Advances in Research on the Biological Activity and Mechanism of Action of Chlorogenic Acid (Postprint)

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Abstract

Chlorogenic acid (CGA) is a widely distributed polyphenolic compound possessing multiple biological functions, including antioxidant, anti-inflammatory, antimicrobial, and hypoglycemic and hypolipidemic activities, and has broad application prospects in animal production and human health. This article briefly reviews the sources and distribution, physicochemical properties, biological activities, and main mechanisms of action of CGA, providing a reference basis for in-depth research and further development and application of CGA.

Full Text

Advances in Research on the Biological Activities and Mechanisms of Action of Chlorogenic Acid

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Abstract: Chlorogenic acid (CGA) is a widely distributed polyphenolic compound with diverse biological functions including antioxidant, anti-

inflammatory, antibacterial, hypoglycemic, and hypolipidemic activities. These properties give it broad application prospects in animal production and human health. This paper briefly reviews the sources, distribution, physicochemical properties, biological activities, and primary mechanisms of action of CGA to provide a reference basis for further research and development.

Keywords: chlorogenic acid; polyphenol; antioxidant; lipid metabolism; mechanism of action; animal product quality

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Chlorogenic acid (CGA) is a phenylpropanoid compound produced through the shikimic acid pathway during aerobic respiration in plants and has attracted considerable scholarly attention since its first successful extraction from apples in the 1950s. CGA has been widely applied in food, cosmetics, pharmaceutical, and chemical industries due to its antioxidant, anti-inflammatory, antibacterial, and anti-radiation properties. Recent studies have also revealed its positive roles in anticancer activity, glucose and lipid regulation, immune modulation, and central nervous system stimulation, though the specific mechanisms remain unclear. Against the backdrop of renewed research enthusiasm for natural plant extracts like artemisinin, coupled with growing public concerns about antibiotics and food safety and increasing demand for high-quality animal products, the development and application of CGA has become a research hotspot. This review summarizes the sources, distribution, physicochemical properties, and biological activities of CGA, discusses its primary mechanisms of action, and explores its application prospects in animal production and human health.

1. Main Sources and Distribution of CGA

CGA is widely distributed throughout the plant kingdom, ranging from dicotyledons to ferns, and is primarily found in plants from the Caprifoliaceae (*Lonicera* L.) and Asteraceae (*Artemisia* L.) families, including *Eucommia ulmoides*, honeysuckle (*Lonicera japonica*), sunflower, wild chrysanthemum, capillary artemisia, and burdock. It is also present in coffee, apples, carrots, green tea, wheat, soybeans, potatoes, and kuding tea. Honeysuckle and *Eucommia ulmoides* contain particularly high CGA concentrations. The content of CGA varies depending on geographical origin, soil conditions, climate, developmental stage, genotype, and plant organ.

China possesses abundant CGA resources, providing a strong foundation for its development and utilization. Honeysuckle, one of the most important CGA sources, is produced in most regions of China, with major production areas including Pingyi in Shandong Province and Longhui in Hunan Province, both designated as "Hometown of Chinese Honeysuckle."Pingyi represents the traditional source and main production area for *Lonicera japonica*, while Longhui has traditionally cultivated *Lonicera macranthoides* since the Qing Dynasty, as recorded in the *Xinhua County Annals* of 1871. Originally a wild species distributed across approximately 5,000 mu (1 mu 666.67 m^2), *Lonicera macranthoides* was

domesticated in the early 1960s with systematic cultivation techniques. The CGA content in *L. macranthoides* flower buds is significantly higher than in traditional honeysuckle varieties, reaching over 4% in Longhui and Xinning counties. The current cultivation area exceeds 200,000 mu with annual production of over 10,000 tons (dry flowers), accounting for more than 50% of national output and ranking first in China. Additionally, *Eucommia ulmoides*, another important CGA source, is abundant in China. As a species endemic to central and southwestern China, Hunan represents one of its central production areas. Cili County in Zhangjiajie, home to China' s largest wild *Eucommia* forest base, was renowned as "China' s *Eucommia* Hometown at the Mysterious 30°N Latitude" as early as 1996, with preserved areas exceeding 150,000 mu. Therefore, investigating the biological activities of CGA and maximizing its application potential in animal production and human health is crucial for fully utilizing China' s natural resources and improving food safety and public health.

