

Antioxidant Properties of Hydroxycinnamic Acids: A Review of Structure-Activity Relationships

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Abstract: Hydroxycinnamic acids (HCAs) are important phytochemicals possessing significant biological properties. Several investigators have studied *in vitro* antioxidant activity of HCAs in detail. In this review, we have gathered the studies focused on the structure-activity relationships (SARs) of these compounds that have used medicinal chemistry to generate more potent antioxidant molecules. Most of the reports indicated that the presence of an unsaturated bond on the side chain of HCAs is vital to their activity. The structural features that were reported to be of importance to the antioxidant activity were categorized as follows: modifications of the aromatic ring, which include alterations in the number and position of hydroxy groups and insertion of electron donating or withdrawing moieties as well as modifications of the carboxylic function that include esterification and amidation process. Furthermore, reports that have addressed the influence of physicochemical properties including redox potential, lipid solubility and dissociation constant on the antioxidant activity were also summarized. Finally, the pro-oxidant effect of HCAs in some test systems was addressed. Most of the investigations concluded that the presence of *ortho*-dihydroxy phenyl group (catechol moiety) is of significant importance to the antioxidant activity, while, the presence of three hydroxy groups does not necessarily improve the activity. Optimization of the structure of molecular leads is an important task of modern medicinal chemistry and its accomplishment relies on the careful assessment of SARs. SAR studies on HCAs can identify the most successful antioxidants that could be useful for management of oxidative stress-related diseases.

Keywords: Antioxidant, hydroxycinnamic acids, *in vitro*, ROS, structure-activity relationships.

OXIDATIVE STRESS AND ANTIOXIDANTS

Reactive oxygen species (ROS) are oxygen derived molecules that readily react with other compounds and macromolecules and oxidize them. Some representative examples of these species include superoxide ($O_2^{\bullet-}$), hydroxy (HO^{\bullet}) and peroxy (ROO^{\bullet}) radicals, hydrogen peroxide (H_2O_2) and singlet oxygen (1O_2) [1-4].

ROS are involved in important physiological processes such as immune response, gene expression, signal transduction and growth regulation [5, 6]; however if they are not kept under tight control by physiological antioxidant systems they will be able to oxidize and damage various biological molecules leading to a condition called oxidative stress [1, 7, 8]. In this regard, oxidative stress has been reported to be involved in the pathogenesis of diseases such as cancer [9], neurodegenerative diseases [10], stroke [11], and others [12, 13].

Since an important source of ROS comes from environment [14], with the industrial development and the change in life style, oxidative stress related diseases need a special attention [15].

Antioxidants operate by preventing or slowing the progression of oxidative damage reactions [16, 17]. An antioxidant has been defined as "any substance that delays, prevents or removes reactive species capable of inducing oxidative damage to a target molecule" [1]. Another requirement is that the compound should also generate a more stable, and therefore less injurious, intermediate molecule upon reaction with a ROS in order to be considered as a good antioxidant [4]. With the recent findings, these definitions should be broadened to encompass also agents that are capable of sequestering transition metal ions (chelation activity), inhibition of enzymes involved in ROS production and induction of endogenous defense mechanisms such as antioxidant enzymes [18].

Large scale epidemiologic cohort studies in different populations have provided evidence that consumption of dietary antioxidants is associated with reduced risks of heart diseases and neurodegeneration [19, 20]. Although a number of interventional trials have failed to prove the usefulness of antioxidants for disease management, the use of disease spe-

cific, target-directed antioxidants in carefully chosen patients with higher levels of oxidative stress may prove useful in management of certain diseases [14, 21, 22].

ANTIOXIDANT ACTIVITY OF HYDROXYCIN- NAMIC ACIDS

In the past few decades, dietary polyphenols, which are one of the most abundant classes of antioxidants in human diet, have received increasing attention [23, 24]. Phenolic acids are an important group of secondary plant metabolites with powerful antioxidant capacities [25-27]. These acids are usually divided in two main groups: benzoic acids, containing seven carbon atoms (C6-C1) and cinnamic acids, consisting of nine carbon atoms (C6-C3) [28]. These natural compounds exist predominantly as hydroxybenzoic and hydroxycinnamic acids (HCAs) that may occur either in their free or conjugated forms. Several types of hydroxybenzoic acids and HCA have been identified in the human diet, and are believed to play important roles due to their abundance

and

functional diversity [29-31].

HCAs have ubiquitous distribution in the plant kingdom [32-37] and are abundantly found in tea leaves, coffee, red wine, various fruits, vegetables, and whole grains [32, 38, 39]. They have been categorized as structural and functional constituents of plant cell walls and also as bioactive ingredients of the diet [40, 41].

HCAs possess a simple chemical backbone consisting of a phenylpropanoid structure (Fig. 1). Natural HCAs usually appear either as free forms or esters being its basic unit the quinic acid or the glucose molecule or as more sophisticated derivatives such as dimer, trimer or mixed glycosidic forms in plants [35]. *Para*-coumaric acid, ferulic acid, sinapic acid, and caffeic acid (Fig. 1) are the most representative HCAs.

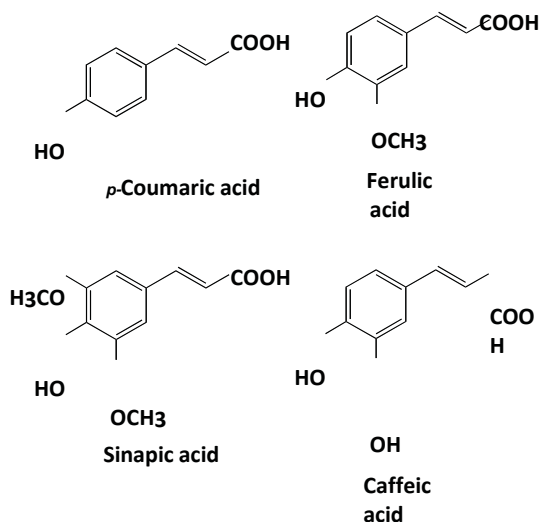


Fig. (1). Chemical structures of the major hydroxycinnamic acids.

