Antioxidant and Antimicrobial Activities of Cinnamic Acid Derivatives

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Abstract: Cinnamic acid is an organic acid occurring naturally in plants that has low toxicity and a broad spectrum of biological activities. In the search for novel pharmacologically active compounds, cinnamic acid derivatives are important and promising compounds with high potential for development into drugs. Many cinnamic acid derivatives, especially those with the phenolic hydroxyl group, are well-known antioxidants and are supposed to have several health benefits due to their strong free radical scavenging properties. It is also well known that cinnamic acid has antimicrobial activity. Cinnamic acid derivatives, both isolated from plant material and synthesized, have been reported to have antibacterial, antiviral and antifungal properties. Acids, esters, amides, hydrazides and related derivatives of cinnamic acid with such activities are here reviewed.

Keywords: Antifungal, antimicrobial, antioxidant, antiviral, cinnamate, cinnamic acid, cinnamic hydrazide, cinnamide.

1. INTRODUCTION

Two large, distinct classes of phenolic acids are known in plants – derivatives of benzoic acid and of cinnamic acid (**1**) [1]. The latter comprise a series of *trans*-phenyl-3-propenoic acids that differ in their ring substitution (Fig. (**1**)). The presence of a benzene ring and a short unsaturated hydrocarbon chain determines their low polarity and low water solubility. They are widely distributed in plants, and are present in fruits, vegetables and beverages (e.g. tea, coffee) at a wide range of concentrations (e.g. 20-675 mg/ml in a cup of coffee) [2-4]. Appropriate polarity and water solubility are achieved by their occurrence as derivatives, most commonly of hydroxycinnamic acid: *p*-coumaric (**2**), caffeic (**3**), ferulic (**4**) and sinapic acids (**5**) (Fig. (**1**)). However, these acids are rarely found in free form and are generally esterified with quinic or tartaric acids or carbohydrate derivatives [1].

In biological chemistry, cinnamic acid is a key intermediate in the shikimate and phenylpropanoid pathways, being a precursor of the flavonoids and the plant structural component lignin [4, 5]. Due to their common occurence in plants and their low toxicity [1-3, 6], cinnamic acid derivatives have been evaluated as pharmacologically active compounds. They show a remarkable variety of biological activities [7-9] and are often used as promising starting compounds for the development of new, highly effective drugs.

The aim of this review is to present the chemical structures (acids, esters, amides, hydrazides and related derivatives) of cinnamic acids with antioxidant and antimicrobial activities. Antibacterial, antiviral and antifungal properties of cinnamic acid derivatives are discussed.

*Address correspondence to this author at the Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, 1000 Ljubljana, Slovenia; Tel: +386-1-4769577; Fax: +386-1-4258031; E-mail: matej.sova@ffa.uni-lj.si

2. ANTIOXIDANT ACTIVITY

2.1. Natural Resources

Phenolic compounds are well known antioxidants due to their high redox potential. They can act as reducing agents, singlet oxygen quenchers, hydrogen donors and metal chelating agents [10, 11]. Some of the common phenolic compounds in plants are hydroxycinnamic acids, which possess high antioxidant activity and several other biological activities [7-14, 17-20]. There are many reports of the strong antioxidant properties of *p*-coumaric (**2**), caffeic (**3**), ferulic (**4**) and sinapic (**5**) acids and their derivatives (Table **1**) [11-24]. The importance of structural features on their potency and their *in vitro* and *in vivo* antioxidant activities is presented in detail in a review by Shahidi and Chandraseka [13]. Caffeic (**3**), ferulic (**4**) and sinapic (**5**) acids are very strong reducing agents, more than butylated hydroxytoluene (BHT) and comparable to Trolox [14]. Hydroxycinnamic acids **2** - **5** are more effective antioxidants than their benzoic counterparts [15, 16]. They have strong antioxidant properties due to a phenolic hydroxyl group that reacts with oxidants and free radicals to form the resonance-stabilized phenoxyl radical, and to the presence of a propenoic side chain, whose conjugated double bond could, by resonance, have a stabilizing effect on the phenoxyl radical (the radical scavenging mechanism is presented in Fig. (**2**)) [16-18]. The antioxidant efficacy of monophenols is strongly enhanced by the introduction of a second hydroxy group and methoxy substituents in the ortho position [15, 16, 19]. The stronger antioxidant activity of dihydroxycinnamic acids (e.g. caffeic acid) can be explained by the intramolecular hydrogen bonding that can occur in ortho substituted phenols (Fig. (**2**)) [17, 20]. The beneficial effects of caffeic acid (**3**) against oxidative stress have been reported. It significantly increases superoxide dismutase, catalase and glutathione peroxidase activities and lowers the hydrogen peroxide and thiobarbituric acid reactive substance levels in the erythrocyte and liver of *db*/*db* mice [21].

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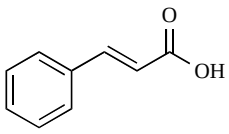
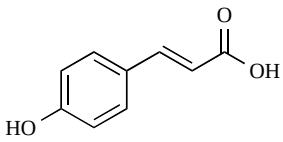
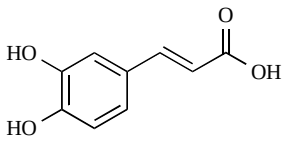


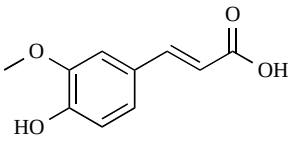
cinnamic acid (**1**)



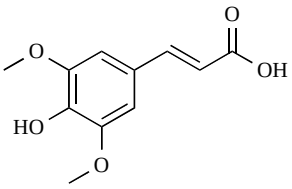
p-coumaric acid (**2**)



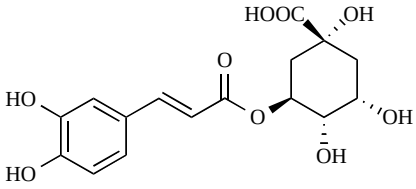
caffeic acid (**3**)



ferulic acid (**4**)



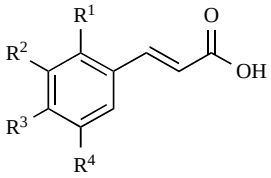
sinapic acid (**5**)



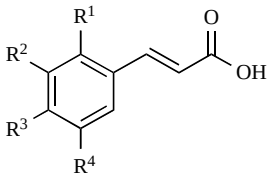
chlorogenic acid (3-caffeoylquinic acid) (**6**)

Fig. (1). Cinnamic acid and its most common derivatives in plants.

Table 1. Substituted Cinnamic Acids (CA) and their Biological Activities

CA					Biological activities and references (*- *in vivo* activity)
	R^1	**R^2**	**R^3**	**R^4**	
1	H	H	H	H	antioxidant [4, 16, 22, 25, 38, 41, 42*]; antibacterial [52-56, 58, 59]; antiviral [9, 85]; antifungal [103, 105-107, 111]
2	H	H	OH	H	antioxidant [9, 11, 12, 13*, 14-16, 19, 20, 22-25, 38, 40, 41, 50]; antibacterial [7, 57]; antifungal [57, 107, 111]
3	H	OH	OH	H	antioxidant [9, 11, 12, 13*, 14-16, 20, 21*, 22-25, 32, 41, 44, 45, 50]; antibacterial [7, 57-60, 67]; antiviral [91]; antifungal [7, 57, 107, 111]
4	H	OCH_3	OH	H	antioxidant [9, 11, 12, 13*, 14-16, 19, 20, 22-25, 40, 41, 44, 45, 50]; antibacterial [7, 57-59]; antifungal [57, 107, 111]
5	H	OCH_3	OH	OCH_3	antioxidant [4, 9, 11, 12, 13*, 14-16, 19, 20, 24, 25, 40, 44]; antibacterial [57]; antifungal [57]
19-23 (Fig. (4))	H	H; OH; $CH_2CH=C(CH_3)_2$; $CO(CH_2)_2Ph$ or $CH_2CH=C(CH_3)CH_2OH$			antioxidant [24, 39, 40]; antibacterial and antifungal [71]
26	OH	H	H	H	antioxidant [14, 22, 23]; antibacterial [58, 59]; antifungal [105]
27	H	OH	H	H	antioxidant [22, 23]; antibacterial [58, 59]; antifungal [105, 106, 111]
28	OCH_2COOH	H	H	H	antioxidant [41]
29	H	3,4-[-OCH_2O-]		H	antioxidant [41]
30	H	COOH	OH	H	antioxidant [41]
31	H	COOH	OCH_2COOH	H	antioxidant [41]
32	H	NH_2	H	H	antioxidant [41]
33	H	H	$N(CH_3)_2$	H	antioxidant [41]

(Table 1). Contd…..

CA					**Biological activities and references** (*- *in vivo* **activity**)
	R^1	**R^2**	**R^3**	**R^4**	
34	H	OCH_3	OCH_3	H	antioxidant [41]; antifungal [111]
35	H	H	CHO	H	antioxidant [41]
36	OH	Br	H	Br	antioxidant [41]
37	H	$C(CH_3)_3$	OH	$C(CH_3)_3$	antioxidant [41]
38	OCH_3	H	H	H	antioxidant [41]
39	H	OCH_3	H	H	antioxidant [41]
40	H	H	OCH_3	H	antioxidant [41]; antibacterial and antifungal [52]
41	H	OCH_2COOH	OCH_2COOH	H	antioxidant [41]
42	H	OH	OCH_3	H	antioxidant [41]
145	H	NO_2	H	H	antibacterial and antifungal [52]
146	H	H	NO_2	H	antibacterial [66]
147	H	H	Cl	H	antibacterial [66]
148	H	H	NH_2	H	antibacterial [66]
149	H	OH	OH	OH	antibacterial [66]
327	H	OH	OH	NO_2	antiviral [98]
331	H	H	SO_3H	H	antiviral [100]
348	CH_3	H	H	H	antifungal [103]
349	H	CH_3	H	H	antifungal [103]
350	H	H	CH_3	H	antifungal [103]
359	H	γ,γ-dimethylallyl	OCH_3	H	antifungal [111]
360	H	γ,γ-dimethylallyl	OAc	H	antifungal [111]

Antioxidant properties of cinnamic acid derivatives have often been determined by their inhibition of lipid oxidation or their scavenging effects on free radicals such as superoxide anion [14, 16-18, 20-25]. Caffeic (**3**), ferulic (**4**) and chlorogenic acid (**6**) exhibit strong superoxide anion (SOA) scavenging effects, while *o*- (**14**), *m*- (**15**) and *p*-coumaric (**2**) acids are only weak SOA scavengers [22, 23]. Furthermore, cinnamic acid (**1**) had no activity, showing that the presence of a phenolic hydroxyl group in the benzene ring is essential for high SOA-scavenging activity. The higher radical scavenging ability of caffeic acid (**3**), in comparison to *p*-coumaric acid (**2**), can be explained by the arrangement of substituents in the molecule to favour reaction with radicals [13]. Similarly, a decrease in radical scavenging reaction is observed when the 3-hydroxy group in caffeic acid (**3**) is replaced by a 3-methoxy group, as in ferulic acid (**4**). On the other hand, sinapic (**5**) and ferulic acids (**4**) are more effective than *p*-coumaric acid (**2**) due to the electron-donating methoxy group(s) which stabilize the phenoxyl radical after hydrogen donation of the hydroxyl group [13, 18, 19].

