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Chlorogenic acid regulates macrophages to improve inflammatory diseases

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Abstract

Chlorogenic acid (CGA) is a polyphenolic compound found primarily in coffee and various plants. It has attracted much attention in recent years due to its significant therapeutic potential for regulating immune responses and alleviating inflammatory diseases. Regulation and fine-tuning of macrophage function are key mechanisms of action of CGA as it can effectively promote the polarization of macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory and tissue-reparative M2 phenotype, thereby reshaping the inflammatory microenvironment. CGA can downregulate the release of key pro-inflammatory cytokines including tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) by inhibiting signaling pathways such as nuclear factor kappa B (NF-κB). On the other hand, its antioxidant properties enable it to eliminate excessive reactive oxygen species and alleviate tissue damage caused by oxidative stress. This review discusses how CGA exerts anti-inflammatory effects through mechanisms such as promoting M2 macrophage polarization, regulating pro-inflammatory cytokine release, and inhibiting oxidative stress. Through both in vitro and in vivo experiments, its efficacy has been established in treating conditions, such as, acute lung injury, inflammatory bowel disease, rheumatoid arthritis, and atherosclerosis. Despite these promising effects, clinical applications of CGA are limited due to its low bioavailability, requiring further research aiming to improve its absorption and delivery. This review also highlights the need for future exploration of its pharmacokinetics, potential systems, such as nanoplatforms, for its precise delivery and identification of metabolic pathways being regulated by it, to enhance its therapeutic value.

Key words chlorogenic acid, macrophages, inflammatory diseases, anti-inflammatory effects, oxidative stress, rheumatoid arthritis, inflammatory bowel disease, atherosclerosis

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Introduction

Inflammation is a rapid and complex defense response that occurs when the body is stimulated by infection or injury. When inflammatory mediators are hyper-activated and continuously released, they can cause abnormal modulation of associated signaling cascades, including pathways such as nuclear factor kappa-B (NF-κB), the mitogen-activated protein kinase (MAPK) system, and Janus kinases (JAK) [1]. At the same time, disrupted immune system leads to tissue damage, causing serious and even life-threatening diseases. Inflammatory pathologies represent a category of persistent systemic conditions caused by abnormal activation of the immune system, including rheumatoid arthritis (RA), inflammatory bowel disease (IBD), atherosclerosis, and chronic obstructive pulmonary disease (COPD) [2-4]. These conditions not only compromise daily functioning, but also impose a huge economic burden on the healthcare system. Abnormal stimulation of immune cells and overproduction of pro-inflammatory factors are the core mechanism of aberrant inflammation. Macrophages contribute as important constituent of the innate immune system [5] which is pivotal in the onset, sustenance, and termination of inflammatory reactions.

Macrophages have high plasticity, and environmental cues within the microenvironment guide the differentiation of these cells into pro-inflammatory M1 or anti-inflammatory M2 subtypes [6]. While M2 macrophages suppress inflammation and encourage tissue repair by secreting anti-inflammatory cytokines like IL-10, TGF-β, and tissue repair factors, M1 macrophages increase inflammation by releasing pro-inflammatory cytokines like TNF-α, IL-6, IL-1β, and promoting reactive oxygen species (ROS) [6, 7]. Therefore, regulating the polarization of macrophages is considered an important strategy for treating inflammatory diseases.

Drugs used for inflammatory diseases mainly include inflammatory cytokine antagonists, nonsteroidal anti-inflammatory drugs, immunosuppressants, and glucocorticoids [8]. However, these drugs have certain side effects, including susceptibility to drug resistance, gastrointestinal reactions, and liver and kidney damage [9]. Therefore, identifying effective therapeutics exhibiting negligible adverse events is an important direction in the ongoing advancements in inflammatory disorders. Over the past several years, natural compounds have received widespread attention based on their role in managing inflammatory disorders, low toxicity, and multi-target properties. With antioxidant, anti-inflammatory, and immunomodulatory properties, CGA is present in coffee, various teas, a spectrum of fruits, and numerous vegetables [10]. It can inhibit the NF-κB and MAPK signaling pathways [11, 12], regulate oxidative stress response, and regulate the polarization of macrophages to exert anti-inflammatory effects [10]. In LPS-induced RAW264.7 macrophages, studies have shown that CGA can dramatically reduce the expression of pro-inflammatory cytokines and encourage M2 macrophage polarization [13]. In addition, CGA has been explored to decrease the size of myocardial infarction and improve survival rate via lowering oxidative stress and inflammatory injury in rats [14].

