Therapeutic potential of caffeic acid phenethyl ester and its anti-inflammatory and immunomodulatory effects (Review)

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Abstract. Caffeic acid phenethyl ester (CAPE), a naturally occurring compound isolated from propolis extract, has been reported to have a number of biological and pharmacological properties, exerting antioxidant, anti-inflammatory, anticarcinogenic, antibacterial and immunomodulatory effects. Recent *in vivo* and *in vitro* study findings have provided novel insights into the molecular mechanisms involved in the anti-inflammatory and immunomodulatory activities of this natural compound. CAPE has been reported to have anti-inflammatory properties involving the inhibition of certain enzyme activities, such as xanthine oxidase, cyclooxygenase and nuclear factor-κB (NF-κB) activation. Since inflammation and immune mechanisms play a crucial role in the onset of several inflammatory diseases, the inhibition of NF-κB represents a rationale for the development of novel and safe anti-inflammatory agents. The primary goal of the present review is to highlight the anti-inflammatory and immunomodulatory activities of CAPE, and critically evaluate its potential therapeutic effects.

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Abbreviations: CAPE, caffeic acid phenethyl ester; CD68, cluster of differentiation 68; COX-2, cyclooxygenase-2; EAE, experimental autoimmune encephalomyelitis; IFN-γ, interferon-γ; IκB-α, κB inhibitor-α; IKK, IκB-kinase; IL-1, interleukin-1; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; MPO, myeloperoxidase; MoDC, monocyte-derived dendritic cell; MS, multiple sclerosis; NF-κB, nuclear factor κB; NO, nitric oxide; Nrf2, nuclear-factor-E2-related factor 2; PAF, platelet-activating factor; PLD1, phospholipase D1; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α; XO, xanthine oxidase

Key words: caffeic acid phenethyl ester, anti-inflammatory activity, immunomodulatory effect

Contents

1. Introduction

Caffeic acid phenethyl ester (CAPE) is an important active component of honeybee propolis extract and has been used in traditional medicine for a number of years. CAPE is a polyphenol that contains hydroxyl groups within a catechol ring, the molecular formula of CAPE is $C_{17}H_{16}O_4$ (1,2) (Fig. 1). It has been shown that this active component of propolis possesses anti-inflammatory, immunomodulatory, antineoplastic, antioxidant and wound-healing properties (1-4). Inflammation is induced by the release of chemical mediators from damaged tissue and migratory cells. Mediators identified in the inflammatory process include biogenic amines, metabolites of arachidonic acid (eicosanoids), platelet aggregation factors, cytokines [interleukins (ILs) and tumor necrosis factor-α (TNF-α)] and free oxygen radicals. These substances are produced by inflammatory cells, such as polymorphonuclear leukocytes (neutrophils, eosinophils and basophils), endothelial cells, mast cells, macrophages, monocytes and lymphocytes (5,6). CAPE inhibits cytokine and chemokine production, the proliferation of T cells and lymphokine production, and thus suppresses the inflammatory process. Specifically, CAPE is a potent and a specific inhibitor of nuclear factor-κB (NF-κB) activation, and this may provide the molecular basis for its multiple anti-inflammatory and immunomodulatory activities (2,7). The aim of this review is to highlight the anti-inflammatory and immunomodulatory activities of CAPE, focusing on the mechanisms of action (already identified) underlying this activity.

2. Overview to the inflammatory response

Inflammation is an immunological response to pathogens and damage that is initiated to protect the body, and contributes

