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Review Article

Caffeic acid phenethyl ester (CAPE): pharmacodynamics and potential for therapeutic application

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Abstract

Caffeic acid phenethyl ester (CAPE) is the major pharmacologically-active component of some propolis types, rich in polyphenols, such as poplar propolis types. CAPE has the potential to be applied as a pharmaceutical as it possesses most of the pharmacological activities of propolis, such as anti-proliferative, antioxidant, immunomodulatory, antidiabetic, anti-inflammatory and antimicrobial. Its advantage is that it lacks some of the downsides of total propolis extracts, such as inability for unified standardization, which is cornerstone for implementing its therapeutic potential as a drug. The current paper provides an overview on the pharmacodynamic principles of CAPE. We present literature search outcomes form ClinicalTrials.gov database and from scientific publications, available on Scopus and Crossref databases. We take a round view of CAPE's potential therapeutic implications in light of approved drugs with related modes of action.

Keywords

Pharmacology, therapeutic application, selective inhibitor of nuclear export, NF-κB activation inhibition

Introduction

CAPE is a major active constituent of some types of propolis, rich in polyphenolics (Murtaza et al. 2014, Zhang et al. 2014, Tolba et al. 2016, Bankova et al. 2018). CAPE is the most studied individual component of propolis at present (Bankova et al. 2018). It has been shown to possess most of the reported biological activities, characteristic to total propolis extracts (Zabaiou et al. 2017), including antimicrobial (Arasoglu et al. 2016), antiproliferative (Akyol et al. 2013), protective against oxidative stress-mediated tissue damage, anti-inflammatory, immunomodulatory (Turan et al. 2015) and antidiabetic (Celik et al. 2009).

Pharmacological mechanisms

Studies in the first decade after the discovery of CAPE proved fruitful in confirming that it possesses broad biological activities, mostly coinciding with those of whole propolis extracts. The cornerstone studies during this stage of CAPE research were introduced in the first part of the current article. CAPE was shown to be most effective as an antineoplastic, antioxidant and anti-inflammatory agent and as inhibitor of some enzymes. This knowledge provided the basis for a boost of research articles in CAPE's underlying mechanisms of action. CAPE was tested on diverse *in vitro* and *in vivo* disease models. Data

on its biological activities has been systematized in extensive review articles regarding its antineoplastic (Ozturk et al. 2012, Akyol et al. 2013, Lin et al. 2013, Kuo et al. 2015, Watanabe and Sforcin 2018), antioxidant and protective towards drug-induced adverse reactions (Akyol et al. 2014, Magnani et al. 2014, Erdemli et al. 2015, Tolba et al. 2016, Anjaly and Tiku 2018), anti-inflammatory (Tolba et al. 2013, Armutcu et al. 2015, Murtaza et al. 2014), antidiabetic (Pittalà et al. 2018) and antiviral (Erdemli et al. 2015) activities. Here, we are going to highlight some therapeutically-relevant pharmacological mechanisms of CAPE. For convenience, we are about to group them as mostly relevant to signal transduction modulation, direct enzyme inhibition and direct antioxidant activities, although CAPE's activity is most probably a combination of the mentioned mechanisms.

