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Current Medicinal Chemistry, 2024, *31*, 6760-6774

REVIEW ARTICLE

Caffeic Acid Phenethyl Ester: A Potential Therapeutic Cancer Agent?

Geir Bjørklund[1,*], Olha Storchylo[2], Massimiliano Peana[3], Tony Hangan[4,*], Roman Lysiuk[5,6], Larysa Lenchyk[7,8], Oleh Koshovyi[8,9], Halyna Antonyak[10], Nataliia Hudz[11,12] and Salvatore Chirumbolo[13,14]

[1]*Council for Nutritional and Environmental Medicine (CONEM), Mo i Rana, Norway;* [2]*Medical Chemistry Department, Odessa National Medical University, Odessa, Ukraine;* [3]*Department of Chemical, Physical, Mathematical and Natural Sciences, University of Sassari, Sassari, Italy;* [4]*Faculty of Medicine, Ovidius University of Constanta, Constanta, Romania;* [5]*Department of Pharmacognosy and Botany, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine;* [6]*Department of Pharmacognosy and Botany, CONEM Ukraine Life Science Research Group, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine;* [7]*Department of Chemistry of Natural Compounds, National University of Pharmacy, Kharkiv, Ukraine;* [8]*CONEM Ukraine Pharmacognosy and Natural Product Chemistry Research Group, National University of Pharmacy, Kharkiv, Ukraine;* [9]*Department of Pharmacognosy, National University of Pharmacy, Kharkiv, Ukraine;* [10]*Department of Ecology, Ivan Franko National University of Lviv, Lviv, Ukraine;* [11]*Department of Drug Technology and Biopharmaceutics, Danylo Halytsky Lviv National Medical University, Lviv, Ukraine;* [12]*Faculty of Chemistry, University of Opole, Opole, Poland;* [13]*Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy;* [14]*CONEM Scientific Secretary, Verona, Italy*

Abstract: ***Background*:** Propolis and its major phenolic compound, caffeic acid phenethyl ester (CAPE), have garnered considerable scientific interest due to their anti-inflammatory properties and potential therapeutic applications.

***Objectives*:** This narrative review explores the potential utility of CAPE in cancer treatment.

***Methods*:** We comprehensively reviewed relevant studies from scientific databases (PubMed and Web of Science) from 2000 to 2022. Our search focused on keywords such as cancer, natural drugs, caffeic acid phenethyl ester, CAPE, cancer cell lines, antitumor effects, and propolis.

***Results*:** CAPE exhibits diverse biological benefits, including antimicrobial, antioxidant, antiviral, anti-inflammatory, cytotoxic, and potentially anti-carcinogenic properties. Numerous studies have demonstrated its wide-ranging antitumor effects on various cancer cell lines, including growth inhibition, apoptosis induction, tumor invasiveness prevention, malignancy suppression, and anti-angiogenic activity.

***Conclusion*:** Following comprehensive preclinical toxicity assessments, further evaluation of CAPE's efficacy and safety through clinical trials is highly recommended to elucidate its potential health benefits in diverse forms of human cancer.

ARTICLE HISTORY

Received: March 12, 2023
Revised: June 20, 2023
Accepted: July 24, 2023

DOI:
10.2174/0109298673252993230921073502

Keywords: Cancer, natural drugs, caffeic acid phenethyl ester, cancer cell lines, antitumor effects, propolis.

1. INTRODUCTION

The role of natural compounds in combating cancer has taken center stage in the ongoing efforts of biomedical sciences to address tumors [1, 2]. Among these compounds, phenolic acids, such as caffeic acid, have emerged as promising tools against various neoplastic disorders, although much of the evidence stems from *in vitro* studies [3-8]. Recent reviews have explored the therapeutic potential of caffeic acid in cancer [9, 10].

A wide array of natural origin medicines possesses anticancer properties. These encompass phytochemicals derived from plant parts, juice components, ground seeds (*e.g.*, milk thistle), as well as derivatives of poly-component systems of non-herbal origin, like

*Address correspondence to these authors at the Council for Nutritional and Environmental Medicine (CONEM), Toften 24, 8610 Mo i Rana, Norway; E-mail: bjorklund@conem.org;
Faculty of Medicine, Ovidius University of Constanta, Aleea Universităţii 1, Campus B, 900470, Constanta, Romania,
E-mail: tony@medcon.ro

1875-533X/24 $65.00+.00

propolis, with noteworthy biochemical potential and the ability to foster beneficial effects on cells [11]. Natural sources of biologically active compounds found in foods, nutrients, and pharmaceutical plants are renowned for their low toxicity, broad spectrum of action, and reduced side effects compared to synthetic medicines [12, 13].

The prevailing notion that plants serve as benign sources of anticancer pro-drugs has its roots in folk and traditional medicine. However, a burgeoning body of literature detailing the effects of various purified components from plant extracts encourages researchers to delve deeper into this subject and broaden the search for potential novel chemopreventive drugs from plant sources. The study of the influence of natural compounds on cancer pathogenesis is recognized as a crucial strategy in developing anticancer medications.

Plant phenolics, particularly flavonoids, have garnered significant scientific interest due to their potential pro-apoptotic and anti-metastatic properties, along with their ability to modulate reactive oxygen species (ROS) signaling, despite the majority of evidence being derived from *in vitro* studies [14-16]. Caffeic acid phenethyl ester (CAPE), for instance, is among the nature-derived substances that have recently captured the attention of researchers due to its myriad biological benefits [17].

The search for novel natural compounds and the investigation of potential antitumor agents of natural origin remain ongoing tasks, necessitating a deeper understanding of their mechanisms of action and biological activity. Numerous reviews have been dedicated to this research area [18-20]. Over the last three decades, one of the components of propolis, CAPE, has undergone extensive study as a potential anticancer agent. This narrative review explores its prospects in cancer treatment, drawing on representative studies from various scientific databases, including PubMed and Web of Science, covering 2000 to 2022. The review focuses on keywords such as cancer, natural drugs, caffeic acid phenethyl ester, CAPE, cancer cell lines, antitumor effects, and propolis.

2. SEARCH METHODOLOGY

We conducted a comprehensive search across multiple scientific databases, including PubMed/Medline, Scopus, Web of Science (WoS), and Embase, using the Medical Subject Headings (MESH) term “caffeic acid phenethyl ester.” This search yielded a total of 1,142 reports. We further narrowed our focus by using the MESH term “caffeic acid phenethyl ester AND cancer,” resulting in 330 reports.

Within this refined dataset, we conducted a more detailed exploration, identifying 38 reviews (of which only five specifically addressed CAPE and cancer), with no meta-analyses or systematic reviews and no clinical trials found. Among the reports, 36 articles were dedicated to *in vitro* experimental studies, with eight studies being duplications. Additionally, other reports examined the antioxidant, anti-inflammatory, and biological activities of CAPE.

To provide a comprehensive view of the research landscape, we expanded our search to include articles related to clinical research. However, it is noteworthy that the majority of eligible reports demonstrating CAPE's effects on cancer cells numbered less than 30.

3. STRUCTURE, ORIGIN, AND DISTRIBUTION OF CAPE

CAPE, in accordance with IUPAC nomenclature, bears the chemical name 2-phenylethyl (2E)-3-(3,4-dihydroxyphenyl) acrylate. This hydrophobic compound belongs to the flavone derivative family, characterized as an α,β-unsaturated heterocyclic ketone and a γ-pyrone derivative (Fig. **1**).

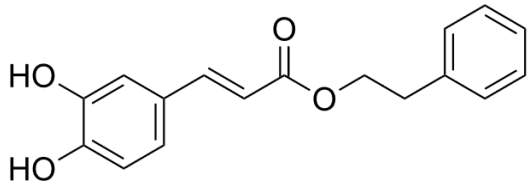

Fig. (1). Chemical structure of caffeic acid phenethyl ester ($C_{17}H_{16}O_4$; molar mass: 284.3 g/mol), a caffeic acid derivative.

Hydroxycinnamic acids, including p-coumaric, caffeic, ferulic, and sinapic acids, are commonly found in various combinations in numerous higher plants. They exist either in a free reactive state (aglycone) or as constituents of glycosides and esters. Among them, caffeic acid and its derivatives, including chlorogenic acid and its isomers, are prevalent and known for their anti-inflammatory and choleretic properties [21]. Notably, chlorogenic acid is abundant in coffee beans, whortleberry leaves, mountain arnica, chamomile flowers, and *Galium verum* herb [22, 23]. The collective action of caffeic, chlorogenic, ferulic, coumaric, and other caffeoylquinic acids contributes to hypoazotemia, improved renal function, and enhanced liver antitoxic activity [24, 25]. These hydroxycinnamic acids also occur in plants such as Echinacea, burdock roots, hawthorn, rhubarb, bird cherry fruits, cherry leaves, and Labrador tea shoots [26-28].

CAPE is naturally present in vegetables, fruits, red wine, and olives. However, it is renowned as a constituent of propolis, a substance safely used as a food additive and in pharmaceutical manufacturing. The chemical composition of propolis varies based on the geographical origin of the propolis sources, influenced by the local vegetation [29]. In a study by Popova *et al.* (2014), more than 60 components were identified in propolis samples using gas chromatography/mass spectrometry, revealing a surprisingly consistent qualitative composition across samples [30]. The main compounds identified in all samples included flavonoids, aromatic acids such as benzoic acid, caffeic acid, p--coumaric acid, phenolic acid esters (coumarates, ferulates/isoferulates, caffeates), flavonoids, and others. CAPE (Fig. **1**) is one of these phenolic compounds present in propolis [30].

Honeybees employ propolis to defend their hives against infections and parasites. Popova *et al.* (2014) observed that honeybee colonies with resistance to mites (Varroa destructor) contained a higher concentration of CAPE in their propolis compared to non-resistant colonies from the same apiary [29]. In a mini-review, Bankova *et al.* (2018) proposed that CAPE is exclusively found in propolis of the poplar type, originating from resinous exudates on buds and young leaves. This compound has been identified in 26 species of the Populus genus, with a predominant presence in *Populus nigra* L. [31]. Furthermore, CAPE has been reported in Serbian unifloral honey [32].

Beyond propolis, honey, and poplar, CAPE has also been detected in certain plants. Bankova *et al.* (2018) noted the presence of CAPE in the leaf exudates of *Baccharis sarothroides* (Asteraceae family), leaves of *Alibertia macrophylla* (Rubiaceae family), roots of *Rhodiola sacra* (Crassulaceae family), aerial parts of *Parastrephia lucida* (Asteraceae family), leaves and flowers of *Melaleuca cajuputi* (Myrtaceae family), and twigs of *Cinnamomum cassia* (Lauraceae family) [31].

