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# Research progress on the pharmacological activity and mechanism of chlorogenic acid in alleviating acute kidney injury in sepsis patients

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## Highlights

- The pharmacological action of chlorogenic acid was summarized.
- The mechanism of acute kidney injury (AKI) was investigated.
- The signaling pathways through which chlorogenic acid plays its role in AKI were summarized for the first time.
- A possible new drug for treating a common perioperative complication, namely sepsis-induced AKI, is revealed.

## Abstract

Sepsis-induced acute kidney injury (SAKI) is a serious perioperative complication and a common clinical syndrome characterized by a rapid deterioration in renal function with a high incidence of 70%. The causes of SAKI include impaired mitochondrial function of renal tubular epithelial cells, oxidative stress, inflammatory reaction and renal microcirculation disorder. Chlorogenic acid, as a natural product of plant origin, has various biological activities, such as antibacterial, antiviral, and anti-tumor, and plays a significant role in the treatment of SAKI. This article reviews the pharmacological activities of chlorogenic acid and the signaling pathways involved in relieving SAKI, in order to provide a theoretical basis for in-depth study of the mechanisms underlying the alleviation of SAKI and the confirmation of potential therapeutic targets.

**Keywords**: Chlorogenic acid, sepsis-induced acute kidney injury, pharmacological activity, mechanism, signaling pathway

## Introduction

As one of the most common perioperative complications, sepsis is a condition characterized by multi-organ dysfunction caused by the host's response to infection, often involving acute kidney injury (AKI). Patients with sepsis usually have a poor prognosis, leading to longer stays in the intensive care unit, higher mortality rates, increased rates of long-term disability, and decreased quality of life [1]. Chlorogenic acid (CGA) is a natural product of 1-bit carboxyl group of caffeic acid and 3-bit hydroxy-condensedated ester of quinic acid. It causes few adverse reactions and can be highly tolerated, offering unique advantages in the treatment of sepsis-induced acute kidney injury (SAKI). At present, CGA is commercially obtained from plants, such as Duzhong leaves, dandelion, honeysuckle, and tobacco leaves [2]. To date, it has been established that CGA has a good therapeutic effect on SAKI, possibly because of its biological activities, such as cardiovascular protection, antioxidant effect, lipid -lowering effect, and anti-inflammatory effect [3-6].

In recent years, CGA has been valued by many scholars. Studies of Zhang and Chen have

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shown that CGA can reduce the small intestine damage of stress-type chickens by inhibiting inflammatory reactions and oxidizing, and can also improve antioxidant capacity [7, 8]. This paper summarizes the pharmacological activities of CGA in alleviating SAKI, aiming to provide reference for in-depth study of mechanisms and related signal pathway of CGA in SAKI.

## Pharmacological activities of CGA

### *Cardiovascular protective effect*

CGA has shown good efficacy in the treatment of cardiovascular and thromboembolic diseases. Myocardial hypertrophy can cause an increase in the incidence and mortality of cardiovascular diseases [9]. Studies have shown that the CGA pretreatment can reduce the apoptosis rate of H9c2 myocardial cells and reduce the reactive oxygen species (ROS) through nuclear factor κappa B (NF-κB) signaling pathway [10]. ROS plays a role in inhibiting myocardial hypertrophy and thus protecting the cardiovascular system. Study has pointed out that CGA reduces the damage of vascular endothelial cells by removing oxygen free radicals and anti-lipid peroxidation, which has a protective effect on the cardiovascular system [11].

