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Natural product chlorogenic acid achieves pharmacological activity and health protection via regulating gut microbiota: a review

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ABSTRACT

Chlorogenic acid (CA) is a natural plant-derived polyphenol compound that is widely present in beverages (coffee and tea), fruits (blueberry, apple, and mulberry), and medicinal plants (*Lonicera japonica*, *Eucommia ulmoides*, and *Cichorium intybus*). In recent years, CA has attracted extensive attention due to its various health benefits, such as anti-inflammatory, immunomodulatory, anti-obesity, anti-diabetes mellitus, and neuroprotection activities. Interestingly, the low bioavailability of CA corresponds to high bioactivity, which raises a key scientific question of how low bioavailability CA can achieve high biological activity. In this review, we highlight the gut microbiota as a key target for connecting the two by summarizing a large amount of evidence. Specifically, the composition and abundance of gut microbiota, its metabolites, intestinal immunity, barrier function and so on were all changed under different pathological conditions such as inflammatory bowel disease, liver disease, kidney disease, cardiovascular disease, diabetes mellitus, obesity, etc. Conversely, these changes could be reversed by CA. In a word, CA could achieve pharmacological activity as well as health-protective effects by modulating intestinal immune and barrier function, gut microbiota composition, gut microbiota metabolites, and signaling pathways. This review provides new targets for the prevention and treatment of diseases by CA. Meanwhile, regulating the composition of the gut microbiota through natural products may be a potential strategy to achieve health protection.

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1. Introduction

There are a large number of microorganisms (10–100 trillion) in the human gastrointestinal tract, which are called gut microbiota^[1]. The gut microbiota is mainly composed of bacteria, forming a

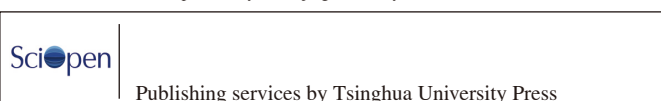
huge and complex ecological community with over 1 000 species. Among them, more than 90% of the species belong to Firmicutes and Bacteroidetes^[2]. Meanwhile, these bacteria can be divided into three categories based on their functions: beneficial (30%), harmful (10%), and conditional pathogenic bacteria (60%)^[3]. For a long time, researchers have believed that there is a symbiotic physiology between the gut microbiota and hosts^[4–5]. In recent years, with the improvement of detection technology and analytical instruments, more and more experimental evidence has revealed that the gut microbiota participates in the regulation of host immune function and metabolic homeostasis^[5–6]. Specifically, the gut microbiota could promote the production of specific types of immune cells (such as regulatory T cells and regulatory B cells) in the gut, thereby regulating

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the balance of the immune response^[7-8]. In addition, metabolites of the gut microbiota, such as short-chain fatty acids (SCFAs) and peptides, could affect the function of immune cells and inflammatory responses, thereby regulating the intensity and direction of immune responses^[9-10].

Polyphenols, a class of plant-derived bioactive components with multiple hydroxyl phenols. They are widely present in daily diet, including grains, vegetables, fruits, and beverages, especially in certain coffee drinks^[11]. Most polyphenols exist in the diet in the form of glycosylation, esters, or polymers, and more than 8 000 polyphenols have been isolated and identified^[12]. Based on the structure of the carbon skeleton, polyphenols are classified into four main categories: phenolic acids, flavonoids, lignans, and stilbenes^[13]. Due to the diversity of polyphenols' structures, their oral bioavailability is low. Therefore, the vast majority of polyphenols cannot be absorbed in the gastrointestinal tract and thus accumulate in the cecum or colon^[14-15]. This situation leads to low bioavailability of polyphenols. However, a large amount of evidence suggests that polyphenols have strong biological activities, including anti-inflammatory, antioxidant, anti-cancer, and neuroprotective activities^[16-20]. From these data, readers should note that the extensive metabolism of polyphenols by the microbiota in the cecum and colon seems to be a key factor in their strong biological activity^[21-22]. In other words, the health benefits exhibited by polyphenols seem to be inseparable from their interaction with the gut microbiota.

Chlorogenic acid (CA, $C_{16}H_{18}O_9$, compound CID: 1794427) is the most abundant natural polyphenol present in the human diet and plants. In the past studies, many pharmacological activities of CA have been widely demonstrated, including anti-obesity^[23], anti-diabetes mellitus^[24], anti-cancer^[25-26], heart protection^[27], liver protection^[28-29], kidneys protection^[30], gut protection^[31-32], and neuroprotection^[33-34]. The multiple pharmacological activities recorded by CA are attributed to their regulation of enzyme activity, cell proliferation, and various signaling pathways (such as anti-inflammatory^[32,35] and antioxidant^[36]). However, as mentioned earlier, gut microbiota may play a crucial role in regulating the biological activity and bioavailability of polyphenols. Even though the various pharmacological activities of CA have been extensively studied by researchers, the interaction between CA and gut microbiota and the health benefits mediated by this interaction are still poorly understood. Therefore, this review mainly focuses on the interaction between gut microbiota and CA, as well as the potential

contribution of this interaction to CA-mediated multi-pharmacological activities and health protection.

2. Chemistry, structure, and sources of CA

CA, also known as caffeoyl quinic acid and caffeitanic acid, is a phenolic acid obtained by the condensation reaction between caffeic acid and quinic acid, and its chemical structure is shown in Fig. 1. Its chemical name is 5-*O*-caffeoylquinic acid (5-CQA), and its molecular formula is $C_{16}H_{18}O_9$. CA has one $-O-$ group at position 3, one $-COOH$ group at position 1, and three $-OH$ groups at positions 1, 4, and 5. Therefore, it is also known as (1*R*,3*R*,4*S*,5*R*)-3-[(*E*)-3-(3,4-dihydroxyphenyl) prop-2-enoyl]oxy-1,4,5-trihydroxycyclohexane-1-carboxylic acid. According to the different esterification reaction sites of quinic acid, CA has a large number of isomeric structures, such as 4-*O*-caffeoylquinic acid (4-CQA, cryptochlorogenic acid), 3-*O*-caffeoylquinic acid (3-CQA, neochlorogenic acid), 3,4-dicafeoylquinic acid (isochlorogenic acid B), 3,5-dicafeoylquinic acid (isochlorogenic acid A), 4,5-dicafeoylquinic acid (isochlorogenic acid C), etc (Fig. 1). Notably, although CA has many isomers, the current term "CA" specifically refers to 5-CQA. Meanwhile, the most abundant isomer present in dietary and plant sources is 5-CQA^[11,37]. In addition, CA is a white or slightly yellow crystalline powder at room temperature and is easily soluble in organic solvents such as ethanol, acetone, and methanol. Interestingly, the solubility of CA in water is low, but the solubility increases with the increase of temperature, and its solubility in water is about 4% at 25 °C. As a polar organic acid, CA has low chemical stability, mainly because its molecular structure contains the *o*-diphenol hydroxyl group, which is the most suitable reaction substrate for phenolase catalysis and is easily oxidized under heat or light conditions^[38-39].

CA is one of the widely distributed polyphenolic compounds in plants and is internationally recognized as "plant gold"^[40]. Its main dietary sources include tea, coffee beans, potatoes, blueberries, apples, mulberries, and so on^[11]. Among them, green coffee beans are considered to have the most abundant CA content in plants, accounting for approximately 6% to 12% (*m/m*) of total CA^[41]. Besides green coffee beans, the content of CA in green tea extract is around 292.3 $\mu\text{g/g}$ ^[42]. For black tea, the content of CA varies greatly depending on the producing area, mainly concentrated between 0 and 530 $\mu\text{g/g}$ ^[43]. Apple (62–385 $\mu\text{g/g}$), mulberry (0–466 $\mu\text{g/g}$) and bilberry

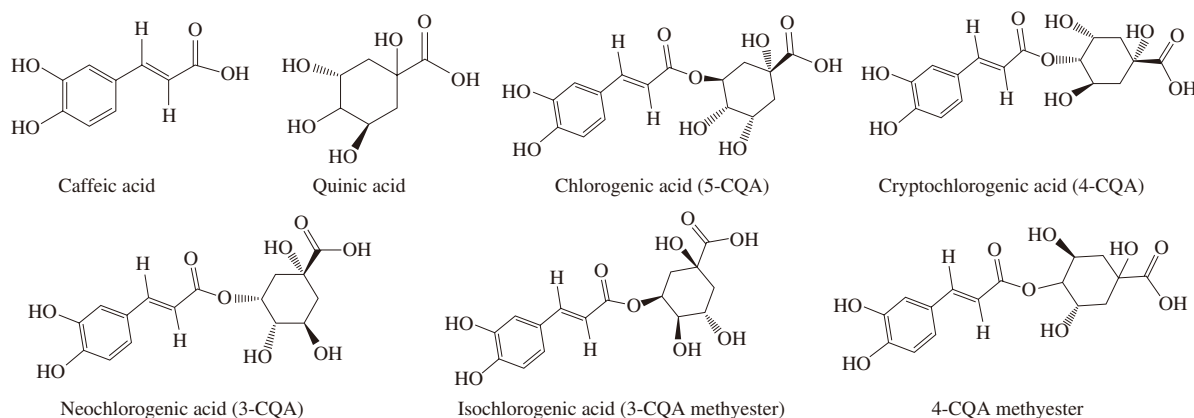


Fig. 1 The chemical structure of caffeic acid, quinic acid, chlorogenic acid (CA), isochlorogenic acid, cryptochlorogenic acid, neochlorogenic acid, and 4-*O*-caffeoylquinic acid methylester. CQA, caffeoylquinic acid.