Although CGA possesses therapeutic potential for inflammatory diseases, its precise mode of action and clinical use require more investigation. This review aims to discuss the recent progress in the regulation of macrophages by CGA to improve inflammatory diseases, and explore its future research directions and application prospects.

Bioactive properties and anti-inflammatory mechanisms of CGA

Chemical structure and bioavailability of CGA

CGA, also known as coffee tannic acid, is found in the form of semi-hydrated yellow or white needle-like crystals which are transformed into an anhydrous state at 110°C. It can be heated with diluted hydrochloric acid to form caffeic acid. It belongs to polyphenol family, and is found in various plant species, but mainly in coffee, tea, apples, pears, and various vegetables. Chemically, it is composed of caffeic acid and quinic acid connected by ester bonds, with two aromatic ring structures and an unstable structure. Its solubility in water at room temperature (25 °C) is about 4%. It is easily soluble in ethanol and acetone, slightly soluble in ethyl acetate, and difficult to dissolve in lipophilic organic solvents such as ether and chloroform [15]. CGA has several biological effects, including antioxidant, anti-inflammatory, and hypoglycemic impacts. The chemical structure of CGA endows it with unique biological activity, and the phenolic hydroxyl and ester bonds in its molecule give it strong antioxidant capacity, which can clear free radicals and inhibit oxidative stress reactions [16]. Its bioavailability in the human body in relatively high. After oral administration, it is absorbed into the intestine and distributed to various tissues across the entire body with multiple polyphenol-derived metabolites measured in human plasma [17].

Metabolism of CGA

CGA is a weak organic acid containing multiple hydroxyl groups. With limited membrane permeability, it exhibits relatively low oral absorption rate. In rats, the absolute bioavailability of orally administered CGA monomer at a dosage of 50 mg/kg is only 4.8% [18]. In humans, CGA is partially absorbed within the small bowel after oral ingestion. The absorption efficiency is potentially influenced by aspects including food categories and individual differences, accounting for about one-third of the total intake [19]. Although the absorption rate is not high, CGA and caffeic acid can still be effectively absorbed in the human body and enter systemic circulation.

In the small intestine, less than 1% of CGA is hydrolyzed by mucosal esterase, producing metabolites including caffeic, quinic, and ferulic acids. About two-thirds of CGA enters the cecum or colon, where the intestinal microbiome plays a significant role [19, 20]. The gut microbiota metabolizes CGA into caffeic acid, ferulic acid, quinic acid, hydroxycinnamic acid, and phenylpropanoid derivatives. There is a complex interaction between CGA and the gut microbiota. This interaction has been shown to affect the structure and function of the gut microbiota, thereby having a positive impact on various diseases. Wang Z.'s research shows that CGA reverses high-fat-diet-induced dysbiosis of the gut microbiota, including significant inhibition of the growth of Desulfoviridae, Ruminococcaceae, Molluscaceae, and Erysipelaceae, as well as increased growth of Bacteroidetes and Lactobacillaceae [21]. This indicates that CGA has potential application value in weight loss, prophylaxis, and pathophysiological modulation of metabolic disorders.

CGA and its metabolites absorbed into the bloodstream are distributed to various tissues and organs throughout the body through blood circulation. In the liver, these compounds undergo further metabolic reactions, predominantly mediated through the cytochrome P450 monooxygenase network, encompassing oxidative transformations, reductive processes, and hydrolytic cleavage. Phase II metabolism includes transformations that encompass glucuronidation and sulfation, which help increase the water solubility of compounds and facilitate their excretion from the body. CGA and its metabolites are mainly excreted from the body along with bile, and some can also be excreted through urine. Overall, CGA has a certain therapeutic effect on various systems