to physiological and pathological processes, such as wound healing and infection at the compromised site. The process is accompanied by adhesion, migration and chemotaxis of leukocytes to the inflammatory environment (6). In response to tissue injury, a multifactorial network of chemical signals initiates and maintains a host response designed to 'heal' the afflicted tissue. The first effectors recruited in the acute inflammatory response are neutrophils. These are followed by monocytes, which undergo differentiation in the tissue into macrophages and migrate to the site of tissue injury under the guidance of chemotactic factors (5,8). The activated leukocytes provide proinflammatory cytokines, reactive oxygen species (ROS) and matrix metalloproteinases to remove the invading pathogen (9). The pathogens and damaged tissue are then phagocytosed, and the inflammatory process is eventually terminated when lipoxins start to overrule the proinflammatory signals (10). In general, IL-1 and TNF target the endothelium and initiate the inflammatory mediator cascade following exposure to certain stimuli, including infection, trauma, ischemia, immune-activated T cells or toxins. The inflammatory cascade can be summarized as follows: i) Activation of inflammatory cytokine-secreting cells, and increases in the levels of proinflammatory cytokines, such as IL-1, TNF-α and interferon-γ (IFN-γ); ii) activation/synthesis of phospholipase A2, cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS); increased endothelial adhesion molecules and synthesis of chemokines; iii) increased platelet-activating factor (PAF), leukotriene, prostanoid (prostaglandin E2) and NO levels, neutrophil endothelial adhesion, and the migration and activation of neutrophils; and iv) inflammation, tissue destruction and loss of function (10-12).

3. Proinflammatory cytokines and signaling pathways

Cytokines are polypeptide regulators of host responses to infection, immune responses, inflammation and trauma. Cytokine secretion by immune cells has a pivotal role in directing the course of an inflammatory response. Cellular cytokine production is regulated at transcriptional and translational levels and via cell signaling (11). Certain cytokines act to enhance the effects of the disease (proinflammatory), whereas others are involved in reducing inflammation and promoting healing (anti-inflammatory). Methods to block potentially harmful cytokines, particularly during an overwhelming infection, have been an area of particular interest. Administration of the proinflammatory cytokines IL-1 and TNF-α to humans can lead to fever, inflammation, tissue destruction and, in certain cases, shock and mortality (9,12). TNF-α is a 'master regulator' among cytokines and is responsible for mediating the inflammatory responses and innate immunity. The major pathways activated by TNF-α include caspases, NF-κB and mitogen-activated protein kinases (MAPKs). Crosstalk between these signaling pathways plays a role in determining the physiological outcome of the responses to TNF-α (13). The network response is further complicated by the phases associated with TNF-α signaling: In the early phase, TNF-α signaling induces the expression of inflammatory cytokines; this then initiates a secondary cytokine-mediated cellular response that contributes to the biological activity of TNF-α (14).

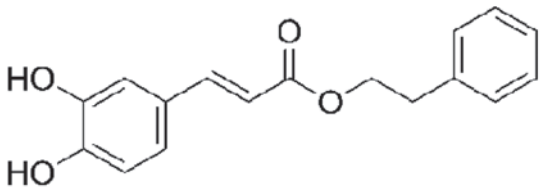

Figure 1. Chemical structure of caffeic acid phenethyl ester.

The transcription factor NF-κB plays a central role in regulating inflammatory, immune and anti-apoptotic responses. It is composed of homodimers and heterodimers of the Rel family of proteins, including p65/RelA, RelB, c-Rel, p50/p105 and p52/p100 (15,16). The activation of inactive NF-κB proteins existing in the cytoplasm is induced by numerous factors, including inflammatory cytokines (IL-1 and TNF-α), bacterial products and protein synthesis inhibitors (17); therefore, agents that can downregulate the activation of NF-κB have potential for therapeutic interventions, whereas the activation of NF-κB promotes inflammation in animals. The binding of TNF-α to cell surface receptors engages multiple signal transduction pathways, including three groups of MAPKs: Extracellular-signal-regulated kinases, c-Jun N-terminal kinases and p38 MAPKs. These MAPK signaling pathways induce a secondary response by increasing the expression of several inflammatory cytokines that contribute to the biological activity of TNF-α. MAPKs, therefore, function both upstream and downstream of signaling by TNF-α receptors (13,18). In almost all cell types, the exposure of the cells to TNF-α induces the activation of NF-κB and leads to the expression of a range of genes associated with inflammation. NF-κB is a protein complex that controls the transcription of DNA and is a central regulator of cellular stress in all cell types in humans. NF-κB plays a key role in regulating the immune response to infection and in acute and chronic inflammation. The activation of NF-κB in rats can induce the expression of IL-1β, which increases the expression of proinflammatory molecules (17,19).

