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Bridging Tradition and Modern Medicine: Caffeic Acid as a Multifunctional Therapeutic Agent in 2025

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KEYWORDS

Caffeic acid, Comprehensive attributes, Source, Antimicrobial activity, Collaborative relevancy, Bioactive compound

ABSTRACT:

Background

Caffeic acid (CA), a naturally occurring hydroxycinnamic acid abundant in coffee, fruits, vegetables, and propolis, represents a molecular bridge between traditional herbal medicine and modern pharmacotherapy. Characterized by both an acrylic acid moiety and a phenolic hydroxyl group, CA and its derivatives—most notably caffeic acid phenethyl ester (CAPE)—exert a wide range of biological activities, including antioxidant, anti-inflammatory, antimicrobial, anticancer, neuroprotective, and cardiometabolic effects. Both naturally isolated and chemically synthesized derivatives have also shown synergistic potential with antibiotics and other therapeutics, positioning CA as a promising multifunctional bioactive compound.

Objectives

This review consolidates recent advances (2022–2025) in understanding the pharmacological potential of caffeic acid, with emphasis on its molecular mechanisms of action, pharmacokinetic challenges, formulation strategies, and therapeutic relevance. Special focus is placed on antimicrobial applications, transcriptional regulation (Nrf2, NF-κB, STAT3),

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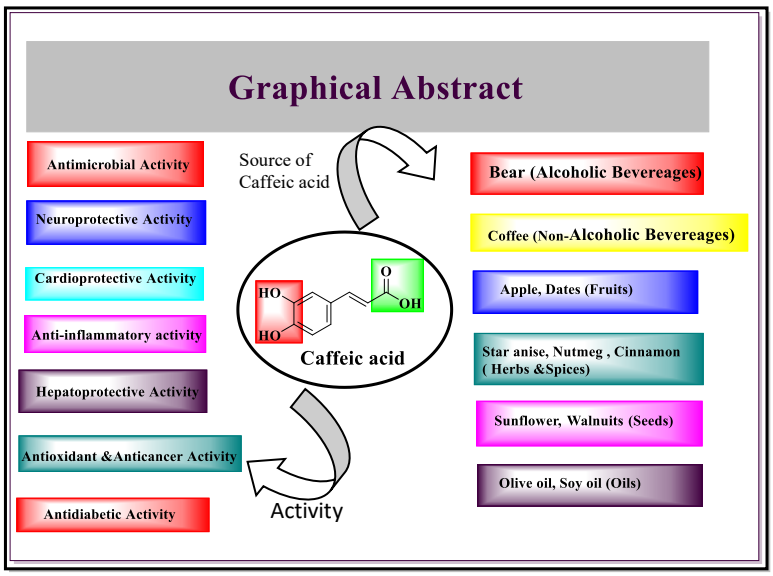
mitochondrial protection, and bioavailability-enhancing approaches, including nanotechnology and medicinal chemistry–driven modifications.

Conclusion

Current evidence highlights CA's diverse pharmacological profile and its dual role as both a traditional remedy and a modern therapeutic candidate. Despite strong preclinical support, translation to clinical practice remains limited by issues of bioavailability, metabolism, and long-term safety. Future directions should prioritize mechanistic studies, synergistic drug-combination strategies, and structure–activity relationship optimization to unlock the full therapeutic potential of CA and its derivatives.



Introduction

Polyphenolic compounds are central to both traditional herbal medicine and modern nutraceutical research. Among these, caffeic acid (3,4-dihydroxycinnamic acid) has attracted growing attention due to its broad pharmacological spectrum and historical presence in herbal remedies. Traditionally, caffeic acid-rich plants (e.g., Echinacea, Salvia, Rosmarinus, and bee propolis) were employed for their tonic, antimicrobial, and anti-inflammatory properties. In modern biomedicine, mechanistic insights demonstrate CA's ability to modulate redox signaling, inflammatory cascades, and oncogenic pathways. Its versatility, spanning antioxidant to anticancer effects, positions it as a unique candidate for bridging ethnopharmacology with evidence-based medicine. [132-136] Caffeic acid (CFA) is a natural phenolic compound (a secondary metabolite of plants), belonging to the family of hydroxycinnamic acids (HCAs).

CFA is biosynthesized in plant tissues via the endogenous shikimate pathway, which is known to be responsible for the production of aromatic amino acids from glucose. Phenylalanine is a precursor for the synthesis of CFA. CFA can be found in many products consumed daily, such as coffee beans, green tea, tomatoes, potatoes, artichokes, carrots, lettuces, dark plums, cherries, gooseberries, blackcurrants, grapes, and herbs (basil, rosemary, oregano) (Fig. 1). CFA and other phenolic compounds are involved in plants' defense mechanism against insects, pathogens, animals (biotic stresses), and environmental conditions, such as excess water, drought, low and high temperatures, salinity, heavy metals, and ultraviolet radiation (abiotic stresses). Numerous in vitro and in vivo studies have shown that CFA has many biological properties, including anti-inflammatory, anticancer, antibacterial, antiviral, antidiabetic, hepatoprotective, and cardio protective activity. [1] The presence of a catechol group with a chain

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of α, β-unsaturated carboxylic acids in the chemical structure of CFA affects its antioxidant properties. This antioxidant mechanism of action is based on the generation of an o-chinone group after the electron donation. Conjugation of the catechol group with the double side binding of o-quinone causes electron delocalization, increasing the stability of the o-quinone radical and the antiradical activity of CFA. CFA can also form complexes with metals (e.g., with iron or copper), inhibiting the decomposition of peroxides, which limits the formation of free radicals and their negative impact on the organism. The excess of free radicals in the organism contributes to unfavorable changes/damage in the structure of proteins, lipids, carbohydrates, and DNA and triggers a number of diseases (e.g., atherosclerosis, asthma, cancer, diabetes, Alzheimer's, and Parkinson's diseases). [131]