2. Physicochemical Properties of CGA

CGA, also known as caffeotannic acid or caffeoylquinic acid, is a depside composed of caffeic acid and quinic acid formed through the shikimic acid pathway during plant aerobic respiration. Based on the esterification position on quinic acid, CGA can be classified into 3-*O*-caffeoylquinic acid (chlorogenic acid), 4-*O*-caffeoylquinic acid (cryptochlorogenic acid), 5-*O*-caffeoylquinic acid (neochlorogenic acid), 3,4-dicaffeoylquinic acid (isochlorogenic acid B), 3,5-dicaffeoylquinic acid (isochlorogenic acid A), and 4,5-dicaffeoylquinic acid (isochlorogenic acid C).

The molecular formula of CGA is C H O with a relative molecular mass of 354.30. Its chemical structure is shown in [Figure 1: see original paper]. The hemihydrate forms white or yellow needle-like crystals that become anhydrous at 110°C, with a melting point of 206–208°C. CGA is widely distributed in traditional Chinese medicinal herbs and foods. Natural CGA in plants often coexists with its isomers, so plant-extracted CGA is typically a mixture, with 5-*O*-caffeoylquinic acid (neochlorogenic acid) being the main component. At room temperature, CGA has low water solubility (approximately 4%) that increases in hot water; it is readily soluble in ethanol, acetone, and methanol, slightly soluble in ethyl acetate, and poorly soluble in lipophilic organic solvents such as chloroform, ether, and benzene. As a polar organic acid, CGA is relatively unstable and prone to isomerization during extraction. The ortho-dihydroxyphenyl group in its molecular structure serves as an optimal substrate for phenolase catalysis and is susceptible to oxidation when exposed to heat or light.

3.1 Antioxidant Activity

Studies have demonstrated that CGA is an effective phenolic antioxidant with stronger antioxidant capacity than common antioxidants such as caffeic acid, *p*-hydroxybenzoic acid, ferulic acid, syringic acid, vitamin C, and vitamin E. The

natural antioxidant properties of CGA depend on its unique molecular structure, which contains five active hydroxyl groups and one carboxyl group that can donate hydrogen radicals to scavenge reactive oxygen species and hydroxyl radicals. The ortho-dihydroxyphenyl group is unstable and readily oxidized, thereby protecting tissues from oxidative damage.

Furthermore, CGA has been reported to inhibit xanthine oxidase (XO) activity and reduce oxygen radical production in vivo, while also upregulating antioxidant enzyme activity and decreasing lipid peroxidation levels. The potential mechanisms of CGA' s antioxidant activity ([Figure 2: see original paper]) include: (1) promoting amino acid metabolism and glutathione metabolic pathways to improve lipid metabolism; (2) upregulating the nuclear factor erythroid 2-related factor 2/antioxidant response element (Nrf2-ARE) signaling pathway by inhibiting ubiquitin-mediated degradation of Nrf2 protein, stabilizing cytoplasmic Nrf2 concentration, enhancing Nrf2 transcriptional activity under stress conditions, and promoting expression of protective genes such as antioxidant proteins and phase II detoxification enzymes; (3) upregulating the phosphatidylinositol 3-kinase/protein kinase B (PI3K-Akt) signaling pathway to promote Akt phosphorylation and expression of forkhead box O transcription factor (FoxO), tumor suppressor gene p53, and anti-apoptotic protein B-cell leukemia/lymphoma 2 (Bcl-2), thereby inhibiting apoptosis; and (4) modulating the mitogen-activated protein kinase (MAPK) signaling pathway by inhibiting phosphorylation of extracellular signal-regulated protein kinase 1/2 (ERK1/2), c-jun N-terminal kinase (JNK), and p38 MAPK.

Abbreviations: CGA, chlorogenic acid; Nrf2-ARE, nuclear factor erythroid 2-related factor 2/antioxidant response element pathway; PI3K-Akt, phosphatidylinositol 3-kinase/protein kinase B pathway; MAPK, mitogen-activated protein kinases pathway; Nrf2, nuclear factor erythroid 2-related factor 2; p-Akt, phosphorylated protein kinase B; FoxO, forkhead box O transcription factor; p53, tumor suppressor gene p53; Bcl-2, B-cell leukemia/lymphoma 2; p-p38, phosphorylated p38 mitogen-activated protein kinase; p-JNK, phosphorylated c-jun N-terminal kinase; p-ERK, phosphorylated extracellular signal-regulated protein kinase.

