Indo Global Journal of Pharmaceutical Sciences, 2021; 11(2): 120-129

INDO GLOBAL JOURNAL OF PHARMACEUTICAL SCIENCES
ISSN 2249- 1023

A Review: p-Coumaric Acid, A Medicinally Important Phenolic Acid Moiety

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Received: 17.01.2020
Accepted: 25.11.2020
Published: 15.04.2021
Keywords
Hydroxycinnamic acids, Phenolic acids, p-Coumaric acid, Antioxidant, Anticancer, Antimicrobial, Antidiabetic.

ABSTRACT: p-Coumaric acid is an ubiquitous natural phenolic phytochemical mainly exist in two forms trans- and cis-p-coumaric acid. It occurs in free as well as in bound forms, is a common dietary polyphenol distributed in fruits, vegetables and cereals. It was considered as a powerful antioxidant and widely reported to demonstrate antimicrobial, antifungal, anticancer, antidiabetic, anti-inflammatory, antiviral, antihypertensive, antiulcer, antiprotozoal and antimelanogenic. This review contains the fundamental information about biological potential, common pathway utilized, SAR, wide source of p-coumaric acid and evidence of their role in disease prevention.

Cite this article as: Sharma, S.; Khatkar, A.; Kakkar, S. A Review: p-Coumaric Acid, A Medicinally Important Phenolic Acid Moiety. Indo Global J. Pharm. Sci., 2021; 11(2): 120-129. **DOI**: http://doi.org/10.35652/IGJPS.2021.112007 .

INTRODUCTION

Natural remedies are considered to be effective and safe. Plants are the rich sources of flavonoids, polytosterols, ellagic acid and gallotannins. Plants are also rich source of hypolipidemic, agents such as phenolic acids and other related polyphenols. Therefore, most of the efforts are now focused on search of potentially useful natural products (1). Phenolic acids are simple molecules and easily absorbed by the human system and are widely found in the plant kingdom (2). They are secondary plant metabolites and a considerable interest has developed in last few years due to their health benefits (3). These acids are easily available in nature in their free and bound forms (4). Phenolic acid can be distinguished into two classes; one is hydroxybenzoic acid viz. gentisic, gallic, salicylic, vanillic and second is hydroxycinnamic acid viz. *p*-coumaric, ferulic, caffeic, sinapic (5). *p*-Coumaric acid exists as a natural phenolic acid in wine, grapes (2) oat groats, hulls (6), brown rice (7), tomatoes (8), coffee (9), jucara fruit (10), grapevine (11), strawberry, blackberry, blueberry (12), bamboo shoot (13), peanut (14) and in morus alba (15). *p*-Coumaric acid is commonly hydroxycinnamic acids which frequently occurs in foods, fruit juices and vegetables (16) as a simple esters with glucose or quinic acid (3). Being a natural compound it is produced by plants as a precursor of cumaroyl –AHL (N-acyl-homoserine lactone) and as a phenylpropanoid intermediate of the lignin pathway (17). The hydroxycinnamic acids approaching a wide variety of chemically diverse phenylpropanoid derivatives with wide variety of biological activities (18). Naturally occurring phenolic acids are of particular interest because of their potential biological properties (19) such as antimicrobial (20), antioxidant (10), anticancer (15), antidiabetic (21), anti-inflammatory (22), antihypertensive (13), antimelanogenic (23) and antiulcer (24). *p*-Coumaric acid is found almost in all food groups viz. beverages (coffee, tea), fruits (berries, grapes), cereals (barley, corn, oats), and vegetables (celery, tomato) (25). Phenolic acids are purported to have numerous health benefits (3). This literature provides the information that correlates high fruit and vegetable diet with maintenance of health and prevention of diseases (26). The present review contains the fundamental information about biological potential, common pathway utilized and SAR (structure activity relationship) of *p*-coumaric acid. From the literature, it was found that various types of review articles have been written on *p*-Coumaric acid which are focused on their pharmacological significance in medicinal filed. However, the current review concentrates on the diverse biological potential of *p*-coumaric acid and its derivatives in the new millennium and no such extensive review article is reported recently.

1. SOURCES OF *P*-COUMARIC ACID

In this review we have mentioned versatile sources of the *p*-coumaric acid. Details are presented in **Table 1**.

Table 1. Various sources of *p*-coumaric acid.