HCAs and their derivatives have a broad spectrum of biological activities including antitumoral [42-45], antimicrobial [46], antioxidant [47-52] and neuroprotective effects [53-55].

One of the most important HCA derivatives is chlorogenic acid (CGA) which has been reported as an efficient antioxidant agent [56, 57].

(CQA) and dicaffeoylquinic acids (diCQA) represent the major CGAs found in nature [59].

CGAs are widely distributed in plant sources [60-62]. Coffee beans are one of the best dietary sources of CGA [59]. Moreover, CGAs possess a variety of biological activities ranging from antifungal [63, 64], antiviral [65, 66] and neuroprotective [67] to antidiabetic [68, 69] and cholesterol lowering [70] effects.

Another important caffeic acid derivative is caffeic acid phenethyl ester (CAPE) (Fig. 2). CAPE is an active component of propolis and has been reported to possess antimutagenic, anticarcinogenic, antiinflammatory, and immunomodulatory properties [71].

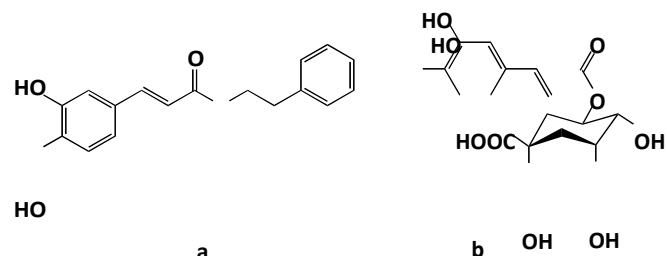


Fig. (2). Chemical structures of **a**) caffeic acid phenethyl ester (CAPE) and **b**) chlorogenic acid (3-CQA).

Due to their structural similarity, several other polyphenols are considered as HCA analogs [72]. For instance, the phenylethanol derivatives, which comprise the 3,4-dihydroxyphenylethanol (hydroxytyrosol) and the 4-hydroxyphenylethanol (tyrosol), the curcumin and derivatives, such as yakuchinone A and yakuchinone B, the capsaicin and dihydrocapsaicin and derivatives, rosmarinic acid and derivatives, [6]-gingerol, [6]-paradol and derivatives are also considered as antioxidant components of diet and a natural inspiration for the development of new potent and effective antioxidants [73-76].

A number of potential health benefits of the HCAs family have largely been connected to their antioxidant properties [77, 78]. HCAs have been shown to be phytochemicals with remarkable antioxidant outlines they are able; a) to increase the resistance of low density lipoprotein (LDL) to lipid peroxidation [56, 79, 80]; b) to protect proteins against oxidation [81]; c) to chelate transition metals that catalyze oxidative reactions [82]; d) to scavenge a variety of ROS [47, 83-86]; e) to inhibit enzymes that are involved in oxidative stress [48, 87].

Several *in vitro* antioxidant assays have been developed

Chlorogenic acids (CGAs) are esters of HCAs and quinic acid. The most common CGA is formed by esterification of caffeic acid to quinic acid (Fig. 2) [58]. Various isomers of CGAs in positions 3, (3-CQA), 4 (4-CQA) and 5 (5-CQA) of the quinic acid have been reported [58]. Caffeoylquinic acids

for assessment of antioxidant activity (Table 1). Readers are advised to read the relevant reviews to get more comprehensive view on the *in vitro* antioxidant methods [88-92].

RATIONAL DESIGN OF ANTIOXIDANTS; STRUCTURE-ACTIVITY RELATIONSHIPS OF HYDROXY-CINNAMIC ACIDS

For decades, natural products have provided an invaluable source of novel lead structures for drug discovery [93]. In recent times, there has been renewed interest in natural products research, mostly motivated by the lower prevalence of undesired side effects of these compounds [23, 44, 94].

Table 1. Most Commonly Used *In Vitro* Antioxidant Assays

No.	Method	Mechanism	Reference	Number of
1	Crocin bleaching assay (CBA)	Crocin bleaches upon oxidation by free radicals	[163]	83
2	Cupric reducing antioxidant capacity	Copper(II)-neocuproine [Cu(II)-Nc] reagent used as the chromogenic oxidizing agent.	[164]	101
3	Ferric Reducing Antioxidant Power	Complex of Fe ²⁺ -TPTZ (tris-pyridyl-triazine) is reduced and measured spectrophotometrically	[165]	2720
4	Oxygen radical absorbance	Peroxy radical is generated by AAPH and decrease in fluorescence of a fluorescent probe is measured	[166]	654
5	Oxygen radical absorbance capacity fluorescent	An improved method of ORAC assay using fluorescein (3',6'-dihydroxyspiro [isobenzofuran-1[3H],9'[9H]-xanthen]-3-one) as the	[167]	599
6	Trolox equivalent antioxidant capacity	Discoloration of the amount of ABTS ^{•+} radical that are scavenged within a fixed time period (6 min) in relation to that of 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox)	[168]	1350
7	Total radical trapping antioxidant	AAPH is used as generator of peroxy radicals, while oxygen uptake, fluorescence of R-phycoerythrin, or absorbance of ABTS ^{•+} are measured to monitor oxidation process	[169]	329
8	ABTS assay	ABTS ^{•+} radical cation has a characteristic color that is measured spectrophotometrically	[170]	3186
9	DPPH method	Spectrophotometric determination of stable free radical DPPH	[171] [172]	2946 2275
10	Hydroxyl radical scavenging	Hydroxyl radical is generated by using Fe ³⁺ /ascorbate/EDTA/H ₂ O ₂ system using Fenton reaction	[173]	574
11	Hydrogen peroxide scavenging	The decrease in of H ₂ O ₂ is measured spectrophotometrically	[174]	1901
12	Peroxynitrite radical	Monitoring the oxidation of dihydrorhodamine by peroxynitrite radical on a microplate fluorescence spectrophotometer	[175]	475
13	Singlet oxygen Scavenging	The decay rate of singlet oxygen phosphorescence at 1270 nm is measured	[176]	543*
14	Superoxide anion scavenging activity	Generation of superoxide anions enzymatically in a hypoxanthine-xanthine oxidase system coupled with nitroblue tetrazolium (NBT) reduction and measurement of the absorbance related to the reduction of nitro blue tetrazolium at 540 nm	[177]	3515
15	<i>β</i> -carotene linoleic acid bleaching assay	Products of linoleic acid oxidation bleach <i>β</i> -carotene in the emulsion	[178]	313
16	Low-density lipoprotein	A gradual increase in absorbance due to formation of conjugated dienes from oxidation of LDL is inhibited by antioxidants	[179]	366

¹ According to the Scopus databank Accessed October 2012. * Citations from Google Scholar.

