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Chemical, Biological, and Pharmacological Prospects of Caffeic Acid

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Abstract: There are many proven beneficial pharmacological effects of polyphenols, and these compounds have been tremendously studied for their role in the human body. Daily intake of polyphenols has shown beneficial effects on the immune system. Polyphenols are the natural compounds present in plants as secondary metabolites. Caffeic acid (CA) is the major one among other compounds of hydroxycinnamic acid, which plays an important role as an antioxidant, anticancer, antidiabetic, antihypertensive, antimicrobial, hepatoprotective, antiviral, etc. It is found in most herbal plants. CA produces its pharmacological effect by altering the activity of various key enzymes. It reduces the blood glucose level by inhibiting enzymes α-amylase and α-glucosidase in type-2 diabetes. It shows anticancer and anti-inflammatory activity by inhibiting various transcript factors. The small part of the esterified form of CA is absorbed in the stomach, and the rest of the part is the breakdown in its free form by the microbial esterases in the colon. It enters intestinal cells via active transport mediated by MCT. The maximum plasma concentration is seen after one hour of food ingestion. Methylation, sulphation, and glucuronidation take place after absorption and are excreted primarily through urine. The purpose of this review is to enhance researchers' knowledge to conduct more studies to reveal and optimize CA's biological and pharmacological properties. Based on its pharmacological activity, this compound can be used as a natural safeguard to replace synthetic antibiotics and other synthetic medicine to reduce the medicinal cost and side effects.

Keywords: phenolics; caffeic acid; pharmacological activity; antioxidant; anticancer; antidiabetic; antihypertensive; antimicrobial; hepatoprotective; antiviral.

1. Introduction

Consumption of polyphenols in daily diet has proven beneficial effects like protection against the disease states [1]. Polyphenols have been shown to possess high antioxidant properties and improve endothelial function [2, 3]. Dietary intake of polyphenols exerts a protective role against pathological conditions like diabetes, cancer, and cardiovascular disease and also has anti-inflammatory, hepatoprotective, and antimicrobial properties [4, 5]. Phenolic compounds are present naturally in the plant kingdom and are categorized as Simple and Polyphenol phenolic compounds [6-8]. Phenolic acids are abundant in polyphenols, in which hydroxybenzoic and hydroxycinnamic acids are principal compounds (Figure 1) [9].

There are six hydroxycinnamic acid compounds, CA, caffeic acid phenyl ester (CAPE), ferulic acid, ferulic acid phenyl ester, rosmarinic acid, and chlorogenic acid [10]. Among these, CA is the principal compound representing the hydroxycinnamic acid, found in the plants as a secondary metabolite of catechol and phenolic acid, which has various derivatives such as amides, glycosides, esters, and sugar esters. It is also known by its chemical name 3,4-Dihydroxycinnamic acid [11]. New analogs with diverse biological properties are found with CA's structural modification, especially when it transforms into ester or amide.

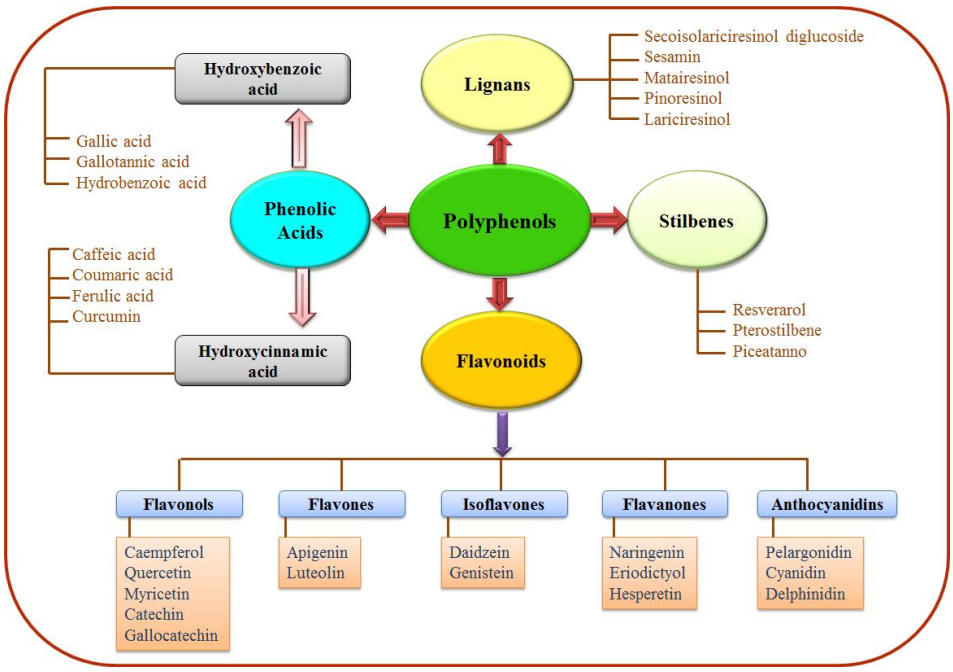


Figure 1. Classification of Polyphenols.

It is abundantly found in *Paraguay tea*, *Melissa officinalis*, and *Baccharis genistelloides*. Other sources include olive oil, white grape wine, spices, potatoes, coffee beans, cabbage, propolis, and carrots [12, 13]. *In vitro* and *in vivo* experiments have proved the pharmacological activities (Figure 2) of CA like antibacterial, antiviral, anti-inflammatory, antioxidant, anti-atherosclerotic, cardioprotective, immunomodulatory, antidiabetic, antiproliferative, hepatoprotective, anticancer, anti-hepatocellular carcinoma and antiviral. The pharmacological activities of this compound are attributed to its action on different enzyme systems of the body. The present review article discusses various pharmacological activities reported for the CA.

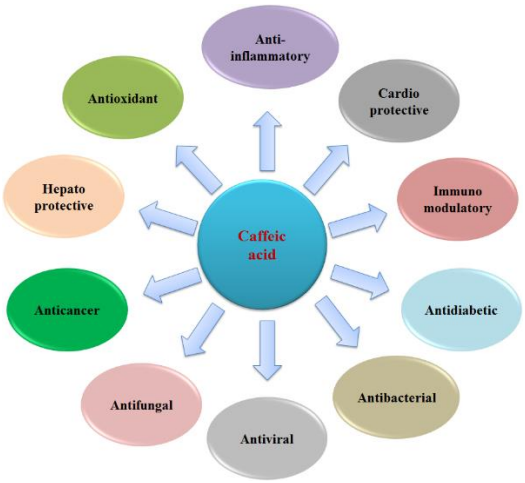


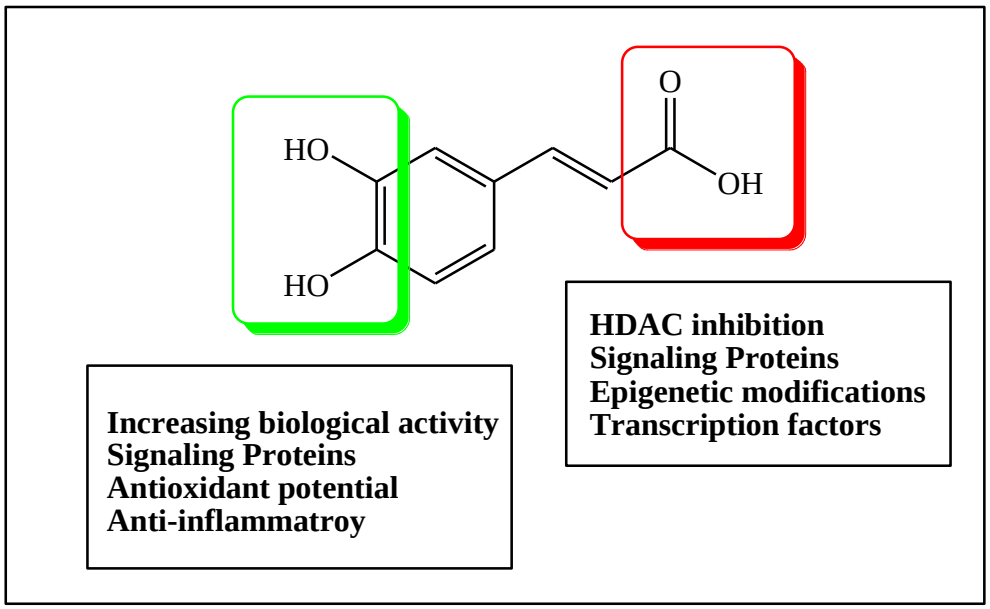
Figure 2. Diagram illustrating the pharmacological properties of Caffeic acid.

