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Chlorogenic Acid's Antioxidant Defense: A Key Pharmacological Mechanism Against Metabolic Diseases

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ABSTRACT
Oxidative stress constitutes a core pathological mechanism in metabolic diseases. Chlorogenic acid (CGA), which is a natural polyphenol, exerts a dual beneficial effect: it enhances the metabolism of both lipids and glucose, and it concurrently acts to mitigate oxidative damage by directly scavenging reactive oxygen species (ROS). By activating the Keap1/Nrf2/ARE pathway to increase endogenous antioxidant enzyme expression (e. g., SOD, GSH), synergistically inhibiting the NF- κB inflammatory pathway, and regulating gut microbiota. This review summarizes the protective mechanisms of CGA in metabolic dysfunction-associated steatohepatitis (MASLD), type 2 diabetes, and polycystic ovary syndrome (PCOS). Although formulation improvements can enhance its bioavailability, individual variability and insufficient clinical evidence still limit its application. Future efforts should integrate multi-omics approaches, novel delivery systems, and precision nutrition strategies to advance its clinical translation.

KEYWORDS
Chlorogenic acid; antioxidant mechanisms; Nrf2 signaling pathway; Metabolic diseases; Gut microbiota; Clinical translation

1 Introduction

Against the backdrop of China's economic leap and profound lifestyle transformations, the prevalence of metabolic diseases—represented by hypertension, diabetes, and hyperuricemia—has continued to rise. These conditions have evolved into a major public health issue that undermines national health and exacerbates the societal burden of healthcare. Extensive research indicates that free radical-induced oxidative stress is one of the core pathological mechanisms underlying the onset and progression of these diseases. Consequently, antioxidants—bioactive substances capable of effectively neutralizing free radicals and mitigating oxidative damage—play a crucial role in preventive and adjunctive therapeutic strategies for related conditions. Chlorogenic acid (CGA), a naturally occurring polyphenolic compound, is ubiquitously present in a wide variety of plants and fruits. Also referred to as 5-caffeoylquinic acid, this extensively distributed phenolic substance has been conclusively demonstrated to possess robust biological activities including potent antioxidant, anti-inflammatory, antihypertensive, and antitumor properties [1]. It effectively scavenges free radicals such as superoxide anion radicals and hydroxyl radicals within the body, mitigating oxidative stress-induced cellular damage and preventing/alleviating stress-related diseases. Chlorogenic acid regulates lipid metabolism by lowering blood triglyceride, cholesterol, and it effectively reduces circulating concentrations of low-density lipoprotein (LDL) while concurrently elevating levels of high-density lipoprotein (HDL). thereby preventing and improving hyperlipidemia. Additionally, it aids in lowering blood glucose through mechanisms such as enhancing insulin sensitivity and modulating the activity of enzymes involved in glucose metabolism, demonstrating positive implications for preventing and treating diabetes and its complications [2].

This review aims to systematically elucidate chlorogenic acid's key pharmacological actions against metabolic diseases through antioxidant defense mechanisms, analyze its multi-targeted mechanisms of action, and explore its application prospects and challenges in clinical translation. It provides theoretical reference for further research and development of chlorogenic acid.

2 Chemical properties and sources of chlorogenic acid

CGA is a family of compounds formed by the combination of 1L-(-)-quinic acid ester with C6-C3 trans-hydroxycinnamic acid. Depending on the substitution position and number of caffeoyl groups on the quinic acid ring, multiple isomers can form. Among these, six primarily exhibit significant biological activity: CGA, cryptoclavic acid, neoclavic acid, isoclavic acid A, isoclavic acid B, and isoclavic acid C [3].

CGA is widely distributed in plants such as Euphorbiaceae, Asteraceae, and Eucommiaceae. Studies indicate exceptionally high CGA content in coffee and Eucommia ulmoides [4], with variations depending on plant species and plant parts.

Multiple extraction methods for chlorogenic acid have been reported, including organic solvent extraction, ultrasonic extraction, enzymatic extraction, and other techniques.