Signal transduction modulation

The source of evidence for the influence of CAPE on signal transduction pathways is predominantly research on its cytotoxic effects on different tumor cell lines. The reason behind the selective cytotoxicity of CAPE towards cells that have undergone chemical/viral transformation compared to non-transformed cells (Grunberger et al. 1988) has been related to its inhibition of the activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (Natarajan et al. 1996). NF-κB is a transcription factor, with a central role in the regulation of different cell functions as cell survival, inflammation, stress response and metabolism as well as tissue development homeostasis and differentiation (Karin 2009, 2012, Aggarwal and Sung 2011, Baker et al. 2011, Lingappan 2018). In the inactive state, NF-κB proteins are retained in the cytoplasm by association with inhibitor of κB (IκB) proteins. NF-κB is activated when IκB becomes phosphorylated by IκB kinases (IKKs), which ultimately lead to its degradation by the proteasome. This in turn leads to the release of the uninhibited, active NF-κB proteins, which can then translocate to the nucleus and exert their effect by activating the transcription of proteins (Moynagh 2005). The state of activation of NF-κB is paramount for the regulation of many signal pathways, which could lead either to cell survival or call death, by activation of caspases and apoptosis or other cell death mechanisms. The interaction between signaling pathways and the fate of the cell depend on the intra- and extracellular biochemical context. An example of such signaling is tumor necrosis factor (TNF), which is one of the strongest inducers of NF-κB activity. TNF functions as a pro-apoptotic factor and an inflammatory cytokine and depending on the biochemical context can either cause apoptosis or cell survival and proliferation. It is generally apoptotic only when NF-κB is blocked (Flusberg and Sorger 2015). The exact mechanism of CAPE's interaction with components of NF-κB-mediated signal transduction is not ultimately clarified. However, CAPE has been shown to block NF-κB activation in tumor (Natarajan et al. 1996, Watabe et al. 2004, Liu et al. 2018) and immune cells (Lalor et al. 2007, Wang et al. 2010). It has been shown to prevent the p65 (one of the active components of NF-κB) from translocation in the nucleus and from binding to DNA (Natarajan et al. 1996, Liu et al. 2018). It has been speculated that CAPE directly inhibits IKK (Lee et al. 2010). Another study infers that the cellular target of CAPE is Exportin 1/ chromosomal maintenance 1 (XPO1/CRM1), a nuclear transporter protein which functions as a nucleocytoplasmic exporter of growth-regulatory factors. CAPE targets specifically a non-catalytic cysteine 528 of XPO1/CRM1, which results in inhibition of its function. (Wang and Liu 2019). Among the target proteins of XPO1/CRM1 are NF-κB, Wnt/β-catenin, PI3K/Akt, p53, FOXOs (Forkhead box proteins), etc. (Wang and Liu 2019). It has been reported that XPO1/CRM1 inhibitors are among the anticancer agents with the broadest spectrum of activity towards diverse malignancies (Wang and Liu 2019). They exert anti-inflammatory effects in preclinical models of neurodegeneration (Haines et al. 2015), which could be also the mechanism of the antineoplastic and anti-inflammatory effects of CAPE. Whether the primary pharmacological mechanism of CAPE is inhibition of XPO1/CRM1 or of NF-κB activity (by inhibition of IKK, p65 translocation or DNA binding), there is non-clinical data, showing that CAPE affects signaling pathways, that are known to be in interplay with all of the discussed mechanisms. For example, CAPE enhances the expression of the tumor suppressor protein p53 in glioma cells (Lee et al. 2003). The tumor suppressor p53 is a transcription factor, regulating DNA-repair and apoptosis. It is the most frequently mutated gene in human cancer (Khoo et al. 2014) and its crosstalk with NF-κB has been implicated in the pathogenesis of stress- and inflammation induced cancer (Schneider and Krämer 2011). CAPE also interferes with FOXO signaling by increasing the levels of the FOXO-1 downstream tumor suppressor in prostate cancer cells (Tolba et al. 2013). FOXO proteins are important transcriptional effectors to the insulin and IGF-1 signaling pathway, they promote the antioxidant defense of cells (Martins et al. 2016) and block NF-κB activity and inflammation (Salminen et al. 2008). In another study, CAPE suppressed TGF-beta induced Akt phosphorylation and the migration of adenocarcinoma cells (Shigeoka et al. 2004). It also inhibited Akt phosphorylation and NF-κB activation in CD4+ T cells (Wang et al. 2010). The PI3K-Akt pathway promotes survival. Its activation leads to NF-κB activation and has been reported to have a role in type 2 diabetes (Carracedo and Pandolfi 2008). Another study shows that CAPE suppressed canonical Wnt signaling of prostate cancer cells, reducing their invasiveness (Tseng et al. 2016). Wnt signaling pathway activation is related to carcinogenesis and promotion of metastasis (Zhan et al. 2017). It's dysregulation predisposes for metabolic dysfunction and type 2 diabetes (Fuster et al. 2015) and is known to interact with NF-κB signaling during inflammation (Ma and Hottiger 2016). Another signaling pathway, regulated by NF-κB and influenced by CAPE, is nuclear factor erythroid 2-related factor 2 (Nrf-2) (Wardyn et al. 2015, Kucukgul 2016). Nrf-

