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REVIEW

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Caffeic acid phenethyl ester: A review on its pharmacological importance, and its association with free radicals, COVID-19, and radiotherapy

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Abstract

Caffeic acid phenethyl ester (CAPE), a main active component of propolis and a flavonoid, is one of the natural products that has attracted attention in recent years. CAPE, which has many properties such as anti-cancer, anti-inflammatory, antioxidant, antibacterial and anti-fungal, has shown many pharmacological potentials, including protective effects on multiple organs. Interestingly, molecular docking studies showed the possibility of binding of CAPE with replication enzyme. In addition, it was seen that in order to increase the binding security of the replication enzyme and CAPE, modifications can be made at three sites on the CAPE molecule, which leads to the possibility of the compound working more powerfully and usefully to prevent the proliferation of cancer cells and reduce its rate. Also, it was found that CAPE has an inhibitory effect against the main protease enzyme and may be effective in the treatment of SARS-CoV-2. This review covers in detail the importance of CAPE in alternative medicine, its pharmacological value, its potential as a cancer anti-proliferative agent, its dual role in radioprotection and radiosensitization, and its use against coronavirus disease 2019 (COVID-19).

KEYWORDS
caffeic acid phenethyl ester, cancer, complementary medicine, coronavirus disease 2019, irradiation, molecular docking study, radiotherapy, therapeutic benefits

1 | INTRODUCTION

Cancer, a heterogeneous group of diseases characterized by excessive cell proliferation or disruption of apoptosis due to the loss of the balance between cell division and cell death, is one of the most dreadful diseases of the 20th century and its incidence is increasing alarmingly due to changing lifestyles, habits and increasing life expectancies. Today, it is spreading further with persistence and increasing incidence, and the situation is so worrying that one out of every four people has a lifetime risk of cancer (Altay et al., 2020; Roy & Saikia, 2016; Taysi, Algburi, Mohammed, Ali, & Taysi, 2022) and has recently been reported as the second cause of death worldwide after cardiovascular disease (Sari, Sumer, & Celep Eyupoglu, 2020). Surgery, radiotherapy (RT), and chemotherapy are traditional approaches to treating cancer. Surgical intervention, which has been used successfully in cancer treatment, is the only curative method for many common solid tumors. However, the most important determinant of successful surgical treatment is the absence of distant metastases and local infiltration. Chemotherapy is the administration of cytotoxic agents, resulting in cytotoxicity to both resting and dividing cells. The goal of cancer chemotherapy is to prevent cancer cells from invading, metastasizing, and killing the patient (Khayyo et al., 2019; Koc, Taysi, Buyukokuroglu, & Bakan, 2003; Roy & Saikia, 2016; Taysi, Koc, Buyukokuroglu, Altinkaynak, & Sahin, 2003).

Beginning in December 2019, the novel coronavirus disease 2019 (nCOVID-19) pandemic has caused enormous economic losses

worldwide, unprecedented health crises, many physical, psychological and social challenges despite the availability of treatment strategies (Dehghan, Ghanbari, Ghaedi Heidari, Mangolian Shahrbabaki, & Zakeri, 2022; Huang et al., 2020). International health systems have responded to this outbreak with low levels of preparedness and emergency response. During the epidemic period, although the emergence of effective vaccines presents Governments, scientific communities and members of the public with a possible way out of the pandemic, effective pharmacotherapy, including immunotherapy, has yet to be established for the prevention and treatment of the epidemic (Paudyal, Sun, Hussain, Abutaleb, & Hedima, 2022). In recent studies, it has been reported that the demand for complementary and alternative medicine information to pharmacists and other health personnel for the prevention, relief of symptoms or treatment of COVID-19 has increased (Paudyal et al., 2022). Natural products and medicines have historically been used for acute respiratory infection and are still used at an increasing rate and generally show acceptable toxicity (Matsunaga et al., 2019; Shi et al., 2022). The stability and ease of scale-up production suitable for oral formulation make these natural products ideal candidates for prophylactic (Huang et al., 2020). In the management of COVID-19, in addition to herbal therapies and nutraceutical drugs, dietary supplements such as vitamins and amino acid derivatives also play an important role (Chavda et al., 2022).

Herbal medicines and phyto-compounds such as propolis, turmeric, ginger, nigella sativa have attracted attention to prevent or reduce the side effects caused by chemotherapy and radiotherapy (Demir et al., 2016; Ercan, Gecesefa, Taysi, Ali Ali, & Taysi, 2021). One of them, caffeic acid phenethyl ester (CAPE), which is one of the most important active components of propolis, many ongoing studies are still being carried out today (Taysi et al., 2021; Taysi, Alafandi, Demir, & Cinar, 2021). Prevention of oral and oropharyngeal mucositis that sometimes requires interruption of treatment, esophagitis that develops in mediastinal irradiations, radiation colitis that develops in abdominal irradiations, and sometimes organs (brain, liver, kidney, bone marrow, lens, salivary glands, etc.) are thought to provide significant clinical benefit and increase the comfort of treatment. In addition, the issue of whether these substances are effective in preventing the harmful effects of ionizing radiation has not been sufficiently investigated (Taysi et al., 2022) .

In this review, we highlight the available information about the effects of antioxidants on the change in the balance of free radicals in cellular radiation response systems and potential treatments to reduce or prevent radiation-related side effects. We analyzed the effects of CAPE, an important antioxidant molecule, both in radiotherapy and its possible effects in the fight against COVID-19, which is an important problem of our time, with the molecular docking program, and we also summarized the researches on the role and importance of CAPE.

2 | FREE RADICALS, OXIDATIVE/ NITROSATIVE STRESS

Free radicals (FRs) are produced in all living things as a result of metabolism and their main source is oxygen-derived radicals (Gul et al., 2006; Gumustekin et al., 2010; Taysi et al., 2010; Uslu, Taysi, & Bakan, 2003). FRs are generally produced such as reactive oxygen species (ROS), reactive nitrogen species (RNS), reactive sulfur species (RSS), reactive carbonyl species (RCS) (Taysi, Tascan, Ugur, & Demir, 2019), reactive selenium species (RSeS) (Sies, Berndt, & Jones, 2017). Overproduction of FRs or a significant decrease in the antioxidant defense system causes reversible or irreversible damage to nucleic acids, proteins, free amino acids, lipids, lipoproteins, carbohydrates and connective tissue biomolecules (Taysi, 2005). Stress in organisms arises as a result of the disruption of the balance between prooxidant-antioxidant and is associated with the pathogenesis of many diseases, including atherosclerosis, mental health diseases, neurodegenerative diseases (Alzheimer's disease and Parkinson's disease), various types of diabetes, cardiovascular diseases and cancers (Karayagmurlu et al., 2022; Kartal, Abbasoglu, & Taysi, 2022). The overproduction of ROS, RNS is referred to as oxidative and nitrosative stress, respectively (Taysi et al., 2019). Recent studies have led to the emergence of the research area "antioxidant and redox regulation of molecular biology", which is one of the most exciting areas of biomedical research. Contrary to the idea that reactive oxygen is mostly a triggering molecule in the oxidative damage of biological structures in most of the studies, ROS, are now stated that at low physiological concentrations, can regulate various key molecular mechanisms that may be associated with important processes such as immune response, cell–cell adhesion, cell proliferation (Sen, 1998).

Radical scavenger molecules (RSM) interact with FR and terminate oxidation chain reactions with different mechanisms, preventing radical damage through an oxidation mechanism or a reduction mechanism of FR. Chain-breaking molecules form the primary protection mechanism by forming stable FR. Inhibitory antiradicals are involved in secondary mechanisms, and this mechanism does not involve direct reactions with FR and does not convert them into more stable products. Tertiary mechanisms restore damaged biomolecules in detoxification or reactions of FR radicals. Also, some molecules classified as multifunctional radical scavenger (RS) may exhibit more than one mechanism. RS is divided into two main classes as enzymatic or non-enzymatic endogenous compounds in the living body and exogenous derived compounds from fruits, vegetables and plants (Taysi et al., 2019).

Some exogenous molecules have been the subject of many experimental and theoretical studies, and it is stated in studies that they can be good antioxidants. Thymoquinone, an important component of Nigella sativa, and CAPE, one of the most effective components of propolis, have been discussed in many studies (Altay et al., 2020; Demir et al., 2016; Demir et al., 2020; Taysi, Okumus, et al., 2021). In this review, we will also touch on the role of CAPE in oxidative/ nitrosative stress and the scavenging mechanism of free radicals.

3 | CAFFEIC ACID PHENETHYL ESTER

CAPE is a powerful antioxidant derived from honey bee propolis. Traditional medicine has employed the described chemical, a well-known

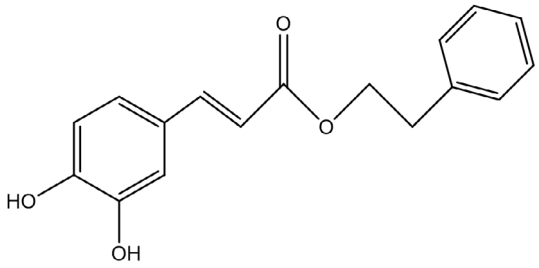


FIGURE 1 Chemical structure of CAPE

nuclear factor kappa B (NF-κB) inhibitor, as an effective anti-inflammatory medication. CAPE possesses anti-viral, anti-bacterial, anti-cancer, immunomodulatory, and wound-healing effects (Olgierd, Kamila, Anna, & Emilia, 2021). The chemical name of CAPE is 2-phenylethyl (2 E)-3-(3,4-dihydroxyphenyl) acrylate (Murtaza et al., 2014). It is also termed as phenylethyl caffeate or phenethyl caffeate. CAPE is a key component of honeybee propolis extract and has been used in traditional medicine for a long time. CAPE is a polyphenol containing hydroxyl groups within a catechol ring, with the chemical formula $C_{17}H_{16}O_4$ (Natarajan, Singh, Burke Jr., Grunberger, & Aggarwal, 1996) (Figure 1).