2. Chemical and Biological aspects

2.1. Molecular formula: $C_9H_8O_4$.

2.2. Molecular structure.

Scheme 1 represents the molecular structure of caffeic acid showing plausible biological and pharmacological performance [14].



Scheme 1. The chemical structure of Caffeic acid showing active functional groups indicates plausible biological and pharmacological performance.

2.3. Biosynthesis.

CA is a moiety of the phenolic acid family with a phenylpropanoid structure in which a 3,4-dihydrolated aromatic ring is attached to a *trans*-ethylene chain [15, 16]. The synthesis of CA in plants occurs by the endogenous shikimate pathway, which produces the aromatic amino acid from glucose (Figure 3) [11, 15].

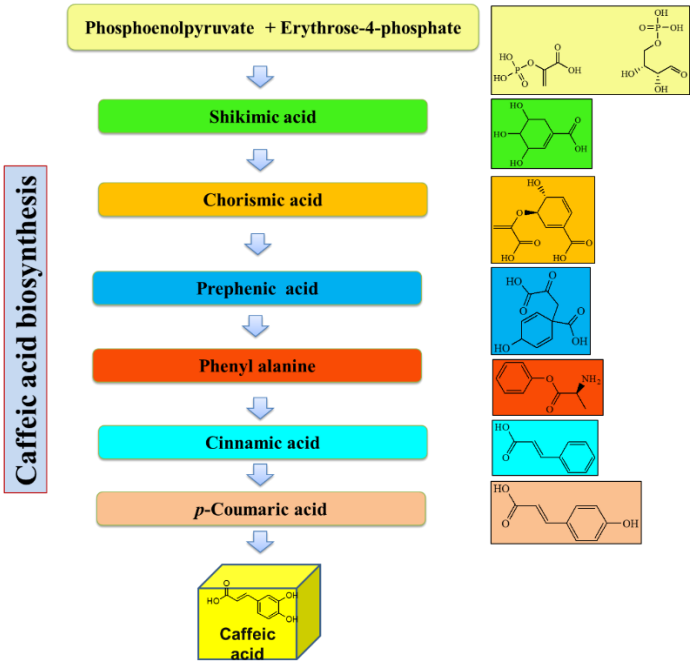


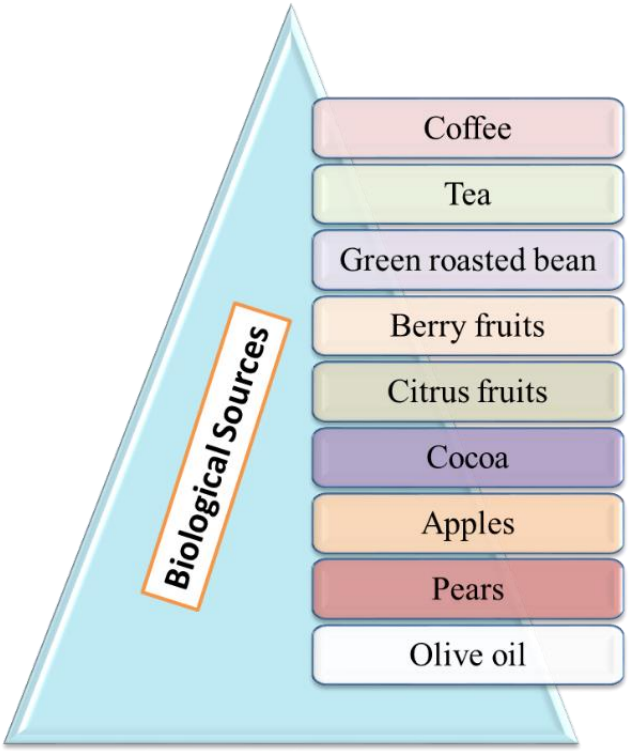
Figure 3. Steps involved in caffeic acid biosynthesis in plants.

2.4. Biological sources.

Hydroxycinnamic acids are the class of phenolic compounds that are consumed abundantly in a normal diet [16, 17]. CA is a prominent member of hydroxycinnamic acid produced as a secondary metabolite of plants [18, 19]. Berry fruits, citrus, tea, coffee, olive oil, cocoa, roasted bean, apples, etc., are the main sources of CA (Table 1) [20–22]. CAPE (caffeic acid phenethyl ester), an ester form of CA, is also a plant-derived polyphenolic active ingredient that can be extracted from honeybee propolis (Scheme 2) [23, 24].

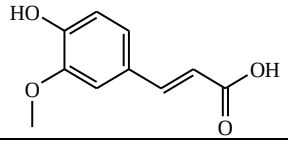
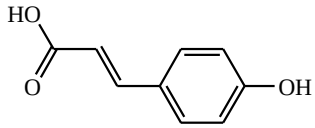
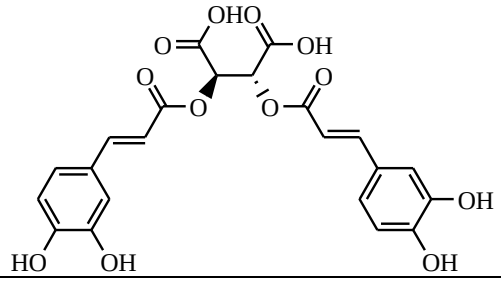
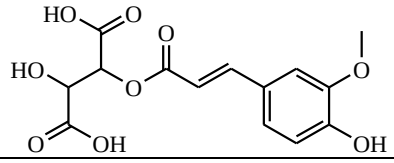
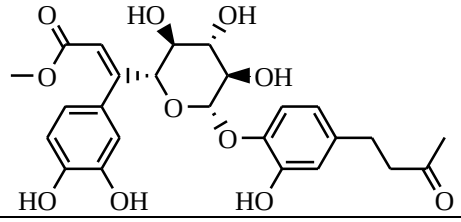
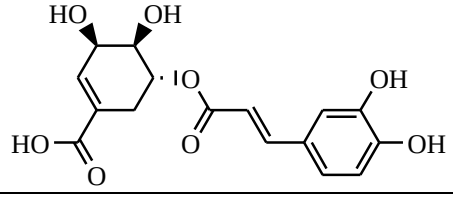
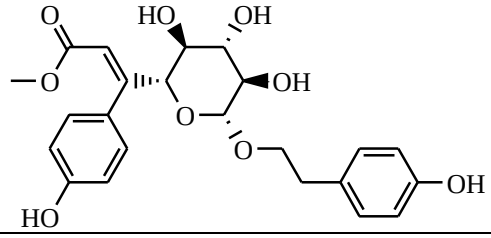
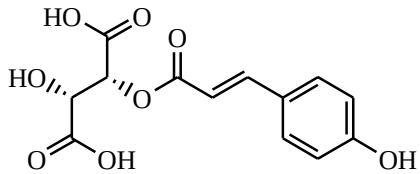
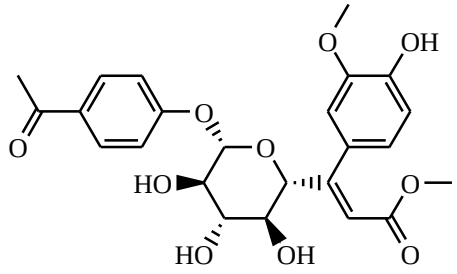
Table 1. Biological sources of caffeic acid.

