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Review Article

Inhibitory mechanism against oxidative stress of caffeic acid

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ABSTRACT

The purpose of this article is to summarize the reported antioxidant activities of a naturally abundant bioactive phenolic acid, caffeic acid (CA, 3,4-dihydroxycinnamic acid), so that new avenues for future research involving CA can be explored. CA is abundantly found in coffee, fruits, vegetables, oils, and tea. CA is among the most potential and abundantly found in nature, hydroxycinnamic acids with the potential of antioxidant behavior. Reactive oxygen species produced as a result of endogenous processes can lead to pathophysiological disturbances in the human body. Foods containing phenolic substances are a potential source for free radical scavenging; these chemicals are known as antioxidants. This review is focused on CA's structure, availability, and potential as an antioxidant along with its mode of action. A brief overview of the literature published about the prooxidant potential of caffeic acid as well as the future perspectives of caffeic acid research is described. CA can be effectively employed as a natural antioxidant in various food products such as oils.

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1. Introduction

Complex metabolic processes occurring in human body result in the production of reactive oxygen species (ROS) such as hydroxyl radicals [1]. These radicals are reported to have different biological functions such as antimicrobial activity [2]. Normally, ROS production in body is balanced by scavengers (antioxidants) but in pathological condition the equilibrium is disturbed due to over-production of ROS, which subsequently reacts with intra- and extracellular species and results in ailments such as aging, cancer and necrosis [1].

Phenolics are a class of compounds isolated from plants and are stated to have free radical scavenging potential due to their stable structure after trapping the free radical. Methoxy and hydroxyl groups can affect the antioxidant potential of the molecule [3]. Hydroxycinnamic acids are aromatic acids, and caffeic acid (CA) is a member of this class. CA (Figure 1) is a phenolic acid and a catechol derivative, isolated from various plants such as *Ilex paraguariensis* (15 mg/100 g), *Melissa officinalis* (39.3 mg/100 g), *Baccharis genistellodes* (8 mg/100 g), and *Achyrocline satureioides* (4 mg/100 g) [4].

CA and its derivatives including ethyl ester and phenyl ester (CAPE) are reported for various pharmacological

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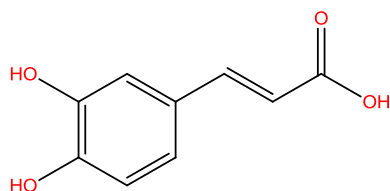


Figure 1 – Structural formula of caffeic acid [15].

activities, e.g. anticancer, anti-AIDS and anti-inflammatory [5,6]. CA is described as an inhibitor for low-density lipoprotein oxidative modification which is thought to be involved in the pathogenesis of atherosclerosis [7]. Moreover, CA is also reported to react (scavenge) more efficiently with peroxyl radical as compared to the drug Trolox, which is used for oxidative stress; however, peroxyl radical involved in lipid peroxidation is a potential threat to cell membranes [8]. Increased antioxidant behavior is attributed to delocalization of the unpaired electrons in the extended conjugated side chain [9]; however, the structure stability of CA is further increased by additional hydrogen bond formation utilizing its *ortho*-dihydroxyl group after breaking the O–H bond [10]. Enhanced antioxidant activity of CA is also associated with the formation of *o*-quinone and regeneration of CA through semiquinone radical primarily generated by the reaction of antioxidant and free radical present in the medium [11].

CA derivatives have been studied and reported for their antioxidant potential: chlorogenic acid, CAPE, caffeic acid methyl ester, caffeic acid ethyl ester, caffeic acid butyl ester, caffeic acid benzyl ester, methyl caffeate (MC), and methyl dihydrocaffeate (MDC), octyl caffeate, and cichoric acid [11–13].

Recently, CA has been reported as an effective antioxidant in vitro assays such as total antioxidant activity by ferric thiocyanate process, lipid peroxidation analysis, reducing efficiency, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid (ABTS⁺) and 2,2-diphenyl-1-picrylhydrazyl (DPPH[•]) scavenging, superoxide anion scavenging analysis, and metal chelating activity against standards such as butylated hydroxyanisole and butylated hydroxytoluene [14].

This review summarizes the recent data published on the antioxidant activity of CA, along with its structural aspects and possible mode of action as an antioxidant agent.