4. Anti-inflammatory effects of CAPE

The transcription factor NF-κB has a pivotal role in a variety of physiological processes throughout the body, including immune responses, cell proliferation and inflammation. NF-κB elicits its effects by promoting the transcription of a range of cytokines, enzymes, chemokines and antiapoptotic and cell growth factors (20). Several *in vitro* and *in vivo* studies have described diverse biological activities of CAPE (at micromolar concentrations), such as a specific inhibition of NF-κB and a suppression of the lipoxygenase pathway of arachidonic acid metabolism during inflammation (2-4). It has also been shown that CAPE acts to suppress the NF-κB activation induced by ROS-generating agents in human histiocytic and coronary artery endothelial cells (2). It is believed that, rather than preventing the degradation of κB inhibitor-α (IκB-α), CAPE suppresses NF-κB activation by inhibiting the interaction between NF-κB proteins and DNA (21) (Fig. 2). Ilhan *et al* (22) suggested that the anti-inflammatory effect of CAPE is most likely due to the inhibition of ROS

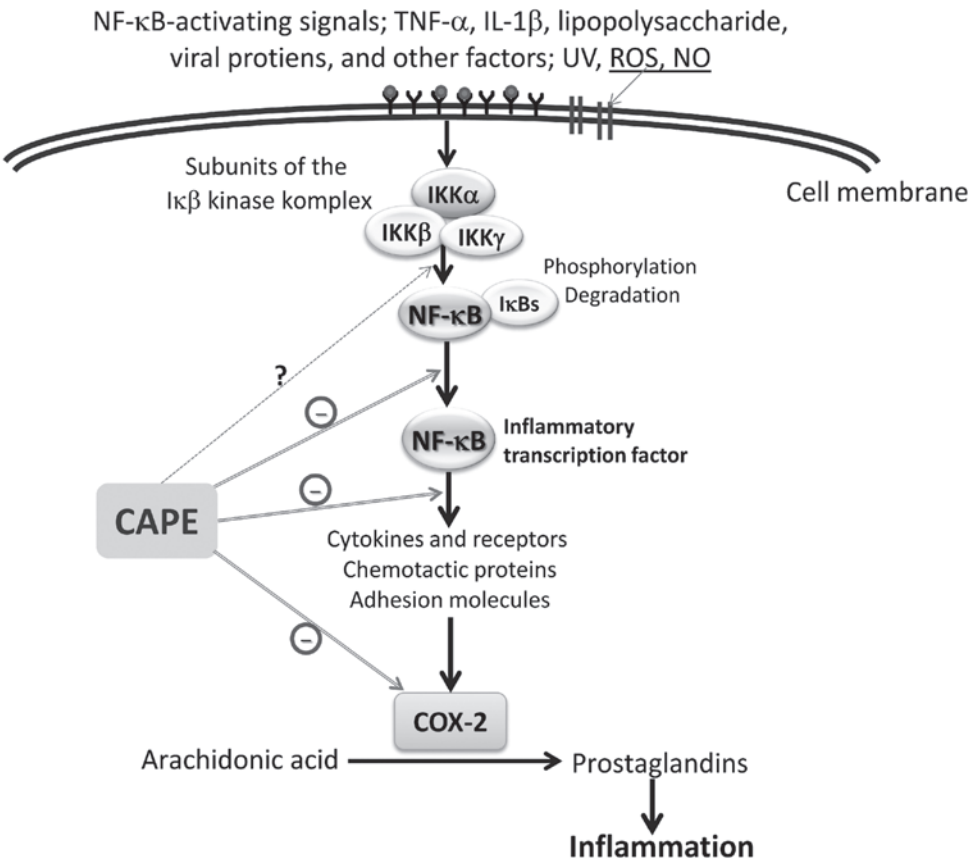

Figure 2. Schematic presentation of the anti-inflammatory effects of CAPE in the inhibition of inflammation. COX-2, cyclooxygenase-2; IκB-α, κB inhibitor-α; IKK, IκB-kinase; IL-1β, interleukin-1β; NF-κB, nuclear factor κB; NO, nitric oxide; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α; UV, ultraviolet.