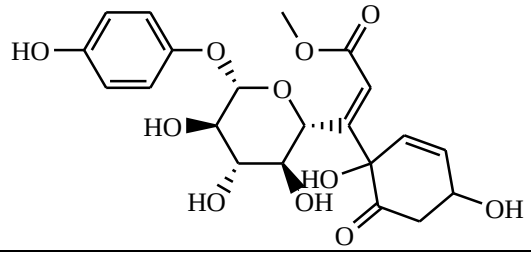
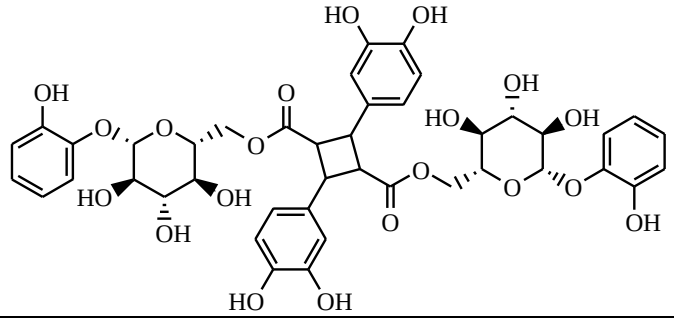
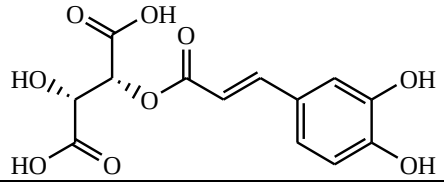
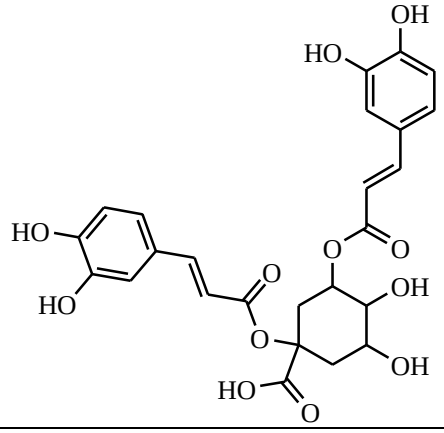
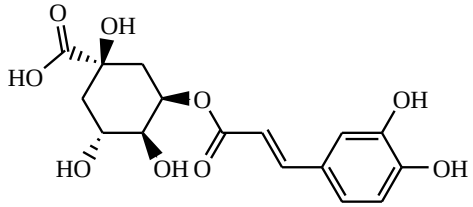
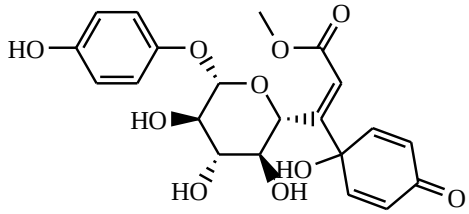
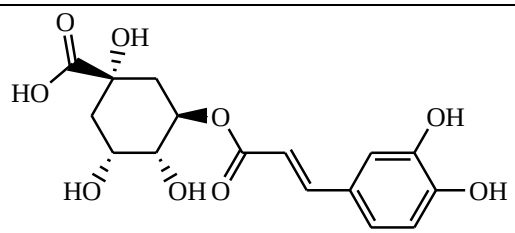
Biological Sources	Common Names	References
Malus domestica	Apples	[25]
Fragaria ananassa	Strawberries	[26]
Brassica oleracea	Cauliflower	[27]
Raphanus sativus	Radish	[28]
Agaricus bisporus	Mushroom	[29]
Brassica oleracea var. sabellica	Kale	[30]
Pyrus communis	Pears	[31]
Olea europaea	Olive oil	[32]
Curcuma longa	Turmeric	[33]
Ocimum basilicum	Basil	[34]
Thymus vulgaris	Thyme	[35]
Origanum vulgare	Oregano	[36]
Brassica oleracea var. capitata	Cabbage	[37]
Salvia officinalis	Sage	[38]
Vitis vinifera	Grapes	[39]
Helianthus annuus	Sunflower seeds	[40]
Myristica fragrans	Nutmeg	[41]
Carum carvi	Caraway	[42]
Cinnamomum verum	Cinnamon	[43]
Coffea Arabica	Coffee beans	[44]
Solanum tuberosum	Potato	[45]
Propolis	Propolis	[46]
Daucus carota subsp. sativus	Carrot	[47]
Zingiber officinale	Ginger	[48]

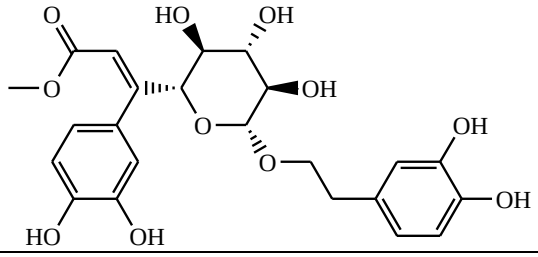
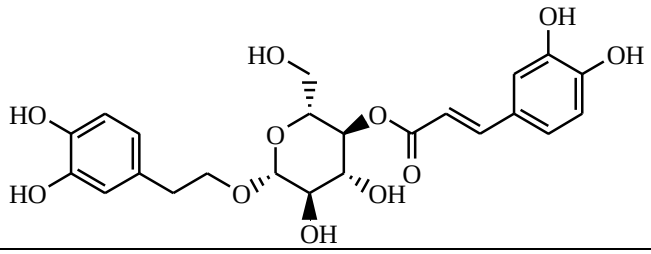
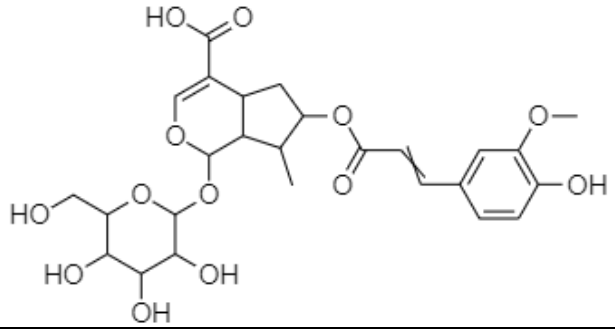
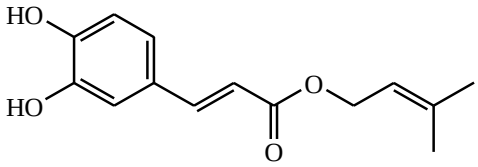
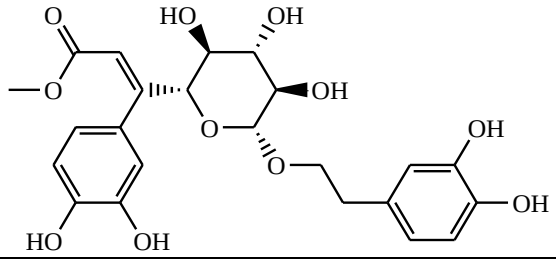
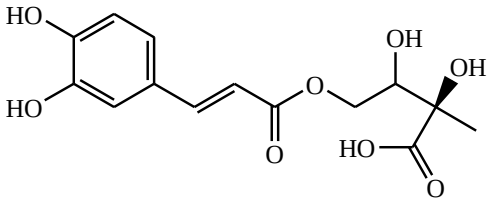
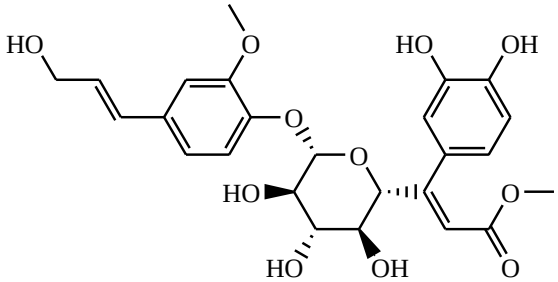


Scheme 2. Common biological sources of caffeic acid and derivatives.