2. Literature search methodology

A rigorous literature search in English language was conducted, using different electronic databases including Science Direct, PLoS One, Medline, PubMed, Science Hub, and EMBASE from 1980 to 2015, using various keywords including *caffeic acid* and *antioxidant* jointly, followed by the use of *caffeic acid* with other keywords including *inflammation*, *cancer*, and *molecular targets*. The literature search was carried out to assess the bibliography of the selected articles to reveal the original research for the preparation of a comprehensive review article.

3. Results and discussion

3.1. Antioxidant activity of caffeic acid

Stability and shelf life are major issues in dietary products; these issues can be overcome by the addition of natural antioxidants such as phenolic acids [15]. CA is also among the hydroxycinnamic acids used to enhance the stability of dietary products [16,17]. However, the antioxidant potential of CA is affected by factors such as nature of oil, food processing, ingredients, and ratio of antioxidants and lipid components [17,18]. Novel dihydro-CA amides have been described for excellent free radical scavenging abilities assessed by the DPPH method, an excellent potential has been reported to protect polyunsaturated oils [11].

Addition of CA has been reported to enhance the stability of various oils by inhibition of lipid oxidation; the results are summarized in Table 1 [16,18–21].

UV radiation is responsible for biological changes such as photoaging and damages normal lymphocytes, resulting in their death. However, lymphocytes pretreated with an amount of CA (1 µg/mL, 5 µg/mL, and 10 µg/mL) for 30 minutes, when irradiated with UV-B (280–320 nm), a photoprotective effect of CA has been reported in terms of decreased lipid peroxidation and reduced DNA damage showing viability of lymphocytes [22]. The maximum protection against photoaging effect has been described with pretreatment using an amount of CA (10 µg/mL) in irradiated lymphocytes [22]. The photoprotective effect of CA may be due to glutathione metabolism, which exhibits free radical scavenging. CA has also been reported to protect phospholipidic membranes [23,24] and resist against vitamin C and vitamin E depletion through the membrane [25]. CA has also been found to have photoprotective activity against UV-B radiation in both in vitro and in vivo studies [26,27]. Furthermore, CA pretreatment leads to considerable decrease in γ radiation-provoked DNA damage in cultured human lymphocytes [26]. CAPE has also been reported to have photoprotective influence against UV-B induced DNA damage [28].

Ischemia/reperfusion (I/R) injury can be caused by ROS [29]. Reported models can be used to study protective effects of antioxidants administered prior to induction of I/R injury [30,31]. CA has been described to have protective effects on I/R injury in rat's small intestine [29] and a successful protection

Table 1 – Caffeic acid and/or its derivatives as antioxidants for stability enhancement of various oils.

Oils	References
Pork lard oil	[16]
Corn oil	[55]
Corn, grape seed, peanut, rapeseed, sesame, and soybean oils	[18,25]
Soybean oil	[17,21]
Sunflower oil	[19,56]
Avocado and coconut oils	[20]
Minced fish muscle	[19,57]
Minced chilled horse mackerel	[58]
Polyunsaturated oils	[11]

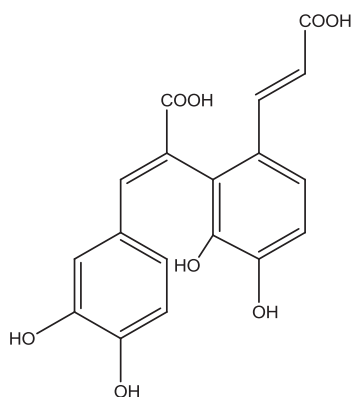


Figure 2 – Structural formula of bis-cafeic acid (SMND-309) [1]

of mouse brain and liver mitochondria from oxidative stress, however, using CAPE and its related phenolic compounds during I/R injury showed more promising results [12]. Moreover, an excellent cytoprotective activity of CAPE and fluorinated CAPE derivatives has been published in a human umbilical vein endothelial cell model of oxidation stress [13].

A comparative *in vitro* study conducted to assess the antioxidant potential of CA and its conjugate SMND-309 (Figure 2) reported 92.1% and 93.4% scavenging activity of CA and SMND-309, respectively, on DPPH radical at the concentration of 20 mg/mL; therefore, a higher antioxidant effect of SMND-309 than CA can be observed [1]. In another study, 61.9% superoxide anion radical scavenging activity at 10 mg/mL has been reported for CA [14].