Several natural hydroxycinnamic acid esters (**6**-**14**, Table **2**) also exhibit promising antioxidant properties [12-15, 25-31]. Chlorogenic acids (esters of cinnamic acids with quinic acid, for example compound **6** in Fig. (**1**)) are well-known antioxidants and are reported to have several health benefits (alleviation of cardiovascular disease, diabetes type 2, Alzheimer's disease) due to their antioxidant and anti-inflammatory properties [25-27]. All three chlorogenic acids, **6**-**8**, exhibit both superoxide scavenging activities and inhibitory effects on xanthine oxidase [27]. Cinnamates **10**-**14**, identified and isolated from Riesling wine, contribute to the total antioxidative activity of white wine [15].

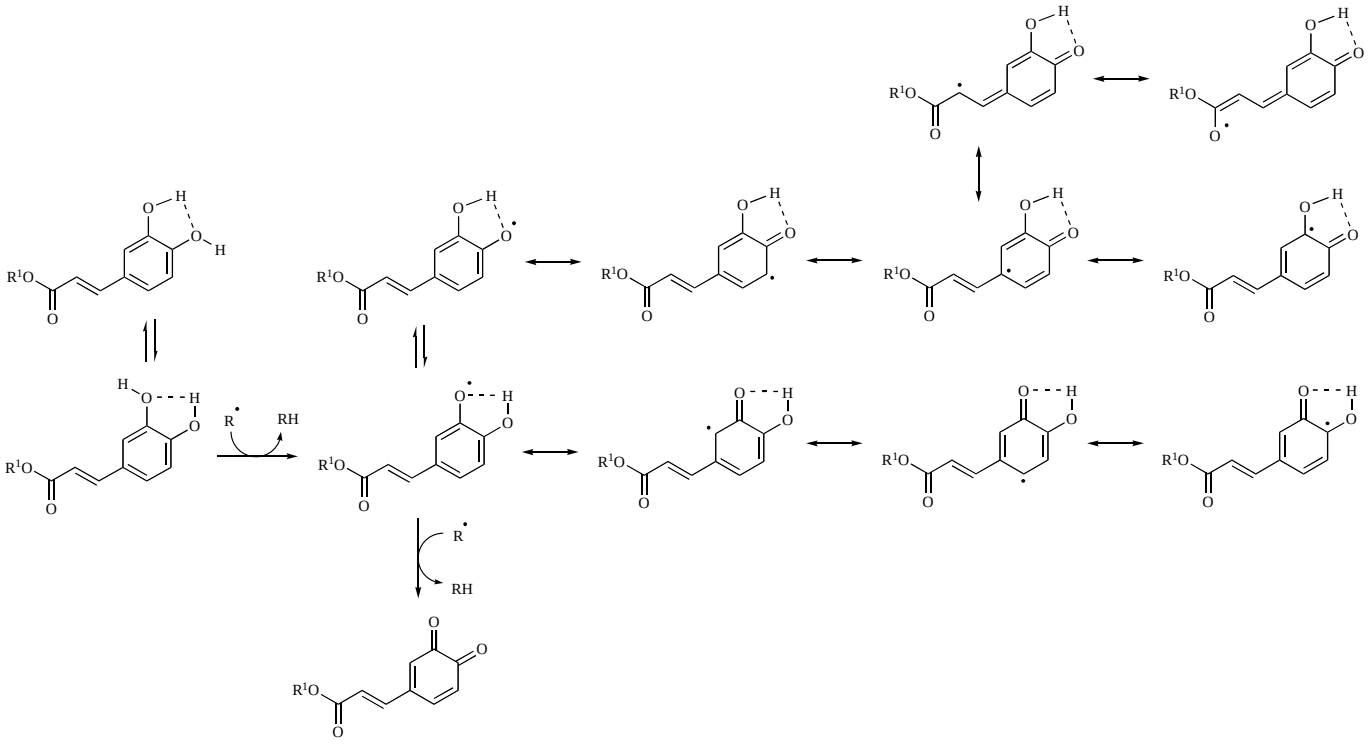
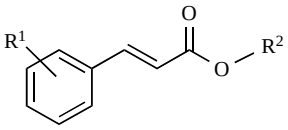
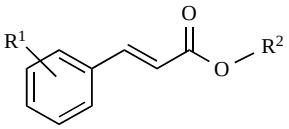


Fig. (2). Radical scavenging mechanism of hydroxylated cinnamic acid derivates including resonance stabilization of a phenoxyl radical by intramolecular hydrogen bonding ($R^{\bullet}$=$HO^{\bullet}$, $LOO^{\bullet}$; R^1=H, alkyl, aryl) [17, 18].

Table 2. Cinnamates with Antioxidant, Antibacterial, Antiviral and Antifungal Activities

Cmpd			Biological activity and reference (*-*in vivo* activity)
	R^1	R^2	
6	3,4-diOH	quinic acid (3-O)	antioxidant [11, 13*, 22, 23, 25-27, 50]; antifungal [108]
7	3,4-diOH	4-methylquinic acid (5-O)	antioxidant [27]
8	3,4-diOH	1-methylquinic acid (3-O)	antioxidant [27]
9	3,4-diOH	3-methyl-2-butenol	antioxidant [25]
10	4-OH	tartaric acid	antioxidant [15]
11	3,4-diOH	tartaric acid	antioxidant [15]
12	3-OCH_3-4-OH	tartaric acid	antioxidant [15]
13	3,4-diOH	ethyl	antioxidant [15]; antiviral [95]
14	3-OCH_3-4-OH	4-O-β-D-glucosyl	antioxidant [15]
15	3,4-diOH	3-(3,4-dihydroxyphenyl)-2-carboxypropyl	antioxidant [13, 31]
43	4-OH	CH_3	antioxidant [12, 14]; antifungal [111, 114]
44	3,4-diOH	CH_3	antioxidant [12]; antiviral [95]; antifungal [111]
45	3-OCH_3-4-OH	CH_3	antioxidant [12, 14]; antifungal [111]

(Table 2). Contd…..

Cmpd			Biological activity and reference (*-*in vivo* activity)
	R[1]	**R[2]**	
46	4-OH	allyl	antioxidant [42*]
47	4-OH	1-naphthylmethyl	antioxidant [42*]
48	3,4-diOH	CH_2CH_2Ph	antioxidant [13, 29]; antiviral [91, 93, 95]
49	3-OCH_3-4-OH	CH_2CH_2Ph	antioxidant [29]; antiviral [93]; antifungal [114]
50	3,4-diOH	3,4-dihydroxyphenethyl	antioxidant [18]
51	3,4-diOH	2-phenoxyethyl	antioxidant [30]
52	3,5-diOCH_3-4-OH	2-hydroxyethyl	antioxidant [43]
53-57	3,4,5-triOCH_3	3-methoxyphenyl; 3-hydrohyl; *m*-tolyl; 2-hydroxyethyl; 2-acetylethyl	antioxidant [43]
58	4-OH	tetradecyl	antioxidant [44]
59-61	3,4-diOH	tetradecyl; hexadecyl; octadecyl	antioxidant [44]
62-64	3-OCH_3-4-OH	tetradecyl; hexadecyl; octadecyl	antioxidant [44]
65-66	3,5-diOCH_3-4-OH	tetradecyl; octadecyl	antioxidant [44]
67	3,4-diOH	hexyl	antioxidant [45]
68	3-OCH_3-4-OH	hexyl	antioxidant [45]
117	H	Et	antibacterial [52, 66]; antifungal [114]
118	H	CH_3	antibacterial [52]; antifungal [104, 111, 114]
119-127	H	*n*-Pr; *i*-Pr; *n*-Bu; *i*-Bu; octyl; $CH_2CH_2(CH_3)_2$; Bn; 8-hydroxy-quinolonyl; Ph	antibacterial [52]; antifungal [114]
256-260	H; 3-OH-4-OCH_3; 3-OCH_3-4-OH; 3,4-diOCH_3; 2,4-diOCH_3	3-phenylprop-2-en-1-yl	antibacterial [80]; antifungal [80]
261-265	H; 3-OH-4-OCH_3; 3-OCH_3-4-OH; 3,4-diOCH_3; 3,4-O-CH_2-O	4-allyl-2,6-dimethoxyphenyl	antibacterial [80]; antifungal [80]
299-300	3,4-diOH	CH_2Ph; $CH_2CH_2CH(CH_3)_2$	antiviral [93, 95]
301-302	3-OCH_3-4-OH	CH_2Ph; $CH_2CH_2CH(CH_3)_2$	antiviral [93]
305-312	3-OH-4-OCH_3; 3,4-diOCH_3; 3,4-diF; 2,5-diOH; 3,4-diOH; 2,3,4-triOH; 3,4,5-triOH; 3,4,6-triOH	phenethyl	antiviral [95]
313-314	3,4-diOH	2-(1-naftyl)-ethyl; 2-(2-naftyl)-ethyl	antiviral [95]
315-317	3,4-diOH; 3-OCH_3-4-OH; 3,4-diOCH_3	CH_2COOH	antiviral [96]
318	3,4-diOH	$CH(CH_3)COOH$	antiviral [96]
325	3,4-diOH	bornyl	antiviral [98]
326	2-NO_2; 3,4-diOH	bornyl	antiviral [98]
328	3,4-diOH, 5-NO_2	phenethyl	antiviral [98]
361-365	4-OCH_3; 3,4-diOCH_3; 3-OH; 3-(γ,γ-dimethylallyl)-4-OCH_3; 3-(γ,γ-dimethylallyl)-4-OH	CH_3	antifungal [111]
366-369	4-Cl; 4-*i*-Pr; 2,4-diCl	CH_3	antifungal [112, 113]
373-374	4-OH	*i*-Pr;Bu	antifungal [114]

