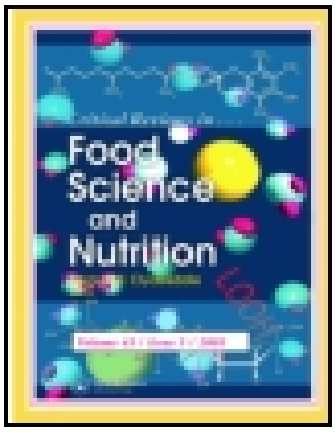

Critical Reviews in Food Science and Nutrition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/bfsn20

Caffeic acid phenethyl ester: A review of its antioxidant activity, protective effects against ischemia-reperfusion injury and drug adverse reactions

Mai F. Tolba[ab], Hany A. Omar[c], Samar S. Azab[a], Amani E. Khalifa[a], Ashraf B. Abdel-Naim[ad] & Sherif Z. Abdel-Rahman[b]

[a] Department of Pharmacology and Toxicology, Faculty of Pharmacy, Ain Shams University, Cairo, 11566, Egypt

[b] Department of Obstetrics and gynecology, The University of Texas Medical Branch, Galveston, Texas, 77555, USA

[c] Department of Pharmacology, Faculty of Pharmacy, Beni-Suef University, 62514, Egypt

[d] Department of Pharmacology and Toxicology, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia

Accepted author version posted online: 03 Nov 2014.

To cite this article: Mai F. Tolba, Hany A. Omar, Samar S. Azab, Amani E. Khalifa, Ashraf B. Abdel-Naim & Sherif Z. Abdel-Rahman (2014): Caffeic acid phenethyl ester: A review of its antioxidant activity, protective effects against ischemia-reperfusion injury and drug adverse reactions, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2013.821967

To link to this article: http://dx.doi.org/10.1080/10408398.2013.821967

Caffeic acid phenethyl ester: A review of its antioxidant activity, protective effects against ischemia-reperfusion injury and drug adverse reactions

Mai F.Tolba[1,2*], Hany A. Omar[3], Samar S. Azab[1], Amani E. Khalifa[1], Ashraf B. Abdel-Naim[1,4], Sherif Z. Abdel-Rahman[2]

[1]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Ain Shams University, Cairo, 11566, Egypt, [2]Department of Obstetrics and gynecology, The University of Texas Medical Branch, Galveston, Texas, 77555, USA, [3]Department of Pharmacology, Faculty of Pharmacy, Beni-Suef University, 62514, Egypt, [4]Department of Pharmacology and Toxicology, Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia

[*]**Corresponding author**

Mai F. Tolba

Department of Obstetrics and gynecology, The University of Texas Medical Branch,

Galveston, Texas, 77555, USA

E-mail: matolba@utmb.edu, tolba.mf@gmail.com

Abstract:

Propolis, a honey bee product, has been used in folk medicine for centuries for the treatment of abscesses, canker sores and for wound healing. Caffeic acid phenethyl ester (CAPE) is one of the most extensively investigated active components of propolis which possess many biological activities, including antibacterial, antiviral, antioxidant, anti-inflammatory, and anti-cancer effects. CAPE is a polyphenolic compound characterized by potent antioxidant and cytoprotective activities and protective effects against ischemia-reperfusion (I/R)-induced injury in multiple tissues such as brain, retina, heart, skeletal muscles, testis, ovaries, intestine, colon and liver. Furthermore, several studies indicated the protective effects of CAPE against chemotherapy-induced adverse drug reactions (ADRs) including several antibiotics (streptomycin, vancomycin, isoniazid, ethambutol) and chemotherapeutic agents (mitomycin, doxorubicin, cisplatin, methotrexate). Due to the broad spectrum of pharmacological activities of CAPE, this review makes a special focus on the recently published data about CAPE antioxidant activity as well as its protective effects against I/R-induced injury and many adverse drug reactions.

Keywords: antioxidant, chemistry, caffeic acid phenethyl ester (CAPE), ischemia/reperfusion (I/R)

1. Introduction:

Natural products played an important role in the process of drug discovery. Polyphenolics comprise an important category of bioactive compounds of natural origin. Propolis, is a naturopathic formula produced by honey bees (*Apis mellifera* L.) that is rich in polyphenolic compounds [Viuda-Martos et al., 2008]. This resinous substance is used safely in folk medicine for its therapeutic effects [Viuda-Martos et al., 2008]. The healing benefits of honey-bee products are also mentioned in The Holy Qur'an [Abdel Haleem et al., 2005; Loukas et al., 2010]. CAPE is a promising component of honey-bee propolis. Several studies elucidated that CAPE has a multitude of beneficial biological properties. It has anti-inflammatory [Toyoda et al., 2009], antioxidant [Gocer and Gulcin, 2011], and anticancer activities [Lin et al., 2012]. CAPE also possesses neuroprotective, hepatopreotective and cardioprotective capacities [Tolba et al., 2013]. This promising compound has strong antioxidant and cytoprotective effects as evidenced *in vitro* and *in vivo*. Furthermore, CAPE exhibited protective effects against ischemia-reperfusion (I/R) injury in multiple target tissues as indicated by a wide range of in vivo studies. Experimental evidence demonstrated that CAPE exerts protective effects against adverse drug reactions (ADRs) including several antibiotics and chemotherapeutic agents. The present review discusses CAPE chemistry, and biological activities with special emphasis on antioxidant activity as well as protection against I/R injury and adverse drug reactions. The information covered in this review encourages further investigation of CAPE in the clinical setting as an adjunct to hinder ROS-induced damages including I/R injuries and ADRs in humans.