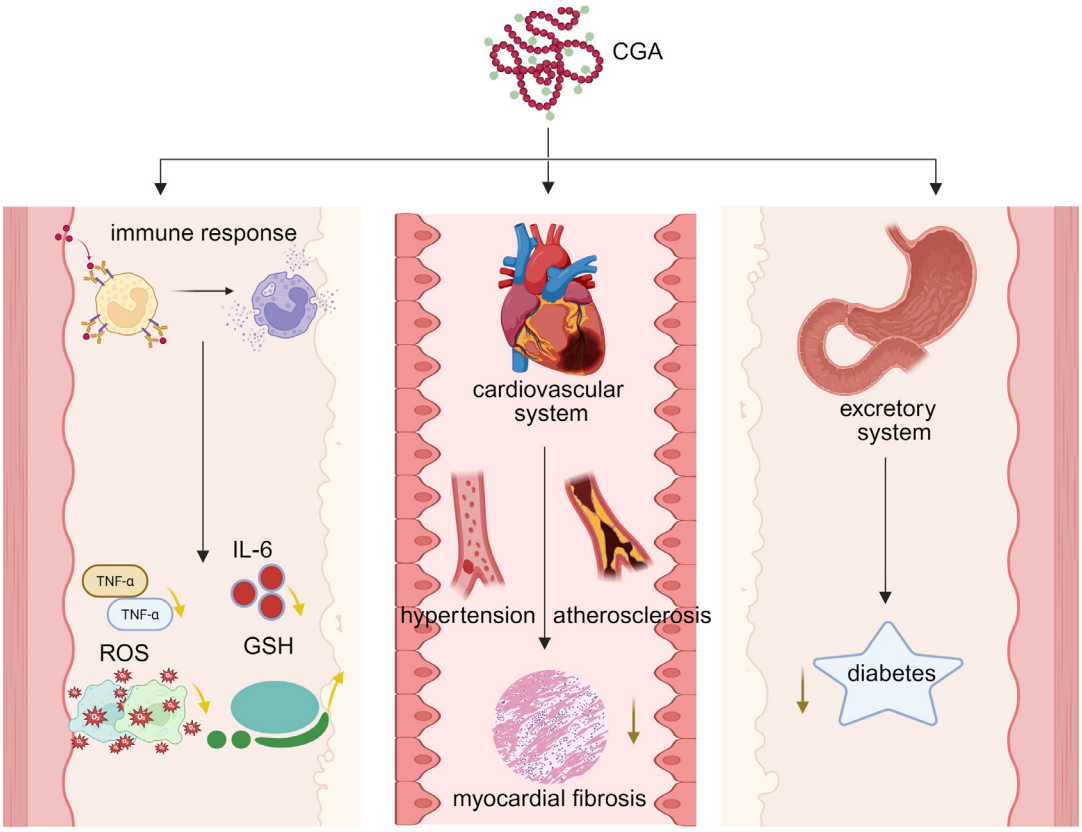

Figure 1. Effects of chlorogenic acid on immune response and systemic health. The multi-system effects of chlorogenic acid (CGA) on immune response and overall health were demonstrated. In the figure, CGA is the core and is expanded from three dimensions. Immune response module: CGA acts on immune cells, triggering the release of inflammatory mediators such as TNF - α and ROS, thereby regulating IL-6 levels and affecting the expression of antioxidant GSH. Cardiovascular system module: CGA participates in the process of blood pressure regulation (hypertension), vascular disease (atherosclerosis) and cardiac fibrosis (myocardial fibrosis). Excretion system module: CGA is associated with the occurrence and development of diabetes. CGA: chlorogenic acid; TNF-α: tumor necrosis factor-alpha; ROS: reactive oxygen species; IL-6: interleukin-6; GSH: glutathione.

in the body **(Figure 1).**

CGA regulates macrophages to improve inflammatory diseases

The role of CGA in improving inflammatory diseases by regulating macrophage function has been validated in multiple experimental studies. These studies include in vitro experiments, animal model experiments, and preliminary clinical studies, covering diverse inflammatory conditions including RA, inflammatory bowel disease, atherosclerosis, and acute lung injury.