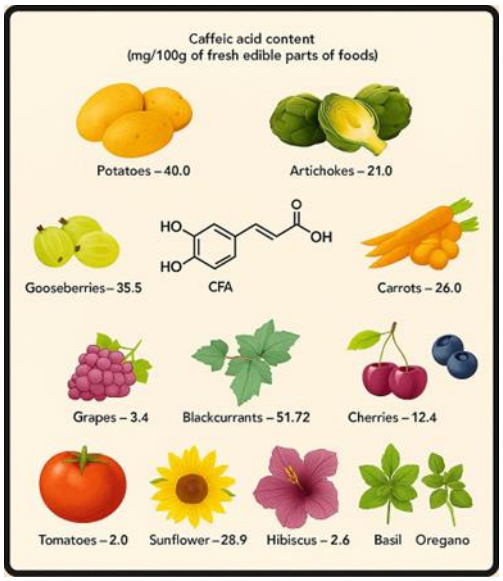

Fig. 1: Source of caffeic acid

Caffeic acid (3, 4-dihydroxy-cinnamic acid) is an organic molecule with hydroxycinnamic acids that appears in food as Chlorogenic acid, a quinic acid ester. A relatively wide class of substances known as polyphenols includes hydroxycinnamic acids as a subclass. These organic compounds, which are distinguished by the presence of many phenols' structural units, serve as the building blocks for special biological, chemical, and physical characteristics. Their bioavailability is significantly impacted by this substantial structural variation. Different harmful microorganisms, such as bacteria, fungi, and viruses that define serious illnesses and disorders, were exposed to both humans and animals [1]. As with chronic or acute infections, some immune-compromised people are also exposed to bacteria that cause disease through contact with food or water, which can result in infection [2]. The invasion of diverse pathogenic pathogens by genetically susceptible people also modifies the makeup of the microbiota [3, 4]. Treatment of microbial infection becomes difficult when attempting to associate with numerous resistance mechanisms [5]. In contrast to conventional antibiotics and other known antimicrobial medicines, bacterial, fungal, and viral infectious agents proliferated [6–8]. Since then, several strategies for dealing with microbial illness and thwarting their antimicrobial agent resistance mechanisms have been developed [9]. Developing effective antibacterial medicines that use phenolic compounds derived from plants to combat human pathogenic microorganisms [10, 11]. Exemplification: Caffeic acid (3, 4-dihydroxy cinnamic acid), the most abundant phenolic ingredient in these plants, is present in fruits, wine, coffee, olive oil, and legumes [12]. Esters, organic esters, glycosides, and amides are certain sugar derivatives that cling to a variety of caffeic acid-like monomeric, dimeric, trimeric, and oligomeric compounds that are thought to be physiologically active antioxidants [13-15]. Therefore, research has been analyzed emphasizing its extra qualities and recognizing it as an antithrombotic, [16] antihypertensive, [17] antidiabetic, [18] anticancer, [19] and anti-inflammatory agent [20]. These studies also acknowledge its additional features as being useful in treating microbial infections. Even with the extensive use of caffeic acid, basic considerations such as water insolubility limit its applicability. Encapsulations into polymeric nanoparticles or grafting to polymeric molecules, which are distinctively different approaches, have been successfully applied in their application to solving solubility problems, and improving modes of action and delivery as well [21-22]. An alternate strategy, known as combination treatment, has been implemented in conjunction with antibiotics or other antimicrobial medicines for higher effectiveness. [23]

Caffeic acid (CA) and its derivatives are widely distributed in the plant kingdom, occurring in free form or conjugated forms (esters, glycosides, amides) across many dietary and medicinal plants. A 2024 review cataloguing plant-derived CA derivatives identified at

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least 17 classes of compounds (e.g. caffeoyl esters, caffeoyl glycosides, caffeoylquinic acids, caffeoyl shikimic acids, caffeoyl tartaric acids) in species from diverse families, underscoring CA's broad distribution and structural diversity in nature. These plants include common dietary sources such as coffee beans, tea leaves, olives, fruits (berries, apples), and herbs, as well as less common species used in traditional medicine. For example, herbal infusions from native Argentine medicinal plants (such as Larrea cuneifolia, Larrea nitida, Grindelia chiloensis) were found to have high phenolic content, including substantial amounts of caffeic acid, correlating with strong antioxidant activity and traditional health-promoting use. Ethnomedically, CA-rich plants and extracts have been used in a variety of preparations. Propolis, a resinous substance produced by bees, has been a long-standing source of caffeic acid phenethyl ester (CAPE) and other CA derivatives in folk remedies, particularly for wound healing, antimicrobial applications, inflammation, and skin ailments. Recent experimental work on CA's analgesic potential, such as in Ximenia americana bark extract, confirms its traditional use for pain relief and supports underlying mechanisms such as interaction with nitric oxide and glutamatergic signaling pathways. Phytochemically, recent studies also show that environmental factors (such as geographical origin, growth conditions, harvesting time) affect CA content in medicinal plants. The 2024 overview of plant-derived CA and derivatives emphasizes that yields of CA and its conjugates vary greatly depending on plant species and part (leaves, flowers, roots), and that structural variants (e.g., caffeoylquinic acids vs. caffeoyl esters) may have distinct pharmacological profiles (Table 2). Traditional relevance is strengthened by modern findings: many CA-rich herbs traditionally used for gastrointestinal, inflammatory, skin, or infectious disorders demonstrate significant antioxidant, antibacterial, hepatoprotective, or cardioprotective effects in recent in vitro/in vivo studies. In food science, CA's anti-ageing action on dermal cells (inhibiting MMPs and pro-inflammatory cytokines under UV-exposed conditions) supports traditional topical uses of CA-bearing herbal extracts for skin protection. [137-140]

The researcher subsequently established the considerable bioactivity of caffeic acid from a variety of sources and its use in a variety of fields, including the chemical scaffolds for the synthesis of numerous derivatives developed in (Fig. 2, 3, and 4) [24-25].

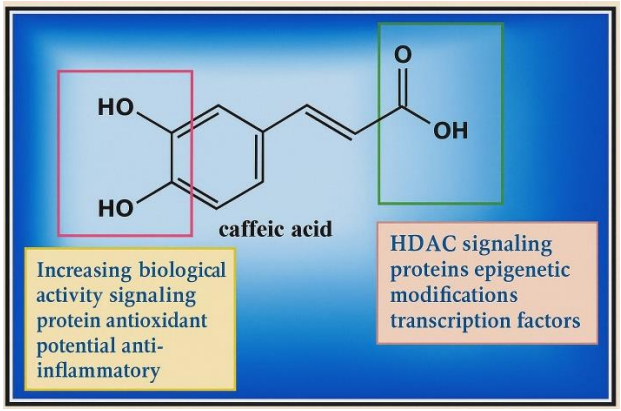

Fig. 2 Depicts the caffeic acid's chemical structure while demonstrating plausible biological and pharmacological effects

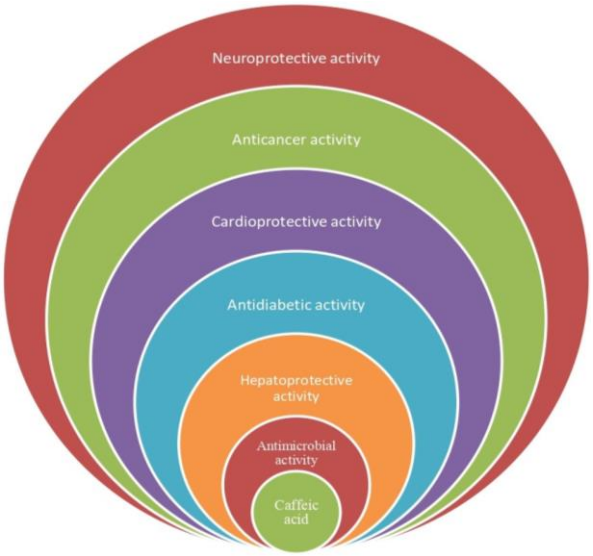

Fig. 3 Pharmacological activity of caffeic acid

Biological Attributes

The group of phenolic chemicals known as hydroxycinnamic acids is frequently found in a typical diet. CA is a well-known form of hydroxycinnamic acid, which is extracted by plants as a secondary metabolite [27]. The primary sources of CA are carrot, ginger, apple, star anise, berry fruits, coffee, olive oil, roasted beans, etc. (Table 1) [28]. The group of phenolic chemicals known as hydroxycinnamic acids is frequently found in a typical diet [29-31].