production at the transcriptional level, through the suppression of NF-κB activation, and the direct inhibition of the catalytic activity of iNOS. Toyoda *et al* (23) reported that CAPE treatment inhibited *Helicobacter pylori*-induced NF-κB activation via the suppression of IκB-α degradation and the phosphorylation of p65 in a gastric cancer cell line. Furthermore, the results clearly demonstrated that the mRNA expression levels of inflammatory factors known to be induced by NF-κB transcriptional activation, such as TNF-α, IFN-γ, IL-2, IL-6, iNOS and KC, an IL-8 homologue chemokine, were all significantly decreased by CAPE treatment in the pyloric mucosa of *H. pylori*-infected Mongolian gerbils (23,24). Colonization of gastric epithelial cells with *H. pylori* induces NF-κB and results in the increased production of the proinflammatory cytokines TNF-α, IL-1, IL-6 and IL-8, all of which are regulated by NF-κB (25,26). It has also been demonstrated that local administration of CAPE leads to increased levels of leukocyte apoptosis and marked reductions in the concentrations of leukocytes, neutrophils and monocytes in the inflammatory site exudate. Furthermore, CAPE decreases the levels of cytosolic IκB-α and increases the nuclear translocation of p65 (27).

CAPE possesses strong antioxidant, anti-inflammatory and healing properties, and its effects on the wound healing have been attributed to the inhibition of NF-κB (28,29). Consistent with these two cited studies, Santos *et al* (30) reported that treatment with CAPE enhanced wound healing, particularly wound healing following burns; decreased inflammatory parameters and oxidative damage; and inhibited the activity of cyclooxygenase and lipooxygenase. Under most inflammatory conditions, such as in thermal injury, NO production is enhanced. In addition to performing histological and biochemical analyses, Santos *et al* (30) evaluated the anti-cluster of differentiation 68 (CD68) and NO levels, as well as myeloperoxidase (MPO) activity. CAPE exhibited an anti-inflammatory action on rat burn healing by reducing MPO activity, NO levels and the number of CD68-positive cells (30). Khan *et al* (31) demonstrated that CAPE reduced neurovascular inflammation and protected the rat brain following transient focal cerebral ischemia by downregulating NF-κB and certain mediators, such as cytokines and iNOS (31).

CAPE classically exerts anti-inflammatory effects by reducing prostaglandin and leukotriene synthesis. Furthermore, it has been suggested that the anti-inflammatory action exhibited by CAPE is a result of the inhibition of arachidonic acid release from the cell membrane. As a consequence of this inhibition, the activity of COX-1 and -2 and the activation of the COX-2 gene expression are suppressed (32,33). Recently, the protective effect of CAPE on a model of eccentric exercise-induced muscle injury was investigated (34). The study results showed that inflammatory skeletal muscle injury enhanced the expression of COX-2 and iNOS, as well as the production of IL-1β and monocyte chemoattractant protein-1 (MCP-1). It was proposed that these pathological changes in the rats were suppressed by

CAPE, which blocked the NF-κB-dependent activation of the inflammatory response (34). In another *in vitro* study, CAPE significantly suppressed the levels of lipopolysaccharide (LPS)-induced IL-1β, TNF-α and MCP-1 from a macrophage cell line, RAW264.7 (35). Furthermore, in a recent study of RAW264.7 murine macrophage *in vivo* models, CAPE reduced the production of cytotoxic molecules, such as NO and peroxynitrite, and thus suppressed the inflammatory responses that could have resulted in cell damage and, potentially, cell death. According to the study results, RAW264.7 cells under LPS/IFNγ stimulation exhibited significantly improved viability following treatment with CAPE, which also inhibited NO production in a similar manner to an iNOS inhibitor. This indicated that CAPE exhibits therapeutic potential in a variety of inflammatory disorders (36).