2. CAPE Chemistry:

CAPE is a diphenolic compound that has the empirical formula $C_{17}H_{16}O_4$, and molecular weight of 284.3. The complete chemical name of CAPE is: (E)-3-(3,4-dihydroxyphenyl)-2-propionic acid, 2-phenylethyl 3-(3,4-dihydroxyphenyl)-2-propenoate [2011; 2012]. The chemical structure of CAPE is shown in Fig.1. CAPE is a white, fine crystalline powder, insoluble in water but freely soluble in ethanol, methanol, acetone and DMSO. The solubility of CAPE in these solvents is about 10 mg/ml [2011]. The use of alcohols as solvents for CAPE in the in vivo experiments should be with caution, as they can produce new caffeic acid esters via transestrification [Celli et al., 2007]. CAPE was first identified as a component of propolis in 1987 [Bankova et al., 1987]. CAPE can be either extracted from propolis by different extraction methods or it can be chemically synthesized by several methods including response surface methodology from caffeic acid and phenethyl alcohols with a molar conversion value of 96% [Chen et al., 2011] and 91.2%.[Chen et al., 2010].

2. Antioxidant activity of CAPE

Oxygen is utilized by the cells as a source of energy through oxidative phosphorylation. In this process, ATP generation is coupled with a reaction in which four electrons and four protons are added to O_2 to form two molecules of H_2O. But when a molecule of O_2 gains only one electron to form superoxide anion ($O_2^{\bullet-}$), this highly reactive oxygen species (ROS) tends to gain three more electrons and four protons to form H_2O. This process involves several reactions and results in the production of other ROS such as hydrogen peroxide (H_2O_2), hydroxyl radical

($OH^{\bullet}$) and peroxynitrite ($ONOO^{-}$). Although the controlled production of ROS has an important physiological role, a high production of ROS that is not counterbalanced by the cellular antioxidant defense produces oxidative stress. Oxidative stress has been proposed to play an important role in the pathogenesis of many diseases including cancer, cardiovascular disease, atherosclerosis, hypertension, ischemia/reperfusion (I/R) injury, diabetes mellitus, neurodegenerative disorders (Alzheimer's disease and Parkinson's disease), rheumatoid arthritis, and ageing [Reuter et al., 2010]. Accordingly, antioxidants may play a significant protective role in various disease conditions.

The antioxidant properties of polyphenols are widely acknowledged. CAPE is a hydroxyl derivative of cinnamic acid. The presence of CH2=CH-COOH group in cinnamic acids ensures greater antioxidant capacity compared to other phenolic acids as benzoic acid. The steric hinderance of the phenolic hydroxyls by a neighbouring inert group such as methyl enhanced its antioxidant activity [Widjaja et al., 2008]. Diphenolics act as antioxidants via inhibiting both free radicals' propagation and formation reactions [Cotelle et al., 1996; Russo et al., 2000]. They have the capacity to chelate the transition metal [van Acker et al., 1996] and/or to inhibit the enzymes implicated in the initiation reactions [Cotelle et al., 1996; Russo et al., 2000]. Propolis extract exhibits interesting antioxidant properties. Russo *et al.* showed that propolis extract (containing CAPE) exhibited more prominent antioxidant properties compared to propolis deprived of CAPE [Russo et al., 2002]. This suggests an important role for CAPE in the antioxidant activity of propolis [Russo et al., 2002]. Consistent with this suggestion, CAPE showed potent ability to inhibit the formation of superoxide anion produced during autoxidation of β-mercaptoethanol and to quench 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical. In the same

study, CAPE also inhibited xanthine oxidase (XO) activity, the well known physiological source of superoxide anions in eucaryotic cells. Moreover, CAPE exhibits a potent antilipoperoxidative cytoprotective and antigenotoxic potential against oxidative damage [Chen et al., 2009; Gocer and Gulcin, 2011; Wang et al., 2008; Wang et al., 2010]. Chen *et al.* [2012] showed that CAPE activated the expression of the antioxidant gene heme oxygenase-1(HO-1) and intercellular adhesion molecule 1 (ICAM-1) gene in retinal cells both in vitro and in vivo. In this study, feeding CAPE to albino rats enhanced the electroretinographic responses and changed the lipid profile in the rats' retinas [Chen et al., 2012]. In a recent study, Sahin *et al.* [2013a] indicated that CAPE treatment alleviated oxidative stress in acute methanol intoxication in the retina and optic nerve and preserved the integrity of the retinal ganglion cell layer as evidenced from histopathological evaluation. Eşrefoğlu *et al.* [2012] reported that CAPE protects kidneys against aging-related oxidative injury in rats. The underlying mechanism was attributed to alleviation of malone dialdehyde (MDA) levels with concurrent elevation in superoxidae dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) activities, and reduced glutathione (GSH) levels in kidney tissues from old rats. Moreover, Yilmaz *et al.* [2004] showed that CAPE protects against lipid peroxidation and replenishes the activities of antioxidant enzymes in the liver tissues of streptozotocin (STZ)-induced diabetic rat model. STZ is used in experimental induction of diabetes and is known to produce oxidative stress in multiple target tissues. This protective capacity was supported by another study by Okutan *et al.* [2005], in which CAPE reversed the oxidative stress in cardiac tissues of STZ-induced diabetic rats. Ozguner *et al.* [2005] elaborated that pretreatment with CAPE can provide significant protection against extracorporeal shock wave lithotripsy-induced free radical damage of renal tissues. The antioxidant activity of CAPE

was believed to protect against lithium-induced oxidative damage in renal tissues in rats [Oktem et al., 2005]. In a recent study, Mansour and Tawfik [2012] demonstrated that 7 days pretreatment with CAPE protected against radiation-induced cardiac tissue damage in rats through reduction of MDA, adenosine deaminase (ADA) and XO activities together with boosting NOx level and SOD activity. Different oxidative-stress targets affected by CAPE are illustrated in Fig. 2