S.no	Scientific name (family)	PartUsed	Pharmacological activity	References
1.	*Apis mellifera*, (Apidae)	Bee hives	Antimicrobial	27
2.	*Coffea arabica L.* (Rubiaceae)	Roasted coffee beans	Antimicrobial	9
3.	*Citrus grandis* (Rutaceae)	Fresh fruits	Antimicrobial and Antioxidant	28
4.	*Plantago major* (Plantaginaceae)	Leaf	Antimicrobial and Antioxidant	29
5.	*Cydonia oblonga Miller* (Rosaceae)	Pulp and peel	Antimicrobial and Antioxidant	30
6.	*Melipona scutellaris* (Apidae)	Wax, soil and resin	Anticancer	31
7.	*Morus alba* (Moraceae)	Fruit	Anticancer	15
8.	*Euterpe edulis* (Arecaceae)	Fruit	Antioxidant	10
9.	*Vitis vinifera* (Vitaceae)	Leaf and root	Antioxidant	11
10.	*Arachis hypogea* (Fabaceae)	Kernel flour	Antioxidant	14
11.	*Fragaria ananassa* (Rosaceae)	Fruit	Antioxidant	12
12.	*Vaccinium virgatum* (Ericaceae)	Fruit	Antioxidant and Antinociceptive	12
13.	*Rubus laciniatus* (Rosaceae)	Fruit	Antioxidant	12
14.	*Vaccinium myrtillus* (Ericaceae)	Fruit & leaf	Anti-inflammatory and Antidiabetic	32
15.	*Centratherum anthelminticum* (Asteraceae)	Seeds	Anti-diabetic, Antimicrobial and Antioxidant	33
16.	*Vigna umbellate* (Fabaceae)	Beans	Antidiabetic	21
17.	*Solanum tuberosum* (solanaceae)	Potatoes	Antioxidant	3
18.	*Brassica oleracea* (Brassicaceae)	Vegetable	Antioxidant	3
19.	*Brassica oleraceavar.botrytis* (Brassicaceae)	Vegetable	Antioxidant	3
21.	*Avena sativa* (Poaceae)	Seeds or grains	Antioxidant	6
22.	*Oryza sativa* (Poaceae)	Grains	Anticancer	1
23.	*Lycopersicum esculentum* (Solanaceae)	Fruit and leaf	Antioxidant and Antibacterial	8
24.	*Allium sativum* (Amaryllidaceae)	Garlic clove	Antioxidant, Anti-inflammatory and Antimicrobial	17
26.	*Malus domestica* (Rosaceae)	Peel and pulp	Antioxidant	34
27.	*Pyrus communis* (Rosaceae)	Peel and pulp	Antioxidant	34
28.	*Cantharellus cibarius* (Cantharellaceae)	Fruit	Antioxidant	35
29.	*Caucalis platycarpos* (Apiaceae)	Above ground parts of the plant	Antitumor	4
30.	Young monovarietal wine	Red wine	Antihypertensive and Antioxidant	36
31.	*Phyllostachys pubescen (Poaceae)*	Young stems	Antioxidant, Antihypertensive and Antibacterial	13
32.	*Baccharis dracunculifolia* (Asteraceae)	Whole Plants	Anti-ulcer	24

2. PATHWAY OF THE ACID

Generally the biosynthesis (**Fig 1**) is carried out by the enzyme called phenylalanine ammonia-lyase (PAL) which catalyses the reaction by deamination of l-alanine to *trans*-cinnamic acid (phenylpropenoic acid). Further reaction process is controlled by cinnamate 4-hydroxylase (C4H), which converts the *trans*-cinnamic acid to *p*-coumaric acid (18; 37).

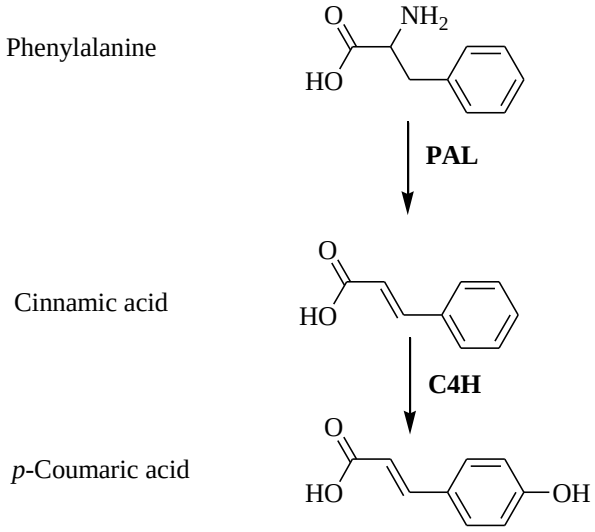
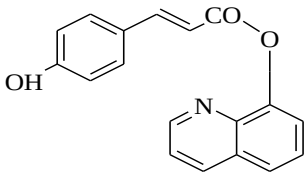


Fig 1: **Biosynthesis of *p*-coumaric acid**

3. DIFFERENT PHARMACOLOGICAL ACTIVITIES OF *P*-COUMARIC ACID

3.1 Antimicrobial potential

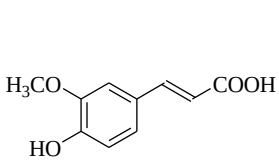
In this study, Khatkar *et al.,* synthesized new *p*-coumaric acid derivatives and evaluated for antimicrobial activity by tube dilution method. Physicochemical parameters were also evaluated. The entire synthesized series were evaluated for the activity against Gram negative and Gram positive bacteria. Among all the compounds, compound **1** was found to be most active (pMICam = 1.73 µM/ml). It was found that anilides having electron withdrawing substituents, esters and amides of *p*-coumaric acid having bulky aromatic groups were more potent than others. Antimicrobial potential of *p*-coumaric acid derivative was further subjected for QSAR studies. (20)



