REVIEW ARTICLE

CINNAMIC ACID AND ITS DERIVATIVES AS POTENTIAL ANTI-TUBERCULAR AGENTS

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ABSTRACT

Cinnamic acid is one of the naturally occurring chemical compounds present in various plants. It is obtained by both isolation from crude drugs, and by the synthetic route. In the last 10 years, many researchers have explored cinnamic acid for its pharmacological activities. Out of this anti-microbial and anti-tubercular activities are mainly focused in this review. Because of the unique structural features of cinnamic acid, various substitutions can be done. This review is an attempt to summarize the chemistry, reactions and pharmacological activities of cinnamic acid with a special focus on its anti-tubercular activity.

Keywords: Cinnamic acid, coumaric acid, antimicrobial, antitubercular, H37Rv, natural etc.

INTRODUCTION

Cinnamic acid is one of the naturally occurring chemical compounds. It comprises of ethylene carboxylic acid substituted on phenyl ring at C3 position. It is called cinnamic acid due to its natural presence in crude drugs from the cinnamon family. It occurs abundantly in cinnamon (*Cinnamon cassia)*, and balsam resins like storax. In plants, the cinnamic acid forms by deamination of phenylalanine. It is one of the intermediates in lignin biosynthesis[1-6]. It is generally synthesized by the famous reaction called as Knoevenagel condensation, by using benzaldehyde as prime substrate and malonic acid as reagent in presence of a weak nucleophilic agent[7-14]. It can be also synthesized by using benzaldehyde and acetyl chloride in presence of a strong base[15-19]. Cinnamic acid is isolated from cinnamon, which belongs to traditional Indian spices[20-22]. Cinnamic acid is used as starting material to prepare substituted cinnamic acid esters, also called cinnamates, which are used as flavouring agents and in perfumes. It is a precursor in the biosynthesis of aspartame sweeteners. It is also used for the enzymatic production of phenylalanine. The sodium salt of cinnamic acid is a corrosion inhibitor for metals. It is a commercial agent, used as brightener in zinc electroplating baths which are cyanide free. It is also used as, heat stabilizer for polyvinyl chlorides. It is also used as a cross-linking agent in the polymer industry[20]. This scaffold is explored for various diseases including antitubercular, antidiabetic, antioxidant, antimicrobial, hepatoprotective, CNS depressant, anticholesterolemic, antifungal, antimalarial, antiviral, anxiolytic, cytotoxic and anti-inflammatory activity[21]. The present review focuses on multiple synthetic routes exploring cinnamic acid scaffold as a basic structure, and its various pharmacological activities.

Cinnamic acid is a well-established scaffold in medicinal chemistry. It is white crystalline powder that melts at 133^{0}C. It is soluble in 100 parts of water and soluble in 10 parts of various organic solvents like ethanol, benzene, toluene, etc. Its freely soluble nature in organic solvents makes it a suitable choice for various chemical reactions. It exhibits a pH of 3.76 at 1.00 mM solution. Other physicochemical characteristics of cinnamic acid, and its alcohol and aldehyde derivatives are depicted in Table I [21-36].

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Other naturally occurring derivatives related to cinnamic acid

4-hydroxycinnamic acid

It is one of the important scaffolds isolated from the cinnamon family. It is also called coumaric acid. It occurs abundantly in the plant *Gnetum cleistostachyum, Gnetaceae* are widely available in Southeast Yunnan. Substitution of the hydroxyl group at the para position gives a wide scope of various substitutions. Its pH is 3.54 at 1.00 nM solution. Other physicochemical characteristics of 4-hydroxycinnamic acid, and its alcohol and aldehyde derivatives are depicted in Table II[23-44].

Caffeic acid

It is 3, 4-dihydroxy cinnamic acid. It is abundantly found in *Eucalyptus globulus, Fam, Myrtacae.* It undergoes various chemical reactions like coumaric acid. Other physicochemical characteristics of caffeic acid and its alcohol and aldehyde derivatives are depicted in Table III, respectively[45-51].

Ferulic Acid

It is 3-methoxy-4-hydroxycinnamic acid. It is named ferulic acid, as it is abundantly occuring in all varieties of *Ferula species.* It is an ether derivative of caffeic acid. The physicochemical properties of ferulic acid, and its alcohol and aldehyde derivatives are depicted in Table IV[52-56].

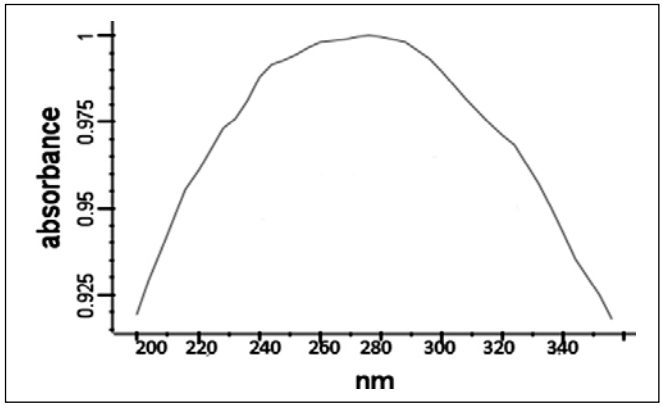


Fig. 1: UV- visible absorption spectrum of cinnamic acid[60]

Table I: Physicochemical properties of cinnamic acid, cinnamyl alcohol and cinnamaldehyde[21-36]

