



# Can propolis and caffeic acid phenethyl ester be promising agents against cyclophosphamide toxicity?

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## ABSTRACT

Propolis is a mixture having hundreds of polyphenols including caffeic acid phenethyl ester (CAPE). They have been using in several medical conditions/diseases in both *in vitro* and *in vivo* experimental setup. Cyclophosphamide (CP) has been used to treat a broad of malignancies including Hodgkin's and non-Hodgkin's lymphoma, Burkitt's lymphoma, chronic lymphocytic leukemia, Ewing's sarcoma, breast cancer, testicular cancer, etc. It may cause several side effects after treatment. In this mini review, the protective effects of propolis and CAPE were compared each other in terms of effectiveness against CP-induced injuries.

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## INTRODUCTION

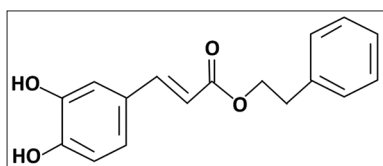
Propolis, having hundreds of polyphenols, is a mixture produced by the honeybee. This sticky, greenish-brown product has different compositions depending on the location of the bees and what trees and flowers they have access to. Propolis from Turkey or Egypt will not have the same chemical properties as propolis from Europe or Brazil. This is because it is very difficult for researchers to come to general conclusions about its health benefits. Caffeic acid phenethyl ester (CAPE) [Figure 1] is one of important compounds found in propolis that has antiviral [1], antioxidant, anti-inflammatory, antiproliferative, antitumor, and immunomodulatory effects [2]. This marvelous compound has been used to prevent oxidative stress-based deterioration in cells/tissues/organs in both cell culture and experimental animals. Lately, the

protection of CAPE on central and peripheral nervous system as well as a reproductive system have been extensively reviewed [3-5]. Cyclophosphamide (CP) is an anticancer chemotherapeutic drug classified as an alkylating agent. It has extensively been used to treat a broad of malignancies including Hodgkin's and non-Hodgkin's lymphoma, Burkitt's lymphoma, chronic lymphocytic leukemia, Ewing's sarcoma, breast cancer, testicular cancer, etc. CP can cause several side effects on treatment. It has toxic effects in almost every system in the human body including the heart, liver, and kidney of which mostly due to its structural properties prone to induce oxidative stress *in vitro* and *in vivo*.

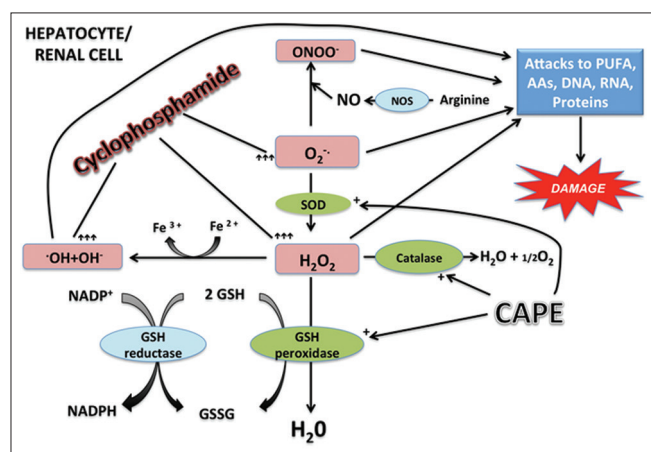
This study aimed to collect data and compare the protective effects of propolis and CAPE against CP-induced injury in animals. There are limited studies in this specific field. Lately,

ameliorative effect of propolis against CP-induced toxicity in mice was studied by El-Naggar *et al.* [6]. It throws light on the side effects of a common anticancer agent, CP, used in the treatment of various malignancies and possible remedies to prevent that type of side effects in vital organs such as liver and kidney. The proposed natural compound propolis has been found to be protective against CP toxicity. Uysal *et al.* [7] conducted an experimental animal study to determine protective role of CAPE on CP-induced hemorrhagic cystitis (HC). While CP-induced HC lead to increase in superoxide dismutase, catalase, and malondialdehyde activities/levels, CAPE significantly reduced these parameters showing the protective effects. In addition to this biochemical effects, CAPE also ameliorates edema, hemorrhage, inflammation, and mucosal ulceration of CP-induced HC.