### *Antioxidant effect*

When the body is exposed to harmful stimuli, the balance of the oxidation system and the antioxidant system can be disrupted [12]. This imbalance leads to the enhancement of the oxidation system, resulting in oxidative stress within the body and the excessive production of ROS and reactive nitrogen species. Study of Ferrare found that CGA has a very strong antioxidant effect, which can accelerate wound repair in diabetic rats by playing an antioxidant role without affecting the levels of superoxide dismutase (SOD) and catalase in wound [13]. It has been shown that CGA can reduce lung tissue damage and reduce the content of malondialdehyde (MDA), ROS and inflammatory factors [14]. Song reported that CGA eliminated and inhibited the production of ROS by enhancing antioxidant stress defense [15]. Other studies have also proven that CGA extracted from honeysuckle leaves and flavonoids can play a good antioxidant role [16, 17]. CGA intervention can inhibit the reduction of the anti-apoptotic protein B-cell lymphoma-2 (Bcl-2) and the increase of the apoptotic protein BCL-2-associated X protein (Bax) [18]. Feng et al. detected the antioxidant effect of CGA in vivo and in vitro, and found that CGA has an anti-inflammatory activity and exerts protective effect against chronic kidney injury [19].

### *Lipid-lowering effect*

CGA is marketed under the trade name Svetol and is incorporated into products such as coffee and chewing gum as additives for weight loss. In the treatment of obesity, research shows that CGA can regulate sugar and lipid metabolism [20]. Shirkhani et al. observed the changes in weight, plasma lipid content and related gene expression in mice fed with a high-fat diet (HFD) for 7 weeks that treated by CGA [21]. The results showed that CGA reduced the increase in weight and fat caused by HFD, improved blood lipid status, reduced plasma toxicity, and regulated the expression of ribonucleic acid related to fat and fat decomposition. It is indicated that CGA can regulate intestinal microbiota and help improve HFD-induced obesity. Study of Ma et al. exhibited that CGA promoted the oxidative degradation of lipids, and inhibiting mouse fat synthesis reduced fat and weight by regulating the expression of liver fat metabolism-related genes and proteins [22].

### *Anti-inflammatory effect*

Inflammatory reaction is a physiological reaction of tissue damage caused by exogenous or endogenous factors [23]. A large number of studies have shown that lipopolysaccharides (LPS) can induce changes in the surface adhesion molecules of neutrophils [24]. After activation, a large number of super-oxides and a series of inflammatory factors are produced to form a cascade of inflammatory response, which mainly causes local tissue and cell damage through free radicals and inflammatory factors. In the study of Gao, CGA administration significantly reduced intestinal inflammation in mice, reduced the levels of pro-inflammatory cytokines interleukin (IL)-1β and IL-6, and increased the expression levels of anti-inflammatory factor IL-10 and antioxidant-related genes catalase, Glutathione Peroxidase 1, Glutathione Peroxidase 2 and SOD 1 [25]. Shimizu showed that CGA enhanced the antioxidant and anti-inflammatory ability of broiler intestines by inhibiting DNA methylation, and its effects on inflammation and DNA methylation lasted until the later stage of growth [26].

## The pathogenesis of SAKI

Sepsis is a life-threatening multi-organ dysfunction caused by the dysfunction of body response to infection [27]. During the progression of sepsis, patients can have multiple organ dysfunction syndrome and even multi-organ

failure, and the kidney is one of the organs that often involved. Studies have shown that the pathogenesis of SAKI is related to oxidative stress injury, inflammation, and microcirculation disorders [28].

*Inflammation*

During sepsis, inflammatory mediators derived from pathogen-associated molecular patterns (PAMPs) and synthesized by activated immune cells release damage-associated molecular patterns (DAMPs), leading to host cell damage. DAMPs and PAMPs can be recognized by renal tubular epithelial cells (RTECs) through transmembrane or intracellular pattern recognition receptors (PRRs) [29].