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Table 1. Biological attributes of caffeic acid

Common Names	Biological Names	Mean Content	Reference
Daucus carota subsp. sativus	Carrot	0.02 mg/100 g FW	[32]
Vitis vinifera	Grapes	0.16 mg/100 ml	[33]
Helianthus annuus	Sunflower seeds	8.17 mg/100 g FW	[34]
Myristica fragrans	Nutmeg	16.30 mg/100 g FW	[35]
Malus domestica	Apple	0.68 mg/100 ml	[36]
Olea europaea	Olive oil	1.33 mg/100 g FW	[37]
Solanum tuberosum	Potato	1.62 mg/100 g FW	[38]
Brassica oleracea	Cauliflower	1.00-02 mg/100 g FW	[39]
Thymus vulgaris	Thyme	11.70 mg/100 g FW	[40]
Zingiber officinale	Ginger	15.50 mg/100 g FW	[41]

Pharmacological Activities

Caffeic acid (CA) exhibits a broad spectrum of pharmacological activities that contribute to its therapeutic potential. Its antioxidant and anti-inflammatory effects are mediated through direct

Table 2. Summary Table: Recent Studies (2022–2025)

Author (Year)	Model	Dose/Formulation	Main finding	Source
Pavlíková et al., 2022	Review (in vitro/in vivo)	N/A	Comprehensive mechanisms: antioxidant, anti-inflammatory, anticancer pathways (Nrf2, NF-κB, PI3K/Akt)	Int J Mol Sci. 2022 (review)
Sun et al., 2022	In vivo (osteoarthritis models)	CAPE (systemic)	Attenuates osteoarthritis via NRF2/HO-1 activation and NF-κB inhibition	Int J Mol Med. 2022.
Fang et al., 2023	In vitro (breast cancer cells)	CAPE	Suppresses metastasis, inhibits migration/invasion and EMT via FGFR1 inactivation	PLOS ONE. 2023.
Park et al., 2023	In vitro (HUVECs)	Caffeic acid methyl ester (CAME)	Anti-inflammatory via HO-1/Nrf2 induction and NF-κB inhibition	PMC Article. 2023.
Jokubaite et al., 2024	Formulation study (in vitro, ex vivo)	Hydrophilic gels (poloxamer/carrier)	Semi-solid formulations improved biological activity and delivery potential	Foods/Pharm Formulation. 2024.

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Gong et al., 2024	In vitro & in vivo (HCC models)	CAPE derivative (CAPE 1')	Enhanced anti-HCC activity compared to sorafenib in models; overcomes resistance mechanisms	Sci Rep. 2024.
Wang et al., 2024	Nanoencapsulation (food-grade peptides)	Self-assembled rice peptide nanocarrier encapsulating CAPE	Improved stability and bioaccessibility of CAPE	Foods. 2024.
Bahrami et al., 2024	In vitro (melanoma A375 cells)	Free CAPE vs Liposomal CAPE	Liposomal CAPE showed higher apoptotic induction and efficacy vs free CAPE	PubMed 2024.

reactive oxygen species (ROS) scavenging, upregulation of cytoprotective pathways such as In the context of anticancer potential, CA induces apoptosis, inhibits the proliferation of cancer cells, and enhances the chemosensitivity of conventional anticancer drugs, demonstrating promising adjuvant effects. Neuroprotective activities are evidenced by improvements in mitochondrial integrity, modulation of neurotransmitter systems, and attenuation of neuroinflammation, highlighting its potential role in neurodegenerative disorders. Additionally, CA confers cardiometabolic benefits by enhancing insulin sensitivity, protecting endothelial function, and reducing lipid accumulation, which may mitigate the risk of metabolic syndrome and cardiovascular diseases. Finally, its antimicrobial and antiviral activities extend to both bacterial and fungal pathogens as well as viral infections, suggesting that CA and its derivatives can serve as effective natural agents against a wide range of infectious diseases. Collectively, these pharmacological effects underline the multifaceted therapeutic potential of caffeic acid and provide a mechanistic basis for its traditional and modern medicinal applications.

Derivatives and Formulation Strategies

Caffeic acid (CA) derivatives have been developed to enhance its pharmacological efficacy and overcome limitations related to bioavailability and stability. Among these, caffeic acid phenethyl ester (CAPE) is one of the most potent, exhibiting superior anti-inflammatory, anticancer, and neuroprotective activities compared to the parent compound. In addition to CAPE, various amides, esters, and hybrid molecules have been synthesized, demonstrating improved biological activity and selectivity in preclinical studies. To further address issues of solubility, stability, and targeted delivery, advanced nanoformulation strategies have been employed, including liposomes, polymeric nanoparticles, and solid dispersions. These formulations not only enhance the physicochemical properties of CA and its derivatives but also improve pharmacokinetic profiles, enabling better tissue distribution and therapeutic efficacy. Collectively, these chemical modifications and innovative delivery systems represent promising approaches to maximize the clinical potential of caffeic acid.

Pharmacokinetics, Safety, and Limitations

Caffeic acid (CA) exhibits limited bioavailability due to rapid metabolism, primarily through glucuronidation and sulfation, which significantly reduces its systemic exposure after oral administration. Despite these pharmacokinetic challenges, preclinical studies have consistently demonstrated a favorable safety profile, with low toxicity observed in cell culture and animal models. However, long-term safety data in humans remain scarce, and comprehensive clinical studies are limited, constraining the direct translation of preclinical findings into therapeutic applications. Additionally, the variability in absorption, metabolism, and distribution across individuals further complicates its clinical use. Therefore, strategies such as chemical modification, formulation optimization, and advanced delivery systems are essential to enhance bioavailability and therapeutic efficacy while ensuring safety.

Anti-microbial action

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Antibiotic use broadens the range and frequency of illnesses that are resistant to treatment, leading to some infections that are incurable in both developed and developing countries. Morbidity, mortality, and healthcare costs all considerably rise as a result of antibacterial resistance [42]. Natural antibiotics provide fewer opportunities for microorganisms to develop resistance against them and can combat microbes that are resistant to current antibiotics. According to reports, some herbal medicines of natural origins contain polyphenolic components that have antibacterial activity. These substances work by stopping or destroying the microorganisms to create their impact. In addition to these polyphenolic elements, CA exhibits potent antibacterial activity both on its own and when combined with other medications. In addition to polyphenolic chemicals from herbal sources, studies have shown that CA plays a significant role in the digestive juice of silkworm larvae [43]. A defense system against dangerous intestinal bacteria is produced by CA in silkworm larvae. The silkworm larvae are affected by Streptococcus faecalis AD-4. Another study used the encapsulation of cyclodextrins to determine the antibacterial property of CA. In this study, CA was enclosed in three different types of cyclodextrins: 2-hydroxypropyl-cyclodextrin (HP-CD), methyl-cyclodextrin (M-CD), and -cyclodextrin (CD) [44]. However, only for CD and HP-CD was the aqueously soluble inclusion complex established. Plenty of investigations have shown that CA has antifungal properties [45]. Three distinct breeds of Candida i.e., C. krusei, C. albicans, and C. tropicalis with several strains served as specimens for this inquiry. Methyl caffeine, Ethyl caffeine, Propyl caffeine, Isopropyl caffeine, and Butyl caffeine were employed in a sequence of five C as esters. In 96-well microplates, the microdilution method was employed to produce the minimum inhibitory concentration (MIC) [46]. Overall, this study's findings showed modest to moderate antifungal activity. The most effective antifungal against all strains of Candida was the CA methyl caffeate ester. In a different CAPE research, fluconazole and an ester version of CA were used alone and in combination to treat Candida albicans. Time-kill micro dilution and the checkerboard test were employed to assess the in vitro interaction between CAPE and Fluconazole [47]. The in vitro Caenorhabditis elegant infection model was employed to assess the antifungal efficacy of the CAPE and fluconazole combination. The outcome demonstrated that when compared to an individual who can utilize CAPE or fluconazole, the combination of the two exhibited great therapeutic potential against fluconazole-resistant C. albicans.

Additionally, CAs have antiviral properties against the poliovirus, the herpes simplex virus, and the influenza virus. Vero cells were used in this investigation, along with MDCK cells. Both viruses were present in Vero cells, while the influenza virus was present in MDCK cells. Individually, CA, quinic acid, caffeine, and chlorogenic acid were applied to the infected cell culture. The results revealed a significant reduction in influenza virus multiplication. It was also demonstrated by CA against antiviral activity. According to these researches, CA has strong antibacterial activities deliberated in Fig. 4 [48].