2 is a transcription factor with cytoplasmic location, which upon activation initiates the expression of genes, coding anti-oxidant, anti-inflammatory and detoxifying proteins, such as heme oxygenase 1 (HO1), superoxide dismutase (SOD), catalase (CAT) and glutathione-s-transferase (GST) (Keum 2012, Loboda et al. 2016). CAPE exerts its antioxidant effects through increased HO1 expression, mediated by Nrf-2 (Stähli et al. 2019). A probable mechanism of Nrf-2 activation by CAPE has been proposed. CAPE's catechol moiety is responsible for it binding to Kelch-like ECH associated protein 1 (Keap1), which keeps Nrf-2 inactive by anchoring it in the cytoplasm. It is supposed that the binding of CAPE to Keap1 results in translocation of Nrf-2 to the nucleus and its activation (Kim et al. 2013). The given examples show the importance of XPO1/CRM1 and NF-κB inhibition in the plethora of effects of CAPE on tumor cells, inflammation and supposedly in metabolic diseases as type 2 diabetes. Based on the presented research, CAPE could be classified as a selective inhibitor of nuclear export (SINE) or, informally as such a pharmacological group has not yet been defined, as an inhibitor of NF-κB signaling. Noteworthy, it has been shown that the mechanism of action of anticancer and anti-inflammatory drugs is related to NF-κB inhibition (Urushibara et al. 2004, Baud and Karin 2009, Gan et al. 2016). Although Baud and Karin (2009) hypothesize that a logical side effect of effective IKK/NF-κB inhibitors should be immunosuppression, a major pitfall could be the pronounced ability of such inhibitors to stimulate the production of interleukin 1 beta (IL-1β) due to overactivation of the inflammasome during bacterial infections. Recently, the first in class SINE - Selexinor was granted accelerated approval by the US Food and Drug Administration (FDA) for "adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody." (Center for Drug Evaluation and Research 2019). Its most common adverse reaction is thrombocytopenia, which is not related to direct cytotoxicity, but rather to delayed maturation of megacaryocytes (Machlus et al. 2017). The existence of approved drugs, with relevant mechanisms of action underlines the good prospects for the clinical application of CAPE in neoplastic and immunopathological conditions.

Target enzyme inhibition

Another group of pharmacodynamic mechanisms of potential clinical importance stem from the ability of CAPE to inhibit the activity of some enzymes. For example, CAPE has been shown to selectively inhibit human matrix metalloproteinase-9 (MMP-9) and matrix metalloproteinase-2 (MMP-2) with IC_{50} values respectively 2 and 5 μM, but it did not inhibit MMP-1, MMP-3, MMP-7 and cathepsin K (Cat K) (Chung et al. 2004). Another study reports that CAPE inhibits MMP-9 at even lower concentrations with IC_{50} of 1–2 nM (Jin et al. 2005). The MMP family's functions are to degrade extracellular matrix – forming proteins. Abnormal MMP activity (of MMP-2 and MMP-9 particularly) has been detected in pathologies such as cancer metastasizing (Iochmann et al. 2009, Li et al. 2017). So far, due to musculoskeletal toxicity, related to lack of specificity (Skiles et al. 2004), only one MMP inhibitor drug has been approved – a subantimicrobial dose doxycycline (Periostat) (Caton and Ryan 2011). The inhibiting activity of CAPE towards MMP-2 and MMP-9 could be promising in dental practice (Table 1), but could also be effective in alleviating tissue damage due to cerebral ischemia and stroke (Dong et al. 2009).