3. *Protective effect of CAPE against ischemia/reperfusion (I/R) injury*

Several studies indicated that CAPE plays an important protective role against I/R injury in multiple tissue types including intestine, colon, retina, heart, ovaries, skeletal muscles, liver, brain and testis. These studies are summarized in Table 1 and Fig. 3. It was demonstrated by Teke *et al.* [2012] that CAPE alleviates the intestinal mucosal injury triggered by superior mesenteric I/R in rats. This was evidenced through improved intestinal mucosal injury scores, intestinal edema, reduced oxidative stress in the intestinal tissues and pro-inflammatory cytokine in plasma. CAPE also boosted the antioxidant parameters in the intestinal tissues. This enhanced the survival rate of CAPE-treated I/R animals. This observation was further substantiated in another study by Teke *et al.* [2013] in which CAPE treatment prevented remote I/R injury-induced delay of colonic anastomotic wound healing. Administration of CAPE reduced oxidative stress markers in colonic anastomotic tissues and plasma pro-inflammatory cytokine levels with subsequent improvement of colonic anastomotic bursting pressures and histopathological scores. Shi *et al.* [2010] demonstrated the protective effect of CAPE against I/R-induced retinal injury in rats. This was attributed to the enhancement of the

activities of the antioxidant enzymes SOD, GPx, and CAT in the retina of CAPE-treated animals. CAPE also, attenuated I/R-induced apoptosis of retinal cells in the inner nuclear and ganglion cells of the retina. In a different study, it was shown that supplementing the cardioplegic solutions with CAPE improved the antioxidant defense system of rat heart during I/R injury. The groups treated with CAPE-supplemented solution showed significant reduction in MPO, Na^+/K^+ ATPase activity [Ozeren et al., 2005]. Kart *et al*. [2009] showed that CAPE ameliorated ovarian I/R damages in rabbits through its antioxidant activity. CAPE prominently reduced the degenerative effects of I/R injury as evidenced by histopathological assessment. CAPE also, exhibited comparable effects to vitamin E in protecting against the harmful effects of hind limb I/R in skeletal muscle [Ozyurt et al., 2007]. The possible protective mechanisms of CAPE were explored in a separate study by Andrade-Silva *et al.* [2009]. The group concluded that CAPE effect may be related to its inhibition of the NF-kB signaling pathway and decreased tissue inflammatory response following skeletal muscle I/R [Andrade-Silva et al., 2009]. Saavedra-Lopes *et al.* [2008] showed that the same mechanism is involved in CAPE amelioration of the acute inflammatory response following I/R in the liver. In 2008, Feng *et al.* reported that CAPE compensates the functional alterations in mitochondria isolated from mouse brain and liver tissues challenged by anoxia-reoxygenation. This was attributed to inhibiting the decrease in membranes fluidity, as well as the increase in lipoperoxidation and protein carbonylation. This is in addition to the blockade of the enhanced release of cardiolipin and cytochrome c [Feng et al., 2008]. CAPE was also reported to provide neuroprotection against cerebral I/R through attenuating the elevation of plasma MDA, CAT and XO content and restoring the levels of plasma GSH and NO [Altug et al., 2008]. CAPE was also reported

to protect the testis against I/R injury [Atik et al., 2006]. It attenuated testicular tissue damage, MPO levels as well as iNOS activity in testicular tissues [Atik et al., 2006]. In another study, Namazi *et al.*, [2009] suggested that the major mechanism for CAPE protective effect against ischemia-reperfusion injury is via decreased expression of lymphocyte function-associated antigen-1 (LFA-1) and intercellular adhesion molecule-1(ICAM-1). Further clinical studies are required to clarify the potential merit of CAPE I/R-induced organ injury that may be encountered during particular surgeries or with disease conditions as myocardial infarction and stroke.

4. Protective effects of CAPE against drug adverse reactions

There is no doubt that the adverse reactions encountered with chemotherapies are major limiting factors for their use. Development of solutions to minimize such toxic effects is a critical issue. Several studies suggested the potential merit of CAPE as a chemopreventive agent against the toxic effects of a wide range of commonly used chemotherapeutic agents. Table 2 summarizes these studies. Recently, Bakir *et al.* [2013] showed that CAPE treatment attenuated streptomycin-induced injury and apoptosis in the inner ear hair cells. The effect was confirmed through histopathological and immunohistochemical examination of cochleas as well as distortion product otoacoustic emissions testing. Ocak *et al.* [2007] indicated that CAPE protects against vancomycin-induced alterations in kidney function and histology through counteracting the elevation in MDA and NO levels in kidney tissues. Sahin *et al.* [2013b] demonstrated that CAPE treatment was able to decrease the oxidative stress in the retina and optic nerve in isoniazid and ethambutol-treated rats and to prevent the shedding of retinal ganglion cell (RGC).

Its interaction with SOD seems crucial for alleviation of ocular oxidative stress and RGCs toxicity [Sahin et al., 2013b].

Sulaiman [2012] reported that CAPE protects against mitomycin-induced clastogenesis. Treatment with CAPE diminished the frequency of chromosomal aberrations and micronuclei induced by mitomycin. It also restored the mitotic activity in the bone marrow cells of mice challenged with mitomycin. This was attributed, at least in part, to CAPE antioxidant effects. Doxorubicin (DOX) is one of the most important chemotherapies against solid tumors. However, its use is limited by dose-related toxicities in different target tissues. It was indicated by Yagmurca *et al.* [2004] that pretreatment of rats with CAPE protected renal tissues against DOX-induced toxic damages. The nephrotoxic action of DOX is attributed to free radical generation which is attenuated by CAPE antioxidant effect. DOX may also induce cardiotoxicity due to the same mechanism of free radical generation. Chlopcikova *et al*. [2004] reported that caffeic acid, the main metabolite of CAPE [Celli et al., 2007] is an effective cytoprotective agent against DOX-induced cardiotoxicity in rats. Fadillioglu *et al.* [2004] indicated that the protective effect of CAPE against DOX- induced cardiotoxicity in rats occurs via ameliorating the changes in oxidant–antioxidant status of heart tissue. This is in addition to reversing the changes in haemodynamics, biochemical parameters, and ultrastructural alterations. Lin *et al.* [2006] demonstrated that CAPE attenuates DOX-induced neuronal injury through its antioxidant properties.