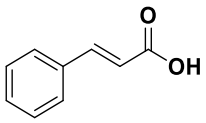
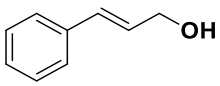
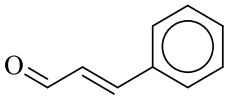
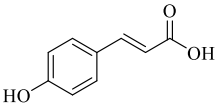
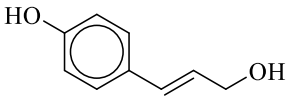
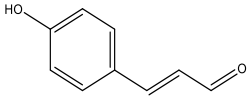
Sr. No.	Parameter	Inference		
		Cinnamic acid	Cinnamyl alcohol	Cinnamaldehyde
1	Structure			
2	Common name	Cinnamic acid, Phenylacrylic acid	Cinnamyl alcohol	Cinnamaldehyde
3	IUPAC name	(2*E*)-3-phenylprop-2-enoic acid	(2*E*)-3-phenylprop-2-en-1-ol	(2*E*)-3-phenylprop-2-enal
4	Chemical formula	$C_9H_8O_2$	$C_9H_{10}O$	C_9H_8O
5	Molecular weight	148.161 g mol^{-1}	134 g mol^{-1}	132.16 g mol^{-1}
6	Appearance	White monoclinic crystals	White crystalline solid	Yellow oily liquid
7	Melting point	133 ^{0}C	133 ^{0}C	–7.5 °C
8	Solubility in water	Slightly soluble (500 mg L^{-1})	Slightly soluble (500 mg L^{-1})	Slightly soluble[30] (1350 mg L^{-1})
9	Solubility in organic solvents	Soluble in ethanol and chloroform	Soluble in ethanol and chloroform	Soluble in ether and chloroform
10	pH	3.76	-	-
11	pKa	4.44	-	-
12	Primary natural source	Cinnamon bark *(Cinnamon cassia,* Lauraceae*)*	Cinnamon leaves *(Cinnamon cassia,* Lauraceae*)*	Cinnamon bark *(Cinnamon cassia,* Lauraceae*)*

Table II: Physicochemical properties of 4-hydroxy cinnamic acid, paracoumaryl alcohol and coumaric aldehyde[23-44]

Sr. No.	Parameter	Inference		
		p-coumaric acid	Paracoumaryl alcohol	coumaric aldehyde
1	Structure			
2	Common name	p-coumaric acid	paracoumaryl alcohol	coumaric aldehyde
3	IUPAC name	(2*E*)-3-(4-hydroxyphenyl) prop-2-enoic acid	4-[(*E*)-3-hydroxyprop-1-enyl] phenol	(*E*)-3-(4-hydroxyphenyl) acrylaldehyde
4	Chemical formula	$C_9H_8O_3$	$C_9H_{10}O_2$	$C_9H_8O_2$
5	Molecular weight	164.1580 g mol^{-1}	150.1745 g mol^{-1}	150.1745 g mol^{-1}
6	Appearance	Crystalline solid	Powder	Powder
7	Melting point	210 to 213°C	213.5 °C	213.5 °C
8	Solubility in water	Slightly soluble	Slightly soluble	Slightly soluble
9	Solubility in organic solvents	Very soluble in ethanol and diethyl ether	Very soluble in ethanol and diethyl ether	Very soluble in ethanol and diethyl ether
10	pH	3.54	-	-
11	pKa	3.89	-	-
12	Primary natural source	Lianas (*Gnetum cleistostachyum,* Gnetaceae)	Lianas (*Gnetum cleistostachyum,* Gnetaceae)	Lianas (*Gnetum cleistostachyum,* Gnetaceae)

Sinapic acid

It is 3,5-Dimethoxy-4- hydroxycinnamic acid. It is naturally occurring prominently in *Vitis vinifera, Vitaceae.* It is a dimethoxy derivative of coumaric acid. Physicochemical properties of sinapinic acid and its alcohol and aldehyde derivatives are depicted in Table V[57-59].

SPECTRAL CHARACTERIZATION OF CINNAMIC ACID

Cinnamic acid shows maximum absorption at 255 nm (Fig. 1)[60]. IR spectroscopy exhibits sharp peaks for a carboxylic group of acid at 1891 cm^{-1}, as it is affected by conjugated double bond present at C_α, also a sharp peak at 1628 cm^{-1} for conjugated double bond, and a

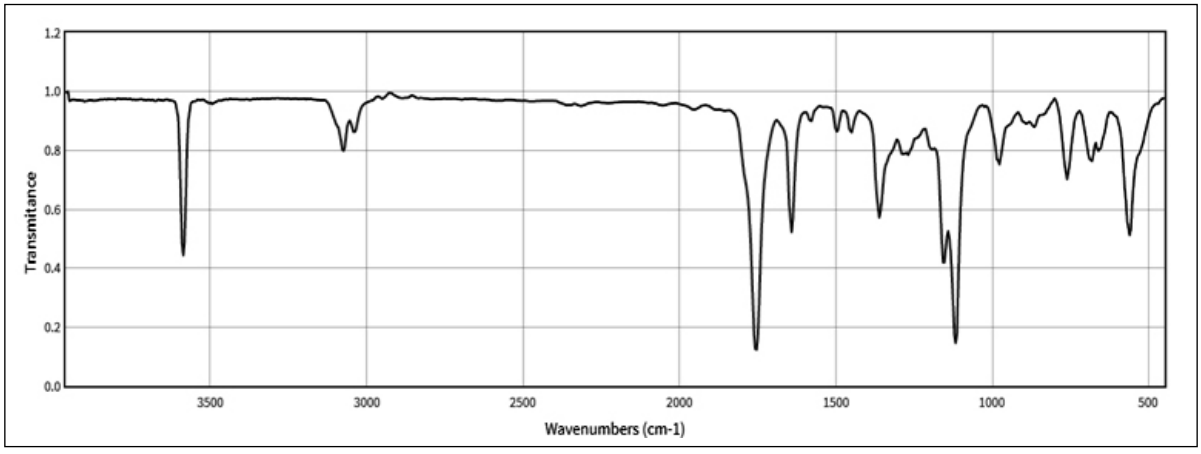
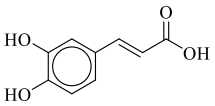
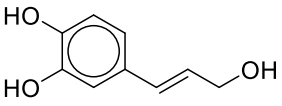
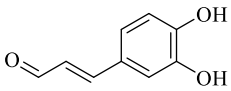


Fig. 2: IR spectrum of cinnamic acid[61]

Table III: Physicochemical properties of caffeic acid, caffeic alcohol and caffeic aldehyde and caffeic aldehyde[45-51]