While CAPE has been reported in some mushrooms, such as *Agaricus bisporus*, *Marasmius oreades*, *Lentulus edodes*, and *Phellinus linteus*, its presence has not been consistently confirmed [31].

Comparatively, the synthetic production of CAPE is more cost-effective and offers higher yields than isolation from raw plant material. As early as 1988, CAPE was synthesized at Columbia University [33]. Since then, various synthetic methods for CAPE production have been developed [31, 34, 35]. This synthetic approach holds promise for the widespread utilization of CAPE in pharmaceutical sciences.

4. INSIGHTS INTO THE BIOLOGICAL EFFECTS OF CAPE, PHARMACOKINETICS, AND TOXICOLOGY

Understanding the toxicological profile of CAPE, particularly L-CAPE, necessitates consideration of CAPE's pharmacokinetics. CAPE's pharmacokinetics are typically associated with its catechol-ring fluorinated derivative (FCAPE). In rat models, administering 5, 10, or 20 mg/kg body weight of CAPE and FCAPE revealed that the area under the time-response curve of plasma concentration increases at a higher level concerning the dose-response behavior within the 5-20 mg/kg range [36].

Clearance values for CAPE across the entire body ranged from 42.1 to 172 ml/min/kg, decreasing with increasing CAPE doses. Similarly, the volume of distribution for CAPE spanned from 1555 to 5209 ml/kg, decreasing as the dose increased. Notably, the elimination half-life for CAPE ranged from 21.2 to 26.7 minutes and remained independent of the amount [36].

Determining CAPE's half-maximal inhibitory concentration (IC_{50}), often evaluated through cell viability assays, varies depending on cell type and experimental models. For instance, in the OV7 cell line, a 100 μM CAPE dose reduced cell survival to 42.3% within 24 hours and 30.7% within 48 hours. The IC_{50} for CAPE, in this case, was 80.08 μM at 24 hours and 49.57 μM at 48 hours [37]. For the MDA-MB-231 cell line, the IC_{50} was found to be 21.05 μM (5.99 μg/ml) at 24 hours, 13.78 μM (3.92 μg/ml) at 48 hours, and 11.69 μM (3.32 μg/ml) using an MTT assay [38]. These data indicate that a 28-30 μg/ml dose is cytotoxic, even for cancer cells.

The biological effects of CAPE encompass its antimicrobial, antioxidant, anti-inflammatory [19, 20, 39, 40], cytotoxic properties and its potential to reduce neuropathic pain and treat lung arterial hypertension [39, 41]. However, the primary focus remains on CAPE's anti-carcinogenic properties [5, 18, 42-44]. Notably, the antiseptic and anti-inflammatory effects of crude drugs from *Parastrephia lucida*, employed in traditional Argentinean medicine, were linked to mixtures of prenyl and phenethyl esters of caffeic and cinnamic acids, including CAPE [45]. Additionally, methanol extracts of *Rhodiola sacra* from Korea demonstrated potent anti-inflammatory activity due to CAPE [46].

CAPE exhibits many properties, including anti-inflammatory, neuroprotective, hepatoprotective, cardioprotective, antioxidant, chemopreventive, cytotoxic, antimetastatic, antitumor, immunomodulatory, and antiviral activities. It has been shown to inhibit lipoxygenase

activities and suppress lipid peroxidation [18, 33, 40, 46]. In antioxidant assessments conducted by Russo *et al.* (2002), propolis extract with CAPE was more efficient than propolis extract without this compound. Furthermore, CAPE alone exhibited high 1,1-diphenyl-2-picrylhydrazine radical scavenging activity [47].

CAPE demonstrates potent cellular protective activity against ROS [48]. Oxidative stress, chronic inflammation, and cancer are closely intertwined, with oxidative stress influencing various stages of cancer. It activates transcription factors, including NF-κB and p53, which play roles in cancer development [49, 50]. Notably, a combination of CAPE, prenyl caffeates, and benzyl caffeate inhibited the growth of bee pathogens [51].

Studies exploring the detoxifying effects of aloe polysaccharides and propolis on smokers, individually and in combination, revealed that aloe polysaccharides were more effective than pure propolis. However, their combined use demonstrated synergistic effects. These components hold promise as potential chemopreventive agents for eliminating carcinogens from smokers' bodies [52].

Promising results have emerged from the administration of propolis in colon cancer prevention. In a pilot, randomized, placebo-controlled, double-blind phase 0/biomarker study, the effectiveness of propolis extract in capsules over three months was confirmed in preventing early-stage colon cancer-related changes [53].

Moreover, in animal experiments, CAPE has exhibited the ability to protect the brain against permanent focal ischemia and reduce ischemia-reperfusion-induced myocardial infarction [54, 55].

5. *IN VITRO* EFFECTS OF CAPE ON CANCER CELLS: INSIGHTS

Like numerous other phenolic acids and polyphenols sourced from nature, CAPE possesses anti-inflammatory and chemopreventive potential. In breast cancer cell lines MCF-7, CAPE triggers apoptosis and cytotoxicity with an IC_{50} range of 6.6 ± 1.0 μM at 24 hours and 6.5 ± 2.9 μM at 48 hours [56]. Notably, this cell line has also reported a synergistic effect of CAPE with 5-FU [56].

In the context of docetaxel-resistant prostate cancer (PCa) cells derived from castration-resistant PCa subjects (CRPC), CAPE demonstrated the ability to suppress proliferation, survival, and tumor growth in PC/DX25 and DU/DX50 CRPC cell lines obtained from PC-3 and DU-145 human PCa cells, respectively [57]. CAPE's effect on PCa may involve the modulation of NF-κB through the mucosa-associated lymphoid tissue-1 gene (MALT-1). In androgen-receptor (AR) positive PCa cells, CAPE downregulates AR and MALT-1 while upregulating p53 [58]. Recent data also indicate that CAPE can block voltage-gated sodium channels, which are typically upregulated by cancer cells, in various cancer cell lines, including breast cancer MDA-MB-231 and MDA-MB-46B lines, colon SW620 cell lines, and non-small lung cell H460 lines [59].

Numerous reviews and reports have highlighted CAPE's anti-cancer properties [18, 60-62]. Furthermore, CAPE has been studied for its potential role in reducing the adverse effects associated with the use of chemopreventive agents, including chemotherapy [63-65].

CAPE's impact extends to the upregulation of metallothionein 2A expression in human bladder cancer, reducing endogenous ROS formation and oxidative stress, thereby mitigating tumor pro-inflammatory effects [66]. Additionally, recent research has reported CAPE's inhibitory effect on NF-κB and its involvement in regulating the NLRP3 inflammasome [67]. This ability of CAPE to inhibit an initial step of inflammation *via* NLRP3 suggests its potential synthesis from starting chemical molecules, paving the way for the development of new targeted compounds against cancer [68]. This presents an exciting challenge to harness the widely available propolis as a source of CAPE for cancer treatment.

The journey from plant pro-drugs to clinical therapy is ongoing, requiring continued efforts and exploration [68].

6. EFFECT OF CAPE AND PROPOLIS ON POST-CANCER ORAL MUCOSITIS

Oral mucositis often arises from chemotherapy in treating various cancer types, presenting patients with discomfort, pain, and disruptions in their normal nutrition, thus extending the recovery period. Unfortunately, effective treatments for this condition are currently lacking. However, there is promise in using propolis, a mixture of diverse components that includes phenolic compounds like flavonoids, hydroxycinnamic acids, and CAPE, which may synergistically enhance its therapeutic potential [69, 70].

A pilot randomized controlled trial yielded positive results when propolis was administered to patients at various stages of breast cancer chemotherapy, making it a viable complementary therapy option [69].

However, the efficacy of propolis in treating mucositis in patients undergoing radiation therapy for head and neck cancer appears to have mixed findings. One double-blind, randomized trial did not confirm its effectiveness [71]. In contrast, another study reported encouraging outcomes among patients receiving chemotherapy for head and neck cancer, with 65% experiencing complete healing and the researchers recommending propolis as a treatment for oral fungal infections [72].

A propolis-based mucoadhesive gel for oral irrigation in open-label trials demonstrated favorable results in oral cancer patients. Patients irrigated their oral cavities with the gel three times daily, starting the day before commencing radiation therapy and continuing for two weeks to prevent radiation-induced oral mucositis. As a result, 83% of patients did not develop mucositis [73].

The effects of honey, either alone or in combination with propolis, were studied in patients with acute lymphoblastic leukemia experiencing oral mucositis of grades 2 and 3. The study noted that honey led to faster healing [74].

However, a double-blind, randomized, placebo-controlled study investigating the use of propolis for severe oral mucositis in children undergoing chemotherapy yielded negative results. While the propolis group experienced a shorter duration and less severe mucositis, the differences were not statistically significant [75].

7. METHODS OF ANTICARCINOGENIC RESEARCH AND DOSAGE

Research on the antitumor activity of CAPE encompasses *in vitro* studies on cell cultures [38] and is complemented by a combination of *in vitro* and *in vivo* methodologies [17, 42]. *In vitro* investigations have unveiled the potent chemopreventive effects of caffeic acid and CAPE. For instance, in an experiment conducted with MCF-7 breast cancer cells, the inhibitory effects on migration were compared between caffeic acid and its phenethyl ether at 50 and 100 μM doses. Both polyphenols exhibited cytostatic effects and induced migration inhibition, but CAPE outperformed caffeic acid at an amount of 50 μM [5]. In another study involving breast cancer cells (MDA-MB-231), the effects of caffeic acid and CAPE were compared across quantities ranging from 10 to 100 μM. The findings indicated that CAPE displayed higher cytotoxic activity than caffeic acid and that the ester possessed stronger apoptotic effects, resulting in cell cycle arrest in the S phase [5].

8. TOXICITY

While there is limited available data regarding CAPE's low toxicity in animal models, it remains essential to conduct further research to assess its impact on the human organism thoroughly.

9. MECHANISM OF CAPE'S ACTIVITY

CAPE's diverse anticancer effects are believed to stem primarily from its potent antioxidant and anti-inflammatory properties. Polyphenols, such as CAPE, serve as effective scavengers of free radicals. In the literature, discussions revolve around the potential of CAPE to induce cell cycle withdrawal and inhibit growth in CRPC cells through the regulation of Skp2, p53, p21Cip1, and p27Kip1 [42]. Furthermore, CAPE has demonstrated dose-dependent and exposure time-dependent inhibition of the growth of MDA-MB-231 and Hs578T breast cancer cell lines [38]. Additionally, HIF-1α and NF-κB are considered alternative targets for CAPE, suggesting its promise as a therapeutic agent [39].

