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Review Article

Caffeic acid phenethyl ester (CAPE): cornerstone pharmacological studies and drug delivery systems

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Abstract

Propolis is a natural product with a plethora of biological effects, utilized by traditional medicine since antiquity. However, its application as a pharmaceutical is hindered by its variable composition and difficult standardization. CAPE has been shown to be a major component of propolis, with a large contribution to its pharmacological effects, among which the anti-inflammatory, antioxidant and antineoplastic have been attracting most attention. The current review article aims to present the cornerstone pharmacological studies of CAPE throughout the years, following its discovery, which confirmed its primary importance among propolis constituents and opened the path to its intensive research as a potential pharmaceutical. We present the diversity of drug delivery systems of CAPE, which have been developed to improve its efficacy in *in vitro* and *in vivo* disease models and discuss their primary promises and weaknesses. The increased interest in recent years over more practical approaches of CAPE research such as its pharmaceutical formulation comes to show that it has a potential to become commercialized as a pharmaceutical.

Keywords

Caffeic acid phenethyl ester, propolis, pharmacological properties, drug delivery systems

Introduction

Propolis is well known for its traditional medical use since antiquity, and its pharmacological activities have been extensively studied in the forms of different extracts and preparations. As for its primary biological function – an antiseptic in the beehives, there is evidence that the antimicrobial activity of the complex mixture of plant metabolites has synergistic activity, which is higher than the activity of any single component (Bankova et al. 2018). However, the use of total propolis extracts has the disadvantage of complicated standardization. It has been proposed that due to propolis' varying chemical composition, influenced by geographical distribution, it is more appropriate to discriminate between propolis types, according to the predominant plant source in the area (Bankova et al. 2018). Another disadvantage of propolis's variable composition is that it complicates furthermore the evaluation and prediction of the allergenic potential of propolis products (Budimir et al. 2012). Caffeic acid phenethyl ester (CAPE) is one of the main biologically active constituents of propolis. It can be easily synthesized, having a relatively simple structure, resolving the characterization and standardization issues. An overview on the potential of CAPE for therapeutic application, focusing on the pharmacodynamic principles, underlying its various pharmacological

activities, as well as registered clinical trials has been presented in a related article (Yordanov 2019). The current review is focused on the discovery of CAPE and its pharmacological potential as well as practical approaches for its pharmaceutical formulation.

Discovery and cornerstone *in vitro* and *in vivo* studies

In order to illustrate the popularity and dynamics of CAPE research over the years, we applied a search in Scopus database (Boyle and Sherman 2006) with keywords "caffeic acid phenethyl ester" by means of a software platform for bibliometric analysis (Harzing 2007). The results of the search (as of 1.7.2019) revealed that a considerable trend towards increasing scientific production, related to CAPE, occurs from the onset of the second millennium, reaching a maximum of 101 publications in 2013 (Fig. 1) An intuitive approach allows us to propose two arbitrary stages in CAPE research. The first period includes the years from its discovery in 1988 until 2000. It is characterized by a relatively small number of cornerstone publications, providing proof of the major pharmacological activities of CAPE, most of which had been already known to be exerted by propolis extracts (Ghisalberti 1979; Hladoń et al. 1980; Neychev et al. 1988; Okonenko et al. 1988).

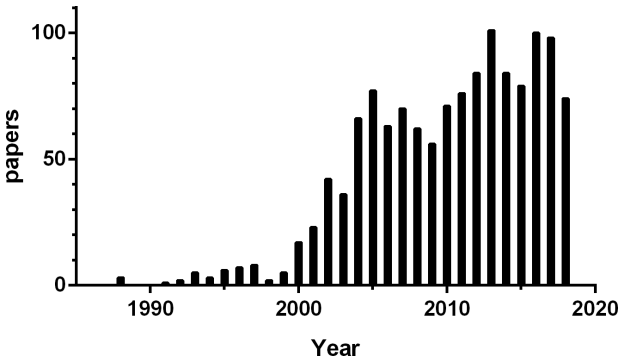

Figure 1. Number of published papers, containing keywords "caffeic acid phenethyl ester", available at Scopus database.

This first period is followed by one of rapidly increasing number of publications, predominantly elucidating the mechanisms behind CAPE's pharmacological activities and proposing new applications for diseases, known to be affected by these activities. This period after the year 2000 and especially the research on the basic principles behind CAPE's impressive diversity of biological effects are the subjects of a related article (Yordanov 2019). Table 1 presents chronologically cornerstone publications on CAPE research, clearly demonstrating its plethora of pharmacological activities. Our literature search in the Scopus online database showed that the first scientific paper on the isolation, identification, synthesis and *in vitro* cytotoxic activity of CAPE was published in 1988 by Grunberger et al. (1988) It describes CAPE as the major component of propolis, originating from Carmel Mountain in Israel. *In vitro* tests show its differential cytotoxicity towards series of transformed cell lines versus cultures of normal and non-transformed cells. This work was shortly followed by a report, describing CAPE as a strong sensitizer, causing propolis allergy (Hausen and Wollenweber 1988) and then, by a subsequent research, describing CAPE synthesis by esterification (Hashimoto et al. 1988). Two years later, in an effort to explain the preferential cytotoxicity of CAPE to the adenovirus-transformed, compared to normal rat embryo fibroblast (CREF) cells, researchers from the institution where CAPE was first isolated (Su et al. 1991) revealed that it also inhibits chemical-viral carcinogenesis of CREF cells. The reports on the preferential activity of CAPE towards transformed cells were the foundation of a study of Guarini et al. (1992) who reported that melanoma cells are more sensitive to CAPE treatment than glioblastoma cells and interestingly, CAPE also appeared to be "an antigenic modulating agent and possibly a differentiation inducing agent.". CAPE's *in vitro* antioxidant effects were first shown on activated human neutrophils, and its 5-lipoxygenase (5-LOX) inhibitory action was reported by Sud'ina et al. (1993). A report on the *in vitro* human immunodeficiency virus-1 (HIV-1) integrase inhibitor activity of CAPE revealed that it possesses antiviral activity. Then, Frenkel et al. (1993) carried out a study on SENCAR mice, confirming its chemopreventive and anti-inflammatory activities *in*

Table 1. Chronology of milestone research publications on the biological activities of CAPE.