Another enzyme that has been researched as a target for CAPE inhibition is human immunodeficiency virus type 1 (HIV-1) integrase (Erdemli et al. 2015). The lentivirus HIV essentially needs the integrase enzyme in order to transfer its genetic material into the host cell's DNA. HIV-1 integrase catalyzes two biochemically and temporally separate steps: the first step consists of cleavage of a 3' terminal dinucleotide of the virus DNA. The second step, catalyzed by HIV-1 integrase is strand transfer, resulting in the integration of virus DNA in specific loci in host DNA. (Andrake and Skalka 2015). It has been shown that CAPE selectively inhibits the second, integration step (Fesen et al. 1994). All approved drugs (first generation: Raltegravir and Elvitegravir; second generation: Dolutegravir), inhibiting the HIV-1 integrase also target the second reaction, that's why they are called integrase strand transfer inhibitors (InSTIs) (Dow and Bartlett 2014). InSTIs are effective when included in antiretroviral polypragmasy and as pre-exposure prophylaxis for individuals in high risk of infection (Günthard et al. 2016). The antiviral activity of CAPE, however is multimodal, as it influences other stages in the retroviral life cycle due to its effects on the signal transduction pathways in the host cell (Erdemli et al. 2015).

CAPE has been shown to inhibit the *in vitro* activity of the cyclooxygenases COX-1 and COX-2, enzymes that are a popular target for non-steroidal anti-inflammatory drugs. The IC_{50} values were 58 μM for both enzymes. However, in the *in vivo* situation, the effect of CAPE on COX activities may be enhanced by its ability to inhibit their gene expression (Michaluart et al. 1999). CAPE has also been shown to inhibit arachidonate 5-lipoxygenase (5-LOX)-catalyzed oxygenation of linoleic acid and arachidonic acid and it has been shown that it inhibits the enzyme by a complete uncompetitive mechanism, related to its antioxidant capacity (Sud'ina et al. 1993). 5-LOX is also an enzyme, which functions in the production of proinflammatory molecules (leukotrienes) and its inhibition is an effective strategy in the treatment of inflammatory disorders. An approved drug for the treatment of asthma, which is an inhibitor of 5-LOX is Zileuton (Aparoy et al. 2012).

CAPE also inhibits xanthine oxidase (XO) by means of competitive inhibition at low concentrations with an IC_{50} of 6.26 μM (Wang et al. 2009). XO's metabolic function is related to purine degradation, but it can also generate reactive oxygen species (Berry and Hare 2004). A clinical trial with the XO inhibitor Allopurinol, used for the treatment

of high blood uric acid levels concludes that it acutely improves the levels of high-energy phosphates as adenosine triphosphate's (ATP) flux through creatine kinase (CK) in the heart of patients with heart failure, which could protect them from disease aggravation (Hirsch et al. 2012).

In order to better understand CAPE's pharmacological action and effectively advance it to the bedside, it is relevant to clarify whether stereoisomerism influences its effects on enzymes and proteins, as such information is unavailable in scientific research databases.

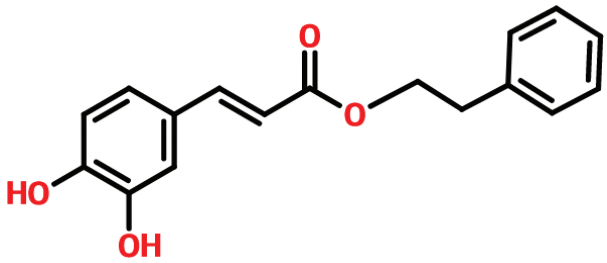

Figure 1. Chemical structure of CAPE.

Direct antioxidant activity

Research on the antioxidant activity of CAPE shows that it is capable of neutralizing oxidative stress (Tolba et al. 2016). Oxidative stress is known to be an important etiological factor in age-related diseases, such as cardiovascular and neurodegenerative disease, also in diseases with an inflammatory component as chronic obstructive pulmonary disease, metabolic diseases and cancer (Liguori et al. 2018). It has been shown that CAPE is the major component of propolis, responsible for its antioxidant activities (Rossi et al. 2002). Presumably, its antioxidant properties are related to its aforementioned effects on signal transduction, immunosuppressive activity and inhibition of enzymes, related to oxidative stress. The same is valid for the activity of CAPE as a protective agent against drug-induced toxicity, mediated by oxidative stress-related toxic mechanisms (Murtaza et al. 2014). Moreover, it has been shown that small molecules with direct antioxidant capacity, such as vitamins and dietary polyphenols can potentially protect against oxidative stress-related pathology (Liguori et al. 2018). CAPE exerts strong antioxidant activity, which is evident from it being an effective radical scavenger in the DPPH (Choi et al. 2019), and ABTS antioxidant tests (Bak et al. 2016). The presence of catechol moiety, the double bond in CAPE's molecule and the high lipophylicity are structural factors, responsible for its excellent antioxidant activity (Razzaghi-Asl et al. 2013).