Shin *et al.* (2017) isolated CAPE from Cinnamomum cassia twigs, a well-regarded anticancer agent in traditional Chinese/Korean medicine. They proposed that CAPE contributed to *C. cassia's* chemopreventive and chemotherapeutic effects by downregulating c-Fos, a property not exhibited by caffeic acid [76].

Motawi *et al.* (2016) suggested CAPE's synergistic role in enhancing tamoxifen's potential in breast cancer treatment [44]. Table **1** summarizes the functions attributed to CAPE in recent years. Many reports have described caffeic acid as an essential cofactor in generating positive outcomes when combined with chemopreventive drugs for cancer therapy. The role of CAPE as an anti-tumoral molecule has been extensively reviewed, and it has been identified as an anti-tumoral agent, even in the absence of tamoxifen. However, concerns regarding its suitability as an ideal anticancer therapy persist [77].

The quest for novel chemotherapeutic drugs derived from the vast realm of plant biochemistry holds significant importance in pharmacology and medicine. It is important to acknowledge that plant-derived phenolic compounds are intricate, multifaceted, multitargeting, and potentially toxic substances, which animal cells may utilize as beneficial molecules through their complex stress response machinery. Intriguingly, the most encouraging results in this field originate from *in vitro* studies with cancer cell lines, which are simpler models than organisms (Table **1**). For clinical evidence of the anticancer effects of caffeic acid and CAPE see Table **2**.

Table 1. ***In vitro*** **and** ***ex vivo*** **anticancer effects of caffeic acid phenethyl ester.**

Experimental Model	Activities	Direction of Effect	Synergic Agent	Reference
Cell lines: breast (MDA-MB-231 and MDA-MB-468), colon (SW620), and non-small cell lung cancer (H460)	Anti-metastatic properties due to blocked voltage-gated sodium channel activity	↓	-	[59]
MCF-7 breast cancer cells	Synergistic cytotoxic effect of tamoxifen, protein levels of Bcl-2 and beclin-1, VEGF level, Angiogenesis	↑ ↓ ↓ ↓	Tamoxifen	[44]
MCF-7, MDA-MB-231, and SKBR3 breast cancer cells	Histone deacetylase, EGFR, in MDA-231 Her2+ protein in SKBR3	↓ ↓ ↓	Honeybee-produced propolis ingredients	[78]
MDA-MB-231 and Hs578T breast cancer cells	Cancer cell viability	↓	Potentiating the action of standard anti-cancer drugs	[38]
MCF-7 and MDA-231 breast cancer cells	Cancer cell cycle growth, apoptosis, angiogenesis, NF-κB, MDR-1 gene, VEGF formation	↓ ↑ ↓ ↓ ↓	-	[33]
Breast cancer stem cells (CSC) from MDA-231 cells	bCSC, Self-renewal progenitor formation, clonal growth, CD44 content	↓ ↓ ↓ ↓	-	[79]
Gastric cancer cell line on tissue culture plastic, laminin, and collagen I	Proliferation, angiogenesis, VEGF, metalloproteinase-9 (MMP-9), thrombospondin-1 (TSP-1)	↓ ↓ ↓ ↓ ↑	-	[80]
In vitro models; influence on expression and activities CYP1A1	3-MC-mediated CYP1A1 expression; AhR and HIF-1α induction	↓ ↓	-	[81]
Human oral cancer cells	Proliferation, survival, metastasis EGFR, COX-2 activity, PI3K-Akt signaling, Skp2	↓ ↓ ↓ ↓ ↓ ↓ ↓	Fluorouracil (*5-FU*)	[82]
Human prostate cancer cells	Cell growth, tumor growth, Akt signaling	↓ ↓ ↓	Chemotherapeutic agents	[43]
C6 glioma cells	Antineoplastic, proliferation, invasion, apoptosis, angiogenesis, the activity of catalase, MMP-2, Pro-MMP 2, MMP-9, Pro-MMP 9, expression of p53, ERK1/2, AKT, EGFR, PCNA	↑ ↓ ↓ ↑ ↓ ↓ ↓	Dasatinib	[83]

(Table 1) contd….

Experimental Model	Activities	Direction of Effect	Synergic Agent	Reference
Human colon cancer cell lines RKO and HC-T-116	Cell proliferation, motility, invasion, pathogenic mutation, apoptosis, autophagy	↓ ↓ ↓ ↓ ↑ ↑	Kaempferol	[84]
Oral squamous cell carcinoma (OSCC)	Cell proliferation, invasion, cell growth, the activity of mitogen-activated protein kinase (MAPK), expression of N-myc downstream-regulated gene (NDRG1)	↓ ↓ ↓ ↑ ↑	-	[85]
Human head and neck squamous carcinoma cells (HNSCC) line (Detroit 562)	Cell viability, apoptosis, cell cycle growth, proliferation	↓ ↑ ↓	Chemotherapeutics	[86]
Breast cancer MDA-MB-231 cells	Cell proliferation, migration, and NO production, apoptosis, autophagy, TLR4 signaling pathway	↓ ↑ ↓	Honeybee-produced propolis ingredients	[87]
Breast cancer MCF-7 cells, PC-3 prostate cancer cells	Cell growth apoptosis,	↓ ↑	-	[88]
MCF-7 breast cancer cells	Cell migration	↓	-	[89]
Triple-negative human caucasian breast adenocarcinoma line cells (MDA-MB-231)	Apoptosis, cell cycle arrest	↑ ↑	-	[5]
Human nasopharyngeal cancer cells	Proliferation, invasion, NDRG1 expression *via* MAPK pathway; phosphorylation of STAT3	↓ ↓ ↑ ↓	-	[90]
Nasopharyngeal carcinoma cells	Cell proliferation, viability, apoptosis, expression of Bcl-XL, irradiation sensitivity of NPC cells synergistic with chemotherapy	↓ ↓ ↓ ↓ ↑	Radiotherapy, chemotherapy	[91]
Ovarian cancer SKOV-3 cells	Viability, migration, invasion, apoptosis, Ki67, PCNA expression, nuclear factor kappa b (NF-κB) pathway	↓ ↑ ↓ ↓	-	[92]
MDA-MB-231 (estrogen receptor-negative), T47D (estrogen receptor-positive) breast cancer cell lines	Cell viability, surviving, radiation-induced DNA damage	↓ ↓ ↑	Radiation sensitivity	[93]
Triple-negative breast cancers (TNBC)	Anti-tumor immunity TGFβ, HGF, EGFR	↑ ↑	-	[94]
Cholangiocarcinoma (CCH) Mz-ChA-1 cells	Cell growth, cell cycle arrest, NF-κB DNA-binding activity, Apoptosis, tumor latency, expression of NF-κB1	↓ ↑ ↓ ↑ ↑ ↓	-	[95]

(Table 1) contd….

Experimental Model	Activities	Direction of Effect	Synergic Agent	Reference
MDA MB-231, N2a, and COLO 320 cell lines	Proliferation, growth, viability, apoptosis	↓ ↓ ↑	-	[96, 97]
Breast cancer cells	Anti-metastasis, mortalin and other key regulators of cell migration, growth arrest, DNA damage signaling	↑ ↓ ↑ ↑	γ- cyclodextrin (γCD)	[98]
SW-480 cancerous cells, CT-26 mouse colon cancer cells	Cell motility, invasion, level of matrix metalloproteinases MMP-2, MMP-9, count of pulmonary nodules	↓ ↓ ↓	-	[99]
Human cancer cells: SKOV3 (ovarian carcinoma), HT1080 (fibrosarcoma), A549 (lung carcinoma), HeLa (cervical carcinoma), U2OS (osteosarcoma), MCF7 and MDA-MB-231 (breast adenocarcinoma; ER-positive and triple-negative, respectively), and IMR32 (neuroblastoma) cells	Cell growth arrest, colony-forming, cell viability, mortalin, p53 tumor suppressor protein; activity for CAPE found only in complex with γ-cyclodextrin	↑ ↓ ↓ ↑	γ-cyclodextrin	[100]

The dual nature of phenolic compounds from plants is well-established. CAPE, in particular, demonstrates a Janus-like behavior as it has been shown to both increase and inhibit vascular endothelial growth factor (VEGF) levels within the tumor microenvironment [44, 80].

Motawi *et al.* (2016) proposed that phenolic acids, plant polyphenols, and other phytochemicals collectively exhibit a common pattern of actions on cancer cells. These actions encompass inhibiting cell growth, inducing cytotoxicity at micromolar concentrations, promoting pro-apoptotic effects, inhibiting NF-κB and other pro-inflammatory pathways, displaying anti-angiogenic activity, and modulating cell cycle progression, among others [44].

Furthermore, in addition to their renowned role in mitigating oxidative stress, phenolic compounds found in phytoestrogens and edible plants, such as honeybee propolis, possess complex mechanisms influencing cell survival. Sometimes, these mechanisms lead to adverse effects, reminding researchers to exercise caution when considering these substances *in vivo*. Evaluating their role in the context of food, rather than as purified or synthetic alternatives, is advisable. Phytochemicals interact with multiple signaling molecules, some of which have seemingly opposing effects, making the cellular machinery more intricate.

The multifaceted interactions of a seemingly simple molecule like CAPE are evident. Motawi *et al.*'s (2016) study demonstrated that CAPE inhibits bcl-2 and beclin-1 proteins [44]. It is well-recognized that bcl-2 anti-apoptotic proteins suppress beclin-1-dependent autophagy, with apoptosis and autophagy being tightly regulated processes in tissue homeostasis and cancer development [101]. Consequently, inhibiting bcl-2 anti-apoptotic proteins can increase beclin-1-mediated autophagy, promoting breast cancer cell survival and tumor growth. This inhibition of autophagy takes on added significance when considering its role in cancer stem cells (CSCs) [102, 103].

Moreover, research indicates that the ubiquitin-proteasome system can impact cancer cell cytotoxicity independently of beclin-1-mediated macroautophagy, suggesting a synergistic mechanism [104]. CAPE has been found to downregulate proteasome subunit alpha 4, exerting anti-cancer effects in colorectal cancer SW480 cells [105]. These findings underscore the pleiotropic nature of plant phenolic substances.