Model system	Major effects	Comment	Ref.
Cell lines (C3H 10T1/2; Ltk-; normal rat 6 cells; CV1; Vero; CREF; wt3A; MCF-7; SK-MEL-28; SK-MEL-170; HT-29; normal 1434 fibroblasts and melanocytes)	*In vitro* differential cytotoxicity towards transformed cells, compared to normal cells	2.5 to 50 μg/ml	(Grunberger et al. 1988)
Adenovirus-transformed, compared to normal rat cloned rat embryo fibroblast (CREF) cells	*In vitro* inhibits chemical-viral carcinogenesis	0.1–5 μg/mL	(Su et al. 1991)
5-LOX, isolated from barley; activated human neutrophils	*In vitro* antioxidant; 5-LOX inhibitor	10 μM	(Sud'ina et al. 1993)
Escherichia coli – produced HIV-1 integrase protein	*In vitro* antiviral; HIV-1 integrase inhibitor	Integration IC50 = 19 μM	(Fesen et al. 1993)
SENCAR mice	*In vivo* inhibits chemical carcinogenesis, anti-inflammatory	–	(Frenkel et al. 1993)
Adenovirus-transformed rat embryo fibroblast cells	*In vitro* proapoptotic to transformed cells	1 μg/mL	(Chiao et al. 1995)
U937 cell line	*In vitro* blocks activation of NF-κB by tumor necrosis factor (TNF)	prevents the translocation of the p65 subunit of NF-κB to the nucleus	(Natarajan et al. 1996)
Rabbits	*In vivo* protective against spinal cord ischemia/reperfusion injury	10 μmol/kg pretreatment	(Ilhan et al. 1999)

vivo. Two years later it was shown that its cytotoxic effects are related to induction of apoptosis (Chiao et al. 1995). CAPE's ability to inhibit the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) was shown by Natarajan et al. (1996). The presence of strong antioxidant activity *in vivo* was demonstrated in a rabbit model of spinal cord ischemia/reperfusion injury (Ilhan et al. 1999). From this point on, as is visible from the time chart, the quantity of research on CAPE's pharmacological activity rapidly increased as it became obvious that it is a major contributor to the biological activities of propolis. As a molecule with a simple structure, the task of revealing its pharmacodynamics interactions became more attainable.

Pharmacokinetics

In order to choose a pharmaceutical approach, that will allow for the effective utilization of the biological effects of CAPE, an in-depth understanding of its pharmacokinetic behavior is essential. Pharmacokinetic studies show a favorable profile of CAPE with the exception of its poor water solubility, the resolution of which is a task, achievable by applying tailored technological approaches for pharmaceutical formulation. CAPE has been shown to be hydrolyzed to caffeic acid in rat plasma, but not in human plasma, which is explained by Wang et al. (2009) with to the lack of carboxylesterase in human plasma (Li et al. 2005; Celli et al. 2007). Human carboxylesterases, capable of hydrolyzing CAPE are highly expressed in most metabolic organs, but not in plasma, which could be advantageous for its therapeutic application (Wang et al. 2018). Experiments on the pharmacokinetics of CAPE show that it is cleared rapidly from rats' plasma after venous administration with half-lives between 21.2 to 26.7 min, shown not to be dependent on the dose (Wang et al. 2009). Probably due to species differences, discussed above, the half-life of a CAPE formulation in solvent (CC100), administered orally to humans is significantly longer, reaching on average 18.5 h with T_{max} of 2.7 h (NCT02050334; https://www.ClinicalTrials.gov). Although information on the solvent system, used for the CAPE formulation of CC100 is not available, the half-life value seems to fit in the optimal range for once-daily oral dosing (Smith et al. 2018). In light of CAPE's multiple biological activities, which are achieved at different CAPE concentrations, its controlled and targeted delivery could be further improved by developing specific pharmaceutical formulations.

Pharmaceutical formulation approaches

In vivo experiments show that CAPE's oral bioavailability is limited due to its poor water solubility (0.021 mg/ml) which could be improved by means of pharmaceutical approaches (Ketkar et al. 2016). Not surprisingly, aqueous solubility is an important factor, determining the successful development of chemical entities, researched by the pharmaceutical industry (Savjani et al. 2012). The dependence of oral bioavailability of drugs on their solubility can be explained with Fick's law, which states that absorption is proportional to the concentration gradient across the membrane (Csáky 1984). Aqueous solubility should also be taken in consideration for intravenous (IV) formulations of drug-candidate molecules. Insoluble molecules could necessitate the use of high quantities of organic solvents or otherwise precipitate, in any of the cases risking toxicity or subtherapeutic plasma concentrations (Di and Kerns 2015). Needless to say, state-of-the-art pharmaceutical formulation strategies allow a great deal of alternative approaches, which could not only resolve solubility problems, but also modify the fate of the drug molecule in the organism (Kalepu and Nekkanti 2015). Such formulation approaches, which have been proposed for CAPE delivery are listed in Table 2.

Cocrystal formation. The development of cocrystals of a drug is a long-known strategy, which however has been undergoing rapid development throughout the last decade (Sun 2013; Duggirala et al. 2016). It is an effective strategy to overcome solubility and stability issues and has the advantage of preserving the chemical structure of the active ingredient, allowing storage in a stable crystal form. Cocrystals could improve physicochemical properties of importance for the formulation of dosage forms, such as tablets (Kumar et al. 2018). Ketkar et al. (2016) reported the successful formation of cocrystals of CAPE with coformers caffeine, isonicotinamide or nicotinamide by means of microwave-assisted cocrystallization. Among the cocrystals, those with nicotinamide were shown to best improve CAPE solubility (17.7 times) and oral bioavailability (2.76 times) in rats. X-ray crystallography revealed an uncommon stabilization of the crystal structure by 1,2-benzenediol-amide heterosynthon.

Synthesis of prodrugs. The two hydroxyl groups of CAPE's catechol moiety make it amenable to conjugation with a variety of molecules, forming prodrugs with potentially improved solubility. In the last decade more than 10% of all FDA-approved small-molecule new chemical entities are prodrugs. Prodrugs have little or no pharmacological activity, but undergo enzymatic and chemical changes in the organism, which lead to their conversion to the active parent drugs (Rautio et al. 2018). Li et al. (2019) report the enzymatic glycosylation of CAPE, mediated by dexYG P473S/P856S. As a result, they isolated a glucoside and a glucosyl-glucoside of CAPE with respectively 35 and 90 times increased aqueous solubility, compared to CAPE. The catechol moiety is known to be important for the pharmacological activity of CAPE, so glycosylation can be expected to render it less active (Kim et al. 2013). Although both glucosides exerted anti-inflammatory effects *in vitro*, they were more pronounced in macrophages, treated with the monoglucoside. Both glucosides exerted lower cytotoxicity than CAPE to tumor cell lines probably due to the time, needed for

Table 2. Strategies for pharmaceutical formulation of CAPE and their effectiveness on biological model systems. Biologically-relevant effects marked with bullets●. Arrows represent comparisons towards CAPE water dispersion: ↑more pronounced effect; ↓decrease of activity/biomarker; → comparable effectiveness; no arrow after bullet – comparison not applicable due to experimental design specifics. *In vitro* studies in normal script, *in vivo* studies represented in **bold** script, and major experimental design characteristics represented in *italic* script.

