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Exploring Pharmacological Potentials of *p*-Coumaric Acid: A Prospective Phytochemical for Drug Discovery

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Abstract

p-coumaric acid, commonly referred to as 4-hydroxycinnamic acid, is a phenolic acid, which has been subjected to much research in recognition of its beneficial properties against several diseases and its widespread distribution in the plant kingdom. This compound can be found in the free-state or coupled with other molecules in nature. It has demonstrated prospective pharmacological effects including antiproliferative, nephroprotective, neuroprotective, antioxidant and antimicrobial effects in addition to other biological properties through numerous *in vivo*, *in vitro* and clinical studies. This review reported a short summary on *p*-coumaric acid to provide fundamental information in its biosynthesis, plant sources, and pharmacological effects which may help in future research and development of novel therapeutics.

Key words: *p*-Coumaric acid, biosynthesis, antiproliferative, neuroprotective, nephroprotective, antioxidant, antimicrobial.

Introduction

Plants provide consistent source of therapeutic chemicals since very ancient age and heal several disorders effectively (Alam *et al.,* 2022a; Emon *et al.*, 2021a). People predicted the therapeutic effects of medicinal herbs before to the development of modern medicines (Alam *et al.,* 2020). Traditional and unfamiliar techniques of treating various illnesses are widely used around the world (Alam *et al.*, 2021a; Chowdhury *et al.*, 2022). Even in the current day, plants may be used to treat significant disorders such as cancer, oxidative stress, diarrhea, depression, fever, and thrombosis (Emon *et al.*, 2020a; Emon *et al.*, 2021b). According to the WHO (World Health Organization), medicinal products based on plants are used by 80% of people as their primary form of healthcare worldwide (Alam *et al.,* 2021b; Islam *et al.,* 2022). Even though there are numerous synthetic drugs that can be purchased on the market to cure illnesses, they come with a lot of harmful side effects. Plant-based medicines, on the other hand, offer more potent therapeutic benefits and fewer side effects (Emon *et al.,* 2020b). So natural plant-based products have recently drawn attention as a substantial way to obtain novel, safe and potent secondary bioactive metabolites with therapeutic possibility (Rudra *et al.*, 2020, Obonti *et al.,* 2021).

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Phenolic compounds are an important family of secondary metabolites extensively present in plant foods and drinks including coffee, tea and fruit juices (Teodoro *et al.,* 2015). Coumaric acid is a phenolic derivative of cinnamic acid that exists in three forms: *o*-coumaric, *m*-coumaric and *p*-coumaric acid, each of which has a hydroxy group as a substituent at one of the aromatic positions (Kiliç and Yeşiloğlu., 2013; Kong *et al.,* 2013). The most abundant isomer found in nature is p-coumaric acid (Kong *et al.,* 2013). The molecular formula of *p*-coumaric acid is $C_9H_8O_3$ and its IUPAC name is (Z)-3-(4-hydroxyphenyl)prop-2-enoic acid (Figure 1).

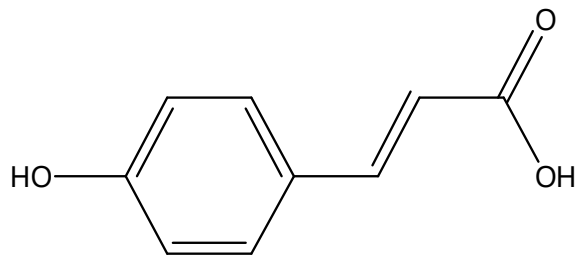

Figure 1. Structure of *p*-coumaric acid.

It is a crystalline yellowish-green powder with a melting point of 211.5 ºC and a molecular mass of 164.16 g/mol. *p*-Coumaric acid is not easily soluble in water or aqueous buffers. On the other hand, it is soluble in organic solvents including ethanol, dimethylformamide and DMSO (Ferreira *et al.,* 2019). Plants have relatively low levels of free *p*-coumaric acid, and the amounts of this molecule vary amongst plant sources. It is commonly identified in plants either as a free molecule or conjugated to other molecules such as organic acids, amines, lignin, mono- or oligosaccharides and alcohols. Surprisingly, bound forms of *p*-coumaric acid are more frequent and have higher biological activity than free *p*-coumaric acid. Many mushroom species like *Ganoderma lucidum*, *Cantharellus cibarius*, *Ganoderma lucidum*, and *Termitomyces heimii* have extremely high levels of free *p*-coumaric acid which is about several milligrams per gram, a thousand times more than that found in fruits (Pei *et al.,* 2016). We have targeted on noteworthy pharmacological potentials of the aforementioned compound in our review aimed to give a head start for the researchers who are looking for potential bioactive compounds for the discovery and development of novel drugs that can be available with few or no side effects than synthetic drugs as there is still a dearth of clinical studies to determine the impact of *p*-coumaric acid concentrations on human health.