Sr. No.	Parameter	Inference		
		Caffeic acid	Caffeyl alcohol	Caffeoyl aldehyde
1	Structure			
2	Common name	Caffeic acid	Caffeyl alcohol	Caffeoyl aldehyde
3	IUPAC name	(2*E*)-3-(3,4-dihydroxyphenyl) prop-2-enoic acid	4-[(1*E*)-3-hydroxy-1-propen-1-yl]-1,2-benzenediol	(*E*)-3-(3,4-dihydroxyphenyl) prop-2-enal
4	Chemical formula	$C_9H_8O_4$	$C_9H_{10}O_3$	$C_9H_8O_3$
5	Molecular weight	180.160 g mol^{-1}	164.160 g mol^{-1}	164.160 g mol^{-1}
6	Appearance	Yellow solid	Yellow solid	Yellow solid
7	Melting point	223 to 225 °C	225 to 227 °C	226 to 228 °C
8	Solubility in water	Slightly soluble in water, and easily soluble in hot water	Slightly soluble in water, and easily soluble in hot water	Slightly soluble in water, and easily soluble in hot water
9	Solubility in organic solvents	Ethanol, ethyl acetate	Ethanol, ethyl acetate	Ethanol, ethyl acetate
10	Primary natural source	Eucalyptus (*Gnetum cleistostachyum,* Gnetaceae)	Eucalyptus (*Gnetum cleistostachyum,* Gnetaceae)	Eucalyptus (*Gnetum cleistostachyum,* Gnetaceae)

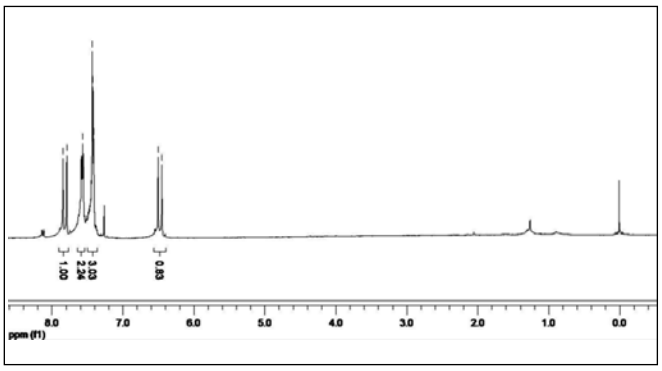


Fig. 3: ^{1}H NMR spectrum of cinnamic acid[62]

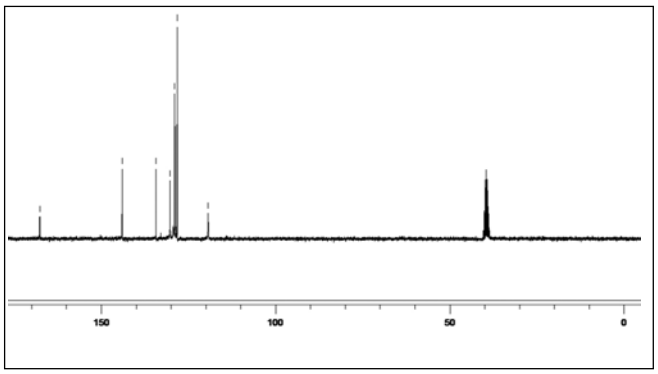


Fig. 4: ^{13}C NMR spectrum of cinnamic acid[62]

broad peak at 3453 cm^{-1} representing the acidic hydroxy group. Various bending vibrations from 700 to 900 cm^{-1} represent the presence of an aromatic region (Fig. 2)[61]. In the ^{1}H NMR analysis, compound exhibits, various multiple peaks in the range of 7.4 to 7.8 ppm which represents aromatic ring; doublet at 6.48 ppm represents double bond near the aromatic system (Fig. 3). 13C NMR exhibits aromatic protons in the range of 128 to 136 ppm. The carboxylic carbon shows a characteristic peak at 167 ppm. Vinylic carbon adjacent to the aromatic ring exhibits a characteristic peak at 144 ppm and vinylic carbon adjacent to the carboxylic group is exhibited at 119 ppm (Fig. 4)[62].

Biosynthetic Pathway of Phenylacrylic Acid and its Analogues

Cinnamic acid is derived from the deamination of phenylalanine by the enzyme Phenylalanine Ammonia Ligase (PAL). It is a crucial rate limiting compound in the

Table IV: Physicochemical properties of ferulic acid, coniferyl alcohol and coniferaldehyde[52-56]