This complexity demonstrates that the efficacy of a specific phenolic compound relies on its simultaneous targeting of multiple signaling pathways in a short time frame. Acting on Bcl-2, beclin-1, or the ubiquitin-proteasome system alone may not be adequate to halt tumor cell growth and induce cell cycle arrest, especially in the MCF-7 breast cancer cell line. For instance, proteasome inhibition by MG132 led to G1/S arrest in normal mammary cells (MCF10A) but G2/M arrest in breast cancer cells (MCF7) [106]. Interestingly, when the proteasome inhibitor was removed, MCF7

Table 2. Some reports on the clinical evidence of anticancer effects of caffeic acid and caffeic acid phenethyl ester.

Clinical Protocol	Activities	Patients Study	Expected Outcomes/Results	Reference
Clinical trial NCT04648917	Caffeic acid as inhibitor of GASC1 in squamous esophageal cell cancer	80 (40+40) May 1 2022	Primary End Point: overall survival (OS)	Protocol
Clinical trial NCT030070262	Caffeic acid in esophagus cancer	300 Dec 2021	Primary End Point: overall survival (OS)	Protocol
Clinical trial NCT02744703	CAPE as metalloproteinase inhibitor	10 May 2015	Determination of structural integrity of hybrid layer in forty restorations on 10 patients using scanning electron microscopy after application of different adhesive strategies and a matrix metalloproteinase inhibitor.	Protocol
Randomized, double-blind, placebo-controlled clinical trial	Propolis with chemotherapy on breast cancer	60	Increase in energy intake and QoL	[38]
Randomized, double-blind, placebo-controlled clinical trial	Propolis and artepillin-C in colon cancer	31 (15+16)	Propolis may have detrimental side effects on muscle tissue, including myocardial cells.	[33]

cells regained their proliferative ability, which was then inhibited by an autophagy inhibitor. These findings highlight the crucial role of the GSK-3β signaling pathway in this process [106].

This discussion covers only one facet of the intricate network of interactions that CAPE engages in within cancer cells. Other phenolic or polyphenolic substances in the source further complicate this interactome. Consuming a variety of phenol-bearing or flavone-bearing molecules from plants in food may lead to interactions with diverse signaling pathways that also affect normal cells.

Propolis, as a source of phenolic compounds, adds to the complexity. It contains coumaric acid derivatives, such as 3,5-diphenyl-p-coumaric acid (artepillin C), which can induce DNA damage and high micronucleus frequencies comparable to methyl methanesulfonate (MMS) in Chinese hamster lung fibroblasts [107]. Additionally, phenolic acids in propolis, including caffeic, ferulic, and cinnamic acids, exhibit significant clastogenic effects but are not genotoxic in hepatoma cells [108]. The flavonoid pinocembrin has been identified as a potential reversal agent in multidrug resistance (MDR) by inhibiting the breast cancer resistance protein (BCRP/ABCG2) [109]. However, pinocembrin's anti-apoptotic effects have also been reported, particularly in SH-SY5Y neuroblastoma cells, where it downregulates p53 expression, decreases the Bax/Bcl2 ratio, and inhibits the release of cytochrome C from mitochondria [110]. This complexity challenges our understanding of propolis-derived phenolics and may explain why some randomized placebo-controlled studies have yielded mixed results [53]. Previous reports have highlighted the efficacy of CAPE but not propolis in tumor prevention [111].

10. CLINICAL EVIDENCE OF CAPE IN CANCER TREATMENT

Clinical evidence regarding the use of CAPE in cancer treatment remains limited, as depicted in Table **2**. A few papers have delved into clinical trials involving CAPE, with some recent protocols and completed studies emerging. It is worth noting that caffeic acid (non-CAPE) has undergone randomized controlled trials against placebos in esophagus cancer and squamous cell esophageal cancer, yielding modest success. However, it is important to recognize that the broader adoption of propolis in cancer treatment is primarily associated with folk and integrative medicine [53, 112]. Further studies and in-depth insights are imperative to establish a more concrete role for CAPE in cancer treatment.

CONCLUSION

Numerous studies have illuminated CAPE's extensive repertoire of antitumor effects across various cancer cell lines. These effects include cell growth arrest, proliferation inhibition, apoptosis induction, invasion impediment, and suppression of angiogenesis. Mechanistically, CAPE's actions are closely tied to the inhibition of NF-kappaB, activation of MAPK family proteins (including p38-regulated Bax proteins and JNK), and modulation of p53, p65, and caspase-3.

However, despite the promising outcomes observed at the molecular level, bridging the gap between laboratory investigations and clinical applications remains a critical challenge. Future research endeavors must encompass both animal studies and *in vitro* experiments to facilitate the translation of CAPE's potential into tangible medical benefits for diverse forms of cancer in human patients. Furthermore, thorough preclinical toxicity assessments should precede clinical trials to ascertain the safety and efficacy of CAPE.

The current body of evidence underscores CAPE as a versatile compound with many potential benefits. This phenolic acid ester exhibits promise as an antimicrobial, antioxidant, antiviral, anti-inflammatory, cytotoxic, and even anti-carcinogenic agent. CAPE's remarkable potential primarily hinges on its antioxidant properties, attributed to a flavone-like ring within its chemical structure.

LIST OF ABBREVIATIONS

ROS	=	Reactive Oxygen Species
CAPE	=	Caffeic Acid Phenethyl Ester
WOS	=	Web of Science
PCA	=	Prostate Cancer
AR	=	Androgen-Receptor
CSC	=	Cancer Stem Cells

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

Massimiliano Peana is the Co Editor of the journal Current Medicinal Chemistry.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Durazzo, A.; Lucarini, M.; Souto, E.B.; Cicala, C.; Caiazzo, E.; Izzo, A.A.; Novellino, E.; Santini, A. Polyphenols: A concise overview on the chemistry, occurrence, and human health. *Phytother. Res.,* **2019**, *33*(9), 2221-2243. http://dx.doi.org/10.1002/ptr.6419 PMID: 31359516

[2] Majidinia, M.; Bishayee, A.; Yousefi, B. Polyphenols: Major regulators of key components of DNA damage response in cancer. *DNA Repair (Amst.),* **2019**, *82*, 102679. http://dx.doi.org/10.1016/j.dnarep.2019.102679 PMID: 31450085

[3] Bułdak, R.J.; Hejmo, T.; Osowski, M.; Bułdak, Ł.; Kukla, M.; Polaniak, R.; Birkner, E. The impact of coffee and its selected bioactive compounds on the development and progression of colorectal cancer *in vivo* and *in vitro*. *Molecules,* **2018**, *23*(12), 3309. http://dx.doi.org/10.3390/molecules23123309 PMID: 30551667

[4] Espíndola, K.M.M.; Ferreira, R.G.; Narvaez, L.E.M.; Silva Rosario, A.C.R.; da Silva, A.H.M.; Silva, A.G.B.; Vieira, A.P.O.; Monteiro, M.C. Chemical and pharmacological aspects of caffeic acid and its activity in hepatocarcinoma. *Front. Oncol.,* **2019**, *9*, 541. http://dx.doi.org/10.3389/fonc.2019.00541 PMID: 31293975

[5] Kabała-Dzik, A.; Rzepecka-Stojko, A.; Kubina, R.; Jastrzębska-Stojko, Ż.; Stojko, R.; Wojtyczka, R.; Stojko, J. Comparison of two components of propolis: Caffeic acid (CA) and caffeic acid phenethyl ester (CAPE) induce apoptosis and cell cycle arrest of breast cancer cells MDA-MB-231. *Molecules,* **2017**, *22*(9), 1554. http://dx.doi.org/10.3390/molecules22091554 PMID: 28926932

[6] Kuo, C.C.; Wang, R.H.; Wang, H.H.; Li, C.H. Meta-analysis of randomized controlled trials of the efficacy of propolis mouthwash in cancer therapy-induced oral mucositis. *Support. Care Cancer,* **2018**, *26*(12), 4001-4009. http://dx.doi.org/10.1007/s00520-018-4344-5 PMID: 30022350

[7] Waheed, M.; Hussain, M.B.; Javed, A.; Mushtaq, Z.; Hassan, S.; Shariati, M.A.; Khan, M.U.; Majeed, M.; Nigam, M.; Mishra, A.P.; Heydari, M. Honey and cancer: A mechanistic review. *Clin. Nutr.,* **2019**, *38*(6), 2499-2503. http://dx.doi.org/10.1016/j.clnu.2018.12.019 PMID: 30639116

[8] Zabaiou, N.; Fouache, A.; Trousson, A.; Baron, S.; Zellagui, A.; Lahouel, M.; Lobaccaro, J.A. Biological properties of propolis extracts: Something new from an ancient product. *Chem Phys Lipids.,* **2017**, *207*(Pt B), 214-222. http://dx.doi.org/10.1016/j.chemphyslip.2017.04.005

[9] Alam, M.; Ahmed, S.; Elasbali, A.M.; Adnan, M.; Alam, S.; Hassan, M.I.; Pasupuleti, V.R. Therapeutic implications of caffeic acid in cancer and neurological diseases. *Front. Oncol.,* **2022**, *12*, 860508. http://dx.doi.org/10.3389/fonc.2022.860508 PMID: 35359383

[10] Mirzaei, S.; Gholami, M.H.; Zabolian, A.; Saleki, H.; Farahani, M.V.; Hamzehlou, S.; Far, F.B.; Sharifzadeh, S.O.; Samarghandian, S.; Khan, H.; Aref, A.R.; Ashrafizadeh, M.; Zarrabi, A.; Sethi, G. Caffeic acid and its derivatives as potential modulators of oncogenic molecular pathways: New hope in the fight against cancer. *Pharmacol. Res.,* **2021**, *171*, 105759. http://dx.doi.org/10.1016/j.phrs.2021.105759 PMID: 34245864

[11] Stohs, S.J. Safety and efficacy of shilajit (mumie, moomiyo). *Phytother. Res.,* **2014**, *28*(4), 475-479. http://dx.doi.org/10.1002/ptr.5018 PMID: 23733436

[12] Boisard, S.; Shahali, Y.; Aumond, M.C.; Derbré, S.; Blanchard, P.; Dadar, M.; Le Ray, A.M.; Richomme, P. Anti-AGE activity of poplar-type propolis: Mechanism of action of main phenolic compounds. *Int. J. Food Sci. Technol.,* **2019**. http://dx.doi.org/10.1111/ijfs.14284

[13] Mainasara, M.M.; Abu Bakar, M.F.; C Linatoc, A.A. Malaysian medicinal plants' potential for breast cancer

therapy. *Asian J. Pharm. Clin. Res.,* **2018**, *11*(6), 101-117. http://dx.doi.org/10.22159/ajpcr.2018.v11i6.24322

[14] Bjørklund, G.; Dadar, M.; Chirumbolo, S.; Lysiuk, R. Flavonoids as detoxifying and pro-survival agents: What's new? *Food Chem. Toxicol.,* **2017**, *110*, 240-250. http://dx.doi.org/10.1016/j.fct.2017.10.039 PMID: 29079495

[15] Chirumbolo, S.; Bjørklund, G.; Lysiuk, R.; Vella, A.; Lenchyk, L.; Upyr, T. Targeting cancer with phytochemicals *via* their fine tuning of the cell survival signaling pathways. *Int. J. Mol. Sci.,* **2018**, *19*(11), 3568. http://dx.doi.org/10.3390/ijms19113568 PMID: 30424557

[16] Lysiuk, R.; Hudz, N. Differential spectrophotometry: Application for quantification of flavonoids in herbal drugs and nutraceuticals. *Int. J Trends. Food Nutr. (Roma),* **2017**, *1*, e102.

