Journal of Intercultural Ethnopharmacology
www.jicep.com
DOI: 10.5455/jice.20150402062823

Review Article

Caffeic acid phenethyl ester as a remedial agent for reproductive functions and oxidative stress-based pathologies of gonads

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Received: March 18, 2015
Accepted: April 03, 2015
Published: April 03, 2015

ABSTRACT

In recent years, the studies on the roles of caffeic acid phenethyl ester (CAPE) in several disease models and cell cultures are tremendously growing. It is such a great molecule that was used by ancient times to ameliorate some diseases and nowadays, it is used by modern medicine to test the effectiveness. In this mini-review article, the protection capability of CAPE, as a liposoluble antioxidant and a potent nuclear factor kappa B inhibitor, on oxidative and non-oxidative ovary, and testis damages has been summarized. In view of our laboratory findings/experience and those reported in the hitherto literature, we suggest that CAPE possesses protective effects for pathologies of the reproductive organs induced by untoward effects of harmful molecules such as free oxygen radicals, pesticides, methotrexate, and MK-801 (dizocilpine).

KEY WORDS: Caffeic acid phenethyl ester, gonads, ovary, oxidative damage, protection, testis

INTRODUCTION

Caffeic acid phenethyl ester (CAPE) [Figure 1] is one of the most active compounds found in propolis. Propolis has been known to be used many ethnic and/or cultural groups as folkloric medicine for hundreds and thousands of years. CAPE is known as a potent antioxidant substance that inhibits the production of xanthine/xanthine oxidase (XO) and free oxygen radicals in human neutrophils [1,2]. Besides its antioxidant and potent Nuclear Factor kappa B (NFκB) inhibitory activities, CAPE has been reported to show some other effects, i.e., vasorelaxant, anti-inflammatory, anticarcinogenic, and immunomodulatory as well. CAPE, as a liposoluble antioxidant and it is used in a number of inflammatory and infectious diseases as traditional medicine. As an antioxidant, CAPE can be used in ischemic/reperfusion injuries or other types of organ damages due to oxidative stress [3-5]. Cells mainly have two defense mechanisms against oxidative damage; one of them pertains to antioxidant enzymes such as catalase (CAT), glutathione peroxidase (GSH-Px), GSH reductase (GSH-Red), superoxide dismutase (SOD), and the other one being antioxidant defense compounds such as GSH, vitamin C, and vitamin E.

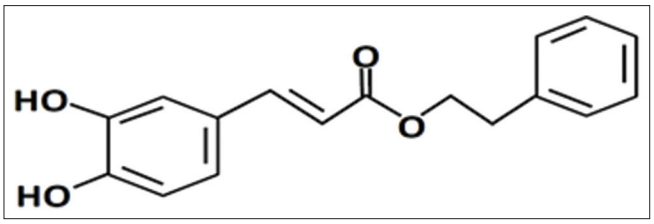

Figure 1: The chemical structure of caffeic acid phenethyl ester

This study aimed to underscore the effects of CAPE on the oxidative and non-oxidative ovary and testicular damages induced by several factors such as free oxygen radicals, pesticides, methotrexate, and MK-801 which have untoward effects on the organs.

Ipsilateral and Contralateral Ischemia Reperfusion (I/R) Injuries in Animal Ovaries and Testes

Torsion of the ovary is an emergency situation in normal individuals or the presence of an ovarian mass. The conservative therapy of twisted ovary is detorsion. However, detorsion has some disadvantages such as the huge amount of reactive oxygen species (ROS) (such as hydrogen peroxide, superoxide anion, hydroxyl radical, and singlet oxygen) produced after detorsion and reperfusion. In the reperfusion phase, xanthine dehydrogenase is converted to XO, which is an enzyme producing huge amounts of ROS, by degrading ATP, ADP, and AMP. Celik *et al.* [6] reported the protective effect of CAPE on rat ovaries injured by I/R. They analyzed GSH, XO, and malondialdehyde (MDA), a lipid peroxidation end product, in the ovarian homogenates obtained from torsion/detorsion (T/D) rats. The MDA level of T/D group was significantly higher compared to those of the control groups. CAPE significantly reduced MDA levels after T/D. CAPE treatment reduced the pathological findings (i.e. acute PMN infiltration, diffuse hemorrhage, edema, and vascular dilatation) detected in the T/D group. Celik *et al.* [6] concluded that CAPE attenuates reperfusion injury in the ovary by decreasing MDA and XO and by increasing GSH. Therefore, the authors suggested the use of CAPE in ovarian T/D injury as well as possibly in some other pathologic conditions related with increased ROS production.