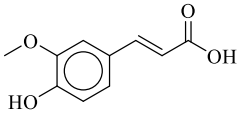
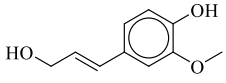
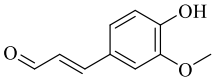
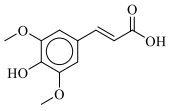
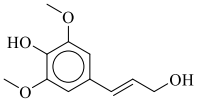
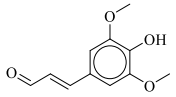
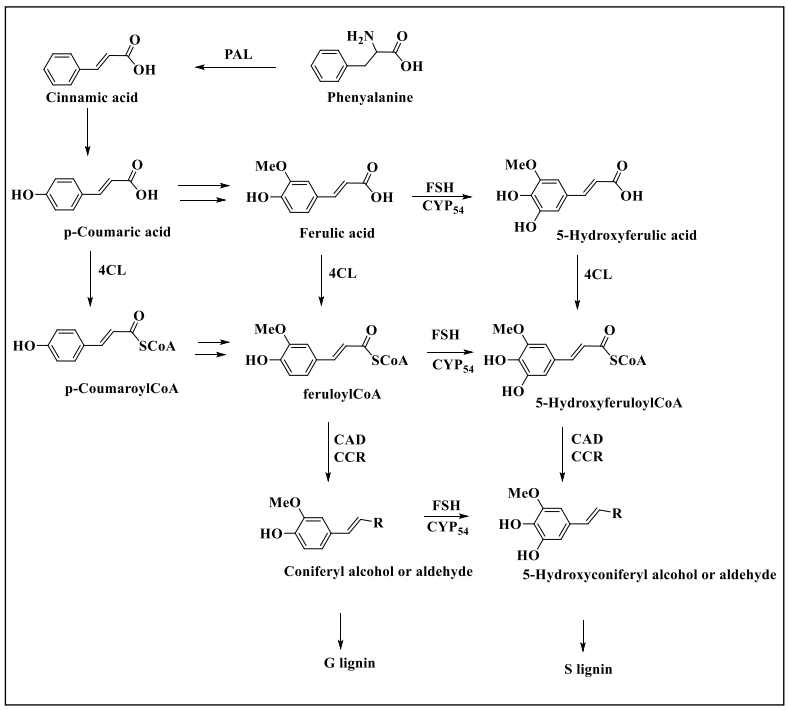
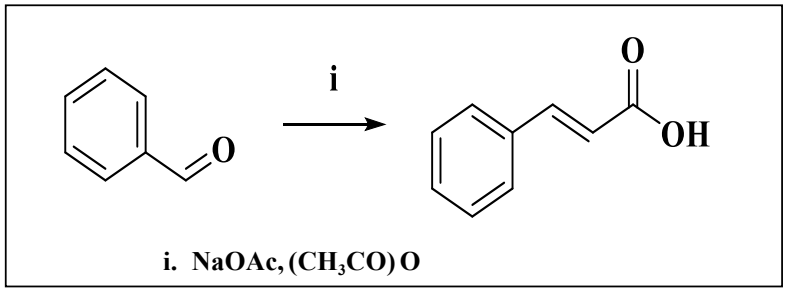
Sr. No.	Parameter	Inference		
		Ferulic acid	Coniferyl alcohol	Coniferaldehyde
1	Structure			
2	Common name	Ferulic acid	Coniferyl alcohol	Coniferaldehyde
3	IUPAC name	(2*E*)-3-(4-hydroxy-3-methoxyphenyl) prop-2-enoic acid	4-[(*E*)-3-hydroxyprop-1-enyl]-2-methoxyphenol	(*E*)-3-(4-hydroxy-3-methoxyphenyl) prop-2-enal
4	Chemical formula	$C_{10}H_{10}O_4$	$C_{10}H_{12}O_3$	$C_{10}H_{10}O_3$
5	Molecular weight	194.18 g mol^{-1}	180.203 g mol^{-1}	178.18 g mol^{-1}
6	Appearance	Slightly yellow powder	Colourless crystalline	White crystalline solid
7	Melting point	168-172 °C	74 °C (165 °F; 347 K)	80 °C
8	Solubility in water	Soluble	Insoluble	Insoluble
9	Solubility in organic solvents	Ethanol, DMSO, DMF	alcohol: moderately soluble	alcohol: moderately soluble
10	Primary natural source	Ferula (*Ferula alliaceae,* Umbelliferae)	Forsythia *(Forsythia intermedia)*	Cork oak tree *(Quercus suber,* Fagaceae*)*

Table V: Physicochemical properties of sinapic acid, sinapyl alcohol and sinapaldehyde[57-59]

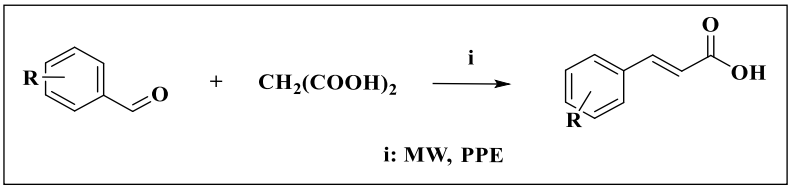
Sr. No.	Parameter	Inference		
		Sinapic acid	Sinapyl alcohol	Sinapaldehyde
1	Structure			
2	Common name	Sinapic acid	Sinapyl alcohol	Sinapaldehyde
3	IUPAC name	3-(4-hydroxy-3,5-dimethoxyphenyl) prop-2-enoic acid	4-(3-hydroxyprop-1-enyl)-2,6-dimethoxyphenol	3-(4-Hydroxy-3,5-dimethoxyphenyl) prop-2-enal
4	Chemical formula	$C_{11}H_{12}O_5$	$C_{11}H_{14}O_4$	$C_{11}H_{12}O_4$
5	Molecular weight	224.21 g mol^{-1}	210.226 g mol^{-1}	208.213 $gmol^{-1}$
6	Appearance	Crystalline solid	Colourless solid	-
7	Melting point	203 to 205 °C	61 to 65 °C	104 to 106 °C
8	Solubility in water	Sparingly soluble in aqueous buffer	Slightly soluble	Insoluble
9	Solubility in organic solvents	DMSO	-	-
10	Primary natural source	Grapes (*Vitis vinifera,* Vitaceae)	Rapeseed *(Brassica napus,* Brassicaceae*)*	Flowers of senra *(Senra incana,* Malvaceac*)*



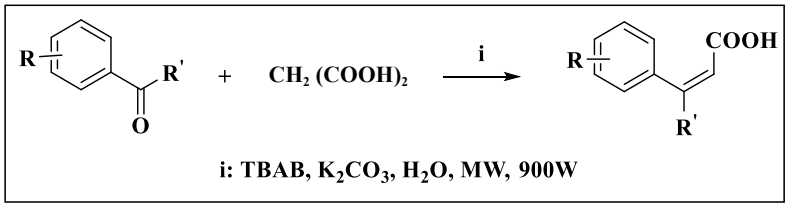
Scheme 1: Biosynthesis of cinnamic acid and its derivatives



Scheme 2: Perkin reaction by conventional synthesis



Scheme 3: Perkin reaction by microwave radiation



Scheme 4: Knoevenagel condensation microwave method

biosynthesis of following naturally occurring biological products:

- Lignan
- Flavonoids
- Isoflavonoids
- Coumarins
- Aurones
- Stilbenes
- Catechin
- Phenylpropanoids

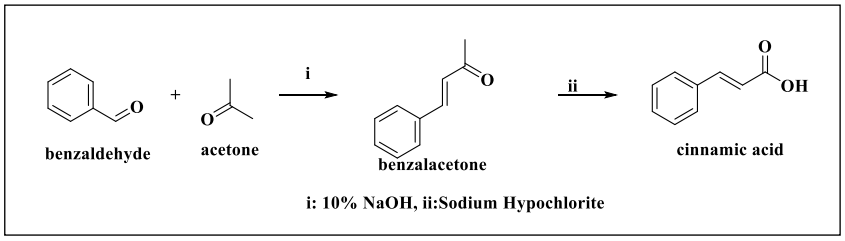
A study was performed on *Photorhabdus luminescens.* It was observed that cinnamic acid autoinduces its own biosynthesis via activation of the enzyme Hca dioxygenase (Scheme 1)[63].