[17] Tolba, M.F.; Azab, S.S.; Khalifa, A.E.; Abdel-Rahman, S.Z.; Abdel-Naim, A.B. Caffeic acid phenethyl ester, a promising component of propolis with a plethora of biological activities: A review on its anti-inflammatory, neuroprotective, hepatoprotective, and cardioprotective effects. *IUBMB Life,* **2013**, *65*(8), 699-709. http://dx.doi.org/10.1002/iub.1189 PMID: 23847089

[18] Akyol, S.; Ozturk, G.; Ginis, Z.; Armutcu, F.; Yigitoglu, M.R.; Akyol, O. *In vivo* and *in vitro* antıneoplastic actions of caffeic acid phenethyl ester (CAPE): Therapeutic perspectives. *Nutr. Cancer,* **2013**, *65*(4), 515-526. http://dx.doi.org/10.1080/01635581.2013.776693 PMID: 23659443

[19] Murtaza, G.; Karim, S.; Akram, M.R.; Khan, S.A.; Azhar, S.; Mumtaz, A.; Bin Asad, M.H.H.; Hassan, M.H. Caffeic acid phenethyl ester and therapeutic potentials. *BioMed Res. Int.,* **2014**, *2014*, 1-9. http://dx.doi.org/10.1155/2014/145342 PMID: 24971312

[20] Murtaza, G.; Sajjad, A.; Mehmood, Z.; Shah, S.H.; Siddiqi, A.R. Possible molecular targets for therapeutic applications of caffeic acid phenethyl ester in inflammation and cancer. *J. Food Drug Anal.,* **2015**, *23*(1), 11-18. http://dx.doi.org/10.1016/j.jfda.2014.06.001 PMID: 28911433

[21] Naveed, M.; Hejazi, V.; Abbas, M.; Kamboh, A.A.; Khan, G.J.; Shumzaid, M.; Ahmad, F.; Babazadeh, D.; FangFang, X.; Modarresi-Ghazani, F.; WenHua, L.; XiaoHui, Z. Chlorogenic acid (CGA): A pharmacological review and call for further research. *Biomed. Pharmacother.,* **2018**, *97*, 67-74. http://dx.doi.org/10.1016/j.biopha.2017.10.064 PMID: 29080460

[22] Koshovyi, O.; Zagayko, A.; Kolychev, I.; Akhmedov, E.Y.; Komissarenko, A. Phytochemical study of the dry extract from bilberry leaves. *Azerbaijan Pharm. Pharmacother. J.,* **2016**, *1*, 18-23.

[23] Shinkovenko, I.L.; Kashpur, N.V.; Ilyina, T.V.; Kovalyova, A.M.; Goryacha, O.V.; Koshovyi, O.M.; Toryanyk, E.L.; Kryvoruchko, O.V. The immunomodulatory activity of the extracts and complexes of biologically active compounds of *Galium verum* L. herb. *Ceska Slov. Farm.,* **2018**, *67*(1), 25-29. PMID: 30157664

[24] Jiang, Y.; Lin, Y.; Hu, Y.J.; Song, X.J.; Pan, H.H.; Zhang, H.J. Caffeoylquinic acid derivatives rich extract from *Gnaphalium pensylvanicum* willd. Ameliorates hyperuricemia and acute gouty arthritis in animal model. *BMC Complement. Altern. Med.,* **2017**, *17*(1), 320. http://dx.doi.org/10.1186/s12906-017-1834-9 PMID: 28623927

[25] Lee, Y.J.; Jang, Y.N.; Han, Y.M.; Kim, H.M.; Jeong, J.M.; Son, M.J.; Jin, C.B.; Kim, H.J.; Seo, H.S. Caffeoylquinic acid-rich extract of Aster glehni F. Schmidt ameliorates nonalcoholic fatty liver through the regulation of PPARdelta and adiponectin in ApoE KO mice. *PPAR Res.,* **2017**, *2017*, 1-19. http://dx.doi.org/10.1155/2017/3912567 PMID: 29201040

[26] Lenchyk, L.; Ovezgeldiyev, D.; Upyr, D. Phytochemical investigation of bird cherry fruits. *Pharm. Lett.,* **2016**, *8*(6), 73-76.

[27] Lenchyk, L.V.; Saidov, N.B. Investigation of phenolic compounds in cherry leaves extract. *Res. J. Pharm. and Tech.,* **2017**, *10*(12), 4402-4406. http://dx.doi.org/10.5958/0974-360X.2017.00811.3

[28] Morton, L.W.; Caccetta, R.A-A.; Puddey, I.B.; Croft, K.D. Chemistry and biological effects of dietary phenolic compounds: Relevance to cardiovascular disease. *Clin. Exp. Pharmacol. Physiol.,* **2000**, *27*(3), 152-159. http://dx.doi.org/10.1046/j.1440-1681.2000.03214.x PMID: 10744340

[29] Kanimozhi, G.; Prasad, N.R. *Coffee in Health and Disease Prevention*; Vr, P., Ed.; Academic Press: Amsterdam, **2015**, pp. 655-661. http://dx.doi.org/10.1016/B978-0-12-409517-5.00073-5

[30] Popova, M.; Reyes, M.; Le Conte, Y.; Bankova, V. Propolis chemical composition and honeybee resistance against *Varroa destructor*. *Nat. Prod. Res.,* **2014**, *28*(11), 788-794. http://dx.doi.org/10.1080/14786419.2014.881366 PMID: 24483289

[31] Bankova, V.; Trusheva, B.; Popova, M. Caffeic acid phenethyl ester (CAPE)-natural sources, analytical procedures and synthetic approaches. *Dokl. Bulg. Akad. Nauk.,* **2018**, *71*(9), 1157-1169. http://dx.doi.org/10.7546/CRABS.2018.09.01

[32] Kečkeš, S.; Gašić, U.; Veličković, T.Ć.; Milojković-Opsenica, D.; Natić, M.; Tešić, Ž. The determination of phenolic profiles of Serbian unifloral honeys using ultra-high-performance liquid chromatography/high resolution accurate mass spectrometry. *Food Chem.,* **2013**, *138*(1), 32-40. http://dx.doi.org/10.1016/j.foodchem.2012.10.025 PMID: 23265452

[33] Wu, J.; Omene, C.; Karkoszka, J.; Bosland, M.; Eckard, J.; Klein, C.B.; Frenkel, K. Caffeic acid phenethyl ester (CAPE), derived from a honeybee product propolis, exhibits a diversity of anti-tumor effects in pre-clinical models of human breast cancer. *Cancer Lett.,* **2011**, *308*(1), 43-53. http://dx.doi.org/10.1016/j.canlet.2011.04.012 PMID: 21570765

[34] Chen, H.C.; Chen, J.H.; Chang, C.; Shieh, C.J. Optimization of ultrasound-accelerated synthesis of enzymatic caffeic acid phenethyl ester by response surface methodology. *Ultrason. Sonochem.,* **2011**, *18*(1), 455-459. http://dx.doi.org/10.1016/j.ultsonch.2010.07.018 PMID: 20797894

[35] Kim, H.; Park, C. Enzymatic synthesis of phenethyl ester from phenethyl alcohol with acyl donors. *Enzyme Microb. Technol.,* **2017**, *100*, 37-44. http://dx.doi.org/10.1016/j.enzmictec.2017.02.004 PMID: 28284310

[36] Wang, X.; Pang, J.; Maffucci, J.A.; Pade, D.S.; Newman, R.A.; Kerwin, S.M.; Bowman, P.D.; Stavchansky, S. Pharmacokinetics of caffeic acid phenethyl ester and its cate-

chol-ring fluorinated derivative following intravenous administration to rats. *Biopharm. Drug Dispos.,* **2009**, *30*(5), 221-228. http://dx.doi.org/10.1002/bdd.657 PMID: 19544289

[37] Kleczka, A.; Kubina, R.; Dzik, R.; Jasik, K.; Stojko, J.; Cholewa, K.; Kabała-Dzik, A. Caffeic acid phenethyl ester (CAPE) induced apoptosis in serous ovarian cancer OV7 cells by deregulation of BCL2/BAX genes. *Molecules,* **2020**, *25*(15), 3514. http://dx.doi.org/10.3390/molecules25153514 PMID: 32752091

[38] Rzepecka-Stojko, A.; Kabała-Dzik, A.; Moździerz, A.; Kubina, R.; Wojtyczka, R.; Stojko, R.; Dziedzic, A.; Jastrzębska-Stojko, Ż.; Jurzak, M.; Buszman, E.; Stojko, J. Caffeic acid phenethyl ester and ethanol extract of propolis induce the complementary cytotoxic effect on triple-negative breast cancer cell lines. *Molecules,* **2015**, *20*(5), 9242-9262. http://dx.doi.org/10.3390/molecules20059242 PMID: 26007182

[39] Cheng, C.C.; Chi, P.L.; Shen, M.C.; Shu, C.W.; Wann, S.R.; Liu, C.P.; Tseng, C.J.; Huang, W.C. Caffeic acid phenethyl ester rescues pulmonary arterial hypertension through the inhibition of AKT/ERK-dependent PDGF/HIF-1α *in vitro* and *in vivo*. *Int. J. Mol. Sci.,* **2019**, *20*(6), 1468. http://dx.doi.org/10.3390/ijms20061468 PMID: 30909527