NF-κB signaling additionally has central roles in precancerous chronic inflammation and cancer-induced inflammation (37). CAPE acts to downregulate inflammation by blocking NF-κB, and affects a variety of mediators, including adhesion molecules, cytokines and iNOS. CAPE is a well-documented inhibitor of NF-κB, which may be an action mechanism for the CAPE-mediated anti-inflammatory and anticancer effects (4,38). Although CAPE has been described to conduct its anti-inflammatory activities by modulating different inflammatory pathways, including inhibition of the transcription factors NF-κB and signal transducer and activator of transcription 3 (acute-phase response factor), the compound has already been evaluated for antitumor efficacy in numerous *in vitro* and *in vivo* studies (39,40). Coimbra *et al* (41), for example, investigated the antitumor efficacy of liposomal formulations of CAPE that are known to interfere with inflammatory signaling pathways and have been described to exert antitumor effects. Furthermore, CAPE has been demonstrated to be selectively cytotoxic to cancer cells (42-44). Previous studies found that CAPE could rapidly enter HL-60 cells and induce glutathione depletion (42), mitochondrial dysfunction and caspase-3 activation (43). In a study by Park *et al* (45) it was observed that CAPE suppressed the expression of phospholipase D1 (PLD1) at the transcriptional level by preventing the binding of NF-κB to the PLD1 promoter. This suggested that the CAPE-induced suppression of matrix metalloproteinase-2 and invasion was mediated by the downregulation of PLD1 by CAPE in glioma cells. Several proposed molecular anti-inflammatory mechanisms of CAPE have been suggested by *in vivo* and *in vitro* studies. Table I (22,23,30,34,35,46-50) summarizes the anti-inflammatory effects of CAPE.

5. Immunomodulatory effects of CAPE

Although the mechanisms underling CAPE-induced NF-κB inhibition have yet to be fully elucidated, the anti-inflammatory and immunomodulatory effects of the compound have been demonstrated in human and experimental models. Immunological studies have indicated that CAPE strongly inhibits mitogen-induced T-cell proliferation, lymphokine production and NF-κB activation (22,27,50). Furthermore, CAPE has been shown to regulate the nuclear binding of the NF-κB subunit p65/RelA, attenuate the expression of cytosolic IκB-α and suppress the dephosphorylation and T-cell transcriptional activity of nuclear factor of activated T cells (51). It has additionally been demonstrated that CAPE can inhibit eicosanoid synthesis, and NF-κB activation may be a causative factor for the increased expression of numerous inflammatory genes in asthma (52,53). NF-κB is expressed in the majority of cell types, and is known to play a central role in immune and inflammatory responses, including asthma. In a study by Jung *et al* (54) CAPE was found to be capable of downregulating NF-κB activity and reducing the levels of eosinophil peroxidase, indicating that CAPE could be considered as an adjuvant therapy for patients with bronchial asthma. Consistent with these observations, Choi *et al* (55) demonstrated the importance of NF-κB in the pathogenesis of asthma in mice. In addition, Park *et al* (56) showed that there was a significant decrease in the cellularity of the spleen and thymus and the thymus weight of mice treated with CAPE at a dose of 20 mg/kg. These results suggested that the treatment of CAPE directly or indirectly caused the immune cells to decrease in cell number, particularly T cells. A different study strongly indicated that the anti-allergy effect of CAPE was a result of the suppression of IgE levels occurring due to the inhibition of NF-κB activation and PAF release (57). Furthermore, it has been reported that CAPE suppresses the contraction of guinea-pig trachea induced by histamine and adenosine. CAPE may therefore be an effective therapeutic agent for allergic diseases (58).