SYNTHESIS OF CINNAMIC ACID

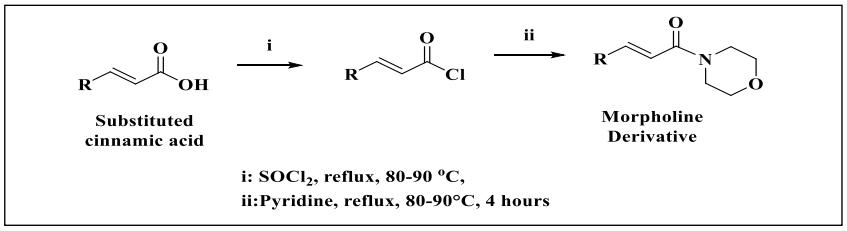
The cinnamic acid is synthesized by various methods, commercially it is synthesized using the Perkin reaction. It can be also synthesized by the Knoevenagel condensation reaction. Some of the synthetic reactions are mentioned below.

Perkin reaction

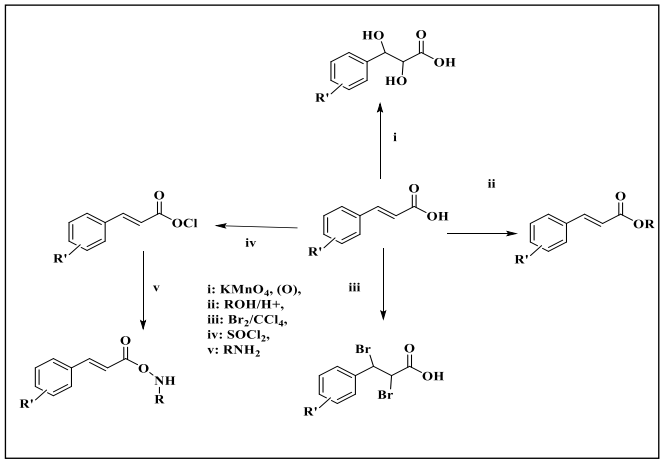
The process involves the condensation of benzaldehyde with acetic anhydride under catalysis of anhydrous alkali acetate. Transfer 0.19 moles of benzaldehyde, 0.29 moles of acetic anhydride and 0.12 moles of fused and finely-powdered CH_3COOK in a dry RBF, equip the reflux condenser with $CaCl_2$ (or cotton wool) guard tube. Reflux the reaction at 180^0 C for 4 h. Transfer the hot reaction mixture to 100 mL of hot water, and add a saturated, Na_2CO_3 solution to the mixture with continuous stirring. Remove residual benzaldehyde by steam distillation and filter off the resinous byproduct. Acidify the filtrate with concentrated HCl acid with continuous shaking till carbon dioxide ceases. Reduce the temperature of reaction mixture and filter the product. Recrystallise using hot water (Scheme 2)[64-65]. The reaction performed using the microwave assisted method by using (PPE) polyphosphate ester as a catalyst, it reduces the reflux time by 60 fold (Scheme 3)[66].



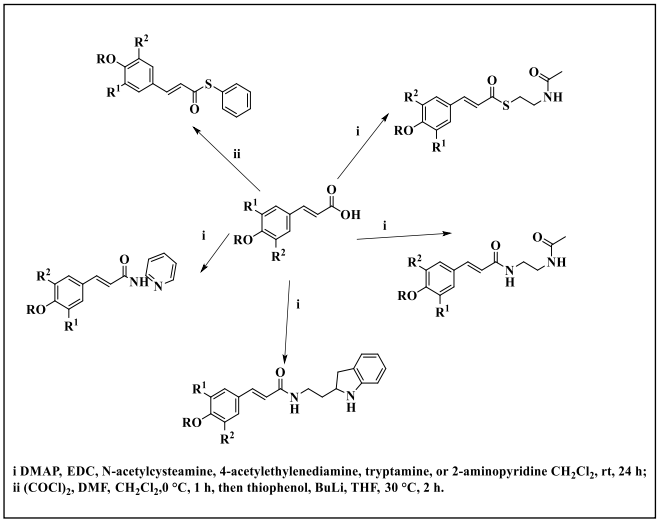
Scheme 5: Cinnamic acid synthesis using condensation of acetone and benzaldehyde



Scheme 6: Synthesis of morpholine derivative



Scheme 7: Synthesis of substituted phenyl acrylic acids, esters and amides



Scheme 8: Synthesis of pseudo cinnamates

Knoevenagel condensation

Prepare an equimolar mixture of benzaldehyde and malonic acid in water. To the mixture, add 2.5 mmol of TBAB (tetra-*n*-butylammonium bromide) and 2.5 mmol of K_2CO_3. Stir the reaction mixture at RT until a uniform solution forms. Irradiate the mixture at 900 Watts in the microwave oven for 5 minutes. Cool the reaction mixture, and acidify with dilute HCl. Filter and recrystallise using ethanol (Scheme 4)[67].