In another study, the role of CAPE was studied in rabbit ovaries T/D injury model by examining the changes in the lipid peroxidation, antioxidant system, and by pathologically [7]. Administration of CAPE one hour before I/R significantly increased ovarian GSH-Px activity and GSH level, on the other hand significantly decreased CAT activity and thiobarbituric acid reactant substances (TBARS). Ovaries of the I/R group that were not treated with CAPE mostly represented grade IV pathological alterations with severe hemorrhage, edema, leukocyte infiltration, and vascular congestion within and around the ovarian medulla. CAPE treatment diminished the pathological changes and reduced the deteriorating changes to Grade 0-III, caused by I/R. As it alleviated the degenerative changes in the ovaries, it was concluded that CAPE might have a therapeutic use additional to the surgery.

To explore the effects of CAPE on I/R model in testis, we have conducted a study using albino rats [8]. In CAPE plus detorsion group, CAPE was applied intra-peritoneally (10 μmol/kg) 30 min before the detorsion. The rats were killed, and bilateral orchiectomy was performed 4 hours after the detorsion. NO levels were analyzed in both twisted ipsilateral and non-twisted contralateral testes. Results of the mentioned study indicate testicular T/D induces significant changes in NO level in the ipsilateral testis while NO level in the contralateral non-T/D testis is not affected. Ischemia led to increases in the concentrations of testicular NO by inducing NOS activity or migration of neutrophils to the testis [9]. Our study also revealed that levels of NO started to diminish with the detorsion process. After the CAPE treatment, NO levels became higher than that of the sham-operated rats with an unknown mechanism, which may suggest the possible protecting role of CAPE in the testicular injury. The possibilities for this finding may be; CAPE directly increases NOS activity, CAPE might have activated the synthesis of cofactors related with NO production or selectively activated neutrophil migration to the testis, which may increase NO synthesis. The most probable and logical explanation for the effect of CAPE is the scavenging effect on ROS together with the other antioxidant enzymes and its preventive effects on the inhibition of NO. Whatever the mechanisms are, the final conclusion is that testicular torsion increases NO level in testis and CAPE administration before testicular ischemia prevents the decrease of NO synthesis during reperfusion. Accordingly, CAPE may be a useful treatment strategy in the I/R injuries of testes.

In another study, the histopathological changes in testicular I/R injury of Wistar rats and the protective effect of CAPE (10 μmol/kg) was investigated [10]. I/R caused an increase in the expression of testicular inducible nitric oxide synthase (iNOS) and myeloperoxidase (MPO) enzymes. CAPE attenuated the increases of MPO and iNOS, leading to normalization of these parameters. The appearance of testicular tissues under the light microscope was normal in CAPE administered group whereas I/R without CAPE administration caused inflammatory infiltration, edema, necrosis, and congestion. These results have a potential to show the pathophysiology of testis I/R injury and also suggest that inhibition of MPO and iNOS activities by CAPE may be a new therapeutic strategy to avoid testicular damage.

I/R Model in Testicular Injury as Remote Organ

I/R injury damages not only in the related initial ischemic tissues and organs, but also in remote unrelated areas [11-13]. To date, the underlying mechanisms of remote organ injury are poorly clarified. In this respect, the effect of oxidative damage on testis following the I/R myocardial injury and also the protective effects of CAPE were reported by Esrefoglu *et al.* [14]. The authors demonstrate that CAPE treatment significantly decrease the elevated serum NO and MDA levels caused by the myocardial I/R. Many testicular pathological changes such as disorganization of the seminiferous epithelium, hyalinization, degeneration, and tubular atrophy were detected in myocardial I/R. Degenerated sertoli cells that were present in the atrophic tubules contained acidophilic cytoplasm and

fragmented nuclei. In the CAPE group, testes demonstrated generally the normal structure of sertoli and germinal cells. CAPE significantly reduced the number of degenerating cells. The authors suggested that involvement of increased NO synthesis in the testicular injury caused by myocardial I/R was a novel finding and more importantly, that inhibition of NO production by potential new agents like CAPE might be a new pharmacological strategy for the prevention of cell damage.