AAPH: 2,2'-azobis(2-amidinopropane) dihydrochloride; ABTS^{•+}: 2,2'-azinobis-(3-ethylbenzthiazoline-6-sulfonic acid); DPPH: 1,1-Diphenyl-2-picrylhydrazyl.

As the design of antioxidant agents cannot rely on receptor-based drug design methods due to the lack of specific molecular targets efforts have been moved towards an analogue-based drug design approach. In fact, identification of molecular leads of natural origin and the optimization of their structure to enhance the activity against different targets is an important task of modern medicinal chemistry. The accomplishment of this task certainly relies on the establishment of structure-activity relationships (SARs), which is

a valuable tool for discovery of more effective molecules [95-97]. Much effort has been directed to the discovery of the ideal pharmacophore and the improvement of the activity in order to generate more potent antioxidants.

The main concept of SAR is that the biological activity of molecules could be attributed to their chemical structure and physico-chemical properties. Analysis of SAR enables the determination of the chemical functional groups respon-

sible for providing a certain effect and allows medicinal chemists to modify the potency of a bioactive compound by changing its chemical structure. SAR analysis focused on natural compounds is of significant importance due to their ever-growing role in human health [98]. Several interesting SAR studies on naturally occurring substances are found in the literature [35, 56, 99, 100]. Our particular interest, several SAR studies have been described that correlate structural characteristics of HCAs to their *in vitro* radical scavenging effects [101-103].

HCAs have two important structural features that make them an interesting scaffold: a) the presence of hydroxy functions on the benzene ring, which can produce a phenoxy radical intermediate that may terminate the free radical chain reaction [104]; b) the ethylenic side chain that contains unsaturated bond being able to stabilize the phenoxy radical or offer an additional site for reaction with ROS [104, 105] (Fig. 3).

The effect of the type of the spacer group between carboxyl moiety and the phenyl ring has been well established in terms of radical scavenging activity [52]. Our previous studies have uncovered the importance of this unsaturated side chain for the antioxidant activity [106], which could be ascribed to the participation of the double bond in stabilization of the phenoxy radicals via increased electron delocalization. However, its role is quite dependent of the type of HCAs, mainly of the substitution pattern of the aromatic moiety.

Studies performed on caffeic acid and its esterified and amidated derivatives demonstrated that the presence of H-donating substituents such as -NH or -SH could also be responsible for the enhancement of the antioxidant activity of HCAs as a result of their hydrogen donating ability [35, 107].

In this paper, we have reviewed *in vitro* studies that have been focused on structure-antioxidant activity relationships of HCAs. In addition, the effect of HCAs physicochemical properties on their antioxidant performance has been also summarized.

The structural features that were of significant importance in SARs of HCAs were divided to two subsections that include the modifications of the aromatic ring and the modifications of the carboxylic function.

MODIFICATIONS OF THE AROMATIC RING

Number of Hydroxy Groups

Antioxidant activity of HCAs seems to be largely influenced by the number of hydroxy groups present on the aromatic ring [83, 108]. This effect can be attributed to the fact that the phenoxy radical that is formed when HCA molecule is oxidized by ROS can be stabilized by the adjacent electron-donating hydroxy groups [56, 83, 109, 110].

Moreover; molecules bearing *ortho*-dihydroxy or 4-hydroxy-3-methoxyl groups possess higher antioxidant activity than those bearing no such functionalities [101].

Trihydroxy Versus Dihydroxy

Increasing the number of hydroxy groups of HCAs usually results in a higher *in vitro* antioxidant capacity in aqueous systems. Several investigations have shown a higher antioxidant activity for trihydroxy (possessing pyrogallol moiety) compared to dihydroxy (possessing catechol moiety) and monohydroxy phenolic acids [52, 81, 111].

We have also shown that 3-(3,4,5-trihydroxyphenyl) propenoic acid has better antioxidant profile than caffeic acid in ABTS and DPPH assays [52]. It should be noted that the order of efficiency may change in lipid peroxidation assays, and dihydroxylated acids may be more potent antioxidants than corresponding trihydroxylated compounds in these systems [52, 112]. Similar trend has been observed among flavonoids [113]. This is possible because the antioxidant activity in membranes also depends on the lipophilicity of the compound [83] and in a more lipophilic media such as the matrix in lipid peroxidation assays, a higher number of phenolic groups may compromise the overall lipophilicity and cause a decrease of the antioxidant capacity [52, 83]. Dihydroxylated cinnamic acids possess higher lipophilicity,