4 | CAPE AS ANTIOXIDANT

CAPE, which is structurally related to flavonoids, is the physiologically active component of honeybee propolis extract and has been used as a local medicine with no negative effects on normal cells. CAPE has many beneficial properties for living organisms, starting with "anti" (Olgierd et al., 2021) (Figure 2).

CAPE is used as a dietary supplement in local medicine to treat a variety of ailments (Tolba, Azab, Khalifa, Abdel-Rahman, & Abdel-Naim, 2013), exerts its beneficial effects by decreasing free oxygen radicals and prevents the consumption of free radical scavenging enzymes by acting in parallel antioxidant enzymes (Ogeturk et al., 2005). CAPE, which is more biologically effective than other natural hydroxycinnamic acid derivatives due to its structural properties, has better bioavailability in lipophilic systems due to its distribution coefficient (Serafim, Milhazes, Borges, & Oliveira, 2015). CAPE is also the ester of caffeic acid, a derivative of phenolic acid (H.-C. Chen, Chen, Chang, & Shieh, 2011).

Phenolic acids are divided into two categories: Hydroxybenzoic acids and hydroxycinnamic acids. Cinnamic acid hydroxyl derivatives are more active antioxidants than benzoic acid hydroxyl derivatives because the $CH_2 = CH–COOH$ group in cinnamic acids assures more antioxidant activity than the COOH group in benzoic acid. The presence of various substituents in the phenol backbone structure influences their antioxidant properties, especially their hydrogen-donating ability. Unsubstituted phenol is inactive as a hydrogen donor in general, and monophenol is a weaker antioxidant than polyphenol. The antioxidant activity of phenol or phenolic acid is increased when an electron-donating group, such as a hydroxyl group, is introduced in the ortho or para position. Its antioxidant activity was also improved by the presence of a carbonyl group, such as aromatic acid, ester, or lactone (Göçer & Gülçin, 2011; Widjaja, Yeh, & Ju, 2008). When a molecule's carbonyl group is removed from the aromatic ring, its antioxidant activity increases as well. Cinnamic acid is more potent as an antioxidant than its benzoic acid counterpart. The antioxidant activity of phenolic hydroxyls was improved by steric hindrance of the phenolic hydroxyls by a nearby inert group, such as methoxyl groups (Widjaja et al., 2008).

CAPE, a polyphenolic compound containing catechol-ring hydroxyl groups, has the ability to actively exchange electrons, thanks to the two functional OH^- groups it contains, and therefore exhibits oxidizing and reducing properties (Olgierd et al., 2021). CAPE, which has a lipophilic character due to long carbon chains in aromatic and aliphatic structure, allows this feature to easily pass-through cell membrane structures and reach the area where it will affect (Göçer & Gülçin, 2011; Widjaja et al., 2008). The best source of antioxidant compounds are fruits and vegetables, which are often used in the human diet. The most important feature of phenolic compounds is to neutralize free radicals. Contrary to the fact that propolis samples obtained from many plant sources have similar qualitative compositions, their CAPE contents vary greatly. CAPE, which does not have a toxic effect, has a significant effect on scavenging free radicals that occur in living organisms (Widjaja et al., 2008).

Studies have reported that CAPE is a potential inhibitor of enzymes such as ornithine carboxylase, 5-α reductase, protease, cyclooxygenase, lipoxygenase, HIV-1 integrase (Son, Lobkowsky, & Lewis, 2001), and also inhibits NF-κB activity, which is a transcription factor (Sforcin & Bankova, 2011). In other studies, it has been reported that CAPE inhibits the production of free radicals formed by the xanthine dehydrogenase/xanthine oxidase system in vitro (Ozyurt, Irmak, Akyol, & Sogut, 2001), prevents lipid peroxidation (LPO) formation, and inhibits tyrosine kinase, cyclooxygenase and lipoxygenase activities (Ozen et al., 2004). Studies have reported that CAPE has many pharmacological activities including free RS, anti-inflammatory, antioxidant (Shao et al., 2020), provides protection against hepatotoxicity caused by multiple exogenous chemicals in mammals, pre-treatment has a protective effect in different experimental animal models (Abdel-Daim & Abdellatief, 2018; Shao et al., 2020). In addition, it has been shown to inhibit LPO without increasing antioxidant enzyme activities (Albukhari, Gashlan, El-Beshbishy, Nagy, & Abdel-Naim, 2009). It is increasingly recognized that compounds containing phenolic groups that are considered potentially oncoprotective may be associated with positive effects on carcinogenesis, primarily due to their antioxidant activity. Since ROS play a role in tumor initiation and progression, antioxidants have attracted attention mainly due to their free radical scavenging activity (Serafim et al., 2015). The mechanisms of free radical scavenging of CAPE can be observed in Figures 3 and 4.

5 | BIOAVAILABILITY OF CAPE

CAPE contains two hydroxyl groups and has high lipophilicity and high membrane permeability due to its phenethyl motif. Although it is an

