MATCHA GREE TEA REVIEW: MATCHA TEA AND GUT-RELATED DISEASES: A REVIEW ON THE LINK BETWEEN PHENOLIC ACIDS AND GUT MICROBIOMES.

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by
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ABSTRACT

Matcha tea (*Camellia sinensis*), a traditional and historical tea, has gained worldwide popularity due to its particular fragrance and potential health benefits. Matcha tea contains various nutrients, such as catechins, caffeine, polyphenols, protein, vitamins, minerals, chlorophyll, fibers, etc. These nutrients bring multiple benefits such as antioxidant, anti-cancer, anti-inflammatory, anti-diabetic, cardioprotective, etc. Phenolic acids, as the main components in Matcha tea, can modulate or impact the gut microbiome to prevent or treat gut-related diseases. This review researched gallic acid, chlorogenic acid, ferulic acid, sinapic acid, ellagic acid, and caffeic acid and their therapeutic effects on the gut microbiome. Gallic acid can modulate the abundance of H.pylori to improve gastric cancer. In addition, Gallic acid can inhibit the biofilm formation of E. coli to show antimicrobial properties. Gallic acid ameliorates colitis by fecal microbiota transplantation. Chlorogenic acid prevents gut aging by reducing colon inflammation and modulating microbiome composition. Moreover, chlorogenic acid benefits post infections-IBS by impacting Firmicutes, Proteobacteria, and another microbiome. Ferulic acid can treat non-alcoholic fatty liver disease by impacting the Prevotella, Alloprevotella, Faecalibacterium, and other microbiomes. Ferulic acid also enhances the colonic intestinal barrier. Sinapic acid provides anti-inflammatory effects and alleviates oxidative stress. Ellagic acid prevents IBD by decreasing E.coli abundance and

increasing other beneficial bacteria. Ellagic acid modulates the gut microbiome to treat ALD as well.

BIOGRAPHICAL SKETCH

Jizhou Lei completed her Bachelor of Science in Pharmaceutical Science degree at the Ohio State University. She decided to switch her major to food science in 2022 because she found she loves natural products more. She will receive a Master of Food Science degree from Cornell University and start the next new life stage.

ACKNOWLEDGMENTS

I would like to express my deepest appreciation to my advisor, Dr. Elad Tako, who helped me greatly this academic year. I am also grateful to my parents that they can afford me to study abroad for many years. Many thanks to myself and congrats to me to finish my education life.

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1. Introduction

In the late twelfth century, Zen Buddhist monks introduced whipped teas to Japan from China (Dreher, 2018). Traditional Matcha tea is whipped, and nowadays, Matcha tea is made from green tea (*Camellia sinensis*) and has been a prevalent tea product worldwide (Dreher, 2018; Horie et al., 2017). The authentic dried leaves called “Tencha” are produced from shaded Camellia sinensis leaves, and after steaming, a special drier -Tencha-ro- is used to dry them. The dried, powdered Tencha ground is Matcha (Horie et al., 2017). Matcha tea is unfermented, and its powder is fine and bright green; the scent is slightly sweet and refreshing; the taste is smooth, bitter, and a little bit sweet; the foam is creamy. The astringency and bitterness of Matcha tea originate from tea polyphenols and caffeine, while the Catechins and tannins bring the bitterness to Matcha (Zhang et al., 2017; Zhang et al., 2020). The traditional Matcha tea often uses a bamboo whisk and tea bowl to whisk Matcha powder and water until the tea is frothy and cream foam on the top (Matchasource, 2024).

Rather than traditional green tea, water-soluble and non-soluble ingredients in Matcha tea can be ingested by humans to improve potential benefits (Wang et al., 2022). Powdered Matcha tea leaves are soluble in water and can be consumed directly without steaming like other tea leaves. Matcha tea beverages are trendy in Japan, and Matcha powders are used in different food products, such as cakes, noodles, and ice creams (Horie et al., 2017). Matcha tea is made with Pale Ale, and Kyoto Matcha IPA has a unique aroma and freshness (Kizakura, 2024). Different grades of Matcha tea contain other active components. Horie showed that higher amounts of theanine would be in the higher-grade Matcha (Horie et al., 2017). The content of Theanine in A1 reaches 3.43 g/100 g DW; this is the main factor that the A1 grade match has the highest grade (Horie et al., 2017).

2. Methods

This review is conducted in the Books and Documents, Clinical Trials, Reviews, Systematic Revies, Randomized Controlled Trials, and Meta-Analysis guide. The article database source was PubMed, and no years were limited. The chemical structures of phenolic acids were from the National Library of Medicine (NIH)- the National Center for Biotechnology Information (NCBI). The search terms and their combinations included “Matcha,” “Matcha tea,” “Gut microbiome,” “Gallic acid,” “Sinapic acid,” “Caffeic acid,” “Ferulic acid,” “Chlorogenic acid,” and “Ellagic acid.” A total of 514 articles were searched through PubMed, and 87 articles were selected finally.