(*E*)-quinolin-8-ylmethyl 3-(4-hydroxyphenyl)acrylate

1

Martínez-Tomé *et al.* evaluated the antimicrobial potential of coffee (*Kenya, Ethiopia, decaffeinated Colombia* and *Coffea arabica*) on pathogenic bacteria such as *S. choleraesius, E. coli, S. aureus, L. monocytogenes, P. aeruginosa* and *E. faecalis.* Coffee contains mixture of phenolic compound viz. *p*-coumaric, ferulic (**2**) and chlorogenic acids (**3**), these three might be responsible for its activity. Microbiological activity of coffee was carried out by using disc diffusion method and activity was measured in mm of diameter by inhibition zone. Chloramphenicol was used as standard drug. Espresso Colombia coffee was found to have superior antimicrobial activity with the difference of ($p<0.05$) than filter and Italian coffee. (9)



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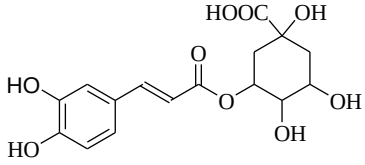

3

In this study, Mokbel *et al.* evaluated the antimicrobial properties of (*Citrus grandis* Osbeck) pummelo fruits by using disc diffusion method. Methanol extract was partitioned off with ethyl acetate (EtOAc) to give basic, acidic, neutral, and phenolic fractions. *p*-Coumaric, caffeic acid (**4**), diasaccharide and monosaccharides were isolated from these fractions. Other compounds like linoleic acid methyl ester, oil buntan compound, meranzin hydrate, nomili, limonin, β-sitosterol, and sigma sterol were isolated from extract and analysed by NMR.

p-Coumaric acid was considered as chief compound which was responsible for maximum antibacterial potential. The inhibitory zone of tested bacteria is shown in **Table 2**. (28)

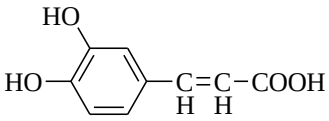

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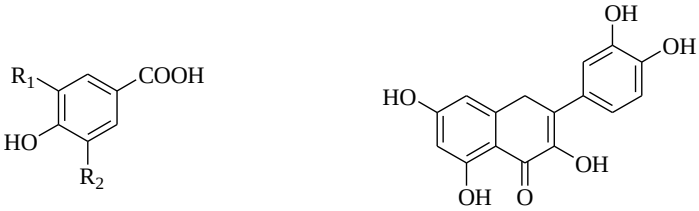
Table 2. Growth inhibition of *p*-coumaric acid

Growth inhibition (mm)			
Gram positive bacteria		**Gram negative bacteria**	
Staphylococcus aureus	13.1 ± 0.3	*Salmonella enteritidis*	12.8± 0.5
Bacillus cereus	15.1± 0.3	*Escherichia coli*	11.6± 0.4
Bacillus subtilis	14.5± 0.1		

Papadopoulou *et al.* reported antimicrobial activity of red and white wine and evaluated their activity against pathogenic strains *E. coli*, *C. albicans* and *S. aureus*, and activity was performed by using agar well diffusion method. Phenolic composition of tested red and white wine extract such as *p*-coumaric acid, ferulic **(2),** syringic **(8)**, vanillic **(7),** chlorogenic **(3)**, caffeic **(4),** *p*-hydroxy-benzoic **(5)** and protocatechuic acid **(6)** showed inhibitory properties towards microbial strains. Other phenolic compound like hydroxytyrosol, resveratrol, and quercetin **(9)** were also found to have antimicrobial activity. All the tested extracts were found to be active against *S. aureus* and less effective against *C. albicans* and *E. coli.* Tested wine extracts discovered that some phenolic components have claim for inhibiting the growth of pathogens (**Fig 2**). (38)



R_1=H, R_2=H: *p*-hydroxybenzoic acid **(5)**

R_1= R_2=OCH_3: Syringic acid **(8)**

R_1=H, R_2=OH: Protocatechuic acid **(6)**

R_1= R_2=OH: Gallic acid **(8a)**

R_1=OCH_3, R_2=H: Vanillic acid**(7)**

Quercetin **(9)**

Fig 2: Phenolic components responsible for inhibiting the growth of pathogens

3.2 Anticancer potential

Da Cunha *et al.* investigated the antiproliferative action of ethanolic fraction of geopropolis (EFGP). *Melipona scutellaris* (stingless bee) was evaluated for its antiproliferative activity. Extract contains *p*-coumaric acid which was confirmed by UV and RP-HPLC. EFGP have shown selectivity in approaches to human cancer cell lines at lower concentration. The extract showed excessive inhibition against melanoma and ovarian cancer lines. The total growth of inhibition is shown in **Table 3**. (31)

Table 3. Total growth inhibition.