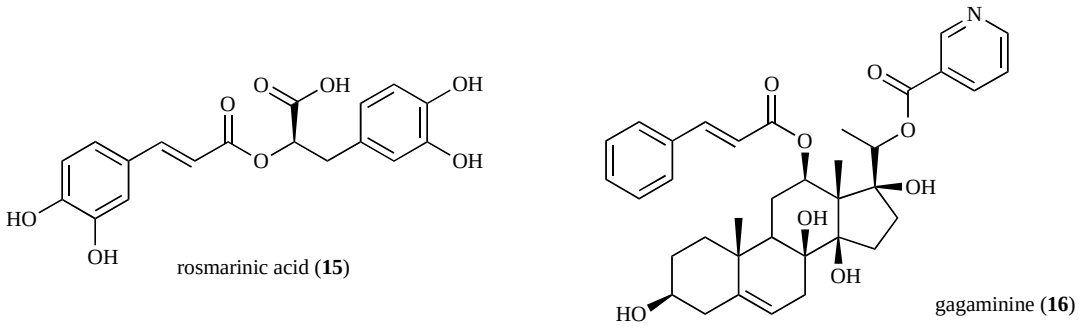


Fig. (3). Structures of rosmarinic acid (**15**) and the potent natural antioxidant gagaminine (**16**).

Rosmarinic acid (**15**, Fig. (**3**)) is a naturally occuring caffeic acid ester and a well-known antioxidant with several beneficial and health promoting effects [13, 31]. It contains four hydroxyl groups which are responsible for its high antioxidative activity [13, 20, 29]. It was reported to inhibit superoxide anion [32] and could be used as an antioxidant supplement in food [33]. It was shown that the scavenging activity of rosmarinic acid is significantly greater than that of ascorbic acid. The structure−activity relationships of caffeic acid derivatives indicated that the presence of an ortho dihydroxyphenyl group is essential for the scavenging effect, which is enhanced by the conjugated double bond [34]. Moreover, rosmarinic acid significantly inhibits both intracellular superoxide and peroxide formation in differentiated HL-60 cells, suggesting that it could be an effective antioxidant in biological systems through the scavenging of superoxide [34].

A potent natural antioxidant, gagaminine (**16**, Fig. (**3**)), a steroid alkaloid isolated from the roots of *Cynanchum wilfordi*, has a cinnamoyl group in its structure, which proved to be critical for the inhibition of hepatic aldehyde oxidase activity, an enzyme that generates highly reactive oxygen species [35].

The Welsh onion has strong antioxidative and antihypertensive activities *in vitro* and *in vivo*. Seo and co-workers isolated four compounds, including two cinnamic amides **17** and **18** (Table **3**), that showed high DPPH radical scavenging activities and therefore may contribute to the antioxidative properties of the Welsh onion [36].

Recently, profile of cinnamic acid derivatives was described in algae and cyanobacteria. They are new sources (together with some fungi) for finding of new cinnamic acid derivatives in future [37, 38]. Furthermore, it was shown that cinnamic acid derivatives present in PLE and PLE-SPE (pressure-liquid with solid-phase extraction) of algal extracts comprise an important proportion of the antioxidant compounds in these extracts [38].

2.2. Prenylated Cinnamic Acids

Ethanolic extracts of Brasilian propolis contain prenylated cinnamic acid derivatives **19**-**23** [8, 24, 39, 40]. In a study of inhibitory activity against peroxidation of linoleic acid in a micelle solution, 3,4-dihydroxy-5-prenylcinnamic acid (**19**) (Fig. (**4**)) showed the highest antioxidant activity of the cinnamic acid derivatives isolated from Brasilian propolis [39]. Comparison of the effects of seven methoxy and prenyl derivatives of cinnamic acid (**19**-**25**, Fig. (**4**)) on the kinetics of lipid bulk phase oxidation showed that sinapic acid (**5**) has the highest antioxidant activity, followed by prenyl cinnamic acid derivatives **20** and **21.** Both are stronger antioxidants than *p*-coumaric (**2**) and ferulic (**4**) acids, due to the greater electron density of the OH-moiety induced by the inductive effect of the prenyl fragment. Compounds **24** and **25** have no antioxidant activity because of transformation of the phenol group due to cyclization [40]. A comparative analysis of radical scavenging (H-donating) and chain-breaking (antioxidant) activity of 15 selected hydroxycinnamic derivatives, including compounds **20** and **21**, was also performed. Three different models were applied to explain the structure-activity relationships of phenolic antioxidants [24].

2.3. Semi-Synthetic and Synthetic Cinnamic Acid Derivatives

Avanesyan and coworkers [41] described the antiradical activity of several cinnamic acid derivatives (**26**-**42**, Table **1**) with different substitutions in the aromatic ring. They found that the nature and position of substituents in the aromatic ring only increase or decrease the activity, the cinnamoyl fragment being the determining factor in antiradical activity.

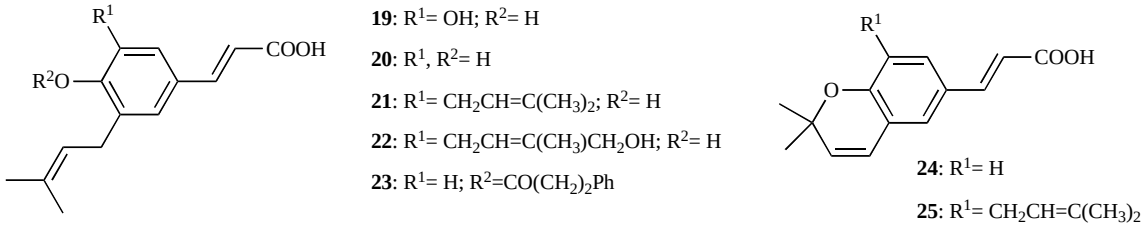
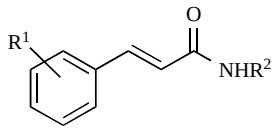


Fig. (4). Prenyl derivatives of cinnamic acid as antioxidants.

Table 3. Antioxidant and Antimicrobial Activities of Cinnamamides, Cinnamic Hydrazides and other Cinnamic Acid Derivatives (CAD)

CAD			Biological activity and reference
	R^1	**R^2**	
17	3-OCH_3-4-OH	2-(3-methoxy-4-hydroxyphenyl)-ethyl	antioxidant [36]
18	4-OH	2-(4-hydroxyphenyl)-ethyl	antioxidant [36]
69	3,4-diOH	hexyl	antioxidant [45]
70	3-OCH_3-4-OH	hexyl	antioxidant [45]
71-91	3,4-diOH	H; NH_3; 3-methylbut-2-enyl; OH; OMe; OEt; *i*-Pr; *i*-Bu; isopentyl; allyl; Ph; 2-OH-Ph; 3-OH-Ph; 4-OH-Ph; Bn; phenethyl; pyrollidinyl; piperidinyl; morpholinyl; $(CH_3)_2$; dopaminyl	antioxidant [25]
92	4-OH	*N*-(2-(4-hydroxyphenyl)ethyl)-*N*-methyl	antioxidant [46]
93	3,4-diOH	2-(4-hydroxyphenyl)-ethyl	antioxidant [46]
94	4-OH	2-(3,4-dihydroxyphenyl)-ethyl	antioxidant [46]
95	3,4-diOH	2-(3,4-dihydroxyphenyl)-ethyl	antioxidant [46]
96-100	3-OCH_3-4-OH	RNH_2: L-Val-OMe; L-Leu-OMe; L-Phe-*t*-Bu; L-Tyr-OMe; L-Phe (4-F-Ph)-Me	antioxidant [47]
101-103	3,5-diOCH_3-4-OH	RNH_2: L-Tyr-OMe; L-Phe (4-F-Ph)-Me; L-Phe-*t*-Bu	antioxidant [47]
128-144	H	NH_2; Ph; 2-NO_2-Ph; 2,4-diNO_2-Ph; 2-Cl-Ph; 3-Cl-Ph; 4-Cl-Ph; 4-OMe-Ph; 2-CH_3-Ph; $N(CH_3)_2$; $N(Et)_2$; $N(C_2H_4OH)_2$; morpholinyl; piperidinyl; *i*-PrNH; *n*-Bu; $NHNH_2$	antibacterial and antifungal [52]
159-168	H; NO_2; OCH_3; OCH_2O; Cl	NHCOPh or NHCOPy (see Fig. (8))	antimycobacterial [72]
201-203	H; 4-OCH_3; 4-O-isopentenyl or geranyl (Fig. (9))	2-(*N*-acetylamino)-ethyl	antibacterial [75]
213-216	4-O-isopentenyl; 4-O-geranyl; 4-OCH_3; 3,4-diOCH_3	NH-(pyridine-2-yl)	antibacterial [75]
217-220	4-O-isopentenyl; 4-O-geranyl; 4-OCH_3; 3,4-diOCH_3	$NH(CH_2)_2$-(indole-3-yl)	antibacterial [75]
241-247	H; 4-OCH_3; 3,4-(O-CH_2-O); 3,4-diOCH_3; 3,5-diOCH_3; 3,4,5-triOCH_3; 2-NO_2	$(CH_3)_2$	antibacterial [77]
319-324	3,4-diOH	RNH_2: Gly; Ala; Val; Phe; Tyr; 3',4'-diOH-Phe	antiviral [96]
370	4-Cl	*i*-Pr	antifungal [112]
371-372	4-*i*-Pr	RNH_2: Gly; Val	antifungal [113]

The compounds substituted with one or two hydroxyl groups showed the highest antiradical activity in the chemiluminescence test.