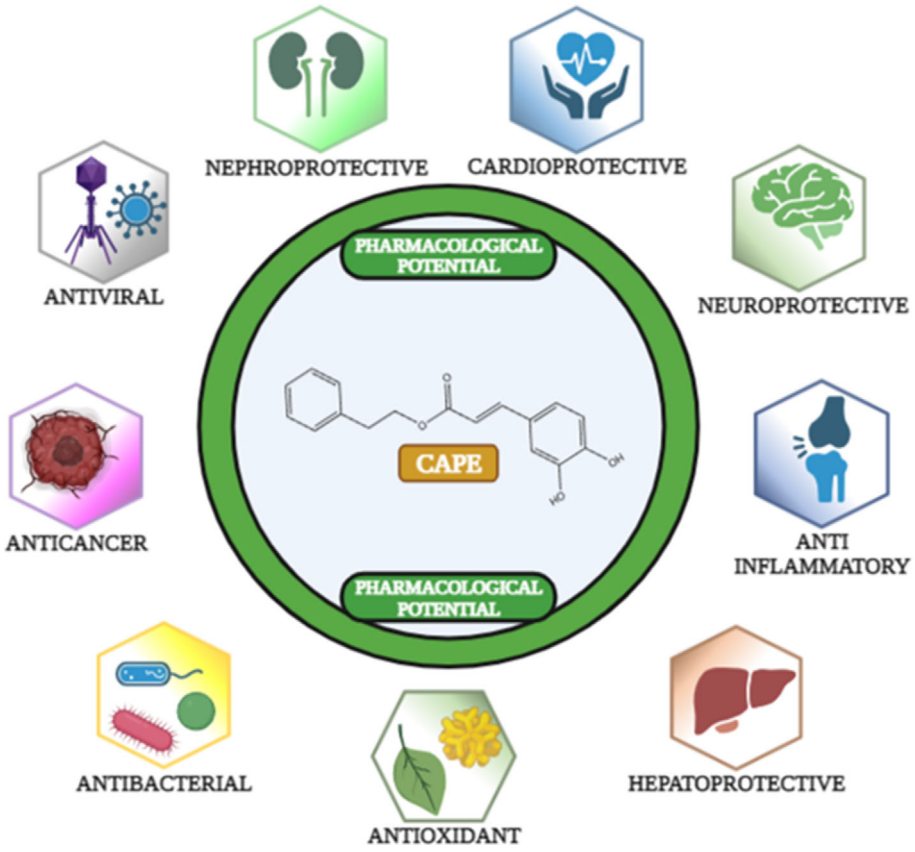


FIGURE 2 The schematic diagram represents pharmacological potential of CAPE

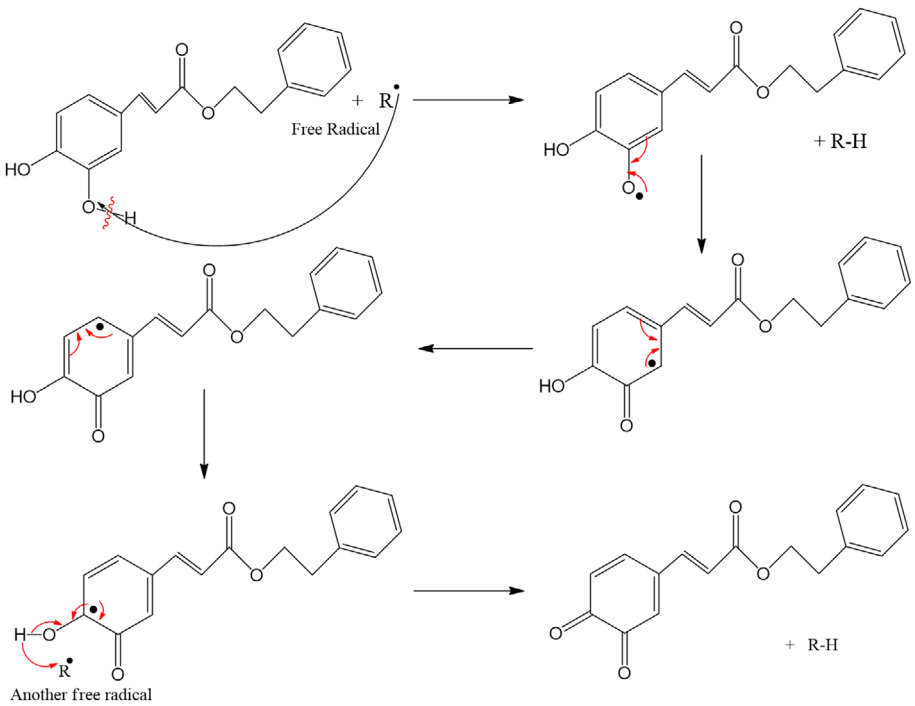


FIGURE 3 The mechanism of free radical scavenging of CAPE

ester of Caffeic Acid, its structure gives it better bioavailability and stability than Caffeic Acid. This feature makes it suitable for various physiological and biological effects (K. Anjaly & Tiku, 2018). The main pharmacokinetic property that makes any drug suitable for therapeutic use is bioavailability. Therefore, a great deal of research has been done on the biological activities of CAPE, both in vivo and in vitro (K. Anjaly & Tiku, 2018). The first research on the subject was in 2004, Celli et al. examined the pharmacokinetic profile of CAPE in rat plasma and urine after oral administration and confirmed their results with LC-ESI/MS. They found that CAPE is rapidly excreted in

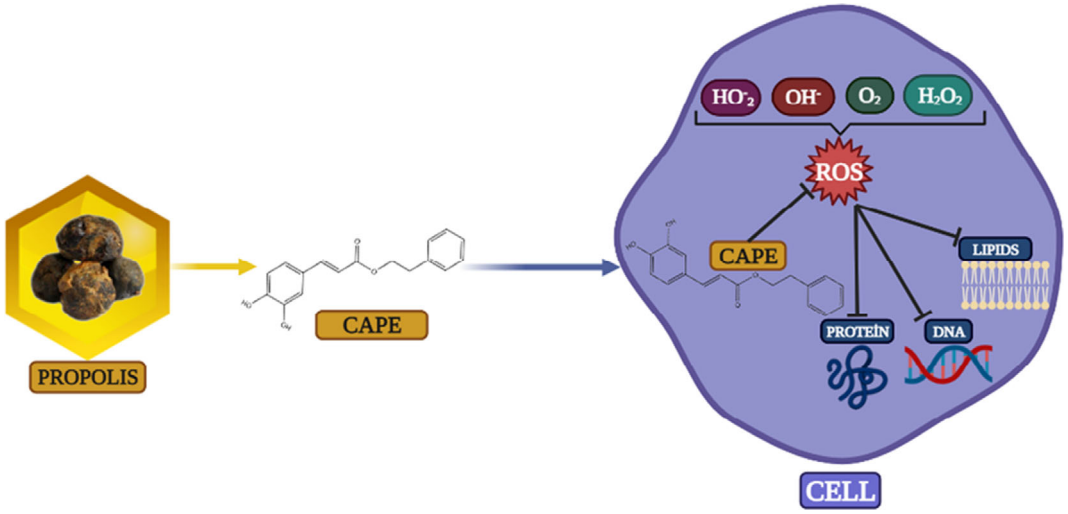


FIGURE 4 The schematic diagram represents the possible radical scavenging activity of CAPE

unmodified molecule form due to rapid hydrolysis by plasma esterases (Celli et al., 2004). In the in vitro study, it was reported that while CAPE was hydrolyzed in rat plasma within 6 h, the stability of CAPE in spiked human plasma was not affected, and its stability in rat and human plasma was different. It has been suggested that this may be because human plasma does not normally contain carboxylesterases containing paraoxonases(PON)/arylesterases and cholinesterases. Among the different plasma esterase inhibitors, in vivo studies, in which carboxylesterase is responsible for the hydrolysis of CAPE, have been reported in rats given CAPE orally at a concentration of 100 mg/kg, with increased CA and lower CAPE levels in the urine after 24 h. This information clearly indicates that CAPE is also hydrolyzed to the main metabolite CA in vivo (Celli, Dragani, Murzilli, Pagliani, & Poggi, 2007). In another in vivo study, it was reported that CAPE has the ability to cross the blood–brain barrier in rats and may be useful in the prevention of Parkinson's disease (Silva et al., 2013).

6 | CAPE AS ANTICANCER

Studies have reported that CAPE is a potential regulator of oncogenic molecular pathways by inhibiting in vitro cell proliferation or in vivo tumor growth in animal models of various carcinoma cells, including breast, lung, colon, pancreatic, cholangiocarcinoma, melanoma and prostate carcinoma cells (Budisan et al., 2019; Chang et al., 2022; Chen et al., 2008; Chen, Wu, Chen, Keng, & Chen, 2004; Chuu et al., 2012; Huang et al., 2019; Kudugunti, Vad, Ekogbo, & Moridani, 2011; Onori et al., 2009). CAPE, the main bioactive component of propolis and a derivative of caffeic acid, specifically inhibits the NF-κB by preventing the displacement of NF-κB subunits to the nucleus (Chang et al., 2022).

In a study with CAPE, which is defined as a potent anticancer agent in multiple cancer types and has dual roles of radioprotection and radiosensitization, Anjaly et al. investigated whether CAPE is radioresistant as well as its radiomodulatory potential in prostate cancer (PCa). For this reason, when they examined the effect of co-treatment of CAPE (5–100 μM) and gamma radiation on androgen-independent DU145 and PC3 cells, they observed that the combination treatment sensitized PCa cells to radiation in a dose-dependent manner and the radiosensitizing effect of CAPE was observed in both cell lines (Km Anjaly & Tiku, 2022).

In another a study investigating the functions and regulatory mechanisms of CAPE in relation to the mucosa-associated lymphoid tissue 1 gene (MALT1), which modulates NF-κB signaling in lymphoma and non-lymphoma cells, they injected 4-week-old male mice intraperitoneally with 10 mg of CAPE once daily for 5 days per week. In prostate carcinoma cells, Chang et al. reported that CAPE effectively and safely suppresses the growth and invasion of prostate carcinoma cells both in vitro and in vivo, this mechanism potentially leading to therapeutic effects on prostate cancer. They found that CAPE attenuated androgen-induced prostate-specific antigen through the androgen receptor (AR), MALT1/NF-κB or p53 signaling pathway in androgen-dependent and androgen-independent prostate carcinoma cells (Chang et al., 2022). In another study, it was reported that CAPE (10 μmoL/kg/day) acts as a protective agent in pancreatic damage after cisplatin administration. The researchers stated that this activity of CAPE is most likely achieved by reducing the production of ROS and, as a result, inhibiting the production of inflammatory mediators that cause damage to cell-building molecules. The results obtained from biomarkers at the biochemical/molecular level, as well as pathohistological analysis, also emphasize that they support these claims (Stošić et al., 2020).

In addition, CAPE has been reported to cause apoptosis of human pancreatic (Chen et al., 2008) and colon cancer cells (Xiang et al., 2006), to have an effect on the growth and antigenic phenotype of the human glioblastoma cell line, and to suppress the growth of the cell line in a dose-dependent manner (Guarini et al., 1992). Induction of apoptosis by chemopreventive agents is the main target, as most therapeutic strategies are designed to induce apoptosis. In C6 glioma cells, it was investigated whether there is a relationship between p53