Cell lines	Total growth inhibition (TGI)	
	EEGP	Dox
Murine normal fibroblast (3T3)*	52.73	0.92
Keratinocytes (HaCaT)*	43.20	0.96
Ovarian (OVCAR-3)	11.93	3.78
Melanoma (UACC-62)	10.90	0.22
Breast (MCF-7)	26.41	2.19
Kidney (786–0)	32.26	1.51
Lung (NCI-H460)	26.72	0.67

*Normal cell lines. Dox- positive control of doxorubicin on human normal and tumour cell lines

Janicke *et al.* investigated the role of *p*-coumaric acid in wholegrain cereals against colon cancer. The effects of acid on metabolic activity and kinetics of the tumour cell line were studied. From study it was observed that after 2-3 days of treatment the acid was effective at 1500 µM and had potential to reduce the number of cells upto 43-75% of control. The acid was also found to be effective on Caco-2 human cancer cells. This study supports the use of cereal bran as a powerful ingredient for protection against colon cancer (**Table 4**). (39)

Table 4. Duration phase study of 2-3 days

Days	Phase	150 µm PCA	1500µm PCA	Control*
1	LI[a]	44.6 (1.3)	54.0(1.0)[b]	44.5 (0.7)
2	LI	48.5 (0.5)	57.0(6.5)[c]	43.4 (3.3)
	Ts	18.8 (1.7)	20.6(3.3)	19.3 (1.2)
	% divided	32.6 (4.3)	20.8(3.0)[c]	38.5 (2.1)
3	LI	41.2 (1.4)	51.6(1.8)[c]	43.2 (1.5)

*Bromodeoxyuridine, LI- DNA synthesize cells are not affect, Ts-S phase duration, % divided-divided cells, [a]-experiments with similar results, [b]-different control ($p < 0.001$), [c]-different control ($p < 0.05$).

Janicke *et al.* studied the role of *p*-coumaric acid as an active ingredient against colon cancer. Dietary fiber having *p*-coumaric acid and hydroxycinnamic acids may protect against gene expression in Caco-2 colon cancer cells. On treatment with PCA, it was found to delay cell cycle regulation and progression. According to this study 901 genes were significantly affected by PCA (**Table 5**). (40)

Table 5. Gene name with symbol

Gene name(symbol)	Fold change	*P* value
G2/mitotic-specific cyclin B1 (CCNB1)	−0.51	0.006
Cyclin-dependent kinase inhibitor 1 (CDKN1A)	1.70	0.030
Proliferating cell nuclear antigen (PCNA)	−0.56	0.001
G2/mitotic-specific cyclin B1 (CCNB1)	−0.51	0.006
Myc proto-oncogene protein (c-myc) (MYC)	−0.68	0.000
M-phase inducer phosphatase 1 (CDC25A)	−0.71	0.001
Cyclin A2 (CCNA2)	−0.80	0.001
Ornithine decarboxylase (ODC1)	−1.06	0.001

Deepa *et al.* reported the antiproliferative action of the methanolic mixture of *Morus alba*. After, analysis of the mixture epicatechin, myricetin, luteolin, quercetin hydrate and kaempferol were found as active components, whereas gallic acid **(8a)**, ascorbic acid,

p-coumaric acid and pelargonidine were reported as minor components. The overall cytotoxic effect of the extract on breast cancer cell lines (MCF-7) showed IC_{50} of 9.2 µg/ml and in human colon cancer (HCT-15) cells IC_{50} was 13.8 µg/ml. Extract induced apoptosis in HCT-15 and MCF-7 cells was significantly traced by morphological changes, upregulation of caspase 3 activities and fragmentation of DNA. (15)

Hudson *et al.* assessed the effect of extract of brown rice along with ethyl acetate on colon and breast tumour. Edphenols present in rice disturbed proliferation or colony-forming ability of colon or breast cells. Bran mixture decreased viability in breast cells, and human colonic epithelial cells. Brown rice and bran contains component with

chemopreventive properties. Brown rice contains phenols and *p*-coumaric acid which might be a prime ingredient of colon or particularly breast cancer chemopreventive activity. Effect of the moiety against breast and colon cell lines is shown in **Table 6** (7).

Table 6. Effect of PCA against colon cell lines and breast cell lines

Effect of PCA on proliferation of Breast and Colon cell lines					
Colon cell lines			Breast cell lines		
HT29	SW480	HCEC	MDA MB468	MCF7	HBL100
86.5	111.2	86.6	100.0	109.3	100.0

3.3 Antioxidant potential

Bicudo *et al.* studied the antioxidant activity of *Euterpe edulis* (*Jucara* fruits) by DPPH assay. Fruits juices were examined for their total antioxidant capacity (TAA), total phenolic acid (TPA), total phenolic content (TPC) and total anthocyanin content (TAC). After conformation of phenolic acid by HPLC it indicated that the presence of *p*-coumaric acid in *Jucara* fruits. From study it was concluded that *Jucara* fruits offered high content of phenolic acid during late May to early June. Composition of *p*-coumaric acid at six different stages is shown in **Table 7** (10).