Pharmaceutical formulation strategy	CAPE preparation	Physico Chemical outcome	Biological outcome *(experimental system)*	Ref.
COCRYSTAL FORMATION	cocrystals with nicotinamide	↑ solubility (17.7×)	●↑**oral bioavailability (2.76×)** ***(rats, 100 mg/kg p.o.)***	(Ketkar et al. 2016)
PRODRUGS	4-O-β-D-glucopyranoside	↑ solubility (35×)	●↓ TNF-α; IL-6; NO *(LPS-induced RAW 264.7 macrophages, 5 μM)*	(Li et al. 2019)
			●↓ cytotoxicity *(A375; SMMC-7721; SGC-7901 A549 cell lines, 100 μM)*	
	4-O-α-D-glucopyranoside	↑ solubility (770×)	●↓NO equally to CAPE	(Moon et al. 2017)
		↑ stability to oxidation and hydrolysis	●↑Nrf-2 activation	
			●Intracellular conversion to CAPE *(LPS-induced RAW 264.7 macrophages, 15 μM)*	
	4-Acylated or 3,4-diacylated	↑lipid solubility	●↑protection against oxidative stress induced cell injury	(Renzong et al. 2013)
			●↑blood-brain barrier permeability *(PC12 cell line)*	
INCLUSION COMPLEXES	hydroxypropyl-β-cyclodextrin	↑ solubility catechol in CD cavity	–	(Garrido et al. 2018)
MICROEMULSIONS	eugenol/water	↑ stability droplets 80–250 nm	●↑cytotoxicity *(HCT-116 cell line, 2 μg/ml)*	(Wang et al. 2017b)
	SPIONs/eugenol/water	↑ stability droplets 100–900 nm	●↑cytotoxicity	(Wang et al. 2017a)
			●↑cytotoxicity upon external magnetic field *(HCT-116 cell line, 2 μg/ml)*	
	peppermint oil/water	↑ stability droplets size - <20 nm	●↑cytotoxicity	(Chen et al. 2019)
			●↑cellular uptake	
			●↓cyclin D expression	
			●↑p53 expression *(HCT-116, MCF-7 cells, 10 μg/ml)*	
LIPOSOMES	EPC-35, cholesterol and PEG2000-DSPE liposomes	↑ stability Size – 100 nm; incorporation in bilayer	–	(Coimbra et al. 2011)
MICELLES	non-ionic surfactant micelles	↑ stability	●↓**plasma histamine, released due to Cremophor RH40** ***(50 μg/kg CAPE; 10 mg/kg solubilizer)***	(Scheller et al. 2000)
			●↑histamine release, compared to solubilizer alone *(isolated peritoneal mast cells; 100 μM CAPE, 20 to 2000 μg/ml solubilizer)*	
	sucrose fatty acid ester micelles	↑ stability particle size<100 nm	●→antioxidant (DPPH; ABTS scavanger)	(Guan et al. 2019)
			●↑cytotoxicity *(HCT-116; MCF-7 cells, 2 μg/ml)*	
	triblock copolymer micelles (PEO-b-PCL-b-PEO)	↑ stability size: 39 nm; narrow size distribution; slightly positive zeta-potential	●↑ protection against oxidative stress induced cell injury *(Hep G2, SH-SY5Y cells, 0.1 μg/ml)*	(Yoncheva et al. 2019)
COPOLYMER NANOPARTICLES	poly(d,l-lactic-co-glycolic acid) NPs	↑ stability Size: 206 nm; highly negative zeta potential	●↑antigenotoxic<ethanol CAPE *(Ames test; 14 μg/ml)*	(Arasoglu et al. 2016, Abamor 2017, Arasoğlu and Derman 2018
			●↑moderate antimicrobial *(S. aureus, 31 μg/ml and MRSA, 61 μg/ml)*	
			●↑antileischmanial on both forms of parasites *(Leishmania infantum promastigotes, IC50=32 μg/ml and amastigotes, IC50=8 μg/ml)*	
	methoxy poly(ethylene glycol)-b-poly(ε-caprolactone) NPs	↑ stability lyophilized and reconstituted at 20 mg/ml; size<300 nm; delayed release	●↑**antimetastatic** ***(CT-26 Pulmonary Metastasis Model on BALb/C mice, 5 mg/kg i.v.)***	(Lee et al. 2015)
			●→weak cytotoxicity *(RAW264.7 cells, 50 μg/ml)*	
			●↑growth inhibition (0.5 μg/ml)	
			●↓migration (1 μg/ml)	
			●→proapoptotic (10 μg/ml)*(CT26 cells,)*	
PROTEIN NANOPARTICLES	Albumin NPs	↑ stability 250–300 nm; negative zeta potential	●↓**p65 and HIF-1α** ***(mouse model of DDS-induced colitis, 20 mg/kg i.p.)***	(Tambuwala et al. 2019)
INCORPORATION IN POLYMER FILMS	CAPE NPs, incorporated in methyl cellulose films	NP size: 50–625 nm; film thickness: 45 to 55 μm	●↓bacterial growth *(S. aureus, MIC = 350 μg/mL and E. faecalis MIC = 700 μg/mL)*	(Saelo et al. 2016)
			●→antioxidant (DPPH, FRAP)	
	electrospun poly(3-hydroxybutyrate), coated with polyvinylpyrrolidone	↑solubility (~1.5×) tunable release profile	●Bactericidal *(S. aureus, 200 μg/mL)*	(Ignatova et al. 2018)
		↑surface area	●Bacteriostatic *(E. coli, 850 μg/mL)*	
MATRIX DRUG DELIVERY SYSTEMS	poly(dimethyl siloxane) matrix	sustained release over 4 weeks	*concept of intraocular lenses as devices for CAPE-delivery*	(Dittrich et al. 2012)

activation. Moon et al. (2017) also reported on the synthesis of a glucoside of CAPE by an enzymatic method, employing amylosucrase from *Deinococcus geothermalis*, which resulted in a glucoside 770 times more soluble than CAPE. The much higher solubility of their caffeic acid phenethyl ester-4-O-α-D-glucopyranoside, compared to the one, synthesized by Li et al. (2019), who present it as a caffeic acid phenethyl ester-4-O-β-D-glucopyranoside is

probably due to both molecules being anomers. Moon et al. (2017) further show that their glucoside is converted to CAPE in RAW 264.7 macrophages. It also stimulates nuclear factor erythroid 2-related factor 2 (Nrf2)-dependent gene expression in lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages to a greater extent than CAPE, and decreases nitrite production to the same extent. Not all attempts to create prodrugs are aimed at improving its aqueous solubility. Renzong et al. (2013) synthesized 4-Acylated and 3,4-diacylated derivatives of CAPE. This modification lead to improved blood-brain permeability and better protective activity towards oxidative stress-damaged PC12 cell in respect to CAPE.

