analysis of randomized controlled trials. *J Integr Complement Med*. March 2022;28(3):218-226. doi: 10.1089/jicm.2021.0226.

The most common causes of acute cough are bronchitis and upper respiratory tract infections (URTIs), whereas chronic cough can occur due to chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma. Currently, several synthetic and alternative therapeutic options are available for relieving cough, but they often offer limited effectiveness and can have adverse effects (AEs). *Eucalyptus globulus*, Myrtaceae) oil has widely been used for its antitussive effects, among other benefits in treating cough and URTIs. However, the evidence to support its efficacy for relieving coughs in humans is lacking. As such, this systematic review and meta-analysis of randomized controlled trials (RCTs) aimed to evaluate the efficacy and safety of eucalyptus on cough.

PubMed, Scopus, Cochrane Library, Embase, EBSCO, Science Direct, ProQuest, and Thai Library Integrated System databases were searched from inception to February 2021, using relevant keywords and phrases. RCTs that evaluated the clinical effects of any eucalyptus formulation on cough in patients having upper or lower respiratory tract infection, bronchitis, or disease related to respiratory tract infection such as acute exacerbation of COPD were eligible for inclusion. Studies that assessed the effects of eucalyptus on cough caused by chronic disease including lung cancer, tuberculosis, severe pneumonia, known immune deficiency, post extubating, and pulmonary fibrosis were excluded. The primary outcome was clinical efficacy defined as the proportion of patients who achieved improvement or resolution of overall cough symptoms as assessed using a verbal rating scale (VRS). Secondary outcomes were frequency and severity of cough, quality of cough, and AEs. With sufficient data, subgroup analyses were performed for types of comparators, age, dosage, and duration of follow-up. The Cochrane risk of bias tool was used to assess the quality of included studies.

A total of 340 studies were identified using the authors' search strategy. After the removal of duplicates (n = 139), irrelevant articles (n = 176), and studies based on exclusion criteria (n = 19), six studies were included in the qualitative and quantitative synthesis. The six studies included 1,866 patients (870 males and 996 females) with an average age of 44.85 years. Most of the studies were conducted in Germany (n = 5), with one conducted in Israel. All

studies were multicenter double-blind randomized controlled trials. The major cause of cough was bronchitis, followed by URTI, and acute exacerbation of COPD. Four studies used eucalyptus in combination formulas, whereas two studies used eucalyptus extract (200 mg three times daily). Among the studies that used a combination formula, three studies used eucalyptus oil mixed with essential oils from lime (*Citrus aurantifolia*, Rutaceae) and pine (*Pinus* spp.) at a dose of 300 mg 3–4 times daily. The remaining studies used eucalyptus oil mixed with aromatic oil spray at a dose of 12 mcg 4–5 times daily. All studies used placebo as a control group. The treatment durations of most studies were < 30 days. Therefore, these data were insufficient to determine longer-term treatment effects (> 30 days). Three of the studies were judged as low risk of bias, whereas the others were judged as high risk of bias, primarily due to missing outcome data and selection bias.

Pooled data from four studies comprised of 1,395 patients revealed that eucalyptus products that were combination products had a statistically significant effect on achieving improvement or resolution of overall cough symptoms compared with placebo (relative risk [RR]: 1.45, 95% confidence interval [CI]: 1.26 to 1.67, $P < 0.001$), with no evidence of heterogeneity. However, this effect was statistically nonsignificant when compared with biologically active controls, such as cefuroxime and ambroxol. Pooled analysis from two studies of eucalyptus alone with high evidence of bias comprising 655 patients reported a statistically significant reduction of cough frequency compared with placebo (weighted mean difference [WMD]: 0.44, 95% CI: 0.28 to 0.60, $P < 0.001$), with mild heterogeneity. Safety data were reported in five studies comprising 1,797 patients. For overall clinical therapeutic efficacy, there was no evidence of small study effect based on the results from the funnel plot and Begg's and Egger's tests. The main effect of eucalyptus on improvement or resolution of overall cough symptoms was unchanged based on the subgroup analysis. The number of AEs reported was comparable between eucalyptus and control groups. The most common AEs reported in the eucalyptus group were mild-to-moderate gastrointestinal symptoms, including heartburn, stomach aches, diarrhea, and nausea.

Based on their findings, the authors conclude eucalyptus (used either alone or in combination with other treatments) may have beneficial effects for relieving cough induced by URTI and related diseases with AEs comparable with other standard interventions. However, the clinical efficacy is minimal, and its relevance in clinical treatment remains uncertain. The mechanisms behind eucalyptus oil on cough remain unknown, but are likely related to its phytochemicals with mucolytic, bronchodilating, antibacterial, antiviral, and anti-inflammatory activities. The authors cite limitations related to the high risk of bias of half of the included studies and the lack of long-term evaluation of efficacy. Most of the studies were also performed in Germany, limiting the generalizability to include other populations. It is also unknown whether the patients in the included studies were receiving co-treatments, be it pharmacotherapy, dietary, or respiratory therapy. In either case, the authors call for further multicenter well-designed RCTs to investigate mechanistic and the long-term effects of eucalyptus products on cough. The authors report no conflicts of interest.

—Gavin Van De Walle, MS, RDN

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