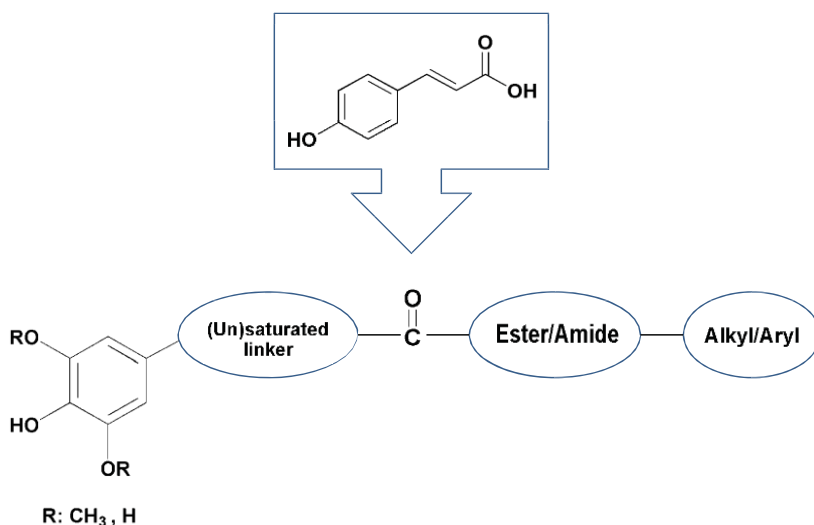


Fig. (3). Schematic representation of structural features of hydroxycinnamic acids that have been modified to improve their antioxidant activity.

measured by oil/water partition coefficient, compared to trihydroxylated cinnamic acids and this property could give them a better protective ability against lipid peroxidation [112]. However, it is important to point out that even in lipophilic systems, in a condition of relatively equal lipophilicities the determinant parameter could be the number of hydroxy groups [35].

Dihydroxy Versus Monohydroxy

Greater hypochlorite scavenging [47] and singlet oxygen quenching abilities [84] of caffeic acid (dihydroxy substituted) over *para*-coumaric acid (monohydroxy substituted) have been previously reported. Also in ferrylmyoglobin-dependent LDL peroxidation assay the activity of HCAs is highly dependent on the number of hydroxy groups: *ortho*-dihydroxy derivatives (caffeic and chlorogenic acids) could act as efficient LDL peroxidation blocking agents when compared to *para*-coumaric acid [114]. The same trend was also observed when HCAs amides were compared; caffeic amides showed superior antioxidant activity compared to the corresponding *para*-coumaric amides in DPPH and microsomal lipid peroxidation assays [115].

Position of Hydroxy Groups

The presence of a catecholic moiety seems to be of great importance to the antioxidant activity of HCAs [101, 103, 116-119]. In this regard, two critical factors have been proposed emphasizing the antiradical activity of HCAs containing catechol moiety bond dissociation energy of O-H bond and ionization potential [52]. The O-H bond dissociation energy is a function of presence of the electron-donating hydroxy group(s) at the *ortho* position [35]. This substitution pattern lowers the O-H bond energy and enhances the rate of H-atom abstraction from the molecule and hence generation of *ortho*-semiquinone radical anion or *ortho*-hydroxy phenoxyl radical (homodisproportionation). This species is more readily oxidized to a final *ortho*-quinone product.

Phenolic compounds bearing catechol behave as chain-breaking antioxidants. In a comparative study performed by Kancheva *et al.* [120], caffeic acid exhibited strongest antioxidant activity in various assays, such as lipid autooxidation and DPPH assay.

In crocin bleaching assay (CBA), the importance of the catechol moiety in providing high antioxidant capacity in HCAs has been demonstrated [100]. It was also emphasized that the positive impact of a catechol moiety could be attributed to the ease of H-atom abstraction from either 3- or 4- OH group leading to the formation of stable semiquinone radicals [100].

It has also been shown recently that radical scavenging ability against DPPH and ABTS radicals is lower for dimethoxycinnamic acid and (*E*)-2-(3-(3,4-dimethoxyphenyl)prop-2-enamido) ethyltriphenylphosphonium methanesulfonate compared to compounds possessing a catechol group [121].

Ortho-Phenolic HCAs Form Intramolecular Hydrogen Bonding

Another distinguished feature of *ortho*-hydroxy substituents is their ability to form intramolecular H-bonds [52, 122].

It was spectrophotometrically demonstrated that the intermediate phenoxyl radical arising from molecules with *ortho*-hydroxy groups would be efficiently stabilized owing to the intramolecular hydrogen bonding [49, 123].

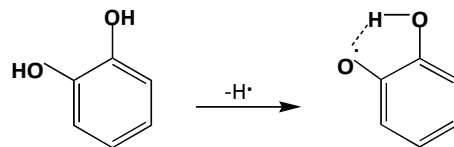


Fig. (4). Intramolecular hydrogen bond that is generated in a hydroxycinnamic acid molecule bearing catechol moiety after hydrogen abstraction.

Introduction of Electron Donating Substituents

Castelluccio *et al.* [111] reported that the antioxidant potency of *para*-coumaric acid against autooxidation of methyl linoleate is dramatically enhanced by insertion of a methoxy group in the *ortho* position to the hydroxy group (as in the structure of ferulic acid Fig. 1). The authors postulated that the enhancement of activity is related to the electron-donation properties of the methoxy moiety that can stabilize the phenoxyl radical formed in the reaction with free radicals. The superior activity of ferulic acid compared to *para*-coumaric acid has been observed also by other authors [47, 124, 125]. Addition of the second methoxy group (as in the structure of sinapic acid Fig. 1) further increases the activity, as deduced from the comparison of sinapic acid with ferulic acid in hypochlorite scavenging [47] and DPPH scavenging assays [125, 126]. Similarly, the results of our group and others have demonstrated that esters of sinapic acid are more active than esters of ferulic acid in β -carotene-linoleic acid system [127] and in DPPH assay [126]. In a study on the kinetics of lipid peroxidation in the presence of HCAs, sinapic acid ensured a longer oxidation stability of lipids when compared to ferulic and *para*-coumaric acid [128]. The higher stability of phenoxyl radicals being surrounded by two methoxy groups rather than one, have been also exploited via combined kinetic and EPR studies [129].

However, when caffeic acid (3,4-dihydroxycinnamic acid) is compared to ferulic acid (3-methoxy-4-hydroxycinnamic acid), the presence of a methoxy substituent usually decreases the activity [47, 130]. For instance, Wu *et al.* [83] have reported that ferulic acid and ethyl ferulate were less efficient than caffeic acid and caffeic acid phenethyl ester in scavenging DPPH and galvinoxyl radicals as the result of methoxylation of 3-hydroxy group and the absence of formation of quinone oxidation products.