Inclusion complexes are formed when a host compound with a hydrophilic exterior and lipophilic cavity, surrounds molecules or parts of molecules of proper size, held in place in the cavity only by van der Waals forces (Challa et al. 2005). Cyclodextrins are cyclic glucopyranose oligosaccharides, which have been successfully utilized for the dissolution of lipophilic drug molecules since the first FDA approval of such a product - oral and IV solution of itraconazole in hydroxy propyl-β-cyclodextrin (HP-β-cyclodextrin), 20 years ago (Kalepu and Nekkanti 2015). Despite α- and β-cyclodextrin cause renal toxicity, γ-cyclodextrin, HP-β-cyclodextrin and sulfobutylether-β-cyclodextrin (SBE-β-cyclodextrin) seem to be safer (Jambhekar and Breen 2016). A study of (Garrido et al. 2018) demonstrates the formation of a stable inclusion complex between CAPE and HP-β-cyclodextrin with the catechol moiety of CAPE fitting in the hydrophobic cavity. Up to date, no biological studies of CAPE in inclusion complexes could be found in the Scopus database. Given the potential advantages of this formulation strategy, toxicological studies could yield data of primary importance.

Microemulsions are thermodynamically stable systems with droplet sizes of about 10 to 100 nm. They can be water-in-oil, oil-in-water or bi-continuous systems, made of water, oil, surfactant and a co-surfactant. Microemulsions are monophasic, transparent and optically isotropic systems. They differ from emulsions by having much lower surface tension values and improved thermodynamic stability (Ita 2017). It has been shown that a commercialized self-microemulsifying drug delivery system of cyclosporine (Neoral) increases its oral bioavailability 6.5-fold compared to the lipid formulation (Sandimmune). Furthermore, in this case the microemulsion allowed for faster intestinal absorption and less variable pharmacokinetic profile (van Mourik et al. 1999). Except for oral formulations, microemulsions hold great potential as transdermal and dermal drug delivery systems (Nastiti et al. 2017). A drawback when considering microemulsion design is the toxicity and irritation of the gastrointestinal tract (GIT) by surfactants, which are in high concentrations. That's why toxicological considerations when choosing surfactants for a microemulsion are of great importance (Rahman et al. 2013). Chen et al. (2019) formulated CAPE in peppermint oil in water microemulsions, emulsified by Tween 20 and lecithin. Droplets were stable for 180 days and were of sizes, smaller than 20 nm. The described CAPE formulation exerted stronger cytotoxic and pro-apoptotic effects on HCT-116 colorectal and MCF-7 breast cancer cells than CAPE. Wang et al. (2017b) reported on the formulation of CAPE in eugenol/water emulsions, by application of an "emulsifying protocol based on guest-host reaction between eugenol and modified without high mechanical energy or surfactant-assistance". It was based on the use of modified rice proteins during emulsification. Formed droplets were of sizes of 80–250 nm and the emulsion was stable over four weeks. Thus formulated, CAPE exerted stronger cytotoxic effects on HTC-116 cells, compared to CAPE, introduced in DMSO (Wang et al. 2017b). An advantage of this approach is that it avoids the use of surfactants, known to be toxic. However, a toxicological evaluation of this formulation is still necessary before it can be applied to humans. In another study of the same group, superparamagnetic iron oxide nanoparticles (SPIONs) were included in the eugenol phase, which resulted in larger droplet sizes and further increased cytotoxicity to HTC-116 cells upon external magnetic field (Wang et al. 2017a). Such an approach could be applied for targeted release of CAPE by localized magnetic field only in the pathological site.

Liposomes are considered the most-successful drug delivery system with many FDA-approved drug products (Bozzuto and Molinari 2015). They are phospholipid bilayer unilamellar or multilamellar structures, which enclose one or more interior water compartments. Liposomes have been shown to be non-toxic and can enclose a great diversity of drugs, modifying their pharmacokinetic profiles. If not surface modified as is in the case of PEG-ylated Doxil (Barenholz 2012), liposomes are phagocytosed after intravenous (IV) application, which can be employed as a 'Trojan horse-like' strategy in the treatment of parasitic diseases which pathogens are normally localized in cells of the mononuclear phagocytic system. A disadvantage of liposomes is the high cost of commercial scale manufacturing and the short plasma half-life of unmodified liposomes (Daraee et al. 2016). Coimbra et al. (2011) showed that CAPE can be incorporated into the phospholipid bilayer of egg phosphatidylcholine-35 (EPC-35), cholesterol and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino(polyethyleneglycol)-2000] (PEG2000-DSPE) liposomes, which resulted in liposome sizes of about 100 nm and stable dispersions. A search in Scopus database revealed no publications, concerning research on the biological effects of liposomal CAPE.

Micelles are dynamic colloidal particles with sizes usually in the range of 5–100 nm in which, unlike liposomes, amphiphilic molecules form monolayers. They consist of core-shell structured aggregates that form when the amphiphilic molecules reach their inherent critical micelle concentration (CMC). The lower the CMC, the more easily micelles are formed. The first study of a CAPE micelle formulation was on non-ionic surfactant dispersions at concentrations close to their CMCs (CMCs in the range of 0.1 mM to 1 mM or 0.01% to 0.05% w/v) and higher,