Table 2. Caffeic acid derivatives with their biological activities.

Derivatives	Chemical structure	Activity	Reference
Ferulic acid		Antioxidant, antibacterial	[49, 50]
p-Coumaric acid		Antiplatelet, antioxidant, antibacterial	[51]
Chicoric acid		Anti-HIV	[52]
Fertaric acid		Gastroprotective, antioxidative	[53]
Vitexfolin A		Vasodilatory and analgesic	[54]
Dactylifric acid		Ant ulcerative, anti-atherogenic	[55]
Eutigoside A		Antiviral (SARs)	[56]
Coutaric acid		Antioxidant	[57]
Scrophuloside B		Antimalarial	[58]

Derivatives	Chemical structure	Activity	Reference
Robustaside E		Antimalarial	[59]
Dodegranoside B		Antihyperglycemic	[60]
Caftaric acid		Antimutagenicity, anti-genotoxic	[61]
Cynarin		Antioxidant	[62]
Neochlorogenic acid		Antioxidant, anti-inflammatory	[63]
Robustaside D		Antimalarial, Antiproliferative	[64, 65]
Chlorogenic acid		Antioxidant and DNA-Protective	[66]

Derivatives	Chemical structure	Activity	Reference
Calceolarioside D		Antioxidant	[67]
Calceolarioside A		Platelet Aggregation	[68]
Khainaoside B		Anti-viral (SARs), Covid-19	[56]
Prenyl caffeate		Antioxidant, Antifungal and Antibacterial	[69]
Calceolarioside B		Cytotoxic, antiproliferation	[70, 71]
(2R)-4-[(E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy-2,3-dihydroxy-2-methylbutanoic acid		Antioxidant and Enzyme Inhibitory, Anti-viral (SARs), Covid-19	[72, 73]
Khainaoside C		SARS/Covid-19	[56]

2.5. Pharmacokinetics.

CA is a major phenolic acid found in foods. Approximately 75-100% of total hydroxycinnamic acid is CA, which exists in free and esterified forms [74]. Generally, phenolic acids absorb through monocarboxylic acid transporter (MCT), which is present in caco-2 cells, but the cinnamic acid derivatives (CA, gallic acid, etc.) show a weak affinity towards MCT. So the absorption of these compounds occurs through paracellular diffusion [17, 75]. The pharmacokinetic process of CA starts with ingesting it in the bound form, i.e., esterified form. After reaching the small stomach, part of this is absorbed. The microbial esterases present in the colon break the ester portion of CA in its free form, which is available for absorption by the intestinal mucosa (approx 95%) [17, 76]. Then CA transmembrane flow into intestinal cells occurs via active transport facilitated by MCT [76]. The maximum plasma concentration of CA is seen only for 1 hour after the ingestion of food containing this compound. After this, plasma concentration decreased rapidly. To maintain the concentration, repeated dose is required every 2 hours [77]. After absorption, CA follows three processes of enzymatic conjugation (also called detoxification) with the help of three enzymes these are methylation (sulfotransferase), sulphation (UDP-glucotransferase), and glucuronidation (catechol-*o*-methyltransferease). Through this process, the compound becomes more hydrophilic. Thus, it reduces its toxicity and facilitates its elimination [78, 79]. CA is primarily excreted through urine (5.9 to27%) [74].

2.6. Biotransformation.

CA is converted into ferulic acid with the help of caffeate O-methyltransferase. CA is rapidly oxidized into tissue extracts by *o*-diphenol oxidases [80].

2.7. Mechanism of action.

Various scientific studies have reported various pharmacological activities of CA [81, 82]. It shows the cardiac protective effect by altering the action of various enzymes playing a crucial role in cardiac activity. Among these, cholinesterase, arginase, and angiotensin-converting enzyme (ACE) are important (Figure 4) [21, 22]. As the *in-vitro assays* of CA show the inhibition of lipid peroxidation of emulsified linoleic acid, it indicates the antioxidant property of this compound [83]. Another *In-vitro* study suggested that CA inhibits the enzyme α-amylase and α-glucosidase linked with type 2 diabetes, reducing the post-prandial increase of blood glucose (Figure 5) [84]. Various scientific studies investigate the anti-carcinogenic and anti-inflammatory properties of CA as it can be used in the treatment of colon cancer, liver cancer, prostate cancer, breast cancer, etc. Nuclear factor-kB (NF-kB) plays an important role in the upregulation of inflammatory cytokines and some enzymes like cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS) [85] etc., which have a significant role in the production of prostaglandin E2 (PGE2), anti-apoptosis, angiogenesis, and metastasis. Inhibiting these transcription factors results in anticancer and anti-inflammatory properties (Figure 6) [86].

3. Pharmacological actions

3.1. Cardioprotective activity.

A number of deaths are reported because of cardiovascular complications throughout the world. Around 5.0 million deaths in developed nations and about 9.0 million deaths in developing nations are due to cardiac disorders [87]. Epidemiological investigations have suggested that intake of flavonoids in daily diet from various sources, mainly from natural sources, has an inverse relationship with long-term mortality from cardiac disorders [88].

Vallance, 2001 reported that the enzymes like ACE, cholinesterase arginase, and nitric oxide synthase are essentially involved in the functioning of the heart [89]. It was reported that CA and its derivatives modulate the renin-angiotensin-aldosterone system (RAAS) through multiple-target (Figure 4) [22, 85]. The prevention of cardiac mitochondrial dysfunction by caffeic acid was reported by Kamaran and Prince in 2010. The oxidative damage was induced by isoproterenol in Wistar rats. These animals showed an increase in serum troponins and heart mitochondrial lipid peroxidation products and an increased level of mitochondrial calcium, cholesterol, free fatty acids, and triglycerides. Whereas a marked decrease in the level of glutathione peroxidase reduced glutathione and a significant decrease in the activity of isocitrate, malate, succinate, α-ketoglutarate, and NADH dehydrogenases and cytochrome-C-oxidase were detected. All these observations indicate myocardial infarction in rats. The pre-treated Wistar rats showed a protective effect against isoproterenol in which all the above biochemical parameters were found to be at a normal level [90].

CAPE an ester form of CA has shown its antihypertensive effect in cadmium (Cd)-induced cardiac impairment in rats by inhibiting the nitric oxide (NO) production in the vessels and decreasing lipid peroxidation [91]. Cyclosporine-induced hypertension was also observed to be recovered by the use of CA in rats. In this study, a significant decrease in heart rates, as well as systolic blood pressure (SBP), was observed in the test drug-treated groups when compared with the standard drug (captopril). CA has shown a significant decrease in the action of Acetylcholinesterase (AChE), Butyrylcholinesterase (BChE), arginase, and ACE. On the other hand, the bioavailability of NO was improved with an increase in the activity of catalase as well as reduced glutathione content increased with a decrease in the level of malondialdehyde (MDA) as compared to cyclosporine-induced hypertensive rats [21]. Another study also revealed the ACE inhibitory activity of CA and oxidative imbalance were also suppressed. This study also showed that CA reduced plasma cholesterols, triglycerides, LDL (low-density lipoprotein) level while increased HDL (high-density lipoprotein) level was observed [92]. Oxidative stress reduction efficacy of CA was also revealed through another research finding in athero-sclerogenic diet-induced rat model. Reduction in atherosclerotic lesions was examined by the aortic staining technique [93, 94]. CA derivative CAPE was also effective in protecting doxorubicin-induced cardiotoxicity and increasing chemotherapeutic efficacy. Doxorubicin is effective against breast cancer, but its clinical use is limited due to its cardiotoxicity. This study has proven CAPE's breast tumor-suppressing and protective activity against doxorubicin-induced cardiotoxicity, which can be a promising approach to treating breast cancer [93].

