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Review Article

Antiviral properties of caffeic acid phenethyl ester and its potential application

Hacı Kemal Erdemli[1], Sumeyya Akyol[2], Ferah Armutcu[3], Omer Akyol[4]

[1]Department of Biochemistry Laboratory, Corum Training and Research Hospital, Corum, Turkey, [2]Department of Medical Biology, Faculty of Medicine, Turgut Ozal University, Ankara, Turkey, [3]Department of Medical Biochemistry, Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey, [4]Department of Medical Biochemistry, Faculty of Medicine, Hacettepe University, Ankara, Turkey

Address for correspondence:
Hacı Kemal Erdemli, Department of Biochemistry Laboratory, Corum Training and Research Hospital, Corum, Turkey.
E-mail: hkemal@hotmail.com

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ABSTRACT

Caffeic acid phenethyl ester (CAPE) is found in a variety of plants and well-known the active ingredient of the honeybee propolis. CAPE showed anti-inflammatory, anticarcinogenic, antimitogenic, antiviral, and immunomodulatory properties in several studies. The beneficial effects of CAPE on different health issues attracted scientists to make more studies on CAPE. Specifically, the anti-viral effects of CAPE and its molecular mechanisms may reveal the important properties of virus-induced diseases. CAPE and its targets may have important roles to design new therapeutics and understand the molecular mechanisms of virus-related diseases. In this mini-review, we summarize the antiviral effects of CAPE under the light of medical and chemical literature.

KEY WORDS: Antiviral effect, caffeic acid phenethyl ester, caffeic acid phenethyl ester-like compounds

INTRODUCTION

Caffeic acid phenethyl ester (CAPE) has been used all over the World, especially in Asian and other geographical areas as a traditional medicine since ancient times. It is an active phenolic component of propolis (Figure 1) of honeybee hives and possesses a plethora of important biological activities. CAPE is thought to be responsible for various well-known effects of propolis, including antibacterial, antioxidant, anti-inflammatory, immunomodulatory, and anticancer activities [1-3]. It is a well-documented inhibitor of nuclear factor kappa B (NF-κB), which may be an action mechanism for CAPE-mediated anti-inflammatory and antineoplastic effects [4,5]. Classically, CAPE reduces prostaglandins and leukotriene synthesis, acting as a potent anti-inflammatory agent. CAPE down-regulates inflammation by blocking NF-κB and influences some mediators including adhesion molecules, cytokines, and inducible nitric oxide synthase [5,6]. Additionally, CAPE used as an antioxidant and anti-inflammatory agent in a number of studies about human diseases. Its beneficial effects have been reported in the treatment of cancer, diabetes, kidney, liver, and neurological diseases [4,7-9]. On the other hand, recent findings provide new insights into the molecular mechanisms involved in the antiviral effect and activities of this natural compound.

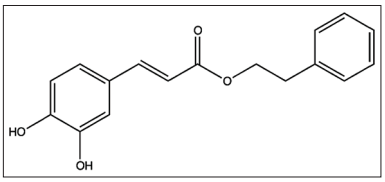

Figure 1: Chemical structure of caffeic acid phenethyl ester

Therefore, the aim of this mini-review article is to highlight the antiviral properties of CAPE, focusing on the mechanisms of action.

GENERAL CHARACTERISTICS OF CAPE

The commercial form of CAPE is a white powder, which is soluble in ethanol, dimethyl sulfoxide, and ethyl acetate (50 mg ml^{-1}). Its empirical formula is $C_{17}H_{16}O_4$ and has 284.3 g mol^{-1} molecular weight. It can be either extracted from propolis by using extraction methods or be synthesized by several methods such as response surface methodology from caffeic acid and phenethyl alcohols [10]. The molar conversion ratio was found to be 96% [11] and 91.2% [12]. According to the current literature, it is asserted that CAPE has no significant toxic effects or minimum toxicity. The pharmacokinetics of CAPE has been characterized; the body clearance values were ranged from 42.1 to 172 ml min^{-1} kg^{-1} decreasing with the higher dose of CAPE. The calculated volume distributions were ranged between 1,555 and 5,209 ml kg^{-1}, which decreases with dose. The estimated elimination half-life was ranged from 21.2 to 26.7 min showing independence from the dose. From this point of view, it can be suggested that CAPE is distributed extensively into the tissues, eliminated very rapidly from the tissue, and has a high volume of distribution and short elimination half-life [13]. The *in vitro* stability of CAPE in different biological samples was investigated. CAPE is hydrolyzed to caffeic acid after 6 h within rat plasma *in vitro* and is hydrolyzed to caffeic acid as the major metabolite *in vivo* [14].