Several hydroxycinnamic acid esters (**43-66**, Table **2**) also exhibit promising antioxidant properties [12-15, 25, 42-44]. Methylated derivatives, compounds **43** and **44,** of coumaric acid (**2**) and caffeic acid (**3**)) are weaker reducing agents and antioxidants than the free forms, with the exception of methyl ferulate (**45**) that possesses only slightly lower antioxidant activity than ferulic acid. Surprisingly, in some measuring systems the ester **36** was an even more effective antioxidant than the free acid [14]. Allyl (**46**) and 1-naphthylmethyl 3-(4-hydroxyl)propanoic acid (**47**) esters exerted lipid-lowering action and antioxidant properties without hepatotoxicity in high-cholesterol fed rats [42]. The antioxidant activities of these cinnamic acid synthetic

derivatives, **46** and **47,** were similar to that of cinnamic acid (**1**). Phenethyl esters **48**-**50** also showed promising antioxidant properties [13, 28, 29]. The activity of 3,4-dihydroxy-cinnamic acid-(2-phenoxyethyl ester) (**51**) was comparable to that of caffeic phenethyl ester (CAPE, **48**) [30]. Several synthetic cinnamates **52**-**57** exhibited potent antioxidant activity in two free radical scavenging models [43]. Due to their antioxidant properties, lipophilicity and capacity to absorb UVB radiation, long chain alkyl hydroxycinnamates **58**-**65** could be used in cosmetics, sunscreens and in topical formulations to treat erythema and other skin diseases [44]. Cinnamic acid esters are more hydrophobic than free acids and generally it was observed that the hydrophilic antioxidants (acids) showed greater antioxidative potency than hydrophobic ones (esters) in bulk oil, while hydrophobic antioxidants showed greater activites than hydrophilic in emulsion [29]. However, caffeic and ferulic acid had stronger antioxidant activitiy in oil-in-water emulsion than their corresponding phenetyl esters [29].

Hexyl esters and amides of caffeic and ferulic acid (**67**-**70**, Tables **2**, **3**) exhibit antioxidant properties that can be related to their lipophilicity and redox behaviour. Due to their appropriate lipophilicity for crossing the blood-brain barrier, some compounds are potential candidates for preventing or reducing the oxidative stress associated with neurodegenerative diseases [45].

In view of the hydrolysis of the ester bond in the gastrointestinal tract, Cos and coworkers synthesized caffeic acid amides (**71**-**91**, Table **3**) and evaluated their free radical scavenging properties, lipid peroxidation inhibiting activity and cytotoxicity [25]. They showed that caffeic acid anilides and caffeic acid dopamine amides still possess high antioxidant activity and low cytotoxicity, which makes them interesting compounds for further investigation of *in vivo* antioxidant properties [25]. Due to their radical scavenging activities, cinnamic acid amides **92**-**95** could be activity active in free radical mediated diseases [46].

The kinetic analysis of the inhibited lipid autoxidation in the presence of hydroxycinnamoyl amides (**96**-**103**, Table **3**) were analysed by Spasova *et al.* [47]. *N*-(feruoyl)- and *N*-(sinapoyl)-L-phenylalanine *t*-butyl ester (**100** and **103**) were the most effective in terminating the oxidation chain and decreasing the oxidation rate during the induction period.

Cinnamoyl ketoamides **104**-**111** (Fig. (**5**)) were synthesized as hybrid structures of antioxidants and calpain inhibitors. Compound **110,** the most potent inhibitor of calpain and with strong antioxidant activities, can be used in neurological disorders (stroke, Alzheimer's disease) to decrease cellular damage [48].

Since the alkaloid glaucine possesses promising photopretective and antioxidant activity, cinnamoyl amides of glaucine (**112**-**116,** (Fig. (**6**)) were synthesized [49]. They showed higher radical scavenging activity than glaucine and 3-aminomethylglaucine which indicates that attachment of the cinnamoyl group increases the antioxidant activity of glaucine. However, the antioxidative effect is still lower than that of free hydroxycinnamic acid [49].

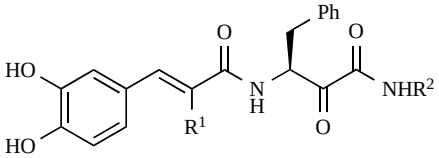
2.4. *In Vitro* Versus *In Vivo* Antoxidant Activity of Cinnamic Acid Derivatives

Several *in vitro* studies have been reported for evaluating the antioxidant activity of cinnamic acid derivatives [11, 13, 50]. *In vivo* information is, however, insufficient. There are a few reports about *in vivo* antioxidant activity for hydroxycinnamic acids, especially for ferulic and caffeic acid derivatives [13]. However, more *in vivo* studies are needed in order to understand the biological role of cinnamic acid derivatives. The *in vitro* antioxidant activity of food phenolics (such as hydroxycinnamates) usually differs from its *in vivo* antioxidant effect. The effect of these antioxidants on the redox balance *in vivo* cannot be simply extrapolated from their activities *in vitro*. The main problems of *in vitro* studies are usually the use of non-physiological conditions (e.g. concentrations of substances) and, furthermore, they do not take into account facts, such as metabolic transformations and interactions, that clearly influence the bioavailability of polyphenols and their activity [50]. Hollman *et al.* [51] showed that direct antioxidant effect of polyphenols *in vivo* is questionable, due to their low concentrations in blood compared with other antioxidants and, additionally, to the fact that their antioxidant activity is lowered by extensive metabolism following ingestion. Thus, the biological relevance of direct antioxidant effects of polyphenols for cardiovascular health has not been established [51].

3. ANTIBACTERIAL ACTIVITY

3.1. Natural Resources

It is well known that cinnamic acid exhibits antimicrobial activity against pathogenic and spoilage bacteria [6, 52-54], but its low water solubility limits its use. Cinnamic (**1**),



104: R^1=H; R^2=Bn

105: R^1=Et; R^2=Bn

106: R^1=Et; R^2=4-methoxyphenethyl

107: R^1=Pr; R^2=Bn

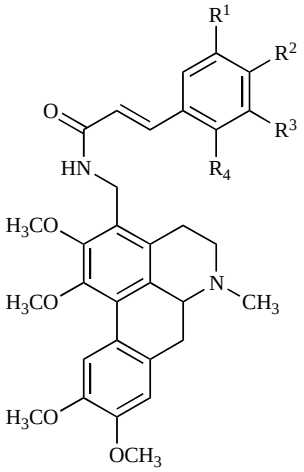
108: R^1=Pr; R^2=4-methoxyphenethyl

109: R^1=Bu; R^2=Bn

110: R^1=Bu; R^2=4-methoxyphenethyl

111: R^1=*i*-Bu; R^2=Bn

Fig. (5). Cinnamoyl ketoamides **104**-**111** as hybrid structures of antioxidants and calpain inhibitors.



112: $R^1=R^2=R^3=R^4=H$

113: $R^1=OCH_3$; $R^2=OH$; $R^3=R^4=H$

114: $R^1=OCH_3$; $R^2=OH$; $R^3=OCH_3$; $R^4=H$

115: $R^1=R^2=R^3=H$; $R^4=OH$

116: $R^1=R^3=R^4=H$; $R^2=OH$

Fig. (6). Cinnamoyl amides of glaucine **112-116** with antioxidative and antiviral activities.

coumaric (**2**), ferulic (**4**) and sinapic (**5**) acids inhibit Gram-positive [55-57] and Gram-negative bacteria *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas syringae* [57]. In contrast to antioxidant activity, ferulic acid (**4**) exhibits the highest antibacterial activity, which shows that the presence of another hydroxyl group is not so important for antibacterial activity as for antioxidant activity [57]. These hydroxycinnamic acids (**2**, **4**, **5**) also showed some weak antifungal activity [57]. Several *Capsicum annuum* L. extracts, which usually contain cinnamic acid derivatives (*trans*-cinnamic acid (**1**), *o*- and *m*-coumaric acid (**14**, **15**), ferulic acid (**4**) and caffeic acid (**3**)), are capable of inhibiting and inactivating certain pathogenic and spoilage bacteria [58, 59]. It was also reported that caffeic acid (**3**) is active against *C. botulinum* spores [60] and has the strongest bactericidal action against *L. monocytogenes* [59]. Comparison of antibacterial activities of cinnamic acid and its derived compounds showed that activity is enhanced by the presence of an αβ double bond and that effectiveness decreases in the order aldehyde>alcohol>acid [6].

Rosmarinic acid (**15**) is also known for its antibacterial activity [31] and shows marked antibacterial activity against *Escherichia coli*, *Bacillus subtilis* and *Micrococcus luteus* [61]. Antibacterial activity was reported for rosemary and other plant extracts and oils containing rosmarinic acid [62-64]. A methanolic extract, containing 30 % carnosic acid, 16 % carnosol and 5 % rosmarinic acid exhibited promising antibacterial activity against Gram negative (MIC between 2 and 60 mug/ml) and Gram positive bacteria (MIC between 2 and 15 μg/ml) [62]. A water extract and pure rosmarinic acid showed activity against *Staphylococcus aureus*. It was suggested that carnosic and rosmarinic acids are the main bioactive antimicrobials in rosemary extracts [62].

3.2. Semi-Synthetic and Synthetic Cinnamic Acid Derivatives

Narasimhan and coauthors [52] synthesized a series of esters, amides and substituted derivatives of cinnamic acid (**40**, **117**-**147**, Tables **1**-**3**) and evaluated their antimicrobial activity *in vitro*. Further, they investigated the relationship between their physicochemical properties and microbiological effects. *Iso*-butylcinnamate (**122)** proved to be the most effective against *S. aureus, B. subtilis* and *E. coli*, presenting an important starting point for future work in antimicrobial research and development [52]. The urea inclusion complex of cinnamic acid also showed moderate activity against those bacteria [65].

The structures of several cinnamic acid related compounds in relation to their antibacterial activity against *B. subtilis* and *E. coli* were investigated by Tonari and coworkers [66]. Of the cinnamic acid derivatives **1**, **117** and **146**-**148** (Tables **1**, **2**), the compound with a substituted phenyl group in ester form (ethyl cinnamate, **117**) exhibited the strongest antibacterial activity against *B. subtilis* and *E. coli*. The structure-antibacterial activity relationships indicated that substituted phenyl groups are stronger in terms of MIC than phenyl and NH_2 or Cl groups are more effective than electron-withdrawing substituent such as NO_2. Furthermore, esters had lower MIC compared to free cinnamic acids [66].

Cinnamic acids **3**, **4** and **149** (Table **1**), analogues of Oenostacin, a naturally occurring, potent antibacterial phenolic acid derivative, were synthesized and evaluated [67]. Free phenolic groups were shown to be essential for antibacterial activity, their protection leading to inactive compounds. 3,4,5-trihydroxycinnamic acid (**149**), the most active cinnamic acid analogue with EC_{50} values of 0.63 μM (*S. epidermidis*) and 1,26 μM (*S. aureus*), is an non-natural analogue of Oenostacin important for further lead optimization [67].