Cisplatin is an anticancer alkylating agent that is basically effective for germ cell tumors. However, its use is limited by dose-related nephrotoxicity. Several studies showed that pretreatment with CAPE abolished cisplatin-induced nephrotoxicity in rats as evidenced by

compensating the alterations in BUN, creatinine, NO, CAT, SOD, GPx, MPO and by histopathology [Ozen et al., 2004; Yilmaz et al., 2005]. In another study, Yilmaz *et al.* [2010] indicated that CAPE significantly decreased the total number of chromosomal aberrations and abnormal metaphases induced by cisplatin. This was attributed to the free radical scavenging effect of CAPE. Iraz *et al.* [2006] reported that CAPE could prevent cisplatin-induced oxidative changes in the liver via boosting the antioxidant defense system and reducing ROS. Furthermore, CAPE was shown to protect against cisplatin-ototoxicity in rats via minimizing the disturbance in XO/xanthine dehydrogenase (XD) system [Kizilay et al., 2004]. XD and XO catalyze the same reaction at the end steps of the purine catabolic pathway. XD enzyme may be converted to XO to produce more superoxide radicals during I/R and oxidizing environment. This pathway is involved in cisplatin-ototoxicity. Methotrexate is one of the most widely used antimetabolites in cancer chemotherapy. Several studies assessed the protective actions of CAPE against methotrexate (MTX)-induced toxic reactions. Previous reports suggested a protective role of CAPE against MTX-induced hepatorenal injury in rats [Cakir et al., 2011; Uz et al., 2005]. This was explained by the ability of CAPE to significantly reduce TNF-α and IL-1β levels in serum in addition to protecting against lipid peroxidation. In a recent study, Cakir *et al*. [2011] suggested that GSH levels and Na^+K^+-ATPase activities in hepatic and renal tissues were restored upon administration of CAPE, showing the protective effect of CAPE on membranes and other subcellular colloidal compartments. Moreover, Uzar *et al.* indicated that CAPE alleviated methotrexate (MTX)-induced alterations in adenosine deaminase (ADA) activity and NO levels that are involved in the pathogenesis of MTX-induced spinal cord toxicity [Uzar et al., 2006b]. It was also reported that CAPE acts as a potential protective agent against cerebellar-oxidative

damage induced by MTX via its antioxidant properties [Uzar et al., 2006a]. Studies by, Armagan *et al.* [2008] indicated that CAPE protects against MTX-induced testicular toxicity.

5. *Conclusions*

CAPE is a polyphenolic component of propolis that is characterized by multiple biological activities. This review addresses the up-to-date studies about CAPE potential antioxidant and cytoprotective activities as well as protection against I/R injury and adverse drug reactions. CAPE is characterized by potent antioxidant and cytoprotective activities. CAPE has demonstrated protective effects against ischemia reperfusion injury in multiple target tissues including brain, retina, heart, skeletal muscles, testis, ovaries, intestine, colon and liver. Several studies indicated the protective effects of CAPE against chemotherapy-induced adverse drug reactions (ADRs) including several antibiotics (streptomycin, vancomycin, isoniazid, ethambutol) and chemotherapeutic agents (mitomycin, doxorubicin, cisplatin, methotrexate,). ROS play an important role in the process of cell senescence and in the pathophysiology of multiple disease states including preeclampsia, cancer, neurodegenerative diseases, myocardial ischemia, and autoimmune diseases. ROS are also important inducers of many adverse drug reactions. Given the potent antioxidant and cytoprotective effects of CAPE, it is suggested as a beneficial dietary supplement to improve human health condition and to protect against adverse health states induced by ROS. It warrants attention that the pleiotropic mechanism of action of CAPE, while offering a therapeutic advantage, might impose adverse effects. In addition, CAPE lacks comprehensive pharmacokinetic studies that are required as a critical preceding step to clinical trials. Consequently, further preclinical safety studies are thus required to determine the

therapeutic index of CAPE before its use in humans. In light of the translational potential of CAPE in fostering effective therapeutic strategies for many diseases, the elucidation of its mechanism of action and safety margins merit continued investigations.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

References:

(2011). Product information: Phenethyl caffeiate. vol. 70750. Cayman Chemical Company, p. 1.

(2012). Caffeic acid phenethyl ester. GENERIC EU MSDS. SIGMA-ALDRICH, p. 1-6.

Abdel Haleem M.A.S., (2005). The Qur'an: A new translation by Abdel Haleem M.A.S., pp. 170. Oxford University Press Inc., New York

Altug M. E., Serarslan Y., Bal R., Kontas T., Ekici F., Melek I. M., Aslan H., Duman T. (2008). Caffeic acid phenethyl ester protects rabbit brains against permanent focal ischemia by antioxidant action: a biochemical and planimetric study. Brain Res 1201, 135-142.

Andrade-Silva AR, Ramalho FS, Ramalho LN, Saavedra-Lopes M, Jordão AA Jr, Vanucchi H, Piccinato CE, Zucoloto S, (2009). Effect of NFkappaB inhibition by CAPE on skeletal muscle ischemia-reperfusion injury. J Surg Res 153, 254-262. .

Armagan A., Uzar E., Uz E., Yilmaz H. R., Kutluhan S., Koyuncuoglu H. R., Soyupek S., Cam H., Serel T .A., (2008). Caffeic acid phenethyl ester modulates methotrexate-induced oxidative stress in testes of rat. Hum Exp Toxicol 27, 547-552.

Atik E., Gorur S., Kiper A. N., (2006). The effect of caffeic acid phenethyl ester (CAPE) on histopathological changes in testicular ischemia-reperfusion injury. Pharmacol Res 54, 293-297.

Bakir S., Ozbay M., Gun R., Yorgancilar E., Kinis V., Keles A., Abakay A., Gokalp O., Topcu I., (2013). The protective role of caffeic acid phenethyl ester against streptomycin ototoxicity . Am J Otolaryngol 34, 16-21.