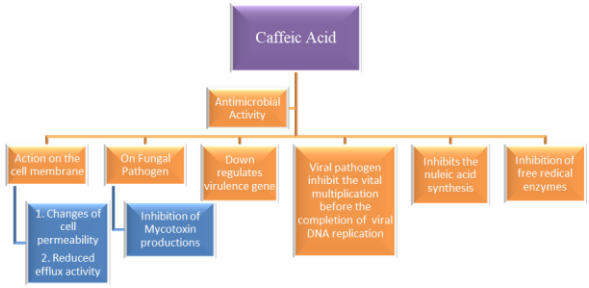

Fig 4. Caffeic acid producing Anti-microbial action

Bone Health and Osteoclastogenesis

Bone Formation and Resorption

Caffeic acid significantly impacts bone metabolism through multiple mechanisms. In adjuvant-induced arthritis models, caffeic acid administration reduced joint swelling, inhibited bone loss, and decreased osteoclastogenesis in a concentration-dependent manner [1]. The compound showed remarkable inhibition of bone loss at 125 mg doses and reduced TRAP-positive multinucleated cells [1].

Novel Derivatives for Bone Disorders

A caffeic acid derivative, N-(4-methoxyphen) methyl caffeamide (MPMCA), suppresses osteoclastogenesis and facilitates osteoclast apoptosis through MAPK pathway inhibition, offering potential for treating bone loss disorders [48]. Additionally, novel caffeic acid

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compounds from Stauntonia hexaphylla demonstrate bone and cartilage formation promoting effects by inhibiting osteoclast differentiation [24].

Antioxidant, Anti-inflammatory effects and Immunomodulatory Activities

Mechanisms of Action

Caffeic acid exerts potent anti-inflammatory effects through multiple pathways. It directly blocks gasdermin D (GSDMD) activation, preventing pyroptosis and reducing pro-inflammatory cytokine secretion [35]. The compound inhibits NF-κB signaling, a key pathway in inflammatory responses, while modulating the expression of inflammatory mediators including TNF-α, IL-1β, and IL-6 [9], [35], [47].

Therapeutic Applications

In experimental models, caffeic acid demonstrates significant anti-inflammatory efficacy. A zinc basic salt/chitosan nanohybrid containing caffeic acid showed excellent anti-edematogenic effects in carrageenan-induced paw edema models [9]. CAPE treatment reduced systemic inflammation in rat trauma models by decreasing IL-1β and IL-6 levels while increasing anti-inflammatory IL-10 [38]. Additionally, CAPE administration reduced enterotoxigenic Bacteroides fragilis-induced colitis through IL-17A/CXCL1 pathway modulation [47].

The reduction of oxidative damage is significantly aided by phenolic acid-rich compounds. An in vitro study on the antioxidant properties of CA recently discovered that it significantly decreased the harm caused by free radicals. By using biological assays to measure the captive properties of hypochlorous acid, radical anion superoxide capture, crocin bleaching, and H_2O_2 capture, the antioxidant action of CA was demonstrated. Rats were used in yet another in vivo and in vitro experiment [49, 50]. In this work, the protective effect against intestinal reperfusion damage in the small rat intestines was evaluated by giving the rats CA and chlorogenic acid. The absorption of CA by Caco-2 cells was shown to be more sensitive than that of chlorogenic acid, resulting in much higher antioxidant activity than chlorogenic acid. As a result, CA was found to be an effective rat protector against intestinal reperfusion injury. Reactive oxygen species (ROS) are widely known to play a substantial part in inflammation development by activating NF-kB and other transcription factors, including AP-1[51]. Nuclear acetylation and de-acetylation also play a key role in many inflammatory diseases. Such conditions can be controlled by including enough antioxidants from polyphenols in the daily diet. Primary bovine mammary epithelial cells (BEC) were used in lipopolysaccharide-induced inflammatory research. When CA was utilized as a test medication, pro-inflammatory cytokines such as IL-8, IL-1, IL-6, and tumor necrosis factor were shown to be greatly reduced. To ascertain CA's locomotor and inflammatory activities, another investigation using the rotenone-induced mice model was conducted [52, 53]. The nigral neurodegeneration caused by rotenone is accompanied by a dose-dependent upregulation of nuclear transcription factor activity via blocking kB inhibitor, as well as degradation and p65 phosphorylation in the NF-Kb pathway and an increase in inflammatory markers and tyrosine hydroxylase (TH) immunostaining. In this study, CA suppressed the production of inflammatory intermediates and decreased the activity of enzymes that break down the cartilage matrix, namely ADAMTS5 MMPs [54, 55]. Additionally, CA inhibited IL-1-induced NF-B activity, activation of the JNK (C-Jun N-terminal kinases) pathway, and degradation of collagen-II and aggrecan in chondrocytes.

Liver Protection Mechanisms

Caffeic acid provides significant hepatoprotective effects through multiple pathways. In cholestatic liver injury models, CAPE improved liver function and reduced inflammation and oxidative stress [21]. The combination of caffeine and silymarin with caffeic acid properties showed enhanced hepatoprotective effects by down-regulating lysophosphatidic acid receptor 3 (LPAR3) expression [22].

Metabolic Liver Disease

Research demonstrates caffeic acid's effectiveness against various liver conditions. Caffeine, sharing similar pathways, attenuated liver damage and improved neurologic signs in hepatic encephalopathy models [37]. The compound's hepatoprotective effects extend to smoking-induced liver injury, where combination treatments showed superior protective effects [32].

The liver is the biggest solid organ and the largest gland in the body and it assists in the metabolism and removal of waste products from the body. After the chemical has

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been absorbed from the digestive system, the liver detoxifies it before it enters the systemic circulation. Due to complete loss of liver function, death happens within minutes [56]. Therefore, it must function properly. For the liver to function properly and to remain healthy, damage such as fatty liver, liver fibrosis, and liver cirrhosis should be avoided. Numerous academic studies have demonstrated that CA protects the liver in a variety of ways. By preventing the 5-lipoxygenase enzyme in rat liver cirrhosis triggered by carbon tetrachloride, CA prevented liver cirrhosis. In this investigation, CA avoided the depletion of glycogen and substantially lowered the markers of lipid peroxidation and liver injury [57]. The poisonous element nickel impairs the operation of many organs including the liver, kidney, brain, lungs, and others. Nickel can enter the body through water, food, or environmental contamination. The liver among these is particularly vulnerable to nickel poisoning [58]. Animal in vivo research has demonstrated the value of CA in preventing nickel-induced liver damage. In the current study, nickel exposure caused oxidative damage that enhanced lipid peroxidation and resulted in lower levels of catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and glutathione S-transferase (GST) [59]. Important liver enzymes such as alanine transaminase (ALT), alkaline phosphatase (ALP), and aspartate transaminase the level and activity of these enzymes to the ideal level when treated with CA. Using a rat model, the phyto-phospholipid complex of CA was also found to have antihyperlipidemic and hepatoprotective effects. According to these researches, CA usage may help avoid liver damage [60].

Metabolic Regulation and Anti-Obesity Effects

Adipocyte Function and Metabolism

Caffeine promotes adipocyte autophagy through the AMPK/SIRT1 signaling pathway, contributing to anti-obesity effects and improving insulin resistance [42]. The compound significantly inhibits fat synthesis proteins and reduces lipid droplet size while enhancing mitochondrial biogenesis [42].