Material and Methods

Articles search strategy: A literature search was conducted using the databases from PubMed, ScienceDirect, Google Scholar, Clinical Trials.gov, Wiley Online Library and Scopus to assemble the information about p-coumaric acid. The phrases used in the searches include '*p*-coumaric acid', 'phenolic compound', 'plant', 'plant-part', 'biosynthesis', 'chemical constituents', 'antiproliferative', 'antimicrobial', 'antioxidants', 'nephroprotective', 'neuroprotective', 'lipid-lowering', 'isolated from' etc. Only peer-reviewed scientific journals were taken into consideration. Only a few papers that met the inclusion criteria were included and reported in this study.

Biosynthesis: Prephanate, the byproduct of the Shikimate pathway, is the main biosynthetic starting point for *p*-coumaric acid (Gao *et al.,* 2021). This prephanate is dehydrogenated into phenylalanine in the presence of prephanate dehydrogenase (Figure 2). Phenylalanine goes through two metabolic steps to produce the *p*-coumaric acid in plants: first, phenylalanine ammonia-lyase catalyzes the conversion of phenylalanine into trans-cinnamic acid, which is then hydroxylated at the para position by trans-cinnamic acid 4-hydroxylase and produced *p*-coumaric acid (Li *et al.,* 2018). Moreover, prephanate can also be converted into tyrosine also, which is further converted into *p*-coumaric acid through the enzymatic action of phenylalanine ammonia-lyase.

Plant source: p-Coumaric acid is a very common bioactive secondary metabolite abundantly found in phyto sources. Here is a list of some plants and plant-parts along with their family names which contain *p*-coumaric acid (Table 1).

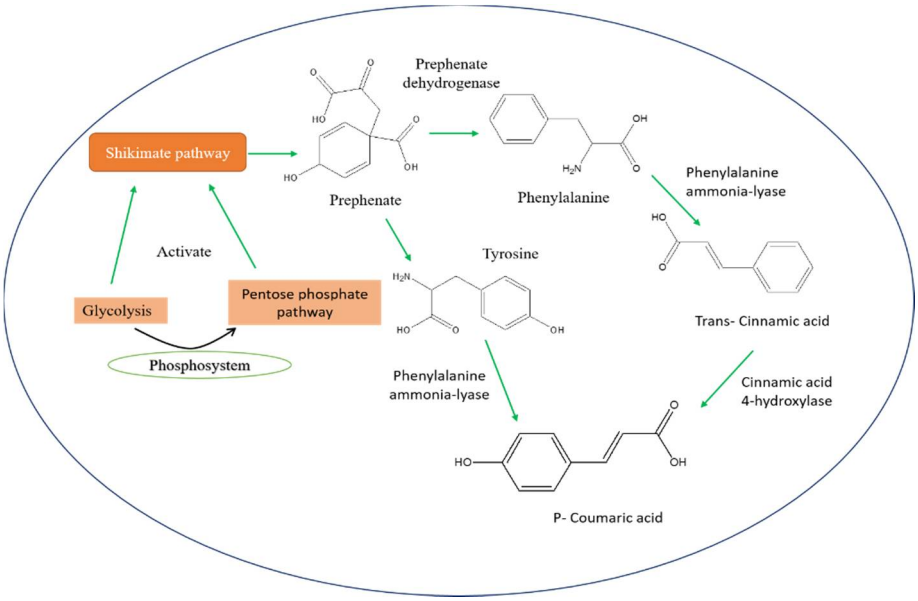

Figure 2: Biosynthesis of *p*- coumaric acid

Table 1. List of some plants and plant-parts along with their family name which contain *p*-coumaric acid.

