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# Chlorogenic Acid: A Promising Natural Agent for Non-Alcoholic Fatty Liver Disease Management

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**Abstract**

Emerging and relatively consistent evidence shows that chlorogenic acid (CGA), a phenolic acid, positively modulates a variety of contributors to the non-alcoholic fatty liver (NAFLD) phenotype, through diverse and complementary mechanisms of action. Therefore, we believe that CGA is a good candidate for the management of NAFLD that deserves a review to aid future research.

**Keywords:** Non-alcoholic fatty liver disease; Liver steatosis; Polyphenol; Chlorogenic acid; Antioxidant; Gut microbiota

**Abbreviations:** NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Non-Alcoholic Steatohepatitis; T2DM: Type 2 Diabetes; IR: Insulin Resistance; CGA: Chlorogenic Acid; LPS: Lipopolysaccharides

## Introduction

As a consequence of the growing epidemics of obesity and Type 2 Diabetes Mellitus (T2DM), Nonalcoholic fatty liver disease (NAFLD) has become the most common form of chronic liver disease in the world [1-3]. NAFLD initially presents as a relatively benign, non-progressive hepatic steatosis, but can, in certain individuals, progress to a potentially serious condition [4]. At the early stages, patients can restore liver function by changing their lifestyle (diet and exercise). However, as the disease progresses, pharmacological intervention or even a liver transplant is required [5]. Despite NAFLD is a major public health problem, it remains difficult to treat, as there is not yet a large, validated treatment [2]. Recent trials suggest that different approaches may be beneficial in subgroups of patients with this condition [4].

Flavonoids and phenolic acids have recently gained substantial attention due to their various biological and pharmacological effects [6]. Accumulating evidence suggests that these bioactive compounds may represent a complementary and integrative natural therapy for the management of obesity and its associated disorders such as T2DM and NAFLD [7-9].

In this review, we explore the medicinal promises of chlorogenic acid (CGA) on NAFLD management based on *in vitro* and *in vivo* reported studies. This phenolic acid is able to positively modulate a variety of steps from NAFLD pathogenesis, through diverse and complementary mechanisms of action.

### Nonalcoholic fatty liver disease

NAFLD is defined by the presence of steatosis in more than 5% of hepatocytes with little or no alcohol consumption [10,11]. The spectrum of the hepatic abnormalities ranging from a simple isolated steatosis to nonalcoholic steatohepatitis (NASH) characterized by steatosis along with hepatocellular injury, inflammation, and varying degrees of fibrosis [12] which sometimes can progress to cirrhosis and hepatocellular carcinoma [13].

The worldwide prevalence of NAFLD increased substantially along with increased rates of obesity and other components of the metabolic syndrome [3,5]. However, a proportion of cases have revealed a normal body mass index (BMI), a phenomenon known as "non-obese NAFLD" [11]. In any case, the presence of T2DM in

patients, displays a very high risk of developing NASH and fatty liver associated complications, evidencing an additive detrimental liver outcome [14].

It is now accepted that the metabolic and molecular changes that lead to NAFLD results from "multiple impacts" on the liver as a consequence of complex interactions between genetic susceptibility, environmental factors, insulin resistance, and changes in the gut microbiota [12,15]. In this sense, several of the triggers of fatty liver can be traced back to events that occur outside the liver in distant organs such as the intestine, adipose tissue, and muscles, among others [12,16]. In this sequence of multiple events, metabolic alterations in lipid homeostasis (free fatty acids, non-HDL-cholesterol) have been reported to precede fatty liver onset [17]. This initial impact results in the development of macrovesicular steatosis with an accumulation of liver fat [18].

Insulin resistance (IR) plays a key role in the development and progression of steatosis / NASH, promoting de novo hepatic lipogenesis and failing to suppress adipose tissue lipolysis, with the consequent rise of fatty acids in the liver [16]. In an attempt to compensate for these changes, both hepatic fatty acid β-oxidation and VLDL secretion are initially upregulated. However, this is insufficient to decrease the continuous flow of fatty acids to the liver that leads to tissue injury [19]. In some patients, steatosis even worsens IR by engaging in a vicious cycle once NAFLD develops. The cytokines derived from the dysfunctional adipose tissue, the free fatty acid-induced ectopic fat deposition, and lipotoxicity increase insulin resistance with the consequent changes in glucose and lipid metabolism [20]. The accumulation of fat in the liver, specifically in the form of triglycerides, impacts the production of reactive oxygen species and endoplasmic reticulum stress along with mitochondrial dysfunction [21]. Excess nutrients overwhelm the endoplasmic reticulum (ER), which activates the unfolded protein response and triggers the development of IR through various mechanisms, including activation and inflammation of c-jun kinase N-terminal (JNKs) [22]. Oxidative stress can promote lipid peroxidation in the hepatocytes and induce the secretion of pro-inflammatory cytokines and the activation of stellate cells through multiple signaling pathways, which in turn lead to fibrosis [4].