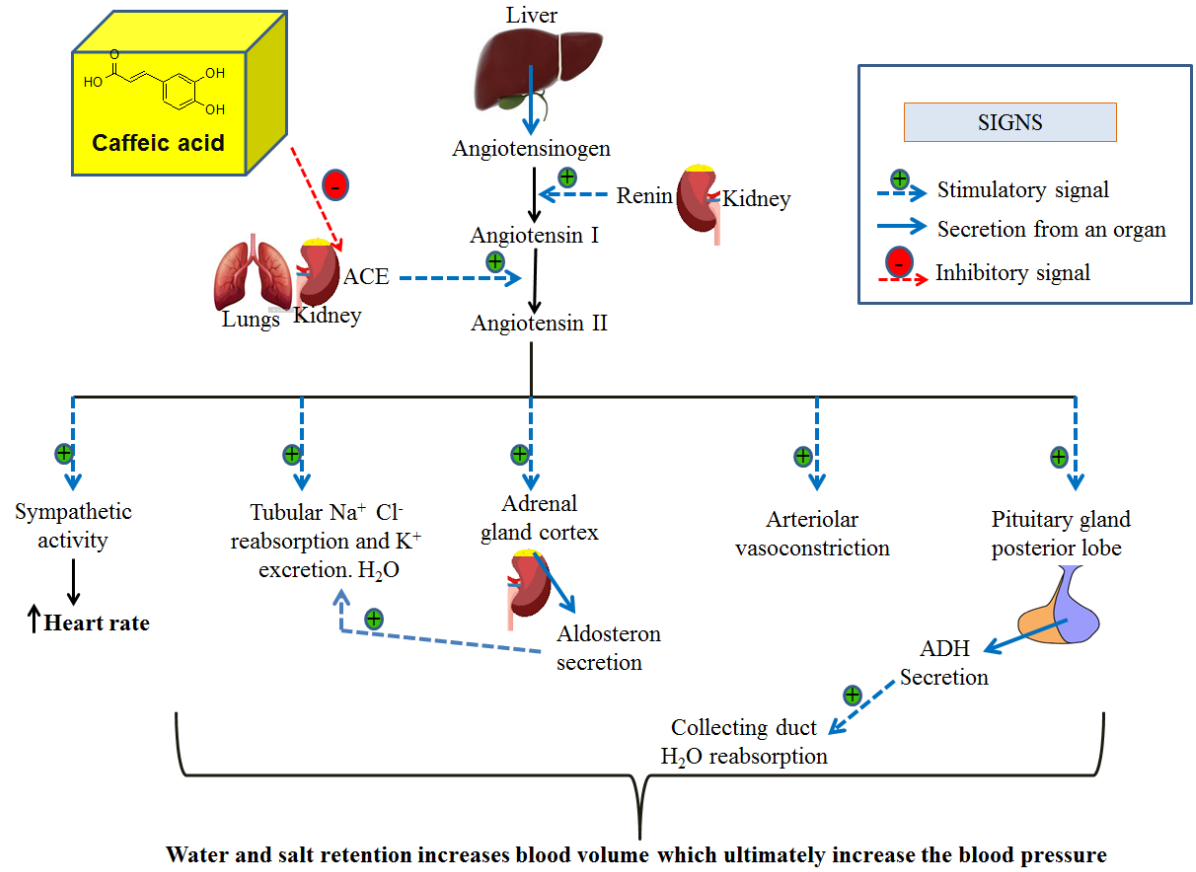


Figure 4. Mechanisms of hypertension and protective mechanism of caffeic acid.

3.2. Anti-inflammatory and antioxidant activity.

Phenolic acid-rich compounds significantly contribute significantly to the inhibition of oxidative damage [95]. A recent *in vitro* study was done on the antioxidant activity of CA in which the damage caused by free radicals was prevented significantly. The antioxidant effect of CA was shown with the help of some biological assays such as radical anion superoxide capture, crocin bleaching evaluation, captive property of hypochlorous acid, H_2O_2 capture, capturing capacity of the $ABTS^{*+}$ /$DPPH^{*+}$, and SOD-like activity [96]. Another *in vivo* and *in vitro* study was done on rats. In this, the protective effect against intestinal reperfusion injury was evaluated in small rat intestines by treating the rat with CA and chlorogenic acid. Caco-2 cell was found more susceptible to the uptake of CA than chlorogenic acid, hence much stronger antioxidant activity than chlorogenic acid. Thus CA was found to be a strong protectant in reperfusion injury in rat intestines [97]. The reactive oxygen species (ROS) is well known to have an important role in inflammation development by activating NF-kB and other transcription factors like AP-1; nuclear acetylation and deacetylation also have a crucial role in numerous inflammatory disorders (Figure 6). Such disorders can be managed by sufficient supplementation of antioxidants from polyphenols in daily diet [98]. A lipopolysaccharide-induced inflammatory study was done using primary bovine mammary epithelial cells (bMEC). CA was used as a test drug and reported a significantly decreased proinflammatory cytokines, *i.e.*, IL-8, IL-1β, IL-6, and tumor necrosis factor α. Other than these also observed the fading in the nuclear transcription factor activity via blocking kB inhibitor as well as α degradation and p65 phosphorylation in the NF-Kb pathway in a dose-dependent manner [99, 100]. Another study was done on the rotenone-induced mouse model to determine CA's locomotor and inflammatory activity. Rotenone results in the nigralneuro-degeneration, increased

inflammatory markers, decreased immunostaining for tyrosine hydroxylase (TH), and upregulation of genes encoding $CD_{11}b$ (a microglial surface antigen, COX-2, iNOS, and NFkB. Administration of CA improved motor activity, reduced microglial expression and inflammatory mediators, amended the nigral TH immunostaining, and improved neuroprotective activity [101]. In another study, researchers reported that CA protects against IL-1β-induced inflammatory responses and cartilage degradation in chondrocytes. In this study, CA blocked the formation of inflammatory intermediates and decreased the activity of cartilage matrix catabolic enzymes like ADAMTS5 MMPs, etc. Other than this, the degradation of collagen-II and aggrecan in chondrocytes induced by IL-1β, NF-κB activity, and the activation of the JNK (C-Jun N-terminal kinases) pathway were also prevented by CA [102]. Fabiola et al. also revealed CA's antioxidant and anti-inflammatory activity using a noise-induced hearing loss model in Wistar rats. The result findings showed its effect by decreasing NF-kB and IL-1 β expression and also prevented oxidative/nitrosative damage induced by noise in the cochlea. In this study, CA prevented cell death in the cochlear turn and protected auditory functions [103].