3. Potential Benefits of Matcha Tea

Matcha tea brings some health benefits, such as antioxidants, anticarcinogenic effects, anti-inflammatory effects, cardioprotective effects, and antiviral properties (Koláčková et al., 2020). Furthermore, Matcha tea has the potential to regulate carbohydrate metabolism, improve cognitive function, and prevent neurodegenerative disorders (Kochman et al., 2021). In a human study, participants were required to take 9 capsules of Matcha for 12 weeks. The results proved that continuous intake of Matcha can improve attention and have anti-stress function (Baba et al., 2021). Green tea consumption has a negative correlation with death from pneumonia among Japanese women, proving that green tea components have the possibility of antiviral and antimicrobial activities against infectious agents (Watanabe et al., 2009). Matcha tea gargling has preventive effects against influenza and acute upper respiratory tract infections (URTI) (Umeda et al., 2021).

3.1 Potential benefits of Matcha tea on obesity

In 2015, obesity affected over 700 million adults and children in more than 70 countries. Besides, there are around 4.0 million people died from high BMI (Afshin et al., 2015). Wang's team, through a mice experiment, explored that matcha tea can help mice to decrease the effects of a high-fat diet (HFD) on weight and liver under the same energy intake (Wang et al., 2022b). Within the supplementation of matcha tea, the lipid accumulation and infiltration in the HFD group can be excessive. Furthermore, matcha tea supplementation can improve lipid droplet accumulation and hepatic steatosis. In Wang's study, Akkermansia muciniphila, which is a probiotic to prevent obesity that was aggregated in a regular diet and HFD. In addition, A. muciniphila can modulate mucus thickness and gut barrier integrity to normalized metabolism (Zhou et al., 2017; Wang et al., 2022b). The anti-obesity effects of Matcha tea often relate to polyphenols, including catechins, quercetin, and polyphenolic extracts (Boccellino&D'Angelo, 2020; Wang et al., 2014). The possible anti-obesity mechanisms of polyphenols should be the inhibition of obesity-related digestive enzymes, modulation of neurohormones or peptides, and improvement of growth of beneficial gut microbiomes and inhibition of pathogenic bacteria (Aloo et al., 2023).

3.2 Potential benefits of Matcha tea on Type 2 Diabetes

Due to diet complexity and unlimited consumption of food, type 2 diabetes has already become a worldwide problem. The study has shown that dietary and metabolic disturbance and high blood sugar in diabetic patients are due to gut microbiota (GM) dysbiosis (He et al., 2015). Matcha tea can potentially increase good bacteria in the gut microbiomes (M.C et al., 2002). In Zhang's study, mice in cornstarch (DM-C) and Matcha tea group (DM-M) did not lose weight compared to mice in DM-C because of the tea polyphenols, caffeine, polysaccharides, EGCG, and other active compounds. Furthermore, the Matcha tea supplementation group can also regulate blood glucose (Zhang Hai-hua et al., 2020). The research data indicated 23.8% differences between the DM-C and DM-M in OTUs. Compared with DM-C, the abundance of Actinobacteria in DM-M was increased, and the abundance of proteobacteria and Cyanobacteria decreased by 58.43% and 62.50%. From the perspective view of family levels, DM-M decreased the levels of Bacteroidaceae and Ruminococcaceae; moreover, the levels of Helicobacteraceae and Enterobacteriaceae decreased by 55.68% and 78.07%, respectively. The increased family levels compared with DM-C were Coriobacteriaceae, Lactobacillaceae (101.81%), Prevotellaceae (80.72%), and Bifidobacteriaceae (155.56%). These data proved that Matcha tea improved gut microbiome composition and bacteria family levels (Zhang Hai-hua et al., 2020).

4. Nutrients and Active Compounds

Matcha tea contains 60-70% insoluble ingredients, which include chlorophylls, proteins, water-insoluble dietary fibers, and so on, and 30-40% soluble ingredients that include polyphenols, caffeine, water-soluble vitamins, minerals, and so on (Maeda-Yamamoto et al., 2013). Koláčková reported that the dry matter contents of matcha tea are between 95.2% and 97.5%, which reaches an agriculture regulation value of 90% (Koláčková et al., 2020; Ministry of Agriculture, 1997). Matcha tea contains multiple nutrients and active compounds, including caffeine, Vitamin C, Chlorophyll, flavonoid, phenolic, and free radicals (Koláčková et al., 2020). Young tea leaves of Matcha will contain high caffeine but low EC and EGC contents but provide higher quality than old tea leaves (Horie et al., 2017; Unno et al., 2018; Ahmed et al., 2013).