In recent years, a crosstalk between the gut microbiota and multiple organs of the host has been demonstrated with a beneficial role in physiological regulation [22]. Nevertheless, changes in the microbiota composition are recognized as key players in the pathogenesis of NAFLD [23]. The intestinal microbiota not only influences the absorption and elimination of nutrients to reach the liver. It also induces changes in the liver microenvironment by supplying gut-derived factors that stimulate hepatocytes to release free oxygen radicals and inflammatory cytokines that activate downstream signaling pathways such as nuclear factor NF-κB [24,25].

## Chlorogenic acid

Chlorogenic acid (CGA) also known as 5-O-caffeoylquinic acid (5-CQA) (IUPAC numbering) or 3-CQA (pre-IUPAC numbering) (Figure 1) [26], is one of the most abundant isomers of caffeoylquinic acid in nature. It is produced by the esterification of caffeic acid and L-quinic acid in certain plant species, in response to environmental stress [27].

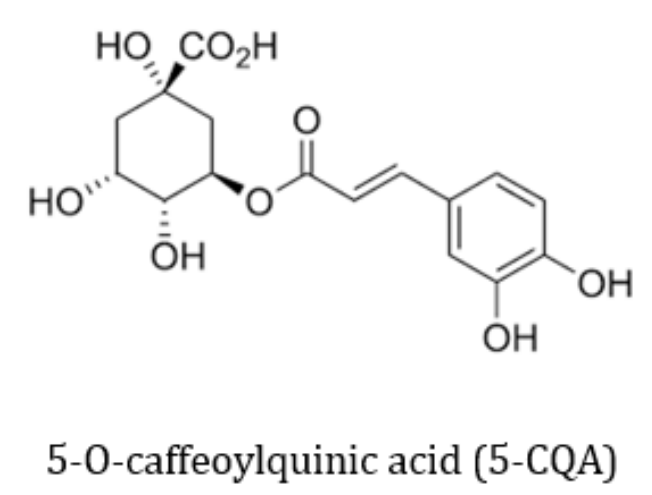


**Figure 1:** Chlorogenic acid.

CGA can be found in varying amounts in seeds, leaves, fruits, roots, and tubers forming part of the human diet [7,28-30]. Substantial amounts of CGA have been reported to be available in green tea and coffee extracts [27] and lower in apples, blueberries, strawberries, tomatoes, and potatoes [8]. Chlorogenic acid is also present in dairy products, as part of the phenolic content of milk influenced by animal grazing [31].


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As a natural plant extract from a wide range of sources, CGA exhibits many biological properties including antioxidant, anti-inflammatory, antimutagenic, anticancer, immunomodulatory, antibacterial, antiviral, particularly hypoglycemic and hypolipidemic effects [32]. Recently, the functions and applications of CGA, in relation to liver metabolism, have been highlighted in both the biological and medical fields [9,33].

## Chlorogenic acid in the line of NAFLD "multiple impacts"

Several lines of evidence indicate that CGA could play vital roles in regulating metabolic dysfunction closely associated with the onset and progression of NAFLD [33,34].

**Impact 1: Improvement of lipid metabolism:** The enhancement of de novo lipogenesis, suppression of β-oxidation, and decreased lipid export from the liver are the major reasons for the promotion of fat accumulation in the liver [18,35]. Recently, Zamani-Garmsiri [36] using a NAFLD rodent model found that CGA alone or in combination with metformin attenuates the expression of the lipogenic genes SREBP-1c and FAS. CGA also induces the expression and strengthens the activity of CPT-1, a fatty acid oxidation speed limit enzyme, and promotes the oxidation of fatty acid. A consequent decrease in plasma and triglyceride liver levels was achieved, demonstrating the antilipidemic function of CGA in HFD-fed mice. In addition, Ma et al. [37] have shown that CGA is able to reduce the transport of long-chain fatty acids into the liver by inhibiting the diet-induced expression of PPARγ and its target genes CD36 and Fabp4. Also, CGA drastically reduces the level of Mgat1 mRNA, shown to be involved in triglyceride synthesis [38]. In addition to the effect on PPARγ, other studies have shown that CGA could enhance PPARα levels in the liver and stimulate lipid utilization through adiponectin receptor-mediated signaling pathway [39-41]. It was also suggested that the effects of CGA could be linked to the modulation of cholesterol metabolism [42]. Some *in vitro* evidence indicates that CGA may indirectly decrease lipid accumulation in the liver by effectively inhibiting HMG-CoA by reducing cholesterol synthesis [43].