3.3. Antidiabetic activity.

Diabetes is a disease due to metabolic imbalance characterized by hyperglycemia. The development of hyperglycemia is due to the reduction or inhibition in the production or activity of insulin, or both may be responsible for the hyperglycemic condition [104]. Chronic diabetes is linked with the deviation in the physiology of vital organs like kidneys, heart, liver, etc., which may cause long-term damage and dysfunctions [105]. According to the "International Diabetes Federation Diabetes Atlas", 9^{th} edition, the estimated worldwide prevalence of diabetes in 2019 is 9.3% (463 million people), which is expected to rise to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 [106]. Diabetic cardiomyopathy is also prevented by CA in diabetic mice using cardiac tissue. CA and ellagic acid were used in this study with a 2% quantity of total normal diet in different groups compared to non-treated ones. Various parameters were examined, such as lipid profile, coagulability, oxidative stress, and inflammation. After 12 weeks, the cardiac tissue of treated animals showed the protective effects treated by these compounds, which caused a decrease in the level of triglyceride, increased plasma insulin level, decreased plasma glucose level, anti-coagulatory effect, antioxidative effect, and anti-inflammatory properties in cardiac tissue. According to this study, supplementation of these compounds might be helpful in diabetic cardiomyopathy prevention [107]. Various studies suggest that CA also is useful in diabetic nephropathy. It happens in diabetic patients due to high blood glucose levels. Sometimes, high blood glucose levels can produce damaging effects on the kidneys, which may affect the filtration process, and the damaged part becomes leaky. Thus, it allows the protein to come into the urine [108]. It has been reported that 40% of total diabetic patients suffer from diabetic nephropathy, which is the major cause of chronic kidney disease and end-stage renal disease all over the world [109]. It is proved by a research study that CA faded diabetic nephropathy via modulation of autophagy pathway through inhibition of autophagy regulatory miRNAs in high-fat diet-induced diabetes in rats [110]. Another *in-vitro* study has shown the antidiabetic activity of CA derivatives containing plants. Leaf extract from *Ocimum gratissimum* L. (Oc) plant and stem bark extract from *Musangacecropoides* R. Br. ex Tedlie (Mu) plant were used as antidiabetic potential. Four different parameters were analyzed to check the activity, (1) Insulin secretion using INS-1 cell line (2) Insulin sensitization(Glut-4 translocation) using L6 myoblast cells (3) Protection

against hydrogen peroxide oxidative stress (Cell mortality) (4) Glucose-6-phosphate (G6P) activity using liver microsomal fraction. The study has shown increased insulin sensitivity and insulin secretion. G6P activity and oxidative stress were found to be decreased with Oc extract. However, no positive response was observed with Mu extract. Oc extract required further *in-vivo* study to justify its anti-diabetic effect. It might be a good approach to curing diabetes in humans [111].

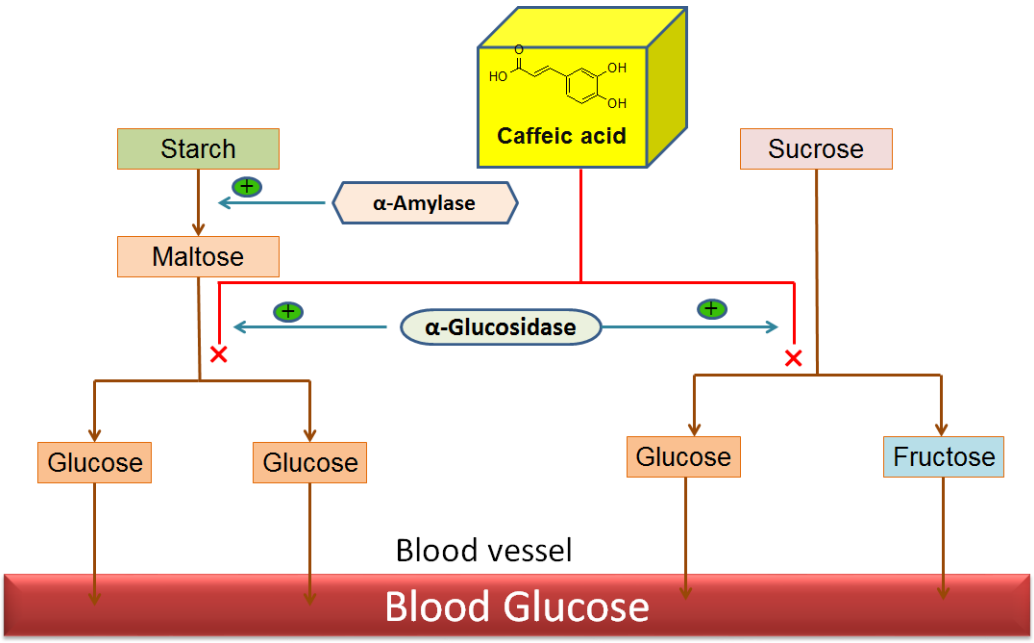


Figure 5. Mechanism of increasing blood glucose level as well as a protective mechanism of caffeic acid.

3.4. Hepatoprotective activity.

The liver is the largest solid organ and the largest gland, which helps in the metabolism and excretion of waste products from the body [112]. The liver detoxifies the substances before going into the systemic circulation after it has been absorbed from the digestive system [113]. Death of the person occurs within minutes due to total loss of liver function. Thus, it has great importance to work properly. To properly function and maintain good health, liver damage, such as fatty liver, liver fibrosis, and liver cirrhosis, should be avoided [112]. Various scientific researchers have proven that CA prevents liver damage through different mechanisms [114]. CA prevented liver cirrhosis by inhibiting the 5-lipoxygenase enzyme in the carbon tetrachloride-induced cirrhosis in rats. In this study CA significantly decreased the marker of liver damage and lipid peroxidation as well as prevented the depletion of glycogen content [115]. Nickel is a toxic metal for the human body which exposed to the body through various ways like water, food, or environmental pollution, which affects the function of various organs like the liver, kidney, brain, lungs, etc. Among these liver is the most susceptible to nickel toxicity [116, 117]. *In vivo* study of animals has shown that CA is also useful to prevent liver damage by nickel. In this study, oxidative damage was induced by nickel which caused hypersecretion of important enzymes present in the liver, such as alanine transaminase (ALT), alkaline phosphatase (ALP), aspartate transaminase (AST), lactate dehydrogenase (LDH), gamma-glutamyltransferase (GGT), etc. and also enhanced the lipid peroxidation as well as caused decreased in the level of catalase (CAT), superoxide dismutase (SOD, glutathione peroxidase (GPx) and glutathione S-transferase (GST). Treated with CAreversed in the level and activities of these enzymes to the optimum level [118]. Antihyperlipidemic and

hepatoprotective activity of phytophospholipid complex of CA was also observed using an animal rat model [119]. These studies suggested that the use of CA might prevent liver damage.

3.5. Anticancer activity.

Cancer is a major cause of death all over the world. Total numbers of cancer cases and deaths are expected to increase as the population increases rapidly [120]. Research findings have shown that the number of cases and the death rate is higher among males as compared to that of females. Studies data in America have shown that the risk of developing cancer is ten times more in persons having the age of over 65 years as compared to younger people. Among cancer cases, lung, breast, prostate, colon, and rectum cancers are most prevalent [121].

Anticancer effect CA was determined using human cervical cancer cells (HeLa). This study suggested that CA produced its antiproliferative effect via a mitochondrial apoptotic pathway in which this compound induced apoptosis by inhibiting Bcl-2 activity, which caused the release of cytochrome c and the activation of caspase-3 resulting in apoptosis [122].