3. The biosynthetic pathway of CA

CA is a phenylpropanoid compound produced by plants through the shikimic acid pathway during aerobic respiration. At present, there are three possible biosynthetic pathways for CA production from phenylalanine^[46-47], as shown in Fig. 2. Phenylalanine is catalyzed by a series of enzymes (phenylalanine ammonia lyase, cinnamate 4-hydroxylase (C4H), and 4-coumarate-CoA ligase (4CL)) to produce

Table 1
The main sources of CA.

Source		Family	Extracted part	References
Latin name	English name			
<i>Coffea arabica</i> L.	Coffee	Rubiaceae	Seed	[48]
<i>Camellia sinensis</i> (L.) O. Ktze.	Tea	Camelliaceae	Leaf	[49]
<i>Malus pumila</i> Mill.	Apple	Rosaceae	Fruit	[50]
<i>Lonicera japonica</i> Thunb.	Honeysuckle	Caprifoliaceae	Bud	[51]
<i>Eucommia ulmoides</i> Oliv.	Eucommiae cortex	Eucommiaceae	Leaf	[52]
<i>Lycium barbarum</i> L.	Matrimony vine	Solanaceae	Leaf	[53]
<i>Solanum tuberosum</i> L.	Potato	Solanaceae	Tuber	[54]
<i>Crataegus pinnatifida</i> Bge.var. <i>major</i> N.E.Br.	Hawthorn	Rosaceae	Leaf	[55]
<i>Vaccinium corymbosum</i> L.	Blueberry	Ericaceae	Leaf	[56]
<i>Morus alba</i> L.	Mulberry	Moraceae	Leaf	[57]
<i>Cichorium intybus</i> L.	Witloof	Compositae	Seed	[58]
<i>Helianthus tuberosus</i> L.	Jerusalem artichoke	Compositae	Tuber	[59]

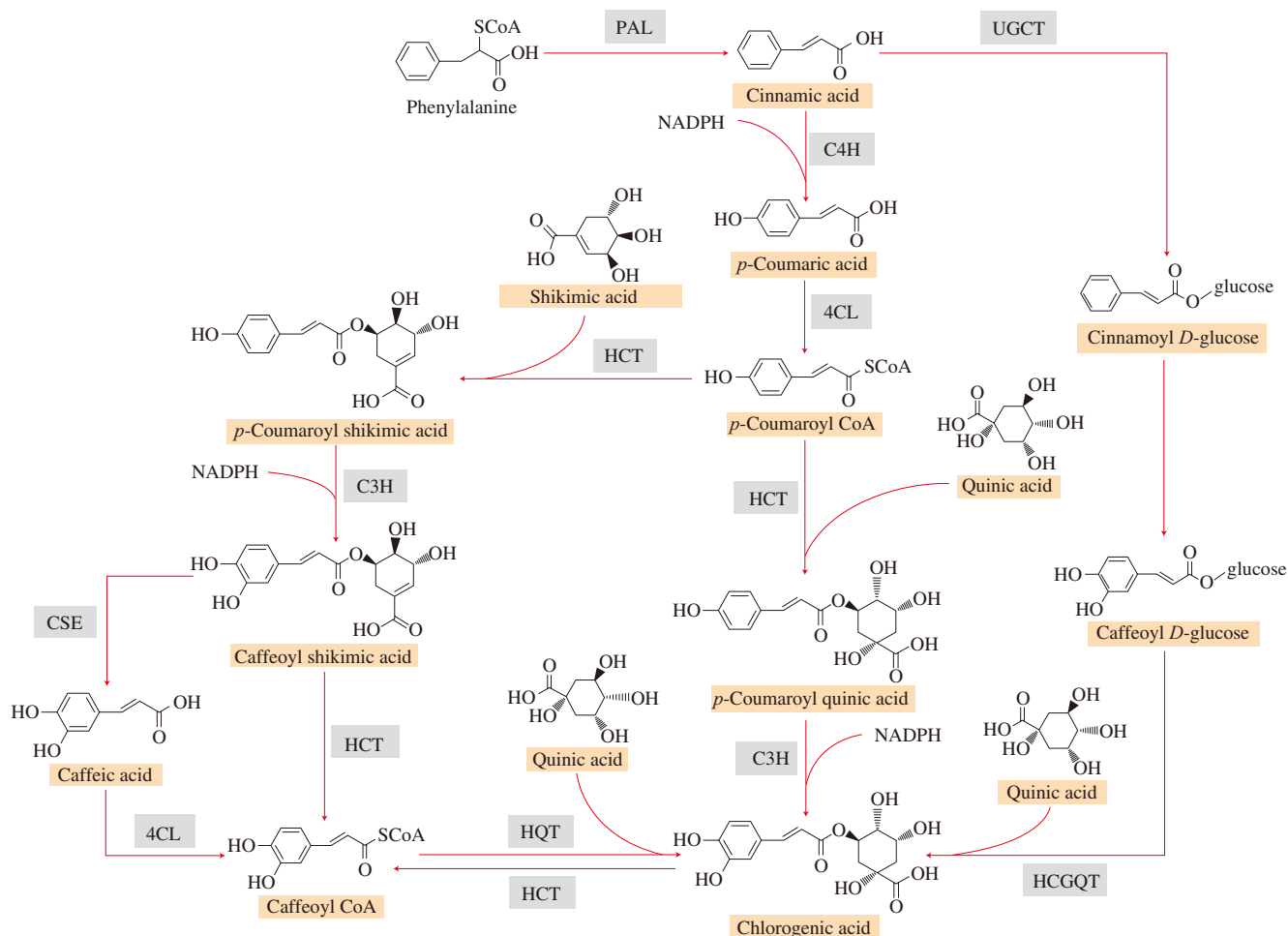


Fig. 2 The biosynthetic pathway of CA. PAL, phenylalanine ammonia lyase; C4H, cinnamate 4-hydroxylase; 4CL, 4-coumarate-CoA ligase; HCT, hydroxycinnamoyl CoA shikimate/quinate hydroxycinnamoyl transferase; C3H, plant coumaric acid-3-hydroxylase; CSE, cystathionine-γ-lyase; HQT, hydroxycinnamoyl-CoA quinate hydroxycinnamoyl transferase; UGCT, UDP glucose:cinnamate glucosyl transferase; HCGQT, hydroxycinnamoyl-D-glucose:quinat hydroxycinnamoyl transferase.

p-coumaroyl CoA. Subsequently, *p*-coumaroyl CoA is condensed with quinic acid and shikimic acid by hydroxycinnamoyl CoA shikimate/quinate hydroxycinnamoyl transferase (HCT) to generate *p*-coumaroyl quinic acid and *p*-coumaroyl shikimic acid, respectively. The former is catalyzed by plant coumaric acid-3-hydroxylase (C3H) and hydroxylated to directly produce CA. The latter produces caffeoyl CoA under the catalysis of a series of enzymes (C3H, HCT, and 4CL, etc.), and finally condensates with quinic acid to form CA. In addition, cinnamic acid can also generate CA under the action of a series of enzymes such as UDP glucose:cinnamate glucosyl transferase and hydroxycinnamoyl-*D*-glucose:quinate hydroxycinnamoyl transferase.

4. Pharmacokinetics

CA is an important dietary polyphenol, but its chemical structure is by no means optimal. This configuration determines the poor water solubility and stability of CA, resulting in poor intestinal absorption and/or bioavailability of CA. In fact, as early as 2001, a clinical study reported that only about one-third ((33 ± 17)%) of CA was absorbed in the small intestine when healthy subjects randomly consumed 2.8 mmol of it on different days, while the majority CA entered the cecum as well as the colon^[60]. Interestingly, in the experiment of infusing CA into the ligated stomach of fasted rats, it was found to be detected in the gastric veins and aorta after 30 min of infusion, which means that CA can be quickly absorbed by the stomach in addition to being absorbed by the small intestine^[61]. Absorbed CA in the blood can be widely distributed in different organs. Among them, the highest levels are found in the liver, followed by the kidneys, lungs, heart, spleen, and brain^[62–63]. CA exhibits differential metabolism throughout the entire gastrointestinal tract, mainly dependent on the composition and activity of the gut microbiota, but the major metabolites are caffeic acid, quinic acid, ferulic acid, and isoferulic acid^[64]. The intake of CA only undergoes slight hydrolysis in the stomach and small intestine of rats (1%)^[61]. Specifically, glycosidases and esterases in the small intestine break the ester bonds of CA, releasing quinic acid and caffeic acid. Subsequently, caffeic acid is absorbed by the gut, and the unabsorbed portion undergoes methylation reactions to produce ferulic acid and isoferulic acid^[11,65]. Besides, approximately 15%–32%

of CA is hydrolyzed into caffeic acid and quinic acid in the cecum or colon^[61]. Similar to the small intestine, part of the unabsorbed caffeic acid generates ferulic acid and isoferulic acid. Meanwhile, under the action of colonic microorganisms, quinic acid metabolizes to produce hippuric acid and coumarin^[66]. It is worth noting that the colon also plays an important role in the conversion of caffeic acid and ferulic acid to dihydroferulic acid^[67] (Fig. 3). Finally, most of the ingested CA is excreted from the urine within 6–24 or 24–48 h^[68].

