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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- κ B, tissue necrosis factor- α , interleukin-6, cyclooxygenase-2, Nrf2, inducible nitric oxide synthase, nuclear factor of activated T cells, hypoxia-inducible factor-1 α , 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.

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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 μ M, CAPE generally inhibits the activated nuclear factor- κ B (NF- κ B) 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.

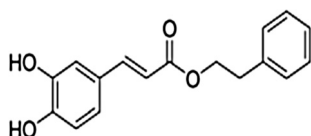


Fig. 1 – Chemical structure of caffeic acid phenethyl ester [9].

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 (μ M) or concentration causing 50% growth inhibition (μ M) 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- κ B activity by limiting the formation of NF- κ B DNA and nuclear factor of activated T cells (NFAT)-DNA complexes and thus retarding NF- κ B-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- κ B, 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

Table 1 – The dose or concentration causing 50% growth inhibition (IC₅₀) of CAPE effective in different cancer cell-lines.

No.	Types of cancer and their cell lines	Dose (μM)	IC ₅₀ (μM)	Refs
1	U973 myeloid leukemia cells	0.4–53	—	[22]
2	GNM neck metastasis of <i>Gingiva carcinoma</i>	25–200	—	[23]
3	TSCC tongue squamous carcinoma cells	25–200	—	[23]
4	Daoy medulloblastoma cells	1–100	—	Lee et al 2005
5	SW480 colon cancer cells	9–18	—	Wang et al 2005
6	HCT116 colon cancer cells	9–182	—	[24]
7	PC-3 prostate cancer cells	88	—	[25]
8	HL-60 leukemia cells	21	—	[26], Chen et al 2001b
9	MCF-7 breast cancer cells	10–100	—	[27]
10	Meng 1 oral epidermal carcinoma cells	50–200	—	[20]
11	H1299 lung cancer cells	—	21.2	Lin et al 2011
12	Nalm6 lymphoma cells	—	3.1	[28]
13	Farage lymphoma cells	—	2.0	[28]
14	Pfeiffer lymphoma cells	—	1.2	[28]
15	Ramos lymphoma cells	—	4.0	[28]
16	HDMAR lymphoma cells	—	2.1	[28]
17	HT-1080 fibrosarcoma cells	—	9.5	[29]
18	HeLa cervical cancer cells	—	2.4	[29]
19	CT26 colon cancer cells	—	35.0	[30]
20	A549 lung cancer cells	—	20.9	[29,31]

attributed to the reduced expression of matrix metalloproteinase and synthesis of vascular endothelial growth factor under the effect of CAPE. In this way, this chemical activity obstructs the angiogenesis and metastasis [56–62].

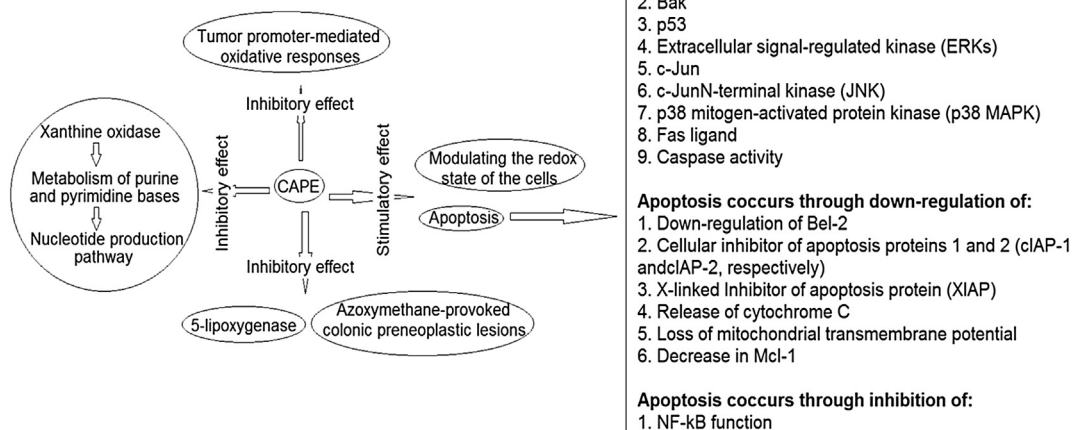
CAPE can suppress apoptosis via inhibiting the activated NF-κB [26], Bak [63], Bcl-2-associated X protein (Bax) [31,63–65], p53 [25,27,63], extracellular signal-regulated kinase [63], c-Jun and p21ap [27], c-JunN-terminal kinase and Fas ligand [65], p38 mitogen-activated protein kinase (p38 MAPK) [25,63], and caspase activity [27,31,63,64]. Moreover, upregulation of Bel-2 [29,66], the cellular inhibitor of apoptosis proteins 1 and 2, and X-linked inhibitor of apoptosis protein [26,31], release of cytochrome C [63,64], loss of mitochondrial transmembrane potential [27], and decrease in Mcl-1 [21,27] by CAPE are also responsible for its antiapoptotic effect.