[40] Yordanov, Y. Caffeic acid phenethyl ester (CAPE): Pharmacodynamics and potential for therapeutic application. *Pharmacia,* **2019**, *66*(3), 107-114. http://dx.doi.org/10.3897/pharmacia.66.e38573

[41] Shen, H.; Yamashita, A.; Nakakoshi, M.; Yokoe, H.; Sudo, M.; Kasai, H.; Tanaka, T.; Fujimoto, Y.; Ikeda, M.; Kato, N.; Sakamoto, N.; Shindo, H.; Maekawa, S.; Enomoto, N.; Tsubuki, M.; Moriishi, K. Inhibitory effects of caffeic acid phenethyl ester derivatives on replication of hepatitis C virus. *PLoS One,* **2013**, *8*(12), e82299. http://dx.doi.org/10.1371/journal.pone.0082299 PMID: 24358168

[42] Lin, H.P.; Lin, C.Y.; Huo, C.; Hsiao, P.H.; Su, L.C.; Jiang, S.S.; Chan, T.M.; Chang, C.H.; Chen, L.T.; Kung, H.J.; Wang, H.D.; Chuu, C.P. Caffeic acid phenethyl ester induced cell cycle arrest and growth inhibition in androgen-independent prostate cancer cells *via* regulation of Skp2, p53, p21Cip1 and p27Kip1. *Oncotarget,* **2015**, *6*(9), 6684-6707. http://dx.doi.org/10.18632/oncotarget.3246 PMID: 25788262

[43] Lin, H.P.; Lin, C.Y.; Liu, C.C.; Su, L.C.; Huo, C.; Kuo, Y.Y.; Tseng, J.C.; Hsu, J.M.; Chen, C.K.; Chuu, C.P. Caffeic acid phenethyl ester as a potential treatment for advanced prostate cancer targeting akt signaling. *Int. J. Mol. Sci.,* **2013**, *14*(3), 5264-5283. http://dx.doi.org/10.3390/ijms14035264 PMID: 23466879

[44] Motawi, T.K.; Abdelazim, S.A.; Darwish, H.A.; Elbaz, E.M.; Shouman, S.A. Could caffeic acid phenethyl ester expand the antitumor effect of tamoxifen in breast carcinoma? *Nutr. Cancer,* **2016**, *68*(3), 435-445. http://dx.doi.org/10.1080/01635581.2016.1153669 PMID: 27007181

[45] D'Almeida, R.E.; Alberto, M.R.; Quispe, C.; Schmeda-Hirschmann, G.; Isla, M.I. Antimicrobial phenylpropanoids from the Argentinean highland plant *Parastrephia lucida* (Meyen) Cabrera. *J. Ethnopharmacol.,* **2012**, *142*(2), 407-414. http://dx.doi.org/10.1016/j.jep.2012.05.010 PMID: 22735664

[46] Jung, W.K.; Lee, D.Y.; Kim, J.H.; Choi, I.; Park, S.G.; Seo, S.K.; Lee, S.W.; Lee, C.M.; Park, Y.M.; Jeon, Y.J.; Lee, C.H.; Jeon, B-T.; Qian, Z-J.; Kim, S-K.; Choi, I-W. Anti-inflammatory activity of caffeic acid phenethyl ester (CAPE) extracted from *Rhodiola sacra* against lipopolysaccharide-induced inflammatory responses in mice. *Process Biochem.,* **2008**, *43*(7), 783-787. http://dx.doi.org/10.1016/j.procbio.2008.03.004

[47] Russo, A.; Longo, R.; Vanella, A. Antioxidant activity of propolis: Role of caffeic acid phenethyl ester and galangin. *Fitoterapia,* **2002**, *73*(Suppl. 1), S21-S29. http://dx.doi.org/10.1016/S0367-326X(02)00187-9 PMID: 12495706

[48] Iraz, M.; Ozerol, E.; Gulec, M.; Tasdemir, S.; Idiz, N.; Fadillioglu, E.; Naziroglu, M.; Akyol, O. Protective effect of caffeic acid phenethyl ester (CAPE) administration on cisplatin-induced oxidative damage to liver in rat. *Cell Biochem. Funct.,* **2006**, *24*(4), 357-361. http://dx.doi.org/10.1002/cbf.1232 PMID: 16437419

[49] Nur, G.; Husunet, M.; Guler, I.; Deveci, A.; Koc, E.; Nur, O.; Kilicle, P. The effect of caffeic acid phenethyl ester (CAPE) on hepatic histopathology and oxidative stress in rats treated with malathion. *Med. Sci. (Turkey),* **2018**, *7*(0), 604-609. http://dx.doi.org/10.5455/medscience.2018.07.8833

[50] Reuter, S.; Gupta, S.C.; Chaturvedi, M.M.; Aggarwal, B.B. Oxidative stress, inflammation, and cancer: How are they linked? *Free Radic. Biol. Med.,* **2010**, *49*(11), 1603-1616. http://dx.doi.org/10.1016/j.freeradbiomed.2010.09.006 PMID: 20840865

[51] Bilikova, K.; Popova, M.; Trusheva, B.; Bankova, V. New anti-Paenibacillus larvae substances purified from propolis. *Apidologie (Celle),* **2013**, *44*(3), 278-285. http://dx.doi.org/10.1007/s13592-012-0178-1

[52] Koo, H.J.; Lee, K.R.; Kim, H.S.; Lee, B.M. Detoxification effects of aloe polysaccharide and propolis on the urinary excretion of metabolites in smokers. *Food Chem. Toxicol.,* **2019**, *130*, 99-108. http://dx.doi.org/10.1016/j.fct.2019.05.029 PMID: 31112706

[53] Ishikawa, H.; Goto, M.; Matsuura, N.; Murakami, Y.; Goto, C.; Sakai, T.; Kanazawa, K. A pilot, randomized, placebo-controlled, double-blind phase 0/biomarker study on effect of artepillin C-rich extract of Brazilian propolis in frequent colorectal adenoma polyp patients. *J. Am. Coll. Nutr.,* **2012**, *31*(5), 327-337. http://dx.doi.org/10.1080/07315724.2012.10720434 PMID: 23529990

[54] Altuğ, M.E.; Serarslan, Y.; Bal, R.; Kontaş, T.; Ekici, F.; Melek, I.M.; Aslan, H.; Duman, T. Caffeic acid phenethyl ester protects rabbit brains against permanent focal ischemia by antioxidant action: A biochemical and planimetric study. *Brain Res.,* **2008**, *1201*, 135-142. http://dx.doi.org/10.1016/j.brainres.2008.01.053 PMID: 18308295

[55] Ozer, M.K.; Parlakpinar, H.; Acet, A. Reduction of ischemia–reperfusion induced myocardial infarct size in rats by caffeic acid phenethyl ester (CAPE). *Clin. Biochem.,* **2004**, *37*(8), 702-705. http://dx.doi.org/10.1016/j.clinbiochem.2004.01.012 PMID: 15302615

[56] Amalia, E.; Diantini, A.; Endang Prabandari, E.; Waluyo, D.; Subarnas, A. Caffeic acid phenethyl ester as a DHODH

inhibitor and its synergistic anticancer properties in combination with 5-fluorouracil in a breast cancer cell line. *J. Exp. Pharmacol.,* **2022**, *14*, 243-253. http://dx.doi.org/10.2147/JEP.S365159 PMID: 35910085

[57] Fu, Y.K.; Wang, B.J.; Tseng, J.C.; Huang, S.H.; Lin, C.Y.; Kuo, Y.Y.; Hour, T.C.; Chuu, C.P. Combination treatment of docetaxel with caffeic acid phenethyl ester suppresses the survival and the proliferation of docetaxel-resistant prostate cancer cells *via* induction of apoptosis and metabolism interference. *J. Biomed. Sci.,* **2022**, *29*(1), 16. http://dx.doi.org/10.1186/s12929-022-00797-z PMID: 35197069

[58] Chang, K.S.; Tsui, K.H.; Hsu, S.Y.; Sung, H.C.; Lin, Y.H.; Hou, C.P.; Yang, P.S.; Chen, C.L.; Feng, T.H.; Juang, H.H. The antitumor effect of caffeic acid phenethyl ester by downregulating mucosa-associated lymphoid tissue 1 *via* ar/p53/nf-kappab signaling in prostate carcinoma cells. *Cancers (Basel),* **2022**, *14*(2), 274. http://dx.doi.org/10.3390/cancers14020274 PMID: 35053438

[59] Fraser, S.P.; Hemsley, F.; Djamgoz, M.B.A. Caffeic acid phenethyl ester: Inhibition of metastatic cell behaviours *via* voltage-gated sodium channel in human breast cancer *in vitro*. *Int. J. Biochem. Cell Biol.,* **2016**, *71*, 111-118. http://dx.doi.org/10.1016/j.biocel.2015.12.012 PMID: 26724521

[60] Demestre, M.; Messerli, S.M.; Celli, N.; Shahhossini, M.; Kluwe, L.; Mautner, V.; Maruta, H. CAPE (caffeic acid phenethyl ester)-based propolis extract (Bio 30) suppresses the growth of human neurofibromatosis (NF) tumor xenografts in mice. *Phytother. Res.,* **2009**, *23*(2), 226-230. http://dx.doi.org/10.1002/ptr.2594 PMID: 18726924

[61] Ozturk, G.; Ginis, Z.; Akyol, S.; Erden, G.; Gurel, A.; Akyol, O. The anticancer mechanism of caffeic acid phenethyl ester (CAPE): Review of melanomas, lung and prostate cancers. *Eur. Rev. Med. Pharmacol. Sci.,* **2012**, *16*(15), 2064-2068. PMID: 23280020

[62] Jiang, X.; Xie, H.; Li, C.; You, M.; Zheng, Y.; Li, G.Q.; Chen, X.; Zhang, C.; Hu, F. Chinese propolis inhibits the proliferation of human gastric cancer cells by inducing apoptosis and cell cycle arrest. *Evid. Based Complement. Alternat. Med.,* **2020**, *2020*, 1-11. http://dx.doi.org/10.1155/2020/2743058 PMID: 32774408

[63] Akyol, S.; Ginis, Z.; Armutcu, F.; Ozturk, G.; Yigitoglu, M.R.; Akyol, O. The potential usage of caffeic acid phenethyl ester (CAPE) against chemotherapy-induced and radiotherapy-induced toxicity. *Cell Biochem. Funct.,* **2012**, *30*(5), 438-443. http://dx.doi.org/10.1002/cbf.2817 PMID: 22431158

