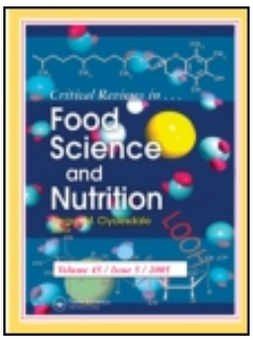

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Caffeic Acid Phenethyl Ester: A Review of Its Antioxidant Activity, Protective Effects against Ischemia-reperfusion Injury and Drug Adverse Reactions

MAI F. TOLBA,[1,2] HANY A. OMAR,[3] SAMAR S. AZAB,[1] AMANI E. KHALIFA,[1] ASHRAF B. ABDEL-NAIM,[1] and SHERIF Z. ABDEL-RAHMAN[2]

[1]Faculty of Pharmacy, Department of Pharmacology and Toxicology, Ain Shams University, Cairo, Egypt
[2]Department of Obstetrics and Gynecology, The University of Texas Medical Branch, Galveston, Texas, USA
[3]Faculty of Pharmacy, Department of Pharmacology, Beni-Suef University, Egypt

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)

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, 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, hepatoprotective, 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

Address correspondence to 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

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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.

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).

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, 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 $CH_2 = CH—COOH$ 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 neighboring 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 eukaryotic cells. Moreover, CAPE exhibits a potent

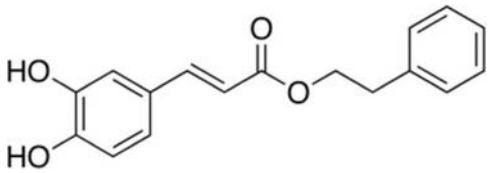

Figure 1 Molecular structure of CAPE.

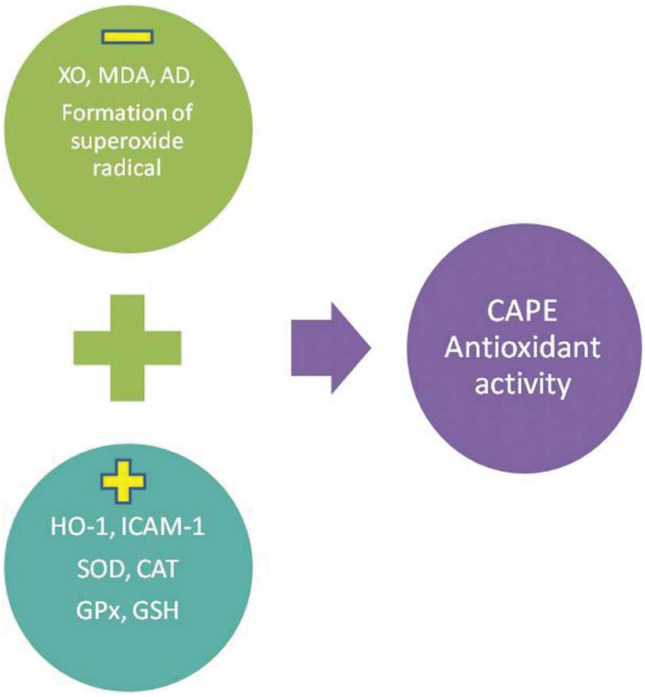

Figure 2 The antioxidant targets of CAPE.

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 hemeoxygenase-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

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

Author/Year	species	Effect of CAPE	CAPE dosing	Stimulus	Molecular targets
Teke et al., 2012	Wistar rats	Reversed intestinal mucosal injury	10 μmol/kg, intravenously 30 min before the beginning of the reperfusion period	60 min of superior mesenteric ischemia followed by 3 hours of reperfusion	MPO XO NOx GSH GPx GR CAT TNF-α IL-1β IL-6
Teke et al., 2013	Wistar rats	Enhanced colonic anastamotic wound healing	10 μmol/kg, intravenously 30 minutes prior to the construction of colonic anastomosis.	60 minutes of superior mesenteric ischemia followed by reperfusion	
Shi et al. 2010	Wistar rats	Protected against retinal injury	10 μmol/kg i.p., before reperfusion and once a day for one or seven days after I/R	Increased intraocular pressure to 110 mmHg for 60 minutes	SOD GPx CAT Apoptosis
Ozeren et al., 2005	Isolated hearts from Wistar rats	Improved cardiac antioxidant defense	0.5μmol /ml solution supplemented St. Thomas solution as cold cardioplegia for 60 min	60 minutes hearts arrest and then reperfused for 15 minutes	MPO Na^+/K^+ ATPase CAT
Kart et al., 2009	New Zealand Rabbits	Ameliorated ovarian injury	8.5 mg/kg, i.p., injected 1 hour before torsion	Ovarian I/R (torsion/ detorsion)	GSH GPx CAT
Ozyurt et al., 2007	Wistar rats	Attenuated skeletal muscles injury	10 μmol/kg, i.p., 1 hour before reperfusion	Unilateral femoral artery clipping for 2 hours followed by 2 hours of reperfusion	NOx SOD
Andrade-Silva et al., 2009	Wistar rats	Protected against skeletal muscle injury	10 μmol/kg, i.p. 30 minutes before reperfusion	120-minutes hind limb ischemia followed by 4-hour reperfusion.	GSH NF-κB p65 Apotosis
Saavedra-Lopes et al., 2008	Wistar rats	Protected against liver injury	10 μmol/kg, i.p. 30 minutes before reperfusion	60 min ischemia of the left lateral and median lobes of the liver followed by reperfusion	GSH NF-κB p65 Apoptosis
Feng et al., 2008	Brain and liver mitochondria isolated from Kunming mice	Reversed the functional alterations in mitochondria	10^{-5}:10 μM before the anoxia or just at reoxygenation	5 minutes anoxia followed by 5 minutes reoxygenation	Membrane anisotropy Respiratory control Cardiolipin Cytochrome c GSH SOD
Altug et al., 2008	New Zealand Rabbits	Neuroprotection	10 μmol/ kg /day, i.p., for seven days after occlusion	Unilateral occlusion of the middle cerebral artery	CAT XO GSH NO
Atik et al., 2006	Wistar rats	Protects against testicular tissue injury	10 μmol/ kg /day, i.p., before detorsion	2 hours torsion followed by 24 hours detorsion	MPO iNOS

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 seven 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

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

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-κB 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.

Table 2 Protective effects of CAPE against ADRs

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

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 I/R 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.

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 hemodynamics, 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.

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.

STATEMENT OF INTEREST

The authors declare that there are no conflicts of interest.

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