Table 7. Harvesting stage of PCA

Composition of PCA at six harvesting stage						
[M–H]− production m/z	HS1[a]	HS2[a]	HS3[a]	HS	HS5[a]	HS6[a]
163/119	3.11 ± 0.18A	2.82 ± 0.13A	2.40 ± 0.12B	2.28 ± 0.06B	1.35 ± 0.02C	1.03 ± 0.01D

[a]The results are shown as mg/100 g dm, Values are significant different ($p < 0.05$), HS- harvesting stage.

In this study, Win *et al.* investigated the antioxidant activity with roasting effects of *Arachis hypogaea L.*(peanut). The results showed change in activity of roasted peanut kernel flour which was determined by total phenolics like thiobarbituric acid test, percent inhibition of linoleic acid oxidation and DPPH free radical-scavenging capacity and compared with unroasted kernel flour. *p*-Coumaric acid was noticed by HPLC for both roasted and unroasted samples. Proper roasting could retain or may enhance the natural antioxidant capacity and phenolics content in peanut. Results revealed that roasting directly affects the activity and phenolic content (**Table 8**). (14)

Odriozola-Serrano *et al.* designed the antioxidant action of strawberry juice processed by High intensity pulse electric fields (HIPEF) or heat treatment and compared with fresh strawberry juice as reference. Phenolic and other components were traced out by HPLC method. HIPEF treated strawberry juice maintained the concentration of *p*-coumaric acid as compared with thermally treated juices during the storage period. HIPEF technology was found to be much effective and safe than thermal. (41)

Madhujith *et al.* tested four types of bean (red, black, white and brown) for their antioxidant activity. Coloured beans were found to be major source of phenolic and polyphenolic compounds and are also a rich source of natural antioxidants. Content of *p-coumaric* from the study is given below in the **Table 9** (42).

Table 8. Roasting time of PCA with skin and without skin

Phenolic acid	0	10	20	30	40	50
Kernel flour without skin (min)						
***p*-Coumaric**	73.38 ± 2.98[a] A	76.00 ± 4.00[a] A	81.88 ± 5.5[A]	75.79 ± 4.33[a] B	59.44 ± 6.67[bc] B	51.62 ± 3.55[c] B
Kernel flour with skin (min)						
***p*-Coumaric**	61.86 ± 6.79[b] A	60.09 ± 9.07[b] A	60.09 ± 1.17[b] B	93.62 ± 6.46[a] A	92.40 ± 1.65[aA]	92.83 ± 2.62[a] A

Values with small and capital letters are not significant ($p<0.05$) different roasting times and ($p<0.05$) difference between the samples respectively

Table 9. Content of PCA in coloured beans

Content of PCA in four types of bean extract	
Extract	**PCA µg/g**
Red hull	1206.±11
Brown hull	209.2±4.2
Black hull	96.2±3.6
White hull	152.4±4.2

Compaore *et al.* studied antioxidant activity of *Bauhinia rufescens* obtained from aqueous acetone extract. Antioxidant activity was performed by ferric-reducing, 2,2-diphenyl-1-picrylhydrazyl and 2,2'-azinobis(3-ethylbenzoline-6-sulphonate) methods. Phenolic content was confirmed by HPLC–MS and indicated the quality of isoquercitrin, rutin, quercetin **(9),** ferulic acid **(2),** *p*-coumaric and hyperoside in the non hydrolysed mixture. *p*-Coumaric acid was identified in the ethyl acetate and n-butanol fractions and responsible for the antioxidant activity. Confirmation of identification is shown in **Table 10**. (43)

Table 10. Identification of PCA in two mixtures

PCA identified by HPLC-ESI-MS (µg Eg^{-1})			
Ethyl acetate fraction		n-Butanol fraction	
Non hydrolysed	Hydrolysed	Non hydrolysed	Hydrolysed
33.5	26.57	-	44.92

3.4 Anti-inflammatory potential

Karlsen *et al.* investigated the polyphenolic principles of bilberries for anti-inflammatory activity by studying the effects of bilberry juice on serum and plasma biomarkers of inflammation. Supplemented polyphenols of billberry may change the inflammation process and give strategy towards prevention and treatment of chronic inflammatory diseases. Specific content of *p*-coumaric in bilberry was found to be 1-9 mg/100g in four weeks and is shown in **Table 11** (32).

Table 11. Content of PCA in bilberry juice

Water n=31			Bilberry juice n=31		
Parameter	**Baseline**	**Change**	**Baseline**	**Change**	**P (change)***
PCA (nmol/l)	13.2 (5.2-155.2)	0.1 (-8.5,13.7)	18.7 (4.7-116.1)	8.7 (5.3,19.9)	0.016

* *P* values refer to observed changes between the groups.