After PRRs combined with PAMPs and DAMPs (**Figure 1**), immune cells are activated to kill microorganisms. They secrete pro-inflammatory factors, such as tumor necrosis factor-α (TNF-α), IL-1α, IL-6 and chemokines, enhance the expression of co-stimulation factors, activate high-efficiency T cells, produce metabolites of arachidonic acid, initiate exogenous coagulation pathways through tissue factors and facilitate the formation of activated thrombin. Subsequently, these processes amplify thrombosis through a cascade reaction of the internal coagulation pathway. Through the LPS-induced SAKI model, Li's research team found that the levels of TNF-α and IL-1β in the model group were higher than those in the pseudo-surgery group [30]. Also, the HE stained pathological sections revealed degeneration and necrosis in the renal tubular epithelial cells in the model group. The renal tubules exhibited a proteinaceous cast formation and significant dilation. Additionally, there was renal interstitial congestion edema, accompanied by infiltration of a large number of inflammatory cells.

The molecular weight of DAMS/PAMPs is small enough to be filtered in the glomerulus. The filtered DAMS/PAMPs entering the renal tubular lumen can be recognized by toll like receptors (TLRs) on the surface of RTECS, and can also affect RTECS through the leakage of adjacent peritubular capillaries. After PAMPs bind to DAMPs, PAMPs/DAMPs can activate signal transduction pathways, and then recognize the TLRs on the surface of RTECS that can increase downstream inflammatory signal cascades, pro-inflammatory cytokines and ROS synthesis [31].

*Oxidative stress injury*

Oxidative stress occurs in the human body when there is an imbalance between oxidation and antioxidant systems. During sepsis, inflammatory mediators and PRRs combine to trigger inflammatory cascade reaction, increase pro-inflammatory factors, cooperate with oxidative stress, and trigger the aggregation of multinucleated neutrophils. Neutrophils can produce superoxide through the complex process of "oxidative burst". The oxidation system mainly includes active free radicals, such as ROS and reactive nitrogen species. The research team of Daenen reported that in the process of sepsis, the outbreak leads to an increase in ROS [32]. This increase results in dysfunction, shedding, or apoptosis of glomerular or renal tubular epithelial cells, and in severe cases, widespread cell death occurs. Neutrophil-induced oxidative enhancement further attracts pro-inflammatory chemokines, promotes the recruitment of leukocytes to tissue injury sites, and initiates a cytokine storm, leading to the further generation of ROS.

*Microcirculation disorder*

The traditional view holds that pre-renal injury is caused by insufficient renal perfusion, that is, the reduction of renal blood flow is one of the main causes of SAKI [33]. However, novel evidence shows that SAKI can occur without low renal perfusion, but along with stable hemodynamics, or even normal or increased renal blood flow [34]. It is suggested that microcirculation dysfunction may play an important role in the development of renal injury.

In sepsis, tissue damage leads to an increase in inducible nitric oxide synthase (iNOS) expression and the uneven distribution of iNOS in the kidney [35]. Simultaneously, the activity of endothelial NO synthase decreases, leading to uneven regional concentration of NO. The dysfunction of NO synthase leads to the reduced NO-mediated endothelium-dependent vasodilation, disrupting the balance of renal microcirculation.

**Mechanisms of CGA in the treatment of SAKI: anti-inflammatory and antioxidant effects**

CGA is one of the active ingredients of many Chinese herbal medicines. It has biological activities such as anti-tumor, antioxidant, and anti-inflammatory, along with advantages of few adverse reactions and good body tolerance in the treatment of a variety of diseases. It is reported that LPS-induced inflammatory cytokines play an important role in the pathogenesis of SAKI. LPS-induced SAKI can lead to severe renal pathological damage, including

destroying glomerular structure, degenerating renal tubular epithelial cells, and decreasing renal function biochemical indicators (such as urea nitrogen, creatinine, kidney injury molecule 1, neutrophil gelatinase-associated lipocalin) and pro-inflammatory cytokines (such as TNF- α and IL-1 β in serum and renal tissue). The renal oxidative stress indexes include ROS, MDA and SOD. A large number of studies have shown that reducing the levels of pro-inflammatory cytokines and oxidative stress indicators can alleviate SAKI. Peng's study confirmed that CGA could regulate inflammation and oxidative stress response, where excessive inflammatory response is an important cause of SAKI [36]. TNF-α, as an important promoter of SAKI, can cause damage to renal tubular epithelial cells, thereby leading to SAKI. IL-1 β and IL-6, alongside TNF-α, are pivotal inflammatory mediators in the cytokine cascade, inducing a cascade reaction that triggers an excessive systemic inflammatory response.