6. Conclusion

In conclusion, CAPE, a compound recognized as the active component of propolis extract, has anti-inflammatory, antioxidant and immunomodulatory properties. Additionally, CAPE inhibits the transcriptional activity of the COX-2 gene in epithelial cells, iNOS gene expression and NO production in macrophage cell lines, and suppresses eicosanoid synthesis and the release of arachidonic acid from cell membranes. In accordance with the above effects, it has been demonstrated that CAPE is a potent and specific inhibitor of NF-κB, lipid peroxidation and lipoxygenase. NF-κB therefore represents a potential target for novel therapeutic agents developed to block the inflammatory response in cases where this process has become chronic or dysregulated. In addition, abnormalities in the NF-κB pathway are frequently observed in a variety of types of human cancer. NF-κB pathway activation is associated with the pathogenesis of chronic inflammatory diseases, including asthma, atherosclerosis, rheumatoid arthritis, inflammatory bowel disease and cancer (59). Furthermore, CAPE demonstrates potential health benefits for the prevention of obesity and associated metabolic disorders and is a potential drug candidate for ischemic stroke treatment due to its inhibition of oxidative stress and inflammation, examples that illustrate how clinically relevant it can be across a wide therapeutic window (49,59). The findings described in this review provide novel insights into the molecular mechanisms underlying the immunomodulatory and anti-inflammatory activities of CAPE. Several of the widely used anti-inflammatory agents inhibit the NF-κB pathway, at least in part, as one of their targets. The effect of CAPE in the treatment of inflammatory diseases may be mediated through the inhibition of NF-κB activation, and it is believed that CAPE is a

Table I. Potential mechanism underlying the effects or progression pathways of CAPE in its anti-inflammatory/immunomodulatory action.

Mechanism for the effect or progression pathway(s)	*In vivo*/*in vitro*	Cells/animals used	Reported outcomes (ref.)
Inhibiting ROS production; suppressing NF-κB activation	*In vivo*, EAE (animal model of MS)	Rats	Inhibited ROS production (XO activity, levels of MDA); reduced infiltration of inflammatory cells (22)
Suppressing inflammation and ocular tissue damage	*In vivo*, LPS-induced inflammation	Rats	Suppressed number of inflammatory cells and MPO activity (46)
Inhibiting NF-κB activation and mRNA expression; preventing degradation of IκB-α and phosphorylation of p65 subunit	*In vitro*, cell culture; *in vivo*, *H. pylori*-induced chronic gastritis	AGS cells, Mongolian gerbils	Inhibited NF-κB activation by suppression of IκB-α degradation and phosphorylation of p65; suppressed NF-κB p50; reduced mRNA expression of TNF-α, IL-2, IL-6, iNOS and KC (23)
Inhibiting NF-κB transcriptional activation	*In vitro*	Jurkat, MT2 human T-cell lines	Inhibited NF-κB transcriptional activation induced by Tax (47)
Inhibiting TNF-α-dependent NF-κB activation via direct inhibition of IKK as well as activation of the Nrf2 pathway	*In vitro*, cell culture	HCT116 (human colon carcinoma) cells	Inhibited NF-κB activation by TNF-α and LPS, and directly inhibited IKK in HCT116 cells. Nrf2 activation is associated with the inhibition of the NF-κB pathway (48)
Inhibiting the inflammatory pathway	*In vivo*	Mice	Reduced NF-κB activation and levels of COX-2 (49)
Inhibiting cytokine and chemokine production associated with the NF-κB signaling pathway	*In vitro*, peripheral blood sampling	MoDCs	Inhibited cytokine and chemokine production, IκB-α phosphorylation and NF-κB activation in human MoDCs (50)
Inhibiting gene expression of proinflammatory cytokines from LPS-stimulated macrophages	*In vitro*, cell culture	LPS-stimulated RAW264.7 cells	Reduced mRNA expression of MCP-1, TNF-α, IL-6 and IL-1β (35)
Blocking NF-κB-dependent activation of the inflammatory responses	*In vivo*, eccentric exercise-induced skeletal muscle injury	Rats	Suppressed high COX-2 and iNOS expression and IL-1β and MCP-1 levels (34)
Anti-inflammatory action on rat burn healing	*In vivo*, burn injury	Rats	Reduced MPO activity, NO levels and CD68 expression; improved wound healing after burn (30)

CAPE, caffeic acid phenethyl ester; CD68, cluster of differentiation 68; COX-2, cyclooxygenase-2; EAE, experimental autoimmune encephalomyelitis; IκB-α, κB inhibitor-α; IKK, IκB-kinase; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; MODC, monocyte-derived dendritic cell; MPO, myeloperoxidase; MS, multiple sclerosis; NF-κB, nuclear factor κB; Nrf2, nuclear-factor-E2-related factor 2; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α; XO, xanthine oxidase.

safe, natural compound and a promising drug candidate for anti-inflammation therapy.

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