which aimed at studying their histamine-releasing potential (Scheller et al. 2000). CAPE was formulated in Tween 80, Solutol HS15, Cremophor RH40 or Cremophor EL. *In vivo*, among the tested solubilizers, only Cremophor EL increased histamine concentrations in rat plasma, which however was countered by CAPE, when solubilized in Cremophor EL. The other three tested solubilizers did not cause increases of histamine levels, compared to control. However, when CAPE was formulated in them, the histamine levels were further lowered even in comparison to controls. This could be the result of the anti-inflammatory and antioxidant activities of CAPE. However, the same was not observed *in vitro* in isolated peritoneal mast cells, in which CAPE solubilized in either of the four solubilizers caused increases in histamine release. Sucrose fatty acid esters (SFAE) are another group of amphiphilic micelle-forming molecules, that have the advantage of being safe for ingestion, which has been confirmed by a chronic/carcinogenicity rat study (Takeda and Flood 2002). Furthermore, in 2004 EFSA established "a group ADI of 40 mg/kg bw/day for sucrose esters of fatty acids" (EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) 2010), which is a high dose, considering the concentrations needed for micelle drug delivery (CMCs in the range 3.26 to 0.012 μM) (Becerra et al. 2008). Guan et al. (2019) formulated CAPE in SFAE, stabilized with propylene glycol, and thymol which improved the loading capacity. The resulting particles were smaller than 100 nm and stable for 30 days at 21 °C. The SFAE micelle dispersion of CAPE, contained 0.15% w/w CAPE in 1.0% w/w SFAE, which can be considered a non-toxic SFAE concentration, based on the ADI. The antioxidant activity of the so-formulated CAPE, evaluated by the DPPH and ABTS radical scavenging assays, remains identical to non-loaded CAPE. The cytotoxic effects of the thymol-stabilized, CAPE-loaded SFAE micelles is somewhat improved in HCT-116 and MCF-7 cells. The formation of micelles by synthetic block copolymers is another approach which allows for very low CMCs (10^{-6} to 10^{-7} M), combined with virtually infinite opportunities for structure modifications. Such drug formulations have proved to be a successful strategy with many copolymer micelle-formulated drugs in clinical trials and several available on the market (Cabral et al. 2018). A search in Scopus database showed that up to date there has been one report on CAPE-loading in copolymer micelles and the physico-chemical and pharmacological evaluation of the formulated drug delivery system (Yoncheva et al. 2019). CAPE was loaded in a poly(ethylene oxide)-b-poly(ε-caprolactone)-b-poly(ethylene oxide) (PEO-b-PCL-b-PEO) triblock copolymer, which resulted in a stable micellar dispersion with particle size of 39 nm, with slightly positive zeta-potential and narrow size distribution. The chosen monomers are known for their biocompatibility, and have been approved for application in pharmaceutical formulations by the FDA (Ulery et al. 2011). CAPE, loaded in the micelles was shown to exert protective effects at very low concentrations on models of oxidative damage of Hep G2 and SH-SY5Y cells.

Copolymer nanoparticles have important advantages, including tunable physicochemical parameters, structural stability, capability to form complex structures by addition of a diverse set of functionalities, slow drug release and potentially - biodegradability (Blanco et al. 2015). They are a promising and versatile strategy for the delivery of drugs with diverse physicochemical properties with many successfully commercialized drugs, showing reduced toxicity, improved efficacy and targeting (Bobo et al. 2016). There have been a series of publications on the formulation and pharmacological evaluation of CAPE, loaded in poly (d,l-lactic-co-glycolic acid) (PLGA) nanoparticles (NPs) by the group of Arasoglu (2016), Abamor (2017) and Derman (2018). The formulated by them CAPE-loaded PLGA NPs had sizes of about 206 nm and a negative zeta potential, which is an indicator of their good stability and favorable pharmacokinetic profile (Clogston and Patri 2011). CAPE-loaded particles exerted antimutagenic activity, in a comparable extent to CAPE in ethanolic solution. It was measured by means of the Ames bacterial reverse mutation assay (Arasoğlu and Derman 2018). Furthermore, CAPE-loaded PLGA NPs were shown to have antiparasitic effects towards both forms of *L. infantum* with better efficacy against amastigotes (Abamor 2017). The same copolymer-CAPE formulation exerted moderate antimicrobial activity towards *S. aureus* and methicillin-resistant Staphylococcus aureus (MRSA) (Arasoglu et al. 2016). Lee et al. (2015) reported on another formulation of CAPE in methoxy poly(ethyleneglycol)-b-poly(ε-caprolactone) NPs with sizes of less than 300 nm, which were stable after liophylisation and reconstitution at concentrations as high as 20 mg/ml. CAPE, loaded in the resulting drug delivery system was effective *in vitro* by causing a commensurate propapoptotic effects with non-loaded CAPE and a better effectiveness in reducing the migration of CT-26 cells. These findings were confirmed *in vivo* with CAPE in NPs being a more effective antimetastatic agent than non-loaded CAPE in a CT-26 Pulmonary Metastasis Model on BALb/C mice.

Protein nanoparticles. Protein nanoparticles allow for the formulation of drug delivery systems with improved biocompatibility, biodegradability, surface modification and cellular uptake. There are several successful protein NP products on the market with undoubtedly the most successful and often pointed out as an example for nanopharmaceutical – Abraxane, which is an albumin-bound paclitaxel (Spicer et al. 2018). Tambuwala et al (2019) loaded CAPE in albumin NPs, characterized by particle sizes of 250–300 nm and negative zeta potential. This CAPE formulation exerted an improved anti-inflammatory effect in a mouse model of dextran sulfate sodium (DDS)-induced colitis, accompanied by a small reduction of p65 and hypoxia-inducible factor 1-alpha (HIF-1α) levels.

Incorporation in polymer films has been researched due to CAPE's antibacterial and antioxidant activities. Such formulations can be applied in food packaging in order to increase the shell life of products at risk of oxidation or bacterial growth or in wound dressings for its antiseptic and anticicatrizing properties. Saelo et al. (2016)

created cellulose films with incorporated nanosized CAPE particles, which retained CAPE's antioxidant properties at higher concentrations and inhibited the growth of *S. aureus* and *E. faecalis*. Ignatova et al. (2018) formulated CAPE in films, made of electrospun poly(3-hydroxybutyrate), coated with polyvinylpyrrolidone, which were shown to be bactericidal towards *S. aureus* and bacteriostatic to *E. coli*.

Matrix drug delivery systems are employed in a variety of pharmaceutical formulations, such as tablets, granules, capsules, films, implants, patches, pellets etc. The matrix is a vehicle, in which the active substance is distributed homogenously or dispersed. These systems have the advantages of being relatively simple and inexpensive for production and allow control of the release profile of the loaded drug (Vasvári et al. 2018). Dittrich et al. (2012) loaded CAPE in a poly(dimethyl siloxane) (PDMS) matrix, which allowed for its sustained release over 4 weeks. It was hypothesized that inclusion of CAPE in PDMS lenses would prevent post-operative capsular opacification by reducing the growth and migration of epithelial cells over the capsular bag.

The listed diversity of drug carriers have been shown to possess the capacity to resolve CAPE's solubility issue while allowing its release in the organism, which are prerequisites for its successful pharmaceutical application. The biocompatibility of CAPE delivery systems for specific routes of administration ought to be tested in a case specific manner before they are applied clinically, with special attention on the toxicological approach for the complex nanosized drug delivery systems (Yordanov et al. 2018).

Conclusion

Research on CAPE in the decade after its discovery was focused mainly on finding proof that it is a major constituent of propolis, being a contributor to its diverse pharmacological effects. As such knowledge amassed the cornerstone research period was followed by a period of intensified research on its pharmacodynamic principles, which is the subject of a related article on CAPE's therapeutic potential. In the recent years there has been a growing interest in approaches to overcome a major obstacle towards CAPE's realization as a drug – its poor aqueous solubility. Formulation approaches of CAPE include diverse strategies to not only make it soluble, but also optimize its pharmacokinetic profile and efficacy in different pathological conditions. The described trends in research publication on different aspects of CAPE is an indication that it has a bright future as a pharmaceutical.