In many cancer cells, CAPE-mediated-cell cycle arrest has been reported through the suppression of various factors including cyclin B1 [28,29]. CAPE-induced necrosis has also been described [22]. In addition, suppression of Akt

phosphorylation is also induced by CAPE, resulting in the inhibition of cancer cell invasiveness [24].

The literature also contains many animal studies that reveal the inhibitory role of CAPE on tumor growth and metastasis. For example, at a dietary level of 0.15% CAPE, C57BL/6J-Min/+ mice having a germ-line mutation exhibit 63% suppression in tumor growth through increased apoptosis and cell proliferation [67]. At a dose of 50 mg/kg, CAPE-treated rats showed the emergence of colon–rectal carcinoma provoked by azoxymethane [44]. In addition, mice with C6 glioma xenografts have exhibited dose-dependent inhibition in tumor metastasis at 1–10 mg intraperitoneal dose of CAPE/kg/day [21]. As far as mechanisms of anticancer activity of CAPE are concerned, CAPE is capable of affecting various processes [32,42,46,60,68–73] as summarized in Fig. 2.

Through numerous experimental studies, the therapeutic potentials of CAPE against various cancers have been explored. The findings of those studies are summarized below and the possible target sites of CAPE action are also described.

**Fig. 2 – Various modes of anticancer activities of caffeic acid phenethyl ester (CAPE).**

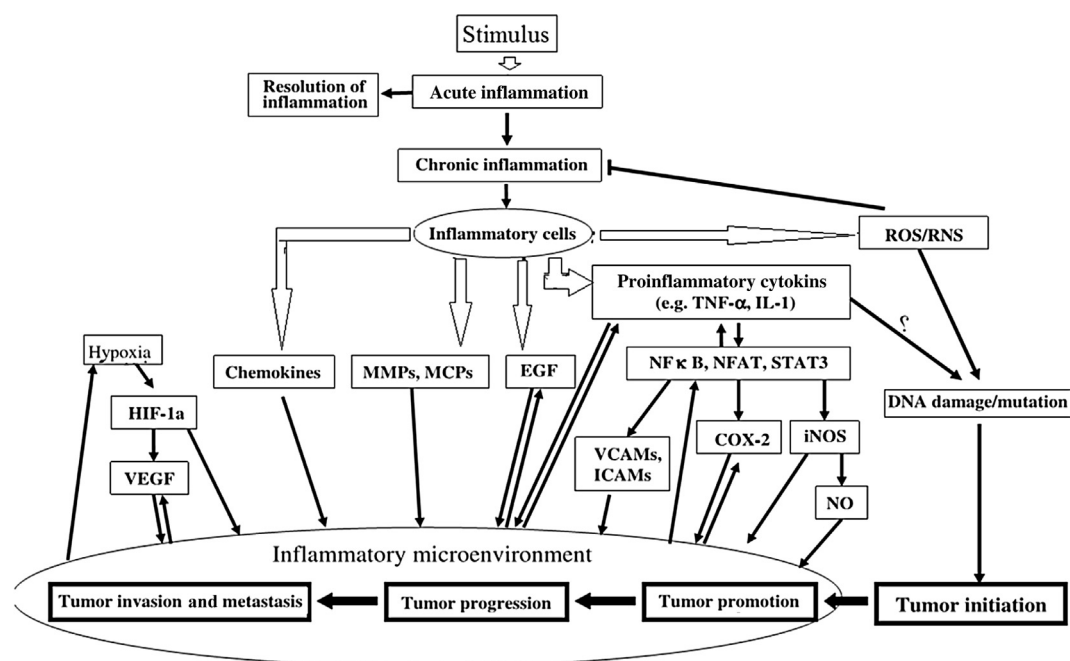


Fig. 3 – A summary of linkage between inflammation and cancer development. Tissue necrosis factor- α (TNF- α), interleukin (IL)-1, hypoxia-inducible factor-1 α (HIF-1 α), vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs), modified citrus pectins (MCPs), endothelial growth factor (EGF), nuclear factor- κ B (NF- κ B), nuclear factor of activated T cells (NFAT), signal transducer and activator of transcription 3 (STAT3), vascular cell adhesion molecules (VCAMs), intercellular adhesion molecules (ICAMs), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), nitric oxide (NO).

In response to a stimulus such as tissue damage, inflammation develops. It is a physiologic phenomenon that may contribute to cancer development through various intermediates (Fig. 3) [74]. Key modulators, which drive inflammation to cancer, include various transcription factors such as NF- κ B, TNF- α , IL-6, COX-2, Nrf2, inducible nitric oxide synthase (iNOS), NFAT, hypoxia-inducible factor-1 α , and signal transducers and activators of transcription [74].

The cytoplasm of all nondiseased B cells contains inactive NF- κ B factor [75]. NF- κ B is a collective term referring to proinflammatory heterotrimer transcription factors, a family of five proteins having Rel-domain. These proteins, including NF- κ B1 (or p50), NF- κ B2 (or p52), Rel A (or p65), Rel B, and c-Rel, remain inactive under the influence of I κ B α , I κ B β , I κ B γ , I κ B δ , and I κ B ϵ ,

bcl-3, p105, and p100 proteins that have the anchoring domain [76].