Pragasam *et al.* assessed the effect of *p*-coumaric acid for acute gouty arthritis. The stage of lysosomal enzymes, lipid peroxidation, paw oedema, histopathological test of ankle joints and enzymatic antioxidants in control and monosodium urate crystal induced inflamed rats were studied. For analgesic effects tail immersion and acetic acid-induced writhing test were used. On treatment with *p*-coumaric acid these biochemical factors were found to be at normal levels, as evidenced by the histopathology of the ankle joints. *p*-Coumaric acid could be considered as a potent and much safer analgesic. (Pragasam *et al.,* 2013)

3.5 Antihypertensive potential

Ortega *et al.* studied the effects of red wine in prevention of cardiovascular diseases. Four monovarietal young red wines (merlot, tempranillo, cabernet-sauvigoan, garnacha) were obtained from grapes and their phenolic composition were identified from HPLC. The concentration of acid in different varieties of wine is shown in **Table 12**.This study displayed that wine induces vasorelaxation and produced antihypertensive effects. (36)

Table 12. Different varieties of wine with PCA concentration

Concentration of PCA (mg/L) in different varieties of wine				
Compound	**Cabernet-Sauvigoan**	**Merlot**	**Tempranillo**	**Garnacha**
***Cis*-PCA**	0.28 ± 0.04	Nil	Nil	Nil
***Trans*-PCA**	0.79 ±0.05	Nil	Nil	Nil

Nil-not detected

Liu *et al.* studied antihypertensive potential of *Phyllostachys pubescens* (bamboo shoot) on spontaneously hypertensive rats. Phenolic content of shoot was confirmed by HPLC method. Bamboo shoot peptide significantly reduced systolic blood pressure with significantly reduction in ACE (Angiotensin converting enzyme) activity in lungs. Extracted *p*-coumaric acid exerts synergistic effects when observed with ACE inhibitor. Reduced systolic blood pressure of spontaneously hypertensive rats was observed in a 30-day antihypertensive test. (13)

3.6. Antidiabetic potential

In this study, Ankolekar *et al.* studied hyperglycaemic effect of cherry juice by fermenting for 72 hours using *Lactobacillus acidophilus* in an *in vitro* model. Analysis was carried out by adjusting pH 6.0 and fermented for 72 hours. Fermented extract along with time was shown in **Table 13**. At initial adjusted pH total phenolics decreased where as it remain constant or increased for natural acidic pH samples. Alpha glucosidase inhibits the activity at decreased adjusted pH samples and increase for neutral pH. From study it was concluded that increase or decrease in alpha glucosidase inhibitory activity was dependent on the variation of pH. Cherry juice containing *p*-coumaric acids can clinically provide potentially novel and low coast approaches to manage hyperglycemia. (44)

Table 13.Fermented extracts of PCA with HPLC analysis

HPLC analysis of PCA of fermented extracts (µg/ml)							
C++				C-+			
0hr	24hr	48hr	72hr	0hr	24hr	48hr	72hr
1.29 ±0.02	1.14 ±0.02	1.09 ±0.01	0.63 ±0.01	1.29 ±0.12	0.91 ±0.04	1.22± 0.002	0.92 ±0.06
C+-				C--			
1.29 ±0.02	1.14 ±0.01	1.1± 0.01	1.38 ±0.16	1.29 ±0.12	1.1± 0.03	1.18± 0.003	1.4± 0.01

Ani *et al.* reported anti hyperglycaemic effect of black/bitter cumin seeds. Extract were tested on postprandial hyperglycaemic in rats, rat intestinal α-glucosidases and human salivary α-amylase. Mixture of polyphenolic compounds with *p*-coumaric acid was identified as good inhibitor for alpha- glucosidase and helpful in management of type- 2 diabetes. (33)

3.7 Antiulcer potential

Gastro-duodenal ulcer and gastric hyperacidity is a very common problem today. These disorders may rise or hike due to imbalance of factors in the stomach, such as mucosal barrier, mucus secretion, blood flow, epidermal growth, acid-pepsin secretion, cellular regeneration, factors and prostaglandins. Smoking, stress, ingestion of NSAIDs and nutritional deficiencies are all factors which trigger gastric ulcer.