A library of hydroxycinnamic acid amides and analogues with the general formula **I** (Fig. (**7**)) were synthesized [68]. However, only dihydrocaffeoyl analogues **150**-**153** were active against methicillin and vancomycin resistant strains of *S. aureus* (MRSA and VRSA) with MIC values between 25 and 50 μg/mL. They were more potent than oxacillin. Oxazolidinones with a cinnamoyl fragment **154**-**156** also showed weak activity against a number of sensitive and resistant bacteria, however, substitution of the acetamidomethyl group with cinnamoyl derivatives led to compounds less active than Ranbezolid [69]. 3ß-amino-(2-aminoethyl)-

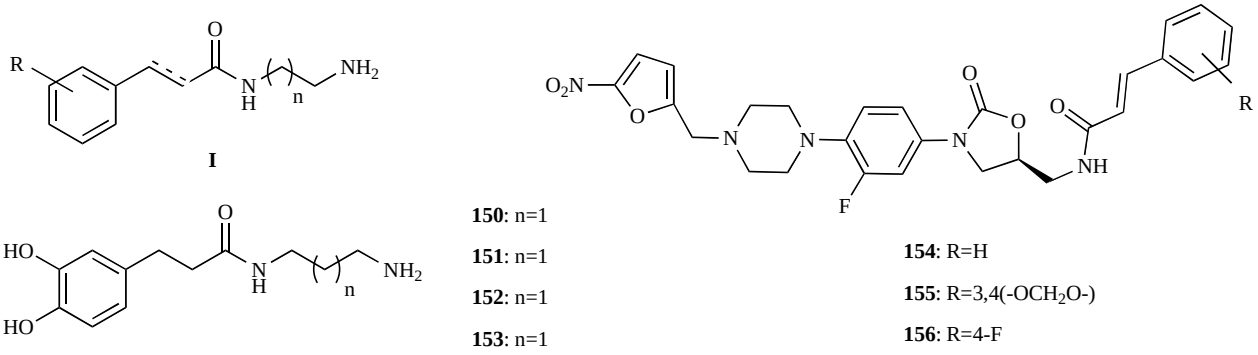


Fig. (7). Cinnamic acid amides (**150**-**156**) with antibacterial activity against resistant strains of bacteria.

cholest-5-ene amides of 4-hydroxycinnamic acid (**157**) and *N*-cholest-5-en-3α-aminoethyl-*bis*(trans-3-phenyl-2-propen) amide (**158**) also showed moderate antibacterial activity against *S. aureus* [70]. It has been already shown (Fig**.** (**4**)) that prenyl derivatives of cinnamic acid (compounds **19**-**23**) have antioxidant properties [24, 39, 40]. The derivatives **20**, **21** and **23**, isolated from the Brasilian propolis, were also identified as antimicrobial agents [71]. Compound **21** shows low MIC values (from 7.8 to 62.5 μg/ml) for several pathogenic bacterial strains. It was shown that the antimicrobial activity of this class of compounds may can be increased by increasing the number of prenyl residues attached [71].

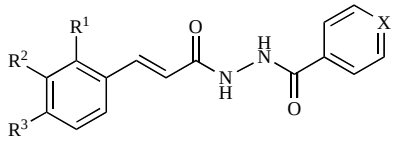
Molecular hybridization between isoniazid and *trans*-cinnamic acid gave *N*-(3-phenyl-acryloyl)-hydrazide derivatives **159**-**168** (Fig. (**8**)) that showed promising antimycobacterial activity, with MIC values between 3.12 and 50.0 μg/ml (Fig. (**8**)) [72]. The isonicotinic moiety contributes to the activity against *M. tuberculosis*. However, in the absence of the pyridine framework, a compensatory effect is promoted by a cinnamic subunit. Cinnamic acid hydrazides **159**-**162** and **166** exhibited activities between 3.12 and 12.5 μg/mL and could be good starting points for finding new lead compounds against the multi-drug resistant tuberculosis. Another molecular hybridization approach was used in the design of antimycobacterials [73, 74]. Phenylacrylamide derivatives **169**-**188** (Fig. (**8**)), incorporating cinnamic acids and guanylhydrazones, showed promising antitubercular activity against *M. tuberculosis* H37Rv [73]. Compound **187,** with a MIC of 6.49 μM and a good safety profile, provides a potential lead for further studies against tuberculosis. Empirical structure–activity relationships indicate that both steric and electronic parameters play a major role in the activity of this series of compounds [73]. Structural features of ethambutol, cerulenin and cinnamic acid gave cinnamides **189**-**200** with MIC values in the range of 5-150 μM and good safety profiles [74]. The most active derivative against *M. tuberculosis*, $H_{37}R_v$ (compound **189**), exhibited synergy with rifampicin. Cinnamic acid derivatives have not been used for treating tuberculosis but they have the potential ability to assist the action of anti-tuberculosis drugs. However, their toxicity problems preclude their use clinically [9].

4-hydroxy and 4-alkoxy substituted cinnamic acid thioesters and amides **201**-**220** (Fig. (**9**), Table **3**) also showed very promising *in vitro* antibacterial activity against *M. tuberculosis* [75]. Although amides were usually less active than the corresponding thioesters, the amide derivative **202** showed the most potent activity (MIC of 0.1 μg/ml) with ClogP less than 5, which means that it is likely to have greater oral bioavailability than the corresponding thioester **205**. These compounds may act on the biosynthesis of mycolic acid (FAS-II system), since their structures are similar to those of known inhibitors.

Some of the twenty synthesized 3-acetoxymethyl cephalosporin derivatives, with various cinnamoyl substituted groups at the 7β-position (**221**-**240**, Fig. (**10**)), showed selective activity against Gram-positive bacteria (*Staphylococcus* and *Enterococcus* sp.) [76]. Substitution on the phenyl ring of the cinnamoyl moiety generally reduced antibacterial activity, however, a *p*-hydroxy group or 2,4-dichloro substitution improved the activity against MRSA. A cyano group on the α position of the cinnamoyl double bond (compound **238**) increased activity against both coagulase-negative *Staphylococcus* and *Enterococcus* sp. and extended the antibacterial spectrum towards Gram-negative bacteria. Attachment of a cinnamoyl moiety to the 7β-amino-3-acetoxymethyl-3-cephem-4-carboxylic acid provides cephalosporins with selective activity against Gram positive bacteria [76].

Pathan *et al.* synthesized *N*-alkyl cinnamamides (**241**-**247**, Table **3**) that were effective against Gram-positive as well as Gram-negative bacteria [77]. Of the *para*-toluenesulfonyloxycinnamamides, compound **248** (Fig. (**11**)) exhibited activity against *E. coli* and *Staphylococci* [78]. Thiazolidine derivatives with a cinnamoyl moiety **249**-**255** (Fig. (**11**)) also showed good *in vitro* activity against *E. coli* and *S. aureus* [79].

Some cinnamic acid derivatives (esters **256**-**265** (Table **2**), ureas **266**-**275**, pyrazoles **276**-**288**, acyl hydrazones, such as compound **289**, benzylidene hydrazides **290**-**291**, Fig. (**12**)) show both antibacterial and antifungal activity [80-84]. Compounds **267**, **276**, **278**-**280**, **282**, **283** and **289** exhibited significant antibacterial activity against *E. coli* and *S. aureus* (high inhibition zones in the agar plate diffusion method) [80-83]. On the other hand, compound **290** was active only against *E. coli* with minimal bactericidal concentration (MBC) of 0.050 μM/ml and compound **291** against *B. subtilis* (MBC of 0.088 μM/ml) [84].



159: R^1, R^2, R^3=H; X=N

160: R^1, R^2=H, R^3=NO_2; X=N

161: R^1, R^2=H, R^3=OCH_3; X=N

162: R=H, R^2 and R^3=OCH_2O; X=N

163: R^1, R^3=Cl, R^2=H; X=N

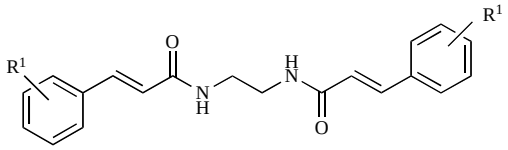
164: R^1, R^2, R^3=H; X=C

165: R^1, R^2=H, R^3=NO_2; X=C

166: R^1, R^2=H, R^3=OCH_3; X=C

167: R=H, R^2 and R^3=OCH_2O; X=C

168: R^1, R^3=Cl, R^2=H; X=C



189: R^1=H

190: R^1=4-CH_3

191: R^1=4-OCH_3

192: R^1=4-Cl

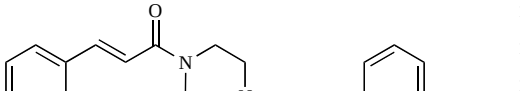
193: R^1=3,4-diCl

194: R^1=2-Cl

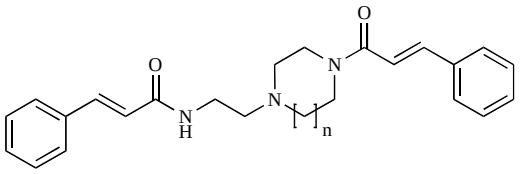
195: R^1=3-NO_2

196: R^1=2-OCH_3

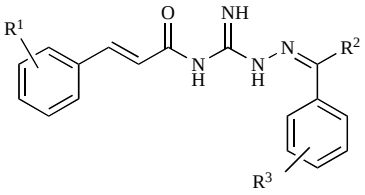
197: R^1=2,6-diCl



198



199: n=1
200: n=2



169: R^1, R^2, R^3=H

170: R^1, R^3=H; R^2=CH_3

171: R^1, R^3=H; R^2=Ph

172: R^1, R^3=H; R^2=4-Cl-Ph

173: R^1=H; R^2=4-Cl-Ph, R^3=4-Cl

174: R^1, R^2=H; R^3=4-OH

175: R^1=H; R^2=CH_3; R^3=4-OH

176: R^1, R^2=H; R^3=3,4-diOCH_3

177: R^1, R^2=H; R^3=3-Cl

178: R^1, R^2=H; R^3=2-Cl

179: R^1=H; R^2=CH_3; R^3=4-Br

180: R^1=H; R^2=CH_3; R^3=4-OCH_3

181: R^1=H; R^2=CH_3; R^3=2-OH

182: R^1=H; R^2=CH_3; R^3=4-F

183: R^1=H; R^2=CH_3; R^3=4-Cl

184: R^1=H; R^2=CH_3; R^3=2,4-diCl

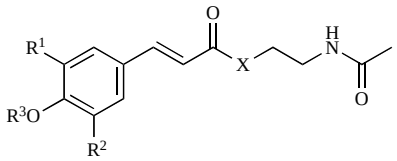
185: R^1=OCH_3; R^2=H; R^3=4-OH

186: R^1=OCH_3; R^2=H; R^3=4-F

187: R^1=OCH_3; R^2=H; R^3=3,4-diOCH_3

188: R^1=OCH_3; R^2=H; R^3=3,4,5-triOCH_3

Fig. (8). Antimycobacterials **159**-**200** designed using the molecular hybridization approach.



