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Cinnamic acid derivatives: A new chapter of various pharmacological activities

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ABSTRACT

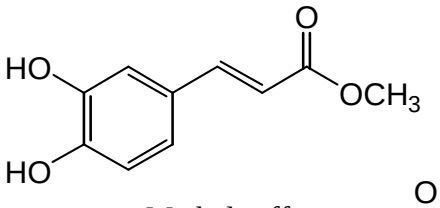
Cinnamic acid derivatives (CADs) are naturally occurring substances found in fruits, vegetables, flowers and are consumed as dietary phenolic compounds. These play a vital role in the formation of commercially important intermediate molecules which are necessary for the production of different pharmaceutical ingradients. In the present review, cinnamic acid and its derivatives are studied for its various biological activities like antioxidant, hepatoprotective, anxiolytic, insect repellent, antidiabetic and anticholesterolemic etc. Different substitutions on basic moiety lead to various pharmacological activities e.g. m- hydroxy or p- methoxy residue on cinnamic acid (CA) is significantly important functional groups as an effective insulin releasing agent while 3, 4-Dihydroxycinnamic acid (caffeic acid, CAF) shows hepatoprotective activity. CADs show variety of pharmacological activities along with their milder to moderate side effects which are always become hurdle for the clinical utilization of this chemical entity. So for the proper utilization of CADs, it is yet to explore to reduce or terminate its adverse effects.

Keywords: Cinnamic acid, Caffeic acid, Adverse effects, Pharmacological activities, Chemical entity, Pharmaceutical products.

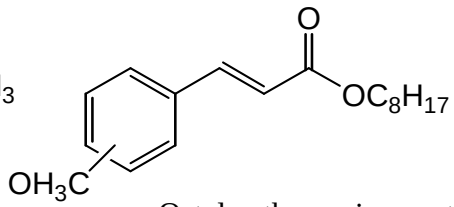
INTRODUCTION

In biological chemistry, cinnamic acid is a key intermediate in shikimate and phenylpropanoid pathways. Shikimic acid is a precursor of many alkaloids, aromatic amino acids, and indole derivatives. It is found both in free form, and especially in the form of esters (ethyl, cinnamyl, benzyl), in various essential oils, resins and balsams, oil of cinnamon, balsam of Peru and balsm of Tolu etc. These are very important intermediates in the biosynthetic pathway of most of the

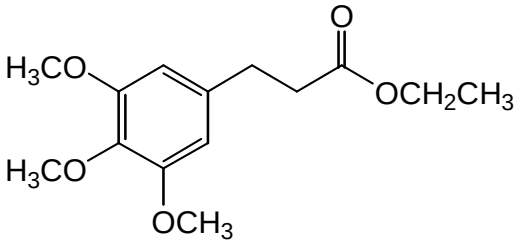
aromatic natural products. These are widely spread in the plants and possess wide range of activities[1]. In addition, cinnamic acids play vital role in the synthesis of other important compounds. For example, cinnamic acid derivatives can be converted into immensely important compounds including styrenes and stilbenes through decarboxylation reaction.



Methyl caffeate



Octylmethoxy cinnamate



Ethyl3, 4, 5-trimethoxycinnamate

Figure 1

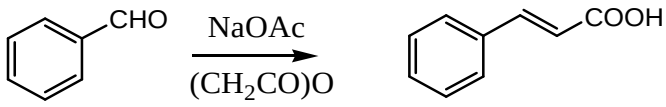
In addition cinnamic acids are also used as precursor for the synthesis of commercially important cinnamic esters. Cinnamic esters are obtained from various plant sources and find application in perfumery, cosmetic industries and in pharmaceutics. For example, methyl caffeate (Figure 1) is found in plant like *Gaillardin pulchella, Gochnatra rusbyana, Netopterygium incisum* and as 4-glycoside in the fruits of *Linum usitatissimum*. The compound is reported to posses antitumour activity against Sarcoma 180 as well as antimicrobial activity[2]. Methoxy substituted cinnamate such as ethyl 3, 4, 5-trimethoxycinnamate (Figure 1) is present in *Piper longum* and plays an important role in controlling inflammatory diseases[3]. Similarly long chain cinnamic ester like methoxy substituted octylcinnamates (Figure 1) are well known sunscreen agent and ideally suited for cosmetic applications since they are non irritating to skin and provide lubricity to prevent drying effect of wind[4].

2. Chemistry

General methods for the synthesis of cinnamic acid and its derivatives are of following:-

2.1 Perkin reaction

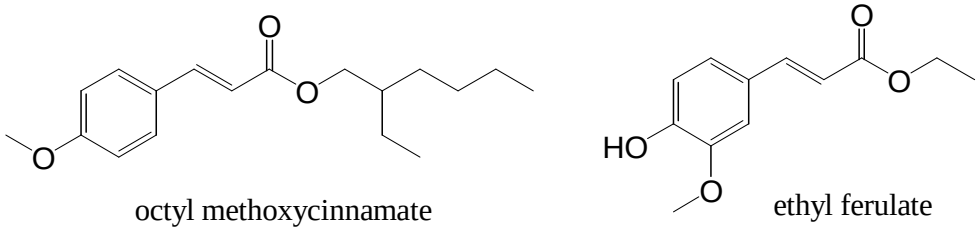
Cinnamic acid is easily prepared by Perkin synthesis using benzaldehyde in acetic anhydride and anhydrous sodium acetate. Perkin reaction is the most frequently method for the preparation of the cinnamic acid and its derivatives but the main disadvantage of this reaction is aldehydes in the presence of base lead to formation of unwanted side products formation.



Scheme 1

2.2 Enzymatic method

Synthesis of two derivatives by using enzymatic method has been carried out by Lee *at al.* using Novozym 435 as a catalyst. They have reported two derivatives of cinnamic acid i.e. the synthesis of ethyl ferulate (EF) from ferulic acid (4-hydroxy 3-methoxy cinnamic acid) and ethanol, and octylmethoxycinnamate (OMC) from *p*-methoxycinnamic acid and 2-ethyl hexanol. This methods is beneficial than others methods reported as there is maximum conversion of reactant to product take place and the enzyme can be reused time and again without any significant loss of activity. The loss of enzyme activity is due to the use of ethanol which ultimate distort the water layer around the enzyme which is necessary for its activity[5].