Bankova V., Dyulgerov A., Popov S., Marekov N., (1987). A GC/MS study of the propolis phenolic constituents. Z Naturforsch 42, 147-151.

Cakir T., Ozkan E., Dulundu E., Topaloglu U., Sehirli A. O., Ercan F., Sener E., Sener G., (201 1). Caffeic acid phenethyl ester (CAPE) prevents methotrexate-induced hepatorenal oxidative injury in rats. J Pharm Pharmacol 63, 1566-1571.

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. J Agric Food Chem 55, 3398–3407.

Chen H., Tran J. T., Anderson R. E., Mandal M. N., (2012). Caffeic acid phenethyl ester protects 661W cells from H2O2-mediated cell death and enhances electroretinography response in dim-reared albino rats. Mol Vis 18, 1325-1338.

Chen HC, Chen JH, Chang C, Shieh CJ, (2011). Optimization of ultrasoundaccelerated synthesis of enzymatic caffeic acid phenethyl ester by response surface methodology. . Ultrason Sonochem 18, 455–459.

Chen HC, Ju HY, Twu YK, Chen JH, Chang CM, Liu YC, Chang C, Shieh CJ, (2010). Optimized enzymatic synthesis of caffeic acid phenethyl ester by RSM. N Biotechnol 27, 89–93.

Chen Y. J., Huang A. C., Chang H. H., Liao H. F., Jiang C. M., Lai L. Y., Chan J. T., Chen Y. Y., Chiang J., (2009). Caffeic acid phenethyl ester, an antioxidant from propolis, protects peripheral blood mononuclear cells of competitive cyclists against hyperthermal stress. J Food Sci 74, H162-167.

Chlopcikova S., Psotova J., Miketova P., Sousek J., Lichnovsky V., Simanek V., (2004). Chemoprotective effect of plant phenolics against anthracycline-induced toxicity on rat cardiomyocytes. Part II. caffeic, chlorogenic and rosmarinic acids. Phytother Res 18, 408-413.

Cotelle N, Bernier JL, Catteau JP ,Pommery J, Wallet JC, Gaydou EM, (1996). Antioxidant properties of hydroxy-flavones. Free Radic Biol Med 20, 35-43.

Eşrefoğlu M, Iraz M, Ateş B, Gül M, (2012). Not only melatonin but also caffeic acid phenethyl ester protects kidneys against aging-related oxidative damage in Sprague Dawley rats. Ultrastruct Pathol 36, 244-251.

Fadillioglu E., Oztas E., Erdogan H., Yagmurca M., Sogut S., Ucar M., Irmak M. K., (2004). Protective effects of caffeic acid phenethyl ester on doxorubicin-induced cardiotoxicity in rats .J Appl Toxicol 24, 47-52.

Feng Y., Lu Y. W., Xu P. H., Long Y., Wu W. M., Li W., Wang R., (2008). Caffeic acid phenethyl ester and its related compounds limit the functional alterations of the isolated mouse brain and liver mitochondria submitted to in vitro anoxia-reoxygenation: relationship to their antioxidant activities. Biochim Biophys Acta 1780, 659-672.

Gocer H., Gulcin I., (2011). Caffeic acid phenethyl ester (CAPE): correlation of structure and antioxidant properties. Int J Food Sci Nutr 62, 821-82.5

Iraz M., Ozerol E., Gulec M., Tasdemir S., Idiz N., Fadillioglu E., Naziroglu M., Akyol O., (2006). Protective effect of caffeic acid phenethyl ester (CAPE) administration on cisplatin-induced oxidative damage to liver in rat. Cell Biochem Funct 24, 357.361-

Kart A., Cigremis Y., Ozen H., Dogan O., (2009). Caffeic acid phenethyl ester prevents ovary ischemia/reperfusion injury in rabbits. Food Chem Toxicol 47, 1980-1984.

Kizilay A., Kalcioglu M. T., Ozerol E., Iraz M., Gulec M., Akyol O., Ozturan O., (2004). Caffeic acid phenethyl ester ameliorated ototoxicity induced by cisplatin in rats. J Chemother 16, 381-387.

Lin H-P, Lin C-Y, Huo C, Su L-C, Chuu C-p, (2012). Anticancer effect of caffeic acid phenethyl ester. Pharmacologia 3, 26-30.

Lin Y. H., Chiu J. H., Tseng W. S., Wong T. T., Chiou S. H., Yen S. H., (2006). Antiproliferation and radiosensitization of caffeic acid phenethyl ester on human medulloblastoma cells. Cancer Chemother Pharmacol 57, 525-532.

Loukas M, Saad Y, Tubbs RS, Shoja MM., (2010). The heart and cardiovascular system in the Qur'an and Hadeeth. Int J Cardiol 140, 19-23.

Mansour H. H., Tawfik S. S., (2012). Early treatment of radiation-induced heart damage in rats by caffeic acid phenethyl ester. Eur J Pharmacol 692, 46-51.

Namazi H., (2009). Decreasing the expression of LFA-1 and ICAM-1 as the major mechanism for the protective effect of caffeic acid phenethyl ester on ischemia-reperfusion injury. J Plast Reconstr Aesthet Surg 62, 550.

Ocak S., Gorur S., Hakverdi S., Celik S., Erdogan S., (2007). Protective effects of caffeic acid phenethyl ester, vitamin C, vitamin E and N-acetylcysteine on vancomycin-induced nephrotoxicity in rats. Basic Clin Pharmacol Toxicol 100, 328-333.

Oktem F., Ozguner F., Sulak O., Olgar S., Akturk O., Yilmaz H. R., Altuntas I., (2005). Lithium-induced renal toxicity in rats: protection by a novel antioxidant caffeic acid phenethyl ester. Mol Cell Biochem 277, 109-115.

Okutan H., Ozcelik N., Yilmaz H. R., Uz E., (2005). Effects of caffeic acid phenethyl ester on lipid peroxidation and antioxidant enzymes in diabetic rat heart. Clin Biochem 38, 191-196.