Other investigators have reported that the performance of the isomers is quite different: 3-hydroxy-4-methoxy (isoferulic acid) is 3-4 folds less efficient than 3-methoxy-4-hydroxy (ferulic acid) in crocin bleaching assay [100].

Introduction of Electron Withdrawing Substituents

There is a paucity of data on the influence of electron withdrawing substituents on the antioxidant activity of HCAs. 3-Nitro-4-hydroxycinnamic acid has been found as a secondary metabolite of marine *Vibrio* strain from the Red Sea [131]. However, some preliminary studies have

shown that the presence of bromine electron withdrawing group at the *ortho* position to the hydroxy group of HCAs has no effect on the antioxidant activity [82].

Iwasaki *et al.* [132] synthesized a nitrated chlorogenic acid (CGA) and demonstrated that it had stronger antioxidant activity than non-nitrated CGA. The observed effects were attributed to the higher ability of nitrocatechol derivatives in sequestering chelated iron compared to catechol. These researchers postulated that nitrated phenolic compounds can bind to metal ion and prevent the generation of hydroxy radical. Del prete *et al.* [133] have demonstrated that 2-cyano-4-hydroxycinnamic acid inhibited glucose oxidation. More studies are required to investigate the effect of this type of substituents on the antioxidant activity.

MODIFICATIONS OF THE CARBOXYLIC FUNCTION

Esterification

Biological properties of HCA ester derivatives have gained much attention and several SAR studies have investigated the effect of esterification on the antioxidant activity of these compounds (Table 2). The effect of esterification on the antioxidant activity of HCAs seems to be dependent on the type of cinnamic acid as well as the ester [126]. It has been found that ester derivatives of caffeic acid possessed stronger biological activity as compared to caffeic acid, ferulic acid and even synthetic Trolox compound in AAPH-induced lipid peroxidation of Tween-emulsified linolenic acid [35]. Petrucci *et al.* [134] have suggested that the oxidation product of ethyl caffeate (*o*-quinone) is more stable than the oxidation products of unesterified HCAs (phenoxy radical). The more stable intermediates of esters may explain their higher antioxidant activity in many test systems. Table 2 summarizes some of the effects on the antioxidant activity of corresponding HCAs as the result of side chain esterification.

Esterification Increases the Lipophilicity

Several HCA esters have been synthesized as antioxidants (Table 2). Ester bond increases lipid solubility of a compound [55] and therefore, alkyl hydroxycinnamates have proven to be efficient ROS scavengers in lipophilic systems [126].

We have previously observed that esterification with short chain (methyl, ethyl, propyl and butyl) alkyls slightly lowered the antioxidant activity of sinapic acid in DPPH and FRAP assays but it had a positive effect on the partition coefficient that could extend the utility of this compound as an antioxidant in more lipophilic media [86]. Similar findings were reported about methyl to dodecyl esters of ferulic acid; the DPPH scavenging effect of the esters was decreased when compared to the parent compound, but their activity in more lipophilic media was considerably increased [125]. In a microsomal lipid peroxidation inhibition assay, ferulic acid was found to be more potent than ethyl ferulate in homogeneous phase; however, it was almost inactive in heterogeneous phase of microsomes [83]. It has also been proposed that esterified derivatives of cinnamic acids can be used as appropriate radical scavenging agents for bulk oil systems due to their increased lipophilicities [135].

Amidation

Synthesis of amide derivatives of HCAs have been a strategy followed by several groups due to the improved *in vivo* stability and solubility of these derivatives [35, 115, 136, 137]. Since esters of HCA may be hydrolyzed by some colonic bacteria [138], it has been suggested that amides may have the advantage of being more suitable for oral use [115].

Several studies can be described in which different types of HCAs amides were synthesized and the antioxidant activity evaluated:

a) Hung *et al.* [139] developed a series of substituted anilides of caffeic acid (Fig. 5). It was shown that all the compounds as well as caffeic acid itself, exhibit an antioxidant activity higher than standard antioxidants (Trolox and vitamin E) in DPPH and ABTS assays. Moreover, the phenethyl amide of caffeic acid displayed a higher antioxidant capacity compared to the analogous caffeic ester derivative, in DPPH assay [35].

An increment of the radical scavenging activity via increasing the number of hydroxyl groups in the phenethyl ring has also been observed [35], an effect that is related with the contribution of amide bond in stabilizing the intermediate radicals. A paradoxical behavior was recorded in an *in vitro* model using AAPH-induced lipid peroxidation of Tween-emulsified linolenic acid in which phenethyl ester of caffeic acid exerted a higher antioxidant activity than the corresponding amide derivative [35].

b) Efforts toward synthesis of new HCA amides bearing a thiazole containing amino acid led to the compounds exhibiting better *in vitro* antioxidant activity than the valine containing thiazole in a DPPH assay (Fig. 6) [140].

Effects of amidation in HCAs are summarized in (Table 3).

Oxidative decomposition of lipids is an adverse reaction leading to harmful health effects [141]. Lipid hydroperoxides (LOOH) may break down into free radicals, which are responsible for subsequent autoxidation reactions. In this regard, phenolic compounds and their derivatives are very efficient substances in avoiding autooxidation processes [128]. For instance, CGA was found to protect human erythrocytes from oxidative stress produced by low levels of lipid hydroperoxides in artificial liposomes [142]. Kortenska *et al.* [128] investigated the kinetics of lipid peroxidation in the presence of cinnamic acid derivatives. For this purpose, the triacylglycerols of sunflower oil were used as lipid samples in lipid oxidation model. This study revealed that the free carboxylic group (COOH) in the structure of HCAs may negatively affect the kinetics of lipid oxidation.

Effect of Physicochemical Properties on the Antioxidant Activity of Hydroxycinnamic Acids

There are several reports which emphasize on the role of physicochemical variables in radical scavenging activity of HCAs [35, 52, 82, 109, 143]. Some of the most important physicochemical parameters will be discussed here.