In this study, Barros *et al.* carried out the antiulcer activity of phenolic compound from Brazilian green propolis like *p*-

coumaric acid. Anti-ulcer property was evaluated by using ethanol-induced, stress-induced and NSAID-induced ulcer protocol. Study proved that the *p*-coumaric acid display antiulcer activity by using different model which are shown in **Table 14**. (24)

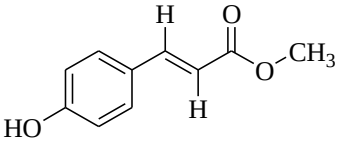
Table 14. Different models show antiulcer activity

On ethanol induced gastric ulcers					
Treatment	**Dose (mg/kg)**	**TAL (mm^2)**	**PLA**	**UI**	**I (%)**
***p*-coumaric**	50	48.09 ± 23.45*	5.22 ± 3.03*	21.48 ± 4.92*	41.40
	250	4.49 ± 1.81*	0.55 ± 0.22*	5.74 ± 1.74*	84.34
On indomethacin-induced gastric ulcers					
***p*-coumaric**	50	28.84 ± 4.83*	3.46 ± 0.60*	36.80 ± 4.68	28.06
	250	20.24 ± 5.77*	3.12 ± 0.84*	23.00 ± 6.70*	55.04
On stress-induced gastric ulcers					
***p*-coumaric**	50	20.91 ± 6.50*	2.10 ± 0.70*	37.80 ± 10.92*	58.77
	250	8.52 ± 1.96*	0.83 ± 0.18*	24.80 ± 5.25*	72.95

*$p < 0.05$ compared with control group, TAL-Total area of lesion, PLA-% of lesion area, UI- Ulcer index, I-inhibition.

3.8 Anti-melanogenic potential

Song *et al.* studied the potential of *p*-coumaric acid and its derivative methyl *p*-coumarate (MPC) as hypopigment agent for topical use. For the evaluation of antimelanogenic activity cellular melanin synthesis and *in vitro* human Tyrosinase (TYR) enzyme activity was used. Study revealed that topical use of PCA can diminish the pigmentation and inflammation due to strong UVB. Study supports the effectiveness of PCA on abnormal skin pigmentation. (23)



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In this study, Jun *et al*. examined the *in vitro* effects of the acid on hypopigmentation in melanocytes gene expression. Melanin content was determined by cell free and cell based assays. *p*-Coumaric acid significantly reduced through inhibition of tyrosinase enzyme activity and also decreased melanogenic gene expression by inhibiting CREB protein phosphorylation. From the study it was concluded that *p*-coumaric acid promotes the development of novel and natural hypopigmentation products. (45)

3.9 Cognitive behavioral therapy

In this study, Kim Hyun-Bum *et al.* found *p*-coumaric acid effects on mental health. The acid had beneficial impact on leaning memory and improved cognitive behaviours. For these finding they used rat and groups were induced with *p*-coumaric acid dose (30mg/kg), with the help of model organotypic hippocampal slice culture. Further, results were confirmed with the help of multi-channel system (MEA), electrophysiology data processing, passive avoidance test, Morris water maze and statistical results followed by one way ANOVA. This study revealed that the moiety has significant therapeutic value to improve memory related problems especially age related. (46)

3.10 Anti-protozoal activity

Lopes *et al.* carried out the study on 12 ester derivatives of *p*-coumaric acid to evaluate their trypanocidal activity. Out of all the tested compounds, pentyl *p*-coumarate was found to be the most active one against the trypanosoma species against both epimastigote and trypomastigote forms (5.16 ± 1.28 μM; 61.63 ± 28.59 μM). These species are responsible for various chronic infections affecting a large part of the population throughout the world. The results were confirmed flow cytometry analysis which showed cell death by necrosis by increase in the percentage of 7-AAD labelled cells, an increase in reactive oxygen species, and a loss of mitochondrial membrane potential. The mechanism of action was confirmed by docking which involved the interaction with two enzymes linked with *Trypanosoma cruzi* i.e. aldo-keto reductases and cruzain. (47)

4. STRUCTURE-ACTIVITY RELATIONSHIP

On the basis of biological activity shown by *p*-coumaric acid derivatives, SAR of each activity might be as follows (**Fig 3**).

Role of hydroxyl group:

In case of electron donating group (-OH) substitution at R_1 position (*m* and *p*-position), consequently were found to improve antioxidant and anticancer potential. This fact was possible by important study of Huang *et al.*, 2012 and Mokbel *et al.*, 2006. Further, hydroxyl group substitution at R_1 position (*m*-position) improved anti-inflammatory activity as depicted by Russell *et al*., 2008.

Role of alkoxy group:

Substitution with alkoxy group (electron releasing group) at R_1 position (*m* and *p*-position) increases anticancer activity which is supported by the results of Madhujith *et al.*, 2004 and Martínez-Tomé *et al.*,2011.

Role of heteroaryl group:

In case of heteroaryl group substitution at R_2 position, it was determined that esters having bulky aromatic group will improve antimicrobial activity. This fact was supported by findings of Khatkar *et al.*, 2013.