3.2. Synergistic effect of caffeic acid

Synergistic studies are important in therapeutic strategies; synergism in the antioxidant activity of CA in the presence of other antioxidants such as cysteinyl thiol, histidine-containing dipeptides, bovine serum albumin (BSA) and chitosan (Ch) are summarized in Tables 2 and 3. In a recent study, the synergistic effect on the antioxidant activity of two caffeates, MC and MDC, in coexistence with cysteinyl thiol was reported [32]. Coexistence of monothiol adducts with MC and of mono- and dithiol adducts with MDC exhibited synergistic antioxidant effect, which was reported to be due to the electronic features of sulfur components [33]. Recently, the enhanced antioxidant activity of CA conjugated to histidine-containing dipeptides has been described; the

Table 2 – *In vitro* studies on synergistic effect of caffeic acid.

Synergistic agent	Objective of study	Background of study	Antioxidant technique	Important results	Conclusion	Reference
Cysteinyl thiol	To study effect of cysteinyl thiol on the antioxidant activity of MC and MDC	MC and MDC can afford various thiol adducts with a recovered catechol structure.	Lipid peroxidation assay	The dependence of synergism upon the length of induction period. The mono-thiol adduct of MC and the mono- and di-thiol adducts of MDC contribute to the synergism in the antioxidant activity of both esters.	Synergistic effect of coexisting thiol on the antioxidant activity of MC and MDC	[32]
Histidine-containing dipeptides	To compare the antioxidant activity of histidine and CA-histidine conjugate with that of CA-β-Ala-His-NH ₂	Histidine naturally exists at high concentrations in mammalian muscle tissue and nervous system.	2,2-Diphenyl-1-picrylhydrazyl radical scavenging assay, Lipid peroxidation assay	The change in the antioxidative activity of CA by changing the position of histidine in CA-histidine conjugate.	The augmented antioxidative effect of conjugated histidine-containing dipeptides.	[34]
Bovine serum albumin (BSA)	To determine the influence of BSA on the total antioxidant activity of CA in model food emulsions	BSA is a minor whey protein (MW 66 kDa) with surfactant features employed for the stabilization of various food emulsions.	Total antioxidant activity	The synergistic increase in stability of the O/W and W/O emulsions containing BSA and CA by 102.9% and 50.4% respectively calculated as 2 × peroxide value + p-anisidine value, with greater synergy calculated if based on formation of headspace volatiles.	A synergistically reduced rate of development of rancidity and considerably reduced concentration of total volatiles, PV and PA for both emulsion types (O/W and W/O) by CA-BSA combination.	[35]

MC = methyl caffeate; MDC = methyl dihydrocaffeate; O = oil; W = water.

Table 3 – In vitro antioxidant activity of chitosan (Ch)–caffeic acid (CA) grafts.

Caffeic acid/ derivative	Grafting agent/ covalent connector	Cross-linker	Objective of study	Antioxidant technique	Important results	Conclusion	Reference
Ch-CA grafts	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride	Not used	To investigate the antioxidant activities of different molecular weights (Mw) and grafting ratios of Ch-CA derivatives	DPPH radical scavenging assay	Maximum IC ₅₀ of radical-scavenging activity (0.064 mg/mL) at the highest CA containing derivative.	Excellent antioxidant activity of Ch-CA grafts	[37]
CA grafted Ch/ CPTMS hybrid scaffolds	Potassium persulfate	CPTMS	To investigate the antioxidant activities of CA grafted Ch/CPTMS hybrid scaffolds	DPPH radical scavenging assay	Increase in the DPPH scavenging activity of CA with increase in CA contents in grafts. The reduction in the antioxidant activity of grafted CA by using potassium sulfate	Higher antioxidant property of biodegradable hybrid polymer (CA grafted Ch/CPTMS hybrid scaffolds)	[38]
Ch-CA-Ge films	Ammonium cerium (IV) nitrate	Ge	To graft CA to Ch for improved antioxidant activity	ABTS radical cation decolorization assay	The higher antioxidant activity of Ch-CA-Ge neutralized films than that of Ch-CA films and the Ch films.	Synergistic improvement in the antioxidant activity of Ch by making its graft with CA and then adding cross-linker, Ge.	[39]
CA-Ch films	Laccase	Not used	To produce synergistically active antioxidant CA-Ch films	ABTS radical cation decolorization Assay	The stronger inhibition of ABTS cation radicals by CA-Ch films as compared to the pure films of Ch. The highest radical scavenging effect of chitosan grafted to CA at pH 4.5	The possibility and feasibility of the preparation of chitosan based novel multifunctional appliances by modifying chitosan functionality with laccase.	[40]

ABTS = 2,2'-azinobis-(3-ethylbenzo-thiazoline-6-sulfonic acid); CPTMS = (3-chloro-propyl)tri-methoxy-silane; DPPH = 2,2-diphenyl-1-picrylhydrazyl; Ge = Genipin.