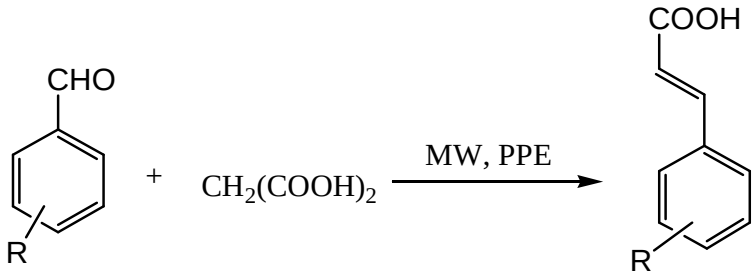
octyl methoxycinnamate (Used as a sunscreen agent)

ethyl ferulate (Antioxidant)

Figure 2

2.3 Microwave irradiation methods (Knoevenagel condensation)

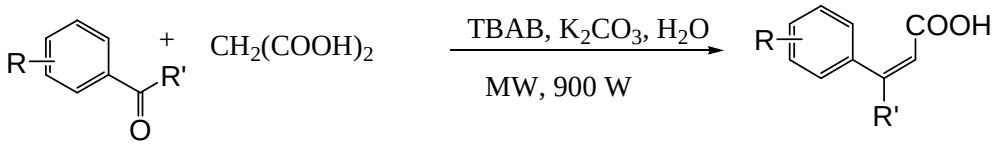
2.3.1 Being an important intermediate in the synthesis of various organic compounds like segontin, cinnarizine etc., and various methods has been reported for the preparation of cinnamic acid and its derivatives. Microwave irradiation of aryl aldehydes and malonic acid with polyphosphate ester (PPE) as the mediator catalyst in solvent less condition produces cinnamic acid and its derivatives[6]. This method is suitable for the synthesis of cinnamic acid with electron donor substituent which overcome the disadvantage of Perkin reaction. Long reaction time is the main disadvantage of this method.



R = 4-Br, 3, 4$(OMe)_2$, 4-OH, 4-NO_2, 2, 5$(OMe)_2$, OMe, 4-Me, 3-Cl, H.

Scheme 3

2.3.2 Aromatic aldehydes or ketones and malonic acid in the presence of tetrabutylammonium bromide and K_2CO_3 in microwave irradiation produce cinnamic acids[7].



R/R' = H/H, 4-OMe/H, 4-NO_2/H, 3-Br/H, 2, 4-Cl/H, 4-OH/H, H/CH_3, 4-Br/CH_3, 4-NO_2/CH_3

Scheme 4

2.4 Phosphorous oxychloride method

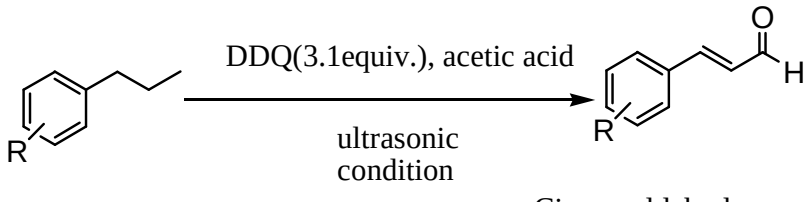
A series of cinnamic acid derivatives were most frequently synthesized by using Perkin reaction. In the presence of electron-donor substituent, the yield of the target product markedly decreases; in such systems the Perkin reaction is not employed for preparative purposes. For the electron donating groups, Knoevenagel and Debner modification reactions lead to the good yields of the final product but the main drawback is that reaction needs long duration of time. Phosphorus oxychloride (POC) act as acid catalyst, which activate both reaction components, since interaction of the aldehydes component with POC may produce the active carbocation[8].

2.5 Industrial preparations of cinnamic acid derivatives

There are numerous methods for the preparation of cinnamic acid derivatives, but industrially it is prepared from 1, 1, 1, 3- tatrachloro-3-*p*-phenylpropane by using CCl_4 as a solvent, which may be destroy the ozonosphere and is harmful to the human body. So this is the main drawback of this method.

2.6 Under ultrasonication method

Cinnamaldehyde having trans selectivity was prepared from arylpropene under one pot two step synthesis by using DDQ (2, 3-Dichloro-5, 6-dicyno-1, 4-benzoquinone), few drops of acetic acid and under ultrasonic condition[9].



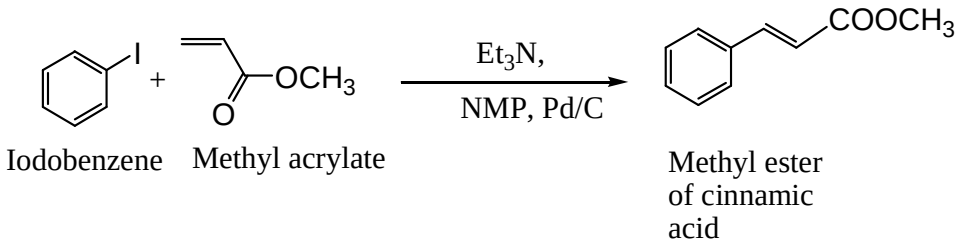
Cinnamaldehyde

Scheme 5

2.7 By using Heck coupling reaction

2.7.1 Using palladium on charcoal as a catalyst

Ambulgekar and co-worker synthesized the methyl ester of CA from iodobenzene and methyl acrylate in NMP (N-methyl pyrolidine) as a solvent and Pd/C as a catalyst under ultrasonic condition[10].

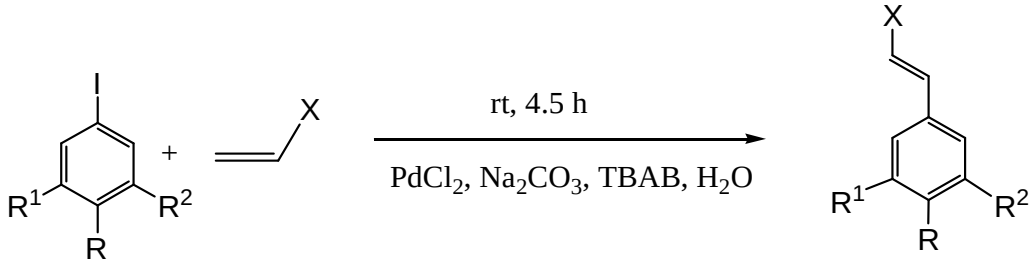


Iodobenzene Methyl acrylate Methyl ester of cinnamic acid

Scheme 6

2.7.2 Using palladium chloride as a catalyst

Cinnamic acid esters was prepared (when X = COOMe) from different aryl halides by using $PdCl_2$ as a catalyst under ultrasonic condition[11]. The role of TBAB (tetra butyl ammonium bromide) as phase transfer catalyst while Na_2CO_3 as a base. Commercial this reaction is very useful reaction as it was carried out under room temperature condition and ultrasonic condition using water as a solvent.