Currently, the regular pattern of blood drug concentration of CA has been clearly revealed in a large number of *in vivo* studies over time. In a study, Qi et al.^[69] administered 50.00 mg/kg of pure CA by gavage to male Wistar rats and measured the dynamic changes of CA in rat plasma over time. The results showed that the pharmacokinetic parameters of CA, such as half-life ($t_{1/2}$), peak concentration (c_{max}), area under the curve (AUC), and clearance (CL), were (1.70 ± 0.24) h, (0.55 ± 0.22) mg/L, 1(.50 ± 0.91) mg·h/L, and (39.00 ± 17.00) L/(h·kg), respectively. In another similar study, rats were given 10.00 mg/kg pure CA intravenously. The $t_{1/2}$, c_{max} , AUC, and mean residence time (MRT) of CA were (7.48 ± 1.90) h, (442.50 ± 29.22) µg/mL, (7 194.09 ± 320.49) µg·min/mL, and (3.61 ± 0.52) h, respectively. Subsequently, the researchers switched the route of administration from intravenous injection to nasal administration and found that the pharmacokinetics of CA in the body varied with the change of administration method^[63]. Specifically, nasal administration significantly reduced c_{max} and AUC, suggesting a decrease in peripheral exposure to CA in plasma^[63]. Besides, evidence has shown that different physiological states can also affect the pharmacokinetic parameters of CA in the body^[70]. In the febrile rat disease model, both the AUC and plasma concentration of CA were significantly higher than those in normal rats^[71]. Consistent with this, the AUC and c_{max} of CA were also significantly increased in the plasma of middle cerebral artery occlusion (MCAO) rats. At the same time, the CL rate of CA in MCAO rats was significantly reduced, while the $t_{1/2}$ was prolonged^[72]. Clinical evidence suggested that there were differences in the absorption and/or metabolism of CA in healthy individuals and the difference varied considerably between individuals^[73]. More importantly, humans in disease states such as tumors can also

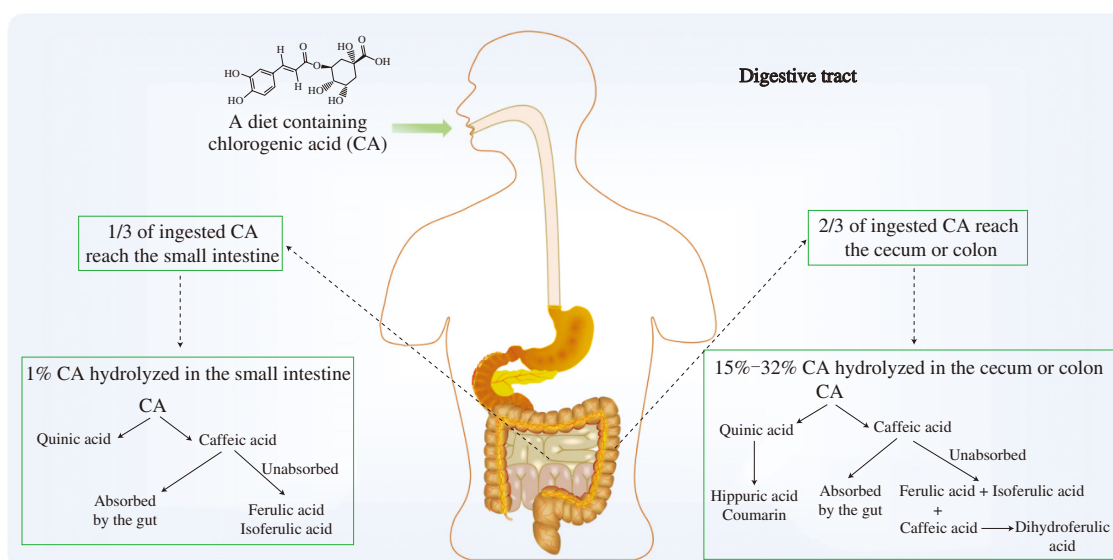


Fig. 3 Absorption and metabolism of CA in human.

significantly affect the pharmacokinetic parameters of CA^[74]. In a word, the pharmacokinetic parameters of CA were affected by different administration methods, different drug doses, and different physiological states.

More detailed information on the pharmacokinetic parameters of CA can be found in Table 2.

5. General effect on the gut microbiota

More and more evidence has suggested that the gut microbiota is a key target for CA to exert various health benefits (such as anti-inflammation, immune regulation, anti-diabetes, anti-obesity, etc.). Actually, CA can interact with the gut microbiota of various organisms to produce beneficial effects, including humans, mice, pigs, chickens, and fish^[82-86]. Therefore, in the following sections, we will discuss in detail the interaction between CA and the gut microbiota, as well as the beneficial effects that arise from it.

5.1 Gut-protective effects

Inflammatory bowel disease (IBD) is a chronic and recurrent gastrointestinal disease characterized by intestinal inflammation. It includes two major forms, Crohn's disease and ulcerative colitis^[87]. The pathophysiological process of IBD is relatively complex and mainly affected by multiple genetic and environmental factors. When these altered factors disrupt the balance between the gastrointestinal microbiota and the intestinal immune system, an immune-mediated inflammatory response is triggered in genetically susceptible individuals^[88-89]. As a natural plant phenolic acid, previous evidence has shown that CA can serve as an effective natural product for the prevention and treatment of IBD, and these effects may be attributed to the regulation of signaling pathways such as nuclear factor κ B (NF- κ B)/NOD-like receptor thermal protein domain associated protein 3, mitogen-activated protein kinase/extracellular regulated protein kinases, signal transducer and activator of transcription 3 (STAT3)/NF- κ B and gut microbiota/lipopolysaccharide (LPS)^[32,90-93].

As mentioned above, regulating the balance between the gut microbiota and the intestinal immune system may be the key to CA's prevention and treatment of IBD. There are many excellent examples here to support this argument. Zhang et al.^[94] found that CA (basal diet with 2% CA) could reverse DSS-induced weight loss, increase disease activity index, pro-inflammatory factors, and colon injury in mice. CA restored the diversity of the gut microbiota, manifested by an increase in the Shannon index. At the same time, CA also ameliorated DSS-induced microbiota imbalance by remodeling the gut microbiota. More importantly, the researchers noticed that CA significantly increased the abundance of *Akkermansia* and *Lactobacillus*, which may be one of the important reasons why CA improved IBD. Similarly, in another study, Zhang et al.^[95] also found that CA (water containing 1 mmol/L CA) improved DSS-induced colitis in proportion to an increase in *Akkermansia*. To confirm this result, the researchers further quantified the content of *Akkermansia* in the feces of normal mice using quantitative polymerase chain reaction technology and consistent with the expected results, CA can significantly increase the proportion of *Akkermansia* in the feces of normal mice. In clinical practice, the relative abundance of *Akkermansia* is negatively correlated with the severity of IBD patients^[96]. The above results reveal that CA can inhibit the pathological process of IBD by regulating the gut microbiota, especially by increasing the relative abundance of *Akkermansia*. Interestingly, Xie et al.^[97] found that the combination of CA (200 mg/kg) and dietary non-starch polysaccharide arabinoxylan promoted more complex changes in the biological function of the gut microbiota and improved *Flavonifractor*, *Coprobacillus*, and *Clostridium_XIVa* and reduced the abundance of *Robinsonella* and *Lactobacillus*. However, the regulatory effect of CA combined with arabinoxylan on the gut microbiota profile was weaker than that of CA. Secondly, arabinoxylan also weakened the beneficial effect of CA on DSS-induced intestinal injury. These potential mechanisms remain to be further investigated in the future.

In a D-galactose-induced intestinal senescence model, Wei et al.^[98] found that CA (20 mg/kg) combined with epigallocatechin-3-gallate was more effective in reducing the level of cytokine tumor necrosis factor- α (TNF- α), interleukin 1 β (IL-1 β), IL-6, and interferon γ

Table 2
Pharmacokinetic studies of CA.