TABLE 1 Applications of CAPE against chemotherapy-induced toxicities

Toxicity inducing drugs	Toxicity	Subject	Outcomes	References
Doxorubicin toxicity	Nephrotoxicity	Rats	Increase in plasma SOD, GSH-Px activities Decrease in plasma NO, MDA levels and XO activities Increase in renal tissue CAT, SOD, GSH-Px activities Decreased renal tissue NO, MDA, Prot. Carbonyl levels and MPO activity	Yagmurca et al. (2004)
Doxorubicin toxicity	Cardiotoxicity	Rats	Increase in heart tissue CAT, SOD and GSH-Px activities Decreased cardiac tissue NO, TBARS, protein carbonyl levels and MPO activity	Fadillioglu et al. (2004)
Doxorubicin toxicity	Neuronal oxidant injury	Rats	Increase in brain tissue CAT, SOD and GSH-Px activities Decreased levels of NO and MDA in brain tissue	Fadillioglu, Erdogan, Iraz, and Yagmurca (2003)
Doxorubicin toxicity	Medulloblastoma cell toxicity	Human	Antiproliferative and radiosensitizing effect of CAPE for Daoy cells	Lin et al. (2006)
Cisplatin toxicity	Nephrotoxicity	Rats	Increase in renal tissue CAT, SOD and GSH-Px activities Decreased renal tissue NO and MDA levels	Ozen et al. (2004)
Cisplatin toxicity	Bone marrow cell toxicity	Rats	The effect of preventing cisplatin-induced chromosomal abnormalities	Yilmaz, Uz, Altunbasak, Sakalli, and Ozcelik (2010)
Cisplatin toxicity	Hepatotoxicity	Rats	Increase in liver tissue CAT, SOD and GSH-Px activities	Iraz et al. (2006)
Cisplatin toxicity	Hepatotoxicity	Rats	Increase in liver tissue CAT, SOD and GSH-Px activities and decrease in NO level	Yilmaz et al. (2005)
Methotrexate toxicity	Neuronal oxidant injury	Human	Decreased NO level and ADA activity	Uzar et al. (2006)
Methotrexate toxicity	Nephrotoxicity	Rats	Decrease in renal tissue MDA level, increase in SOD, CAT and GSH-Px activities	Öktem et al. (2006)
Methotrexate toxicity	Cerebellar oxidative stress	Rats	Decrease in MDA level	Uzar et al. (2006)
Methotrexate toxicity	Testicular toxicity	Rats	Decrease in MDA level, increase in CAT activity	Armagan et al. (2008)
Methotrexate toxicity	Nephrotoxicity	Rats	Decreased NO level, XO and ADA activity	Uz, Öktem, Yılmaz, Uzar, and Özgüner (2005)
Methotrexate toxicity	Hepatorenal oxidative injury	Rats	Decreased TNF-α, IL-1 β, MDA levels, MPO, Na^+/K^+-ATPase activities and increased GSH level	Çakır et al. (2011)
Bleomycin toxicity	Lung fibrosis	Rats	Decreased NO, MDA levels and MPO activity, increased SOD and CAT activities	Özyurt et al. (2004)
Tamoxifen toxicity	Hepatotoxicity	Rats	Decreased TNF-α, TBARS levels, increase in GSH, GSSG levels, GRD, GSH-Px, CAT and SOD activities	Albukhari et al. (2009)

Abbreviations: ADA, adenosine deaminase; CAT, catalase; GRD, glutathione reductase; GSH, glutathione; GSH-Px, glutathione peroxidase; GSSG, oxidized glutathione; IL-1β, interleukin-1 beta; MDA, malondialdehyde; MPO, myeloperoxidase; Na^+/K^+-ATPase, sodium potassium ATPase; NO, nitric oxide; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances; TNF-α, tumor necrosis factor alpha.

and mitogen-activated protein kinases (MAPKs) signaling pathway in the regulation of CAPE (50 μM)-induced apoptosis, and it has been reported in studies that CAPE causes apoptosis (Y. J. Lee et al., 2003). Lee et al., reported that the tumor suppressor protein p53 and p38 mitogen-activated protein kinase (p38 MAPK) play an important role in CAPE-induced apoptotic cell death, which may contribute to the antitumor effects of CAPE (Y. J. Lee et al., 2003). In a study investigating its effects on aggressive breast cancer cells, it was reported that CAPE with doses of from 10 to 100 mM, for periods of 24 and 48 h showed significant toxicity, inhibited the apoptotic profile and cell cycle (Kabala-Dzik et al., 2017), showed a dose-dependent effect against free radicals, inhibited xanthine oxidase activity, and displayed

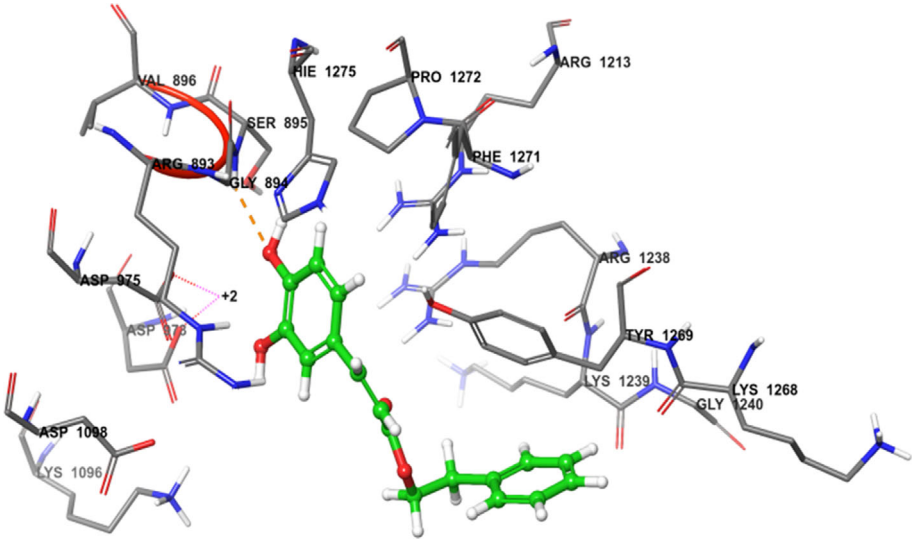


FIGURE 5 3D of CAPE with DNA polymerase III active site

antioxidant properties by blocking lipoperoxidation (Russo, Longo, & Vanella, 2002). In another study, CAPE was found to be more effective than its derivative, caffeic acid (CA), in reducing the viability of osteosarcoma cells (UMR-106) and reducing cell migration. Moreover, CAPE has been shown to exhibit 44-fold higher toxicity than CA for half-maximum inhibitory concentration calculated after 72 h of treatment (Pagnan et al., 2022). In addition, the efficacy of CAPE for head and neck squamous carcinoma was 2 times higher than CA (Dziedzic, Kubina, Kabala-Dzik, & Tanasiewicz, 2017), the same trend was found using triple-negative breast adenocarcinoma cells (MDA-MB-231) (Kabala-Dzik et al., 2017) and breast cancer cells (MCF-7) (Kabala-Dzik et al., 2018). A possible explanation for the much better anticancer activity than CA, of which CAPE is a derivative, may be that the addition of an ester or amide linkage reduces its hydrophilicity and therefore increases its lipophilicity.

Multiple cancer medicines disrupt the physiological balance of many organs, including the kidneys and liver, due to free radical production and oxidant toxicity (Akyol et al., 2012; Sulaiman, Al-Amiery, & Bagnati, 2014). It lowers the therapeutic efficacy of anticancer medications and generates unwanted side effects, such as nephrotoxicity in doxorubicin and cisplatin, and hepatotoxicity in tamoxifen. Methotrexate promotes mucosal barrier damage by activating NF-κB. Their use as an anticancer chemotherapeutic is limited due to these adverse effects. Table 1 covers research that looked into the role of CAPE in reducing the side effects of anticancer drugs such doxorubicin, cisplatin, methotrexate, bleomycin, and tamoxifen.

7 | MOLECULAR DOCKING OF CAPE

The structures of DNA polymerase III were obtained from (RCSB protein Data Bank [PDB]) under the symbol (2F2B). The process of Docking between CAPE and the replication enzyme DNA polymerase III was carried out using Schrödinger Maestro version 12.5.139 version (Kumar, Dhanjal, Kaul, Wadhwa, & Sundar, 2021; Schrodinger Release, 2020).

The results that performed from Docking show the possibility of linking CAPE with the replication enzyme to stop the spread of cancer cells, as in Figures 5 and 6.

8 | SUGGESTED MODULATIONS FOR INCREASING THE DOCKING SCORE

In order to increase the safety of CAPE binding with the replication enzyme, modifications can be made at three sites on the CAPE molecule (Figure 7) that cause the possibility of the compound to work more powerfully and usefully to prevent the multiplication of cancer cells and reduce the speed of their spread in the host, as shown in Table 2.

The results of the Molecular docking show that the highest docking score can be reached when substituting the hydroxyl group in the benzene ring (C) and the site (A) together.

9 | CAPE AND IRRADIATION

Cancer, a hyperproliferative disease involving transformation, dysregulation of apoptosis, proliferation, invasion, angiogenesis, and metastasis, has in recent years revealed much about its biology (Prasad, Muthusamy, Shanmugam, & Ambudkar, 2016). Especially in cancer patients who do not respond to surgical resection, chemotherapy and radiotherapy constitute the mainstay of treatment (Taysi et al., 2022). Radiotherapy, which is one of the indispensable treatment methods in cancer treatment, approximately 2/3 of cancer patients receive this treatment at some stage of their disease (Altay et al., 2020; Khayyo et al., 2019). While increasing the total dose required to provide local control with RT, damage occurs in the normal tissues within the irradiation area (Emin Buyukokuroglu, Taysi, Koc, & Bakan, 2003; Ertekin et al., 2004; Karslioglu et al., 2004; Koc, Taysi, Sezen, & Bakan, 2003). Today, various radiotherapy techniques such as three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, image-