[64] Cauli, O. Oxidative stress and cognitive alterations induced by cancer chemotherapy drugs: A scoping review. *Antioxidants,* **2021**, *10*(7), 1116. http://dx.doi.org/10.3390/antiox10071116 PMID: 34356349

[65] Luo, C.; Xu, X.; Wei, X.; Feng, W.; Huang, H.; Liu, H.; Xu, R.; Lin, J.; Han, L.; Zhang, D. Natural medicines for the treatment of fatigue: Bioactive components, pharmacology, and mechanisms. *Pharmacol. Res.,* **2019**, *148*, 104409. http://dx.doi.org/10.1016/j.phrs.2019.104409 PMID: 31446039

[66] Sung, H.C.; Chang, K.S.; Chen, S.T.; Hsu, S.Y.; Lin, Y.H.; Hou, C.P.; Feng, T.H.; Tsui, K.H.; Juang, H.H. Metallothionein 2A with antioxidant and antitumor activity is up-regulated by caffeic acid phenethyl ester in human bladder carcinoma cells. *Antioxidants,* **2022**, *11*(8), 1509. http://dx.doi.org/10.3390/antiox11081509 PMID: 36009228

[67] Gong, Z.; Gao, X.; Yang, Q.; Lun, J.; Xiao, H.; Zhong, J.; Cao, H. Phosphorylation of ERK-dependent NF-κB triggers NLRP3 inflammasome mediated by vimentin in EV71-infected glioblastoma cells. *Molecules,* **2022**, *27*(13), 4190. http://dx.doi.org/10.3390/molecules27134190 PMID: 35807435

[68] Sucu, B.O.; Koc, E.B.; Savlug Ipek, O.; Mirat, A.; Almas, F.; Guzel, M.A.; Dogan, B.; Uludag, D.; Karakas, N.; Durdagi, S.; Guzel, M. Design and synthesis of novel caffeic acid phenethyl ester (CAPE) derivatives and their biological activity studies in glioblastoma multiforme (GBM) cancer cell lines. *J. Mol. Graph. Model.,* **2022**, *113*, 108160. http://dx.doi.org/10.1016/j.jmgm.2022.108160 PMID: 35248814

[69] Piredda, M.; Facchinetti, G.; Biagioli, V.; Giannarelli, D.; Armento, G.; Tonini, G.; De Marinis, M.G. Propolis in the prevention of oral mucositis in breast cancer patients receiving adjuvant chemotherapy: A pilot randomised controlled trial. *Eur. J. Cancer Care (Engl.),* **2017**, *26*(6), e12757. http://dx.doi.org/10.1111/ecc.12757 PMID: 28840622

[70] Sforcin, J.M. Propolis and the immune system: A review. *J. Ethnopharmacol.,* **2007**, *113*(1), 1-14. http://dx.doi.org/10.1016/j.jep.2007.05.012 PMID: 17580109

[71] Marucci, L.; Farneti, A.; Di Ridolfi, P.; Pinnaro, P.; Pellini, R.; Giannarelli, D.; Vici, P.; Conte, M.; Landoni, V.; Sanguineti, G. Double-blind randomized phase III study comparing a mixture of natural agents *versus* placebo in the prevention of acute mucositis during chemoradiotherapy for head and neck cancer. *Head Neck,* **2017**, *39*(9), 1761-1769. http://dx.doi.org/10.1002/hed.24832 PMID: 28560780

[72] Randomized double blind placebo controlled trial of propolis for oral mucositis in patients receiving chemotherapy for head and neck cancer. *Asian Pac. J. Cancer Prev.,* **2016**, *17*(7), 3611-3614. PMID: 27510017

[73] Noronha, V.; Araujo, G.; Gomes, R.; Iwanaga, S.; Barbosa, M.; Abdo, E.; e Ferreira, E.; Viana, A.; Souza, A.; Abreu, S.; Santos, V. Mucoadhesive propolis gel for prevention of radiation-induced oral mucositis. *Curr. Clin. Pharmacol.,* **2014**, *9*(4), 359-364. http://dx.doi.org/10.2174/1574884709666140205210051 PMID: 24502424

[74] Abdulrhman, M.; Samir Elbarbary, N.; Ahmed Amin, D.; Saeid Ebrahim, R. Honey and a mixture of honey, beeswax, and olive oil-propolis extract in treatment of chemotherapy-induced oral mucositis: A randomized controlled pilot study. *Pediatr. Hematol. Oncol.,* **2012**, *29*(3), 285-292. http://dx.doi.org/10.3109/08880018.2012.669026 PMID: 22475306

[75] Tomaževič, T.; Jazbec, J. A double blind randomised placebo controlled study of propolis (bee glue) effectiveness in the treatment of severe oral mucositis in chemotherapy treated children. *Complement. Ther. Med.,* **2013**, *21*(4), 306-312. http://dx.doi.org/10.1016/j.ctim.2013.04.002 PMID:

23876561

[76] Shin, S.H.; Lee, S.R.; Lee, E.; Kim, K.H.; Byun, S. Caffeic acid phenethyl ester from the twigs of *Cinnamomum cassia* inhibits malignant cell transformation by inducing c--Fos degradation. *J. Nat. Prod.,* **2017**, *80*(7), 2124-2130. http://dx.doi.org/10.1021/acs.jnatprod.7b00433 PMID: 28682072

[77] Erdis, E. Can CAPE be used as ideal antitumor agent "safely"? *Eur. Rev. Med. Pharmacol. Sci.,* **2013**, *17*(4), 567. PMID: 23467961

[78] Omene, C.; Kalac, M.; Wu, J.; Marchi, E.; Frenkel, K.; O'-Connor, O.A. Propolis and its active component, caffeic acid phenethyl ester (CAPE), modulate breast cancer therapeutic targets *via* an epigenetically mediated mechanism of action. *J. Cancer Sci. Ther.,* **2013**, *5*(10), 334-342. PMID: 24466386

[79] Omene, C.O.; Wu, J.; Frenkel, K. Caffeic Acid Phenethyl Ester (CAPE) derived from propolis, a honeybee product, inhibits growth of breast cancer stem cells. *Invest. New Drugs,* **2012**, *30*(4), 1279-1288. http://dx.doi.org/10.1007/s10637-011-9667-8 PMID: 21537887

[80] Kosova, F.; Kurt, F.O.; Olmez, E.; Tuğlu, I.; Arı, Z. Effects of caffeic acid phenethyl ester on matrix molecules and angiogenetic and anti-angiogenetic factors in gastric cancer cells cultured on different substrates. *Biotech. Histochem.,* **2016**, *91*(1), 38-47. http://dx.doi.org/10.3109/10520295.2015.1072769 PMID: 26523612

[81] Kim, H.G.; Han, E.H.; Im, J.H.; Lee, E.J.; Jin, S.W.; Jeong, H.G. Caffeic acid phenethyl ester inhibits 3-MC-induced CYP1A1 expression through induction of hypoxia-inducible factor-1α. *Biochem. Biophys. Res. Commun.,* **2015**, *465*(3), 562-568. http://dx.doi.org/10.1016/j.bbrc.2015.08.060 PMID: 26296470

[82] Kuo, Y.Y.; Jim, W.T.; Su, L.C.; Chung, C.J.; Lin, C.Y.; Huo, C.; Tseng, J.C.; Huang, S.H.; Lai, C.J.; Chen, B.C.; Wang, B.J.; Chan, T.M.; Lin, H.P.; Chang, W.S.; Chang, C.R.; Chuu, C.P. Caffeic acid phenethyl ester is a potential therapeutic agent for oral cancer. *Int. J. Mol. Sci.,* **2015**, *16*(12), 10748-10766. http://dx.doi.org/10.3390/ijms160510748 PMID: 25984601

[83] Balkhi, H.M.; Gul, T.; Sana, S.; Haq, E. Potential synergism of caffeic acid phenethyl ester and dasatinib in c6 glioma cell model: Adumbrating the molecular mechanism. *Brain Disord. Ther.,* **2018**, *7*(2), 2. http://dx.doi.org/10.4172/2168-975X.1000245

[84] Budisan, L.; Gulei, D.; Jurj, A.; Braicu, C.; Zanoaga, O.; Cojocneanu, R.; Pop, L.; Raduly, L.; Barbat, A.; Moldovan, A.; Moldovan, C.; Tigu, A.; Ionescu, C.; Atanasov, A.; Irimie, A.; Berindan-Neagoe, I. Inhibitory effect of cape and kaempferol in colon cancer cell lines—possible implications in new therapeutic strategies. *Int. J. Mol. Sci.,* **2019**, *20*(5), 1199. http://dx.doi.org/10.3390/ijms20051199 PMID: 30857282

[85] Chung, L.C.; Chiang, K.C.; Feng, T.H.; Chang, K.S.; Chuang, S.T.; Chen, Y.J.; Tsui, K.H.; Lee, J.C.; Juang, H.H. Caffeic acid phenethyl ester upregulates N-myc downstream regulated gene 1 *via* ERK pathway to inhibit human oral cancer cell growth *in vitro* and *in vivo*. *Mol. Nutr. Food Res.,* **2017**, *61*(9), 1600842. http://dx.doi.org/10.1002/mnfr.201600842 PMID: 28181403

[86] Dziedzic, A.; Kubina, R.; Kabała-Dzik, A.; Tanasiewicz, M. Induction of cell cycle arrest and apoptotic response of head and neck squamous carcinoma cells (Detroit 562) by caffeic acid and caffeic acid phenethyl ester derivative. *Evid. Based Complement. Alternat. Med.,* **2017**, *2017*, 1-10. http://dx.doi.org/10.1155/2017/6793456 PMID: 28167973

[87] Chang, H.; Wang, Y.; Yin, X.; Liu, X.; Xuan, H. Ethanol extract of propolis and its constituent caffeic acid phenethyl ester inhibit breast cancer cells proliferation in inflammatory microenvironment by inhibiting TLR4 signal pathway and inducing apoptosis and autophagy. *BMC Complement. Altern. Med.,* **2017**, *17*(1), 471. http://dx.doi.org/10.1186/s12906-017-1984-9 PMID: 28950845

[88] Imai, M.; Yokoe, H.; Tsubuki, M.; Takahashi, N. Growth inhibition of human breast and prostate cancer cells by cinnamic acid derivatives and their mechanism of action. *Biol. Pharm. Bull.,* **2019**, *42*(7), 1134-1139. http://dx.doi.org/10.1248/bpb.b18-01002 PMID: 30982786