Angiogenesis in Ovaries

In recent years, several studies report that a number of phytochemical substances or their synthetic derivatives represent angiogenesis inhibitory effects, which is very important for preventing or delaying cancer by suppressing its neovascularization [15]. Apers *et al.* [16] recently reported the novel derivatives of caffeic acid esters by biomimetic dimerization in order to obtain antiangiogenic lignans. Similarly, Basini *et al.* [17]. 2012 studied the potential antiangiogenic effect of a synthetic CAPE derivative, benzo (k,l) xanthene lignan synthesized through the biomimetic dimerization in ovarian cell line and an angiogenesis bioassay. Granulosa cells of swine ovaries were aseptically harvested by aspiration of large follicles, and they were grown in culture medium to test the synthesis of vasculoepithelial growth factor (VEGF). CAPE-derived lignan significantly inhibited the secretion of VEGF by granulosa cells, which suggested this compound as a novel potential angiogenesis inhibitor.

Estrogens have a vital role on the reproductive tissues in respect to growth, differentiation, and function. Additional to the reproduction system, estrogen receptors are also present in other tissues, for example estrogen receptor β (ERβ) has important functions in the differentiation of epithelial cells and it has been reported that ERβ is the major ER expressed in colon [18]. Estrogen loss during the postmenopausal period is related with physiological changes and an increase in ROS that may be associated with several pathologic conditions [19,20]. Ovariectomy itself is used as an experimental model for oxidative stress [21,22]. Finally, evidence indicates that some kind of ROS such as hydrogen peroxide and superoxide anion are involved in the pathogenesis of inflammatory bowel disease [23]. The effect of CAPE has been studied in an inflammatory bowel disease model produced by 2,4,6-trinitrobenzene sulfonic acid (TNBS) in ovariectomized rats [24]. CAPE at the doses of 10 and 30 mg/kg significantly diminished the colon damage caused by TNBS compared to that of the vehicle-treated group. Levels of GSH, CAT, and MDA were significantly altered in the CAPE group compared to colitis and vehicle control groups. Authors concluded that CAPE had those effects through anti-inflammatory and antioxidant mechanisms and that it might be used as an adjunct therapy in colitis in ovariectomized female rats.

Effects of Smoking on Testicular Functions and Oxidant/Antioxidant Balance

Testicular tissue has been known as a highly vascular tissue and because of the blood supply cigarette smoke may deteriorate the balance between oxidant and antioxidant enzyme systems. Oxidative stress can cause the production of abnormal spermatozoa and affect sperm functions [25]. The assessment of infertility of males is usually based on the evaluation of several semen parameters which can easily be affected by smoking [26]. Histological changes in the seminiferous tubules, sperm counts, and sperm morphology are seriously affected by smoking [27]. In one previous report, 21 rats were exposed to cigarette smoke, intra-peritoneal CAPE was applied for 60 days, and testicular NO, SOD, GSH-Px, catalase, and MDA were studied [28]. It was found that CAT and SOD activities were significantly high and GSH-Px activity was significantly low in smoking group whereas they were normalized in CAPE applied group. Increased MDA and NO levels in the testicular tissue in the smoking group were reversed by CAPE application, showing the protective role of CAPE on smoking-related damage.

Effects of Pesticides on Testes

Pesticides have a toxic effect on testes mostly due to induction of oxidative stress because of production of high levels of ROS. Spermatozoa is especially affected by oxidative stress because of high levels of polyunsaturated fatty acids in the membranes [29] and low levels of antioxidant enzymes in their cytoplasms. λ cyhalothrin (LC) is a new generation of insecticide, which is effective against a large variety of arthropods. Abdallah *et al*. studied the adverse effects of LC on reproductive organs and fertility in male rats and evaluated the protective role of CAPE [30]. The authors studied testicular oxidative status, epididymal sperm characteristics, and testicular pathology. LC declined the sperm quality by increasing oxidative stress. CAPE treatment reduced testicular oxidative stress and the deleterious effects of LC on male fertility due to its antioxidant properties.

Effect of Methotrexate (MTX) on Testes

Methotrexate is a widely used chemotherapeutic agent for the treatment of different diseases such as several cancer types (osteosarcoma, acute lymphoblastic leukemia, lymphoma, head and neck cancer, bladder cancer, and breast cancer) and non-malignant diseases (psoriasis, rheumatoid arthritis, and graft versus host disease).