**Impact 2: Improvement of oxidative status:** The appearance and persistence of oxidative stress in the liver seem to play a fundamental role in the development of inflammation and NAFLD progression to more severe stages [3]. In fact, higher production of oxygen and nitrogen radical species, a lack of endogenous antioxidant defenses, and mitochondrial structural defects within hepatocytes were observed in patients with NASH [24]. So, targeting oxidative stress and inflammation could represent one of the main pathways of innovative NAFLD therapies [44].

Several studies *in vivo* and *in vitro* have found that plant extracts containing CGA have anti-inflammatory and antioxidant activities [45-48]. It has been shown that CGA up-regulates cellular antioxidant enzymes and suppresses ROS-mediated NF-κB, AP-1, and MAPK activation *in vitro* [45]. Also, CGA could promote scavenge free radical, up-regulate the expression and stimulate antioxidant enzymatic activities of SOD and GPx, CAT to attenuate NAFLD *in vivo* [47,49]. Additionally, Budryn et al. [50] showed a high reduced to oxidized glutathione (GSH/GSSG) ratio in the liver and a high concentration of the antioxidants in blood serum, as a result of the consumption of diets containing microencapsulated CGA.

**Impact 3: Improvement of inflammation:** Abnormal lipid accumulation in hepatocytes increases oxidative stress and leads to lipotoxicity, which triggers liver inflammation [24]. The secretion of pro-inflammatory cytokines in the hepatocytes is accompanied by macrophage infiltration and a change in macrophage phenotype M2 (anti-inflammatory) to M1 (pro-inflammatory) in the infiltrated tissues, key players in the metabolic inflammation observed in NAFLD [4]. CGA reduces the transcription of TNF-α, IL-6, MCP-1, and CRR2, suppressing the NF-κB activity, reducing inflammatory responses in the liver of HFD mice [37,38]. The modulating action of CGA on the NF-kB signaling was previously demonstrated by [51] in a lipopolysaccharide (LPS)-challenge in mice. In addition, CGA also could reverse the HFD-induced activation of TLR4 signaling pathway in liver [21] and decrease macrophage marker genes (including F4/80, CD68, CD11b and CD11c) and pro-inflammatory mediator genes (MCP-1 and TNF-α) in the liver and adipose tissues [36]. Recently, it was determined that CGA is capable of suppressing inflammation by inhibiting the activation of TLR4 / sphingosine (SPK / S1P), highlighting the role of CGA in preventing progression to NASH [49].

**Impact 4: Improvement of insulin sensitivity:** Insulin resistance is at the core of the pathophysiology of metabolic syndrome and T2DM. CGA is able to exert vital roles in the regulation of metabolic abnormalities closely associated with the occurrence and progression of NAFLD [52]. Accumulating evidence suggests that CGA may improve adipose tissue dysfunction and in turn reduce the development of obesity-linked IR [6,53]. According to Ma et al. [36], CGA is able to sensitize peripheral tissues for insulin response by attenuating inflammatory phenotypes in both adipose and liver tissues of obese mice.

On the other hand, hepatic IR is known to be associated with dysregulated glucose metabolism, as a consequence of an increase in gluconeogenesis and a reduction in glycogen synthesis. Recent findings showed that AMP-activated protein kinase (AMPK) plays a major role in the control of hepatic metabolism [54]. AMPK activation in the liver has metabolic consequences on lipids and glucose due to its ability to integrate nutritional and hormonal signals [55]. CGA has been shown to regulate glucose overproduction by inhibiting glucose-6-phosphatase (G-6-Pass) activity through AMPK stimulation [56]. Meanwhile, by specific binding to AKT, CGA is able to promote glucose uptake in liver cells by stimulating glycogen synthesis through phosphorylation of molecules downstream of GSK3β / FOXO1 signaling [57]. In addition, the increased expression and translocation of glucose transporter type-4 (GLUT-4) in skeletal muscle mediated by AMPK


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activation, could also facilitate glucose clearance in peripheral tissues, maintaining fasting glucose levels, glucose tolerance, and insulin sensitivity [35,58]. In this way, CGA could be considered a novel insulin sensitizer capable of maintaining glucose homeostasis similar to metformin [59].