[89] Kabała-Dzik, A.; Rzepecka-Stojko, A.; Kubina, R.; Wojtyczka, R.D.; Buszman, E.; Stojko, J. Caffeic acid *versus* caffeic acid phenethyl ester in the treatment of breast cancer MCF-7 cells: Migration rate inhibition. *Integr. Cancer Ther.,* **2018**, *17*(4), 1247-1259. http://dx.doi.org/10.1177/1534735418801521 PMID: 30246565

[90] Chiang, K.C.; Yang, S.W.; Chang, K.P.; Feng, T.H.; Chang, K.S.; Tsui, K.H.; Shin, Y.S.; Chen, C.C.; Chao, M.; Juang, H.H. Caffeic acid phenethyl ester induces N-myc downstream regulated gene 1 to inhibit cell proliferation and invasion of human nasopharyngeal cancer cells. *Int. J. Mol. Sci.,* **2018**, *19*(5), 1397. http://dx.doi.org/10.3390/ijms19051397 PMID: 29738439

[91] Liang, Y.; Feng, G.; Wu, L.; Zhong, S.; Gao, X.; Tong, Y.; Cui, W.; Qin, Y.; Xu, W.; Xiao, X.; Zhang, Z.; Huang, G.; Zhou, X. Caffeic acid phenethyl ester suppressed growth and metastasis of nasopharyngeal carcinoma cells by inactivating the NF-κB pathway. *Drug Des. Devel. Ther.,* **2019**, *13*, 1335-1345. http://dx.doi.org/10.2147/DDDT.S199182 PMID: 31118570

[92] Liu, G.L.; Han, N.Z.; Liu, S.S. Caffeic acid phenethyl ester inhibits the progression of ovarian cancer by regulating NF-κB signaling. *Biomed. Pharmacother.,* **2018**, *99*, 825-831. http://dx.doi.org/10.1016/j.biopha.2018.01.129 PMID: 29710481

[93] Khoram, N.M.; Bigdeli, B.; Nikoofar, A.; Goliaei, B. Caffeic acid phenethyl ester increases radiosensitivity of estrogen receptor-positive and-negative breast cancer cells by prolonging radiation-induced DNA damage. *J. Breast Cancer,* **2016**, *19*(1), 18-25. http://dx.doi.org/10.4048/jbc.2016.19.1.18 PMID: 27066092

[94] Omene, C.; Patel, M.; Karagoz, K.; Gatza, M.L.; Barcellos-Hoff, M.H. Abstract P4-07-03: Immunomodulation of triple negative breast cancer by caffeic acid phenethyl ester (CAPE). *Cancer Res.,* **2019**, *79*(4_Supplement), P4-07-03. http://dx.doi.org/10.1158/1538-7445.SABCS18-P4-07-03

[95] Onori, P.; DeMorrow, S.; Gaudio, E.; Franchitto, A.; Mancinelli, R.; Venter, J.; Kopriva, S.; Ueno, Y.; Alvaro, D.; Savage, J.; Alpini, G.; Francis, H. Caffeic acid phenethyl ester decreases cholangiocarcinoma growth by inhibition of NF-κB and induction of apoptosis. *Int. J.*

Cancer, **2009**, *125*(3), 565-576. http://dx.doi.org/10.1002/ijc.24271 PMID: 19358267

[96] Fırat, F.; Özgül, M.; Türköz Uluer, E.; Inan, S. Effects of caffeic acid phenethyl ester (CAPE) on angiogenesis, apoptosis and oxidatıve stress ın various cancer cell lines. *Biotech. Histochem.,* **2019**, *94*(7), 491-497. http://dx.doi.org/10.1080/10520295.2019.1589574 PMID: 30991851

[97] Kurauchi, Y.; Hisatsune, A.; Isohama, Y.; Mishima, S.; Katsuki, H. Caffeic acid phenethyl ester protects nigral dopaminergic neurons *via* dual mechanisms involving haem oxygenase-1 and brain-derived neurotrophic factor. *Br. J. Pharmacol.,* **2012**, *166*(3), 1151-1168. http://dx.doi.org/10.1111/j.1476-5381.2012.01833.x PMID: 22224485

[98] Wadhwa, R.; Nigam, N.; Bhargava, P.; Dhanjal, J.K.; Goyal, S.; Grover, A.; Sundar, D.; Ishida, Y.; Terao, K.; Kaul, S.C. Molecular characterization and enhancement of anticancer activity of caffeic acid phenethyl ester by γ cyclodextrin. *J. Cancer,* **2016**, *7*(13), 1755-1771. http://dx.doi.org/10.7150/jca.15170 PMID: 27698914

[99] Wu, W.; Gao, F.; Song, X.H.F.; Zhao, Y.; Xu, M.; Zhang, X.; Yang, Z.; Yang, Z. Caffeic Acid Phenethyl Ester (CAPE) mediated decrease in metastasis of colon cancer cells: An *in vitro* and *in vivo* study. *Afr. J. Tradit. Complement. Altern. Med.,* **2017**, *14*(5), 63-71. http://dx.doi.org/10.21010/ajtcam.v14i5.9

[100] Ishida, Y.; Gao, R.; Shah, N.; Bhargava, P.; Furune, T.; Kaul, S.C.; Terao, K.; Wadhwa, R. Anticancer activity in honeybee propolis: Functional insights to the role of caffeic acid phenethyl ester and its complex with γ-cyclodextrin. *Integr. Cancer Ther.,* **2018**, *17*(3), 867-873. http://dx.doi.org/10.1177/1534735417753545 PMID: 29390900

[101] Pattingre, S.; Levine, B. Bcl-2 inhibition of autophagy: A new route to cancer? *Cancer Res.,* **2006**, *66*(6), 2885-2888. http://dx.doi.org/10.1158/0008-5472.CAN-05-4412 PMID: 16540632

[102] Gong, C.; Bauvy, C.; Tonelli, G.; Yue, W.; Deloménie, C.; Nicolas, V.; Zhu, Y.; Domergue, V.; Marin-Esteban, V.; Tharinger, H.; Delbos, L.; Gary-Gouy, H.; Morel, A-P.; Ghavami, S.; Song, E.; Codogno, P.; Mehrpour, M. Beclin 1 and autophagy are required for the tumorigenicity of breast cancer stem-like/progenitor cells. *Oncogene,* **2013**, *32*(18), 2261-2272, 1-11. http://dx.doi.org/10.1038/onc.2012.252 PMID: 22733132

[103] Gong, C.; Song, E.; Codogno, P.; Mehrpour, M. The roles of BECN1 and autophagy in cancer are context dependent. *Autophagy,* **2012**, *8*(12), 1853-1855. http://dx.doi.org/10.4161/auto.21996 PMID: 22960473

[104] Hui, B.; Shi, Y.H.; Ding, Z.B.; Zhou, J.; Gu, C.Y.; Peng, Y.F.; Yang, H.; Liu, W.R.; Shi, G.M.; Fan, J. Proteasome inhibitor interacts synergistically with autophagy inhibitor to suppress proliferation and induce apoptosis in hepatocellular carcinoma. *Cancer,* **2012**, *118*(22), 5560-5571. http://dx.doi.org/10.1002/cncr.27586 PMID: 22517429

[105] He, Y.J.; Li, W-L.; Liu, B-H.; Dong, H.; Mou, Z-R.; Wu, Y-Z. Identification of differential proteins in colorectal cancer cells treated with caffeic acid phenethyl ester. *World J. Gastroenterol.,* **2014**, *20*(33), 11840-11849. http://dx.doi.org/10.3748/wjg.v20.i33.11840 PMID: 25206290

[106] Gavilán, E.; Giráldez, S.; Sánchez-Aguayo, I.; Romero, F.; Ruano, D.; Daza, P. Breast cancer cell line MCF7 escapes from G1/S arrest induced by proteasome inhibition through a GSK-3β dependent mechanism. *Sci. Rep.,* **2015**, *5*(1), 10027. http://dx.doi.org/10.1038/srep10027 PMID: 25941117

[107] Francielli de Oliveira, P.; Lima, I.M.S.; Monteiro Neto, M.A.B.; Bastos, J.K.; da Silva Filho, A.A.; Tavares, D.C. Evaluation of genotoxicity and antigenotoxicity of artepillin C in V79 cells by the comet and micronucleus assays. *Nutr. Cancer,* **2013**, *65*(7), 1098-1103. http://dx.doi.org/10.1080/01635581.2013.815233 PMID: 23915392

[108] Maistro, E.L.; Angeli, J.P.F.; Andrade, S.F.; Mantovani, M.S. *In vitro* genotoxicity assessment of caffeic, cinnamic and ferulic acids. *Genet. Mol. Res.,* **2011**, *10*(2), 1130-1140. http://dx.doi.org/10.4238/vol10-2gmr1278 PMID: 21710465

[109] Tan, K.W.; Li, Y.; Paxton, J.W.; Birch, N.P.; Scheepens, A. Identification of novel dietary phytochemicals inhibiting the efflux transporter breast cancer resistance protein (BCRP/ABCG2). *Food Chem.,* **2013**, *138*(4), 2267-2274. http://dx.doi.org/10.1016/j.foodchem.2012.12.021 PMID: 23497885

[110] Gao, M.; Zhang, W.; Liu, Q.; Hu, J.; Liu, G.; Du, G. Pinocembrin prevents glutamate-induced apoptosis in SH-SY5Y neuronal cells *via* decrease of bax/bcl-2 ratio. *Eur. J. Pharmacol.,* **2008**, *591*(1-3), 73-79. http://dx.doi.org/10.1016/j.ejphar.2008.06.071 PMID: 18625218

[111] Borrelli, F.; Izzo, A.A.; Di Carlo, G.; Maffia, P.; Russo, A.; Maiello, F.M.; Capasso, F.; Mascolo, N. Effect of a propolis extract and caffeic acid phenethyl ester on formation of aberrant crypt foci and tumors in the rat colon. *Fitoterapia,* **2002**, *73*(Suppl. 1), S38-S43. http://dx.doi.org/10.1016/S0367-326X(02)00189-2 PMID: 12495708

[112] Davoodi, S.H.; Yousefinejad, V.; Ghaderi, B.; Akbari, M.E.; Darvishi, S.; Mehrabi, Y.; Darvishi, N. Oral propolis, nutritional status and quality of life with chemotherapy for breast cancer: A randomized, double-blind clinical trial. *Nutr. Cancer,* **2022**, *74*(6), 2029-2037. http://dx.doi.org/10.1080/01635581.2021.1988118 PMID: 34622721