We published a review article about toxicities of some therapeutic compounds and the protective effect of CAPE on chemotherapy- and radiotherapy-induced toxicity [8]. We have shown that CAPE has protective effects on oxidative stress-induced toxicities by doxorubicin (nephrotoxicity) [9], cisplatin (nephrotoxicity, ototoxicity, and hepatotoxicity) [10-13], and bleomycin (lung fibrosis) [14].



**Figure 1:** The chemical illustration of caffeic acid phenethyl ester



**Figure 2:** Proposed mechanism of how cyclophosphamide-induced oxidative stress is blocked by antioxidant enzymes in several parts of hepatocytes and renal cells and how CAPE shows its protective effects against oxidative stress. AAs: Amino acids, CAPE: Caffeic acid phenethyl ester, CAT: Catalase, Fe<sup>2+</sup>: Ferrous iron, GPx: Glutathione peroxidase, GSH: Reduced glutathione, GR: Glutathione reductase, GSSG: Oxidized glutathione, H<sub>2</sub>O: Water, NADP<sup>+</sup>: Oxidized nicotinamide adenine dinucleotide phosphate, NADPH: Reduced nicotinamide adenine dinucleotide phosphate, O<sub>2</sub>: Molecular oxygen, O<sub>2</sub><sup>•-</sup>: Superoxide anion radical, OH<sup>-</sup>: Hydroxyl ion, OH: Hydroxyl radical, ONOO<sup>-</sup>: Peroxynitrite, NO: Nitric oxide, NOS: Nitric oxide synthase, PUFA: Polyunsaturated fatty acid, SOD: Superoxide dismutase

Currently, there is no medically recommended dose for propolis, since the mixture of propolis is subjected to change depending on its source. The most successful medical application field of propolis is beauty and skin care, especially in acne vulgaris because of its antibacterial, antiviral, antifungal, and anti-inflammatory properties. Despite the fact that both water and ethanolic extractions of propolis have been used in the *in vivo* and *in vitro* experiments, water-soluble extracts of propolis exhibit higher antioxidant and inhibitory activities as compared ethanolic extract *in vitro* [15]. In this perspective, even though the extraction method selection is dependent on the authors' desire, it would be expected for authors to study propolis for their experiments comparatively by selecting propolis extracted by both extraction methods. CAPE is the most potent antioxidant agent of propolis mixture having free radical scavenging activity and potent inhibition of NF-κB. So, the protective antioxidant effect of ethanol extract of propolis on organs depends mostly on CAPE rather than other polyphenolic compounds such as flavonoids, phenolic acids, and their esters [Figure 2]. CAPE was shown to completely block the production of reactive oxygen species in human neutrophils and in the xanthine/xanthine oxidase systems at 10 μM concentration by its competent antioxidant capacity [16]. Indeed, CAPE has a regulatory effect on antioxidant enzyme activities such as catalase, superoxide dismutase, and glutathione peroxidase [7,17] [Figure 2].

It has been shown that CAPE application to the rats modifies the enzyme activity of cytochrome P450 (CYP) isoforms involved in the activation of diethylnitrosamine such as CYP1A1/2 and CYP2B12 [18]. Furthermore, treatment with CAPE of carbon tetrachloride-induced hepatotoxicity in mice blocks CYP2E1-mediated CCl<sub>4</sub> bioactivation and protects against fas/FasL-mediated apoptosis [19]. It will be very interesting to see the effect of CAPE on CYP2B6, which constitutes 3-6% of total hepatic CYP content and metabolizes several pharmaceuticals including CP [20]. To achieve this, further studies on the every single bioactive constituent of propolis such as CAPE and some other polyphenols are necessary to identify interactions mediating their biological effects on CYP2B6, since there are roughly 150 different polyphenolic compounds within propolis.

As a conclusion, studying propolis to prevent CP-induced oxidative stress in animals has several limitations since the proposed effect cannot be specified to one or several molecules within the mixture. In that case, every single bioactive constituent of propolis needs to be studied to show the source of real effects and the molecular mechanisms of this effects.

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