References

Abamor ES (2017) Antileishmanial activities of caffeic acid phenethyl ester loaded PLGA nanoparticles against Leishmania infantum promastigotes and amastigotes in vitro. Asian Pacific Journal of Tropical Medicine 10: 25–34. https://doi.org/10.1016/j.apjtm.2016.12.006

Arasoğlu T, Derman S (2018) Assessment of the Antigenotoxic Activity of Poly(D , L -lactic- *co* -glycolic acid) Nanoparticles Loaded with Caffeic Acid Phenethyl Ester Using the Ames *Salmonella* /Microsome Assay. Journal of Agricultural and Food Chemistry 66: 6196–6204. https://doi.org/10.1021/acs.jafc.8b01622

Arasoglu T, Derman S, Mansuroglu B (2016) Comparative evaluation of antibacterial activity of caffeic acid phenethyl ester and PLGA nanoparticle formulation by different methods. Nanotechnology 27: 025103. https://doi.org/10.1088/0957-4484/27/2/025103

Bankova V, Popova M, Trusheva B (2018) The phytochemistry of the honeybee. Phytochemistry 155: 1–11. https://doi.org/10.1016/j.phytochem.2018.07.007

Barenholz Y (Chezy) (2012) Doxil – The first FDA-approved nano-drug: Lessons learned. Journal of Controlled Release 160: 117–134. https://doi.org/10.1016/j.jconrel.2012.03.020

Becerra N, Toro C, Zanocco AL, Lemp E, Günther G (2008) Characterization of micelles formed by sucrose 6-O-monoesters. Colloids and Surfaces A: Physicochemical and Engineering Aspects 327: 134–139. https://doi.org/10.1016/j.colsurfa.2008.06.012

Blanco E, Shen H, Ferrari M (2015) Principles of nanoparticle design for overcoming biological barriers to drug delivery. Nature biotechnology 33: 941–951. https://doi.org/10.1038/nbt.3330

Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR (2016) Nanoparticle-Based Medicines: A Review of FDA-Approved Materials and Clinical Trials to Date. Pharmaceutical Research 33: 2373–2387. https://doi.org/10.1007/s11095-016-1958-5

Boyle F, Sherman D (2006) Scopus: The Product and Its Development. The Serials Librarian 49: 147–153. https://doi.org/10.1300/J123v49n03_12

Bozzuto G, Molinari A (2015) Liposomes as nanomedical devices. International Journal of Nanomedicine 10: 975–999. https://doi.org/10.2147/IJN.S68861

Budimir V, Brailo V, Alajbeg I, Vučićević Boras V, Budimir J (2012) Allergic contact cheilitis and perioral dermatitis caused by propolis: case report. Acta dermatovenerologica Croatica: ADC 20: 187–190.

Cabral H, Miyata K, Osada K, Kataoka K (2018) Block Copolymer Micelles in Nanomedicine Applications. Chemical Reviews 118: 6844–6892. https://doi.org/10.1021/acs.chemrev.8b00199

Celli N, Dragani LK, Murzilli S, Pagliani T, Poggi A (2007) In vitro and in vivo stability of caffeic acid phenethyl ester, a bioactive compound of propolis. Journal of Agricultural and Food Chemistry 55: 3398–3407. https://doi.org/10.1021/jf063477o

Challa R, Ahuja A, Ali J, Khar RK (2005) Cyclodextrins in drug delivery: An updated review. AAPS PharmSciTech 6: E329–E357. https://doi.org/10.1208/pt060243

Chen H, Guan Y, Baek SJ, Zhong Q (2019) Caffeic Acid Phenethyl Ester Loaded in Microemulsions: Enhanced In Vitro Activity against Colon and Breast Cancer Cells and Possible Cellular Mechanisms. Food Biophysics 14: 80–89. https://doi.org/10.1007/s11483-018-9559-y

Chiao C, Carothers AM, Grunberger D, Solomon G, Preston GA, Barrett JC (1995) Apoptosis and Altered Redox State Induced by Caffeic Acid Phenethyl Ester (CAPE) in Transformed Rat Fibroblast Cells. 55: 3576–3583.

Clogston JD, Patri AK (2011) Zeta potential measurement. Methods in Molecular Biology (Clifton, N.J.) 697: 63–70. https://doi.org/10.1007/978-1-60327-198-1_6

Coimbra M, Isacchi B, van Bloois L, Torano JS, Ket A, Wu X, Broere F, Metselaar JM, Rijcken CJF, Storm G, Bilia R, Schiffelers RM (2011) Improving solubility and chemical stability of natural compounds for medicinal use by incorporation into liposomes. International Journal of Pharmaceutics 416: 433–442. https://doi.org/10.1016/j.ijpharm.2011.01.056

Daraee H, Etemadi A, Kouhi M, Alimirzalu S, Akbarzadeh A (2016) Application of liposomes in medicine and drug delivery. Artificial Cells, Nanomedicine, and Biotechnology 44: 381–391. https://doi.org/10.3109/21691401.2014.953633

Dittrich B, Koch B, van Kooten T, Kastner C, Guthoff R, Sternberg K, Möller M (2012) Drug delivery system for sustained delivery of caffeic acid phenethyl ester within lens capsule after cataract surgery. Biomedical Engineering / Biomedizinische Technik 57. https://doi.org/10.1515/bmt-2012-4474

Duggirala NK, Perry ML, Almarsson Ö, Zaworotko MJ (2016) Pharmaceutical cocrystals: along the path to improved medicines. Chemical Communications 52: 640–655. https://doi.org/10.1039/C5CC08216A

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) (2010) Scientific Opinion on the safety of sucrose esters of fatty acids prepared from vinyl esters of fatty acids and on the extension of use of sucrose esters of fatty acids in flavourings. EFSA Journal 8. https://doi.org/10.2903/j.efsa.2010.1512

Fesen MR, Kohn KW, Pommier Y (1993) Inhibitors of human immunodeficiency virus integrase. Proceeding of the National Academy of Sciences of the USA: 1–5. https://doi.org/10.1073/pnas.90.6.2399

Frenkel K, Wei H, Bhimani R, Ye J, Zadunaisky JA, Huang MT, Ferraro T, Conney AH, Grunberger D (1993) Inhibition of tumor promoter-mediated processes in mouse skin and bovine lens by caffeic acid phenethyl ester. Cancer Research 53: 1255–1261.