The mechanism of MTX toxicity is related with oxidative stress. Testicular toxicity is one of the important adverse effects of MTX. It may infertility via the inhibition DNA synthesis by the increased production of ROS [31], decreasing GSH level [32], SOD, CAT and GSH-Px activities [33,34]. MTX may cause chromosomal changes which may result in oligozoospermia [35]. The rich polyunsaturated fatty acid content of the testicular tissue makes this organ more vulnerable to oxidative damage [36]. MTX decreases antioxidant mechanisms, alters the function of pro-inflammatory cytokine system, and increases the formation of ROS due to the stimulation of phagocytic cells [33]. In one study, authors aimed to evaluate whether there is any change in the ROS production and oxidative stress by MTX administration in rat testes and whether CAPE treatment

stops this abnormal condition [34]. Mean body and testicular weight, antioxidant enzyme activities, lipid peroxidation parameters were studied to test this hypothesis. The level of lipid peroxidation and the activities of SOD were significantly higher in the MTX group. These were decreased after CAPE administration. CAT activity in MTX group decreased insignificantly although its activity was significantly increased by CAPE administration. Altogether, it was concluded that CAPE administration with MTX treatment has a protective effect on MTX-induced oxidative injury on testes.

Effect of MK-801-induced Psychosis on Testicular Oxidative Balance

Gonadal functions have been reported to be abnormal in schizophrenic men. On the other hand, none of the studies have been conducted to show the association between schizophrenia and oxidative stress on testicular tissues in relation to gonadal dysfunction. ROS may have a role in the pathophysiology of neuropsychiatric disorders because it is involved in membrane pathologies in the central nervous system. Oxidative stress in blood, cerebrospinal fluid, and postmortem brain tissues has been extensively studied in the literature. MK-801 (dizocilpine) has been used to create animal models of schizophrenia. Pharmacologically, it is an uncompetitive antagonist of the N-Methyl-D-aspartate receptor. Ozyurt *et al*. [37] reported the oxidative changes in the testicular tissues of MK-801-induced schizophrenia model in rats for the first time. Biochemical parameters of oxidative damage and pathological changes in testicular tissues have been studied in this schizophrenia model. A significant increased oxidative stress has been noted in testicular tissues of rats in response to MK-801-induced psychosis. Treatment of the animals with CAPE decreased the oxidative stress and normalized the histological changes caused by the MK-801 administration (disorganization and degeneration of the seminiferous epithelium, hyalinization, and tubular atrophy). CAPE treatment reduced the disorganization, degeneration of the germinal cells, and tubular atrophy.

CONCLUSION

In general, it is obvious that a significant oxidative stress has been noted in all of the pathological models of the reproductive organs such as ovary I/R, testicular I/R, methotrexate-induced testicular injury, MK-801-induced testicular injury, and cigarette smoke-induced injury. The administration of some harmful compounds as well as I/R injuries in both reproductive organs cause the elevation of oxidative stress and pretreatment with CAPE has protecting effects on the oxidative stress in testis and ovaries. Overall, the findings of the aforementioned studies clearly display that CAPE has a protective effect on testicular and ovarian I/R as well as medicine-induced injury, and that this effect is shared by two of the most possible pathways; inhibition of neutrophil-mediated injury, and scavenging of ROS extensively by CAPE [Figure 2]. Clinical studies are needed to validate the correct usage of CAPE either alone or in combination with existing alternative therapies.

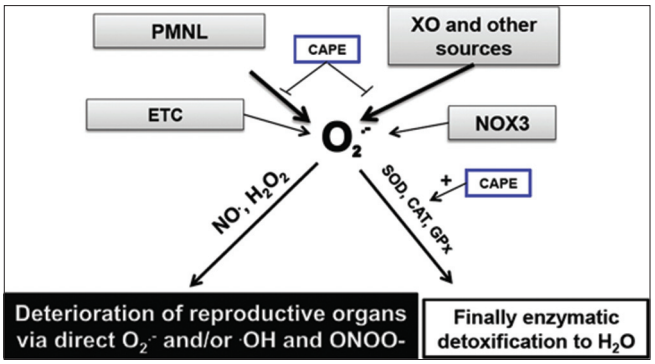

Figure 2: Proposed mechanism for the relationship between oxidative stress and the protective effect of caffeic acid phenethyl ester on reproductive organs

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Source of Support: Nil, Conflict of Interest: None declared.