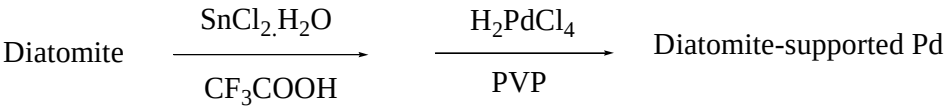
Yield = 43-93 %

R = H, OMe, Cl, Br, OMOM, NHCOMe, or NO2
R^1= I, CHO, H
R^2= I or H
X = CO_2Me, COOH, CN or Ph

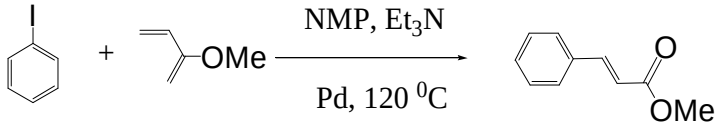
Scheme 7

2.7.3 Using Diatomite-Supported Pd Nanoparticles

Solid supported palladium, gold, nickel etc. play a very crucial role in the C-C bond formation reactions. Diatomite-supported palladium nanoparticles has been prepared by following way



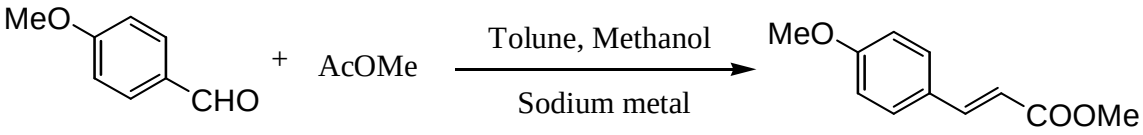
The above prepared Pd-nanoparticles are used for the synthesis of CADs. Aryl halides reacted with methyl acrylate to form various cinnamic acid derivatives using NMP (*N*-Methyl pyrolidine) as a solvent and triethylamine as a base produces good yield[12].



Scheme 8

2.8 Claisen–Schmidt Condensations

A variety of (*E*)-cinnamic acid derivatives are prepared in high yields through the Claisen–Schmidt condensation in the presence of sodium metal and a catalytic amount of methanol with toluene employed as the co-solvent.



Scheme 9

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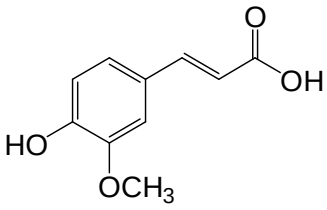
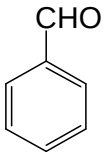
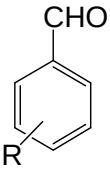
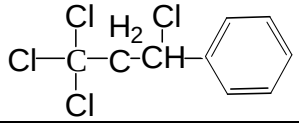
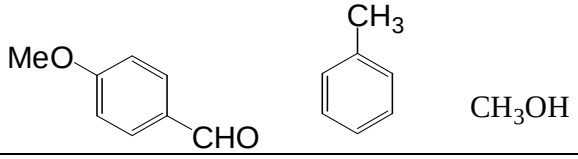
Table 1 Various methods of synthesis of Cinnamic acid and their derivatives along with drawbacks of each method

S. No.	Name of the reaction	Reactant involved	Disadvantages
1	Enzymatic method	Ferulic acid (4-hydroxy 3-methoxy cinnamic acid) and ethanol using Novozym 435 as a catalyst  and CH_3CH_2OH ferulic acid	Ethanol is responsible for the significant loss of catalytic activity of enzyme
2	Perkin reaction	Benzaldehyde in acetic anhydride and anhydrous sodium acetate  + $CH_2(COO)_2O$ + NaOAc	Not suitable for electron donor substituent as it leads to low yield.
3	Knoevenagel condensation	Aryl aldehydes and malonic acid with polyphosphate ester  and $CH_2(COOH)_2$	Long duration of reaction time and considerable amount of solvents are required
4	Phosphorous oxychloride method	Similar as used in Perkin and Knoevenagel condensation reaction	Low yield obtained except $-OCH_3$

5	Industrial preparations	1,1,1,3- tatrachloro-3-p-phenylpropane and CCl_4 	CCl_4 causes ozone layer depletion
6	Claisen–Schmidt Condensations	Aryl aldehydes in the presence of sodium metal and a catalytic amount of methanol with toluene 	Problem of handling of sodium metal

3. Biological activities of cinnamic acid derivatives

The CA derivatives are extremely versatile and have featured in various drugs. The wide range of pharmacological profile shown by cinnamic acid derivatives can be classified into the following categories.

1. Anti TB
2. Antidiabetic
3. Antioxidant
4. Antimicrobial
5. As a fragrance material
6. Hepatoprotective
7. CNS depressant
8. Anticholesterolemic
9. Antifungal and Fungitoxic
10. Antihyperglycemic
11. Antimalerial
12. Antiviral
13. Anxiolytic
14. Cytotoxic
15. Anti-inflammatory
16. UV rays absorbent