Gut Microbiota Modulation

Caffeic acid combined with dietary fibers like β-glucan demonstrates synergistic anti-obesity effects by modulating gut microbiota composition, increasing beneficial bacteria such as Bifidobacterium, and reversing high-fat diet-induced metabolic changes [58].

Hyperuricemia Treatment

Caffeic acid shows significant antihyperuricemic activity through xanthine oxidase inhibition. In experimental models, caffeic acid treatment resulted in 52.7-81.0% inhibition of xanthine oxidase activity and 38.8-72.5% reduction in uric acid levels [4].

Diabetic prevention

Diabetes is a condition brought on by a metabolic imbalance that is hyperglycemic. The reduction or inhibition of insulin's synthesis or action, or both of these factors combined, is what causes hyperglycemia to occur. Chronic diabetes is associated with physiologic abnormalities in important organs like the kidneys, heart, liver, and others that may result in long-term damage and dysfunction [61]. The 9th edition of the "International Diabetes Federation Diabetes Atlas" estimates that there will be 463 million individuals with diabetes worldwide in 2019. This prevalence is predicted to increase to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045. In diabetic mice employing cardiac tissue, CA also prevents the development of diabetic cardiomyopathy [62]. In this study, CA and ellagic acid were employed in various groups in comparison to those who weren't treated with 2% of the entire amount of a typical diet. Inflammation, oxidative stress, coagulability, and lipid profiles were only a few of the variables that were looked at. After 12 weeks, the treated animals' cardiac tissue displayed the protective effects of the compounds, which led to changes in triglyceride levels, plasma insulin levels, glucose levels, and the heart tissue's anti-coagulatory, antioxidant, and anti-inflammatory characteristics [63]. This study suggests that supplementing with these substances may aid in preventing diabetic cardiomyopathy. Numerous types of research imply that CA is helpful in diabetic nephropathy as well. Diabetes patients experience it as a result of high amounts of blood sugar [64]. High blood sugar levels can occasionally harm the kidneys, which can impair the filtering process and cause the injured area to leak. As a result, it enables the protein to enter the urine. According to reports, diabetic nephropathy, the primary factor contributing to end-stage renal disease and chronic kidney disease globally, impacts 40% of all diabetic individuals [65]. According to a study, CA reduced

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diabetic nephropathy in rats with high-fat diet-induced diabetes by modulating the autophagy pathway and inhibiting the autophagy regulatory miRNAs. The anti-diabetic properties of plants that contain CA derivatives have been demonstrated in another in vitro investigation i.e., extract of Ocimum gratissimum L. leaves [66].

Cardiovascular protection

CAPE demonstrates superior cardioprotective effects compared to common antioxidants like vitamin C and coenzyme Q10. In cardiomyocyte studies, CAPE significantly reduced H2O2-induced cell damage in a dose-dependent manner, suggesting potential benefits for maintaining cardiovascular health [28].

Systematic Cardiovascular Benefits

Comprehensive reviews indicate that caffeic acid and CAPE positively affect various cardiovascular aspects, including atherosclerotic diseases, myocardial infarction, hypertension, and cardiac arrhythmias through antioxidant, cytostatic, and anti-inflammatory processes [51].

Around the world, cardiovascular problems are said to have contributed to a lot of deaths. Cardiovascular diseases are responsible for roughly 5.0 million fatalities in industrialized countries and 9.0 million deaths in poor countries. Epidemiological studies have found a negative relationship between flavonoids consumed in the diet from a range of sources, especially from natural sources, and long-term mortality from heart diseases [67]. According to Vallance (2001), ACE, cholinesterase arginase, and nitric oxide synthase are the main enzymes that control the heart's function. According to CA and its derivatives, the renin-angiotensin-aldosterone system (RAAS) is controlled by them through a variety of targets [68]. In Wistar rats, isoproterenol-induced oxidative damage. These animals had higher levels of serum troponins, cardiac mitochondrial lipid peroxidation products, mitochondrial calcium, cholesterol, free fatty acids, and triglycerides. Isocitrate, malate, succinate, -ketoglutarate, NADH dehydrogenases, and Cytochrome C-oxidase activity all showed notable reductions, although glutathione peroxidase lowered glutathione levels dramatically decreased. All of these findings support rat myocardial infarction [69]. The pre-treated Wistar rats showed a protective effect against isoproterenol, as evidenced by the discovery that all the aforementioned biochemical markers were present at normal levels in these animals.

In cadmium (Cd)-induced cardiac injury in rats, CAPE, an ester form of CA, has established its antihypertensive activity by limiting the production of nitric oxide (NO) in the arteries and reducing lipid peroxidation. CA was also observed to alleviate cyclosporine-induced hypertension in rats. In this study, systolic blood pressure (SBP) and heart rates were significantly lower in the groups receiving the test drug compared to the control drug (captopril). Acetylcholinesterase (AChE), Butyrylcholinesterase (BChE), arginase, and ACE activity have all significantly decreased in CA. As opposed to cyclosporine-induced hypertensive rats, the bioavailability of NO was improved with increased catalase activity and reduced glutathione content rose with decreased malondialdehyde (MDA) levels. Another study found that CA also decreased oxidative imbalance and its ACE inhibitor function [70]. The current research has also shown that CA increased plasma levels of HDL (high-density lipoprotein) while lowering levels of LDL (low-density lipoprotein) and triglycerides. Another study results in a rat model of athero-sclerogenic diet-induced atherosclerosis likewise demonstrated the effectiveness of CA in reducing oxidative stress. Aortic staining was used to examine any decrease in atherosclerotic lesions. The CA derivative CAPE was also beneficial in lowering doxorubicin-induced cardiotoxicity and improving chemotherapeutic effectiveness. Although doxorubicin is effective against breast cancer, its cardiotoxicity restricts its clinical use. The suppression of breast tumors and protection from doxorubicin-induced cardiotoxicity demonstrated by this study make CAPE a potentially effective treatment for breast cancer [71].

Anti-cancer action

The most prevalent cause of death worldwide is cancer. As the population grows fast, it is projected that the overall number of cancer cases and fatalities would rise. According to research, men have more cases and die from the disease at a higher rate than women. According to an American study, people over 65 have a tenfold higher chance of having cancer than people under that age. The most prevalent malignancies are those of the lung, breast, prostate, colon, and rectum [72].

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Human cervical cancer cells (HeLa) were used to assess the anticancer impact of CA. Following this study, CA had an anti-proliferative effect via lowering Bcl-2 activity, which caused the release of cytochrome and the activation of caspase-3, which resulted in apoptosis [73]. In another investigation, this substance's anticancer efficacy was determined using the human fibro-sarcoma cell line HT-1080. The anti-proliferative impact of CA was assessed using this MTT assay, while oxidative stress was identified using lipid peroxidation. In comparison to controls, lipid peroxidation indicators such as TBARS, CD, and LHP were greater in the cells following CA treatment, and increased DCF fluorescence indicated higher ROS levels in HT-1080 cell lines. Treatment with CA also changed the potential of the mitochondrial membrane in HT-1080 cell lines [74]. Apoptotic morphological alterations and increased DNA damage were also noted. These investigations suggested that CA had a potent anticancer effect on HT-1080 cell lines and human cervical cancer cells [75]. A different study was conducted to assess the anticancer efficacy of ashwagandha extract combined with CAPE. The anti-metastasis activity of this combination was found through research. As a result, it can function as an anticancer agent [76].