Acute lung injury

Infection by pathogenic microorganisms, weakened immunity, and other factors can lead to pneumonia. The accumulation of M1 macrophages and the generation of elevated concentrations of inflammation-related substances, forming an inflammatory cytokine storm, are considered the primary contributors to the progression of this condition. Lv B.'s study found that CGA improves LPS-elicited acute pulmonary injury by suppressing the lysine acetyltransferase 2A gene and suppressing the inflammatory cytokine storm [22]. They established a model of acute pulmonary injury through the administration of lipopolysaccharide into mice via the tail vein. The results showed that CGA inhibited inflammation and significantly improved respiratory function decline in mice resulting from the administration of lipopolysaccharide, through the inhibition of KAT2A expression [22]. Liu C. investigated the mechanism by which CGA attenuates lipopolysaccharide-induced acute pulmonary injury in murine models by modulating the miR-223/NLRP3 pathway. It was found that CGA can effectively alleviate lung injury and the inflammatory response [23].

The NLRP3 inflammasome constitutes a crucial element in the inflammatory reaction, and its activation leads to the maturation and release of IL-1β and IL-18 [24]. Chai X. reported that CGA prevents suppression of Lnc Neat1 gene expression, and NLRP3 inflammasome activation mitigates ischemia-reperfusion-induced myocardial damage and pyroptosis [25]. Although not directly applied in acute lung injury models, it also has certain reference value for acute lung injury. Subsequently, Xu Y. also discovered the characterization of NLRP3 inflammasome small molecule inhibitors and their potential use in acute lung injury [26].

Shi A. reported that an increase in Nrf2 activation was observed upon CGA treatment, and this enhanced transcription of Nrf2-associated antioxidant genes such as HO-1, NQO1, and GCLC [24]. Zeng J. studied the operational principle of CGA in combating Klebsiella pneumoniae-induced pneumonia in mouse experiments and found that CGA significantly inhibited the triggering of the NLRP3 inflammasome. The findings suggest that consuming CGA or foods rich in CGA in the diet improves Klebsiella

pneumoniae-alleviated pneumonia, leading to the down-regulation of NLRP3 inflammasome activation [27].

In addition, Li QR infected mice with Klebsiella pneumoniae and treated them with CGA and a silencing information regulatory factor 1 (SIRT1) inhibitor (Selisistat). The results showed that CGA can regulate macrophage polarization in pneumonia, activate silent information regulator 1 (SIRT1), resulting in diminished acetylation and nuclear import of high mobility group protein B1 (HMGB1), which subsequently facilitates the acquisition of an anti-inflammatory phenotype in alveolar macrophages, and alleviates pneumonia [28]. Jain S.'s research demonstrated that CGA targets TLR4/3 to alleviate oxidative stress-induced NLRP3/NF-κB axis and improve acute respiratory distress syndrome. Studies have shown that CGA treatment normalized immune cell migration, reduced elevated levels of pro-inflammatory cytokines, and lowered the serum biomarker D-dimer for intravascular coagulation after CGA treatment [29]. He F. et al. showed that in vitro, CGA significantly suppresses LPS-induced inflammatory responses and enhances phagocytic activity in RAW264.7 cells. In vivo, CGA administration significantly alleviates lung inflammation and tissue damage, reduces lung bacterial load, promotes alveolar macrophage phagocytosis, improves the survival rate of CLP-induced ARDS mice, and significantly upregulates GPR37 expression both in vivo and in vitro [30]. CGA can enhance the phagocytosis of alveolar giant cells and improve acute respiratory distress syndrome through the activation of G-protein coupled receptor 37 (GPR37).

Inflammatory bowel disease

A collection of non-specific, long-term intestinal inflammatory illnesses, IBD mostly consists of Crohn's disease (CD) and ulcerative colitis (UC) [31, 32]. These two diseases have similar clinical symptoms, but there are differences in the location of onset, pathological features, and complications.

Continuous exposure to cadmium (Cd) is responsible for significant impairment of the hepatic and digestive systems. CGA has been demonstrated in earlier research to strengthen the intestinal barrier in weanling rats. Xue Y investigated the ameliorative influence of CGA, both in isolated form and within sunflower seed extract (SSE), on the growth dynamics, oxidative stress parameters, inflammation indicators, and gut barrier robustness in rats subjected to cadmium exposure [33]. The findings indicated that both CGA and SSE diminished Cd accumulation in the jejunum and augmented fecal Cd excretion. Combined treatment with CGA or SSE in rats was associated with a reduction in inflammation, an improvement in villous damage, a restoration of tight junction integrity, and a regain of