The production of macrophages in sepsis can induce the synthesis of a large number of free radicals, leading to oxidative stress. However, renal antioxidant system lacks the capacity to adequately remove these excessive free radicals, resulting in an imbalance in oxidation/antioxidation of the kidney, which attacks the cellular lipid substances. MDA is the end product of lipid peroxidation process, and its level can reflect the extent of lipid peroxidation damage in the body. ROS-induced oxidative damage can promote the development and progression of SAKI.

Study of Zhou showed that CGA could effectively improve the inflammatory response induced by AKI in a dose dependent manner through TNF-α and IL-1β in rat serum [37]. Han's team found that CGA pretreatment could reduce the expression of inflammatory factors and the levels of ROS and MDA and increase the activity of SOD [38]. CGA may be achieved by regulating nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase 1 (HO-1) signaling pathway.

## Signaling pathways

### *Nrf2/NLRP3 signaling pathway*

Nrf2 is a basic leucine zipper redox-sensitive transcription factor with anti-inflammatory effect, serving as the primary regulatory factor for genetic protection in various cells. Under static conditions, Nrf2 remains inactive as it interacts with Kelch-like ECH-associated protein 1 (Keap1). In response to oxidative and inflammatory stress, Nrf2 is released from Keap1 and transported to the nucleus to trans-activate the expression of cell protection genes such as HO-1 and quinoneoxidoreductase (NQO1) so as to eliminate oxidative stress and inflammation. Study showed that CGA significantly increased the expression of Nrf2, promoted its entry into the nucleus, and increased the expression of HO-1 and NQO1 proteins [39]. According to the research results of Zheng et al., CGA can inhibit oxidative stress and inflammation by activating the Nrf2/HO-1 signaling pathway [40]. As one of the most studied and important members of the Nod-like receptor family of PRRs, Nod-like receptor family 3 (NLRP3) inflammasome consists of NLRP3, apoptosis-associated speck-like protein containing a CARD and cysteinyl aspartate specific proteinase(caspase)-1 preforms, and its central role is to activate the aspartic proteolytic enzyme containing cysteine [41]. Active cleaved caspase-1 is produced, which cleaves the pro-inflammatory cytokines IL-1β and IL-18 to be biologically active. Nrf2 inhibits the production of ROS, which has a positive regulatory relationship with the activity of the NLRP3 inflammasome, and ROS is required for the activation of the NLRP3 inflammasome [42, 43]. ROS, serving as an intermediate in the activation of Nrf2 and NLRP3 inflammasome, can counter the NLRP3 inflammasome by reducing ROS production. Nrf2 has a protective effect against oxidative and inflammatory damage by inhibiting the activity of NLRP3 inflammasome. Some studies have reported that CGA can inhibit the activation of NLRP3 inflammasome [44]. In summary, CGA plays an important role in Nrf2/NLRP3 signaling pathway. Specifically, CGA activates HO-1/Nrf2 signaling pathway through Nrf2, promotes protein expression of Nrf2, HO-1 and NQO1, inhibits production of ROS and activation of NLRP3 inflammasome, and reduces the level of inflammatory factors, thereby improving renal function (**Figure 1**).