Table 2. Effect of Esterification of Hydroxycinnamic Acids, Carboxylic Function on the Antioxidant Activity

No	Reference	Compounds	Methods	Results
1	[55]	Methyl, ethyl, propyl and butyl esters of ferulic and caffeic acids	- FRAP assay - DPPH assay	Ferulate esters had lower antioxidant activity, while caffeate esters had higher activity compared to
2	[126]	Long chain (C14-C18) alkyl esters of <i>para</i> -coumaric acid, caffeic acid, ferulic acid and	- DPPH assay - ABTS assay	The esterification did not considerably alter the antioxidant activity.
3	[26]	Methyl, ethyl, propyl, butyl and hexyl esters of ferulic acid and caffeic acid	- Sunflower oil protection measured by Rancimat method	Esterification (<i>n</i> -alkylation) increased the protection factor of sunflower oil in the following order: Caffeic acids: butyl>hexyl>ethyl>propyl>methyl
4	[86]	Methyl, ethyl, propyl and butyl esters of sinapic acid	- FRAP assay - DPPH assay	Esterification decreased the activity.
5	[180]	Ferulic acid, Arbutin ferulate, dihydrocholesterol ferulate, 3 <i>P</i> - <i>O</i> -feruloyl-17 <i>P</i> -hydroxy-5 <i>α</i> - androstane	- DPPH assay - TEAC assay - LDL peroxidation assay	Arbutin ferulate had a higher activity against ABTS radical and inhibited LDL peroxidation more efficiently compared to ferulic acid. All derivatives of ferulic acid were better
6	[106]	Trihydroxycinnamic acid and two esters	- DPPH assay - ABTS assay - Lipid peroxidation assay in liposomes	<i>Trans</i> -ethyl-3-(3,4,5-trihydroxyphenyl)-2-propenoate and diethyl 2-(3,4,5-trihydroxyphenylmethylene) Malonate exhibited a higher radical scavenging
7	[181]	Glycoside esters of ferulic acid and sinapic acid	- DPPH assay - Inhibition of lipid peroxidation in soybean lecithin emulsion and	The antioxidant effect of sinapoyl and feruloyl glycosides depends on the nature of conjugation.
8	[83]	Caffeic acid, ferulic acid, CAPE, ethyl ferulate	- DPPH assay - Galvinoxyl radical scavenging - Inhibition of AAPH-induced erythrocyte hemolysis - Inhibition of hydroxyl radical induced	1) The direct scavenging effects toward DPPH radicals and galvinoxyl radicals were in the following order: CAPE > caffeic acid > ferulic acid > ethyl ferulate. 2) The order of lipoperoxidation inhibition in liver microsomes was in accordance with the observed priority in human erythrocytes: CAPE > ethyl
9	[182]	Methyl ferulate, ferulic acid, coniferyl aldehyde and isoferulic	- Carotene-linoleate model	Methyl ferulate possessed stronger antiradical activity than ferulic acid, coniferyl aldehyde and
10	[183]	CAPE, and 5 of its derivatives	- DPPH assay - AAPH-induced lipid peroxidation assay - Peroxynitrite radical scavenging assay	1) 3,4-dihydroxy-benzoic acid-(2-phenoxyethyl ester), and 5 [3,4-dihydroxy-cinnamic acid-(2-phenoxyethyl ester)] exhibited comparable antioxidant activity to CAPE in the DPPH assay. 2) CAPE showed lower antioxidant activity than 2,5-dihydroxy-benzoic acid-(2-phenoxyethyl ester)
11	[125]	19 Ferulate esters (C1-C12)	- DPPH assay - Linoleic acid hydroperoxide formation inhibition - AAPH-induced	1) Esterification of ferulic acid decreased DPPH scavenging activity but increased linoleic acid oxidation inhibition efficiency 2) Hexyl, octyl, and 2-ethyl-1-hexyl ferulates were the most active compounds in AAPH-induced
12	[35]	N- <i>trans</i> -Caffeoyl-L-cysteine methyl ester, CAPE, caffeic acid,	- AAPH-induced lipid peroxidation of Tween-emulsified	Synthetic ester analogues of caffeic acid possess stronger biological activity compared to caffeic acid, ferulic acid and synthetic Trolox C.

No	Reference	Compounds	Methods	Results
13	[184]	Caffeic acid, sinapic acid, ferulic acid and their ethyl esters	- Copper-induced low-density lipoprotein (LDL) oxidation	Ethyl esterification increased lipophilicity and antioxidant properties of caffeic, sinapic and
14	[185]	Propyl esters of caffeic acid, hydro- caffeic acid, ferulic acid, isoferulic acid and gallic acid	- Sunflower oil protection measured by Rancimat method - DPPH assay	A chain-breaking mechanism was proposed for propyl esters.
15	[109]	Caffeic acid, methyl caffeate, ethyl caffeate, propyl caffeate	- DPPH assay	Esters of caffeic acid exhibited similar potencies and were superior to caffeic acid.
16	[186]	Caffeic acid, caftaric acid, chloro- genic acid, neochlorogenic acid, ferulic, fertyric acid, <i>para</i> -coumaric	- Human LDL oxidation assay	1) Esterification to tartaric acid slightly increased the anti- oxidant activity of <i>para</i> -coumaric and ferulic acids 2) Esterification of caffeic acid to quinic acid (as in chloro- genic and neochlorogenic acid) had no

AAPH: 2,2'-azobis(2-amidinopropane) dihydrochloride; ABTS^{•+}: 2,2'-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid); CAPE: Caffeic acid phenethyl ester; DPPH: 1,1-Diphenyl-2-picrylhydrazyl; FRAP: Ferric Reducing Antioxidant Power; LDL: Low density lipoprotein.