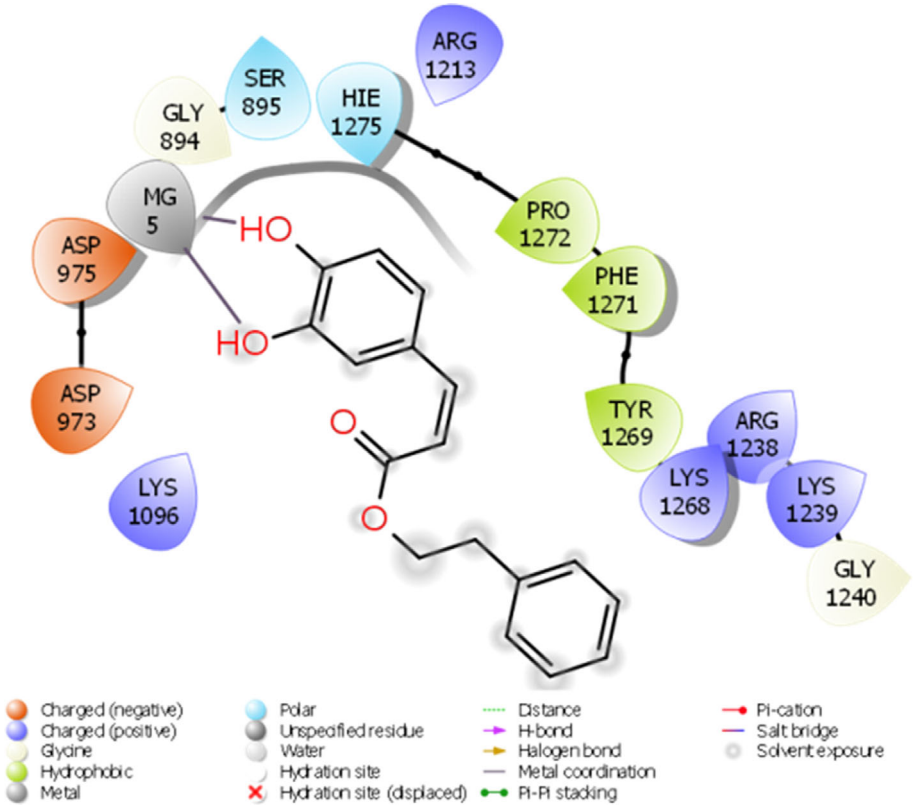


FIGURE 6 2D of CAPE with DNA polymerase III active site

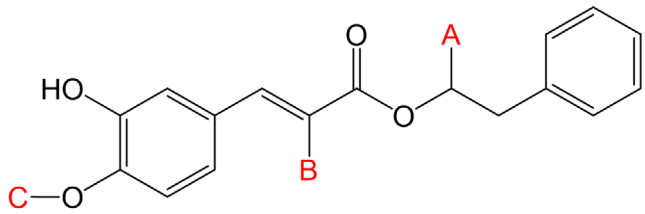


FIGURE 7 Modification sites at three sites on the CAPE molecule, which makes the compound more likely to work more potently and usefully to prevent and slow down the proliferation of cancer cells

guided radiotherapy, stereotactic radiotherapy and proton therapy are used to reduce complications in normal tissue (Akyuz et al., 2017; Demir et al., 2016; Prasanna et al., 2021). Ionizing radiation acts by generating free radicals. Free radicals formed in RT cause cell death by causing DNA breaks as well as causing many damages to the tissue. Another approach to reduce radiation-related side effects is the systemic use of radiosensitizing or radioprotectant agents that protect normal tissue against radiation but do not have a protective effect on the tumor (Choi et al., 2021; Taysi et al., 2022).

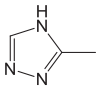
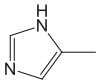
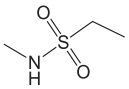
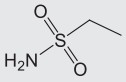
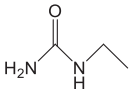
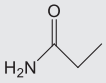
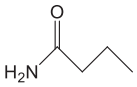
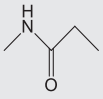
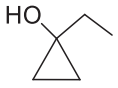
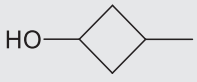
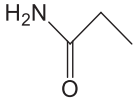
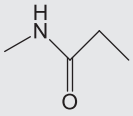
Three generations of chemosensitizers have been developed to date, and unfortunately, all of them are toxic and cause side effects in patients receiving the treatment. Phytochemicals derived from medicinal plants, which are considered as fourth-generation chemosensitizers to overcome resistance in therapy, have received considerable attention (Prasad et al., 2016).

Of all molecules, polyphenols are biologically active and have diverse pharmacological activities, and are the most abundant and most studied. They have been the subject of research in many areas because they show an effective protection against the harmful effects of ionizing radiation and can be applied at high doses with less toxicity (Ercan et al., 2021; Taysi et al., 2022). Some natural agents with both antioxidant and pro-oxidant properties have been studied for their radiomodulatory potential as possible suitable candidates for radiation therapy (K. Anjaly & Tiku, 2018; Prasad et al., 2016). Combination of CAPE, a powerful antioxidant, with radiotherapy can provide an effective treatment strategy to protect normal tissues against radiation damage.

10 | CAPE IN THE PREVENTION OF RADIATION-INDUCED CATARACTS

In recent years, especially with the help of rapid developments in genetics and cell biology, the biochemical processes in cataract formation have begun to be clarified more. It does not seem possible to escape from radiation in many areas developing with technology (Cui, Yang, & Yang, 2020; Izzotti, 2003; Taysi et al., 2022). Many complex processes play a role in the formation of cataract, which is defined as a progressive opacity of the eye lens that eventually leads to vision loss (Ainsbury et al., 2016). Cataracts are divided into three different groups according to their primary causes: age-related, pediatric or secondary cataracts. In addition, it can be divided into three groups as nuclear, cortical or posterior subcapsular according to the anatomical

TABLE 2 Modulations on the CAPE molecule and docking score values

Comp. No.	A	B	C	Docking score kcal/mole
1	H	H	H	−7.091
2		H	H	−7.773
3		H	H	−7.984
4		H	H	−8.021
5		H	H	−8.064
6		H	H	−7.965
7		H	H	−7.942
8		H	H	−7.922
9		H	H	−7.947
10		H	H	−8.187
11		H	H	−8.141
12		H	H	−8.039
13		H	H	−8.078
14		H	H	−7.734
15		H	H	−7.385
16		H	H	−7.503
17		H	H	−7.950
18		H	H	−7.956

(Continues)

TABLE 2 (Continued)

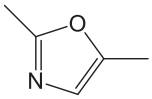
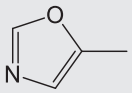
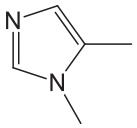
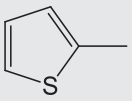
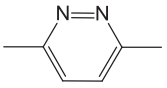
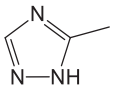
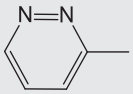
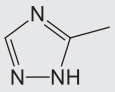
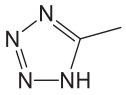
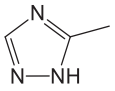
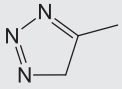
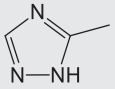
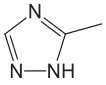
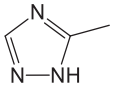
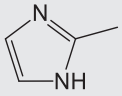
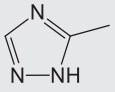
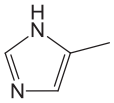
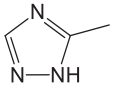
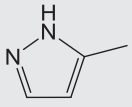
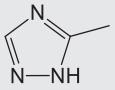
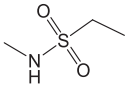
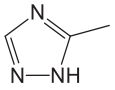
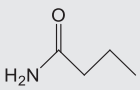
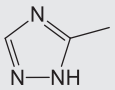
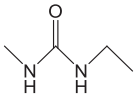
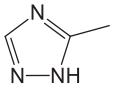
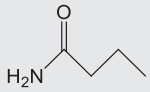
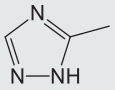
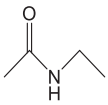
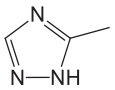
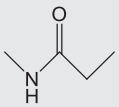
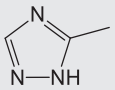
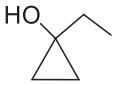
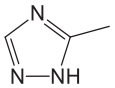
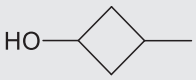
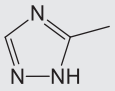
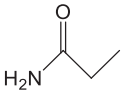
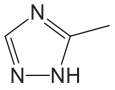
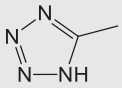
Comp. No.	A	B	C	Docking score kcal/mole
19	H		H	−8.098
20	H		H	−7.999
21	H		H	−7.644
22	H		H	−7.626
23	H			−9.158
24	H			−9.434
25		H		−9.088
26		H		−9.177
27		H		−9.178
28		H		−9.075
29		H		−9.080
30		H		−9.077
31		H		−8.795
32		H		−8.862
33		H		−9.144

TABLE 2 (Continued)

Comp. No.	A	B	C	Docking score kcal/mole
34		H		−8.821
35		H		−8.588
36		H		−8.890
37		H		−8.577
38		H		−8.577
39		H		−9.007
40	H	H		−7.593

location or appearance within the lens (Barnard & Hamada, 2022; Kleiman, Stewart, & Hall, 2017).