Clinical trials

CAPE has a simple chemical structure (Fig. 1) and possesses the most utilized pharmacological activities of propolis, some of which at very low concentrations (antiproliferative and antioxidant), therefore it could be utilized as a medicine with greater success than propolis total extracts. Although the aim of the current review is not to extensively evaluate clinical data on propolis, in order to exemplify the interest towards its pharmaceutical application and the abundance of such data, we did a quick search in one of the biggest clinical trials' databases – https://clinicaltrials.gov with the keyword "propolis" in the search feature box, where drug information should be included. The search (as of 1.7.2019) resulted in 40 hits, dominated by dental products, related to its antibacterial, anti-inflammatory and analgesic properties (21 hits), followed by diabetic foot treatments (4 hits), skin and wound conditioning (4 hits), vaginal application (2 hits), and oral food supplementation for glycemic control in diabetes mellitus type 2 (2 hits), and other conditions, including chronic kidney disease, stable angina pectoris, common cold, gastroenteritis, chronic thrombocytopenic purpura and mild cognitive impairment. Noteworthy, this search revealed only one study with published results. However, at present the majority of clinical trials are not listed in the publicly available specialized databases (Glanville et al. 2014). Concerning the published clinical trial data in research articles, most of the data on propolis efficacy in oral health applications is of poor methodological quality and doesn't allow drawing significant conclusions (Hwu and Lin 2014, Sung et al. 2017). The same conclusion is applicable for studies on skin and genital diseases (Sung et al. 2017). However, a meta-analysis of propolis treatment in cancer therapy-induced oral mucositis concludes that it is effective and safe (Kuo et al. 2018). Another meta-analysis concludes that the use of propolis as a supplement may be effective in the control of blood glucose concentrations in patients with type 2 diabetes mellitus (Karimian et al. 2019). The overview on clinical data points to the existence of sound interest on propolis pharmaceutical application, probably based on the tradition of apitherapy (Hellner et al. 2008). However, propolis products have been considered not sufficiently characterized in order to substantiate effects on health conditions (EFSA Panel on Dietetic Products and Allergies (NDA) 2010), which could also be among the reasons for the reported lack of reproducibility and poor methodological quality of clinical studies.

So far, the clinical potential of CAPE seems to remain relatively unexplored compared to propolis formulations. A quick search in the online database ClinicalTrials.gov with keywords caffeic acid phenethyl ester resulted in only one registered clinical study (ID:NCT02744703) on its properties as a matrix metalloproteinase inhibitor (Comlekoglu 2016). Not surprisingly, the pursuit towards finding applications in dentistry coincides with the abundance of clinical trials of total propolis extracts for dental application. The authors of the aforementioned study hypothesize that CAPE pretreatment of dentin would improve the binding of resin material to tooth substrate. The researchers summarize that dentin pretreatment with 5% CAPE solution "significantly increased the composite resin restorations' bond strengths to dentin applied with either total-etch or self-etch adhesive system". However,

Table 1. Clinical trials of CAPE and caffeic acid, listed in ClinicalTrials.org database as of 1.7.2019.

Treatment	Condition/Procedure	Outcome	ClinicalTrials.gov Identifier, Phase and Status
CAPE solution (5%)	Restorative dentistry	Pretreatment improves bond strengths of nanohybrid resin restorations to dentin	NCT02744703; Completed
Single increasing oral doses of CC100 (CAPE in solvent 2 to 20 mg)	Healthy volunteers	No serious adverse events, T_{max} at 2.7h; $T_{1/2}$ at 18.5 h	NCT02050334; Phase I Completed;
Multiple oral doses of CC100 (CAPE in solvent 250 to 1000 mg once daily)	Patients with amyotrophic lateral sclerosis	Anticipated results on safety, pharmacokinetics and pharmacodynamics	NCT03049046; Phase I; Recruiting;
Dexamethasone; Caffeic acid 300 mg, tablets, three times daily;	Patients with immune thrombocytopenia	Improves platelet count values; mild adverse effects	NCT02351622; Phase III; Completed; (Qin et al. 2015)
Dexamethasone; Caffeic acid 300 mg, tablets, three times daily;	Patients with immune thrombocytopenia	Anticipated results on sustained patient response after 6 months since the treatment started	NCT02556814; Phase IV; Unknown
Caffeic acid 300 mg, tablets, three times daily;	Patients with advanced esophageal squamous cell cancer	Anticipated results on 3 months' progression free survival and 1 year overall survival	NCT03070262; Phase III; Enrolling by invitation