Neuroprotective effect

The focus of most current research is on neurodegenerative conditions including Parkinson's and Alzheimer's. These illnesses are the most prevalent and lethal in the world. In several age-related neurodegenerative disease subgroups, reactive oxygen species (ROS) production has been associated with neuronal death. ROS are normally produced as a result of regular oxygen metabolism in a healthy state and are crucial for preserving homeostasis and cell communication [77]. The structure and operation of cell membranes can be considerably changed by ROS, and tissues and organs can suffer oxidative damage as a result. The hippocampus is one of the areas of the brain that is most susceptible to oxidative stress, according to a study. Neurodegenerative illnesses eventually develop when neurons in the hippocampus are repeatedly damaged. In the neurological system, high ROS affect a variety of signaling targets such as protein kinase A (PKA) and cyclic AMP response element-binding protein, according to a study (CREB). It has been demonstrated that caffeic acid has neuroprotective effects in behavioral studies [78]. Caffeic acid, which is found in several phenolic substances and has been connected to anti-cholinesterase in tissues or animal models as well as in cell line research. Neurological diseases that are brought on by rotenone typically appear in people who are exposed to pesticides like rotenone. Rotenone tends to inhibit mitochondrial complexes and change the activity of dopaminergic neurons. Rotenone enhances the release of cytokines, nitric oxide synthase, and nitric oxides and causes toxicity. Caffeic acid reduces the control of nitric oxide synthase, suppresses microglia cells, and enhances locomotion by blocking cytokines [79]. The chemical Caffeic acid has the potential to treat liver, lung, kidney, and other organ damage conditions as well as neurodegenerative diseases. It might have a possible neuroprotective impact due to its anti-inflammatory qualities. The study aims to examine how coffee affects the activation of microglia and the impairment of locomotion in rotenone Parkinsonian rats [80, 81].

In different dosage groups of the treatment, rotenone was also given in addition to caffeic acid. Additional behavioral testing included locomotor, pole, rota-rod, and cylinder tests. Lower striatal dopamine levels were associated with the behavioral impairments discovered in the current investigation, as has been previously reported [82]. Caffeic acid (10 mg/kg) raised the motor functions activity score in comparison to the rotenone group and the rotenone + caffeic acid (2.5 mg/kg) group. Furthermore, ELISA tests revealed that striatal COX-2, iNOS, and NFB levels in the rotenone group were greater than those in the vehicle group (3.28-fold, 10.82-fold, and 3.2-fold increases, respectively) than those in the vehicle group. Higher dosages of caffeic acid (5 or 10 mg/kg) reduced the expression of striatal COX-2, iNOS, and NFB in contrast to the rotenone control group. These beneficial effects supported the neuroprotective properties of caffeic acid and the increases in locomotor activity, at least in part [83, 84].

Caffeic Acid and Its Derivatives Combinatorial Relevance in Light of Anti-Microbial Action

Caffeic acid was chosen as a key platform for the discovery of novel antimicrobial medicines carried out under structure-antimicrobial activity relationship (SAR) investigations because of its rising antimicrobial-resistant strains [85]. For example, caffeoyl glucosides,

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caffeoyl 5, 6-anhydroquinic acid, and caffeic acid phenethyl ester exhibit potential antibacterial action towards many pathogens, including the human immunodeficiency virus (HIV) [86, 87]. The importance of several derivatives, such as caffeic acid phenethyl ester and caffeic acid n-octyl ester, which have been studied as anti-HCV (hepatitis C virus) drugs, is highlighted [88, 89]. Additionally, it enhances the synergistic effects of other anti-HCV medications such as interferon-alpha 2b [90], daclatasvir [91], and VX-222 [92]. In accordance, the antibacterial potential against the bacterial, fungal, and viral pathogens are best demonstrated by caffeic acid in combination with esterified and amidated derivatives [93]. Regarding numerous pathogenic microorganisms, including both Gram-positive and Gram-negative, fungal (Candida albicans), and viruses (influenza and hepatitis C virus), it is important to note that ester derivatives, including caffeic acid phenethyl ester (CAPE), demonstrate various attributes like antioxidant, antimicrobial, anti-inflammatory, and anticancer Fig. 5 and 6 [94].

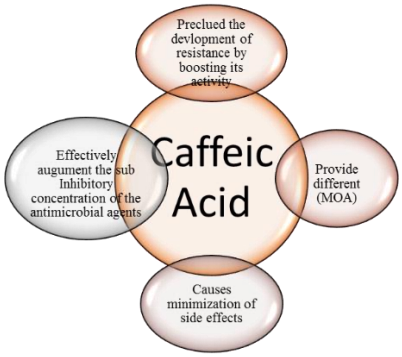

Fig. 5: Relevancy of Caffeic acid

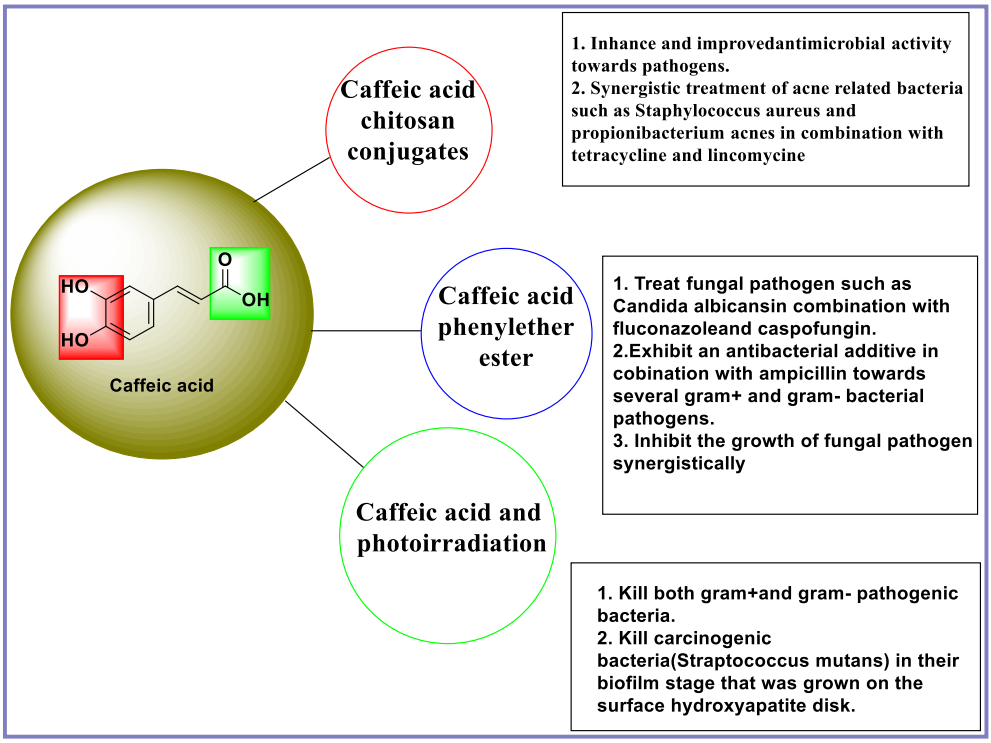

Fig. 6: Caffeic acid and its derivatives collaborative

Perspectives About the Effectiveness of Caffeic Acid as an Anti-Microbial Against Pathogenic Microorganisms

Phenolic acids (75–100% of the total hydroxycinnamic acid) are constrained by a copious supply where caffeic acid is supplied from various sources of plant goods including coffee, vegetables, and fruits. The bacterial P450 CYP199A2 enzyme converts p-coumaric acid to caffeine acid. By using the tyrosine substrate and the modified E. coli, a significant amount of caffeic acid has been produced [97]. Through adventitious and hairy roots, the Echinacea species have been used