The improvement in systemic glucose control can also be attributed to CGA inhibitory action on glucose-6-phosphate translocase that delays absorption in the small intestine [60]. It was reported that CGA also inhibited the activities of $\alpha$-amylase and $\alpha$-glucosidase contributing to reducing the glycemic impact of food and chronically lowering blood glucose levels in patients with T2DM at high risk of developing NAFLD [61,62].

**Impact 5: Improvement of the gut–liver axis:** The gut microbiota and intestinal permeability have been demonstrated to be the key players in the gut-liver cross-talk in NAFLD [63]. In NAFLD, overgrowth of the gut microbiota contributes to the disease progression, through the leaky gut barrier [64]. The increased permeability allows translocation of intestinal luminal antigens, including LPS to the liver, where they bind to their specific CD14 and TLR4 receptors on Kupffer cells aggravating inflammation and oxidative stress damage in the liver [65]. So, targeting the gut-liver axis and modulation of gut microbiota metabolites using specific prebiotics could represent an additional therapeutic approach for the treatment of NAFLD [66]. In line with this, several studies showed that CGA is able to reverse intestinal dysbiosis, increasing the metabolic activity and/or numbers of the beneficial Bifidobacterium spp. in both humans and mice [39,66-68]. Simultaneously, it was found that CGA in combination with Genistoside could enhance the intestinal barrier function, preventing leakage of LPS derived from the intestine and reducing plasma D-lactate in NAFLD [69]. The reduction of gut permeability by CGA is closely related to the restoration of the expression of the tight junction proteins occludin, claudin-1, and zonula occludens-1 (ZO-1) in the intestinal mucosa, together with the inhibition of tight junction disassembly promoted by down-regulation of RhoA/ ROCK signaling [25].

Furthermore, the interactions between the CGA and the gut microbiota can impact intestinal L-cell metabolism, increasing the GLP-1 levels in the portal vein [25]. An abnormal incretin system has been found in nondiabetic NAFLD and NASH patients [70]. By binding to GLP-1R, GLP-1 could act on β-cells, through cAMP-dependent mechanisms, helping to maintain the response capacity of these cells to increased plasma glucose [71]. GLP-1 could also improve NAFLD, increasing liver lipid oxidation, improving insulin sensitivity and inhibiting liver fat synthesis through AMPK-activation [72].

**Impact 6: Improvement of progression to liver fibrosis:** As seen above, oxidative and ER stresses play an important role in the development of liver complications [73]. NASH is characterized by fatty liver, liver inflammation and substantial hepatocyte cell death. The activation of hepatic stellate cells (HSCs) by apoptotic bodies, ROS, or by TGFβ from activated-kupffer cells, produces liver collagen accumulation leading to fibrosis. In the line with this, Shi et al. [47] showed that CGA could significantly improve liver matrix remodeling reducing hydroxyproline content and collagen ⍰, collagen ⍰, and TIMP-1 expression in CCl4-injected rats. Moreover CGA, also prevents HSCs activation, by suppressing PDGF/ROS generation in these cells, suggesting that the anti-fibrogenic mechanisms might be related to CGA-antioxidant and anti-apoptotic effects.

At last, it is well established that apoptotic hepatocytes define the progression of the severity of liver disease [20]. Thus, limiting liver injury could be a therapeutic way to prevent the progression of hepatic complications. Recent evidence indicates that CGA is able to reduce oxidative stress-mediated cell death via Nrf2 activation in HepG2 cells [74]. Consistent with this, the consumption of products with a high CGA content, improves oxidative stress and reduce liver cell death constituting promising agents for NAFLD management [27,30,46,48,75].

## Conclusion

Based on the results obtained from various studies, we believe that CGA, a prebiotic phenolic compound with multifunctional properties, protects against steatosis, oxidative stress, and liver inflammation. The combination of these health benefits makes CGA an excellent candidate for the prevention and treatment of NAFLD. Future research should focus both on stimulating clinical studies on NAFLD and on analyzing the inclusion of CGA in different matrices to ensure its bioavailability.

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