3 Core pharmacological mechanisms of chlorogenic acid's antioxidant defense

3.1 Activation of the nrf2 antioxidant pathway

Nrf2 is a central pathway in antioxidant stress response, and its activation is crucial for the body's defense against oxidative stress. Nrf2 serves as a key transcription factor regulating redox balance [5]. Under normal conditions, under basal conditions, the transcription factor Nrf2 is bound to its cytosolic repressor, Kelch-like ECH-associated protein 1 (Keap1), which facilitates its ubiquitination and proteasomal degradation, thereby maintaining its stable cytoplasmic localization and preventing its nuclear translocation. Keap1 inhibits Nrf2 activity by promoting its degradation. Under oxidative stress, reactive oxygen species (ROS) generated by oxidative reactions induce a conformational change in Keap1, preventing its degradation of Nrf2. Following its activation, Nrf2 undergoes nuclear translocation, where it heterodimerizes with small Maf proteins and binds to antioxidant response elements (AREs) in the promoter regions of target genes, thereby initiating the transcription of a broad array of cytoprotective enzymes, including those involved in antioxidant defense. These genes include those encoding antioxidant enzymes (such as superoxide dismutase SOD and glutathione peroxidase GPx) and detoxifying enzymes (such as quinone reductase 1 NQO1). These enzymes effectively scavenge ROS, repair oxidative damage, and maintain cellular redox homeostasis [6-8].

Research by Han [9]demonstrated that Chlorogenic acid exerts a protective effect against hydrogen peroxide-induced oxidative insult in osteoblasts through the activation of the Nrf2 signaling pathway. Its mechanism involves promoting Nrf2 dissociation from Keap1 and nuclear translocation, where it binds to AREs to initiate antioxidant enzyme gene expression [10]. This pathway not only directly scavenges free radicals but also strengthens the cell's endogenous antioxidant defense system, establishing a long-lasting protective mechanism.

3.2 Inhibition of the nf-κb inflammatory pathway

Chlorogenic acid finds extensive application in food, pharmaceutical, and feed processing industries. Anti-inflammatory and antioxidant drugs typically exhibit effects of inhibiting oxidative damage and protecting tissues and cells [11]. Research by Wan Fan [12]. revealed that chlorogenic acid supplementation alleviates LPS-induced inflammatory responses in PEC-J2 cells. The potential mechanism involves microautophagy and through suppression of the NF- κB signaling cascade, this compound mediates its anti-inflammatory activity by impeding the nuclear translocation of p65 and subsequent pro-inflammatory gene expression. Thus, chlorogenic acid reduces chronic inflammatory states by suppressing NF-κB pathway activation and decreasing production of multiple pro-inflammatory cytokines.

3.3 Enhancement of intestinal barrier function and microbiota regulation

Zhuo Chunliu et al [13]. observed that supplementing 2 g/L stevia chlorogenic acid starting at 7 days of age significantly regulated gut microbiota balance and enhanced immune function in broiler chicks. JIN et al [14]. observed that compared to controls, CGA supplementation significantly improved growth performance indicators in fish, markedly elevated intestinal digestive enzyme activity ($P < 0.01$), and increased nonspecific immunoglobulin enzyme activity in intestinal and hepatic tissues. Thus, dietary supplementation with 800 mg/kg CGA enhances intestinal structural integrity, improves intestinal epithelial function, and modulates gut microbiota composition and diversity.

4 Antioxidant effects of chlorogenic acid in specific metabolic disorders

4.1 Metabolic dysfunction-associated steatohepatitis (MASLD)

Metabolic dysfunction-associated steatohepatitis (MASLD), a nomenclature recently adopted in place of non-alcoholic fatty liver disease (NAFLD), describes a chronic hepatic disorder pathologically defined by excessive lipid deposition within the liver. This condition arises from metabolic dysregulation (e.g., obesity, insulin resistance, dyslipidemia) after in the absence of significant alcohol intake and after the exclusion of other established etiologies of hepatic injury [15]. The liver is a vital organ regulating lipid metabolism. Conditions like obesity and insulin resistance can disrupt hepatic lipid metabolism and trigger chronic inflammatory responses, thereby accelerating the progression of hepatic lesions to steatohepatitis, and potentially to cirrhosis, hepatocellular carcinoma, or even death [16]. Hepatic inflammation is a critical link in this progression.

Yu Yujuan's research [17]demonstrated that chlorogenic acid (CGA) exerts protective effects against multi-organ damage induced by a high-fat diet. CGA reduced body weight and fat mass in mice, lowered blood lipids, and suppressed expression of pro-inflammatory factors such as IL-6, TNF- α, MCP-1, and COX-2 in the liver. Histopathological findings further demonstrated that CGA significantly alleviated liver damage. Its protective mechanism is associated with reducing lipid accumulation and inhibiting inflammatory responses.