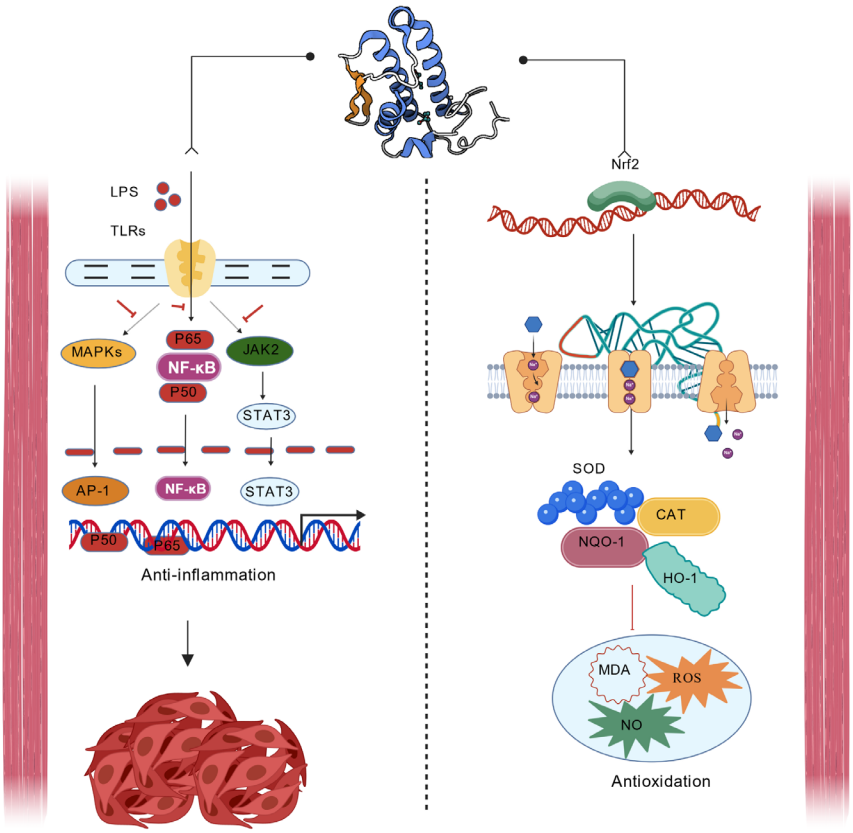

Figure 2. Molecular mechanisms of chlorogenic acid in anti-inflammation and antioxidation. Anti-inflammatory mechanism: LPS activate signaling pathways such as MAPKs, PI3K, JAK2 by binding to TLRs, thereby regulating transcription factors such as NF-κB, STAT3, AP-1 and ultimately inhibiting inflammatory responses; Antioxidant mechanism: After Nrf2 enters the nucleus, it initiates the expression of antioxidant enzymes such as SOD, CAT, NQO-1, HO-1, etc., which help clear oxidative products such as MDA, ROS and NO and exerting antioxidant effects. LPS: lipopolysaccharide; TLRs: toll-like receptors; MAPKs: mitogen-activated protein kinases; PI3K: phosphoinositide 3-kinase; JAK2: janus kinase 2; NF-κB: nuclear-factor kappa-B; STAT3: signal transducer and activator of transcription 3; AP-1: activator protein-1; Nrf2: nuclear factor erythroid 2-related factor 2; SOD: superoxide dismutase; CAT: catalase; NQO-1: NAD(P)H quinone dehydrogenase 1; HO-1: heme oxygenase-1; MDA: malondialdehyde; ROS: reactive oxygen species; NO: nitric oxide.

body weight [33]. Zhang Z. demonstrated that CGA attenuated multiple effects of dextran sodium sulfate the symptoms of DSS-induced colitis included weight loss, a higher disease activity index and aggravated mucosal lesions by inhibiting the active NF-KB signaling pathway. Besides, CGA significantly inhibited the secretion of IFNγ, TNFα, and IL-6, and reduced the infiltration of CD3+ T cells, F4/80+ macrophages, and CD177+ neutrophils in the colon, which is caused by NF-κB pathway inhibition and an increased abundance of mucinophilic Akkermansia spp. contributing to the improvement of experimental colitis [34]. The MAPK signaling cascade is profoundly linked to the development of ulcerative colitis. Gao W. reported that CGA alleviates DSS-triggered ulcerative colitis in murine subjects substantially alleviating tissue inflammation and apoptotic events wherein the operative mechanism involves the MAPK/ERK/JNK signaling cascade [11].