3.1 Anti TB activity

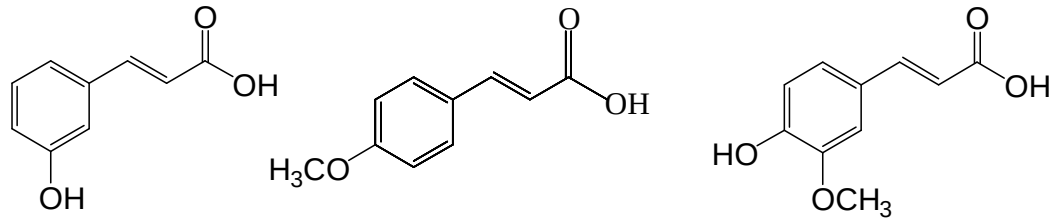
There are many drugs which are used against the *Mycobectrium tuberclosis*, but the main disadvantages of these drugs are that they develop resistance more abruptly. Rastogi *et al.*[13] investigated cerulenin, an inhibitor of fatty acid and trans-cinnamic acid, which was recently shown to augment the activity of various antibiotic drugs against *M. avium*. Cerulenin is a known inhibitor of fatty acid synthetase[14, 15] and has been reported to inhibit the biosynthesis of both unsaturated and saturated fatty acids as well as that of total phospholipids in M. smegmatis. Trans-cinnamic acid is a bacteriostatic even at concentrations as high as 200 μg ml^{-1}, whereas cerulenin was bacteriostatic until 50 μg ml^{-1}. Ethambutol resulted in synergistic activity in 12/30 drug combinations, as compared to 15/36 for cerulenin and 10/18 for trans-cinnamic acid while clofazimine, did not show any synergistic activity with ethambutol or cerulenin. Berwa R and co-

workers synthesized 20 novel phenylacrylamide derivatives incorporating cinnamic acids and guanylhydrazones by using microwave assisted synthesis. Activity of the synthesized compounds was evaluated using resazurin microtitre plate assay (REMA) against *M. tuberculosis* H37Rv. (2*E*)-*N*-((-2-(3,4-dimethoxybenzylidene) hydrazinyl) (imino) methyl)-3-(4-methoxyphenyl) acryl amide showed MIC of 6.49 μM along with good safety profile of >50-fold in VERO cell line[16]. Cinnamic acid derivatives are not used as anti TB agent but they can only assist the action of various anti TB drugs. Clinically they are not used due to its toxicity problems.

3.2 Antidiabetic activity

Insulin is a primary hormone that regulates glucose metabolism either by stimulating peripheral glucose uptake or by suppressing hepatic glucose production[17].

m- hydroxy or *p*-methoxy residues of cinnamic acid were significantly important substituent as an effective insulin releasing agent in both in-vivo and in-vitro. The introduction of *p*-hydroxy and *m*-methoxy substituted groups in cinnamic acid (ferulic acid) structure displayed the most potent insulin secreting agent among those of cinnamic acid derivatives. Sulfonylurea based drugs are generally used against diabetes, but the main disadvantage of these are drugs are that they cause hypoglycemia and failure of insulin secretion. Ferulic acid is the most effective insulin-secreting agent among the cinnamic acid derivatives. *m- Hydroxy* or *p*-methoxy residues on cinnamic acid also shows good insulin releasing activity when Glibenclamide was used as a positive control in the experiment[18].



m-hydroxy cinnamic acid | p-methoxy cinnamic acid | ferulic acid

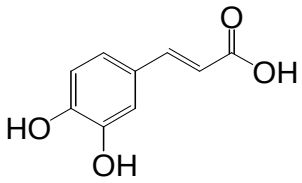
Figure 2

3.3 Antioxidant Activity

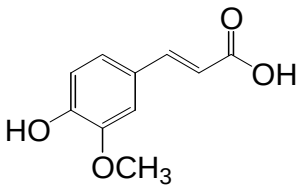
Cinnamic acid derivatives exhibit high antioxidant activity that is due to the presence of vinyl fragments. This property attracts attention to the study of these compounds as potential drugs for the treatment of pathologies related to the lipid peroxidation in cellular membranes. However, the reactive center (vinyl fragment) is significantly affected by substituent present in various positions of the benzene nucleus[19]. According to Jiang *et al* Caffeic acid and ferulic acid and their respective phenyl ethyl ester derivatives shows antioxidant activity[20].

Derivatives of benzoic acid with the homologous cinnamic acid derivatives by using competition kinetic test and in vitro oxidative modification of human low-density lipoprotein (LDL) and showed the increased antioxidant activity in the following sequence *p*-hydroxy < *p*-hydroxymethoxy < dihydroxy < *p*- hydroxydimethoxy. The four derivatives of benzoic acid used by Natella *et al* were *p*- hydroxybenzoic, protocatechuic, vanillic and syringic acid while

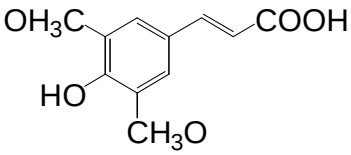
cinnamic acid derivatives used were *p*- coumeric acid, caffeic acid, ferulic acid and sinapic acid[21].



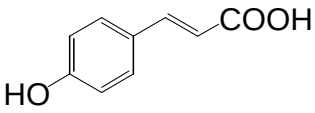
Caffeic acid



Ferulic acid



Sinapic acid

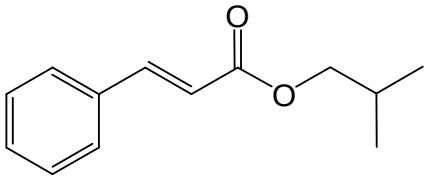


p-coumaric acid

Figure 3

3.4 Antimicrobial activity

Antimicrobial activity of CA derivatives is due to the presence ester and amide groups. Narasimhan and co-workers have reported the antibacterial activity against *Escherichia coli and Staphylococcus aureus, Bacillus subtilis* (Gram negative and Gram positive respectively) and antifungal activity against *Candida albicans* and *Aspergillus niger*. Isobutyl cinnamate and dibromo cinnamic acid exhibited strong antibacterial activity against Gram positive and Gram negative bacteria and good antifungal properties. Author has observed that addition of halogens to the side chain caused remarkable increase in growth inhibitory effect of cinnamic acid whereas addition of hydroxy groups to the side chain double bond did not remarkably enhance the antimicrobial activity[22].



Isobutyl cinnamate

Figure 4

3.5 In cosmetology and as a fragrance material

CA is a fragrance ingredient used in many fragrance compounds. It may be found in fragrances used in shampoos, fine fragrances, decorative cosmetics, toilet soaps and other toiletries as well as in non-cosmetic products such as household cleaners and detergents. Its use worldwide is in the region of 1–10 metric tonnes per annum[23]. Although, cinnamic acid is not considered an important odorant, it serves as a precursor for derivatives such as the esters[24] which have

pleasant long-lasting aromas. Methyl cinnamate used widely and is found in flavour and fragrance compositions created for products which include soaps and cosmetics as well as beverages, baked goods, and convenience foods. Reported applications for cinnamic acid and its derivatives also include: preparation of herbicidal compositions; as a raw material in the synthesis of heterocyclic color complexes.