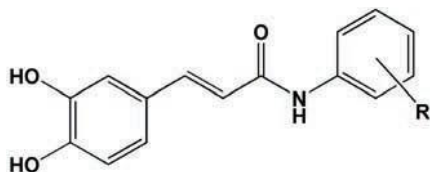


Fig. (5). General structures of caffeic acid anilides.

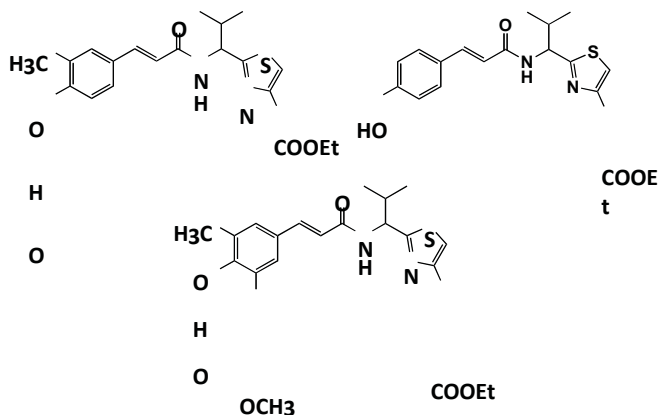


Fig. (6). Chemical structures of thiazole containing amino acid-based HCA amides.

Redox Potential

Electrochemical techniques provide powerful tools for the study of electron transfer in oxidation reactions and provide useful information about the reaction mechanisms as well as intermediates. The use of cyclic voltammetry as an instrumental tool for the evaluation of the total antioxidant capacity of the low-molecular-weight antioxidants in *in vitro* systems is also well known [144, 145].

For a variety of natural and synthetic compounds, good correlations exist between antioxidant activity and oxidation potentials [146]. HCAs exert their antioxidant effects via

activity of different molecules [146]. Studies performed by our group and others on synthesized and natural HCAs have demonstrated that redox potential is closely related with the *in vitro* antioxidant activity of HCAs [82, 135]. Differential pulse and cyclic voltammetry techniques have revealed that the structural characteristics of HCAs may influence the reduction-oxidation potential [121].

Our SAR studies on a set of synthesized HCAs including caffeic acid, ferulic and related compounds have shown that

derivatives with higher antioxidant efficacy (including caffeic acid and related compounds) have lower redox potential and those with lower antioxidant capacity (including ferulic acid and related derivatives) are associated with higher redox potentials [147]. We have also observed that methoxylation of ferulic acid leads to an increase in redox potential and a decrease in the antioxidant activity [82]. Other investigators

have similarly reported that the reduction potential of HCAs is inversely correlated with their quenching ability of singlet reduction (electron transfer) of ROS and knowledge on their inherent oxidation ability could be obtained by the study of their redox potentials [134]. Various reports have indicated that redox potentials can provide an index of antioxidant

molecular oxygen [84].

Lipid Solubility

The antioxidant capacity of compounds per se does not predict the ability to protect cells exposed to oxidative their stress [121, 148]. Lipophilic antioxidants can penetrate cell membranes and may prevent oxidative damage to cells through membrane-related partitioning effects that supplement their chemical activities [121]. Compounds possessing sufficient lipophilic character would also be able to cross the blood-brain barrier (BBB) and hence act as potential radical scavenging agents for protection against oxidative stress in the central nervous system [147]. On the other hand, inefficiency of dietary HCAs in relieving neuronal oxidative stress has been related mainly to their inability to pass through BBB [149]. Therefore, lipophilicity remains as one of the most important physicochemical variables in developing efficient radical scavenging agents.

Table 3. Effect of Amidation of Hydroxycinnamic Acids, Carboxylic Function on the Antioxidant Activity

No.	References	Compounds	Methods	Results
1	[137]	Three hydroxycinnamic acid derivatives conjugated with glycine-containing oxazole	- DPPH assay	Sinapic acid amide had the highest activity
2	[140]	p-Coumaroyl-2-valyl-thiazole-4-carboxylic acid ethyl ester, Feruloyl-2-valyl-thiazole-4-carboxylic acid ethyl ester, and Sinapoyl-2-valyl-thiazole-4-carboxylic acid ethyl ester	- DPPH assay	Amides were less active than the parental compounds.
3	[187]	p-Coumaroylputrescine, caffeoylputrescine and feruloylputrescine	- Singlet oxygen scavenging assay	Amides were more potent than parental compounds.
4	[188]	Sinapoyl and feruloyl C-protected amino acid amides	- Bulk phase lipid autoxidation assay	All feruloyl-amide showed higher antioxidant efficiency compared to ferulic acid. The highest activity was observed for (E)- N-(sinapoyl)-L-phenylalanine t-butyl ester and (E)- N-(feruloyl)-L-phenylalanine t-butyl
5	[139]	Caffeic acid anilides	- DPPH assay - ABTS assay	3-(3,4-Dihydroxy-phenyl)-N-(4-hydroxy-phenyl)-acrylamide was the most efficient agent in ABTS assay. N-(3-Bromo-phenyl)-3-(3,4-dihydroxy-phenyl)-acrylamide was
6	[35]	N-trans-Caffeoyldopamine, N-trans-caffeoyltyramine, N-trans-caffeoyl- α -phenethylamine, caffeic acid and ferulic acid	- AAPH-induced lipid peroxidation of Tween-emulsified	Amides of caffeic acid were stronger than caffeic acid and ferulic acid.
7	[115]	Caffeic acid amides containing aromatic and aliphatic amines	- DPPH assay - Microsomal lipid peroxidation assay	Lipid peroxidation inhibition of the caffeic acid amides containing aromatic amines was better than the amides with aliphatic amines. Caffeic acid anilides and caffeic acid
8	[189]	N-Aryl/alkyl caffeic acid amides	- Lipid peroxidation assay in liposomes	Caffeic anilides were strong inhibitors of lipid peroxidation.

AAPH: 2,2'-azobis(2-amidinopropane) dihydrochloride; ABTS^{•+}: 2,2'-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid); CAPE: Caffeic acid phenethyl ester; DPPH: 1,1-Diphenyl-2-picrylhydrazyl; FRAP: Ferric Reducing Antioxidant Power; LDL: Low density lipoprotein.