Table 4 – Studies showing antioxidant and pro-oxidant activity of caffeic acid (CA).

CA/derivative	Objective of study	Background of study	Antioxidant technique	Important results	Conclusion	Reference
CA	To explore the possible mechanisms involved in the antioxidant and prooxidant activities of CA	Concentration-dependent antioxidant or prooxidant effects of some dietary components	DPPH radical scavenging assay, Lipid peroxidation assay	CA exhibits: 1. ROS-scavenging after 2. 2,20-azobis-aminopropane dihydrochloride-induced damage in splenic lymphocytes and the inhibition of lipid peroxidation in mouse liver microsomes.	Concentration-dependent antioxidant and prooxidant effects of CA	[43]
Decomposition products of CA	To study the CA products obtained through thermal decomposition for possible antioxidant potential	Enhanced oxidative reactions due to the presence of prooxidant molecules	DPPH radical scavenging assay	On low heating at the start of CA decomposition, an enhanced prooxidant capacity due to the development of prooxidants. On higher heating, a reduction in the prooxidant components.	Prooxidant behavior of thermal decomposition products of CA	[44]

DPPH = 2,2-diphenyl-1-picrylhydrazyl; ROS = reactive oxygen species.

synergism found was possibly due to the presence of a radical scavenging moiety, imidazole in histidine. However, the highest antioxidant action has been reported for CA-Pro-His-NH₂, where the existence of proline facilitates histidine for stabilizing the hydroxyl groups of CA, resulting in the synergistic antioxidant effect in both aqueous and oily systems [34]. The antioxidant potential of CA has been described in emulsions (5 mmol/kg of emulsion) of 30% sunflower oil-in-water (O/W) and 20% water-in-sunflower oil (W/O) at pH 5.4 during storage at 50°C [35]. BSA is known to possess a slight antioxidant activity (0.2%), however, a synergistically reduced rancidity by the CA-BSA blend in both W/O and O/W emulsions has been reported; CA-BSA increases the stability of both O/W and W/O emulsions by 102.9% and 50.4%, respectively; therefore, it acts more efficiently in W/O emulsions [35,36].

In a comparative study [37], Ch with various molecular weights was mixed with CA in different ratios to prepare Ch-CA graft. Subsequently, these grafts were subjected to DPPH radical-scavenging activity assay based on reducing ability of DPPH. Half inhibition concentrations of Ch-CA samples were < 1 mg/mL but those of low-, medium- and high-molecular-weight Ch were over 10 mg/mL and radical scavenging activity appeared to be entirely dependent on the CA concentration of the polymer [37]. Moreover, the grafting between CA and Ch occurs through bond development between amine group of Ch and carboxyl group of CA; therefore, radical-scavenging activities of CA and Ch-CA were identical in the same CA concentrations. Consequently, the antioxidant activity of CA and Ch-CA directly depends upon phenol group, because carboxyl group is already engaged and thus inactivated in Ch-CA [37].

CA grafting with CSC1.0 (a Ch-based hybrid scaffold) resulted in biodegradable hybrid polymers with a higher antioxidant potential than the CSC1.0 alone [38]. Antioxidant activity has also been described for Ch, Ch cross-linked with genipin (Ch-Ge), Ch grafted with CA (Ch-CA), and Ch cross-linked with Ge and grafted with CA (Ch-CA-Ge) films [39]. The Ch-CA-Ge neutralized films exhibited 40% higher antioxidant activity than the Ch-CA films and 80% higher than the films made up of Ch alone. The improvement in antioxidant activity of Ch films made by grafting to CA, the activity was further synergistically increased by adding cross-linking agent, Ge [39]. Recently, CA-Ch films were reported to strongly inhibit the ABTS cation radicals compared to the films made up of Ch alone [40]. This improved radical scavenging effect could be due to the reproduced oxidizable hydroxyl groups in the polymeric compounds as well as their branched structure and improved stability of radicals owing to the elevated electron delocalization. The branched structure of the polymeric compounds offered the steric obstruction to the moving free radicals making their access difficult to the active sites; Ch was grafted to CA at different pH (4.5, 5.5, and 6.5) was given codes accordingly Ch4.5, Ch5.5, and Ch6.5; Ch4.5 was shown to have the highest radical scavenging effect. In Ch5.5 and Ch6.5 graft, covalent bond formation occurred between CA and Ch resulting in steric hindrance that reduced the accessibility of CA [40]. *In vitro* studies performed using Ch and CA grafts are summarized in Table 3.