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to create caffeic acid derivatives such as cynarin, caftaric acid (2-O-caffeoyltartaric acid), cichoric acid, chlorogenic acid (5-Ocaffeoylquinic acid), and echinacoside. Caffeic acid, which has significant antioxidant properties, promotes better health by preventing illness when consumed [98]. It is utilized as a food preservative against S. aureus (Fig. 7**)** because it contains one or more hydroxyl groups, and it also has antibacterial properties due to its phenolic ring [99]. Due to the potential modes of action listed in (Table 3) [100]. Caffeic acid has antibacterial properties that manifest against bacteria, viruses, and fungi, in addition to their active

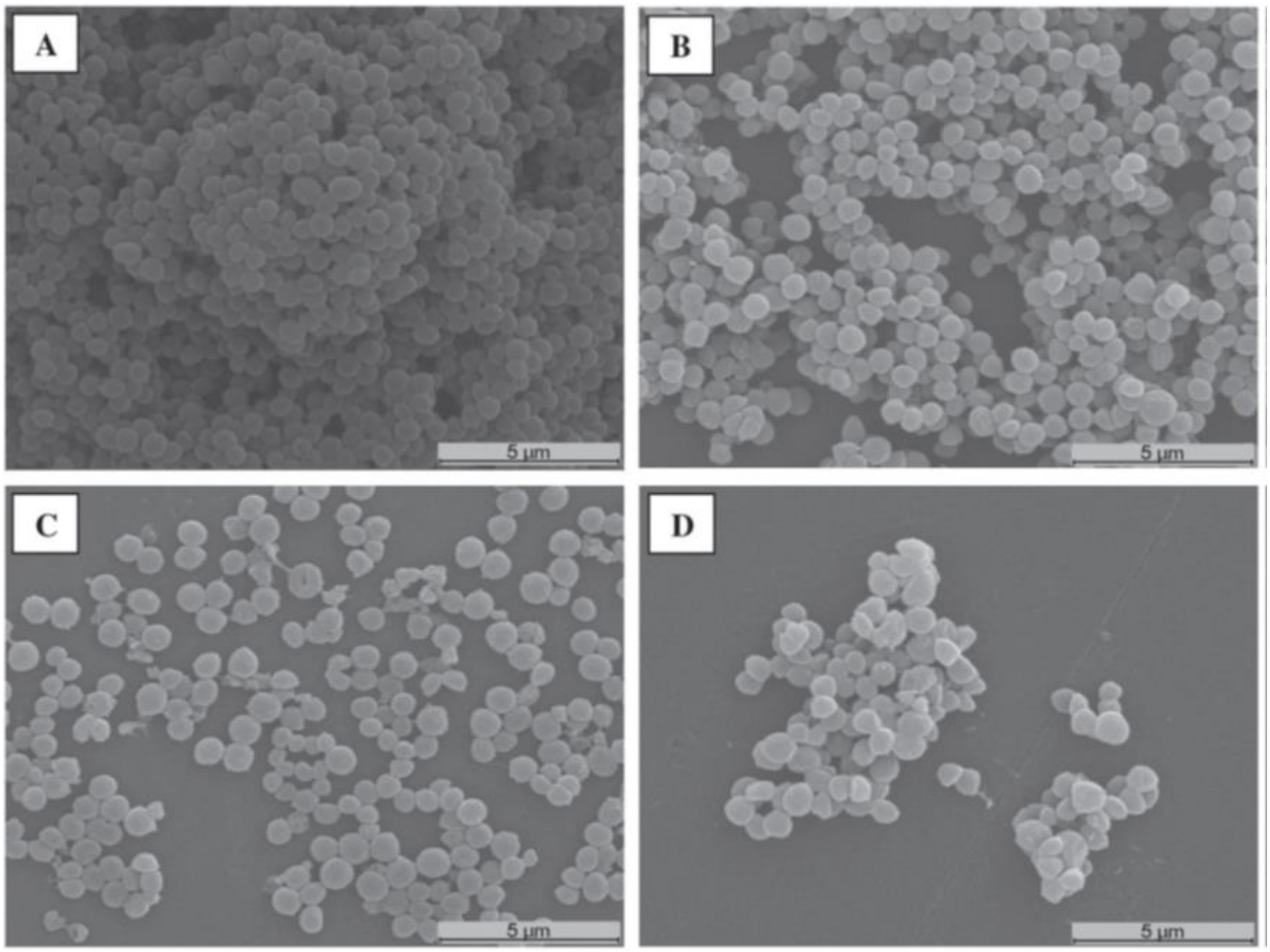

Fig. 7: SEM images: A = uniformly distributed S. aureus ATCC 25923 bio-film on polystyrene coupons (positive control); B = Biofilm formed in the presence of Gallic acid;

C = Bio-film formed in the presence of Caffeic acid; D = Bio-film formed in the presence of Chlorogenic acid [104].

concentrations. Both Gram-positive and Gram-negative pathogenic bacteria have been utilized in studies to test the antibacterial activity of caffeic acid [101]. Verticillium species, a reputable fungal pathogen, were used to assess the antifungal action of caffeic acid, although only a small number of fungal pathogens were considered. The primary features largely impacted by the antibacterial action of caffeic acid towards bacterial and fungal pathogens were alteration of membrane permeability, suppression of enzyme activity, damage to the protein structure, and DNA [102].

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Table 3. Summarizes activity against various bacteria and one virus [113]

Infectious agents	Active concentration	Mode of expression	Method	References
S. aureus	Inhibition zone (>12 mm)	Oxidative phosphorylation restrain	Agar-Diffusion Assay	[103]
S. aureus clinical strains and culture	MIC (between 62.5 and 250 g/mL)	elevated permeability of the cell membrane	Proline assay	[104]
Hepatitis C virus	IC50 100 ± 20 µM CC50 1600 ± 30 µM	Inhibited virus replication Stabilized HO-1 and Nrf2 initiation	HCV sub-genomic replicon assay	[105]
Viral canine distemper	59–86% less RNA was synthesized at 24–72 hours.	prevented viral RNA from accumulating during the replication cycle.	Cytotoxicity assay	[106]
C. f. reundii	200 to 400 µg/Ml ranging rate of IC50	Antimicrobial activity execution	Alkaline Hydrolysates of UP (AHUP)	[107]
Influenza virus type A	100-fold less viral replication when the concentration is 4 mM.	Prevented the spread of viruses. the virus showed evidence of Cytotoxicity	Plaque assay	[108]
Citrobacter f. reundii	At 2 mg/mL, inhibition zones range from 7.0 0.5 mm to 10.00 0.9 mm.	altered the cell membrane's form and function	Microtiter plate method	[109]
Type 1 HSV (Herpes Simplex Virus)	8 mM antiviral activity	Before viral replication, the virus's multiplication was down regulated.	Dye-exclusion method	[110]
Thrombocytopenia syndrome virus (SFTSV)	IC50 0.048 mM	Retardation of SFTSV Cellular Binding	Virus-binding assay	[111]
MRSA culture and clinical strains	The range of 52 to 1024 g/mL (MIC)	Inhibitory resistant pathway	Broth microdilution method	[112]

Reported Data on the Bioactivity of Caffeic Acid

Regarding caffeic acid's health advantages, it is important to note that it has anti-inflammatory, anticancer, and antiviral properties as well as substantial advantages since the body's naturally occurring free radicals can reduce oxidative stress specifically, antioxidants [114-117]. The emergence or aggravation of oxidative imbalance-related human illnesses is attributed to conditions including cancer, atherosclerosis, cardiovascular disorders, Parkinson's disease, Alzheimer's disease, and many others [118,119]. Caffeic acid has a protective impact on low-density lipoproteins (LDL) by acting as an antioxidant that helps -tocopherol [120]. Working collaboratively with certain derivatives to occupy more antioxidant action, such as caffeic acid and chlorogenic acid. i.e., chlorogenic acid attempts to play a significant protective function against ischemia-reperfusion damage both in vitro and in vivo [121, 122]. Despite all of these benefits, it also functions as a potential photo-protective agent and has been utilized in skin care products because hydroxycinnamic acids are present and protect the skin from photo-oxidative damage [123].