X= NH

201: R^1, R^2=H; R^3= isopentenyl

202: R^1, R^2=H; R^3= geranyl

203: R^1, R^2=H; R^3= CH_3

211: R^1, R^2, R^3= H;

212: R^1= OCH_3; R^2, R^3= H;

X= S

204: R^1, R^2=H; R^3= isopentenyl

205: R^1, R^2=H; R^3= geranyl

206: R^1, R^2=H; R^3= farnesyl

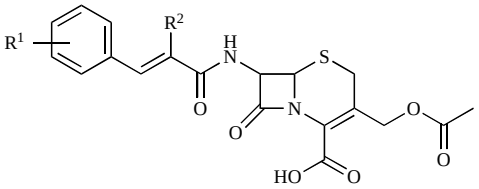
207: R^1, R^2=H; R^3= CH_3

208: R^1, R^2, R^3= H

209: R^1= OCH_3; R^2, R^3= H

210: R^1, R^2= OCH_3; R^3= H

Fig. (9). Cinnamic acid thioesters and amides **201**-**212** as antituberculosis agents.



221: R^1, R^2=H

222: R^1=H; R^2=CH_3

223: R^1=2-Cl, R^2=H

224: R^1=3-Cl; R^2=H

225: R^1=4-Cl; R^2=H

226: R^1=2,4-di-Cl; R^2=H

227: R^1=2-NO_2; R^2=H

228: R^1=3-NO_2; R^2=H

229: R^1=4-NO_2; R^2=H

230: R^1=2-OCH_3; R^2=H

231: R^1=3-OCH_3; R^2=H

232: R^1=4-OCH_3, R^2=H

233: R^1=3,4-di-OCH_3; R^2=H

234: R^1=3-OH-4-OCH_3; R^2=H

235: R^1=3-OCH_3-4-OH; R^2=H

236: R^1=3-OH; R^2=H

237: R^1=4-OH; R^2=H

238: R^1=4-OH; R^2=CN

239: R^1=4-CH_3; R^2=H

240: R^1=4-$(NCH_3)_2$; R^2=H

Fig. (10). Antibacterial 3-acetoxymethyl cephalosporin derivatives **221**-**240** against *Staphylococcus* and *Enterococcus* sp.

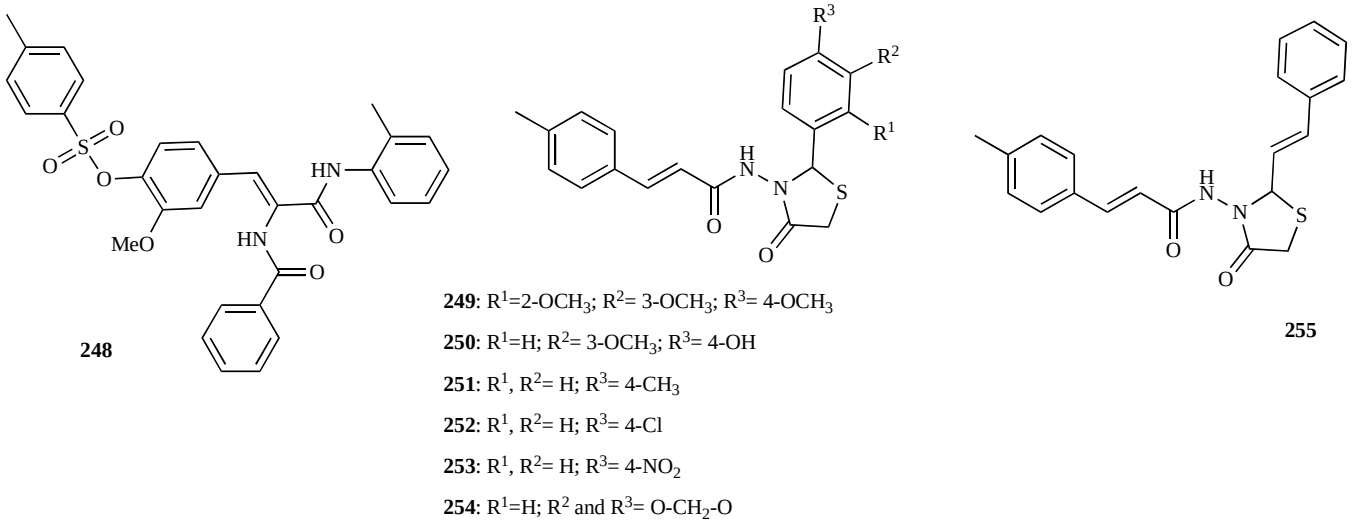


Fig. (11). Cinnamamide **248** and thiazolidines **249**-**255** with antibacterial activity against *E. coli* and *Staphylococci*.

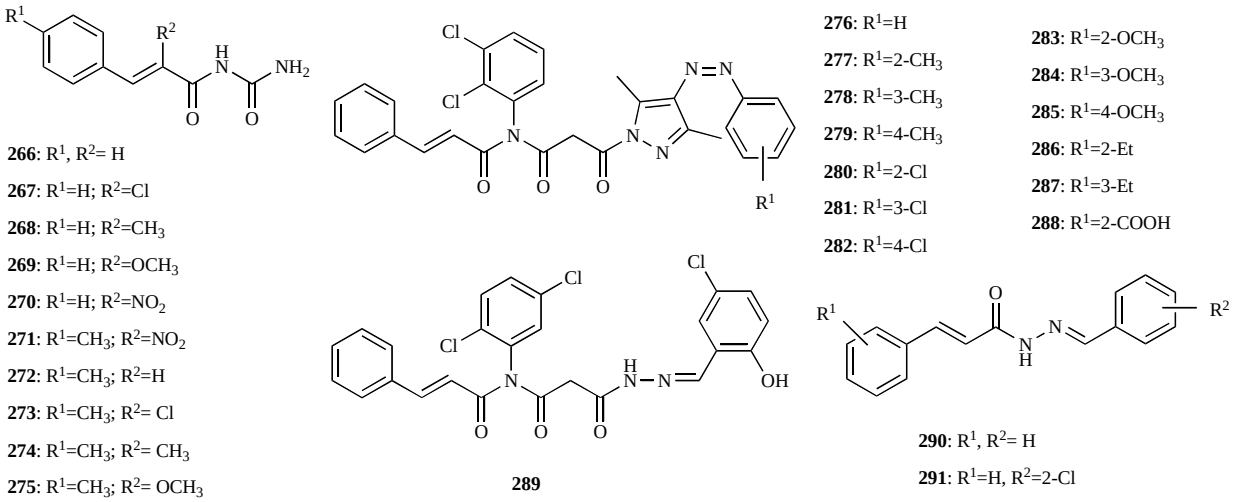


Fig. (12). Cinnamic acid derivatives **266**-**291** with antibacterial and antifungal activity.

4. ANTIVIRAL ACTIVITY

4.1. Natural Resources

Cinnamic acid inhibited viral replication of *equid herpes virus 1*. However, virucidal activity was not observed [85].

In addition to antioxidant and antibacterial properties, rosmarinic acid (**15**) also possesses antiviral activity that can be used in the therapy of *Herpes simplex* infections, using extracts of *Melissa officinalis* containing rosmarinic acid [31]. In another study, rosmarinic acid (**15**) showed potent *in vivo* antiviral activity in mice infected with Japanese encephalitis. It reduces viral replication within the brain and was, therefore, recommended as a strong candidate for further consideration as a therapeutic measure to reduce the neurological complications observed in Japanese encephalitis patients [86].

Inhibitors of HIV-1 integrase, an obligatory enzyme for HIV replication, were also found among natural cinnamic acid derivatives [87-91]. L-chicoric acid (**292**), 3,5-dicaffeoylquinic acid (**293**) and 1-methoxyoxalyl-3,5-dicaffeoylquinic acid (**294**) (Fig. (**13**)) are potent HIV-1 integrase inhibitors [87]. Furthermore, they inhibit HIV-1 replication in tissue culture at 1-4 μg/mL. Since their toxic concentrations are 100-fold greater than their antiviral concentrations and both are specific for HIV-1 integrase and active against HIV-1 in tissue culture, they constitute promising leads to new anti-HIV therapeutics [87]. Rosmarinic acid (**15**) and its methyl ester (**295**) were also reported as potent inhibitors of HIV-1 integrase [88]. Furthermore, nitration of rosmarinic acid (6′-nitro- and 6′,6″-dinitrorosmarinic acids, **296**-**297**) greatly improved the HIV-1 integrase inhibition and the antiviral activity, without increasing the cellular toxicity [89]. In another study, rosmarinic acid (**15**) directly inhibited reverse transcriptase and targeted very early reverse transcription in intact virions [90].

Rosmarinic (**15**) and chicoric acid (**292**) are important as future multitarget anti-HIV leads, however, they are not expected to replace the actual antiretroviral therapy but,

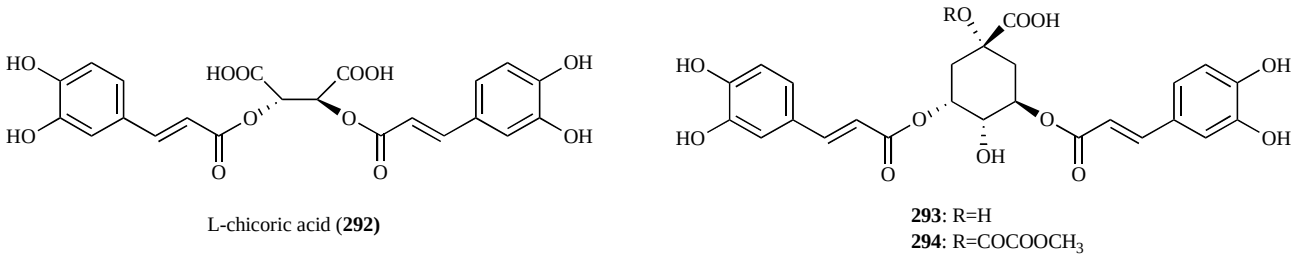


Fig. (13). L-chicoric acid (**292**), 3,5-dicaffeoylquinic acid (**293**) and 1-methoxyoxalyl-3,5-dicaffeoylquinic acid (**294**) as potent HIV-1 integrase inhibitors.

more likely, to complete and perhaps lighten it by adapted diet [91]. Due to insufficient data about their bioavailability, such as plasma levels, there is no evidence that dietary intake of caffeic acid derivatives will provide adequate blood levels to affect HIV viral loads *in vivo* [91].