Additionally, Wan F. demonstrated that CGA exerts antioxidant and anti-inflammatory effects and restores intestinal barrier function by activating the Nrf2/heme oxygenase-1 (HO-1) pathway, thereby effectively improving DSS-induced colitis. These results suggest that DSS-induced colitis can be improved through the attenuation of oxidative stress and inflammation, as well as the restoration of the intestinal barrier [35]. In summary, CGA regulates inflammatory and oxidative molecular mechanisms via multiple signaling pathways **(Figure 2).**

Rheumatoid arthritis (RA)

RA, a continuous and comprehensive autoimmune disease, typically attacks the synovium of the joints, resulting in joint damage that worsens over time, destruction and dysfunction, and may also cause systemic damage. It is characterized by joint swelling, pain, morning stiffness (lasting ≥1 hour), synovial hyperplasia, and formation of vascular cataracts, and gradual erosion of cartilage and bone, leading to joint deformity.

CGA is the main component of Caulis Lonicerae, an herbal medicine utilized in the therapy of RA. Lou, L showed that CGA had the capacity to block IL-6-mediated inhibition of inflammatory cell proliferation in RSC-364 cells by inducing programmed cell death, and suppressed the activation of the JAK/STAT and NF-κB signaling pathways in the inflammatory response through IL-6-mediated signaling, as well as the expression levels of important components in these signaling pathways, thereby inhibiting inflammatory proliferation of synovial cells. STAT and NF-κB molecular signaling routes were also affected, and the activation of these signaling pathways during the inflammatory response was prevented by blocking IL-6-mediated signaling, thereby inhibiting the inflammatory proliferation of synovial cells [36]. The current results suggest that CGA could be used as a new medicinal substance to inhibit synovial inflammatory proliferation by inducing synovial cell apoptosis in RA patients. Furthermore, Lou L. has revealed that CGA exhibits the potential to prevent IL-6-mediated signaling. It effectively suppressed the production of important molecules in the JAK/STAT and NF-κB signaling pathways, as well as inhibited the initiation of these signaling pathways involved in the inflammatory response via suppressing IL-6 signaling. It also induced apoptosis in RSC-364 cells, thereby limiting their expansion in response to inflammation [36]. Fu X. has reported that CGA can inhibit TNF-α-induced BAFF expression, and promote apoptosis in MH7A cells in a dose-dependent manner. It indicates that the presence of the NF-κB binding site in the BAFF promoter region is necessary for regulating this process [37]. The findings suggest that CGA could offer a new strategy for treating RA by focusing on BAFF as a key target of CGA.

Macrophages have been reported to be functionally heterogeneous in RA, as they can release both pro-inflammatory cytokines including TNF and IL-1β to encourage inflammatory reactions, and anti-inflammatory cytokines such as IL-10. Metabolic reprogramming of macrophages may be an important mechanism for the regulation of their functions [38]. Liu Q. synthesized calcium CGA nanoparticles (Ca-CGA NPs) by binding small molecules of CGA to Ca^{2+}. Under the low pH conditions of lysosomes, the internalized Ca-CGA NPs were capable of dissolving to liberate free CGA and Ca^{2+}. Findings from controlled in vitro tests showed that not only did Ca-CGA NPs improve BMSC osteogenic differentiation, but also promoted the phenotypic transition of macrophages from M1 to M2. In addition, in vivo tests verified that administering Ca-CGA NPs aided in the recuperation of a rat cranial bone defect model with osteogenic induction and immunomodulation [39]. In order to speed bone healing, a novel method based on Ca-CGA NPs was devised in this study to stimulate BMSC differentiation into osteoblasts and macrophage polarization into the M2 phenotype.