In tumor cells, as well as proliferating thymocytes, monocytes, astrocytes, T cells, and B cells, NF- κ B is reported to be activated after phosphorylation and removal of I κ B α by I κ B α kinase (IKK; Fig. 4). The IKK family consists of three enzymes (IKK α , IKK β , and IKK γ), of which, IKK β is proposed to be involved in NF- κ B activation by cytokines (tissue necrosis factor, IL-6, growth factors, and differentiation factors) and many other carcinogens and tumor promoters [76–78]. Shishodia et al [79] demonstrated tissue necrosis factor as the strongest NF- κ B activator, under the influence of which tumor cells proliferate, invade, metastasize, and suppress apoptosis. Matrix metalloproteinases, urokinase type of plasminogen activator, and IL-8 are examples of NF- κ B-regulated gene products that regulate the invasion of tumor cells [79–82]. Metastasis of tumor cells is regulated by NF- κ B and is mediated through the expression of different adhesion molecules, including intercellular adhesion molecule-1, vascular cell adhesion molecule-1, endothelium leukocyte adhesion molecule-1, and iNOS [83,84].

Immediately after activation, translocation of NF- κ B occurs from the cytoplasm to the nucleus of the cell followed by the binding of NF- κ B to its particular harmonized site consisting of 10 base pairs, GGGPuNNPyPyCC [85,86]. The active NF- κ B, in normal physiology, controls the expression of many genes that regulate the immune, growth, and inflammation features of cell.

By contrast, the excessive and improper activation of NF- κ B can intervene inflammation and tumorigenesis. In addition, NF- κ B acts as a linkage between inflammation and

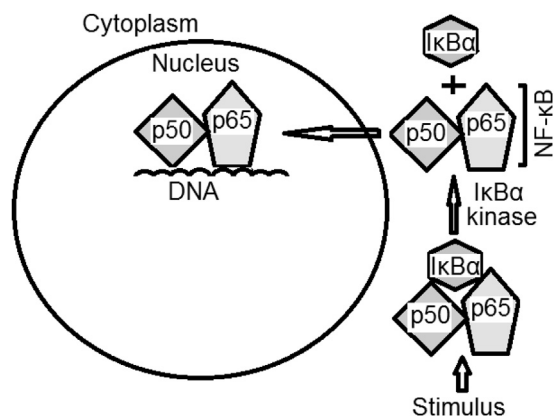


Fig. 4 – An illustrative summary of the nuclear factor (NF)- κ B activation route.

cancer remembering that cancer is a proinflammatory disease [45,87]. Thus, activation of NF- κ B by any inflammatory agents can produce inflammation that is mediated through adhesion molecules, such as intercellular adhesion molecule-1 [88]. Similarly, suppression of NF- κ B by any anti-inflammatory agents can reduce inflammation and proliferation causing cell cycle arrest, eventually leading to apoptosis [45]. The microenvironment of tumors, as well as different inflammatory agents, carcinogens, and tumor promoters may activate the NF- κ B [76]. There are some members of the NF- κ B group that are oncogenic in nature and can intervene their effects by activating NF- κ B [76,89].

Various stimuli, such as lipopolysaccharide, proinflammatory cytokines (e.g., IL-1 and tissue necrosis factor), and growth factors (e.g., epidermal growth factor), have been found to be involved in expression of COX-2, which acts on arachidonic acids and produces prostaglandins, the crucial mediators of inflammation. Moreover, COX-2 is overexpressed in cancer [74,90,91]. Various antioxidant genes are regulated by Nrf2's role in inflammation; this effect of Nrf2 can be attributed to the involvement of prostaglandins and/or NO leading to the diminished susceptibility to apoptotic factors including TNF- α . Nrf2 is reported to exhibit protection against DNA damage and carcinogenesis [92,93]. Likewise, iNOS, an enzyme that catalyzes the production of NO, is also overexpressed in inflammation and cancer [29,94,95]. In addition, NFAT is proposed to play a crucial role in inflammatory responses through the expression of various proinflammatory cytokines, including IL-2, IL-3, IL-4, IL-5, IL-13, and TNF- α . NFAT is involved in COX-2 expression induced by TNF- α [96,97]. By contrast, inflammation is always accompanied by hypoxia due to metabolic shifts during inflammation. In response to hypoxia, hypoxia-inducible factor-1 α , a heterodimeric transcription factor, activates various molecules including erythropoietin, iNOS, vascular endothelial growth factor, and glucose transporter-1 [98–100]. Signal transducers and activators of transcription factors are also activated by various cytokines in inflammation and cancer [29].

4. Conclusion

This literature mining study revealed anti-inflammatory and anticancer activities of CAPE. The possible molecular targets for the action of CAPE in inflammation and cancer include various transcription factors such as NF- κ B. Based on the valuable data about the above presented bioactivities, clinical studies of CAPE should be conducted to explore its toxicities, if any.

Conflicts of interest

All authors declare no conflicts of interest.

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