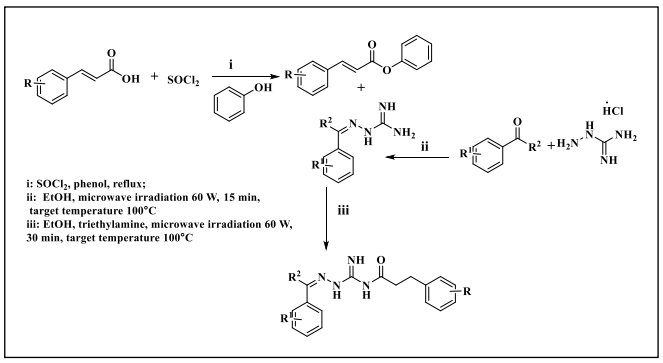
Synthesis by condensation of benzaldehyde and acetone

It is one of the commercial methods for the synthesis of cinnamic acid. The reaction is performed at a low temperature. A three-necked RBF(Round bottom flask) is equipped with a dropping funnel and thermometer blanketed with ice and salt mixture. A mixture of 0.12 moles of benzaldehyde and 0.20 moles of acetone is introduced in the RBF. 1% sodium hydroxide solution is added dropwise to the solution. Continue stirring for 20 minutes. Kept the reaction mixture still for 48 h. Then neutralise the reaction with 20% acetic acid. Distil the excess acetone. Filter the mixture and collect the benzyl-acetone crystals to a new three-necked RBF, transfer benzyl-acetone and sodium hypochlorite solution. Stir the reaction mixture for 6 h. Keep the reaction mixture still overnight. Separate the chloroform formed in the reaction and precipitate cinnamic acid by adding 20 % sulphuric acid (Scheme 5)[68].

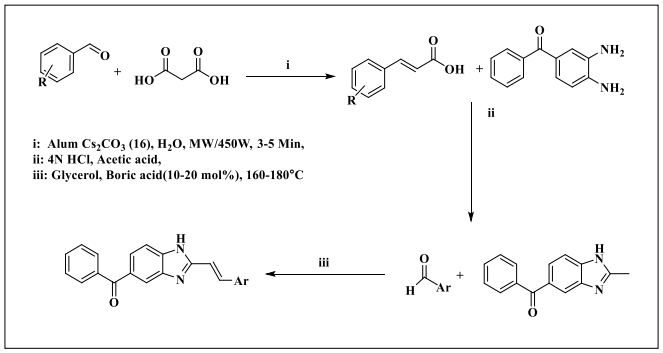
PHARMACOLOGICAL PROFILE OF CINNAMIC ACID

Cinnamic acid is a versatile scaffold, usually present in a combined form with various other chemically important scaffolds. Its pharmacological usage ranges from cosmeceuticals to CNS active agents. Its pharmacological activities can be classified as follows;

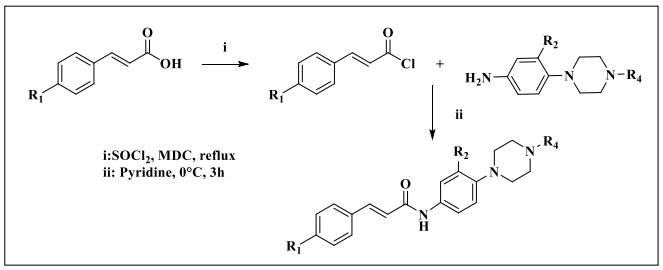
- Cosmeceuticals
- Antioxidant
- Antimicrobial
- Hepatoprotective
- Cardiovascular
- Action on CNS
- Antihyperglycemic
- Anti-tubercular



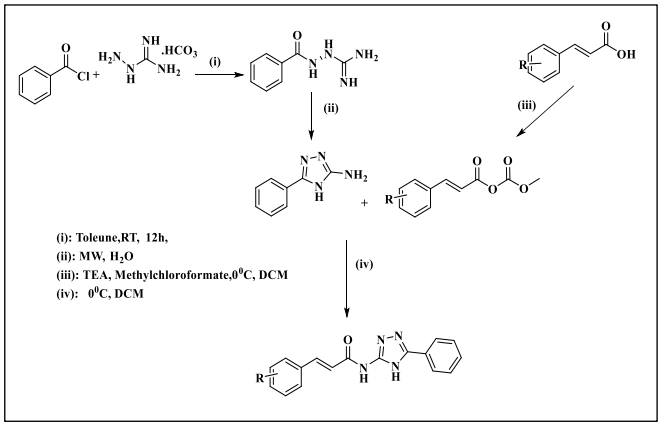
Scheme 9: Synthesis of phenyl acrylamide derivatives



Scheme 10: Synthesis of 2-heterostyrylbenzimidazoles



Scheme 11: Synthesis of *N*-[4-(piperazin-1-yl) phenyl] cinnamamide derivatives



Scheme 12: Synthetic route for triazole substituted cinnamamide derivatives

Cosmeceuticals: Fragrance and dermatological products

Cinnamic acid and cinnamic acid esters are used as fragrance materials in various pharmacological products like fine fragrances, shampoos, toilet soaps, body lotions, face creams, fragrance creams, antiperspirants, shower gel, hair sprays and many more. A detailed toxicity study on cinnamic acid was performed by Letizia *et. al.* in 2005. It was performed on mice, rabbits and then on human skin. Results indicated that cinnamic acid is a safe and non-irritant cosmeceutical ingredient in acute quantity, and its antioxidant property enhances the quality of the cosmetics[69].

Antioxidant and antimicrobial activity

In presence of vinyl fragments, cinnamic acid exhibits high antioxidant activity. Due to this property, it can be considered a potent candidate for lipid peroxidation in the cellular membrane. Substituted cinnamic acids like 3,4-dihydroxy phenyl acrylic acid (caffeic acid), 4-hydroxy-3-methoxyphenyl acrylic acid (ferulic acid) and their phenyl esters exhibit potent antioxidant activity and anti-tubercular activity[70-73].

Jiang *et. al.*[66] performed antioxidant activity of hydroxycinnamic acid derivatives by the DPPH assay method, in which rosmarinic acid exhibited the highest antioxidant activity 20 µg mL^{-1}. Gangadhara *et. al.* synthesized morpholine substituted cinnamic acid derivatives and screened for antioxidant and antimicrobial activity, out of which dimethoxy and trimethoxy phenyl acrylic acid-containing compounds exhibited potent radical scavenging activity against DPPH, and potent antibacterial activity, whereas, chloro-cinnamic acid exhibited potent antifungal activity (scheme 6)[74-76].