TARGETS IN ANTIVIRAL THERAPY AND ANTIVIRAL EFFECTS OF CAPE

Although fewer drugs were licensed for the treatment of viral infections up to now, the current antiviral drugs repertoire has been increasing. Antiviral drugs are generally divided into four classes; (i) drugs that inhibit uncoating of viral RNA (amantadine, rimantadine, and gamma globulins); (ii) drugs that inhibit viral nucleic acid synthesis (DNA polymerase inhibitors; entecavir, acyclovir, idoxouridine, vidarabine, etc.); (iii) drugs that inhibit late protein synthesis and processing (protease inhibitors); and (iv) immunomodulators (interferons). There are various strategies for antiviral drug development including inhibition of virus adsorption, virus-cell fusion, viral DNA or RNA synthesis (viral DNA polymerase, reverse transcriptase), IMP dehydrogenase, S-adenosylhomocysteine hydrolase, and inhibition of viral enzymes such as protease and neuraminidase [15]. At the earliest, Sud'ina *et al.* suggested various activities and molecular targets of CAPE including antiviral effect inhibiting HIV-1 integrase [1]. Therefore, CAPE is believed to have a potential for anti-HIV therapy. At the same time frame, Fesen *et al.* reported that the integration step is efficiently inhibited by CAPE than the initial cleavage step by HIV-1 integrase (Figure 2) [16]. According to their results, CAPE was the only compound that inhibited the integration step to a substantially greater degree than the initial cleavage step of the enzyme. It was confirmed by another study that CAPE had been found to inhibit the activity of HIV-1 [17]. The mechanism of this inhibition is attributed to the unique molecular structure of CAPE which inhibited the reaction involved by NF-κB [2], and interrupted the method of the treatment of multiple growing points in the life cycle of HIV [18]. CAPE was demonstrated to inhibit the integration step relative to the cleavage step of integration reaction selectively. CAPE was unable to bind DNA significantly [15]. Moreover, it is reported that the effect of CAPE derivatives on hepatitis C virus (HCV) proliferation has been investigated to develop more effective anti-HCV compounds [16]. As it was mentioned before, CAPE inhibits the enzyme activity of some endogenous and viral proteins as well as a transcription of NF-κB. CAPE also suppresses HCV replication enhanced by morphine mediated NF-κB activation [19]. However, the molecular mechanisms of this action have not been fully understood. Shen *et al.* examined chemical structure and antiviral activity suggested that the length of the n-alkyl side chain and catechol moiety is responsible for the anti-HCV activity of CAPE [20]. Their study revealed that CAPE and its analog possess a significant inhibitory effect on HCV replication. HCV NS3, which is a viral protease, was decreased at the protein level by treatment with CAPE in a dose-dependent manner, corresponding to the viral replication. In addition, CAPE and its esters, in a concentration range of 1.0 to 109.6 mM, have also been tested in an HCV replicon cell line of genotype 1b and found effective against replication of HCV. These studies suggest that CAPE and CAPE-like esters are promising therapeutic reagents for HCV treatment [21]. On the other hand, HTLV-1 is an etiologic agent for aggressive, the lethal malignancy of CD4 T-lymphocytes called adult T-cell leukemia and some other clinical disorders[22]. The viral tax protein has been accepted as a key factor in HTLV-1 pathogenicity. Shvarzbeyn and Huleihel found that CAPE strongly prevented both tax binding to inhibitor of κBα and its induced degradation by Tax, whereas it did not interfere in the nuclear transport of tax or NF-κB proteins (Figure 2) [22].