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Hsu *et al.* [124] examined the efficient use of caffeine using the streptozotocin-instigate and insulin-resistant rat models. Caffeic acid was administered intravenously to diabetic rats as part of the experiment, and a dose-related decline in plasma glucose was observed. Reduced plasma glucose levels have also been seen in experiments on insulin-resistant rats. To reduce plasma glucose levels, caffeic acid must thus increase the amount of glucose it uses. Caffeic acid and ellagic acid, two of the examined substances, showed evidence of anti-inflammatory qualities and a cardio protective impact in opposition to dyslipidemia, hypercoagulability, oxidative stress, and inflammation in diabetic mice evaluated by Chao *et al*. [125] Using dietary supplements of caffeic and ellagic acid to improve lipid metabolism and glycemic control in diabetic mice results in anti-oxidative, anti-inflammatory, triglyceride-lowering, and anti-coagulatory protection.

Similarly, Lee *et al.* [126] concluded that caffeic acid phenethyl ester, the most representative component of propolis, has antidepressant properties.

Prospected by Kanimozhi *et al.* [127] Consuming foods high in caffeic acid protects against the development of cancer thanks to its two important qualities as an antioxidant and pro-oxidant. Cancer cells' DNA (deoxyribonucleic acid) is negatively associated with pro-oxidative qualities by inducing apoptosis in those cells, which is followed by signaling. Additionally, an increased quantity of reactive oxygen species and changed mitochondrial membrane potential have been identified in this experiment.

Rosendahl *et al.* [128] authorized experiments on MCF-7, T47D, and MDA-MB-231 breast cancer cells, as well as cell cycle continuation using coffee and caffeic acid. Resulting in the discovery of estrogen-positive MCF-7 cells that killed off the growth of breast cancer cells using caffeic acid to its fullest extent. The anticancer activity of this compound now shows a positive effect against hepatic carcinoma along with antioxidant and pro-oxidant properties. It helps kill tumor cells by DNA oxidation and angiogenesis by reducing VEGF-induced vascularization, and it suppresses MMP-2 as well as MMP-9 expression preventing excessive ROS formation.

A comparative study done by Kabała-Dzik *et al.* [129] incorporating caffeic acid and its phenethyl ester, inhibited triple-negative MDA-MB-231 breast cancer line cells by cytotoxic activity and migration rate at two exposure dosages of 50 and 100 m. When compared to other treatments, caffeic acid phenethyl ester slows the proliferation of breast cancer cells. Additionally, caffeic acid was shown to inhibit head and neck squamous carcinoma cells as well as the viability and migration of oral cancer, or SCC-25 cells.

Delineated by Bastianini *et al.* [130] Because of its greater bioavailability, caffeic acid is a novel raw material for cosmetic applications. It is vehiculated into anionic clay for the marketing of the cosmetic endeavor as a promising and effective hybrid as well as sustained antioxidant activity.

Bridging Traditional and Modern Perspectives

Caffeic acid (CA) exemplifies the intersection between traditional herbal medicine and modern therapeutic development. Historically, CA-rich plants, including coffee, propolis, and various medicinal herbs, were utilized for their antioxidant, antimicrobial, anti-inflammatory, and wound-healing properties. Modern research has validated many of these traditional uses, demonstrating CA's ability to modulate molecular targets such as Nrf2, NF-κB, and STAT3, regulate oxidative stress, and protect mitochondria in preclinical models. [132, 134] Additionally, derivatives like caffeic acid phenethyl ester (CAPE) and synthetic analogs enhance pharmacological potency, bridging natural remedies with contemporary medicinal chemistry approaches. [133, 135] These findings underscore the value of ethnopharmacological knowledge as a foundation for rational drug development, highlighting how natural compounds can inform modern therapeutic strategies.

Future Directions

Despite promising preclinical evidence, translation of caffeic acid into clinical use remains limited. Future research should prioritize mechanistic studies to elucidate precise molecular targets and signaling pathways involved in its pharmacological effects. Optimization of pharmacokinetics through advanced delivery systems such as nanoparticles, liposomes, and solid dispersions is essential to overcome rapid metabolism and improve bioavailability. [135] Additionally, exploring synergistic drug combinations and conducting structure–activity relationship (SAR)

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analyses can maximize efficacy while minimizing potential side effects. [133-136] Well-designed randomized controlled clinical trials are urgently needed to confirm safety, therapeutic doses, and efficacy in humans, facilitating translation from bench to bedside.

Conclusion

Caffeic acid (CA) is a naturally occurring bioactive compound with a multifaceted pharmacological profile, making it a promising therapeutic agent for the prevention and management of a wide range of diseases. Its extensive activities—including antioxidant, anti-inflammatory, anticancer, neuroprotective, cardiometabolic, and antimicrobial effects—are well substantiated by recent preclinical studies. Derivatives such as caffeic acid phenethyl ester (CAPE), along with advanced formulation strategies like nanoparticles, liposomes, and solid dispersions, have been developed to overcome limitations of solubility, stability, and bioavailability, thereby enhancing therapeutic efficacy.

The strong antimicrobial and potential antiulcer activities of CA further underscore its broad scientific and clinical relevance, positioning it as a candidate for novel therapeutic interventions. Despite these advances, long-term safety, clinical efficacy, and optimal dosing strategies remain to be fully elucidated. Future research should focus on mechanistic studies, synergistic drug-combination approaches, structure–activity relationship optimization, and rigorous clinical trials to translate preclinical promise into effective human therapies. By bridging traditional medicinal knowledge with modern pharmacology, caffeic acid offers a versatile platform for drug discovery, serving not only as a natural therapeutic agent but also as a template for designing next-generation bioactive compounds with enhanced clinical potential.

List of Abbreviation

ROS=Reactive oxygen species, **DNA**= Deoxyribose nucleic acid, **MIC**=Minimum inhibitory concentration, **MBC**=Minimum bactericidal concentration, **MRSA**=Methicillin resistant staphylococcus aureus, **SFTSV**=Severe fever with thrombocytopenia syndrome virus-induced macrophages, **LDL**=Low-density lipoprotein, **MCF**=Malignant catarrhal fever, **MMP**=Matrix metalloproteinase, **SCC-25**=Squamous cell carcinoma-25, **MDA-MB-231**=Epithelial human breast cancer cell line-231, **VEGF-induced** = Vascular endothelial growth factor, **MMP-2** = Matrix metalloproteinase 2, **MMP-9** = Matrix metalloproteinase 9

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Author Contribution

Gulam Muheyuddeen: Conceptualization, Methodology, Investigation, Writing - Original Draft. Tanzeem Ahmad: Methodology, Investigation, Formal Analysis. Dr. Mohammad Khushtar: Supervision, Validation, Writing - Review & Editing. Ching-Yuan Lin: Resources, Software, Formal Analysis. Dong-Jin Li: Resources, Data Curation. Mohd Yaqub Khan: Formal Analysis, Visualization. Ming-Chen Wang: Supervision, Project Administration.

Ethical Approval

This study did not involve human subjects or animal experiments, and therefore, ethics approval was not required.

Consent to Participate: Not Applicable.

Consent to Publish: All authors have reviewed and approved the manuscript for publication in the Journal of Medical and Biological Engineering and consent to its publication.

Data Availability: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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