Balasubramanian *et. al.* developed novel series of phenyl acrylic acid esters, amides and aryl analogues. Out of 32 derivatives synthesized compounds containing isobutyl, dibromo substitutions exhibited potent antimicrobial activity against *C. albicans, A. niger, B. subtilis, E. coli* and *S. aureus* (scheme 7)[77].

Hepatoprotective activity

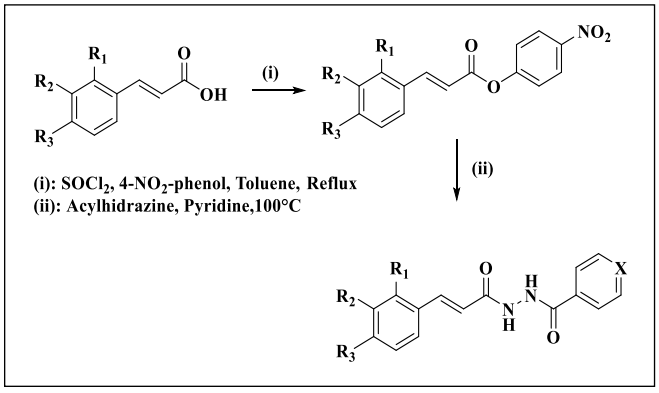
Alvarez *et. al.* performed hepatoprotective activity of phenyl acetic acid and its hydroxy-substituted analogues on CCl_4 derived liver damaged male Wistar rats. Out of 5 derivatives tested, caffeic acid was more hepatoprotective. The structural activity study suggested the presence of aryl hydroxyl groups which provide hepatoprotective activity[78-80].

Cardiovascular activity

Mortan *et. al.* have studied the effect of dietary supplements containing polyphenolic acids on the cardiovascular system. The study suggested that consumption of fruits rich in cinnamic, coumaric, caffeic, gallic, ellagic acids and their esters decreases the risk of cardiovascular diseases[81-83].

Action on CNS

Yabe *et. al.* investigated pharmacological action of cinnamic acid derivatives on the proliferation of neural stem cells, which are also called progenitor cells. The activity was tested *in vitro* on cells isolated telencephalon of Wistar rats at E14.5 and *in vivo* on stress-induced adult male ddY mice. Authors have given the first evidence that ferulic acid increases the neural stem cells proliferation. The results give a new pharmacophore for the treatment of CNS disorders like depression[84-88].



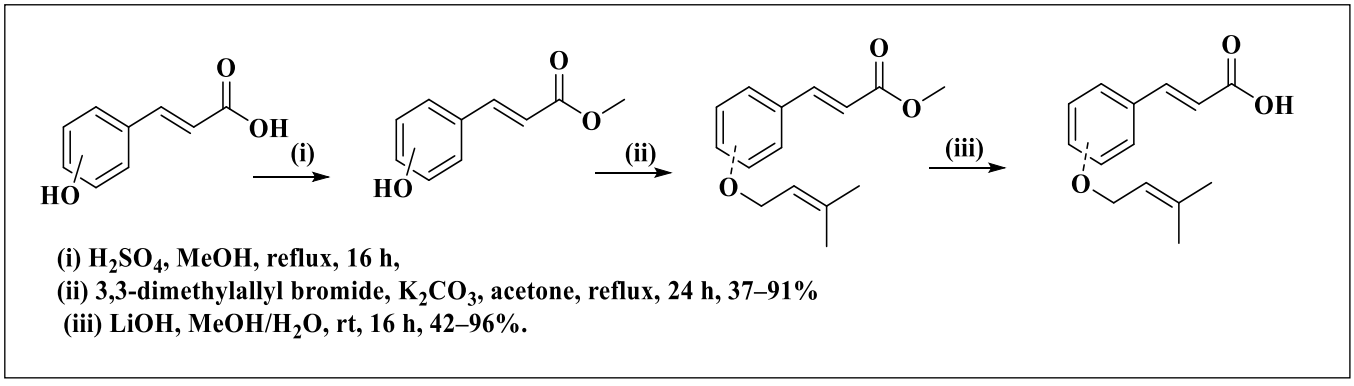
Scheme 13: Scheme of synthesis of heterocyclic acid substituted analogues

Antihyperglycemic activity

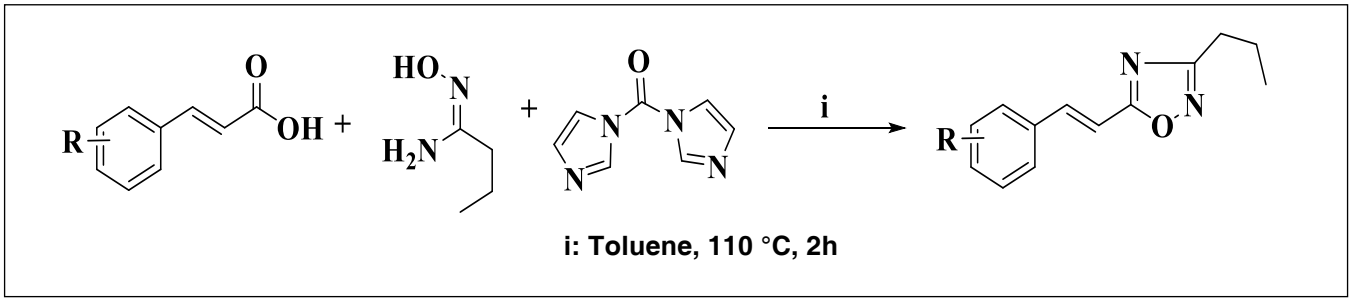
Adisakwattana *et. al.* studied the modulation of insulin secretion by using cinnamic acid analogues. It was observed that potential stimulation of insulin secretion from pancreatic β-cells was done excellently by ferulic acid and p-methoxy cinnamic acid. It can be predicted that dietary intake of these compounds can be a feasible therapeutic strategy for treatment as well as preventive measure for patients with type 2 diabetes mellitus[89-92].