One of the most interesting uses for cinnamic acid in recent years has been as a raw material in the preparation of L-phenylalanine the key intermediate for the aspartame[25] (synthetic dipeptide sweetener).

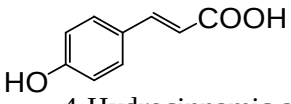
More than 95% of the consumption of cinnamaldehyde occurs in flavor applications where a spicy, cinnamon character is required. It is used in a wide range of products including bakery goods, confection, and beverages as well as in toothpastes, mouthwashes, and chewing gum. It is also used effectively in air fresheners.

In electroplating processes, cinnamaldehyde is utilized as a brightener. In addition to these applications, it is used as an animal repellent, its use in compositions to attract insects. Cinnamaldehyde has been efficiently isolated in high purity by fractional distillation from cassia and cinnamon bark essential oils. This material has been utilized in several manufacturing protocols for the preparation of natural benzaldehyde through a retro-aldol process. Since the late 1970s the demand for natural flavors has increased dramatically. This demand has led to a corresponding requirement for a more extensive line of readily available natural aroma chemicals for flavor creation.

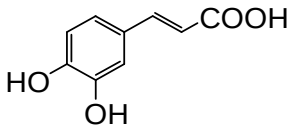
Cinnamyl alcohol and its esters, especially cinnamyl acetate, are widely employed in perfumery because of their excellent sensory and fixative properties. They are also used in blossom compositions such as jasmine, lilac, lily of the valley, gardenia and hyacinth to impart balsamic and oriental notes to the fragrance. In addition, they are utilized as modifiers in berry, nut, and spice flavor systems. The value of cinnamyl alcohol has also been mentioned in a variety of applications which include the production of photosensitive polymers, the creation of inks for multicolor printing, the formulation of animal repellent compositions, and the development of effective insect attractants[26].

3.6 Hepatoprotective

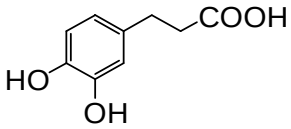
3, 4-Dihyhroxycinnamic acid (caffeic acid) is a natural product containing catechol with an α, β-unsaturated carboxylic acid chain that has hepatoprotective properties[27]. Alvarez and co-workers have determined the effects of the various substituents like 4-hydroxy, 3-hydroxy, 3, 4-dihydroxy and the double bond moiety on the hepatoprotective activity in which the liver damage was produced by the CCl_4[28].



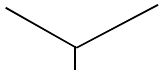
4-Hydrocinnamic acid



3, 4-dihydroxycinnamic acid



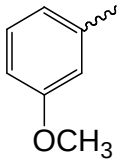
3, 4-dihyrdroxyhydrocinnamic acid



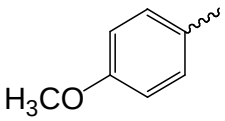
no significantly difference between these two indicates α-β unsaturated carboxylic acid chain double bond has no effects on hepatoprotective activity

Figure 5

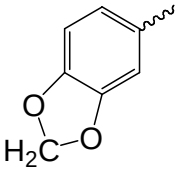
Fernandez *et al* also reported the hepatoprotective activity for 15 cinnamic acid derivatives in the CCl_4 induced acute liver damage model (depend upon oxidative stress mechanism). Compounds with a methoxy group at position 3 or 4, or a 3,4-methylenedioxy moiety were the most active ones. They reported that bulkier the group, lesser will be the hepatoprotective activity[29].



3-methoxy moiety



4-methoxy moiety



3, 4-methylene dioxy moiety

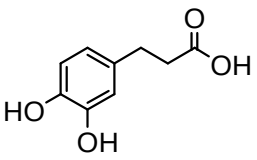
Figure 6

3.7 CNS depressant activity

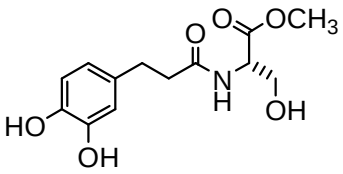
Halogenated cinnamic acid derivatives showed the highest CNS depressant activity[30]. Yabe *et al* reported the effect of ferulic acid on the proliferation neural stem cell. Oral administration of ferulic acid also increases the cAMP response element binding protein phosphorylation[31].

3.8 Anticholesterolemic activity

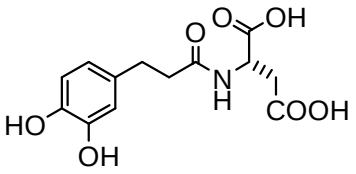
Hypercholesterolemia is considered to be a major cause of the diseases associated with atherosclerosis, and a number of hypercholesterolemic drugs have already been developed to improve the plasma lipid levels in patients. Lipid lowering efficacy (anticholesteremic) of two derivatives of 3, 4-dihydrocinnamate i, e. 3, 4-dihydrophenylpropionic amide (L-serine methyl ester) and 3, 4-dihydrophenylpropionic amide (L-aspartic acid) has been reported by Kim and co-workers using clofibrate as a positive control.



3, 4-di(OH)-hydricinnamate (HC)



3, 4-di(OH)-phenylpropionic acid (L-serine methyl ester) amide

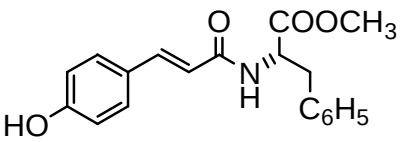


3, 4-di(OH)-phenylpropionic acid (L-aspartic acid) amide

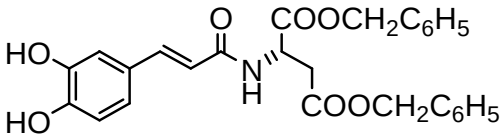
Figure 7

HC and its amide derivatives had lowered atherogenic index and increased the ratio of HDL-cholesterol to the total plasma cholesterol in the same fashion as the clofibrate done. Author had also observed that hepatic cholesterol level was lowered in liver[32].

Two other derivatives of cinnamic acid [4-hydroxycinnamic acid (L-phenylalanine methyl ester) amide (a) and 3,4-dihydroxyhydrocinammic acid (L-aspartic acid dibenzyl ester) amide (b)] inhibit human acyl-CoA :cholesterol acyltransferase-1 and -2. So these two compounds a and b act as useful anti-atherosclerotic agent by inhibiting the cellular cholesterol storage, inhibiting the LDL-oxidation and HDL particle size rearrangement[33].