1-cinnamoyl-3,11-dihydroxymeliacarpin (**298**, Fig. (**14**)), isolated from the leaf extracts of *Melia azedarach*, inhibited vesicular stomatitis virus and herpes simplex virus type 1 multiplication *in vitro* when added after infection, with no cytotoxic effect [92].

4.2. Semi-Synthetic and Synthetic Cinnamic Acid Derivatives

Along with natural cinnamic acid derivatives, six synthetic esters of substituted cinnamic acid (**299**-**302**, Table **2**), identical to or analogous to some of the constituents of the diethyl ether fraction of Bulgarian propolis, showed promising anti-influenza activity [93]. Isopentyl ferulate **302** suppressed the reproduction of influenza virus A/Hong Kong *in vitro* and *in ovo*. The study offered some new information concerning the anti-influenza activity of propolis and decoded the active ingredients therein. Antiviral activity was observed in compounds containing α-aminophosphonate and cinnamoyl moieties (**303**-**304**, Fig. (**14**)) [94]. Compound **306** showed high antiviral activity *in vivo* against *Tobacco mosaic virus*, with an EC_{50} value of 65.2 μg/ml.

In addition to natural resources, several synthetic cinnamates (**13**, **44**, **48**, **49**, **299**, **300**, **302**, **305**-**314** (Table **2**)) showed potent inhibitory activity against HIV-1 integrase [93, 95-98]. Phenethyl esters **308**-**312** had IC_{50} values in the low micromolar range. The major requirement for potent inhibition is two vicinal hydroxyl groups on the aromatic ring. Several mechanisms of action were proposed, such as chelation of an enzyme-bound divalent metal ion and hydroxyls functioning as H-bond donors [95]. Lee *et al.* [96] synthesized caffeoylglycolic and caffeoylamino acid derivatives **315**-**324** as halfmers of L-chicoric acid (**292**). Two compounds, **315** and **324** (Fig. (**15**)), showed HIV-1 integrase inhibitory activity that was equal to or slightly greater than that of **292**, showing that the inhibitory activity can be retained or even increased upon simplification of L-chicoric (**292**) acid to halfmeric structures. However, more SAR studies are needed, since compounds **315** and **324** did not show anti-HIV activity in cell culture assays. Several other analogues of **292**, linked by aliphatic, alicyclic or aromatic spacers, were also prepared and their antiviral and HIV-1 integrase inhibitory activities determined [97]. In the series of *trans*-caffeate analogues, bornyl caffeate (**325**), bornyl 2-nitrocaffeate (**326**), 5-nitrocaffeic acid (**327**) and 5-nitrocaffeic acid phenethyl ester (**328**) possess good HIV integrase inhibitory activity, with IC_{50} values of 19.9, 26.8, 25.0 and 13.5 μM, respectively [98].

Of thirteen steryl esters of cinnamic acid derivatives, two compounds, cholesteryl 3,4-dimethoxycinnamate (**329**) and *o*-coumaroyl ester of beta-(2'-hydroxyethoxy)-cholesten-5-en (**330**), exhibited marked activity against poliovirus type 1 [99]. The anti-adhesive compound *p*-sulfoxy-cinnamic acid (**331**), obtained from the temperate marine eelgrass, *Zostera marina*, showed antiviral properties against dengue virus in a focus forming unit reduction assay [100].

Cinnamoyl- and hydroxycinnamoyl amides of glaucine (**112**-**116**, Fig. (**6**)), exhibited strong radical scavenging activity [49]. Their activity *in vitro* against viruses belonging to different taxonomic groups (enteroviruses, human rhinoviruses (HRV), influenza virus, respiratory syncytial virus (RSV)) was also tested by the cytopathic effect inhibition test in the viral multicycle growth setup [49]. *p*-Coumaroyl amide (**116**) inhibited the replication of echovirus 13 (IC_{50}= 32 μM), HRV-14 (IC_{50}= 13 μM) and RSV (IC_{50}= 18 μM) with good selectivity indices [49].

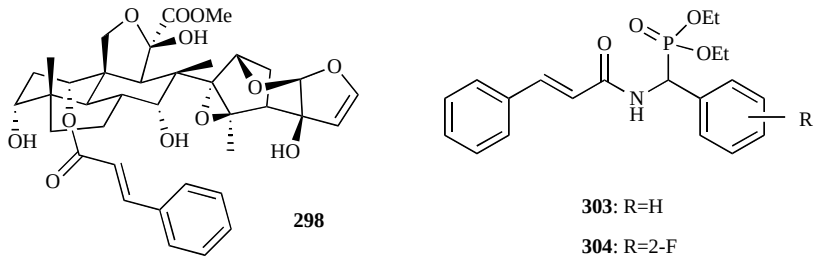
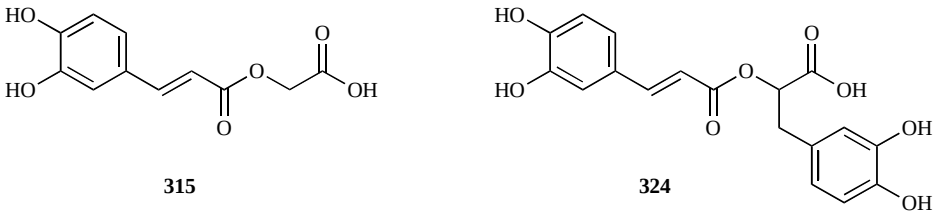
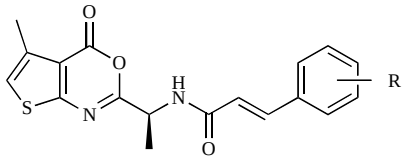


Fig. (14). 1-cinnamoyl-3,11-dihydroxymeliacarpin (**298**) and α-aminophosphonate **303**-**304** as antiviral agents.



315 **324**

Fig. (15). Two compounds, **315** and **324**, designed as halfmers of L-chicoric acid (**292**), with promising HIV-1 integrase inhibitory activity.



		IC_{50} (μM)					IC_{50} (μM)		
	R	HSV-2	VZV	CMV		**R**	HSV-2	VZV	CMV
332	H	0.3	0.038	0.5	**340**	2-Cl, 6-F	0.52	0.036	2.0
333	2-Cl	0.61	0.035	0.38	**341**	2,6-diCl	1.97	0.01	>34
334	2-Br	0.48	0.039	0.38	**342**	2,6-diMeO	1.3	0.18	21
335	2-Me	1.5	0.036	20	**343**	3-Cl	0.98	0.042	0.96
336	2-NO_2	0.72	0.076	2.2	**344**	3,5-diMeO	0.35	0.021	8.5
337	2-EtO	0.56	0.015	0.51	**345**	4-CHO	0.53	0.094	2.4
338	2-Cl-4-OH	0.23	0.015	0.19	**346**	4-NMe_2	0.57	0.038	1.8
339	2,6-diF	0.63	0.06	1.7	**347**	4-NO_2	0.94	0.060	3.6

Fig. (16). Antiviral activity of thieno[2,3-d]oxazinones (**332**-**347**) against herpes simplex virus type 2 (HSV-2), varicella zoster virus (VZV) and cytomegalovirus (CMV) [101].

Cinnamyl derivatives of thieno[2,3-d]oxazinones (**332**-**347**, Fig. (**16**)) inhibited herpes simplex virus type 2, varicella zoster virus and cytomegalovirus proteases with nanomolar potency, with good rates of inactivation and prolonged rates of reactivation [101]. The 2-chloro-4-hydroxy di-substituted aromatic (**338**) showed stronger antiviral activity than the 2-chloro derivative (**333**), providing the highest activity in this series of compounds. This indicates that introduction of 4-hydroxyl group is important for the potency against all enzymes [101].

5. ANTIFUNGAL ACTIVITY

5.1. Natural Resources

Cinnamic acid and its derivatives also have promising potential as antifungal agents. The possible use of cosmetic compositions containing cinnamic acid or buffered acidic lotions and shampoos in the treatment of *M. ovalis* infections of the scalp has been described [102]. Moreover, a urea inclusion complex of cinnamic acid showed moderate activity against *Candida albicans* and *Aspergillus niger* [65], while cinnamic (**1**) and 2-, 3- or 4-methyl cinnamic acids (**348**-**350**, Table **1**) are toxic to wood-rot fungi *Lenzies betulina* and *Laetiporus sulphureus* [103]. (*E*)-methyl cinnamate (**118**) was found to be the most active component of hexane and chloroform extracts of *C. impressicostatum* and *C. pubescens* against several bacteria and fungi, being most active against *C. albicans* and *S. cerevisiae* [104]. Cinnamic acid (**1**) was also shown to display significantly higher antifungal activity against *S. cerevisiae* and *A. flavus* than caffeic acid (dihydroxy acid) (**3**). In contrast, three coumaric acids, **2**, **26** and **27**, showed moderate levels of antifungal activity [105]. Based on these results it can be concluded that introduction of a hydroxyl group leads to reduced antifungal activity. Combined application of phenolics (such as *m*-coumaric acid (**27**) or cinnamic acid (**1**)) with inhibitors of mitochondrial respiration can effectively suppress the growth of fungi [106]. It was shown that cinnamic acid (**1**) also inhibits the growth of *Neurospora crassa* [107]. Chlorogenic acid (**6**), *p*-coumaric acid (**2**) and other cinnamic acid derivatives were active against several fungal pathogens commonly found during the storage of fruits and vegetables [108].