Anti-tubercular activity

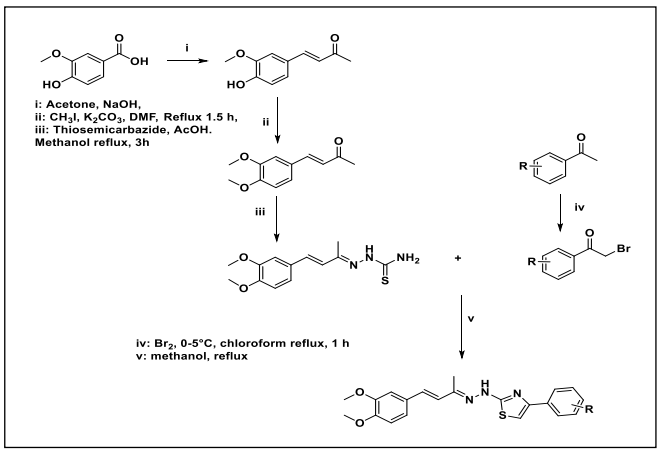
Cinnamic acid derivatives are reported for antibacterial and antimicrobial properties. Its reported activity against DNA gyrase prompted researchers to explore its activity against mycobacteria. Yoya *et. al.* have synthesized pseudo-cinnamates containing nitrogen and/or sulphur and heterocyclic substitutions in the carboxylic functional group. Acrylamide derivatives have exhibited good antitubercular activity (Scheme 8)[71-73,93-99].



Scheme 14: Scheme of synthesis prenylation of the structural isomers of coumaric acid



Scheme 15: Synthetic route of oxadiazole substituted cinnamic acid analogues



Scheme 16: Synthesis of styryl hydrazine thiazole

Ranjeet *et. al.* synthesised 20 phenyl acrylamide derivatives incorporating cinnamic acid with guanyl hydrazones by microwave-assisted methods. The compounds were screened for antitubercular activity by using REMA analysis (resazurin microtiter plate assay) against *Mycobacterium tuberculosis* H37Rv[96-99,114]. Dimethoxy benzylidene substituted acrylamide exhibited 6.49 IM with acceptable safety parameters in VERO cell lines (Scheme 9)[95].

Mohan *et. al*. developed a group of new 2-heterostyrylbenzimidazole derivatives, cyclisation of cinnamic acid, (3,4-diamino phenyl) (phenyl)methanone and glycerol were in high amount. These compounds were screened against *M. tuberculosis* H37Rv and MIC was found to be in acceptable range. Out of them, *N*-[4-(piperazin-1-yl) phenyl] cinnamamide bearing derivative exhibited promising inhibition to the *M. tuberculosis* H37Rv strain (Scheme 10)[100].

Ravikumar *et. al.* synthesised analogues of *N*-[4-(piperazin-1-yl) phenyl] cinnamamide. The scheme was developed using hybridization approach, the part C was bridged by carbamate and amide functionality which improves biophysical properties and regulates ADME behaviour. The optimisation at Part C for exploring SAR of antimycobacterial cinnamamide was conducted. Total 52 compounds were screened for their antimycobacterial activity against *M. tuberculosis* using REMA analysis. Trifluoromethyl substituted compound exerted good antimycobacterial activity and piperazinyl substituted cinnamamide exhibits promising antiTB activity (3.125 mg mL^{-1}) (Scheme 11)[100].

Manoj *et. al.* developed series of triazole substituted cinnamamides as FAS II inhibitors mimetics. *In silico* optimisation based on Topliss operational method was undertaken in further research work. On the basis of *in silico* research work, the series as developed was screened for antitubercular activity by REMA analysis. All compounds had MIC in range of 5- 95 µg mL^{-1} as well as good safety profiles (Scheme 12)[101-102]. Samir *et. al.* developed a series of heterocyclic acid substituted trans cinnamic acid analogues by molecular hybridization approach. Antimycobacterial activity of ether and nitro substituted compounds was found in range of 3.2 to 12.5 lg mL^{-1}, which can be a potential scaffold for MDR tuberculosis (Scheme 13)[103].

Jouan *et. al.* functionalised various hydroxycinnamic acids by adding amide and 5 membered heterocyclic rings. The starting materials, intermediates and final products were screened for antiTB action against *M. tuberculosis* H37Rv by SPOTi (spot culture growth inhibition assay). Out of all substituted compounds, 2-coumaryl derivatives exhibited potential anti-tubercular activity (Scheme 14)[104].

Abhay *et. al.* synthesized oxadiazole based cinnamates. The series was developed by reaction with amidoximes. The compounds were screened *in vitro* against *M. tuberculosis* H37Ra. Out of them 4-carboxyl substituted derivatives exhibited potential antitubercular activity (Scheme 15)[105].

Girish *et. al.* developed dehydrozingerone (DZG) inspired styryl hydrazine thiazole hybrids (Scheme 16). AntiTb activity was evaluated against *M. tuberculosis* H37Rv strain. Amongst various substituted compounds, nitro substituted hybrids had significant antimycobacterial effect. Further, comparative studies on hypoxic and regular oxygenated strains of mycobacteria resistant to isoniazid and rifampicin exhibited considerable antimycobacterial activity. The presence of electron-releasing groups on the phenyl ring from thiazole ring has a direct correlation with pharmacological effect. The study comments on development of DZG clubbed thiazole hydrazine hybrids as prospective antimycobacterial scaffold[106].

CONCLUSION

Cinnamic acid is one of the privileged scaffolds in the medicinal world, it can be isolated from natural sources and can be prepared using synthetic methods commercially. The naturally occurring hydroxy and methoxy substituted cinnamic acid exhibit potential antioxidant, antifungal, antibacterial, antidiabetic, hepatoprotective and antitubercular activities[107-110]. The cinnamic acid-derived ethers, esters, amines, amides, polycyclic and heterocyclic compounds exhibit multiple pharmacological activities and especially antitubercular activity is interesting and should be explored in the near future[111-114].

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