Atherosclerosis

Atherosclerosis, a prolonged inflammatory illness which is defined by the disruption of unstable atherosclerotic plaques, stenosis, or occlusion due to thrombosis and platelet aggregation, causes acute cardiovascular illness [40, 41]. Over the last few years, the role of CGA, a natural polyphenolic compound, in regulating the process of atherosclerosis (AS) has received increasing attention. In addition, caffeoylquinic acid (CQA) and feruloylquinic acid (FQA), two of its isomers which can raise antioxidant activity and dramatically lower total blood cholesterol, have shown promise. According to the docking results, the energy binding of CGA compounds and their isomers is less than that of the drug ibuprofen, which suggests that CGA compounds and their isomers are superior to the drug ibuprofen, and therefore they have anti-inflammatory potential and can be used to prevent atherosclerosis formation [42]. Meng C. found that CGA maintains cholesterol homeostasis by regulating NPC1L1 and HMGCR expression through PXR and SREBP2 signaling, along with their interaction with HSP90. This suggests that CGA has a potential role in regulating the atherosclerotic process [43]. Steinbauer S. found that components of elderberry (Sambucus nigra), including CGA, were able to prevent foam cell development without increasing hepatic lipogenesis by a high-content screen, a finding that supports the potential role of CGA in attenuating atherosclerotic lesions [44].

Atherosclerosis is a chronic inflammatory disease brought on by artery endothelial dysfunction, and macrophages are essential to the onset and course of the illness [45]. CGA significantly ameliorates the pathological process of atherosclerosis by modulating macrophage function. Francisco V showed that CGA can possess anti-inflammatory qualities via inhibiting the NF-κB pathway, cytokine production, and proteasomes, which supports the anti-inflammatory action of polyphenols in physiologically relevant cells [46]. CGA possesses antioxidant and anti-inflammatory effects and is capable of inhibiting the inflammatory response induced by atherosclerosis. Furthermore, little is known about the chemical processes that underlie the suppression of oxLDL-driven oxidative damage in human endothelial cells. Recently, according to data from Tsai, K., CGA pretreatment increased the level of SIRT1 deacetylase activity, reduced oxidative stress and mitochondrial biogenesis failure brought on by oxLDL, and corrected oxLDL-impaired SIRT1 and AMPK/PGC-1 activity [47]. This finding provides fresh insight into the potential molecular pathways by which CGA inhibits mitochondrial dysfunction and endothelial oxidative stress brought on by oxLDL by activating SIRT1 and modifying the AMPK/PGC-1 signaling pathway.

Table 1. Research on the application of chlorogenic acid in diseases.

Disease type	Animal/Cell models	Result	References
Liver injury	Mice	CGA counteracts AP-induced liver injury at different levels by preventing cell apoptosis and oxidative stress damage; The GSH and Trx antioxidant systems, as well as the mitogen activated MAPK signaling cascade, are involved in the protective mechanism.	[49]
Liver inflammation and fibrosis	Rat	Inhibition of CCl4-induced rat liver fibrosis may have a protective effect due to inhibition of the TLR4/MyD88/NF-κB signaling pathway.	[51]
Obesity	3T3-L1 cells	The main colonic metabolite of CGA can counteract TNF α- induced inflammation and oxidative stress in 3T3-L1 cell lines, and has the potential to combat obesity.	[52]
Healthy development of intestines	Weaned piglets	CGA improves intestinal development by inhibiting mucosal inflammation and cell apoptosis in weaned piglets.	[53]
Inflammatory injury	RAW264.7 macrophages	By regulating CD36/AMPK/PGC-1 α to alleviate oxidative stress, it can contribute to the development of inflammatory diseases.	[54]
Acute liver injury	Mice	CGA affects the kinase activity of IRAK4, inhibits the autophosphorylation of IRAK4 stimulated by various TLR agonists, IL-1 α, or high mobility box-1 in peritoneal macrophages of C57BL/6 or C3H/HeJ mice, and enhances the transcriptional activity of NF-κB or AP-1.	[50]

In addition to the use of CGA alone, there have been attempts to see if the combination would be more effective. In order to investigate whether CGA and caffeic acid (CA) could reduce the ability of macrophages to accumulate lipids, Marino, M. conducted a study. The results showed that the CGA + CA mixture reduced the ability to store lipids in macrophages, and further studies revealed that the reduction in lipid storage was mediated by diminished levels of the transcription factors C/EBPβ and PPAR-γ [48]. In addition, CGA has proven to be beneficial for the treatment of various other diseases, such as liver injury [49, 50], liver inflammation and fibrosis [51], obesity [52], healthy gut development [53], inflammatory damage [54] (**Table 1**).