Route of administration	Species	Dose (equivalent to CA)	$t_{1/2}$ (h)	C_{max}	AUC	CLs	MRT _{0-∞} (h)	References
i.v.	Rat	10 mg/kg (pure CA)	7.48 $\pm$ 1.90	(442.50 $\pm$ 29.22) μ g/mL	(7 194.09 $\pm$ 320.49) μ g·min/mL	N/A	3.61 $\pm$ 0.52	[63]
i.n.	Rat	10 mg/kg (pure CA)	9.66 $\pm$ 1.97	(128.14 $\pm$ 31.33) μ g/mL	(1 803.36 $\pm$ 297.46) μ g·min/mL	N/A	NA	
Oral	Rat	50.00 mg/kg (pure CA)	1.70 $\pm$ 0.24	(0.55 $\pm$ 0.22) μ g/mL	(1.50 $\pm$ 0.91) mg·h/L	(39.00 $\pm$ 17.00) L/(h·kg)	NA	[69]
		50.00 mg/kg	1.70 $\pm$ 0.20	(0.37 $\pm$ 0.12) mg/L	(0.76 $\pm$ 0.26) mg·h/L	(65.00 $\pm$ 21.00) L/(h·kg)	NA	
		1.20 mg/kg	N/A	(3.11 $\pm$ 0.96) ng/mL	(4.29 $\pm$ 1.92) ng·h/mL	N/A	1.19 $\pm$ 0.22	
Oral	Rat	2.40 mg/kg	N/A	(5.59 $\pm$ 1.61) ng/mL	(8.16 $\pm$ 3.65) ng·h/mL	N/A	1.48 $\pm$ 0.50	[75]
		4.80 mg/kg	1.52 $\pm$ 0.79	(8.73 $\pm$ 2.83) ng/mL	(14.38 $\pm$ 5.06) ng·h/mL	N/A	1.67 $\pm$ 0.63	
		492.48 μ g/kg	3.36 $\pm$ 0.97	N/A	(155.43 $\pm$ 23.39) ng·h/mL	(2.53 $\pm$ 0.43) L/h	3.30 $\pm$ 0.99	
i.v.	Rat	60.00 mg/kg (pure CA)	0.91 $\pm$ 0.19	(2.35 $\pm$ 0.48) μ g/mL	(5.59 $\pm$ 1.41) μ g·h/mL	N/A	N/A	[77]
Oral	Beagle	60.00 mg/kg	1.20 $\pm$ 0.31	(1.66 $\pm$ 0.58) μ g/mL	(5.33 $\pm$ 1.34) μ g·h/mL	N/A	N/A	
		60.00 mg/kg	1.09 $\pm$ 0.19	(2.33 $\pm$ 0.61) μ g/mL	(3.79 $\pm$ 1.79) μ g·h/mL	N/A	N/A	
i.v.	Rat	36.30 mg/kg	0.83 $\pm$ 0.06	N/A	(25.60 $\pm$ 3.40) μ g·h/mL	(1 462.00 $\pm$ 247.00) mL/(h·kg)	0.64 $\pm$ 0.11	[78]
Oral	Rat	(212.73 $\pm$ 2.73) mg/kg	7.26 $\pm$ 2.03	(359.91 $\pm$ 170.79) ng/mL	(782.85 $\pm$ 295.50) ng·h/mL	N/A	N/A	[79]
Oral	Rat	60 mg/kg	4.34 $\pm$ 1.24	(0.26 $\pm$ 0.08) μ g/mL	(1.22 $\pm$ 0.34) μ g·h/mL	N/A	5.95 $\pm$ 1.54	[71]
		60 mg/kg	3.42 $\pm$ 1.74	(0.42 $\pm$ 0.17) μ g/mL	(2.25 $\pm$ 0.72) μ g·h/mL	N/A	6.16 $\pm$ 2.65	
i.v.	Human	7.4 mg	1.35 $\pm$ 0.53	(255.70 $\pm$ 66.43) μ g/L	(403.62 $\pm$ 109.30) μ g/(L·h)	(0.37 $\pm$ 0.11) L/(h·kg)	1.26 $\pm$ 0.12	[80]
Oral	Human	3.64 mg	1.30 $\pm$ 0.60	(0.76 $\pm$ 0.54) μ g/L	(1.14 $\pm$ 0.45) ng·h/L	(3 211.00 $\pm$ 1 296.00) L/h	N/A	[81]

Note: i.v., intravenous administration; i.n., intranasal administration; Oral, oral administration; N/A, not applicable.

(IFN- γ) as well as increasing the total antioxidant capacity, thus protecting the intestine from inflammatory damage. Meanwhile, CA combined with epigallocatechin-3-gallate can more effectively restore the disordered gut microbiota in aged mice compared to CA alone. Among them, the *g_Candidatus_oleiferrea* is considered to play a key role in anti-inflammatory and maintaining intestinal homeostasis. More importantly, CA exerts gut-protective effects not only by directly modulating the composition of the gut microbiota but also by promoting the production of SCFAs, a metabolite product of the gut microbiota. In a rat colon mucosal injury model induced by a high-fat diet (HFD), CA (100 mg/kg) increased the abundance of *Ruminococcus*, which is the main bacterial group producing butyric acid. This promotes the production of SCFAs (especially butyric acid) in the intestine. Subsequently, the increase in butyric acid induced related anti-inflammatory effects to alleviate HFD-induced intestinal inflammation^[99].

Indomethacin is a non-steroidal anti-inflammatory drug mainly used in clinical practice to treat diseases such as arthritis, gout, bursitis, tendinitis, and scapulohumeral periarthritis. However, when using indomethacin, it usually causes gastrointestinal reactions including indigestion, nausea, and vomiting. To investigate the role of CA in alleviating indomethacin-induced intestinal injury, Yan et al.^[93] administered CA by gavage to indomethacin treated mice. The results showed that CA (50 mg/kg) alleviated indomethacin-induced intestinal injury, inflammation, and changes in intestinal microbial structure in mice. Subsequently, the researchers aimed to further determine whether the gut microbiota played an important role in indomethacin-induced intestinal injury. Therefore, they used antibiotics to deplete the microbiota in the mice's intestines and found that the intestinal protective effect of CA was reversed. More importantly, in the gut microbiota transplantation experiment, researchers found that germ-free mice transplanted with CA derived microbiota could more effectively prevent indomethacin-induced intestinal morphological damage and barrier dysfunction. Meanwhile, CA derived microbiota can also inhibit intestinal inflammation and the growth of LPS-producing bacteria. Thus, it is evident that the regulation of the gut microbiota plays a key role in alleviating indomethacin-induced intestinal damage in CA.

Salmonella pullorum is a Gram-negative small bacterium that mainly harms chicks within one week of age, resulting in a higher mortality rate. When chicks are infected with this pathogen, the bacteria often spread throughout their internal organs (such as the liver, lungs, gallbladder, and intestines), leading to the occurrence of most diseases, including intestinal barrier dysfunction, inflammation, and impaired chicken productive performance^[100-101]. Honeysuckle extract (1 000 mg/kg, CA is the main component) could reduce serum endotoxin levels and *S. pullorum* positive organ frequency. Meanwhile, it also reduced the levels of inflammatory factors such as IFN- γ , TNF- α , IL-8, and IL-1 β in the ileum^[102]. In addition, the researchers have found that the regulation of intestinal microbiota by honeysuckle extract was closely related to intestinal inflammation and the productive performance of chicks. Among them, the decrease of Firmicutes abundance and the increase of Bacteroidetes abundance were positively correlated with intestinal inflammation. This was similar to the positive correlation between increased abundance of *Bacteroides* and Prevotellaceae and improved productive performance^[102]. As reported, acute heat stress is another factor that

threatens the intestinal health and production performance of poultry. For this, Chen et al.^[103] established a model of young hens with acute heat stress to evaluate the effects of dietary CA supplementation on intestinal health and microbiota composition. The results showed that CA (300, 600 mg/kg) alleviated the decrease of total antioxidant capacity and total SOD activities and the increase of IL-1 β and TNF- α induced by heat stress. At the same time, CA increased the abundance of beneficial bacterial groups, such as Rikenellaceae RC 9_gut_group, Ruminococcaceae UCG-005, and Christensenellaceae R-7_group. More importantly, CA also reduced the abundance of inflammatory-associated gut microbiota such as *Sutterella*. In summary, CA can protect the intestinal health of poultry by down-regulating inflammation related and up-regulating beneficial gut microbiota.

5.2 Other organo-protective effects

Above, we have discussed in detail the protective effects of CA on intestinal function, barrier, and inflammation. What's more, this protective effect is closely linked to the regulation of the gut microbiota and their metabolites. In addition, CA also shows protection to other organs, including the liver, kidneys, and heart.

5.2.1 Hepatoprotective effects

The strong expression of inflammation, disruption of the intestinal barrier, and disruption of the gut microbiota are significant features of the HFD-induced non-alcoholic fatty liver disease (NAFLD) model. However, intervention with CA (60 mg/kg) can significantly inhibit the expression of inflammatory factors TNF- α and IL-6 and the infiltration of macrophage in the liver. The level of LPS in serum was also suppressed by the intervention of CA. Meanwhile, CA increased the expression of tight junction proteins (occludin and ZO-1), thereby protecting the intestinal barrier from damage. More importantly, CA contributed to changes in the structural composition of the gut microbiota, including an increase in *Bifidobacteria* abundance and a decrease in *Escherichia coli* abundance^[104]. In a clinical study of 26 patients with diabetes and NAFLD, the researchers found that a supplement of 200 mg CA and 200 mg caffeine for 12 consecutive weeks can effectively reduce the metabolic disorder of patients. This beneficial effect may partially come from the regulation of the gut microbiota *Bifidobacteria*. However, this study only showed statistical significance in cases of weight loss. Therefore, more direct evidence is needed to further assess whether CA achieves liver protection through the regulation of the gut microbiota^[82]. Similar to NAFLD, alcoholic liver disease (ALD) can also cause disruption of the gut microbiota, including a decrease in the abundance of beneficial bacteria Muribaculaceae, *Bacteroides*, *Alloprevotella*, and *Parabacteroides*, as well as an increase in the abundance of opportunistic pathogens. And the abundance of these bacteria could be reversed by administering CA (60 mg/kg) intervention. In addition, the content of SCFAs, a metabolite of the gut microbiota, could also significantly increase through CA intervention, of which it is worth mentioning that the content of *n*-butyric acid was increased by nearly 3 times^[105]. Overall, CA increases the expression of tight junction proteins and maintains intestinal barrier function by regulating the homeostasis of the gut microbiota, thereby avoiding harmful microbiota and LPS crossing the intestinal barrier to stimulate the immune system and induce

immune cell inflammation. Meanwhile, *n*-butyric acid can also alleviate intestinal and systemic inflammation and maintain intestinal immune homeostasis^[106-107]. Ultimately, it effectively avoids the transition of NAFLD and ALD to liver fibrosis and even cirrhosis.