### *TLR4/NF-κB signaling pathway*

As an important cell membrane receptor, TLR4 plays a key role in the process of inflammation reaction. As a downstream effector of TLR4 signaling pathway, recombinant NF-κB is bound to the inhibitor of NF-κB (IκB) in normal physiological state by heterodimer composed of inactive NF-κB p65 and p50. In a pathological state, IκB kinase can specifically phosphorylate IκB and promote the transfer of NF-κB p65 into the nucleus, causing the body to release inflammatory factors that trigger inflammatory response. Studies have shown that CGA can effectively down-regulate the expression of TLR4 protein in renal tissue and inhibit the phosphorylation of-

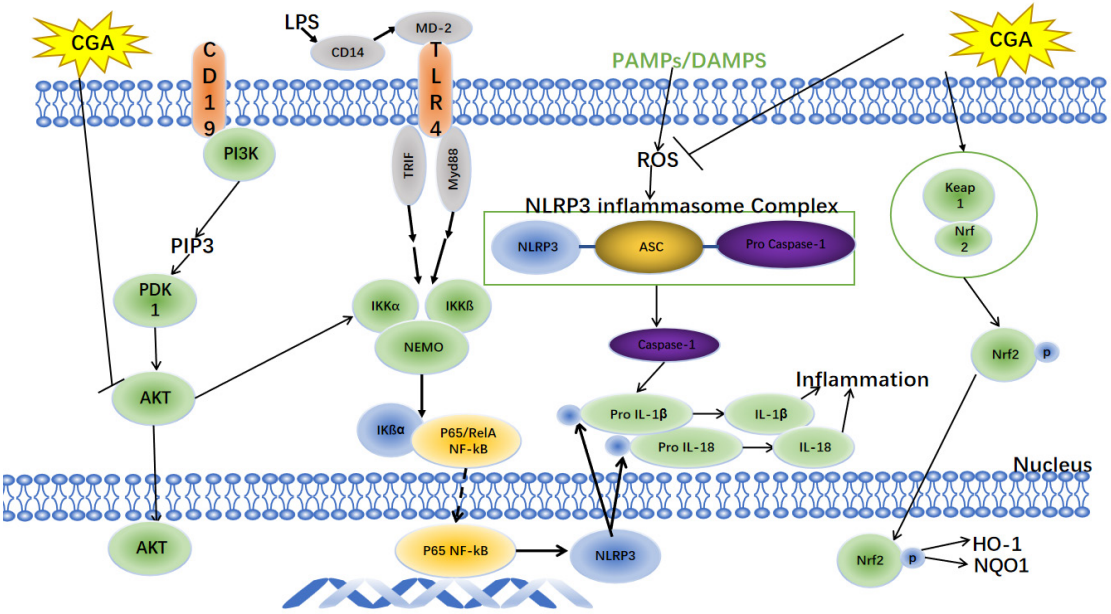


**Figure1. Signaling pathway involved in CGA-mediated treatment of SAKI.** SAKI, sepsis-induced acute kidney injury; CGA, chlorogenic acid; LPS, lipopolysaccharides; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; TLR4, toll like receptor 4; ROS, reactive oxygen species; NF-κB, nuclear factor κappa B; Nrf2, nuclear factor erythroid 2-related factor 2; NLRP3, Nod-like receptor family 3; IL, interleukin; HO-1, heme oxygenase 1; NQO1, quinoneoxidoreductase; IκBα, inhibitor kappa B α; IKKβ, inhibitor of kappa B kinase; IKKα, IκB kinase α; TRIF, Toll/IL-1 receptor domain containing adaptor inducing IFN-β; Myd88, myeloid differentiation primary response gene 88; Keap1, Kelch-like ECH-associated protein 1; caspase-1, cysteinyl aspartate specific proteinase 1; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; PDK1, pyruvate dehydrogenase kinase isozyme 1; CD19, B-lymphocyte antigen CD19 precursor; CD14, cluster of differentiation 14; PIP3, 3-phosphate phosphatidylinositol; ASC, apoptosis-associated speck-like protein containing a caspase-recruitment domain; MD-2, myeloid differentiation protein-2; NEMO, nuclear factor-κappa B essential modulator.