Sl.	Plant name	Family	Plant part	Reference
1	*Cynodon dactylon* (L.) Pers.	Poaceae	Whole plant	Karthikeyan *et al.*, 2015
2	*Cucumis sativus* L.	Cucurbitaceae	Leaves	Daayf *et al.*, 1997
3	*Daucus carota* L.	Apiaceae	Root	Kreutzmann *et al.*, 2008
4	*Osteospermum ecklonis* (DC.) Norl.	Compositae	Aerial parts	Jewely and Abdul-Jalil., 2022
5	*Tanacetum longifolium*	Compositae	Aerial parts and Root	Mahmood *et al.*, 2003
6	*Tithonia diversifolia* (Hemsl.) A.Gray	Compositae	Leaves	Devi *et al.*, 2022
7	*Vaccinium bracteatum* Thunb.	Ericaceae	Leaves	Oh *et al.*, 2021
8	*Panax ginseng* C.A.Mey.	Araliaceae	Leaves	Lim *et al.*, 1999
9	*Cannabis sativa* L.	Cannabaceae	Root	Oh *et al.*, 2022
10	*Peltophorum africanum* Sond.	Leguminosae	Bark	Mebe and Makuhunga., 1992
11	*Lavandula angustifolia* Mill.	Lamiaceae	Flowers	TopÇu *et al.*, 2007
12	*Lavatera trimestris* L.	Malvaceae	Flowers	Skalicka-Woźniak *et al.*, 2007.
13	*Juniperus phoenicea* L.	Cupressaceae	Aerial parts	Abdel Raoof and Mahmoud., 2023
14	*Musa textilis* Née	Musaceae	Leaf fibers	del Río *et al.*, 2004
15	*Baccharis dracunculifolia* DC.	Compositae	Leaves	Bankova *et al.*, 1999
16	*Araucaria angustifolia* (Bertol.) Kuntze	Araucariaceae	Leaves	Bankova *et al.*, 1999

17	*Eucalyptus citriodora* Hook.	Myrtaceae	Trunk	Bankova *et al.*, 1999
18	*Triticum aestivum* L.	Poaceae	Seed	Wu *et al.*, 1999
19	*Solanum lycopersicum* L.	Solanaceae	Fruit	Hunt and Baker., 1980
20	*Panicum virgatum* L.	Poaceae	Stem	Yan *et al.*, 2010
21	*Camellia sinensis* (L.) Kuntze	Theaceae	Leaves	Azevedo *et al.*, 2019
22	*Coffea arabica* L.	Rubiaceae	Seed	Aissaoui *et al.*, 2020
23	*Malus domestica* Borkh.	Rosaceae	Fruit (Peel & Pulp)	Veberic *et al.*, 2005
24	*Citrus sinensis* (L.) Osbeck	Rutaceae	Fruit	Kelebek and Selli., 2011
25	*Allium cepa* L.	Amaryllidaceae	Bulb	Lachman *et al.*, 2003
26	*Solanum tuberosum* L.	Solanaceae	Tuber	Vaitkevičienė *et al.*, 2020
27	*Phaseolus vulgaris* L.	Leguminosae	Beans	Luthria and Pastor-Corrales., 2006
28	*Pyrus communis* L.	Rosaceae	Fruit	Öztürk *et al.*, 2015
29	*Avena sativa* L.	Poaceae	Kernels	Multari *et al.*, 2018
30	*Zea mays* L.	Poaceae	Kernels	Del Pozo-Insfran *et al.*, 2006

Results and Discussion

Pharmacological activities

Anti-proliferative effect: According to an antiproliferative assay, *p*-coumaric acid displayed an inhibiting impact on HT 29 and HCT 15 cells, having an IC_{50} (concentration for 50% inhibition) value of 1600 and 1400 µmol/l, respectively. Colony forming assay showed that *p*-coumaric acid-treated HCT 15 and HT 29 cells were inhibited in a time-dependent manner. After HCT 15 cells were treated with *p*-coumaric acid, and propidium iodide staining revealed an increase in the number of apoptotic cells (37.45 ± 1.98 vs 1.07 ± 1.01) accumulating at the sub-G_1 phase of the cell cycle. After being exposed to *p*-coumaric acid, HCT-15 cells were examined under a photomicrograph and a scanning electron microscope which revealed blabbing and shrinkage as a sign of apoptosis. Studies on the lipid layer indicated that lipid layer breakdowns were correlated with the growth inhibition of *p*-coumaric acid. In the *p*-coumaric acid-treated cells, a decrease in mitochondrial membrane potential and an increase in ROS production were seen. Furthermore, apoptosis assessed by YO-PRO-1 staining similarly revealed the time-dependent increase of apoptotic cells after treatment (Jaganathan *et al.*, 2013).