Discussion

The role of CGA in regulating macrophages and improving inflammatory diseases has been widely validated through in vitro experiments, animal model experiments, and preliminary clinical studies. Its mechanism involves multiple aspects, like reducing the release of cytokines that promote inflammation, promoting M2 polarization of macrophages, inhibiting oxidative stress, and regulating inflammasome activation. Although additional trials are warrented, CGA, as a natural compound, has shown great potential in the treatment of inflammatory diseases. Future research must focus on in-depth analysis of its mechanism of action and optimization of clinical applications. Following issues also pertain in drug development:

(1) CGA has low oral bioavailability, a short retention time in the body, and needs repeated administration. If injected intravenously, it will lead to excessive local CGA, and excessive CGA may bind to protein groups and cause allergic adverse reactions [55].

(2) Caffeic acid and ferulic acid, which are metabolites of CGA, also exhibit anti-inflammatory activity, and their mechanisms for exerting CGA activity need to be further investigated [56].

(3) The primary active component of many traditional Chinese medications is CGA, but the effects of other ingredients in traditional Chinese medicines and compound formulations on their pharmacokinetics are unknown [57].

An early stage of cirrhosis that affects many people is liver fibrosis, posing a serious health risk for which there is no viable treatment. The polyphenol monomer CGA was delivered to the wounded liver for the first time in this study using tetrahedral framework nucleic acid nanoparticles as carriers. Through this delivery approach, CGA's bioavailability and stability were enhanced, laying the foundation for its antifibrotic and antioxidant effects [58]. In addition, studies have shown that nanogels are promising drug delivery frameworks for targeting collagen protein-induced arthritis, utilizing chitosan and interconnections used to encapsulate CGAs [59]. Zhou H. made phospholipid-based in situ gels with CGA-PG. In vitro and in vivo, CGA-PG demonstrated appropriate slow-release behavior, high drug loading capacity, good fluidity, and easy injectability. The results demonstrated that CGA-PG could stop tumor growth without causing any serious side effects [60]. All things considered, CGA-PG might be a potential long-term medication administration method with superior therapeutic outcomes for gliomas and hepatocellular cancer, whether it will again continue to be modified for applications in inflammatory diseases remains to be seen. Encapsulation of CGA utilizing a self-microemulsifying drug delivery approach increased its oral bioavailability and promoted drug accumulation in the mesenteric lymph nodes to achieve amelioration of inflammation [61]. Specific targeting of nanoparticles for colonic inflammation is controlled by loading CGA using combined ultrasonic emulsification. The metabolites

of CGA, including caffeic acid and ferulic acid, also possess anti-inflammatory properties. This is followed by degradation of pectin by colonic flora and pectinase generated by a magnetic field applied to the colon, and this oral colonic nano-delivery system could have a promising future as a new therapeutic modality [62].

Prospect

After extensive research on the role of CGA in modulating macrophages to ameliorate inflammatory diseases, future studies should aim to investigate its underlying mechanism and improve its application in clinical practice. Despite extensive research has established the role of CGA in reducing inflammation through various mechanisms, such as by inhibiting the release of pro-inflammatory cytokines, by promoting the polarization of M2-type macrophages, and by regulating oxidative stress, the specific cellular signaling pathways and molecular mechanisms still need to be fully elucidated. For example, how CGA functions in different immune cell populations, and how its regulatory effect on the gut microbiota affects inflammatory diseases, are directions that need to be focused on in future studies.

In addition, the low oral bioavailability of CGA and the anti-inflammatory function of its metabolites are among the bottlenecks limiting its clinical application. How to improve the bioavailability of CGA, extend its half-life in vivo, and reduce the side effects through drug delivery systems are key tasks for future research. Nanotechnology and targeted drug delivery systems may provide new solutions to enhance the efficacy of CGA.

CGA, as a natural polyphenolic compound, has been preliminarily demonstrated to have potential application in a variety of inflammatory diseases. Future clinical studies are necessary to validate the effectiveness and safety of CGA through multicenter, large-sample randomized controlled trials, with the aim of providing a new therapeutic option associated with mild side effects for the management of inflammatory diseases.

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Ethics approval

No applicable.

Data availability

The data will be available upon request.

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Authors' contribution

The entire article was drafted and revised by Ahmed Karim, who also created the tables and charts and submitted the final version.

Competing interests

The authors declare no competing interests.

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