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Review Article

Possible molecular targets for therapeutic applications of caffeic acid phenethyl ester in inflammation and cancer

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ABSTRACT

Of the various derivatives of caffeic acid, caffeic acid phenethyl ester (CAPE) is a hydrophobic, bioactive polyphenolic ester obtained from propolis extract. The objective in writing this review article was to summarize all published studies on therapeutics of CAPE in inflammation and cancer to extract direction for future research. The possible molecular targets for the action of CAPE, include various transcription factors such as nuclear factor-κB, tissue necrosis factor-α, interleukin-6, cyclooxygenase-2, Nrf2, inducible nitric oxide synthase, nuclear factor of activated T cells, hypoxia-inducible factor-1α, and signal transducers and activators of transcription. Based on the valuable data on its therapeutics in inflammation and cancer, clinical studies of CAPE should also be conducted to explore its toxicities, if any.

1. Introduction

Due to the lethal side effects of synthetic chemical-based drugs, enthusiastic efforts are currently being applied to explore natural therapeutic agents with minimum toxicity. In this context, plant or herbal origin compounds are being studied to investigate the bioactivities of their natural active compounds. Polyphenols represent one of the most intensively studied groups of natural compounds.

Caffeic acid has been proposed to act as a multipurpose active polyphenol and its derivatives have also been subjected to considerable study. One of the derivatives of caffeic acid is caffeic acid phenethyl ester (CAPE), which possesses promising therapeutic potential against various pathologies such as inflammation, cancer, infection, and neurodegeneration

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[1–5]. This naturally bioactive, hydrophobic polyphenolic ester occurs in numerous plants [6–9] and propolis [10] and can also be prepared by reacting caffeic acid with phenethyl alcohols [1–3]. The molecular formula of CAPE is $C_{17}H_{16}O_4$ and is chemically recognized as 2-phenylethyl (2E)-3-(3,4-dihydroxyphenyl)acrylate (commonly termed as phenylethyl caffeate or phenethyl caffeate) [4].

To achieve biological effects, CAPE should be administered at a therapeutic concentration so that prolonged maintenance of blood CAPE-concentration at a particular level could be achieved. Thus pharmacokinetic and bioavailability study of CAPE is crucial for determining its route of administration. Fig. 1 depicts the chemical structure of CAPE consisting of a catechol ring and two hydroxyl groups; the former is considered to be responsible for its therapeutic features [5]. It has been proposed that metabolism of CAPE is a saturable process because an increase in the area under the plasma concentration–time curve for CAPE was observed in a proportion higher than the increase in its dose. Moreover, volume of distribution and total body clearance values for CAPE were found to be in the ranges of 1555–5209 mL/kg and 42–172 mL/minute/kg, respectively, proposing that these values are in an inverse relationship with the dose of CAPE. Additionally, no relationship was observed between the values of elimination half-life (21.24–26.71 minutes) of CAPE and its dose. Pharmacokinetic study of CAPE showed its high values of volume of distribution and short elimination half-life, revealing its extensive distribution and swift elimination from the body after intravenous administration [11]. Another pharmacokinetic study of CAPE showed comparable results [12]. Furthermore, pharmacokinetic analysis of CAPE and its metabolites should also be carried out after its oral administration. Another study has revealed that CAPE can efficiently cross the blood–brain barrier in rats [13]. Besides, although CAPE is stable for 6 hours in rat plasma, after which it hydrolyzes to caffeic acid, CAPE hydrolysis does not occur in human plasma showing its stability, possibly owing to the absence of carboxylesterase in this biofluid [14,15].

After an extensive search, no data were found about toxicity study of CAPE. Rather, slight toxicity of propolis was seen in a range of 2000–7300 g of propolis/kg in mice that is an origin of CAPE [16,17]. At a dose of approximately 80 μM, CAPE generally inhibits the activated nuclear factor-κB (NF-κB) and other transcription factors via suppressing their binding with DNA [15].

The objective in writing this review article was to summarize various published studies on the therapeutics of CAPE in inflammation and cancer, especially focusing on their molecular targets that are responsible for therapeutic effect of CAPE.

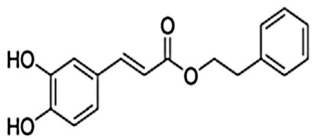

Fig. 1 – Chemical structure of caffeic acid phenethyl ester [9].

2. Literature search methodology

An extensive literature search in English was conducted, using various electronic databases including Medline (1966–2014) and EMBASE (1980–2014). An initial search was made using terms *caffeic acid phenethyl ester* and *activity* jointly. Then, other terms such as *inflammation*, *cancer*, and *molecular targets* were combined with *caffeic acid phenethyl ester* and *activity* for an advanced search. The literature investigation was done by assessing the bibliography of the selected publications showing original research to make a quality review article.

3. Results and discussion

There are many studies in the literature that elaborate the anti-inflammatory activity of CAPE [18,19]. Moreover, CAPE-induced inhibition of normal cell transformation to the neoplastic cell has also been reported [20,21]. Table 1 [20,22–32] elaborates the dose (μM) or concentration causing 50% growth inhibition (μM) of CAPE effective in different cancer cell-lines. In addition, CAPE selectively destroys the cancerous cells leaving noncancer cells unaffected as observed in human immortal lung fibroblast WI-38 cells [29].

These studies hypothesize that CAPE inhibits the release of arachidonic acid from the cell membrane, and moreover, suppresses the gene responsible for cyclooxygenase-2 (COX-2) expression [33–36]. Moreover, CAPE suppresses NF-κB activity by limiting the formation of NF-κB DNA and nuclear factor of activated T cells (NFAT)-DNA complexes and thus retarding NF-κB-dependent transcription in Jurkat cells [37–42]. In 2005, Abdel-Latif et al presented anticancer and anti-inflammatory activities of CAPE in a gastric epithelial cell line, claiming that CAPE inhibits the production of tissue necrosis factor-α (TNF-α) and interleukin (IL)-8; it eventually retards the expression of NF-κB, AP-1, and COX-2 [43]. It is noteworthy to mention here that CAPE does not influence other tissues of body, and thus the usage of this natural anticancer agent is free of side effects with effective chemopreventive feature [44–47]. This outcome elaborates the nutritional importance of CAPE, particularly for patients whose tumors express gradually elevated levels of above given activated transcription factors.

Lipopolysaccharide-mediated inflammation in human neutrophils has also been combated using CAPE which suppresses the synthesis of TNF-α and IL-6 [48]. The same authors also found that CAPE attenuates the phosphorylation of extracellular signal-regulated kinase 1/2 and c-JunN-terminal kinase [48]. Raso et al [49] found that CAPE has potential for reducing inflammation through inhibiting IL-2 gene in activated T-cells that are normally the source of inflammation [34].

Biological studies have also revealed the activity of CAPE against angiogenesis, tumor invasion, metastasis, proliferation, and apoptosis in different cancers such as human pancreatic and colon cancer [23,35,44,50–55]. The improvement in the viability of colon adenocarcinoma cells (CT26) has been noted in a dose-dependent manner when these cells are treated with CAPE [30]. This cytotoxic effect of CAPE has been