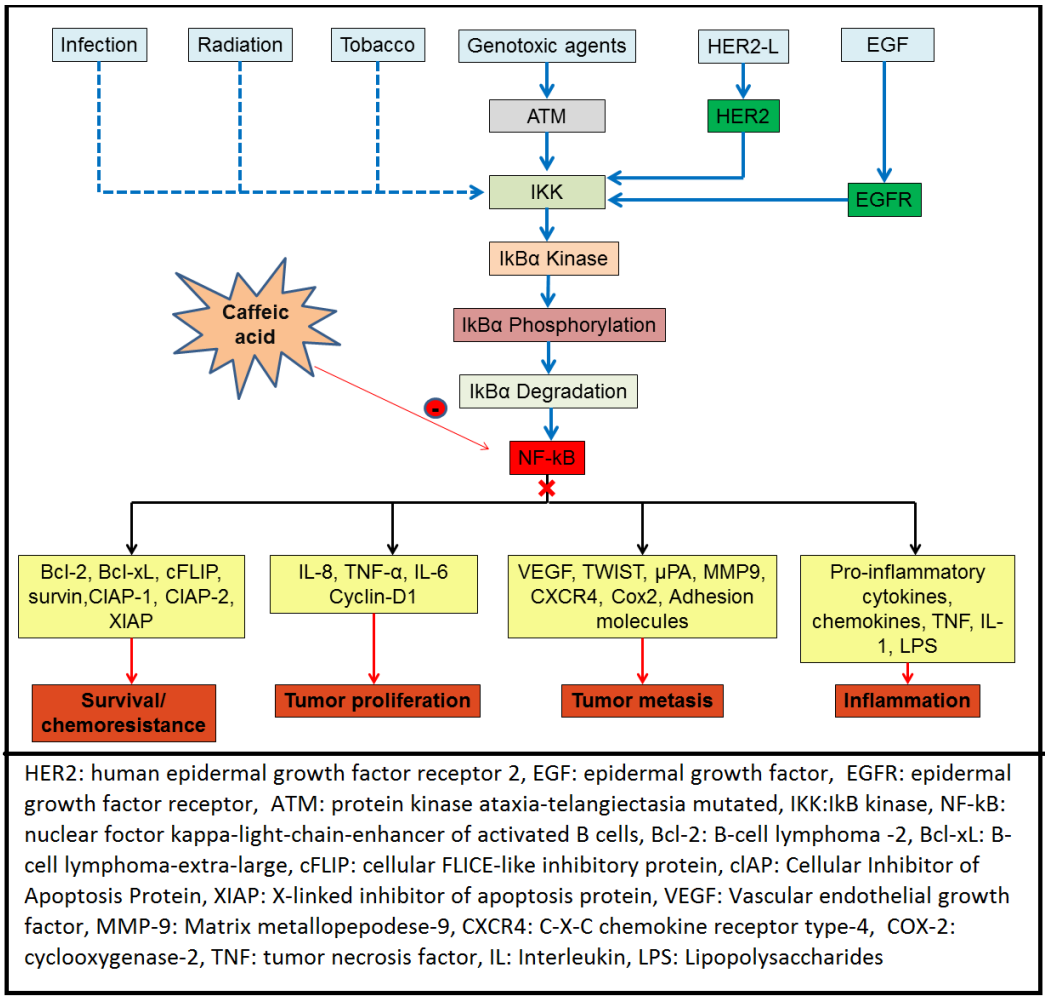


Figure 6. Mechanism of development of inflammation and cancer with the defence mechanism of caffeic acid.

HT-1080 human fibrosarcoma cell lines were used in another study for the determination of the anticancer activity of this compound. This MTT assay was done to evaluate the antiproliferative effect of CA, and oxidative stress was determined by lipid peroxidation. When the cells were treated with CA, the lipid peroxidation markers like TBARS, CD, and LHP were increased than control's, and increased DCF fluorescence witnessed the enhanced ROS level in HT-1080 cell lines. The mitochondrial membrane potential of HT-1080 cell lines was also altered when treated with CA. Increased DNA damage and apoptotic

morphological changes were also observed [123]. These studies suggested that CA has a strong anticancer effect on human cervical cancer cells and HT-1080 cell lines. Another study was performed using the combination of ashwagandha extract and CAPE to evaluate its anticancer activity. Research findings revealed the anti-metastasis activity of this combination [124]. Thus it may be used as an anticancer agent.

3.6. Antimicrobial effect.

The use of antimicrobial drugs increases the frequency and spectrum of antimicrobial-resistant infections in the community, resulting in certain untreatable infections in the developing and the United States. Antibacterial resistance significantly increases morbidity, mortality, and health care cost [125]. Antibiotics obtained from natural sources can act against the microbes that are resistant to modern antibiotics and have lower chances for the microbes to get resistance against these [126]. It has been reported that there are a number of natural-origin herbal drugs containing polyphenolic compounds that are available which have antimicrobial activity. These compounds produced their effect by inhibiting or killing the micro-organisms. Among these polyphenolic compounds, CA has strong antimicrobial activity alone or in combination with other drugs [127, 128]. Studies reported that besides polyphenolic compounds from herbal sources, CA is also an important component of the digestive juice of silkworm larvae. CA in silkworm larvae produces a defense mechanism against harmful intestinal bacteria. *Streptococcus faecalis* AD-4 affects the silkworm larvae [129]. Another study determined the antibacterial property of CA with the help of β-cyclodextrins encapsulation. In this study, CA was encapsulated with three types of cyclodextrins, β-cyclodextrin (βCD), 2-hydroxypropyl-β-cyclodextrin (HPβCD), methyl-β-cyclodextrin (MβCD). Still, the aqueous soluble inclusion complex was confirmed only for βCD and HPβCD. CA in its simple form was found more efficacious against *S. epidermidis than K. pneumoniae or S. aureus* than in encapsulated form. Still, both encapsulated forms of CA were found to be more effective than that without encapsulated form. As the βCD/CA has better stability, it may be a good choice as an antibacterial agent against skin infections [130]. Various research findings have shown the antifungal activity of CA [131]. An *in vitro* research revealed the antifungal activity of the esters of CA. In this study, a series of five esters of Cas, i.e., Methyl caffeate, Ethyl caffeate, Propyl caffeate, Isopropyl caffeate, and Butyl caffeate, were used against three different species of *Candida* (*C. albicans, C. tropicalis,* and *C. krusei*.) with different strains. To obtain the minimal inhibitory concentration (MIC) microdilution method was used in 96-well microplates. The overall findings of this study revealed weak to moderate antifungal activity. Methyl caffeate ester of CA presented the best antifungal against all strains of *Candida* species [132]. In another study of CAPE, an ester form of CA was made in combination with fluconazole and alone against *Candida albicans*. For the evaluation of *in vitro* interaction between CAPE and Fluconazole, time-kill microdilution and checkerboard assay were used. *Caenorhabditis elegans in vitro* model of infection was used for the evaluation of the antifungal activity of CAPE and fluconazole combination. The result confirmed that the combination of both showed considerable therapeutic potential against fluconazole-resistant *C. albicans* compared to that of an individual who can use CAPE or fluconazole [133].

Other than antibacterial and antifungal, CAs also exhibits antiviral activity against the influenza virus, herpes simplex virus (DNA virus), and poliovirus (RNA virus). This study was carried out on MDCK and Vero cells. Vero cells were infected with poliovirus and herpes simplex virus, while MDCK cells were infected with influenza virus. The infected cell culture

was treated with CA, quinic acid, caffeine, and chlorogenic acid individually. The results showed a marked inhibition in the growth of the influenza virus, whereas quinic acid, caffeine, and chlorogenic acid do not. The antiviral activity against herpes simplex and poliovirus also was shown by CA [134]. Another antimicrobial study was also performed using the combination of two phenolic combined (1) Caffeic acid and (2) Ferulic acid. Both the phenolic combined showed antimicrobial activity as an individual as well as in the combination of both against *Escherichia coli* and *Listeria monocytogenes* [135]. These studies suggested that CA exhibits potent antimicrobial properties.