Sesquiterpene dialdehyde cinnamates from *Pseudo-wintera axillaris* (**351**-**358**, Fig. (**17**)) showed fungicidal activity against a range of important food crop pathogens such as *Phytophthora infestans*. A structure-activity study revealed that the cinnamate group is important for fungicidal activity [109].

Rosmarinic acid (**15**) has been reported to have antifungal properties against *Candida albicans* (MIC of 250 μg/ml) [110].

5.2. Semi-Synthetic and Synthetic Cinnamic Acid Derivatives

A structure-antifungal activity relationship study of 18 related cinnamic acid derivatives (**1**-**4**, **19**, **27**, **34**, **43**-**45**, **359**-**365**; Table **1**, **2**) was carried out by Bisogno *et al*. [111].

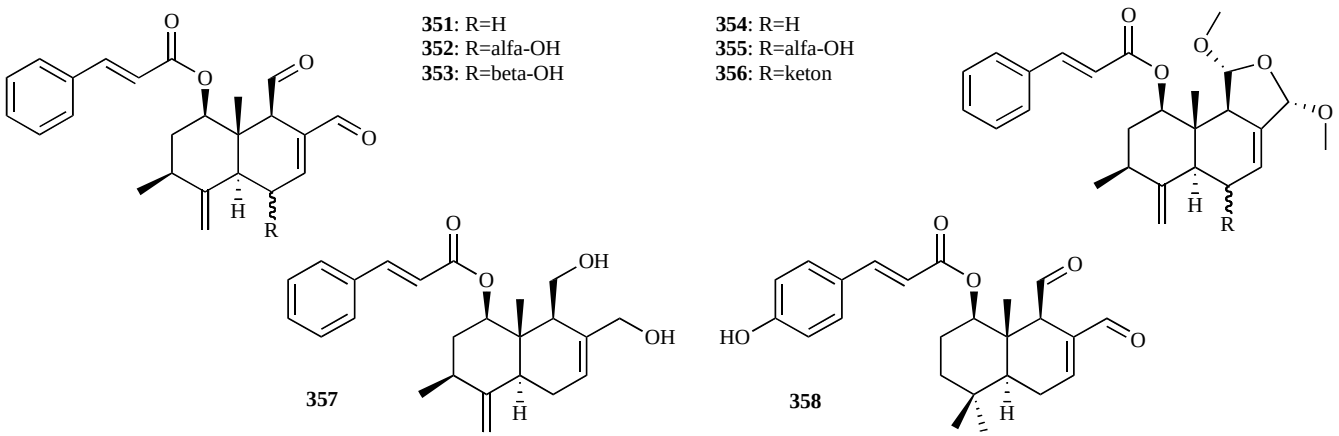


Fig. (17). Sesquiterpene dialdehyde cinnamates from *Pseudowintera axillaris* (**351**-**358**) with fungicidal activity against a range of important food crop pathogens.

Of these, (*E*)-3-(4-methoxy-3-(3-methylbut-2-enyl)phenyl) acrylic acid (**359**) exhibited remarkable antifungal activity against *A. terreus*, *A. niger*, and *A. flavus* (MICs 31.25, 1.95 and 62.5 μg/ml, respectively) with low toxicity against fish and amphibians, which raises hope for development of nontoxic antifungal agents. A structure-antifungal activity relationship indicated that the double bond in the side chain is essential for activity, that esters are less active than acids and that a *p*-methoxy group on the aromtic ring usually increases activity [111].

A large library of cinnamates and cinnamides (representative compounds **43**, **49**, **118**-**123**, **366**-**376**; Tables **2**, **3**; Fig. (**18**)) has been prepared [112-115]. Fungitoxicities towards *Corticium rolfsii* and *Phytium* species are markedly sensitive to the ring substituents. Isopropyl or chloro groups at the 4-position enhance the toxicity while 2,4-dichloro derivatives have lower toxicities than 4-chloro derivatives. On the other hand, cinnamamides with lower alkyl groups on the amino moiety (such as compound **370**) are more fungitoxic than anilide derivatives [112]. Of the *N*-cinnamoyl-α-amino acid esters (for example, compounds **371** and **372**) the antifungal activities are generally as follows: 4-isopropyl > 2,4-dichloro > 4-chloro > H [113]. In another study, isopropyl 4-hydroxycinnamate (**373**) and butyl 4-hydroxycinnamate (**374**) were found to be the most active antifungal compounds against *Pythium* sp., with similar activity to the commercial fungicide iprobenfos [114]. Of 22 pyranyl-substituted cinnamates, isopropyl derivatives **375** and **376** (Fig. (**18**)) showed the highest antifungal activity against *Rhizoctonia solani* and *Sclerotium dellfinii* [115].

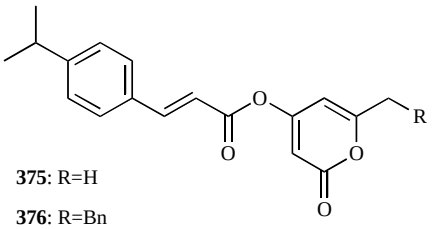


Fig. (18). Pyranyl-substituted cinnamates **375**-**376** with antifungal activity against *Rhizoctonia solani* and *Sclerotium dellfinii*.

A large number of triazoles with cinnamoyl moieties (general formula **II** in Fig. (**19**)) were shown to be active against eight human pathogenic fungi [116, 117]. The greatest antifungal activity was observed for compounds **377** (R^1= CF_3, R^2=H) [116] and **378** (R^1= F, R^2=3-NO_2) [117], with MIC_{80} values ranging from 0.00097 to 4 μg/ml. The molecular model resulting from a computational docking simulation helped to explain the observations that the piperazinyl side chain and the trifluoromethyl group greatly enhance the antifungal activity against different *Candida* species. The cinnamoyl group was suggested to form hydrophobic and van der waals interactions with surrounding hydrophobic residues in the active site of CACYP51 [116, 117].

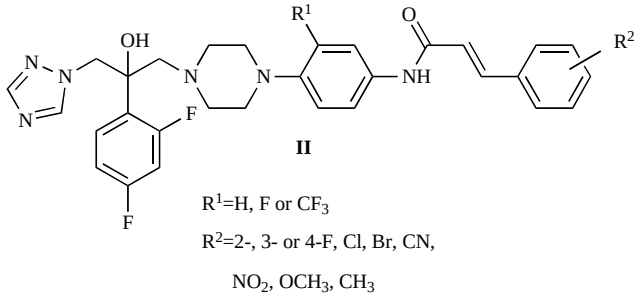


Fig. (19). Triazoles with a cinnamoyl moiety (general formula **II**) having broad spectrum antifungal activity.

Cinnamic acyl thiourea derivatives (**379**-**388**, Fig. (**20**)) showed inhibitory activity against *Gibberella zeae* (wheat scab fungus) and *Rhizoctonia solani* [118]. A hybrid molecule 3β-cinnamoyloleanolic acid (**389**, Fig. (**20**)) was synthesized and its *in vitro* inhibition of candidosis studied against 7 candida species and two moulds, using the well-in-plate agar diffusion and microdilution methods [119]. The MIC and MFC (minimum fungicidal concentration) values indicate that concentrations of 1.25 mg/mL inhibited and 2.5 mg/mL completely killed these organisms and, furthermore, that the concentration that inhibited the growth of *Candida guielemondi* was even lower than that of the antimycotic drug fluconazole.

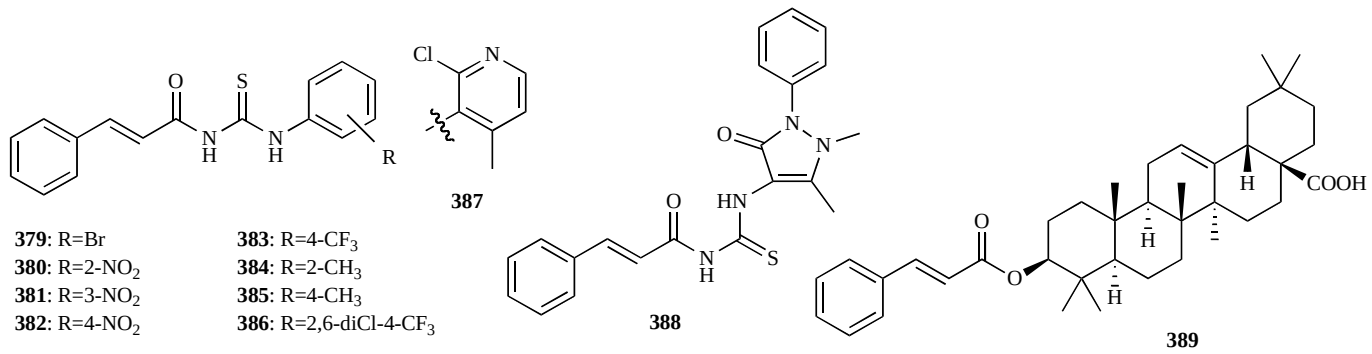


Fig. (20). Cinnamic acyl thiourea derivatives (**379**-**388**) and 3β-cinnamoyloleanolic acid (**389**) as antifungal compounds.

CONCLUSION

Cinnamic acid and its derivatives exhibit a broad spectrum of biological activities. Hydroxycinnamic acid derivatives, widely distributed in food and beverages, are well-known antioxidants with several health benefits. Cinnamic (**1**), coumaric (**2**), ferulic (**4**) and sinapic acid (**5**) show inhibitory activity against several Gram-positive and Gram-negative bacteria. Many cinnamic acid derivatives (thioesters, amides and hydrazides) show promising antimycobacterial activity. HIV-1 integrase inhibitory activity has been reported among cinnamates. Along with *in vitro* antiviral activity against viruses belonging to different taxonomic groups, antifungal properties of cinnamates and cinnamamides have also been observed. Thus, cinnamic acid derivatives, with their antioxidant and antimicrobial activities, are important and promising compounds with high potential for development into drugs. However, lack of information about toxicity, pharmacokinetic properties, their mode of action and understanding of molecular mechanisms are probably the main reasons that cinnamic acids derivatives have not been introduced to human or veterinary medicine. More *in vivo* studies of antioxidant and antimicrobial activites are needed, since the majority of *in vitro* results cannot be directly extrapolated to activities of cinnamic acid derivatives in the organism.

To conclude, obtaining more *in vivo* data for known derivatives, isolation of new substances from new natural sources and determination of their biological effects are essential for the development and successful application of cinnamic acid derivatives.

CONFLICT OF INTEREST

None declared.

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