3.2 Anti-inflammatory Activity

Anti-inflammatory activity represents another important biological function of CGA and a key characteristic for its widespread application beyond antioxidant properties. CGA can participate in the Janus kinase/signal transducer and activator of transcription 3 (JAK-STAT3) signaling pathway by inhibiting expression of interleukin-6 (IL-6) receptor subunit (gp130), Janus kinase 1 (JAK1), and phosphorylated STAT3 (p-STAT3) under oxidative stress conditions, thereby negatively regulating inflammatory factor expression and secretion. Inflammatory responses are crucial manifestations of autoimmunity, and the nuclear factor kappa B (NF- B) pathway is closely associated with autoimmunity, playing a key regulatory role in secretion of pro-inflammatory

cytokines, chemokines, and adhesion molecules. Studies have shown that CGA can inhibit carbon tetrachloride (CCl)- and lipopolysaccharide (LPS)-induced expression of interleukin-1 (IL-1), IL-6, and tumor necrosis factor- (TNF-) by suppressing NF- B, and can also alleviate inflammation by inhibiting NF- B activation. Additionally, Toll-like receptor (TLR) signaling pathways represent important regulatory mechanisms for CGA' s anti-inflammatory effects. CGA can inhibit TLR4 pathway activation, downregulate expression of TLR4, myeloid differentiation factor 88 (MyD88), inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2), and upregulate BMP and activin membrane-bound inhibitor (BAMBI) expression, thereby inhibiting secretion of TNF- , IL-6, and IL-1 and alleviating hepatic inflammatory injury and fibrosis. Subsequent studies have found that CGA can also improve inflammatory responses by inhibiting TLR2, TLR3, and TLR9 signaling pathways.

3.3 Antimicrobial and Antiviral Activity

CGA is one of the primary active antibacterial components in traditional Chinese medicinal herbs such as honeysuckle and *Eucommia ulmoides*. Research demonstrates that CGA exhibits broad-spectrum antimicrobial activity with strong inhibitory and bactericidal effects against various pathogenic bacteria and fungi, showing greater efficacy against fungi than bacteria with dose-dependent effects. The antimicrobial mechanisms of purified CGA compounds remain unclear, and systematic studies are scarce. Based on available literature, potential mechanisms may include: (1) CGA' s phenolic hydroxyl groups serve as optimal substrates for phenolase catalysis, affecting metabolic enzyme activity and reducing material and energy metabolism levels, thereby blocking metabolic processes and inhibiting bacterial activity. Evidence suggests CGA may be an effective non-competitive inhibitor of arylamine acetyltransferase in gastrointestinal bacteria such as *Escherichia coli*, affecting bacterial metabolism and inhibiting sugar metabolism to cause energy deficiency and impair growth and reproduction. (2) The strong polarity of CGA molecules enables high affinity for macromolecules like lipids, allowing binding to bacterial surfaces and altering membrane structure, increasing cell membrane permeability, and causing leakage of DNA, RNA, electrolytes, enzymes, and nutrients, thereby affecting protein synthesis. (3) Beyond biofilm stability, bacterial drug resistance and infectivity are closely related to swarming ability. CGA may exert antimicrobial effects by inhibiting bacterial flagella synthesis, reducing flagella numbers, and decreasing swarming motility.

Research on CGA' s antiviral effects is relatively limited, and the mechanisms remain unclear. Reports indicate that CGA significantly blocks and inhibits influenza A virus FM1 strain, herpes simplex virus (HSV), porcine parvovirus (PPV) in vitro, and porcine reproductive and respiratory syndrome virus (PRRSV). The mechanism may involve inhibiting expression of certain proteins required for virus-host binding, thereby preventing viral entry and release of progeny virions, though further investigation is needed. Additionally,

chlorogenic acid ethyl ester exhibits auxin-like activity, suggesting CGA may serve as a potential lead compound for anti-HIV drug development.

3.4 Hypoglycemic and Hypolipidemic Effects

Metabolic diseases such as type II diabetes, triggered by obesity, have become major threats to human health with rapidly increasing prevalence. Reducing excessive fat deposition represents an important strategy for addressing these issues, while regulating fat deposition also improves meat quality in animal production. CGA has been identified as the first novel specific inhibitor of glucose-6-phosphate translocase in rat liver microsomes. Since this enzyme plays a crucial role in endogenous glucose formation through gluconeogenesis and glycogenolysis, CGA intake may help reduce excessive hepatic glucose output in type II diabetes, making it a potential therapeutic option. CGA can also reduce fat deposition and decrease lipid content in blood and liver by inhibiting expression of peroxisome proliferator-activated receptor- 2 (PPAR- 2) and CCAAT enhancer binding protein (C/EBP), which are transcription factors associated with adipocyte differentiation. Moreover, CGA participates in the AMP-activated protein kinase (AMPK) signaling pathway, which plays vital biological roles in metabolism and cell development. AMPK serves as a key sensor of cellular energy status and a major regulator of lipid homeostasis in the liver and whole body, representing an important target for diabetes and related metabolic diseases.