Cadmium and lead are two typical heavy metal elements that widely exist in industrial production and daily life. At the same time, as environmental pollutants, if they accumulate in large amounts in the body, they can damage the immune, liver, kidney, and nervous systems of the human body^[108]. Researchers found that cadmium could induce inflammation and oxidative damage to the liver and kidney and increase the production of NO and myeloperoxidase in the liver and kidney in mice with acute cadmium exposure. Fortunately, when CA (500 mg/kg) was administered intraperitoneally to acute cadmium exposed mice, the inflammatory signal Toll-like receptor 4 (TLR4)/myeloid differentiation factor 88 (MyD88)/NF- κ B was significantly inhibited, thereby alleviating the aforementioned damage^[109]. Meanwhile, CA (30 mg/kg) was administered orally to the model mice, which restored the imbalance of the gut microbiota, including a decrease in the proportion of Firmicutes/Bacteroidetes and the increase in bacterial abundances such as *Ruminiclostridium_9*, *Alloprevotella*, and *Rikenella*^[109]. Similar to this study, CA (30 mg/kg)

could also significantly alleviate lead-induced cognitive dysfunction and hepatorenal toxicity in mice. In addition, the researchers conducted sequencing analysis of the V3–V4 region of the 16S rRNA gene in the gut microbiota of mice, revealing that lead could induce a decrease in *Helicobacter* abundance (from 8.22% to 2.95%) and an increase in the abundance of Lachnospiraceae_NK4A136_group (from 1.85% to 7.09%). After administering CA (30 mg/kg), the changes in the abundance of these bacterial communities were reversed, with the abundance of *Helicobacter* and Lachnospiraceae_NK4A136_group changing to 11.24% and 2.68%^[110], respectively. In conclusion, all evidence suggests that CA can alleviate heavy metal-induced liver and kidney damage by reshaping the structure of the gut microbiota and maintaining inflammatory homeostasis.

L-Carnitine is a type of amino acid that is widely present in red meat. It plays a crucial role in lipid metabolism as an essential cofactor for the intracellular transport of fatty acids^[111-112]. Recently, Zhang et al.^[113] found that a high intake of *L*-carnitine can be derived into a metabolite trimethylamine *N*-oxide (TMAO) under the action of the gut microbiota. However, TMAO can cause liver dysfunction, release liver inflammation, and abnormal blood lipids. On the contrary, CA (200, 400 mg/kg) intervention significantly alleviated

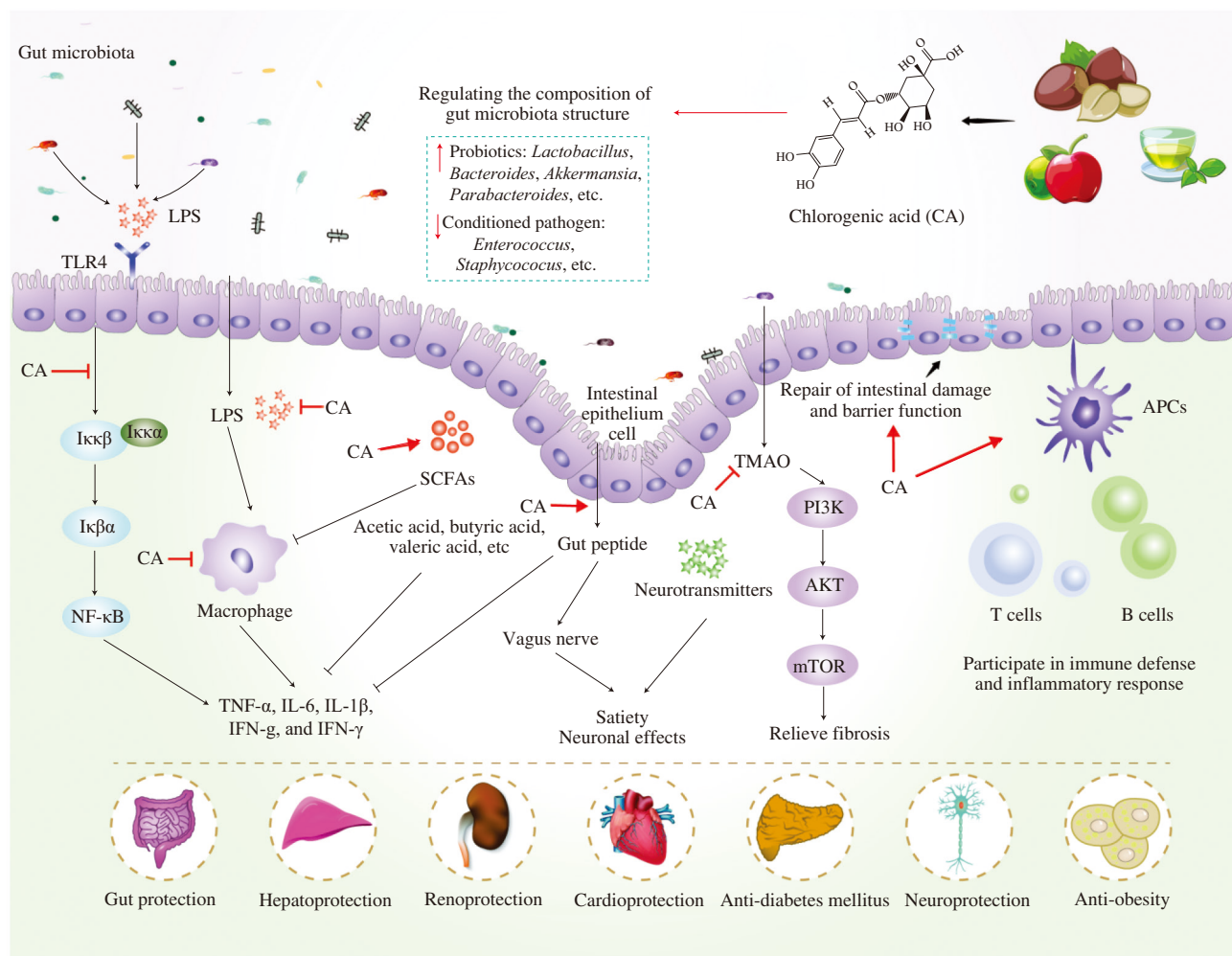


Fig. 4 The health protection effects achieved by CA benefits from its interaction with gut microbiota. CA reversed the composition and abundance of gut microbiota in disease states, and regulated intestinal immunity and barrier function; CA promoted the production of gut microbiota metabolites SCFAs, thereby regulating immune balance and lipid metabolism; CA regulated signaling pathways closely related to gut microbiota, such as microbiota/LPS/TLR4/NF- κ B, microbiota/TMAO/PI3K/AKT signaling pathways.

liver function (manifested by a decrease in aspartate transaminase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP)) and inflammation (manifested by a decrease in IL-6, TNF- α , and TNF- β). More importantly, CA reversed the disruption of the gut microbiota homeostasis by TMAO. At the phylum level, CA reversed the increase in Firmicutes, Proteobacteria, and Bacteroidetes abundance induced by TMAO. At the genus level, CA reduced the populations of *Erysipelatoclostridium*, *Faecalibaculum*, and Erysipelotrichaceae, but increased the abundance of *Akkermansia* and *Bacteroides*. In a word, the structural changes of the gut microbiota play an important role in TMAO-induced liver injury. Notably, similar to the above description, CA mediates this protective effect by modulating the structure of microorganisms and maintaining inflammatory balance.

5.2.2 Reno-protective effects

As mentioned earlier, CA can regulate heavy metal-induced liver and kidney damage by reshaping the structure of the gut microbiota and maintaining inflammatory homeostasis. In addition to this, CA also shows a therapeutic potential for hyperuricemia nephropathy. This has been demonstrated in two excellent studies. First, Zhou et al.^[114] induced a hyperuricemia mice model using hypoxanthine and potassium oxonate. Subsequently, they administered 30 and 60 mg/kg CA orally to the mice with hypoxanthine. The results showed that CA significantly reduced serum LPS levels and renal *IL-1 β* , *TNF- α* , and *NLRP3* mRNAs expression, and blocked the transmission of TLR4/MyD88/NF- κ B, an inflammatory pathway in the kidney. Meanwhile, intestinal tight junction proteins ZO-1, as well as occludin were significantly increased after CA intervention. Furthermore, they found that CA increased the abundance of *Bacteroides*, Prevotellaceae_UCG-001, and *Butyricimonas*. And the increase in the abundance of these colonies was proportional to the production of SCFAs. To further explore the role of the gut microbiota in hyperuricemia nephropathy in depth, Zhou et al.^[115] designed and completed another experimental study. In this study, they noticed a significant increase in TMAO levels in the serum of mice with hyperuricemia nephropathy. To determine whether this change was related to the gut microbiota, they further analyzed the composition of the gut microbiota in hyperuricemia nephropathy mice. Interestingly, the bacterial communities associated with TMAO synthesis, such as *Blautia*, *Enterococcus*, and *Faecalibaculum*, were significantly increased. At the meantime, phosphoinositide 3 kinase (PI3K), protein kinase B (AKT), and mammalian target of rapamycin (mTOR) proteins were highly expressed in hyperuricemia nephropathy mice. In contrast, all these alterations were reversed by CA (40 mg/kg). Overall, the two studies not only illustrated that CA maintains the intestinal barrier by remodeling the gut microbiota, thereby reducing LPS entry into the serum and avoiding the activation of inflammatory pathway but also further proved that CA can regulate the microorganism/TMAO/PI3K/AKT/mTOR axis to improve hyperuricemia nephropathy.