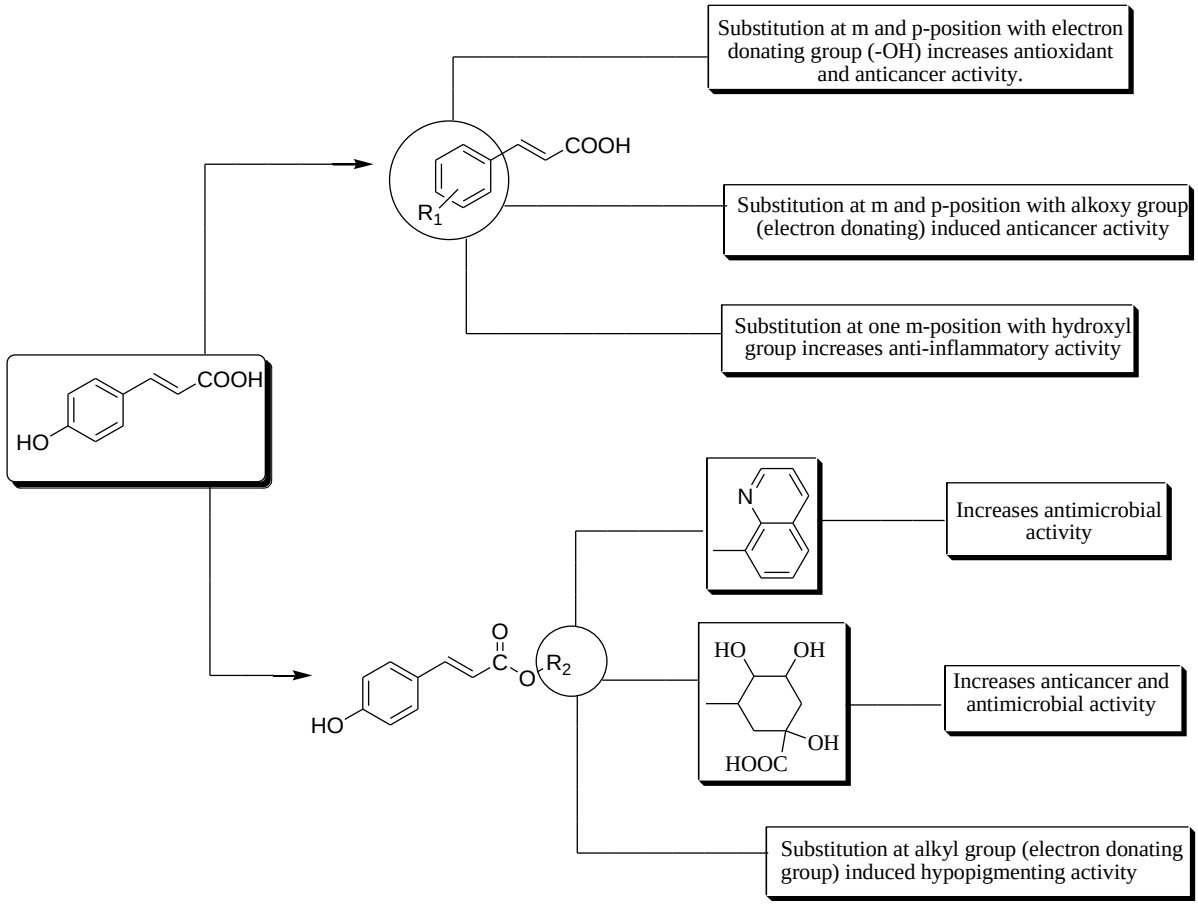

Fig 3: SAR of biological activities of *p*-coumaric acid derivatives

Role of cyclohexanyl group:

In case of cyclohexanyl group substitution at R_2 position, which indicated that esters having bulky group will highly improve anticancer and antimicrobial activity supported by Martínez-Tomé *et al.*, 2011.

Role of alkyl group:

In case of alkyl group substitution at R_2 position, it was determined that esters having bulky group will highly improve hypo pigmenting activity as shown by Song *et al.*, 2011.

DISCUSSION AND CONCLUSION

p-Coumaric acid is a common natural compound which is widely distributed in fruits, vegetables and cereals**.** The literature revealed that *p*-coumaric acid is a hydroxycinnamic acid and has great potential for the development of new substitutes for the treatment of various infectious diseases, cancer, diabetes and skin disorders as well inflammatory conditions. This review has reported the vast applications of PCA and their derivatives for the formation of other important compounds like ferulic acid, chlorogenic acid, caffeic acid, vanillic acid, synergic acid, *p*-hydroxybenzoic acid, protocatechuic acid and ellagic acid. The aforementioned information is helpful to provide organized outline regarding natural sources, application of PCA in cosmetics, metabolism and other industries. This literature provides vast information to the researchers who focused their interest on natural products and will try to provide potent natural remedies for curing diseases. In summary, the present article aims to review the work reported on therapeutic potentials of *p*-coumaric acid and its derivatives which are valuable for medical applications during new millennium. The moiety is versatile in nature and offers the medicinal chemist to explore more about it and the data mentioned in this article will be a great help to prospective researchers working in this area for further study of this scaffold. Thus, by studying the derivatives of the *p*-coumaric acid it will be an interesting pathway for future development of new and natural drugs against many pathological conditions.

ACKNOWLEDGEMENT

Not declared.

CONFLICT OF INTEREST

The authors have no conflict of interest.

FUNDING SOURCE

No external funding source has been disclosed.

DATA AVAILABILITY

Not declared.

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