Epidemiological findings regarding the lens of the eye, one of the most radiosensitive tissues in the human body, have reported that lens opacities from exposures to ionizing radiation are probably induced at lower doses than previously thought (Ainsbury et al., 2009; McCarron et al., 2022). The precise mechanisms of radiation cataractogenesis are still poorly understood. Cataract may develop as a result of radiotherapy of tumors located in the head and neck, brain or eye. Today, the only treatment for cataract formation is surgery. However, a 10-year delay in cataract formation or development is predicted to cut cataract surgeries in half (Demir et al., 2016; Suryanarayana et al., 2005). Therefore, alternative treatment models are important. Although cataract is a multifactorial disease, almost all studies have agreed that oxidative stress is an initiating factor. Oxidation and reduction events play an important role in the lens (Ahmadi, Barnard, Ainsbury, & Kadhim, 2022; Taysi, Okumus, et al., 2021). Oxidative damage leads to a series of molecular changes that result in cataracts, resulting in the need for reducing systems in the lens as well as detoxification enzymes such as catalase (CAT) and superoxide dismutase (SOD) (Ertekin et al., 2004). GSH plays the most important role in protecting the lens from oxidative damage. In many types of cataracts, the ability of the lens to resist oxidative stress decreases as a result of the decrease in GSH levels. Therefore, studies on free radical formation as a result of oxidative stress and the role of antioxidants in this mechanism are important. Although antioxidants are produced by the body, their levels in the blood decrease with aging, lifestyle and environmental factors (Muranov & Ostrovsky, 2022; Yu, Wang, & Yang, 2007). Demir et al. (2016) in a study conducted on the lens tissue of rats after a single dose of 5 Gy total head irradiation, found that 80% developed cataracts in the radiotherapy group. They reported that in the group given 10 μmol CAPE every day for 10 days, the rate of cataract formation after radiation decreased to 40% and remained limited to grades 1 and 2. In the radiotherapy group, malondialdehyde (MDA) level and xanthine oxidase (XO) enzyme activity, which are oxidant parameters, were significantly higher than all other groups. They found that, among the antioxidant parameters, SOD activity was lower in the radiotherapy group than in the other groups, while glutathione peroxidase (GSH-Px) enzyme activity was higher than in all other groups. In this study, they suggested that the high rate of cataract observed in the radiotherapy group and the decrease in the rate of cataracts in the group given CAPE before and after radiation were the result of the protective effect of this agent against radiation (Demir et al., 2016). In another study, the possible effect of nitrosative stress caused by radiotherapy on the development of cataracts was investigated. Nitric oxide synthase (NOS) activity, nitric oxide and peroxynitrite levels, which are nitrosative stress parameters, were found to be significantly higher in the radiotherapy group than in the other groups. They reported that these parameters decreased in the group given 10 μmol CAPE and were at the same level as the control group. They suggested that CAPE prevents nitrosative stress caused by radiotherapy (Taysi, Okumus, et al., 2021).

In a study investigating the potential effects of CAPE against oxidative stress in rat retinas exposed to mobile phones emitting 900 MHz electromagnetic radiation (EMR) for a long time, a group of rats exposed to EMR at 30 minutes/day for 60 days received 10 mM/kg/day CAPE for the 60-day study. It was found that EMR increased retinal MDA and nitric oxide (NO) levels and caused a decrease in SOD, CAT and GSH-Px activities. It has been reported that the retinal MDA and NO levels decreased in the CAPE group and increased SOD, CAT and GSH-Px activities, the antioxidant enzymes, by keeping them within normal ranges. They suggested that this stress was prevented by the effective free radical scavenging activity of CAPE (Ozguner, Bardak, & Comlekci, 2006). In the light of studies, it has been reported that CAPE can prevent cataractogenesis and strengthen antioxidant defense in cataracts caused by ionizing radiation in rat lenses.

11 | CAPE AS A RADIO PROTECTOR IN HEAD AND NECK CANCERS

Cancers arising from the oral cavity, pharynx, larynx, paranasal sinuses, nasal cavity and salivary glands constitute head and neck cancers and are the sixth most common cancer, affecting 650,000 people worldwide and causing 350,000 deaths annually (Altay et al., 2020; Kuo et al., 2015). Oral cancer, the most common type of head and neck cancer, was reported to cause 135,000 deaths worldwide in 2013. Oral and oropharyngeal squamous cell carcinoma (OSCC) account for 90% of oral cancers, its poor prognosis is due to the low response rate to current therapeutic drugs (Kuo et al., 2015). In a study investigating the antitumor effect and mechanism of CAPE in laryngeal carcinoma cells, it was reported that CAPE showed potent antitumor activity against HEp2 cells by reducing cell proliferation in vitro at a concentration of 23.8 ± 0.7 μM for 72 h. It has been reported to induce S phase arrest and inhibit cell proliferation by regulating the signal transducer and activator of the transcription (STAT)-3/Polo-like kinase 1 pathway (Ren et al., 2019).

Studies have shown that CAPE therapy can effectively suppress proliferation, survival and metastasis of oral cancer cells. In addition, CAPE has been reported to inhibit Akt signaling, cell cycle regulatory proteins, NF-κB function, as well as the activity of matrix metalloproteinase (MMPs), epidermal growth factor receptor (EGFR) and Cyclooxygenase-2 (COX-2) (Bussink, van der Kogel, & Kaanders, 2008; Kuo et al., 2015). Possible effects on tongue tissue were examined in a study using total head irradiation in rats. When the radiotherapy group was compared with the other groups, it was reported that statistically significant differences were detected in the oxidative stress parameters in the tongue tissue, and XO activity, lipid hydroperoxides (LOOH), total oxidant status (TOS), oxidative stress index (OSI) levels were significantly higher. This shows that 10 μmol CAPE reversed oxidative stress in irradiated rats and this natural agent protected the rats from ionizing radiation. In terms of its effect on XO activity and LOOH levels, this protection seems even more pronounced (Altay et al., 2020). In another study, the possible effects on brain tissue were discussed, and when evaluated in terms of TOS, OSI and LOOH levels, statistically significant changes were detected, and it was reported that oxidative stress parameters were significantly increased in the radiotherapy group compared to all other groups. However, the total SH level in the brain tissue of the rats given CAPE before and after radiotherapy was found to be significantly higher than the radiotherapy group. In their findings, it was suggested that 10 μmol CAPE has an antioxidant effect against the oxidative damage that may occur in the brain due to radiation in rats, however, supportive pharmacological and toxicological studies are needed to confirm these findings (Khayyo et al., 2019).

There are many studies investigating the parameters that change in the oxidation state of the brain due to radiation, and there are different opinions. In a study investigating the effects of whole-body radiotherapy on brain tissue LPO and antioxidant system parameters in rats of different age groups, radiotherapy was applied to 1-week, 4-week, 12-week and 1-year-old rats. This approach is based on the assumption that 1-week-old rats can correspond to newborn humans, 4-week-old rats to adolescent, 12-week-old rats to adult, and 1-year-old rats to elderly. It was found that SOD activity decreased significantly in 1-week-old rats, the decrease in GSH-Px and CAT activity was more pronounced in 1-week-old and 1-year-old rats, and there were no significant changes in adolescent and adult rats. It has been reported that an increase in MDA levels was observed in all age groups and the highest MDA level was in 1-year-old rats. They reported that ionizing radiation used in radiotherapy affects antioxidant systems and increases tissue MDA levels, and these changes are more common in 1-week-old and 1-year-old rats. They suggested that this may be due to the incompleteness of many systems in newborn rats and the loss of physiological capacity due to aging in 1-year-old rats (Uyumlu, Erkal, Batcioglu, Serin, & Yucel, 2009). In a study using 10 μmol CAPE, it was found that brain tissue SOD activity was the lowest in the rats in the radiotherapy group compared to the other groups, and the highest in the CAPE group. When compared in terms of MDA level, it was reported that the MDA level was the highest in the radiotherapy group, while the MDA level was the lowest in the rats receiving CAPE (Alkis et al., 2015).

In a study investigating the antiproliferative and radiosensitizing effects of CAPE on medulloblastoma (MB) Daoy cells, different concentrations of CAPE were used on Daoy cells and evaluated in terms of cell viability, apoptosis, cell cycles, cyclin B1 expressions, radiosensitization and chemosensitization. In addition, human astroglia SVGp12 cells were treated with CAPE to determine whether CAPE has possible protective or complicating effects on normal tissues. Various concentrations of CAPE (0.3, 1, 3, 10, 30 μM) have been reported to inhibit the growth of Daoy cells in a time- and concentration-dependent manner. Researchers have suggested that CAPE has antiproliferative and radiosensitizing effects for Daoy cells, and in this respect, it may improve the treatment of MB (Lin et al., 2006). In another study, Lee et al. reported that CAPE inhibited the growth of Daoy cells, effectively decreased glutathione reductase (GRD), and significantly increased GSH-Px activity. They emphasized that CAPE performs its anti-proliferative and radiosensitizing effects by

decreasing glutathione (GSH), increasing ROS activity and inhibiting NF-KB activity (Y. Y. Lee et al., 2008).

It has been reported that CAPE strengthens antioxidant defense in Head & Neck cancers, reduces oxidants and therefore LPO, plays a positive role by reducing both glutathione and its synthesizing enzyme activity and increasing ROS activity in cancer cells. Therefore, this aspect of CAPE can create suitable working grounds for better results in the future.