3.3. Antioxidant and prooxidant activity of caffeic acid

Antioxidant and prooxidant effects of CA and its derivatives have been reported through a combination of mechanisms:

i.e. radical scavenging activity, inhibition of lipid peroxidation and shielding against LDL oxidation [41,42]. However, CAPE was described to inhibit autoxidation of pyrogallol more efficiently than the CA and efficiently scavenge $O_2^{\bullet-}$ in both nonenzymatic and enzymatic reactions [42]. To evaluate antioxidant and prooxidant potential of CA in a concentration-dependent bleaching of $ABTS^{+\bullet}$, ferulic acid (a derivative of CA) was designated to show better results for $ABTS^{+\bullet}$ scavenging than CA; however, in hydroxyl radical scavenging, CA is described to act as antioxidant up to dose of $5\mu M$; after that it behaves as prooxidant [43]. CA shows a change in oxidative properties under thermal conditions; thermally decomposed products of CA are reported to act as prooxidant [44]. Studies performed to establish the antioxidant and prooxidant activity of caffeic acid are summarized in Table 4.

3.4. In vivo antioxidant activity of caffeic acid against chemical-induced toxicity

Toxic metals such as nickel are environmental pollutants and potential threats for humans. In a study, performed on rat liver with induced toxicity by intraperitoneally administrated Ni for 20 days (20 mg/kg body weight), CA has been reported to reduce the oxidative stress caused by Ni toxicity [45]. However, literature reveals that not only CA but also its derivatives such as CAPE can be effective against carbon tetrachloride-, cisplatin-, and cadmium-induced toxicity of liver and kidney in various animals such as mice, rabbit, and rats [46–53]. In a recently published study, CA was found effective at a dose level 250 mg/kg body weight in rats previously treated with cisplatin, which causes oxidative stress and alters activity of many antioxidant enzymes present in the small intestine of rat [54]. Furthermore, in vivo studies performed using CA and CAPE found them to be effective against various chemically induced toxicities (Table 5).

4. Conclusion

CA-Ch grafts exhibit synergism in their antioxidant effect. Newer grafting agents/covalent connectors and cross-linkers should be explored to exponentially increase the antioxidant action of grafts. The antioxidant activity of CA and its derivatives should also be investigated against various toxicities

induced by other metals such as arsenic, chromium, and lead. Some antioxidants such as cysteinyl thiol, histidine-containing dipeptides, bovine serum albumin and chitosan have been described to synergistically improve the antioxidant activity of CA; similarly, the antioxidant activity of CA can also be synergistically enhanced by other antioxidants. The use of antioxidants can also show signs of concentration-dependent prooxidative effect, which may lead to oxidative damage of cells, considerable health implications should be designed and adopted where CA is being consumed. CA can be effectively employed as a natural antioxidant in various food products such as oils.

Conflict of interests

There is no conflict of interests among authors over the contents of this article.

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Table 5 – In vivo antioxidant activity of caffeic acid against chemical induced toxicity.

CA or its derivative	Toxic chemical(s)	Organ studied	Reference
CA	CCl_4 and alcohol	Rodent liver	[3]
CA	Nickel	Rat liver	[45]
CAPE	Cisplatin	Rabbit liver	[47]
CAPE	CCl_4	Rat liver	[48]
CAPE	CCl_4	Rat kidney	[49]
CAPE	CCl_4	Mice liver	[50]
CAPE	Cadmium	Mice liver	[52]
CA	Cisplatin	Rat intestine	[54]

CA = caffeic acid; CAPE = caffeic acid phenyl ester.

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