Studies have shown that CGA can activate AMPK, upregulate glucose transporter 4 (GLUT4) expression, stimulate glucose uptake in skeletal muscle, downregulate glucose-6-phosphate translocase expression, inhibit gluconeogenesis, and suppress fatty acid synthesis. CGA has also been demonstrated to reduce fatty acid synthesis and decrease fat deposition in animals by downregulating expression of aconitase (ACO), catalase (CAT), fatty acid synthetase (FAS), and peroxisome proliferator-activated receptor- 2 (PPAR- 2). Pancreatic lipase (PL), secreted by the pancreas, is responsible for 50–70% of dietary fat digestion. CGA and other plant extracts are natural PL inhibitors that can be used for obesity and diabetes intervention.

Furthermore, CGA' s hypoglycemic effects have been confirmed, with potential mechanisms including: (1) stimulating glucagon-like peptide-1 (GLP-1)-mediated insulin secretion, and (2) activating AMPK to promote GLUT4 translocation to the cell membrane, thereby enhancing glucose uptake.

4.1 Broad Application Prospects of CGA in Animal Production

As a widely sourced natural plant extract with multiple biological functions and no pollution or toxic side effects, CGA can improve intestinal microflora structure and redox balance, alleviate adverse effects of various stress factors during animal production, regulate fat deposition, and enhance immunity and

disease resistance. It represents an ideal feed additive to replace antibiotics and hormones, holding significant importance for reducing antibiotic use and improving production efficiency and product quality. Adding 300 mg/kg CGA (85% purity) to weaned piglet diets significantly increases plasma glutathione peroxidase (GSH-Px) and CAT activities, reduces malondialdehyde (MDA) content, enhances plasma hydroxyl radical scavenging capacity, and improves antioxidant capacity to alleviate oxidative stress damage, likely due to CGA' s phenolic hydroxyl groups forming stable semiquinone structures with free radicals. Similar results were obtained in sow studies, where 300 mg/kg dietary CGA (90% purity) improved antioxidant capacity in sows and newborn piglets, significantly increased piglet birth weight, litter size, and 21-day litter weight, and reduced sow backfat loss during lactation, effectively alleviating farrowing stress and improving sow health and production efficiency. Adding 0.08% *Eucommia* leaf polyphenol extract (containing 33.7% CGA) to finishing pig diets significantly increased final body weight and average daily gain, reduced feed-to-gain ratio, improved growth performance, enhanced dietary protein utilization, regulated lipid metabolism, and improved meat quality. Beyond swine production, studies have shown that dietary CGA supplementation can improve growth performance, alleviate stress, enhance immunity, and improve product quality in poultry and aquatic animals, providing a solid foundation for CGA application in animal production.

4.2 Promising Breakthroughs for CGA in Human Health

Numerous studies and applications have demonstrated CGA' s free radical scavenging, antibacterial, and anti-inflammatory effects. According to incomplete statistics, over 170 traditional Chinese patent medicines recorded in the Ministry of Health' s Drug Standards for heat-clearing, detoxifying, antibacterial, and anti-inflammatory purposes contain CGA as a major component, making it an important quality control indicator in products such as Shuanghuanglian preparations. CGA is also widely used as a primary active ingredient in preservatives, cosmetics, and daily chemical products. With advancing research and medical technology, more application values of CGA are being discovered, and future breakthroughs are anticipated in curbing the spread of nutritional metabolic diseases (obesity, diabetes), treating immunodeficiency diseases (HIV), and enhancing natural immunity.

In summary, CGA possesses multiple biological functions with broad application foundations in animal production and human health. However, several issues currently limit its deeper development and utilization: (1) immature preparation technology and high costs for isolating pure CGA from plants; (2) unclear metabolic pathways and low bioavailability requiring improvement; (3) unclear mechanisms of action; and (4) limited application in animal production with need for further research on optimal utilization. Therefore, systematic investigation of CGA biosynthesis methods and elucidation of its metabolic pathways and molecular mechanisms are urgently needed to maximize the development

potential of CGA-rich plant resources.

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Note: Figure translations are in progress. See original paper for figures.