results' data is not yet publicly available. As caffeic acid is a metabolite of CAPE, we broadened the search in ClinicalTrials.gov database by applying the keywords "caffeic acid". This resulted in two more registered clinical trials of CAPE of synthetic origin, reconstituted in an unspecified diluent, administered orally. The first study, trialing the safety and tolerability of single increasing doses (2 to 20 mg), with dosing occurring every 2 to 7 days and a study duration of 5 to 15 days in healthy adults with a placebo group to which 2 increasing doses were administered and the third and highest dose was substituted with placebo (NCT02050334). The study has been completed and shows that there were no observed serious adverse events in none of the groups and there was no increase of the overall occurrence of other (not including-serious) adverse events in the high dose treatment group, compared to the lower dose treatment group, which confirms the notion of its tolerability from non-clinical data (Armutcu et al. 2015). The pharmacokinetic outcomes showed that the time to reach maximum observed plasma concentration (T_{max}) was on average 2.7 hours and the plasma decay half-life ($T_{1/2}$) was on average 18.5 hours. Probably, as a result of the favorable outcomes of this study, another clinical trial with the same CAPE formulation has been registered (NCT03049046) which has a status of recruiting subjects, suffering from amyotrophic lateral sclerosis for studying CAPE's multiple-dose safety and tolerability in doses up to 1000 mg. There have been numerous reports on the therapeutic potential of antioxidants as CAPE in the treatment of neurodegenerative diseases (Matteo and Esposito 2003, Fontanilla et al. 2012, Gandhi and Abramov 2012) This study plans to follow the effect of CAPE on some secondary outcome measures of pharmacodynamics, related to the condition of amyotrophic lateral sclerosis, namely the inflammation biomarker monocyte chemotactic protein 1 and the excitotoxicity/oxidative stress biomarkers heme oxygenase-1, thioredoxin and heat-shock protein 70. In an attempt to find non-listed in the searched database clinical trials, published in scientific articles, an additional literature search was undertaken in the following search engines: Scopus, Google Scholar and Crossref, applying as keywords "caffeic acid phenethyl ester" AND "clinical trial" by means of a software platform for bibliometric analysis (A. W. Harzing 2007). It failed to identify other clinical trials of CAPE.

The search in the ClinicalTrials.gov database with keywords "caffeic acid" resulted in two studies on the use of caffeic acid in the polypragmasy of immune thrombocytopenia (NCT02556814; NCT02351622) and one, applying caffeic acid for the treatment of esophageal cancer (NCT03070262). Unfortunately, no results are still available in the searched database. However, there is a publication, authored by the responsible party of both trials on the treatment of immune thrombocytopenia, reporting that treatment with 300 mg tablets of CAPE, three times daily for 12 weeks is "effective in patients with ITP with few and mild adverse effects" (Qin et al. 2015).

Conclusion

In conclusion, CAPE is the most researched and promising component of propolis, exerting most of the known pharmacological effects of total propolis extract. Due to its simple structure, it lacks the disadvantage of the inherently complex standardization of propolis. Historically, the initial phase in scientific research of CAPE, following its discovery, was marked by cornerstone research enterprises, providing evidence for its diverse biological activities. In the new millennium many of the mechanisms, underlying the biological effects of CAPE have been clarified, despite some important knowledge gaps. CAPE exerts its pharmacological activities by influencing the cellular signaling pathways, known to be in interplay with NF-κB and XPO1/CRM1. It is an effective inhibitor of enzymes, which are targeted by commercialized drugs and is a free radical scavenger. As information about the pharmacology of CAPE mounts, it is evident that it already attracting attention as a drug candidate molecule, which we exemplified with some recent clinical trials.

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