4.2 Insulin resistance and type 2 diabetes

Insulin resistance (IR) is a pathophysiological state characterized by decreased sensitivity to insulin in target organs such as the liver, muscles, and adipose tissue, leading to impaired glucose uptake and utilization. To compensate for this defect, the body reflexively stimulates the pancreas to secrete excessive insulin. Without early intervention, IR may progress to type 2 diabetes mellitus (T2DM), severely impacting patient health.

Obesity is a major risk factor for increased incidence and mortality in T2DM patients. CGA specifically inhibits G-6-phosphate dehydrogenase (G-6-PD) [18], downregulates G-6-PD mRNA expression [19], and reduces hepatic glucose output. Alonso-Castro et al [20]. found that CGA significantly enhances 3T3 adipocyte uptake of 2-deoxyfluorodeoxyglucose under both insulin-sensitive and insulin-resistant conditions. This indicates CGA enhances insulin sensitivity by increasing glucose uptake in adipose tissue [21].

4.3 Polycystic Ovary Syndrome (PCOS)

Polycystic ovary syndrome (PCOS) represents a prevalent endocrine disorder, clinically defined by the core features of hyperandrogenism and chronic ovulatory dysfunction and polycystic ovarian changes. Its clinical presentation exhibits high heterogeneity, and the etiology remains unclear. The disorder frequently coexists with menstrual irregularities, infertility, insulin resistance, and other metabolic abnormalities, significantly impacting patients' mental health and quality of life. Shah MZUH et al [22]. investigated the effects of chlorogenic acid (CGA) on endocrine and metabolic dysregulation in letrozole-induced PCOS mice. By establishing a PCOS model followed by CGA intervention, it was found that chlorogenic acid (CGA) improves endocrine and metabolic disorders in PCOS mice by regulating adiponectin and its receptor (Adipor1), while also influencing key downstream genes (including MLXIPL, PPARGC1, and Pparg, which regulate glucose and lipid metabolism).

5 Clinical translation challenges and future directions

Despite numerous studies demonstrating chlorogenic acid's significant potential in metabolic disorders, its clinical translation faces multiple challenges.

5.1 Low bioavailability

Chlorogenic acid exhibits poor oral bioavailability, primarily due to low gastrointestinal absorption and susceptibility to metabolism by gut microbiota and intestinal enzymes. To address this issue, Yingshu Feng et al. proposed a formulation system composed of cholesterol and phosphatidylcholine for preparing effective chlorogenic acid-loaded liposomes. This approach significantly enhances oral bioavailability and increases the antioxidant activity of chlorogenic acid in vivo [23].

5.2 Individual variability and precision nutrition

Individuals exhibit variable responses to chlorogenic acid, primarily due to differences in gut microbiota composition, which affects metabolic capacity and ultimately outcomes. Additionally, genetic diversity related to chlorogenic acid metabolism and target sites may contribute to inter-individual variation. Future research should therefore focus on personalized strategies to identify populations most likely to benefit from chlorogenic acid interventions, enabling precision nutrition.

5.3 Future research directions

Future chlorogenic acid research should advance in three key areas: First, conducting large-scale, long-term randomized controlled trials to establish its efficacy and safety in preventing and treating metabolic diseases. Second, integrating multi-omics, molecular docking, and gene editing technologies to elucidate its molecular mechanisms and target sites, thereby supporting precision interventions. Third, exploring synergistic effects with other bioactive compounds or drugs to enhance therapeutic outcomes. Through systematic research, chlorogenic acid should be transformed from a natural compound into an effective disease prevention and treatment strategy.

6 Conclusions and significance

This study demonstrates that chlorogenic acid (CGA) effectively alleviates oxidative stress through multidimensional mechanisms, including direct radical scavenging and activation of the Nrf2 antioxidant pathway. It exerts protective

effects in various metabolic disorders such as metabolic dysfunction-associated steatohepatitis (MASLD), insulin resistance, and polycystic ovary syndrome (PCOS). Its effects involve multiple pathways, including regulating lipid metabolism, suppressing inflammatory responses, and improving gut microbiota. Although formulation improvement strategies like liposomes can enhance its bioavailability, individual variability and clinical translation remain current challenges. Future efforts should integrate multi-omics technologies with precision intervention strategies to advance chlorogenic acid from basic research to clinical application, providing novel natural compound solutions for the prevention and treatment of metabolic diseases.

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