12 | CAPE AS A RADIOPROTECTOR IN THE GASTROINTESTINAL SYSTEM

In studies, it has been reported that the incidence of pancreatic, colon-rectum, liver and stomach cancers in humans is highly correlated with lifestyle and this relationship plays an important role in the increase or decrease of gastrointestinal system cancers (Lv, Cui, Ma, Liu, & Yang, 2021). It has been reported that CAPE (7.5–120 μM), which significantly inhibits human neutrophil elastase activity, causes inhibition of cell growth and migration of pancreatic cancer cells (Duan et al., 2017). In a study investigating the radioprotective effects of CAPE on intestinal damage caused by X-ray radiation, rats were first given 10 mol/kg/day CAPE intragastrically for 7 consecutive days, and then a single dose of 9 Gy X-ray irradiation was applied to the abdomen. The experimental study was terminated after 72 h. Jin et al reported that CAPE administered before ionizing radiation effectively reduced intestinal pathology changes, apoptosis, oxidative stress, nitric oxide and myeloperoxidase content, as well as plasma tumor necrosis factor-α concentration. They also found that CAPE reversed the activation of p38MAPK and increased expression of the intercellular adhesion molecule-1 induced by radiation in the intestinal mucosa. Their findings suggested that CAPE given before treatment could be a promising candidate to treat radiation-induced intestinal injury (Jin et al., 2015).

In a study evaluating the protective effect of CAPE against acute radiation-induced liver injury, Chu et al administered a single dose of 30 Gy beta-ray to the upper abdomen after intraperitoneal administration of CAPE (30 mg/kg) to rats for 3 consecutive days. They found that CAPE given before treatment significantly reduced serum levels of alanine aminotransferase and aspartate aminotransferase, which are liver function tests, and increased SOD activity and GSH levels. They showed that CAPE also protected against radiation-induced hepatotoxicity and inhibited hepatocyte apoptosis. They also found that it reduced the activity of tumor necrosis factor-α, NO, and inducible NOS, which are nitrosative stress markers. In their results, they reported that CAPE given before treatment protected against radiation-induced liver damage (Chu et al., 2015).

In an experimental study, Cikman et al. examined the possible protective effects of 10 μmol CAPE supplementation on the oxidant and antioxidant system in the liver tissue of irradiated rats in irradiated rats. They found that liver tissue TOS, LOOH level and OSI parameters of irradiated rats increased significantly, while total antioxidant status (TAS), sulfhydryl levels and PON activity decreased significantly. They reported that CAPE given before and after ionizing radiation therapy kept oxidative stress parameters at the level of control group values, prevented oxidative stress caused by radiation with its radioprotective effect, and had antioxidant effects that increase antioxidant capacity in liver tissue (Cikman et al., 2015a). In another study, liver tissue total superoxide scavenging activity (TSSA), non-enzymatic superoxide scavenging activity (NSSA), glutathione-S-transferase (GST) activity, markers of antioxidant, were found to be statistically low in the irradiated group. However, XO, NOS activities, NO and MDA levels, markers of oxidant, were found to be statistically significantly higher when compared with all other groups (Cikman et al., 2015b). In a study, it was reported that 20 μmol CAPE acts by decreasing proteasome function to increase the sensitivity of gastric cancer cells to doxorubicin and cisplatin, which is anticancer drugs (Matsunaga et al., 2019). In other studies, regarding drug resistance, which is one of the challenges of chemo-radiotherapy, it has been reported that various doses (0, 0.5, 1, 2, 4, 6, 8, and 25 μg/ml) of CAPE, a strong inhibitor of NF-κB, sensitizes colorectal tumor cells to radiation by depleting glutathione and inhibiting NF-kB activity (Chen, Liao, Tsai, Wang, & Shiao, 2005). To summarize, CAPE may represent a promising new adjuvant for the treatment of drug resistance in gastrointestinal tract cancers, one of the challenges of chemo-radiotherapy.

13 | CAFFEIC ACID PHENETHYL ESTER AND COVID-19

Coronaviruses, discovered in 1960, are infectious strains of viruses named for their crown-like appearance under the electron microscope due to glycoprotein projections on their envelope and placed into the family Coronaviridae; order Nidovirales. They enter the respiratory system through the nose. They induce the symptoms of a moderate common cold/bronchitis in avian and mammalian species during a 3–7 day incubation period (nasal blockage, sneezing, runny nose, cough, headache, fever, pneumonia, asthenia, and inflammation in the airway) (Chen et al., 2008; Kumar et al., 2021; Natarajan et al., 1996). Understanding the molecular mechanisms of viral replication and packaging into infectious particles in host cells, their release, the identification of antiviral target proteins, and the generation of inhibitors are all necessary for designing and developing antiviral therapy. Coronaviruses have been found to infect and multiply in differentiated respiratory epithelial cells, causing vacuolation, cilia destruction, local inflammation, swelling, sneezing, and fever (Graham, Donaldson, & Baric, 2013). Severe Acute Respiratory Syndrome Coronavirus 2 is a new coronavirus that has killed numerous people all over the world. Understanding this novel virus and developing preventative and therapeutic medications is critical. Because drug creation is an expensive, time-consuming, and intensive process, timely repurposing of existing medications is frequently pursued, with research areas such as genomics, bioinformatics, and molecular modeling approaches providing considerable advantages (Kumar et al., 2021). It has been reported in studies that honeybee propolis is used extensively in traditional home

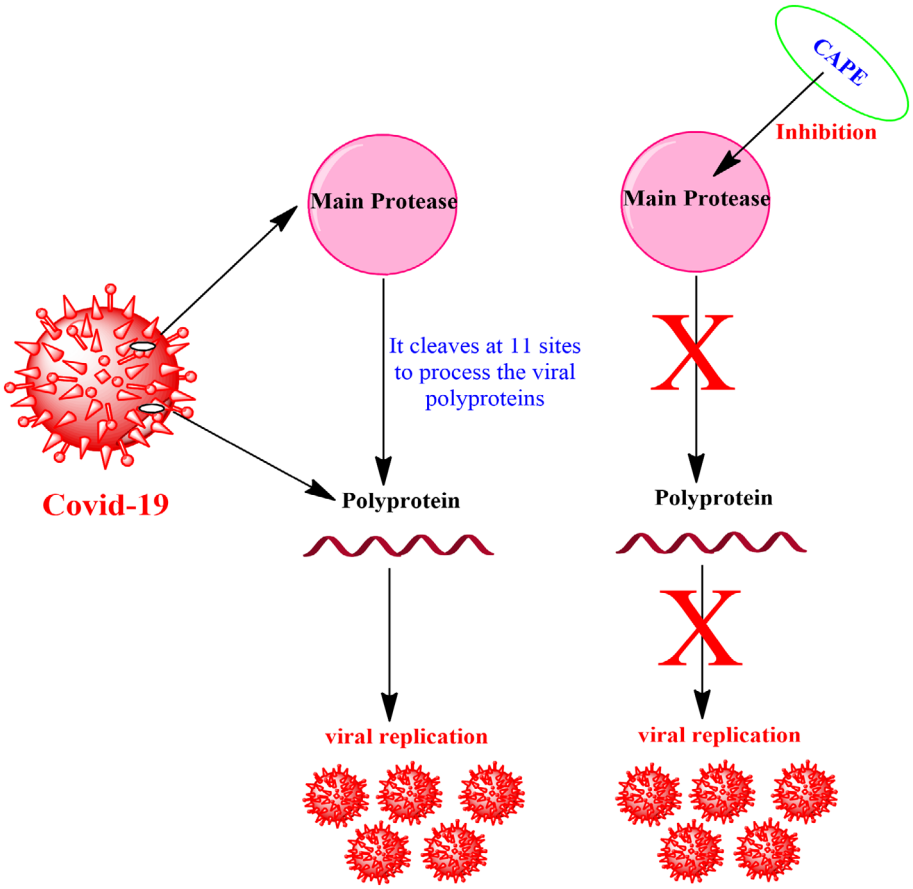


FIGURE 8 Effect of main protease inhibition by CAPE on replication of COVID-19

medicine systems, strengthens immune function, and has various prophylactic and therapeutic activities (Akyol et al., 2013; Anjaly & Tiku, 2018; Kumar et al., 2021). Studies have reported evidence that honeybee propolis inhibits a variety of viruses, including herpes simplex virus, human cytomegalovirus, dengue virus type-2, influenza virus A1 and rhinovirus (Kumar et al., 2021; Kwon, Shin, Perumalsamy, Wang, & Ahn, 2020; Serkedjieva, Manolova, & Bankova, 1992; Zandi et al., 2011).

We examined the potential of CAPE (Figure 8) from honeybee propolis against SARS-CoV with molecular docking tools. Since the major viral proteases isolated from different coronaviruses are mainly conserved in sequence and structure, we used an important viral enzyme Major Protease as a target in this molecular docking program. It showed interactions with highly conserved residues of CAPE coronavirus proteases, demonstrating its inhibitory potential for SARS-CoV-2 protease and its therapeutic importance for the novel SARS-CoV-2 coronavirus.

14 | MOLECULAR DOCKING OF CAPE WITH MAIN PROTEASE

The sudden outbreak of 2019 novel coronavirus (2019-nCoV, later named SARS-CoV-2) rapidly turned into an unprecedented pandemic of coronavirus disease 2019 (COVID-19). This global healthcare emergency marked the third occurrence of a deadly coronavirus (CoV) into the human society after entering the new millennium, which overwhelmed the worldwide healthcare system and affected the global economy. However, therapeutic options for COVID-19 are still very limited. Developing drugs targeting vital proteins in viral life cycle is a feasible approach to overcome this dilemma. Main protease plays a dominant role in processing CoV-encoded polyproteins which mediate the assembly of replication-transcription machinery and is thus recognized as an ideal antiviral target (Cui et al., 2020; Segueni, Keskin, Kadour, Kolaylı, & Salah, 2021).