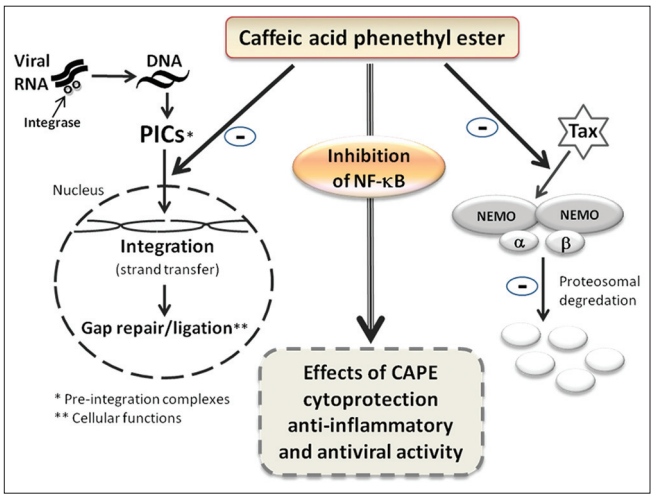

Figure 2: Featured two hypothetical opinions about the antiviral effects of caffeic acid phenethyl ester (CAPE). Integration step is efficiently inhibited by CAPE than the initial cleavage step by HIV-1 integrase (on the left), and CAPE strongly prevents both Tax binding to IκBα and its induced degradation by Tax (on the right)

ANTIVIRAL AND INHIBITORY EFFECTS OF CAPE DERIVATIVES AND CAPE-LIKE COMPOUNDS

CAPE and four CAPE-like compounds (methyl caffeate; ethyl 3-(3,4-dihydroxyphenyl)acrylate; phenethyl dimethyl caffeate, and phenethyl 3-(4-bromophenyl)acrylic) synthesized from commercial caffeic acid were investigated for their anti-HIV replication *in vitro* and immune modulation effects *in vivo* [23]. In these studies, CAPE and other derivatives significantly inhibited HIV replication although the mechanism was unknown. The different effects of treatment on HIV replication and cytokine modulation are guided that the compounds had a virological and immunological response by different mechanisms. Among them, CAPE can selectively inhibit virus-transformed and oncogene-transformed rodent cells and human tumor cells. Two decades ago, it was found that the integrase is essential for viral replication and a possible target for antiviral agents [24,25]. However, most of these compounds possess little or no activities in tissue cultures and have no selectivity in their action mechanisms. These results indicate that CAPE-like compounds do not selectivity eliminate the activation of HIV integrases or the compounds inhibiting HIV integrase do not enter the cells [23]. In a study, 30 different compounds have been tested as HIV integrase inhibitors based on the structural lead provided by CAPE [26]. All of them were designed to test specific properties of the parent CAPE structure, which might be important for activity. The examined properties that have a potential to inhibit integrase were side chain length and composition, rigs substitution, and phenyl ring conformational orientation. Dinucleotide cleavage and strand transfer, which were two sequential steps in the measured combined effects, were found to be lower in the analogs than those of CAPE. Additionally, in literature, there are other studies on other viral agents including influenza and adenovirus [27]. Kishimoto *et al*. [28] reported that CAPE at 8.8 μM inhibited the growth of Type A and B influenza virus by 95% and 92%, respectively. In the other study, treatment of the cells with an anti-IL-6 receptor antibody and CAPE reduced the detached cell number, viral titers, and improved cell viability after infection with the pandemic influenza virüs [29].

CONCLUSION

Modern medicines currently available for antiviral treatment are very expensive and sometimes ineffective; therefore, the alternative agents from natural sources need to be extensively investigated. CAPE seems to be one of such promising agents for antiviral treatment because of accumulating *in vivo* and *in vitro* data. In this regard, clinical trials are needed to test the availability of CAPE alone and in combination with existing regimens.

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