Garrido EMPJ, Cerqueira AS, Chavarria D, Silva T, Borges F, Garrido JMPJ (2018) Microencapsulation of caffeic acid phenethyl ester and caffeic acid phenethyl amide by inclusion in hydroxypropyl-β-cyclodextrin. Food Chemistry 254: 260–265. https://doi.org/10.1016/j.foodchem.2018.02.007

Ghisalberti EL (1979) Propolis: A Review. Bee World 60: 59–84. https://doi.org/10.1080/0005772X.1979.11097738

Grunberger D, Banerjee R, Eisinger K, Oltz EM, Efros L, Caldwell M, Estevez V, Nakanishi K (1988) Preferential cytotoxicity on tumor cells by caffeic acid phenethyl ester isolated from propolis. Experientia 44: 230–232. https://doi.org/10.1007/BF01941717

Guan Y, Chen H, Zhong Q (2019) Nanoencapsulation of caffeic acid phenethyl ester in sucrose fatty acid esters to improve activities against cancer cells. Journal of Food Engineering 246: 125–133. https://doi.org/10.1016/j.jfoodeng.2018.11.008

Guarini L, Su ZZ, Zucker S, Lin J, Grunberger D, Fisher PB (1992) Growth inhibition and modulation of antigenic phenotype in human melanoma and glioblastoma multiforme cells by caffeic acid phenethyl ester (CAPE). Cellular and Molecular Biology 38: 513–527.

Harzing A-W (2007) Publish or Perish. https://harzing.com/resources/publish-or-perish

Hashimoto T, Tori M, Asakawa Y, Wollenweber E (1988) Synthesis of Two Allergenic Constituents of Propolis and Poplar Bud Excretion. Zeitschrift für Naturforschung C 43: 470–472. https://doi.org/10.1515/znc-1988-5-625

Hausen BM, Wollenweber E (1988) Propolis allergy. (III). Sensitization studies with minor constituents. Contact Dermatitis 19: 296–303. https://doi.org/10.1111/j.1600-0536.1988.tb02931.x

Hladoń B, Bylka W, Ellnain-Wojtaszek M, Skrzypczak L, Szafarek P, Chodera A, Kowalewski Z (1980) In vitro studies on the cytostatic activity of propolis extracts. Arzneimittel-Forschung 30: 1847–1848.

Ignatova M, Manolova N, Rashkov I, Markova N (2018) Antibacterial and antioxidant electrospun materials from poly(3-hydroxybutyrate) and polyvinylpyrrolidone containing caffeic acid phenethyl ester – "in" and "on" strategies for enhanced solubility. International Journal of Pharmaceutics 545: 342–356. https://doi.org/10.1016/j.ijpharm.2018.05.013

Ilhan A, Koltuksuz U, Ozen S, Uz E, Ciralik H, Akyol O (1999) The effects of caffeic acid phenethyl ester (CAPE) on spinal cord ischemia/reperfusion injury in rabbits. European Journal of Cardio-Thoracic Surgery 16: 458–463. https://doi.org/10.1016/S1010-7940(99)00246-8

Ita K (2017) Progress in the use of microemulsions for transdermal and dermal drug delivery. Pharmaceutical Development and Technology 22: 467–475. https://doi.org/10.3109/10837450.2016.1148722

Jambhekar SS, Breen P (2016) Cyclodextrins in pharmaceutical formulations I: structure and physicochemical properties, formation of complexes, and types of complex. Drug Discovery Today 21: 356–362. https://doi.org/10.1016/j.drudis.2015.11.017

Kalepu S, Nekkanti V (2015) Insoluble drug delivery strategies: review of recent advances and business prospects. Acta Pharmaceutica Sinica B 5: 442–453. https://doi.org/10.1016/j.apsb.2015.07.003

Ketkar S, Pagire SK, Goud NR, Mahadik K, Nangia A, Paradkar A (2016) Tracing the Architecture of Caffeic Acid Phenethyl Ester Cocrystals: Studies on Crystal Structure, Solubility, and Bioavailability Implications. Crystal Growth & Design 16: 5710–5716. https://doi.org/10.1021/acs.cgd.6b00759

Kim H, Kim W, Yum S, Hong S, Oh J-E, Lee J-W, Kwak M-K, Park EJ, Na DH, Jung Y (2013) Caffeic acid phenethyl ester activation of Nrf2 pathway is enhanced under oxidative state: Structural analysis and potential as a pathologically targeted therapeutic agent in treatment of colonic inflammation. Free Radical Biology and Medicine 65: 552–562. https://doi.org/10.1016/j.freeradbiomed.2013.07.015

Kumar S, Nanda A (2018) Pharmaceutical Cocrystals: An Overview. Indian Journal of Pharmaceutical Sciences 79: 858–871. https://doi.org/10.4172/pharmaceutical-sciences.1000302

Lee H-Y, Jeong Y-I, Kim EJ, Lee KD, Choi S-H, Kim YJ, Kim DH, Choi K-C (2015) Preparation of Caffeic Acid Phenethyl Ester-Incorporated Nanoparticles and Their Biological Activity. Journal of Pharmaceutical Sciences 104: 144–154. https://doi.org/10.1002/jps.24278

Li B, Sedlacek M, Manoharan I, Boopathy R, Duysen EG, Masson P, Lockridge O (2005) Butyrylcholinesterase, paraoxonase, and albumin esterase, but not carboxylesterase, are present in human plasma. Biochemical Pharmacology 70: 1673–1684. https://doi.org/10.1016/j.bcp.2005.09.002

Li Y, Liu L, Yu X, Zhang Y, Yang J, Hu X, Zhang H (2019) Transglycosylation Improved Caffeic Acid Phenethyl Ester Anti-Inflammatory Activity and Water Solubility by *Leuconostoc mesenteroides* Dextransucrase. Journal of Agricultural and Food Chemistry 67: 4505–4512. https://doi.org/10.1021/acs.jafc.9b01143

Moon K-O, Park S, Joo M, Ha K-T, Baek N-I, Park C-S, Cha J (2017) Glycosylation Enhances the Physicochemical Properties of Caffeic Acid Phenethyl Ester. Journal of Microbiology and Biotechnology 27: 1916–1924. https://doi.org/10.4014/jmb.1706.06017

van Mourik ID, Thomson M, Kelly DA (1999) Comparison of pharmacokinetics of Neoral and Sandimmune in stable pediatric liver transplant recipients. Liver Transplantation and Surgery: Official Publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 5: 107–111. https://doi.org/10.1002/lt.500050203

Nastiti C, Ponto T, Abd E, Grice J, Benson H, Roberts M (2017) Topical Nano and Microemulsions for Skin Delivery. Pharmaceutics 9: 1–37. https://doi.org/10.3390/pharmaceutics9040037

Natarajan K, Singh S, Burke TR, Grunberger D, Aggarwal BB (1996) Caffeic acid phenethyl ester is a potent and specific inhibitor of activation of nuclear transcription factor NF-kappa B. Proceedings of the National Academy of Sciences 93: 9090–9095. https://doi.org/10.1073/pnas.93.17.9090

Neychev H, Dimov V, Vuleva V, Shirova L, Slavcheva E, Gegova G, Manolova N, Bankova V (1988) Immunomodulatory action of propolis. II. Effect of water-soluble fraction on influenza infection in mice. Acta Microbiologica Bulgarica 23: 58–62.