5.2.3 Cardioprotective effects

From previous studies, CA can achieve cardioprotective effects through multiple pathways such as anti-inflammatory, antioxidant, and immune regulation^[116-118]. A recent study pointed out that the

main component CA (10 μ g/mL) from *Saussurea involucreata* could promote the production of the gut microbiota metabolites SCFAs (including acetic acid, proionic acid, butyric acid, and isovaleric acid) to alleviate myocardial ischemia^[119]. SCFAs have prominent anti-inflammatory and immunomodulatory effects^[120-121]. It can be seen that the cardioprotective effect of CA is highly likely mediated by the gut microbiota metabolite SCFAs. In addition, CA can also alleviate structural and functional changes in the cardiovascular system by increasing the diversity of the gut microbiota^[117]. However, the limited evidence does not yet indicate a direct correlation between the gut microbiota and the cardioprotective function of CA. At the same time, it is also unknown how CA exerts cardioprotective effects by regulating the gut microbiota in terms of mechanism. Therefore, these questions need to be addressed in future research.

5.3 Anti-diabetic effects

Diabetes is divided into type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), special type diabetes, and gestational diabetes. Among them, T1DM and T2DM are the two most common subtypes of diabetes. T1DM is characterized by an absolute insufficient in insulin secretion due to immune-mediated destruction of pancreatic β -cells, while T2DM is mainly associated with a relative insufficient in insulin secretion and insulin resistance. Consistently, their main feature is the presence of hyperglycemia^[122-123]. Over the past 30 years, the number of patients with diabetes worldwide has soared. More importantly, T2DM accounts for approximately 90% of the total number of diabetes patients. Among them, China and India have become the main regions for the global prevalence of T2DM^[124]. Therefore, it is essential to take scientific measures to prevent and treat diabetes, especially T2DM. Related studies have shown that the addition of CA (1.3 g/100 g) to a daily diet can effectively reduce postprandial blood sugar levels in rats and improve antioxidant status in the liver and kidneys^[125]. Meanwhile, some foods containing CA, such as coffee and mangoes, could also effectively reduce the level of glycosylated hemoglobin^[126-127]. Recently, a study indicated that CA (80 mg/kg) could prevent and delay the development of T2DM. Specifically, in the prediabetic rat model induced by HFD, CA reduced the content of saturated fatty acid-containing DAG species, low-density lipoprotein cholesterol, and total cholesterol in the blood, and increased the level of blood very-long-chain fatty-acid-containing ceramides species. At the same time, CA increased the expression of adiponectin receptors (AdipoR1 and AdipoR2) and peroxisome proliferation-activated receptor alpha (PPAR α) in the liver and enhanced the downstream adenosine 5'-monophosphate-activated protein kinase (AMPK) activity^[128].

In recent years, increasing evidence has shown that the regulation of the gut microbiota is another important way of preventing and treating T2DM^[129-131]. Fortunately, CA, a natural polyphenol with multiple health benefits, can target and regulate the gut microbiota to inhibit the occurrence and development of T2DM. For example, in *db/db* mice with T2DM, the gut microbiota exhibited a disordered state. This included a decrease in the abundance of *Lactobacillus* and an increase in the abundance of *Blautia*, *Robinsonella*, and *Enterococcus*^[132]. On the contrary, CA supplementation (250 mg/kg) not only increased the α - and β -diversity of bacteria in the mice cecum but also restored the abundance of *Lactobacillus*, *Blautia*,

Robinsoniella, and *Enterococcus*. Similarly, the extract of *Lycium barbarum* L. leaves rich in CA can effectively reverse the ecological imbalance of the gut microbiota induced by T2DM^[53]. However, further experiments (including antibiotic consumption of the gut microbiota and fecal transplantation experiments) are needed to verify whether CA mediated changes in the gut microbiota are directly related to the improvement of T2DM.

In addition, Zhou et al.^[133] designed a myofibrillar protein-CA (MP-CA) complex. They administered the MP-CA complex (2.65 mg CA/10 mg MP, 10 mg MP/kg body weight) orally to T2DM rats. This compound improved hyperglycemia and hyperlipidemia in T2DM rats and reduced intestinal inflammation and barrier damage. Meanwhile, the MP-CA complex also reshaped the gut microbiota of T2DM rats. This included an upregulation of the abundance of probiotics *Bacteroides*, *Akkermansia*, and *Parabacteroides*, as well as a downregulation of the abundance of conditionally pathogenic bacteria *Enterococcus* and *Staphylococcus*. In addition, they also reported that the MP-CA complex up-regulated the content of intestinal SCFAs (including butyric acid, valeric acid, and isobutyric acid) in T2DM rats. And the increased SCFAs (especially butyric acid) produced a positive regulation in T2DM rats. More importantly, the MP-CA complex exhibited better pharmacological activities than CA and MP alone^[133]. In a word, these results not only demonstrate that the MP-CA complex alleviates T2DM by regulating the gut microbiota and related metabolites, but also opens up new avenues for the future development of protein polyphenol complexes.

5.4 Neuro-protective effects

Considering the multiple health benefits of CA (especially the strong anti-inflammatory activity), its neuroprotective effect is not surprising. As expected, evidence suggests that CA can attenuate cerebral ischemia-induced neuroinflammation by inhibiting the activation of nuclear factor NF- κ B^[134]. Also, CA can modulate the Nrf2/NF- κ B inflammatory signaling pathway through activation of Sirt1 to achieve neuroprotective effects in a hypoxic-ischemic brain injury model^[33]. On the basis of these and as mentioned in the previous sections, CA achieves its protective effects on organs such as the intestine, liver, kidneys, and heart by regulating the gut microbiota. Therefore, we are looking forward to revealing the connection between its neuroprotective effect and its regulatory role in the gut microbiota.

Trimethyltin chloride (TMT) is a chemical substance known to have strong neurotoxicity, particularly in the hippocampus^[135]. To investigate whether CA could protect mice from TMT-induced neurotoxicity, Xi et al.^[136] administered TMT to mice through intraperitoneal injection and found that TMT-induced cognitive impairment, neuroinflammation, and the gut microbiota disorder in mice. On the contrary, when treated with CA (30 mg/kg), the cognitive impairment and neuroinflammation of mice were effectively alleviated. Microbiome analysis further showed that the gut microbiota of mice recovered after CA intervention. Previous evidence has shown that *Lactobacillus* is a well-known probiotic that can affect neurotransmitter levels in mice and protect them from toxin-induced neurobehavioral disorders^[137-138]. In this study, they further found that CA upregulated the relative abundance of probiotic *Lactobacillus* and restored the disorder of neurotransmitters

(especially DL-kynurenine and acetylcholine chloride) induced by TMT in the mice hippocampus. These changes seem to be closely related to CA-mediated neuroprotection^[136].

SCFAs, the main metabolites of the gut microbiota, participate in the occurrence and development of nervous system disease by regulating synaptic function and neuroinflammation^[139]. In a mice model of cognitive impairment induced by a high fat and high fructose diet, CA (150 mg/kg) could significantly improve synaptic dysfunction and cognitive behavioral disorders. Furthermore, the researchers found that CA treatment increased the diversity of the gut microbiota and levels of SCFAs-producing bacterial genera (including Lachnospiraceae_NK4A136, *Bifidobacterium*, *Streptococcus*, and *Ruminococcus_9*, among others). More importantly, through multi-omics analysis, the researchers further found a close correlation among the gut microbiota, synaptic transmission genes, and neurotransmission in the group supplemented with CA^[140]. Similarly, CA (30 mg/kg) can also achieve a neuroprotective effect by increasing the content of SCFAs in the hippocampus of mice^[136]. In general, these results support the ability of CA to improve cognitive impairment in mice by regulating the gut microbiota and its metabolites.

Li et al.^[141] designed a new flowerlike selenium nanocluster (TGN-CA@SeNCs) by using the brain targeting peptide (TGN peptide) and CA. This nanomaterial can significantly improve the solubility and stability of CA. Subsequently, in APP/PS1 mice, researchers found that TGN-CA@SeNCs exhibited a better regulatory ability on the gut microbiota compared to using CA alone. Specifically, TGN-CA@SeNCs significantly increased the abundance of *Turicibacter*, *Colidextribacter*, *Ruminococcus*, *Alloprevotella*, and *Alistipes*. Notably, the changes of the gut microbiota were negatively correlated with inflammation and oxidative stress. In addition, TGN-CA@SeNCs had a better effect in modulating A β aggregation and improving brain glucose homeostasis compared to CA administration separately. This may be attributed to the higher bioavailability of TGN-CA@SeNCs and their ability to target the disease across the blood-brain barrier. In summary, these data reveal that TGN-CA@SeNCs can more effectively target the gut microbiota to achieve neuroprotective effects on APP/PS1 mice. What's more, it points out the development direction for the further improvement of CA stability and biological activity.