4.1 Catechins

Catechins, a phenolic compound in Matcha tea, can benefit people with antioxidant benefits (Kochman et al., 2021). (-)-epicatechin (EC), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG), and (-)-epigallocatechin-3-gallate (EGCG) are the four main catechins in green tea; EGCG is the most abundant catechin that reaches to approximate

60% (Reygaert, 2018). Even though matcha tea has lower catechin content than other traditional green tea due to the limited sunlight before harvesting, matcha tea powders dissolved in water can produce three times more catechins than traditional loose-leaf green teas (Goto et al.,1996; Ikegaya et al., 1984; Fujioka et al., 2016).

Catechins have the potential for antibacterial and antiviral activity. The possible mechanism of action is that catechins has interact with the lipid bilayer and cell membrane (Renzetti et al., 2020; Sirk et al., 2009). Consuming tea catechin can help prevent viral respiratory infections like influenza and acute URTIs (Umeda et al., 2021). In addition, Takabayashi proved that catechins can be an agent to inhibit H.pylori infection by presenting a decreased number of Helicobacter pylori in the stomachs of Mongolian gerbils (Takabayashi et al., 2004). Furthermore, catechins can inhibit the growth of pathogenic bacteria, such as Salmonella and Clostridium. Bacillus and other harmful bacteria (Cabrera et al., 2006). Sasagawa demonstrated that 20 mg/mL Matcha tea can fight against Streptococcus pneumonia, and catechins inhibit the oligomerization of pneumolysin that is a pore-forming toxin that works on pneumococcal pneumonia (Sasagawa et al., 2021)

A rats experiment found that EGCG has the ability to reduce plasma cholesterol levels and non-HDL cholesterol levels by inhibiting cholesterol absorption. Furthermore, the mechanism of EGCG can modify the structure of lecithin and cholesterol in these micelles to the displacement of cholesterol from the mixed micelle phase. This is the possible mechanism for lowering cholesterol level (Raederstorff et al., 2003).

4.2 Caffeine

In the study of Koláčková, the data showed that matcha teas often have caffeine contents between 14.4-34.1 mg/g, while most coffee beans only contain 10.0-12.0 mg caffeine/g. (Koláčková et al., 2020). Caffeine contents depend on the tea leaves freshness, climatic conditions, and plucking season; meanwhile, caffeine as an antioxidant positively correlates with water extraction (Koláčková et al., 2020; Adnan et al., 2013).

An interesting randomized placebo-controlled study presented that when people suffer from psychological stress, consuming Matcha with caffeine better improves attention and work performance than with caffeine alone (Baba et al., 2021). The mechanisms of action to prove the psychological function of caffeine include adenosine A2A receptor blockade, modulation of neurotransmitter release, and stimulation of dopamine receptors (Baba et al., 2021). Caffeine also shows various potential benefits, including inhibiting enzyme activity to slow down starch digestibility (Li et al., 2021); reducing lipid accumulation and increasing fat oxidation to lowering lipid (Zhou et al., 2020; Willems et al., 2018).

4.3 Vitamin C

Vitamin C contents vary from 1.63 to 3.98 mg/g in various regions and types of Matcha, but two times higher than other green tea (Koláčková et al., 2020). The water temperature still alters the Vitamin C content from 32.12 to 44.8 mg/L when brewed

Matcha (Jakubczyk et al., 2020).

Vitamin C deficiency is the fourth nutrient deficiency in the United States, and daily intake is necessary. Vitamin C, as a cofactor for numerous biosynthetic and gene regulatory enzymes, likely contributes significantly to its ability to modulate the immune system. Vitamin C aids in immune defense by bolstering the cellular functions of both the innate and adaptive immune systems (Carr et al., 2017). Besides, a study proved that vitamin C intake can reduce the risk of gall bladder cancer (GBC) (Panda et al., 2013). Not only gall bladder cancer but vitamin C still protects against gastric, colon, esophageal, and other cancers due to inhibiting the formation of carcinogens from precursor compounds, but the evidence supporting this assertion is lacking (Panda et al., 2013).

4.4 Phenolic Acids

Koláčková reported that the total phenolic contents in the total methanol extraction are in the range of 169-273 mg GAE/g (Koláčková et al., 2020). Among the 12 different types of matches, the following lists are the most significant content of different phenolic acids in each type: Kissa: gallic acid — 423.0 μg/g; Don Matcha: protocatechuic acid — 299.0 μg/g; Whittard: *P*-hydroxybenzoic acid — 243.0 μg/g; Asagiri: chlorogenic acid — 4800 μg/g; Hisui: caffeic acid — 223.0 μg/g; Royal Pharma: ferulic acid — 289.0 μg/g; Bio Matcha: sinapic acid — 1400.0 μg/g; Mo Cha Fen: ellagic acid — 371.0 μg/g (Koláčková et al., 2020).