Okonenko LB, Aĭdarkhanov BB, Rakhmetova AA, Zhakisheva SS, Iksymbaeva ZS (1988) Vitamin E and propolis as antioxidants after excessive administration of polyunsaturated fatty acids. Voprosy pitaniia: 68–70.

Rahman MdA, Hussain A, Hussain MdS, Mirza MohdA, Iqbal Z (2013) Role of excipients in successful development of self-emulsifying/microemulsifying drug delivery system (SEDDS/SMEDDS). Drug Development and Industrial Pharmacy 39: 1–19. https://doi.org/10.3109/03639045.2012.660949

Rautio J, Meanwell NA, Di L, Hageman MJ (2018) The expanding role of prodrugs in contemporary drug design and development. Nature Reviews Drug Discovery 17: 559–587. https://doi.org/10.1038/nrd.2018.46

Renzong Z, Xianling N, Zhili Z, et. al. (2013) Design, synthesis and pharmacological evaluation of caffeic acid phenethyl ester acylation as multifunctional neuroprotective agents against oxidative stress injury. Journal of Chinese Pharmaceutical Sciences 22: 475–482.

Saelo S, Assatarakul K, Sane A, Suppakul P (2016) Fabrication of Novel Bioactive Cellulose-Based Films Derived from Caffeic Acid Phenethyl Ester-Loaded Nanoparticles via a Rapid Expansion Process: RESOLV. Journal of Agricultural and Food Chemistry 64: 6694–6707. https://doi.org/10.1021/acs.jafc.6b02197

Scheller S, Dworniczak S, Pogorzelska T, Rajca M, Shani J (2000) Effect of Quercetin, Caffeic Acid and Caffeic Acid Phenylethyl Ester, Solubilized in Non-ionic Surfactants, on Histamine Release in vivo and in vitro. Arzneimittelforschung 50: 72–76. https://doi.org/10.1055/s-0031-1300166

Smith DA, Beaumont K, Maurer TS, Di L (2018) Relevance of Half-Life in Drug Design: Miniperspective. Journal of Medicinal Chemistry 61: 4273–4282. https://doi.org/10.1021/acs.jmedchem.7b00969

Spicer CD, Jumeaux C, Gupta B, Stevens MM (2018) Peptide and protein nanoparticle conjugates: versatile platforms for biomedical applications. Chemical Society Reviews 47: 3574–3620. https://doi.org/10.1039/C7CS00877E

Su Z-Z, Grunberger D, Fisher PB (1991) Suppression of adenovirus type 5 E1A-mediated transformation and expression of the transformed phenotype by caffeic acid phenethyl ester (CAPE). Molecular Carcinogenesis 4: 231–242. https://doi.org/10.1002/mc.2940040310

Sud'ina GF, Mirzoeva OK, Pushkareva MA, Korshunova GA, Sumbatyan NV, Varfolomeev SD (1993) Caffeic acid phenethyl ester as a lipoxygenase inhibitor with antioxidant properties. FEBS Letters 329: 21–24. https://doi.org/10.1016/0014-5793(93)80184-V

Sun CC (2013) Cocrystallization for successful drug delivery. Expert Opinion on Drug Delivery 10: 201–213. https://doi.org/10.1517/17425247.2013.747508

Takeda K, Flood M (2002) Chronic Toxicity and Carcinogenicity of Sucrose Fatty Acid Esters in Fischer 344/DuCrj Rats. Regulatory Toxicology and Pharmacology 35: 157–164. https://doi.org/10.1006/rtph.2001.1502

Tambuwala MM, Khan MN, Thompson P, McCarron PA (2019) Albumin nano-encapsulation of caffeic acid phenethyl ester and piceatannol potentiated its ability to modulate HIF and NF-kB pathways and improves therapeutic outcome in experimental colitis. Drug Delivery and Translational Research 9: 14–24. https://doi.org/10.1007/s13346-018-00597-9

Ulery BD, Nair LS, Laurencin CT (2011) Biomedical Applications of Biodegradable Polymers. Journal of polymer science. Part B, Polymer physics 49: 832–864. https://doi.org/10.1002/polb.22259

Vasvári G, Kalmár J, Veres P, Vecsernyés M, Bácskay I, Fehér P, Ujhelyi Z, Haimhoffer Á, Rusznyák Á, Fenyvesi F, Váradi J (2018) Matrix systems for oral drug delivery: Formulations and drug release. Drug Discovery Today: Technologies 27: 71–80. https://doi.org/10.1016/j.ddtec.2018.06.009

Wang D, Zou L, Jin Q, Hou J, Ge G, Yang L (2018) Human carboxylesterases: a comprehensive review. Acta Pharmaceutica Sinica B 8: 699–712. https://doi.org/10.1016/j.apsb.2018.05.005

Wang T, Wang R, Chen Z, Zhong Q (2017a) Magnetization of eugenol to fabricate magnetic-responsive emulsions for targeted delivery of caffeic acid phenethyl ester. RSC Advances 7: 43455–43463. https://doi.org/10.1039/C7RA08167G

Wang T, Chen H, Wang R, Chen Z, Zhong Q (2017b) Self-emulsification of eugenol by modified rice proteins to design nano delivery systems for controlled release of caffeic acid phenethyl ester. RSC Advances 7: 49953–49961. https://doi.org/10.1039/C7RA09712C

Wang X, Pang J, Maffucci JA, Pade DS, Newman RA, Kerwin SM, Bowman PD, Stavchansky S (2009) Pharmacokinetics of caffeic acid phenethyl ester and its catechol-ring fluorinated derivative following intravenous administration to rats. Biopharmaceutics & Drug Disposition 30: 221–228. https://doi.org/10.1002/bdd.657

Yoncheva K, Tzankova V, Yordanov Y, Tzankov B, Grancharov G, Aluani D, Bankova V, Popova M, Trusheva B, Kondeva-Burdina M, Petrov P (2019) Evaluation of antioxidant activity of caffeic acid phenethyl ester loaded block copolymer micelles. Biotechnology & Biotechnological Equipment: 1–11. https://doi.org/10.1080/13102818.2018.1537753

Yordanov Y, Tzankova V, Yoncheva K (2018) Nanotoxicology: factors, affecting toxicity. Pharmacia 65: 63–71.

Yordanov Y (2019) Caffeic acid phenethyl ester (CAPE): pharmacodynamics and potential for therapeutic application. Pharmacia 66: 107–114. https://doi.org/10.3897/pharmacia.66.e38573