Ozen S., Akyol O., Iraz M., Sogut S., Ozugurlu F., Ozyurt H., Odaci E., Yildirim Z., (2004). Role of caffeic acid phenethyl ester, an active component of propolis, against cisplatin-induced nephrotoxicity in rats. J Appl Toxicol 24, 27-35.

Ozeren M., Sucu N., Tamer L., Aytacoglu B., Bayri O., Dondas A., Ayaz L., Dikmengil M., (2005). Caffeic acid phenethyl ester (CAPE) supplemented St. Thomas' hospital cardioplegic solution improves the antioxidant defense system of rat myocardium during ischemia-reperfusion injury. Pharmacol Res 52, 258-263.

Ozguner, F., Armagan, A., Koyu, A., Caliskan, S., Koylu, H., (2005). A novel antioxidant agent caffeic acid phenethyl ester prevents shock wave-induced renal tubular oxidative stress. Urol Res 33, 239-243.

Ozyurt H., Ozyurt B., Koca K., Ozgocmen S., (2007). Caffeic acid phenethyl ester (CAPE) protects rat skeletal muscle against ischemia-reperfusion-induced oxidative stress. Vascul Pharmacol 47, 10.112-8

Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB., (2010). Oxidative stress, inflammation, and cancer: how are they linked? Free Radic Biol Med 49, 1603-1616.

Russo A, Acquaviva R, Campisi A, Sorrenti V, Di Giacomo C, Virgata G, Barcellona ML, Vanella A, (2000). Bioflavonoids as antiradicals, antioxidants and DNA cleavage protectors. Cell Biol Toxicol 16, 91-98.

Russo A., Longo R., Vanella A., (2002). Antioxidant activity of propolis: role of caffeic acid phenethyl ester and galangin. Fitoterapia 73 Suppl 1, S21-29.

Saavedra-Lopes M, Ramalho FS, Ramalho LN, Andrade-Silva A, Martinelli AL, Jordão AA Jr, Castro-e-Silva O, Zucoloto S, (2008). The protective effect of CAPE on hepatic ischemia/reperfusion injury in rats. J Surg Res 150, 271-277.

Sahin A., Kaya S., Turkcu G., Cingu A. K., Yuksel H., Turkcu F. M., Cinar Y., Ari S., Sahin M., Caca I., Gokalp O., (2013a). The effects of caffeic acid phenethyl ester in acute methanol toxicity on rat retina and optic nerve. Cutan Ocul Toxicol.

Sahin A., Kursat Cingu A., Kaya S., Turkcu G., Ari S., Evliyaoglu O., Cinar Y., Turkcu F. M., Yuksel H., Murat M., Caca I., Gokalp O., (2013b). The protective effects of caffeic acid phenethyl ester in isoniazid and ethambutol-induced ocular toxicity of rats. Cutan Ocul Toxicol.

Shi Y., Wu X., Gong Y., Qiu Y., Zhang H., Huang Z., Su K ,.(2010). Protective effects of caffeic acid phenethyl ester on retinal ischemia/reperfusion injury in rats. Curr Eye Res 35, 930-937.

Sulaiman G. M., (2012). Role of caffeic acid phenethyl ester on mitomycin C induced clastogenesis: analysis of chromosome aberrations, micronucleus, mitotic index and adenosine deaminase activity in vivo. J Appl Genet 53, 213-219.

Teke Z., Bostanci E. B., Yenisey C., Kelten E. C., Sacar M., Simsek N. G., Duzcan S. E., Akoglu M., (2013). Caffeic Acid phenethyl ester prevents detrimental effects of remote ischemia-reperfusion injury on healing of colonic anastomoses. J Invest Surg 26, 16-29.

Teke Z., Bostanci E. B., Yenisey C., Sacar M., Simsek N. G., Akoglu M., (2012). Caffeic Acid phenethyl ester alleviates mesenteric ischemia/reperfusion injury. J Invest Surg 25, 354-365.

Tolba, MF, Azab, SS, Khalifa A. E., Abdel-Rahman SZ., Abdel-Naim AB. (2013). 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 (in press)

Toyoda, T., Tsukamoto, T., Takasu, S., Shi, L., Hirano, N., Ban, H., Kumagai, T., Tatematsu, M., (2009). Anti-inflammatory effects of caffeic acid phenethyl ester (CAPE), a nuclear factor-kappaB inhibitor, on Helicobacter pylori-induced gastritis in Mongolian gerbils. International journal of cancer Journal international du cancer 125, 1786-1795.

Uz E., Oktem F., Yilmaz H. R., Uzar E., Ozguner F., (2005). The activities of purine-catabolizing enzymes and the level of nitric oxide in rat kidneys subjected to methotrexate: protective effect of caffeic acid phenethyl ester. Mol Cell Biochem 277, 165-170.

Uzar E., Koyuncuoglu H. R., Uz E., Yilmaz H. R., Kutluhan S., Kilbas S., Gultekin F., (2006a). The activities of antioxidant enzymes and the level of malondialdehyde in cerebellum of rats subjected to methotrexate: protective effect of caffeic acid phenethyl ester. Mol Cell Biochem 291, 63-68.

Uzar E., Sahin O., Koyuncuoglu H. R., Uz E., Bas O., Kilbas S., Yilmaz H. R., Yurekli V. A., Kucuker H., Songur A., (2006b). The activity of adenosine deaminase and the level of nitric oxide in spinal cord of methotrexate administered rats: protective effect of caffeic acid phenethyl ester. Toxicology 218, 125-133.

van Acker SA, van den Berg DJ, Tromp MN, Griffioen DH, van Bennekom WP, van der Vijgh WJ, Bast A, (1996). Structural aspects of antioxidant activity of flavonoids. Free Radic Biol Med 20, 331-342.