The structures of the main protease were obtained from [(RCSB PDB)] under the symbol (5R7Y). The process of Docking between CAPE and the main protease was carried out using Schrödinger Maestro version 12.5.139, MMshare 5.1.139 version. Molecular docking results are shown in Figures 3 and 4, where it was found that the binding energy between the protein and the ligand was −7.091 and the RMSD value was 0.044, and this indicates the high potential of CAPE to bind with the target enzyme and inhibit its action, as the types of bonding forces were the presence of two hydrogen bonds between the two hydroxyl groups on the benzene ring in the CAPE and the amino acid Glu166 located in the active site of the enzyme. It was also observed that there is an ionic bonding strength between the benzene ring and the ester group to which the double bond is linked with the amino acid residues His41, Ser46, Thr24 and Asn142 (Figures 9 and 10).

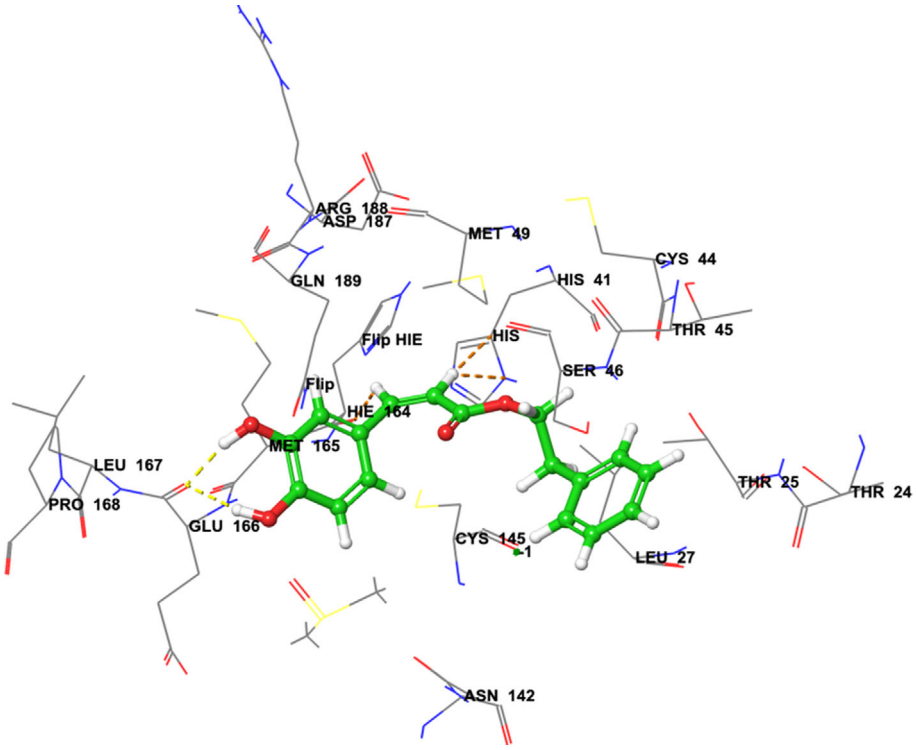


FIGURE 9 3D of CAPE with main protease active site

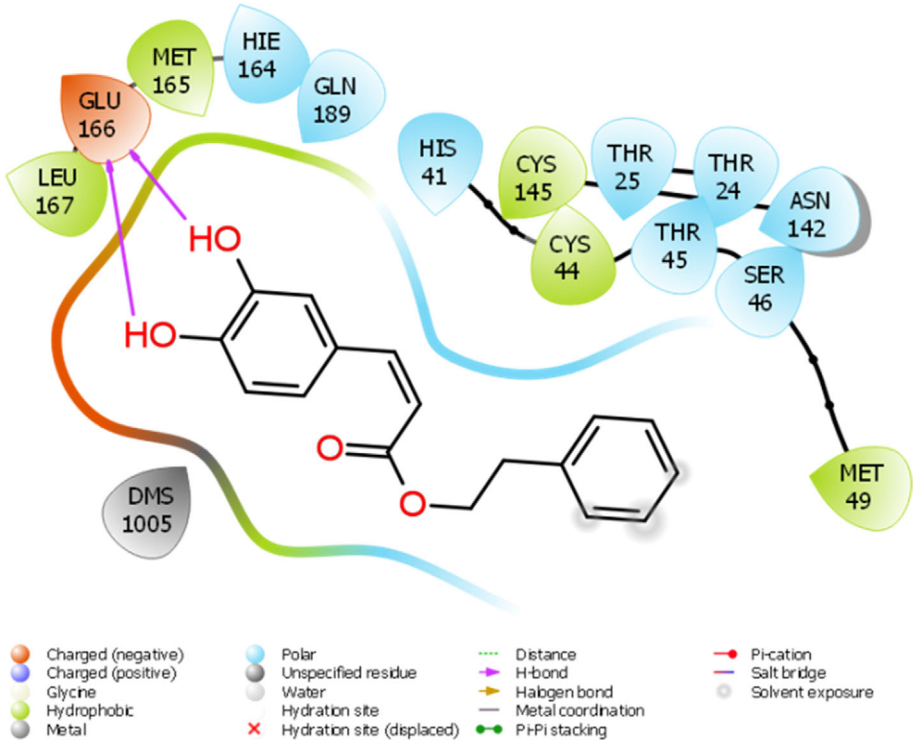


FIGURE 10 2D of CAPE with main protease active site

15 | DISCUSSION

Cancer, which is a multifactorial disease that requires different treatments including radiotherapy and chemotherapy, is one of the most problematic diseases in the world and its cells gain resistance to radiotherapy and chemotherapy by different mechanisms (Prasad et al., 2016). Patients receiving cancer treatment suffer because of its high cost, rate of side effects, and recurrence of the disease. For this reason, natural, economical, safer therapeutic and preventive measures are important in research subjects (Sari et al., 2022). Since most of the radiosensitizing and chemo-sensitizing agents exhibit adverse reactions in non-target organs, medicinal compounds considered to

be naturally occurring, non-toxic fourth-generation chemosensitizers are of great interest to research, and many also show radiosensitivity properties (Prasad et al., 2016).

Natural antioxidants, which have the potential to eliminate and detoxify harmful molecules that cause stress, are constantly being researched for their health benefits. However, concurrent research findings reveal that these substances may also have dark aspects that can be harmful to human health. Maintaining an appropriate balance in therapy with the addition of antioxidants should be available based on the accumulating evidence of recent research reports. Natural herbs and products have received a lot of attention due to various factors such as easy availability, low cost, safety and effectiveness (Shi et al., 2022).CAPE, the most effective main component of propolis, is an important area of interest in these studies. CAPE exhibits a variety of potent therapeutic activities by reversing chemo and radioresistance, inhibiting proliferation, angiogenesis and metastasis, inducing apoptosis and regulating autophagy in cancers (Sari et al., 2022). Pyroptosis, another programmed cell death different from apoptosis, is a newly recognized type of inflammatory programmed cell death that differs in part from other forms of cell death by its unique morphological and biochemical features, and characterized by swollen cells, formation of holes in plasma membranes, and release of proinflammatory cytokines (Fink & Cookson, 2006; Huang et al., 2022). Tumors attempt to prevent or limit the cell death pathway using multiple strategies (Cerella, Teiten, Radogna, Dicato, & Diederich, 2014; Yu et al., 2021). Widely studied apoptosis and other forms of death function as important anticancer defense mechanisms. However, the relationship between pyroptosis and cancer has not been fully understood until now (Pezuk, 2019; Yu et al., 2021). The relationship between pyroptosis and tumors is becoming increasingly clear in research, which may lead to some strategies for clinical treatments (Yu et al., 2021).

As in Figures 5 and 6, results from molecular docking show the possibility of binding CAPE with replication enzyme to stop the spread of cancer cells. Also, in order to increase the binding security of the replication enzyme and CAPE, modifications can be made at three sites on the CAPE molecule, causing the compound to work more potently and usefully to inhibit the proliferation of cancer cells and reduce its rate. Also, it is seen that CAPE has an inhibitory effect against the main protease enzyme and may be effective in the treatment of SARS-CoV-2 (Figures 3 and 4).

Antioxidants derived from natural plants, which have gained popularity as dietary supplements with few side effects, are one of the most important issues that have received much attention recently, and the use of naturally occurring substances as prophylaxis or to prevent recurrence of malignancies and other disorders has been widely accepted.

16 | CONCLUSION AND FUTURE PERSPECTIVE

In light of all this information, obviously, the available information regarding CAPE, a promising new naturopathic agent based on remarkable pharmacodynamic effects, mainly comes from cellular and experimental animal models. However, there are no clinical data on its use in humans and there is insufficient information on how it acts in the body. Therefore, extensive clinical studies are needed to address key aspects of CAPE's efficacy and safety in vivo based on pharmacodynamics and pharmacokinetics.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

Availability of data and materials All data analyzed and generated during this study are included in this article.

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