5.5 Anti-obesity effects

In order to explore the potential molecular mechanism underlying the anti-obesity effect of CA, an HFD-induced obesity mouse model was successfully established. In a state of obesity, mice have elevated blood lipid levels and abnormal expression of genes related to fat production and decomposition. At the same time, the balance of the gut microbiota (diversity and abundance) was destroyed. Subsequently, CA (150 mg/kg) was used for intervention, and all the above symptoms were alleviated. More importantly, CA reversed the imbalance of the gut microbiota, including the inhibition of the abundance of Desulfovibrionaceae, Ruminococcaceae, Lachnospiraceae, and Erysipelotrichaceae, and the increase of the abundance of Bacteroidaceae and Lactobacillaceae^[142]. The increased beneficial microbiota contributed to the production of SCFAs, thereby regulating fat metabolism^[121,143]. In another similar study, the researchers administered CA (100 mg/kg) by gavage to

HFD-induced obese mice. The results showed that the abundance and diversity of the gut microbiota were altered, promoting the production of SCFAs (especially butyric acid)^[144]. Meanwhile, the generated SCFAs enhanced the barrier immune function of the intestinal mucosa and activated the expression of G protein-coupled receptor 43 in fat and immune cells, thereby regulating lipid metabolism and immune balance in mice^[144]. In summary, CA regulated the homeostasis of the gut microbiota, thereby promoting the production of its metabolites, and improving obesity and intestinal immune imbalance in mice.

5.6 Other effects

In addition to the above discussion, we also found that health benefits of CA in anti-depressant, anti-hypertensive, and anti-endotoxemia are closely related to the regulation of the gut microbiota.

The regulation of CA in depression model rats induced by adrenocorticotrophic hormone mainly benefits from the impact on the structure of the gut microbiota. Specifically, CA (500 mg/kg) improved the decrease of fecal microbiota diversity in rats caused by adrenocorticotrophic hormone. Especially at the genus level, changes in the relative abundance of Desulfovibrionales, *Desulfovibrio*, *Klebsiella*, Burkholderiales, and Bifidobacterium were reversed by CA^[84]. Similarly, Zhu et al.^[145] found that CA (100 mg/kg) ameliorated the occurrence and development of hypertension by reshaping the gut microbiota of hypertensive mice. What's more, they administered *Klebsiella* to hypertensive mice by gavage and further found that the upregulation of *Klebsiella* relative abundance was an important reason for the antihypertensive effect of CA. In addition, CA (150 mg/kg) could also increase the metabolite SCFAs of the gut microbiota (such as *Dubosella*, *Romboutsia*, *Mucispirillum*, and *Faecalibaculum*) to improve the intestinal barrier function, thus exerting the role of anti-endotoxemia effect^[146].

In addition, detailed data is presented in Table 3.

6. CA-mediated changes in the gut microbiota are closely related to diseases

The use of antibiotics to deplete microorganisms and fecal microbiota transplantation experiments are important means to verify the close relationship between the gut microbiota and diseases^[149-150]. As mentioned earlier, the microbiota in the gut was depleted by antibiotics, and the protective effect of CA on indomethacin-induced gut inflammation and damage was offset. Besides, transplanting CA-treated mouse feces to sterile mice could more effectively prevent indomethacin-induced gut morphological damage and barrier dysfunction^[93]. In another similar study, the researchers gavaged normal mice and HFD-induced obese mice with CA, and after 4 weeks, fresh feces from mice were collected daily using sterile centrifuge tubes. Subsequently, fecal bacterial suspension containing CA was gavaged to obese mice. The results showed that all fecal bacterial suspensions containing CA could regulate the composition (diversity and community richness) of the gut microbiota and lipid metabolism, thereby alleviating obesity in mice^[144]. Clearly, the

evidence showed that the regulation of the gut microbiota played a crucial role between CA and disease.

7. General summary and conclusions

In this review, we described that CA can help maintain the intestinal immune function, alleviate intestinal injury, and improve diabetes and nervous system diseases by regulating the proportion of beneficial and harmful bacteria. As previously reported, probiotics such as *Lactobacillus* and *Bifidobacterium* could regulate the function of the intestinal immune system and contribute to the treatment or improvement of diseases^[151]. At the same time, we also pointed out that the regulation of the gut microbiota diversity by CA was closely related to the maintenance of cardiac structure and function. Besides, additional evidence suggested that abnormal changes in the gut microbiota could lead to mucosal immune dysfunction, leading to the occurrence of IBD in genetically susceptible hosts^[152]. On the contrary, CA maintained immune homeostasis by restoring the homeostasis of the gut microbiota, thereby protecting the host from the invasion of IBD. Furthermore, CA regulated the homeostasis of the gut microbiota and increased the expression of tight junction proteins, thereby reducing the production of LPS and preventing its further transfer to the bloodstream. Ultimately, systemic inflammation was alleviated. Notably, CA could also block LPS binding to TLR4 receptors on the surface of organs such as the liver and kidneys, further protecting the liver and kidneys from inflammatory damage. More importantly, gut microbiota metabolites SCFAs alleviated the occurrence of inflammatory reactions. Meanwhile, they could also regulate lipid metabolism and immune balance. These effects of SCFAs enabled CA to play a positive role in anti-obesity, anti-diabetes and nervous system, liver and kidney protection.

In summary, CA achieved health protection through gut microbiota mainly due to the following factors (Fig. 4): 1) CA reversed the composition and abundance of gut microbiota in disease states, and regulated intestinal immunity and barrier function; 2) CA promoted the production of gut microbiota metabolites SCFAs, thereby regulating immune balance and lipid metabolism; 3) CA regulated signaling pathways closely related to gut microbiota, such as microbiota/LPS/TLR4/NF- κ B, microbiota/TMAO/PI3K/AKT signaling pathways.

Although we have determined that health benefits of CA are closely related to its interaction with the gut microbiota. However, from numerous studies, we find that dose setting is a key issue in the use of CA. In particular, for the same biological activity, there is a significant difference in the dosage of CA. Whether this difference in dosage has a significant impact on the gut microbiota is the thing that needs to be focused on for further scientific research in the future^[153]. In addition, we should also consider what dosage of CA can achieve the expected effect and avoid the side effects caused by excessive intake of it. More importantly, in the future, it should also be considered that more clinical trials should be conducted. Because the current work mainly focuses on preclinical animal studies, clinical data are still very lacking. This situation could greatly limit the development of therapeutic methods based on CA.

Table 3
The various health benefits of CA benefit from targeting the gut microbiota.