Viuda-Martos M., Ruiz-Navajas Y., Fernandez-Lopez J., Perez-Alvarez J. A., (2008). Functional properties of honey, propolis, and royal jelly. J Food Sci 73, R117-124.

Wang T., Chen L., Wu W., Long Y., Wang R., (2008). Potential cytoprotection: antioxidant defence by caffeic acid phenethyl ester against free radical-induced damage of lipids, DNA, and proteins. Can J Physiol Pharmacol 86, 279-287.

Wang X., Stavchansky S., Kerwin S. M., Bowman P. D., (2010). Structure-activity relationships in the cytoprotective effect of caffeic acid phenethyl ester (CAPE) and fluorinated derivatives: effects on heme oxygenase-1 induction and antioxidant activities. Eur J Pharmacol 635, 16-22.

Widjaja A, Yeh TH, Ju YH, (2008). Enzymatic synthesis of caffeic acid phenethyl ester. J Chin Inst Chem Eng 39, 413-418.

Yagmurca M., Erdogan H., Iraz M., Songur A., Ucar M., Fadillioglu E., (2004). Caffeic acid phenethyl ester as a protective agent against doxorubicin nephrotoxicity in rats. Clin Chim Acta 348, 27-34.

Yilmaz H. R., Sogut S., Ozyurt B., Ozugurlu F., Sahin S., Isik B., Uz E., Ozyurt H., (2005). The activities of liver adenosine deaminase, xanthine oxidase, catalase, superoxide dismutase enzymes and the levels of malondialdehyde and nitric oxide after cisplatin toxicity in rats: protective effect of caffeic acid phenethyl ester. Toxicol Ind Health 21, 67-73.

Yilmaz H. R., Uz E., Altunbasak A., Sakalli E., Ozcelik N., (2010). Anticlastogenic effect of caffeic acid phenethyl ester on cisplatin-induced chromosome aberrations in rat bone marrow cells. Toxicol Ind Health 26, 33-37.

Yilmaz H. R., Uz E., Yucel N., Altuntas I., Ozcelik N., (2004). Protective effect of caffeic acid phenethyl ester (CAPE) on lipid peroxidation and antioxidant enzymes in diabetic rat liver. J Biochem Mol Toxicol 18, 234-238.