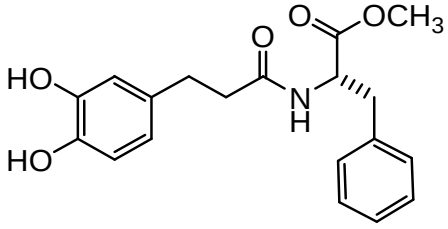
a



b

Figure 8

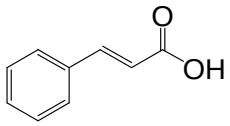
3, 4-di (OH)-cinnamate i, e. 3, 4-Di (OH)-phenylpropionic acid (L-phenyl alanine methyl ester) amide is also effective in lowering the plasma lipids and improving the antioxidant enzyme system[34].



3, 4-Di(OH)-phenylpropionic acid(L-pheny alanine methyl ester)amide

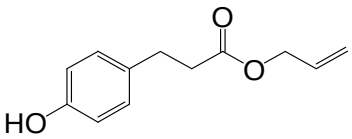
Figure 9

Compound b and c significantly lowered cholesterol and triglyceride levels in the plasma and liver with a simultaneous increase in the HDL-cholesterol concentration, whereas cinnamic acid only lowered the plasma cholesterol concentration. Cinnamic acid lowered hepatic HMG-CoA reductase activity in high cholesterol fed rats, however, its synthetic derivatives (a and b) did not affect HMG-CoA reductase activity compared to the control group[35].



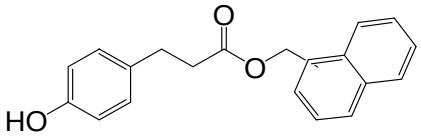
Cinnamic acid

a



(Allyl 3-(4-hydroxyphenyl)propanoate)

b



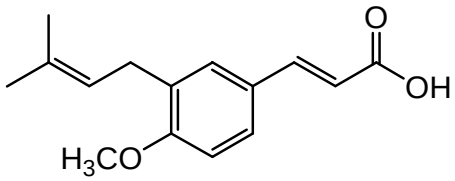
(1-naphthylmethyl 3-(4-hydroxy phenyl)propanoate)

c

Figure 10

3.9 Antifungal activity

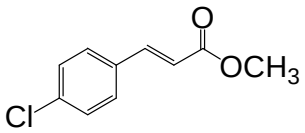
(*E*)-3-(4-Methoxy-3-(3-methylbut-2-enyl)phenyl)acrylic acid exhibited highest antifungal activity against *A. niger*, comparable to that of miconazole and a significant antifungal effect against *A. flavus* and *A. terreus*, while caffeic acid was inactive to the antifungal activity[36].



(E)-3-(4-Methoxy-3-(3-methylbut-2-enyl)phenyl)acrylic acid

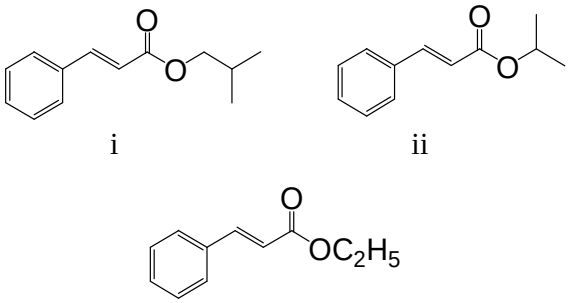
Figure 11

In an another study Kim *et al.* reported that cinnamic acids were having more antifungal effects than coumaric acids[37]. Compound i, ii and iii showed the 40 % fungitoxic activity at 10 ppm, while Methyl 4-chloro cinnamate showedthe highest activity.against *C. rolfsii*



Methyl 4-chloro cinnamate

Figure 12

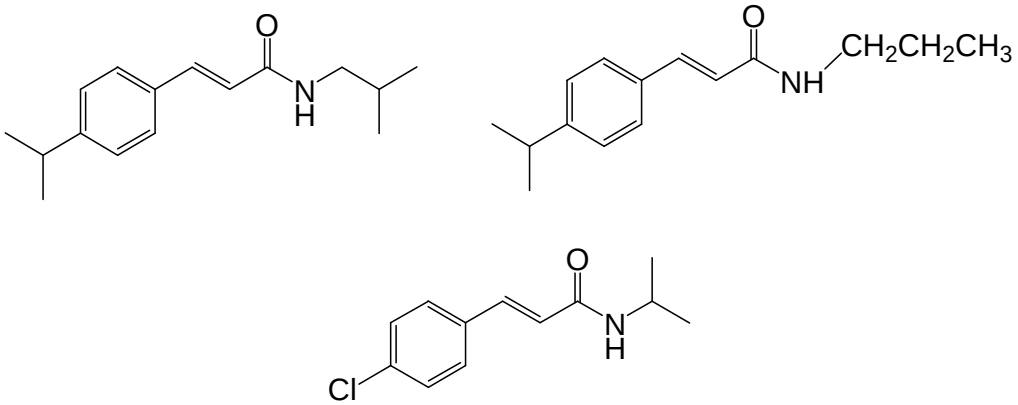


i ii

iii

Figure 13

While in amide derivatives 4-isopropylcinnamamide derivatives showed the highest fungi toxic activity (40 % inhibition against *Pythium* sp. and 30 % against *C. rolfsi*)[38].

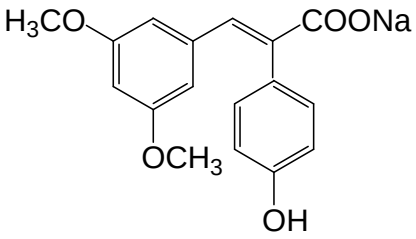


N- isopropyl-4-chlorocinnamamide (highest fungitoxic activity 66 %)

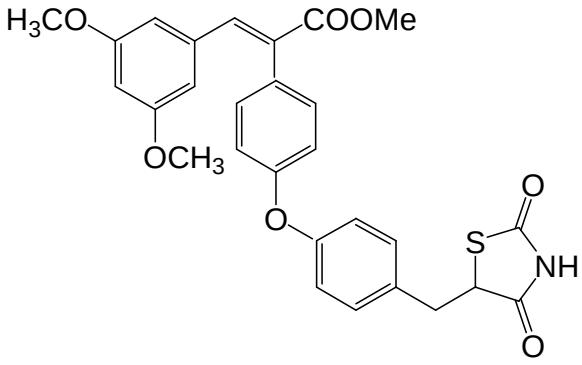
Figure 14

3.10 Antihyperglycemic activity

A new series of thiazolidine-1, 4-dione substituted α-phenyl cinnamic acid with moderate PPARγ agonist activity showing strong oral glucose lowering effects in animal model of type 2 diabetes. The presence of double bond and the geometry of cinnamic acid is necessary for its PPAR agonistic activity. α-phenyl substituted cinnamic acid derivatives possess a weak antihyperglycemic activity while its 2,4-thiazolidinedione analogues and related cinnamic and phenyl propionic acid and esters were having good activity[39].