On the other hand, one main restriction to the formulation of HCAs into food or cosmetic products is their hydrophilic character, which makes it difficult to integrate them into fat or oil matrices [82].

A way of increasing the lipophilicity of HCA molecules is the preparation of ester and amide derivatives [126], which facilitates their penetration through membranes and may also make them more suitable to be formulated into topical and skin preparations.

Dissociation Constant

Dissociation constant of HCAs also plays an important role in the antioxidant profile in various *in vitro* and *in vivo* systems [147]. In fact, the acidity of the phenolic moiety in HCAs may be affected by the electron donating/withdrawal nature of different substituents [109].

We have used the potentiometric method to determine the dissociation constants of caffeic acid, dihydrocaffeic acid and their methyl, ethyl and propyl esters and have observed that pKa values (*para*-OH) were lower for caffeic acid derivatives [109].

Chelation Activity of Hydroxycinnamic Acids

Transition metals play a very important role in generation of oxygen free radicals within the body of living organisms leading to lipid peroxidation, protein modification and DNA damage [150]. Hence metal sequestering agents may potentially protect the harmful effects of metal ions. In this regard, one of the preventive antioxidative mechanisms for HCAs may be metal chelation, i.e. formation of complexes with the metal ions [141, 151].

Some studies dealt with the complexation of metal ions with caffeic acid in various media and have been reported in the literature [152]. Psotova *et al.* [153] studied the chelation

ability of ferulic, chlorogenic and caffeic acids with Cu(II), Fe(II) and Fe(III) ions using phosphate buffer–saline solutions mimicking reaction conditions used for cell culture experiments. Two types of complexes were detected with the stoichiometry of metal : ligand of = 1 : 1 and 1 : 2, while both complex types were stable. Caffeic acid did not form any complex with ferric ions, while *trans*-ferulic acid did not exhibit chelation activity at all.

In another report, chlorogenic acid was described to be efficient in forming a stable complex with Fe(II) ions. Chlorogenic acid and caffeic acid exhibited better chelation activity when compared to hydroxybenzoic acids [150]. The authors emphasized the importance of *ortho*-dihydroxy (catecholic) moiety in efficient binding to the metal ions. Compounds without catechol groups did not exhibit any complex formation. However, the place of chelation may be dependent on the metal ion, since Kalinowska *et al.* [154] synthesized manganese (II), copper (II) and cadmium (II) complexes of *para*-coumaric acid and characterized them with elemental and thermogravimetric analysis. The proposed binding site for these bidentate metal ions was the carboxylate moiety of *para*-coumaric acid.

Pro-oxidant Effects of Hydroxycinnamic acids

HCA may act as pro-oxidants under certain circumstances [155]. Some results supported the hypothesis that anticancer mechanism of plant polyphenols involved mobilization of endogenous copper and consequent pro-oxidant action [156, 157].

HCA have the ability to act as pro-oxidants in systems containing redox-active metals [158, 159]. Redox cycling of HCA can be catalyzed by transition metals in the presence of oxygen, producing organic radicals along with ROS that may damage biological macromolecules [160].

A study on different model systems containing fish lipids showed that the pro-oxidative effect of caffeic acid in food emulsions and liposomes is highly dependent on the pH, the applied emulsifier and type of prooxidants present [161]. The obtained results proved that caffeic acid can act as a prooxidant agent in the presence of Fe(II).

Maurya *et al.* [162] indicated that the antioxidant or pro-oxidant effect of ferulic acid and caffeic acid may depend on their concentration; these compounds show high antioxidant potential at lower concentrations, while exhibiting pro-oxidant behavior at higher concentrations. The pro-oxidant activity of ferulic acid and caffeic acid was attributed to their iron reducing properties [162].

CONCLUDING REMARKS

Much effort has been directed to the improvement of the activity of HCA in order to generate more potent antioxidants. There is an inherent difficulty in choosing an appropriate antioxidant assay method, because various methodologies provide different findings according to the applied target, probe and test conditions. In this regard, the use of a battery of *in vitro* assays that use dissimilar conditions may provide more reliable outcomes.

In general, the presence of the catechol moiety on the ring that has a role in stabilization of phenoxy radical as well as a double bond on the side chain that confers increased electron delocalization are the two most consistent structural properties that help improve the antioxidant profile in SAR studies. Certain esters such as caffeic acid phenethyl ester (CAPE) and chlorogenic acids (CGAs) have improved properties compared to parent compounds, however, in general, esterification or amidation have various effects on the activity of HCA, which depends on the type of HCA, applied assay and also the type of ester or amide. Lipophilicity is generally increased due to esterification and amidation, which increases the antioxidant capacity in lipophilic systems.

Finally, physicochemical properties of HCA should also be taken into consideration in order to generate more feasible antioxidants for biological systems. SAR studies are very useful in providing a series of highly potent antioxidants that could be useful for management of oxidative stress-related diseases.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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ABBREVIATIONS

AAPH	=	2,2'-azobis(2-amidinopropane) hydrochloride
ABTS	=	2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonic acid)
CAPE	=	Caffeic acid phenethyl ester
CBA	=	Crocin bleaching assay
CGAs	=	Chlorogenic acids
CQA	=	Caffeoylquinic acid
CUPRAC	=	Cupric reducing antioxidant capacity
LDL	=	Low density lipoprotein
DPPH	=	1,1-Diphenyl-2-picrylhydrazyl
FRAP	=	Ferric reducing antioxidant power
HCA	=	Hydroxycinnamic acid
ORAC	=	Oxygen radical absorbance capacity
ROS	=	Reactive oxygen species
RAE	=	Relative antioxidant efficiency
SAR	=	Structure-activity relationship
TAC	=	Total antioxidant capacity
TEAC	=	Trolox equivalent antioxidant capacity
TRAP	=	Total radical trapping antioxidant parameter

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