Nephroprotective effect: Research was carried out to clarify the role of *p*-coumaric acid, a common dietary polyphenol, in protecting rats against cadmium-induced nephrotoxicity. For comparative purposes, silymarin (50 mg/kg body weight) was utilized as a standard reference medication. In the experiment, the animals were split into four groups of six each. The animals of Group I received saline and were considered as a control group and Group II received cadmium chloride (3 mg/kg body weight) subcutaneously once on a daily basis for 3 weeks. On the other hand, Group III and IV animals received cadmium chloride followed by *p*-coumaric acid at the dose of 100 mg/kg body weight and silymarin at the dose of 50 mg/kg body weight, respectively, daily orally for 3 weeks. The results demonstrated that urea, uric acid, and creatinine levels were considerably higher in serum and lower in urine samples from rats treated with cadmium chloride alone in comparison to the control and drug-treated rats. On the contrary, the administration of *p*-coumaric acid proving its nephroprotective effect successfully protected the biochemical alterations by restoring the levels of kidney functioning indicators in cadmium-treated rats (Navaneethan and Rasool, 2014).

Neuroprotective effect: Till to date, cerebral ischemia (IR) is a major clinical issue that can result

in permanent neurological damage. Primary injury (edema, contusion, and pressure) invariably results in cell death and permanent harm (Guven *et al.,* 2015). An investigation was done to look at how *p*-coumaric acid could protect mice with cerebral ischemiareperfusion damage which can lead to disability and cognitive decline. 30 male ICR mice were divided into three groups randomly: Sham that received vehicle and not induced IR, Control-IR that received vehicle and induced IR and PC-IR that received 100 mg/kg body weight *p*-coumaric acid and induced IR. Vehicle or *p*-coumaric acid (100 mg/kg body weight) was orally administered for 2 weeks before developing the cerebral IR injuries utilizing a bilateral common carotid artery blockage for 30 minutes followed by a 45 minutes reperfusion. The whole-brain infarction volume was studied by 2, 3, 5-triethyltetrazoliumchloride staining of sections. A histological investigation of the susceptible neuronal population in the dorsal hippocampus was performed by staining brain sections with 0.1% cresyl violet. The findings showed that IR increased the levels of calcium, MDA (malondialdehyde), whole-brain infarction volume and hippocampus neuronal death significantly. But pretreatment with *p*-coumaric acid markedly lowered MDA level, whole-braininfarction volume and hippocampal neuronal death as well as elevated catalase and superoxide dismutase actions. So, it can be concluded that pretreatment of animals with p-coumaric acid can diminish the extent of infarction size, IR-induced brain oxidative stress, andneuronal vulnerability (Sakamula and Thong-Asa, 2018).

Antioxidant activity: The antioxidant activities of phenolic compounds are well recognized as they neutralize reactive oxygen species (ROS) and manage endogenous antioxidant enzymes protecting biomolecules from oxidative damage (Abdel-Wahab *et al.,* 2003). Different analytical techniques were used to clarify the in vitro radical scavenging and antioxidant properties of *p*-coumaric acid such as total antioxidant activity determination by ferric thiocyanate, 1,1-diphenyl-2-picrylhydrazyl free radical (DPPH) scavenging, hydrogen peroxide scavenging, 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) radical scavenging activity, superoxide anion radical scavenging, ferrous ions (Fe2+) chelating activity and ferric ions (Fe3+) reducing capacity. At a concentration of 45 µg/mL, *p*-coumaric acid prevented 71.2% lipid peroxidation of a linoleic acid emulsion. On the contrary, BHA (butylated hydroxyanisole), BHT (butylated hydroxytoluene), ascorbic acid, and α-tocopherol displayed 66.8, 69.8, 59.7 and 64.5% inhibition on the peroxidation of linoleic acid emulsion, respectively, at the same concentration. Additionally, *p*-coumaric acid had potent DPPH scavenging, ABTS·+ scavenging, hydrogen peroxide scavenging, superoxide anion radical scavenging, ferric ions (Fe^{3+}) reducing activity as well as ferrous ions (Fe^{2+}) chelating effect. Furthermore, the different antioxidant activities were evaluated in comparison with BHA, BHT, ascorbic acid and α-tocopherol as reference antioxidant substances. These findings proved that the characteristics of *p*-coumaric acid make it suitable for usage in the pharmaceutical and food industries (Kiliç and Yeşiloğlu., 2013).