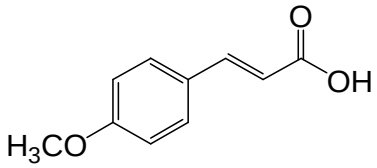
weak antihyperglycemic activity



strong glucose lowering activity

Figure 15

Antihyperglycemic effect of *p*-methoxycinnamic acid (*p*-MCA) have been reported by Adisakwattana and co-workers[40].



p-methoxy cinnamic acid

Figure 16

3.11 Antimalerial activity

Compound (Figure 17) has been proved as a novel class of anti-malarial agents. Replacement of the 3-phenylpropionyl moiety of the lead structure (i) by a 4-propoxycinnamic acid residue resulted in a significant improvement in anti-malarial activity[41].

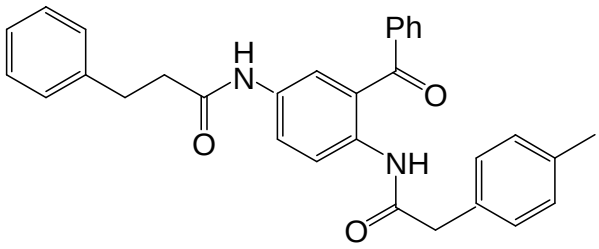
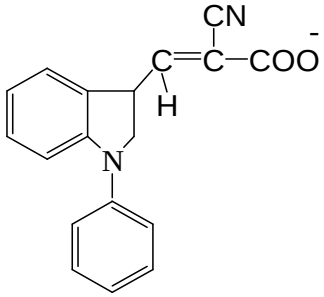


Figure 17

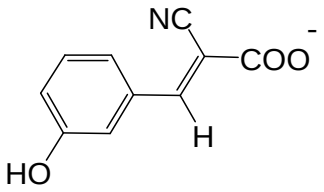
Cinnamic acid derivatives (CADs) inhibit the transport of monocarboxylate across erythrocyte and mitochondrial membranes. They also inhibit parasite growth and that they are equally effective at the young (ring) and the mature (trophozoite) stages of parasite development.

The alteration of parasite growth by CADs could be due to inhibition of lactate transport or of mitochondrial respiration. It must be emphasized that since cinnamic acid derivatives are also

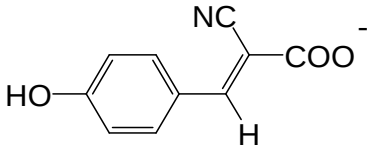
noxious to host cells, they could not be used as novel antimalarial drugs. They have been used as tools for the investigation of lactate disposal and for the detection of possible new targets for chemotherapeutic onslaught[42].



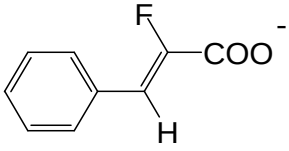
[α-Cyno-β–(1–phenylindol-3-yl) acrylate]



α–Cyno–3–hydroxycinnamate



α–Cyno–4–hydroxycinnamate



α–Fluorocinnamate

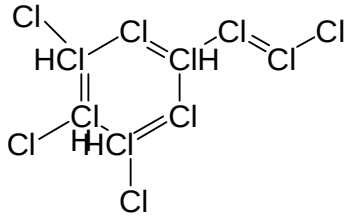
Figure 18

3.12 Antiviral activity

Gravina *et al.* proposed the antiviral for *trans*-cinnamic acid. *Trans*-cinnamic acid did not show virucidal activity but inhibited the viral replication cycle. In addition to this author has also reported the antiviral activity for quercetin and morin against *equid herpesvirus 1* (EHV-1)[43].

3.13 Anxiolytic activity

Sinapic acid shows anti-anxiety action and was confirmed by Adisakwattana *et al.* using elevated plus-maze apparatus (EPM) test and diazepam as a positive control. Anxiolytic like effects of Sinapic acid is mediated via $GABA_A$ receptors and potentiating Cl^- currents.



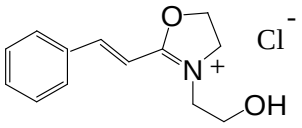
Sinnapic acid

Figure 19

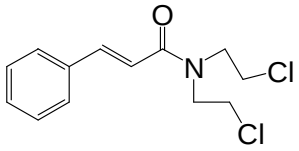
It is unlikely that it has side-effects that are severe enough to prevent its pharmacological activities alone or in combination with other agents. Moreover, sinapic acid may be viewed as a lead compound for the development of more selective anxiolytic agents[44].

3.14 Cytotoxic activity

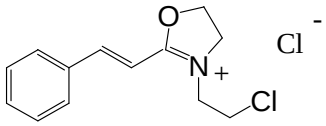
Cinnamoyl chloride, when converted into (2-hydroxyethyl)-oxazolinium chlorides (i), *N, N*-bis-(2-chloroethyl) amides (ii) and (2-chloroethyl)-oxazolinium chlorides (iii), show the cytotoxic activity[45].



i

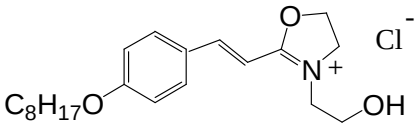


ii



iii

substitution at phenyl ring with electron donating group (methyl, methoxy) is having more potent than substitution with electron withdrawing group (chloro, nitro etc.)