Fig. 1 Molecular structure of CAPE

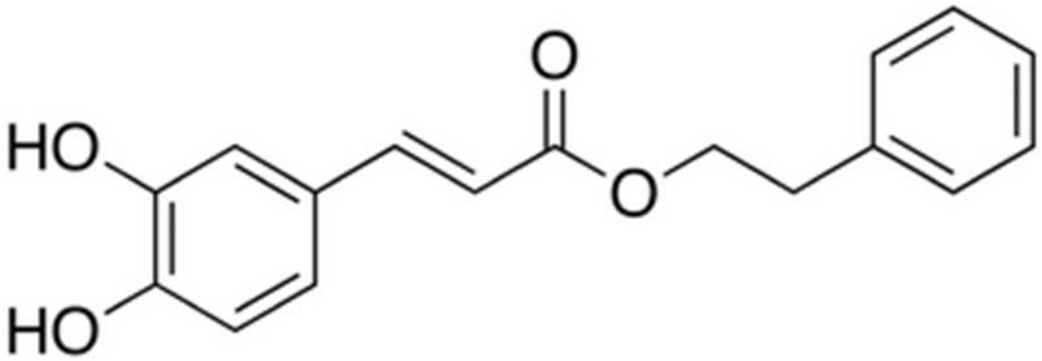

Fig. 2 The antioxidant targets of CAPE

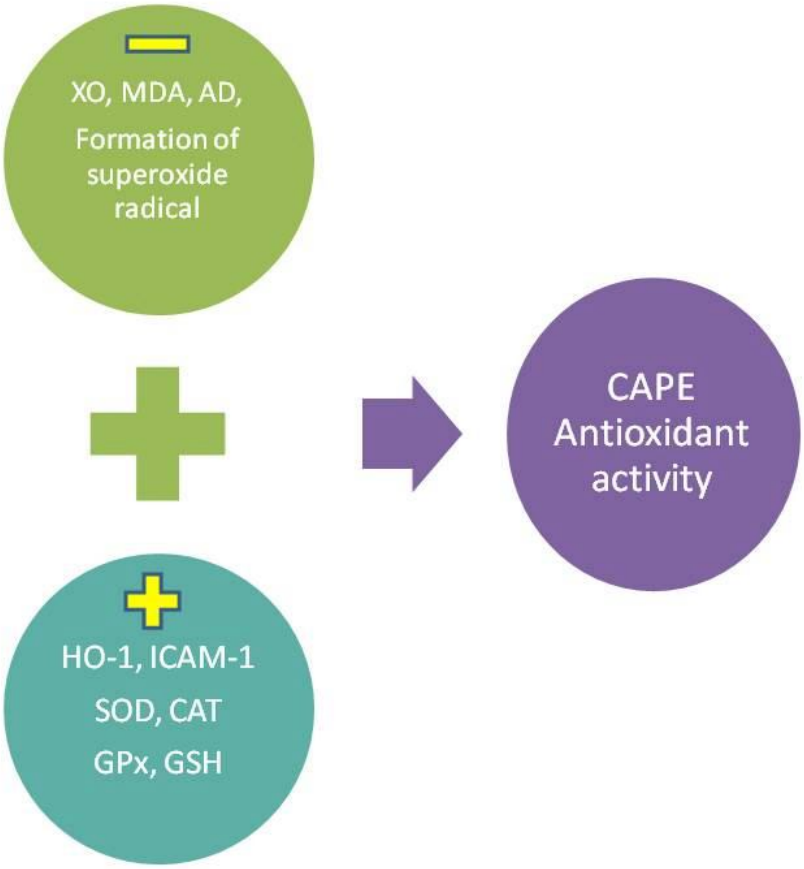

Fig. 3 CAPE protects against I/R injury in different target tissues

Table 1 Protection against ischemia/reperfusion (I/R) injury by CAPE

Molecular targets	Stimulus	CAPE dosing	Effect of CAPE	species	Author/Year
MPO XO NOx GSH GPx GR CAT TNF-α IL-1β IL-6	60 min of superior mesenteric ischemia followed by 3 hr of reperfusion	10 µmol/kg, intravenously 30 min before the beginning of the reperfusion period	Reversed intestinal mucosal injury	Wistar rats	Teke *et al.*, 2012
	60 min of superior mesenteric ischemia followed by reperfusion	10 µmol/kg, intravenously 30 min prior to the construction of colonic anastomosis.	Enhanced colonic anastamotic wound healing	Wistar rats	Teke *et al.*, 2013
SOD GPx CAT Apoptosis	Increased intraocular pressure to 110 mmHg for 60 min	10 µmol/kg i.p., before reperfusion and once a day for one or seven days after I/R	Protected against retinal injury	Wistar rats	Shi *et al*. 2010
MPO Na^+/K^+ ATPase CAT	60 min hearts arrest and then reperfused for 15 min	0.5µmol /ml solution supplemented St. Thomas solution as cold cardioplegia for 60 min	Improved cardiac antioxidant defense	Isolated hearts from Wistar rats	Ozeren *et al*., 2005
GSH GPx CAT	Ovarian I/R (torsion/detorsion)	8.5 mg/kg, i.p., injected 1 h before torsion	Ameliorated ovarian injury	New Zealand Rabbits	Kart *et al* ., 2009
NOx SOD	Unilateral femoral artery clipping for	10 µmol/kg , i.p., 1 h	Attenuated skeletal muscles	Wistar rats	Ozyurt *et al* ., 2007

	2 h followed by 2 h of reperfusion	before reperfusion	injury		
GSH NF-kB p65 Apotosis	120-min hindlimb ischemia followed by 4-h reperfusion.	10 µmol/kg, i.p. 30 min before reperfusion	Protected against skeletal muscle injury	Wistar rats	Andrade-Silva *et al*., 2009
GSH NF-kB p65 Apoptosis	60 min ischemia of the left lateral and median lobes of the liver followed by reperfusion	10 µmol/kg, i.p. 30 min before reperfusion	Protected against liver injury	Wistar rats	Saavedra-Lopes *et al* ., 2008
Membrane anisotropy Respiratory control Cardiolipin Cytochrome c	5 min anoxia followed by 5 min reoxygenation	10^{-5}:10 µM before the anoxia or just at reoxygenation	Reversed the functional alterations in mitochondria	Brain and liver mitochondria isolated from Kunming mice	Feng *et al*., 2008
GSH SOD CAT XO GSH NO	Unilateral occlusion of the middle cerebral artery	10 µmol/ kg /day, i.p., for 7 days after occlusion	Neuroprotection	New Zealand Rabbits	Altug *et al*., 2008
MPO iNOS	2h torsion followed by 24 h detorsion	10 µmol/ kg /day, i.p., before detorsion	Protects against testicular tissue injury	Wistar rats	Atik *et al*., 2006

Table 2 Protective effects of CAPE against ADRs

Drug	Effect of CAPE	CAPE dose	Species	Author/Year
Mitomycin	Inhibit mitomycin-induced clastogenesis	5 or 10 mg/kg/day four days pretreatment or post-treatment	Balb/c Swiss mice	Sulaiman 2012
Streptomycin	Inhibit streptomycin-induced ototoxicity	10 µmol/ kg /day, i.p., for 45 days	Wistar rats	Bakir *et al.*, 2013
Vancomycin	Inhibit vancomycin-induced nephrotoxicity	10 µmol/ kg /day, i.p., for 8 days	Wistar rats	Ocak *et al.*, 2007
Isoniazid	Inhibit isoniazid-induced ocular toxicity	10 µmol/ kg /day, i.p., for 30 days	Sprague–Dawley rats	Sahin *et al.*, 2013b
Ethambutol	Inhibit ethambutol-induced ocular toxicity			
Doxorubicin (DOX)	Inhibit DOX-induced nephrotoxicity	10 µmol/ kg /day, i.p., Started 48 h before DOX	Sprague–Dawley rats	Yagmurca *et al.*, 2004
	Inhibit DOX-induced cardiotoxicity		Sprague–Dawley rats	Fadillioglu *et al.*, 2004
Cisplatin	Inhibit cisplatin-induced nephrotoxicity	10 µmol/ kg /day, i.p., Started 24 h before cisplatin	Wistar rats	Ozen *et al.*, 2004 Yilmaz *et al.*, 2005
	Inhibit cisplatin-induced chromosomal aberrations	10 µmol/ kg /day, i.p., Started 24 h before cisplatin	Sprague-Dawley rat bone marrow cell system	Yilmaz *et al.*, 2010
	Inhibit cisplatin-induced hepatotoxicity	10 µmol/ kg /day, i.p., 1 day before and for 5 days after cisplatin	Wistar rats	Iraz *et al.*, 2006
	Inhibit cisplatin-induced ototoxicity	10 µmol/kg/day, i.p. 24 h before and at the same time of cisplatin injection and every 24 h for 5 days	Wistar rats	Kizilay *et al.*, 2004
Methotrexate (MTX)	Inhibit MTX-induced nephrotoxicity	10 µmol/ kg /day, i.p., for 7 days	Wistar rats	Uz *et al.*, 2005
	Inhibit MTX-induced hepatorenal oxidative injury	10 µmol/ kg /day, i.p., for 5 days after MTX	Wistar rats	Cakir *et al.*, 2011
	Inhibit MTX-induced spinal cord injury	10 µmol/ kg /day, i.p., for 7 days	Wistar rats	Uzar *et al.*, 2006b
	Inhibit MTX-induced cerebellar oxidative injury		Wistar rats	Uzar *et al.*, 2006a
	Inhibit MTX-induced testicular toxicity		Wistar rats	Armagan *et al.*, 2008