Antimicrobial activity: In an era of rising bacterial resistance to conventional antibacterial agents, it has been predicted that the growth of resistance to known antibiotics could possibly be overcome by discovering new drug targets via genomic research, boosting current antibiotics, and especially by discovering fresh antibacterial drugs with novel structures and modes of action. This will always be the major objective (Salahuddin *et al.,* 2009). Simple organic acids have well-established antibacterial properties in the literature and *p*-coumaric acid is one of them (Khatkar *et al.,* 2017). The mechanism of action of *p*-coumaric acid against Gram-positive and Gram-negative pathogenic bacteria was studied. Six strains- *Staphylococcus aureus, Bacillus subtilis, Streptococcus pneumoniae, Escherichia coli, Salmonella typhimurium* and *Shigella dysenteriae* were used to investigate to find out the ability of *p*-coumaric acid to bind with the bacterial DNA and permeate the external membrane of the bacterial cell wall. The most potent

antimicrobial effect was seen against *Shigella dysenteriae*. The results also demonstrated that *p*-coumaric acid destroyed pathogenic bacterial strains by binding to DNA, which prevented cellular activities and by inducing irreversible permeability alterations in the cell membrane which causes incapability to maintain cytoplasmic macromolecules (Lou *et al.,* 2012).

Secondary metabolites are a diverse group of chemical elements that are produced by plants, although they play no direct function in plant growth or reproduction (Sultana *et al.,* 2022; Chakrabarty *et al.,* 2022; Islam *et al.,* 2022b). These chemicals showed pharmacological effects on the human body due to their significant biological activities (Ashrafi *et al.,* 2022a, Ashrafi *et al.,* 2022b). Phytomedicines are also thought to have fewer negative effects, hence about 80% of medication moieties are directly plant-extracted or their adjusted equivalents (Alam *et al.,* 2022b, Ashrafi *et al.,* 2023). *p*-coumaric acid is one of the most frequently found isomers in nature. *p*-coumaric acid, categorized as a phytochemical and nutraceutical, can be found in a number of edible plants (Boz, 2015). The present review has discussed some pharmacological properties showed by *p*-coumaric acid. *In vitro* and *in vivo* studies demonstrated that *p*-coumaric acid has a higher bioavailability than the other phenolic acids. *p*-coumaric acid can exhibit anticancer effects by different mechanisms such as inducing apoptosis, modulating inflammation and oxidative stress, altering cellular proliferation pathways, halting cell cycle progression, and enhancing sensitivity to chemotherapeutic drugs. These characteristics make *p*-coumaric acid an appealing nutraceutical option for phytochemical-based colorectal cancer incidence and morbidity reduction techniques (Tehami *et al.,* 2023). *p*-coumaric acid also offers a defense against the development of diabetic nephropathy which is a chronic inflammatory disease resulting from hyperglycemia-induced alterations and causes renal fibrosis and end-stage renal disease. *p*-coumaric acid markedly reduced BUN (blood urea nitrogen), serum creatinine and total proteinuria while raising creatinine clearance (Zabad *et al.,* 2019). It has been revealed that *p*-coumaric acid protects the liver from damage brought on by ischemia-reperfusion by enhancing liver antioxidants, liver functional tests and suppressing the apoptotic gene protein caspase-3 (Parvizi *et al.,* 2020). *p*-coumaric acid exerted neuroprotective activities against scopolamine and 5-S-cysteinyldopamine-induced neurotoxicity (Kim *et al.,* 2017; Vauzour *et al.,* 2010). Moreover, *p*-coumaric acid has exhibited numerous physiological effects including a gastro protective effect (Boeing *et al.,* 2021), antimelanogenic effect (Boo, 2019), antiangiogenic effect (Kong *et al.,* 2013), anti-inflammatory and immunomodulatory effect (Pragasam *et al.,* 2013). Therefore, it can be a natural alternative to these illnesses instead of synthetic additives.

Conclusion

p-Coumaric acid consists of a unique chemical structure, and has various biological traits that make it a good candidate for its use. *p*-coumaric acid can be a prospective candidate in the upcoming therapeutics to treat disorders. It can also be exploited as a precursor of flavonoids, phenolic acids, lignin and many other secondary metabolites. The advancement in *p*-coumaric acid research still demands a lot of attention as despite being a notable drug like candidate very few researches have been conducted upon it. Finally, further investigations are still recommended to provide in depth information about its different pharmacological potentials as well as their exact mechanism.

Declarations

All authors have read and approved the article for submission. The entire document has never been published, and it is not currently under consideration for publication in any journal in any portion.

Conflict of interest

The authors claim that none of their competing interests appeared to have influenced the research presented in this study.

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