Model	Dosage and duration	Key finding (Mainly focused on the changes involving the species and abundance of microflora following the action of CA)	References
Gut-protective effects			
Dextran sulfate sodium (DSS)-induced colitis in mice	200 mg/kg; 14 days	Suppress colon shortening and histological damage; increase the relative abundance of <i>Flavonifractor</i> , <i>Coprobacillus</i> , and <i>Clostridium</i> _XIVa; decrease the abundance of <i>Robinsoniella</i> and <i>Lactobacillus</i>	[97]
DSS-induced colitis in mice	100 mg/kg; 9 days	Reduce the expression of myeloperoxidase and increase SOD level in colon tissue; regulate the abundance of Actinobacteriota, <i>Lactobacillus</i> , <i>Bifidobacterium</i> , <i>Bacteroides</i> , <i>Subdoligranulum</i> , and <i>Streptococcus</i>	[147]
Acute heat stress in young hens	300, 600 mg/kg; 14 days	Decrease the expression of interleukin-1 β (IL-1 β) and tumour necrosis factor- α (TNF- α) in duodenum; increase the activities of total antioxidant capacity and decrease the content of MDA in duodenum; increase the relative abundance of Rikenellaceae RC9_gut_group, Ruminococcaceae UCG-005, and Christensenellaceae R-7_group; decrease the abundance of <i>Sutterella</i> species	[103]
DSS-induced colitis in mice	2%; 20 days	Reduce the level of TNF- α in colon tissue; increase the abundance of <i>Lactobacillus</i>	[94]
HFD-induced colitis in obesity rat	100 mg/kg; 7 weeks	Decrease MCP-1 and IL-6 levels and increase the expression of intestinal epithelial tight junction protein occludin and IL-10 in colon tissue; decrease the abundance of <i>Blautia</i> and <i>Sutterella</i>	[99]
D-Galactose-induced colitis in aging mice	20 mg/kg; 8 weeks	Improve colon structure and reduce lymphocyte infiltration in the colon region; decrease gut permeability; decrease the level of IL-1 β and malondialdehyde (MDA) and increase catalase (CAT) activity in colon tissue; decrease the abundance of Lactobacillaceae, Erysipelotrichaceae, and Deferribacteraceae; increase the abundance of Lachnospiraceae	[98]
DSS-induced colitis in mice	1 mmol/L; 15 days	Suppress the colonic infiltration of F4/80 ⁺ macrophages, CD3 ⁺ T cells, and CD177 ⁺ neutrophils; decrease the proportions of Firmicutes and Bacteroidetes; increase the proportions of Verrucomicrobia	[95]
Indomethacin-induced colitis in mice	50 mg/kg; 12 days	Decrease the level of IL-8, eosinophil peroxidase (EPO), and myeloperoxidase (MPO) in colon tissue; increase the expression of occludin and claudin-1 in colon tissue; increase Firmicutes/Bacteroidetes ratio; decrease the LPS level in colon tissue and cecum	[93]
Other organo-protective effects			
Hepatoprotective effects			
L-Carnitine-induced liver injury in mice	200 and 400 mg/kg; 12 weeks	Reduce TMAO formation; inhibit the abundance of Firmicutes, Proteobacteria, <i>Erysipelatoclostridium</i> , <i>Faecalibaculum</i> , and Erysipelotrichaceae; promote the abundance of Bacteroidetes, <i>Akkermansia</i> and <i>Bacteroides</i>	[113]
Cd-induced hepatorenal injury in mice	30 mg/kg; 8 weeks	Decrease the Firmicutes to Bacteroidetes ratio; enhance the relative abundances of <i>Ruminiclostridium</i> _9, <i>Alloprevotella</i> , and <i>Rikenella</i>	[109]
Non-alcoholic fatty liver disease (NAFLD) and diabetes in patients	200 mg; 12 weeks	Increase the gut <i>Bifidobacteria</i>	[82]
High-carbohydrate and high-fat diet (HFD)-induced metabolic syndrome in rat	100 mg/kg; 8 weeks	Decrease the abundance of Bacteroidetes, Lachnospiraceae, <i>Oscillospira</i> S24-7, and Lachnospiraceae; increase the abundance of Firmicutes and <i>Turicibacter</i>	[117]
HFD-induced NAFLD in mice	60 mg/kg; 12 weeks	Increase the content of <i>Bifidobacterium</i> ; reduce the content of <i>Escherichia coli</i> ; increase the expression of occludin and zonula occludens-1 (ZO-1); reduce LPS level, and increase GLP-1 level	[104]
Pb-induced hepatorenal toxicity in mice	30 mg/kg; 8 weeks	Increase the proportion of <i>Helicobacter</i> ; decrease the proportion of Lachnospiraceae_NK4A136_group; increase the concentrations of acetate, propionate, and butyrate	[110]
Ethanol-induced ALD in mice	60 mg/kg; 21 days	Increase <i>n</i> -butyric acid production; increase the relative abundances of Muribaculaceae, <i>Bacteroides</i> , <i>Alloprevotella</i> , and <i>Parabacteroides</i> ; decrease the abundances of <i>Eubacterium_nodatum</i> , <i>Eubacterium_ruminantium</i> , and <i>Anaerotruncus</i>	[105]
Renoprotective effects			
PO and adenine-induced hyperuricemia in rat	40 mg/kg; 2 weeks	Increased the α -diversity of the gut microbiota; decrease the relative abundance of Firmicutes, Actinobacteria, <i>Blautia</i> , Coriobacteriaceae UCG-002, <i>Dubosiella</i> , <i>Faecalibaculum</i> , <i>Holdemania</i> , <i>Enterococcus</i> , and <i>Eisenbergiella</i> ; increase Bacteroidetes, Lachnospiraceae NK4A136 group, <i>Butyrivimonas</i> , <i>Bifidobacterium</i> , and <i>Phascolarctobacterium</i>	[115]
Potassium oxonate-induced hyperuricemia in mice	30 and 60 mg/kg; 19 days	Decrease serum LPS level and ileal IL-1 β and IL-6 expression; increase the expression of ZO-1 and occludin; increase the relative abundance of <i>Bacteroides</i> , <i>Alistipes</i> , and <i>Butyrivimonas</i> ; decrease the relative abundance of Firmicutes, <i>Muribaculum</i> , <i>Faecalibaculum</i> , and <i>Aeromonas</i>	[114]
Cardioprotective effects			
Sprague Dawley adult male rats	10 μ g/mL; 24 h	Increase the abundance of acetic acid, propionic acid, butyric acid, and isovaleric acid (<i>in vitro</i>)	[119]

Table 3 (Continued)

Model	Dosage and duration	Key finding (Mainly focused on the changes involving the species and abundance of microflora following the action of CA)	References
High-carbohydrate and HFD-induced metabolic syndrome in rat			
Anti-diabetic effects			
Type 2 diabetes mellitus (T2DM) rats	100 mg/kg; 8 weeks	Decrease the abundance of Bacteroidetes, Lachnospiraceae, Lachnospiraceae, and <i>Oscillospira</i> ; increase the abundance of Firmicutes and <i>Turicibacter</i>	[117]
	1.04 and 2.08 g/kg (<i>Lycium barbarum</i> extract); 4 weeks	Decrease the abundance of <i>Marvinbryantia</i> , <i>Parasutterella</i> , Prevotellaceae_NK3B31_group, <i>Blautia</i> , <i>Ruminococcus_1</i> , and <i>Coproccoccus_2</i>	[53]
HFD-induced oxidative stress in rats	0.5% of diet intake (g/day); 4 weeks	Increase short-chain fatty acids (SCFAs) concentration (including acetic, propionic, and butyric acids); decrease the abundance of <i>Bacteroides</i> , <i>Enterococcus</i> , <i>Escherichia</i> , <i>Clostridium</i> , and <i>Staphylococcus</i> ; decrease the activity of β -glucosidase, β -galactosidase, β -glucuronidase and the concentration of putrefactive SCFAs (PSCFA, the sum of isobutyric, isovaleric and valeric acids)	[125]
Diabetic <i>db/db</i> mice	250 mg/kg; 18 days	Decrease the abundance of Proteobacteria, <i>Blautia</i> , <i>Robinsoniella</i> , and <i>Enterococcus</i> ; increase the abundance of Bacteroidetes, <i>Lactobacillus</i>	[132]
T2DM rats	2.65 mg CA/10 mg MP, 10 mg MP/kg	Increase the abundance of probiotics <i>Bacteroides</i> , <i>Akkermansia</i> , and <i>Parabacteroides</i> ; decrease the abundance of conditional pathogenic bacteria <i>Enterococcus</i> and <i>Staphylococcus</i> ; increase the content of intestinal SCFAs (including butyric acid, valeric acid, and isobutyric acid)	[133]
Neuro-protective effects			
HFD and high-fructose diet-induced obesity in mice	150 mg/kg; 14 weeks	Decrease the proportion of Firmicutes, <i>Bacteroides</i> , and <i>Dubosiella</i> ; increase the proportion of Bacteroidetes, Lachnospiraceae NK4A136 group, <i>Lactobacillus</i> , <i>Alistipes</i> , <i>Odoribacter</i> , <i>Helicobacter</i> , <i>Alloprevotella</i> , and SCFAs	[140]
TMT-induced neurobehavioral dysfunctions in mice	30 mg/kg; 11 days	Increase the abundance of <i>Lactobacillus</i> , Firmicutes, and the content of SCFAs (such as propionic acid, and isobutyric acid); decrease the abundance of <i>Bacteroides</i>	[136]
ICR mice	80 mg/kg; 1 week	Increased the relative abundance of <i>Turicibacter</i> , <i>Colidextribacter</i> , <i>Ruminococcus</i> , <i>Alloprevotella</i> , and <i>Alistipes</i>	[141]
Anti-obesity effects			
HFD-induced obesity in mice	100 mg/kg; 12 weeks	Increase the level of ZO-1 and claudin-1, decrease colon IFN- γ and IL-1 β levels, and the abundance of Firmicutes, <i>Bacteroides</i> , and Proteobacteria	[144]
HFD-induced obesity in mice	150 mg/kg; 6 weeks	Decrease the growth of Desulfovibrionaceae, Ruminococcaceae, Lachnospiraceae, and Erysipelotrichaceae; increase the abundance of Bacteroidaceae, Lactobacillaceae	[142]
HFD-induced obesity in mice	100 mg/kg; 13 weeks	Regulate the abundance of unique bacterial community	[148]
Other effects			
High fructose-induced hypertension in mice	50, 100, and 200 mg/kg; 8 weeks	Increase the abundance of <i>Klebsiella</i> and colonic farnesoid X receptor levels	[145]
HFD-induced obesity in mice	150 mg/kg; 20 weeks	Increase the tight-junction proteins (ZO-1, occludin, and claudin-1) and the abundance of <i>Dubosiella</i> , <i>Romboutsia</i> , <i>Mucispirillum</i> , and <i>Faecalibaculum</i>	[146]
Adrenocorticotrophic hormone-induced major depressive disorder in rats	500 mg/kg; 14 days	Decrease the relative abundance of Firmicutes, Proteobacteria, Desulfovibrionales, Deltaproteobacteria, <i>Oscillospira</i> , <i>Wautersiella</i> , <i>Desulfovibrio</i> , <i>Anaeroplasm</i> , and <i>Klebsiella</i> ; increase the abundance of <i>Pseudoxanthomonas</i> , <i>Gallionella</i> , <i>Phenyllobacterium</i> , <i>Lysoacter</i> , <i>Streptococcus</i> , <i>Rothia</i> , <i>Bifidobacterium</i> , <i>Haemophilus</i> , <i>Neisseria</i> and <i>Steroidobacter</i>	[84]

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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