



EDITORIAL

Caffeic Acid Phenethyl Ester Possessing Various Immunomodulatory Effects Is a Potentially Effective Therapy for Asthma

Asthma is one of the most common chronic disorders in childhood, which imposes a growing burden on society in terms of morbidity, quality of life, and health care costs. In addition to current medications, such as bronchodilator, inhalation of corticosteroid, leukotriene modifier, and anti-immunoglobulin E (IgE) antibody, some traditional medicines have also shown the therapeutic effect on asthma. Propolis, a natural resinous product collected by honeybees, has exhibited various biological activities. In an ovalbumin-sensitized airway inflammatory animal model, propolis extracts could suppress the serum levels of ovalbumin-specific IgE and immunoglobulin G1 (IgG1) and airway hyperresponsiveness.¹ Moreover, propolis was used as an adjuvant to treat patients with mild to moderate asthma in a clinical trial. The results showed that the number of nocturnal asthma attacks significantly decreased and the lung function improved in patients receiving propolis.²

Although propolis appears to be effective in asthma treatment, the clinical application of it is not currently suggested. The major concern is the highly variable composition of propolis that limits the standardization and raises the safety issues. Propolis contains resin and vegetable balsam, wax, essential and aromatic oils, pollen, minerals, and a mixture of biologically active chemicals, including terpenes, cinnamic acid, caffeic acid and their esters, amino acids, and flavonoids. Of them, caffeic acid phenethyl ester (CAPE) is extensively studied and found to have antitumor, antioxidant, anti-inflammatory, and other immunomodulatory properties.^{3,4} CAPE has been shown to inhibit mitogen-induced human T-cell proliferation and the production of cytokines, such as interferon- γ and interleukin (IL)-5. It can also induce active caspase-3 expression in CD4⁺ T cells, especially Type 2 T helper cells.³ In this issue of the journal, Sy et al⁵ found that CAPE could further enhance transforming growth factor- β production by

peripheral blood mononuclear cells from asthmatic children. Of note, transforming growth factor- β is a powerful anti-inflammatory cytokine that can efficiently block the Type 2 T helper cell-related inflammation.

During the process of allergic inflammation, allergens are captured, processed, and presented to T cells by antigen presenting cells. Dendritic cells are professional antigen presenting cells, and the effect of CAPE on functions of human monocyte-derived dendritic cells (MoDCs) has been well studied. The results showed that CAPE significantly inhibited IL-12, IL-10, and immune protein-10 production by MoDCs derived from healthy controls, whereas it inhibited IL-10 and immune protein-10 but not IL-12 expression in allergic patients' MoDCs stimulated by crude mite extract. CAPE was also found to interfere with inhibitor of kappa B- α (I κ B α) phosphorylation and nuclear factor- κ B activation in human MoDCs, indicated by blocking the NF- κ B signaling pathway; CAPE has the ability to inhibit cytokine and chemokine production by MoDCs.⁴ In addition to immune cells, CAPE could affect other cells. Through signal transducer and activator of transcription 6 inhibition, Lin et al⁶ recently revealed that CAPE suppressed the production of eotaxin in cytokine-stimulated human lung fibroblasts in a dose-dependent manner that may subsequently decrease the influx of eosinophils.

Taken together, CAPE with certain immunomodulatory functions may provide another therapeutic option for asthma. In the future, it is needed to conduct more animal studies and human clinical trials to investigate the safety and clinical effectiveness of CAPE in the treatment of asthma.

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References

1. Sy LB, Wu YL, Chiang BL, Wang YH, Wu WM. Propolis extracts exhibit an immunoregulatory activity in an OVA-sensitized airway inflammatory animal model. *Int Immunopharmacol* 2006;**6**:1053–60.
2. Khayyal MT, el-Ghazaly MA, el-Khatib AS, et al. A clinical pharmacological study of the potential beneficial effects of a propolis food product as an adjuvant in asthmatic patients. *Fundam Clin Pharmacol* 2003;**17**:93–102.
3. Wang LC, Chu KH, Liang YC, Lin YL, Chiang BL. Caffeic acid phenethyl ester inhibits nuclear factor-kappaB and protein kinase B signalling pathways and induces caspase-3 expression in primary human CD4⁺ T cells. *Clin Exp Immunol* 2010;**160**: 223–32.
4. Wang LC, Lin YL, Liang YC, et al. The effect of caffeic acid phenethyl ester on the functions of human monocyte-derived dendritic cells. *BMC Immunol* 2009;**10**:39.
5. Sy LB, Yang LK, Chiu CJ, Wu WM. The immunoregulatory effects of caffeic acid phenethyl ester on the cytokine secretion of peripheral blood mononuclear cells from asthmatic children. *Pediatr Neonatol* 2011;**52**:327–31.
6. Lin YT, Hsu JY, Chen CJ, Chu JJ, Fu LS. Caffeic acid phenethyl ester suppresses eotaxin secretion and nuclear p-STAT6 in human lung fibroblast cells. *J Microbiol Immunol Infect* 2011 [Epub ahead of print].