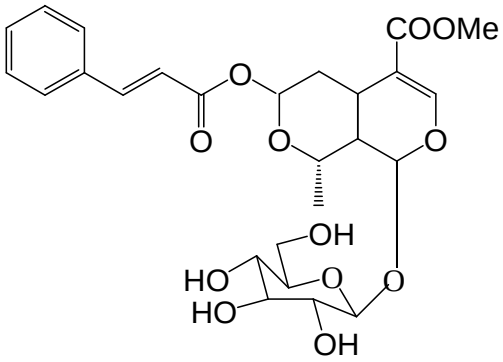


compound with 4-octyloxy-phenyl-substituent(most potent) as it is more lipophilic

Figure 20

3.15 Anti-inflammatory activity

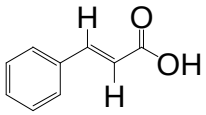
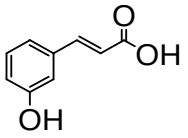
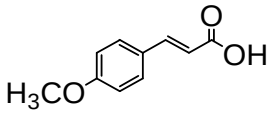
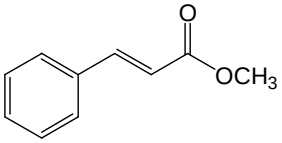
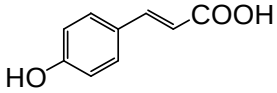
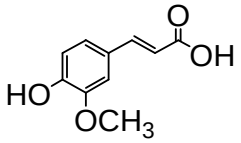
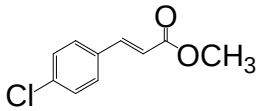
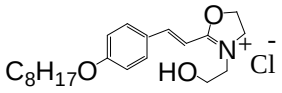
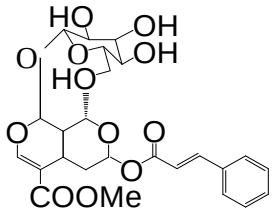
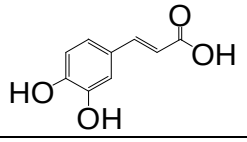
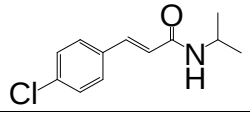
Morroniside cinnamic acid conjugate showed the anti-inflammatory activity on E-selectin mediated cell–cell adhesion. Compound 7-*O*-Cinnamoylmorroniside exhibited excellent anti-inflammatory activity and was observed to be a potent inhibitor of TNF-α-induced E-selectin expression[46].

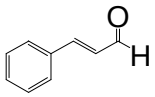
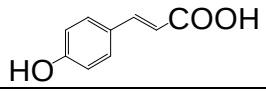
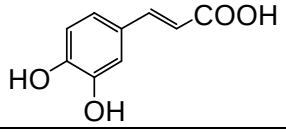
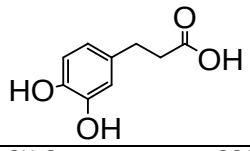
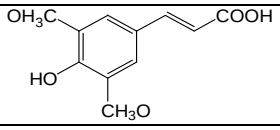
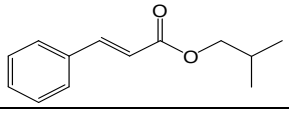
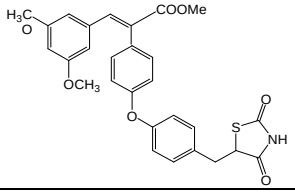


7-O-cinnamoylmorroniside

Figure 21

Table 2 Various derivatives of cinnamic acid along with different pharmacological activities and mechanism of action

S. No.	Cinnamic acid derivatives	Structure	Pharmacological activity	Mechanism of Action
1	*Trans*-cinnamic acid with cerulin		Anti TB, Antiviral	i) inhibits the transfer of mycolic acid ii) inhibited the viral replication cycle
2	*m*- hydroxy cinnamic acid		Antidiabetic activity	stimulating peripheral glucose uptake
3	*p*-methoxy cinnamic acid		Antidiabetic, Hepatoprotective, Antihyperglycemic, Sunscreen agent	PPAR agonistic activity, UV absorption property
4	Methyl cinnmate		As a flavoring agent and used in composition of soap.	-
5	4- Hydroxy cinnamic acid		Hepatoprotective	5-lipoxygenase inhibition activity
6	Ferulic acid		Antioxidant, Antidiabetic activity	inhibit LDL –oxidation, PPAR agonistic activity
7	Methyl-4-chlorocinnamate		Antifungal activity	Alteration in permeability of fungal cell membrane
8	Cinnamic acid derived oxazolinium ions		Cytotoxic activity	Act as alkylating agents
9	7-*O*-cinnamoyl morronniside		Anti-inflammatory activity	inhibitor of TNF-α-induced E-selectin expression
10	Caffeic acid		Antioxidant, Hepatoprotective	-
11	4- isopropyl cinnamate derivatives		Fungitoxic activity	

12	Cinnamaldehyde		Widely used as flavoring agent	-
13	*p*- coumaric acid		Antioxidant	inhibit LDL -oxidation
14	3, 4-dihydroxy cinnamic acid		Hepatoprotective	-
15	3, 4-di(OH)-hydrocinnamate		Anticholestrolemic activity	hepatic HMG-CoA reductase activity
16	Sinapic acid		Anxiolytic and Antioxidant	$GABA_A$ receptors and potentiating Cl^- currents
17	Isobutyl cinnamate		Antimicrobial activity	interaction (strictly related to the hydrophobic character of the molecules) on protein thiol groups.
18	Thiazolidine1, 4-dione substituted α-phenyl cinnamic acid derivatives		Antihyperglycemic activity	PPARγ agonist activity

3.16 UV rays absorbent

When cinnamic acid and *p*-methoxycinnamic acid intercalated into ZnAl layered double hydroxide by co-precipitation reaction, then it show UV rays absorption property. In addition to this methoxy substituted octyl -cinnamates is having excellent property of UV absorption that is why these are used in sunscreen composition.

CONCLUSION

Although Cinnamic acid derivatives has been prepared by various methods starting from Perkin reaction, but each mehods have its own loopholes like low yield, tedious synthetic procedure, long duration of reaction time etc. It is cleared from the chemistry part of this review that modern Heck reaction using various novel supported catalysts is important for the synthesis of CADs. The various positions of cinnamic acid derivatives are needed to be explored to achieve the clinically used drugs.

In this context, tabular depiction of various methods of synthesis and their pharmacological activities of CADs make the information more simple and give the ultimate blend of chemistry with the pharmacological activities.

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