3.7. Antiviral activity.

At the end of 2019, a severe respiratory coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) developed as a pandemic [136]. WHO report stated that by July 2020, SARS-CoV-2 had infected more than 13 million people and killed more than 0.5 million [137]. COVID-19 is the third life-threatening coronavirus outbreak to strike the human population in the twenty-first century [138]. Polyphenols are proving to be valuable as lead molecules for drug development against various human ailments, according to mounting data [139]. Polyphenols have been shown in recent research to have the ability to fight COVID-19 [140]. Caffeic acids, which have two phenolic hydroxyl moieties and are found in coffee, fruits, and vegetables, are one of the most prevalent plant-based Polyphenols [141]. Caffeic acids have been shown to exhibit substantial virucidal effects against the herpes simplex virus [142], the influenza virus [134], and the SFTS (severe fever with thrombocytopenia syndrome) virus [143]. 27 caffeic acid derivatives were screened from a library for the discovery of novel naturally occurring anti-COVID-19 compounds towards 5 distinct SARs-CoV-2 therapeutic targets, along with binding affinities analysis and docking were performed by Molegro Virtual Docker software [144]. Using the following website http://www.swissadme.ch, an in silico ADME analysis was performed to explore the physicochemical features of powerful hits, such as water solubility, lipophilicity, and pharmacokinetics [145]. Most of the caffeic acid derivatives manifest good binding affinities with distinct SARs-CoV-2 targets. Calceolarioside B was found to be a potent compound among all 27 caffeic acid derivatives. Furthermore, calceolarioside B has anti-RSV (respiratory syncytial virus) properties, implying that calceolarioside B-rich foods might be a feasible alternative method for COVID-19 prevention and therapy. It has the ability to decrease IL-6 synthesis in order to exhibit anti-inflammatory characteristics in addition to its antiviral capabilities.

While some of the most effective caffeic acid derivatives may be found in vegetables and fruits, including Spinach (*Spinacea oleracea*), a popular green vegetable, which has been discovered to be high in CAFDs such as Spinacetin and Pluletin [146]. Blueberry (*Vaccinium dunali anumas*), rich in 6′-*o*-caffeoylarbutin, is widely used in traditional medicine [147]. Research on sunflower (Helianthus annuus) suggested that cynarin as a constituent is profoundly found in sunflower [148]. So these foods are enriched with natural-health supplements that strengthen the immunity and treatment efficiency of COVID-19 patients by 1) CAFDs' effectiveness in lowering the viral load and decreasing the infectious time, 2) optimum dosage regimen depending upon the viremia effect. 3) In COVID-19 patients, the effect on antibody production, inflammatory signaling, and oxidative stress was studied [56].

3.8. Neuroprotective activity.

The current state of study is primarily focused on neurodegenerative disorders such as Parkinson's and Alzheimer's. These are the most prone diseases in the world, and they are incurable. The production of reactive oxygen species (ROS) has been shown to play a role in neuronal death in various age-related neurodegenerative disease complements. ROS are produced as a natural consequence of regular oxygen metabolism in a healthy state and play crucial roles in cell signaling and homeostasis [149]. ROS can significantly alter the structure and function of cell membranes and cause oxidative damage to tissues and organs. The hippocampus has been demonstrated to be one of the most sensitive areas of the brain to oxidative stress, and neuronal cells in the hippocampus that are constantly destroyed will eventually cause neurodegenerative illnesses [150]. Increased ROS modifies a number of signaling targets in the nervous system, including protein kinase A (PKA) and cyclic AMP response element-binding protein, according to studies (CREB) [151, 152]. Some phenolic compounds contain caffeic acid, which has neuroprotective activity in behavioral studies, is related to anti-cholinesterase in tissues or animal models, and also in cell line studies [153].

Rotenone-induced neurodegenerative diseases are very much common in people who are exposed to the pesticides like rotenone. Rotenone tends to inhibit the mitochondrial complexes and alter dopaminergic neurons' activity [154]. Rotenone leads to toxicity and increases cytokines and nitric oxide synthase or nitic oxides release. Caffeic acid suppresses the microglia cells and decreases the regulation of nitric oxide synthase; it also improves locomotor activity by inhibiting cytokines [155].

Caffeic acid is a potential molecule for treating neurodegenerative illnesses and other organ damage issues such as lung, kidney, and liver [156]. Based on its anti-inflammatory properties, it may have a potential neuroprotective effect [157]. The study's goals are to look at how caffeic acid affects locomotor impairment and microglia activation in rotenone Parkinsonian rats [158].

Caffeic acid was administered in addition to rotenone in treatment groups with different dosage regimes. Further, behavioral activities like locomotor, pole, rota-rod, and cylinder tests were performed. These behavioral abnormalities identified in the current study were linked to lower striatal dopamine levels, as previously documented [159]. Caffeic acid (10 mg/kg) raised the motor functions activity score and reared compared to the rotenone group and the rotenone + caffeic acid (2.5 mg/kg) group. Furthermore, ELISA measurements of striatal COX-2, iNOS, and NFB revealed higher levels in the rotenone group compared to the vehicle (3.28-fold, 10.82-fold, and 3.2-fold increases, respectively). Caffeic acid at higher dosages (5 or 10 mg/kg) inhibited the expression of striatal COX-2, iNOS, and NFB in contrast to the rotenone control group. These beneficial effects led, at least in part, to caffeic acid's neuroprotective properties and the improvements in locomotor activity [101].

4. Toxicity aspects

4.1. Reproductive and developmental toxicity study of CA in mice.

Reproductive toxicity study was done using 80 virgin female mice (7 weeks old, 25-31 g) and 80 male mice for mating (10 weeks old, 33-40 g). Animals were divided into four groups, namely the control group (0 mg/kg/day), low dose group (0.15 mg/kg/day), mid-dose group (5 mg/kg/day), and high dose group (150 mg/kg/day) in which dose of CA was administered in

female mice using gavage. The dosing was started before 14 days of mating and continued until the end of the lactation period. The result found that 5 mg/kg/day and 150 mg/kg/day dose of CA had anti-implantation activity during early pregnancy in mice and also affected fetal weight gain. No maternal toxicity, fetal teratogenesis, or post-natal effects on pup development were observed at any above-mentioned CA dose. 0.15 mg/kg/day dose of CA had shown no-observed-adverse-effect level (NOAEL) for pregnant female mice in this study [160].

Table 3. Completed and active Clinical trials on caffeic acid [161-163].

Treatment	Condition/ Procedure	Outcomes	Phase	Status	Clinical trials Identifier
Dexamethasone, Caffeic acid 300 mg tablets, three times a day	Patients with immune thrombocytopenia	Improves platelet count values; mild adverse effects	Phase III	Completed	NCT02351622
Dexamethasone, Caffeic acid 300 mg tablets, three times a day	Patients with immune thrombocytopenia	Anticipated results on sustained patients response after 6 months since the treatment started	Phase IV	Completed	NCT02556814
Caffeic acid 300 mg, Tablets, Three times a day	Patients with advanced esophageal squamous cell cancer	Anticipated results on 3 months progression-free survival and 1-year overall survival	Phase III	Active	NCT03070262

5. Conclusions

The published data by numerous scientific studies have confirmed that CA exerts beneficial effects on the human body's immune system. It also exhibits complex pharmacological behaviors additionally to immunity. This compound's antioxidant effects mitigate the risk of multiple infectious diseases. CA was proposed as a pure and healthy food additive substitute that could be used to replace toxic chemicals used for the production of various antibiotics, growth promoters, and other therapeutics formulations that have multiple side effects. The use of CA could save the cost of the pharmaceutical of expensive medicines. However, to date, there are studies on the beneficial performance of CA, but also the requirement to fully elucidate the more support from clinical works so that it may be utilized as FDA approved naturally-origin drug. We also recommend further works on new vista as nanomedicine with systematic combinations with other nano-drug carriers and nanoassemblies.

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Conflicts of Interest

The authors declare no conflict of interest.

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