**Table1. Mechanism and signaling pathway of CGA in treating SAKI**

| Medicine | Types of signaling pathway | Molecular substances | Pharmacology |
|---|---|---|---|
| CGA | Nrf2/NLRP3 signaling pathway | Nrf2, Keap1, HO-1, NQO1, ROS, NLRP3, cleaved caspase-1, IL-18, IL-1β | Oxidative stress and inflammation |
| | TLR4/NF-κB signaling pathway | TLR4, Myd88, P65 NF-κB, IκBα | inflammation |
| | PI3K/AKT signaling pathway | PI3K, AKT, p-AKT, Bcl-2, ROS | Oxidative stress |

Note: CGA, chlorogenic acid; SAKI, sepsis-induced acute kidney injury; Nrf2, Nuclear Factor erythroid 2-Related Factor 2; NLRP3, Nod-like receptor family 3; TLR4, toll like receptor 4; NF-κB, recombinant nuclear factor kappa B; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; Keap1, Kelch-like ECH-associated protein 1; HO-1, heme oxygenase 1; NQO1, quinoneoxidoreductase; ROS, reactive oxygen species; caspase-1, cysteinyl aspartate specific proteinase 1; IL, interleukin; Myd88, myeloid differentiation primary response gene 88; IκBα, ecombinant inhibitory subunit of NF kappa Bα; Bcl-2, B-cell lymphoma-2.

NF-κB p65 and IκBα [45]. Studies have reported that TLR4/NF-κB signaling pathway plays a role in diseases such as acute kidney injury [46]. Zhou et al. suggested that CGA could inhibit TLR4/NF-κB pathway to alleviate acute kidney injury in sepsis patients (**Figure 1**) [37].

***Phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway***

The PI3K/AKT signal pathway is involved in the onset of various diseases, including cancer, cardiovascular disease, nerve disease, endocrine disorders, etc. As a proto-oncogene, AKT protein kinase is an important downstream component of PI3K, which is activated upstream to produce the second messenger phosphatidylinositol 3,4,5-triphosphate (PI-3,4,5-P3). PI3K binds to

the N-terminal pleckstrin homology domain of AKT, facilitating the translocation of AKT from the cytoplasm to cell membrane. Moreover, AKT is activated through pyruvate dehydrogenase kinase isozyme 1-mediated phosphorylation site. The activation of the PI3K/AKT signaling pathway can lead to the onset of diseases. Studies have demonstrated that CGA can significantly inhibit the expression of p-PI3K, p-Akt and Bcl-2 proteins, while inducing an increase in Bax protein expression [47]. The higher the concentration of CGA, the more obvious the changes in protein expression. In addition, CGA can reduce the activation of PI3K/Akt signaling pathway and interfere with the PI3K/AKT pathway, leading to a decrease in p65 entering into the nucleus, as well as a reduction in the production of inflammatory factors and ROS [48]. Zhou proposed the potential of CGA to prevent hyperuricemic nephropathy (CKD) by regulating PI3K/Akt pathway (**Figure 1**) [37].

## Conclusion

CGA is a low-cost and easily obtained natural product with various biological activities. However, in China, the biosynthesis of CGA, its pharmacological activities, as well as research and development are relatively undeveloped. Despite having abundant CGA plant sources, China has not fully utilized this rich resource, resulting in significantly lower utilization efficiency compared to developed countries. As CGA research continues to advance, our understanding of its potential benefits grows more comprehensive. It is hoped that CGA can be utilized not only as a therapeutic drug for diseases such as SAKI in clinical practice, but also be processed into medicinal diets to promote the overall well-being of people.

In **Table 1**, we summarize the pharmacological effects and signaling pathways of CGA in alleviating SAKI, as well as the molecular substances involved in the mechanism of action: CGA exerts anti-inflammatory and antioxidant effects on SAKI via the Nrf2/NLRP3 signaling pathway, CGA plays an anti-inflammatory role in the treatment of SAKI via TLR4/NF-κB signaling pathway, and CGA fulfills an antioxidant role in SAKI through the PI3K/AKT signaling pathway.

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