5. Therapeutic Effects of Phenolic Acids on Gut Microbiomes

Approximate 3.8*10 ^{13} microbial cells in a 70 Kg human body, especially in the gastrointestinal tract (Sender et al., 2016b; Gill et al., 2006). Gut microbiota includes bacteria, archaea, and eukaryotes within various species and phyla (Cheng et al., 2023). There are 10^{12} bacteria in the extraintestinal body and 3.8×10^{13} bacteria in the intestine; the overall intestinal microorganisms can be classified into 12 phyla and 2172 species (Sender et al., 2016; Sender et al., 2016b; Zhang et al., 2021b). Over 90% of bacterial phylum are Bacteroidetes and Firmicutes in the gut (Tanaka et al., 2017). In the small intestine, the Bacilli class of Firmicutes and Actinobacteria are highly enriched, while in the colon, Bacteroidetes and Lachnospiraceae family of the Firmicutes are abundant (Sekirov et al., 2010). The gut microbiota compositions can use α-diversity to test the changes in richness and diversity and β-diversity to test the alteration of the microorganism community (Cheng et al., 2023).

As the major part of polyphenols, phenolic acids have essential functions in regulating gut microbiota. The possible mechanisms of action are modulating microbiota composition, interfering with bacterial quorum sensing, and impacting gut metabolism and immunity (Kasorzak-Drozd et al., 2021). Matcha tea mainly contains gallic acid, chlorogenic acid, ferulic acid, sinapic acid, ellagic acid, and caffeic acid. These phenolic acids have potential therapeutic effects on gut-related diseases.

5.1 Gallic Acid

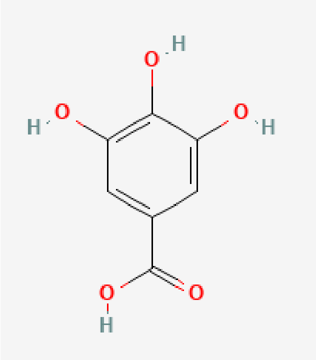

Figure 1: 2D structure of Gallic acid (PubChem Compound Summary for CID 5281855, Ellagic Acid, 2024)

As a polyphenol compound, gallic acid (GA) is a significant component in Matcha tea. GA and gut microbiota are closely related and deeply impact intestinal diseases (Yang et al., 2020). Some studies proved that GA had beneficial effects on Gastric cancer, colorectal cancer, and inflammatory bowel disease (IBD) (Yang et al., 2020). Helicobacter. pylori infection is the primary risk factor for gastric cancer development. A ginger aqueous extract (GA and cinnamic acid) demonstrated potential in protecting the gastric mucosa against stress-induced lesions by suppressing H. Pylori activity, inhibiting H+, K+-ATPase function, and providing antioxidant defense. This proved that GA can potentially prevent and treat gastric cancer by reducing H. Pylori abundance. Some studies also showed that GA intake can increase the abundance of *Lactobacillus spp., Lactobacillus plantarum, Lactobacillus reuteri*, and *Lactobacillus lactis* these beneficial bacteria to improve gut health (Kim et al., 2020; Yang et al., 2020).

GA has also been proven to have antimicrobial properties. GA can inhibit the biofilm formation of Escherichia coli (E. coli) by regulating pgaABCD gene expression (Kang et al., 2018). Moreover, GA has an anti-biofilm effect on Staphylococcus aureus by regulating the expression of the *ica* operon (Liu et al., 2017). Biofilms have a risk of increasing food contamination. GA has important benefits in the food industry in decreasing the growth of bacteria.

A study proved that GA has therapeutic effects on colitis through a DSS-induced mouse model (Pandurangan AK et al., 2015). DSS-induced Mice had obvious rectal bleeding; besides, the colon length of infected mice was significantly shortened. However, the colon length of GA-treated mice did not have the evident shortened. Furthermore, through histological scoring, the administration of GA reduced inflammation, ulceration, and neutrophil infiltration symptoms from DSS-induced mice (Pandurangan AK et al., 2015).

Meanwhile, GA can improve DSS-induced microbiota dysbiosis to ameliorate colitis. In Peng's study, the GA group increased the α-diversity, abundance of all major phyla except Actinobacteria, and the abundance of Clostridiales, Enterobacterales, and Bacteroidals at the order level (Peng et al., 2024). Furthermore, fecal microbiota transplantation (FMT)-GA mice had improved colitis phenotypes and histopathological changes. The intestinal permeability was increased compared to FMT-DSS mice (Peng et al., 2024).

5.2 Chlorogenic Acid

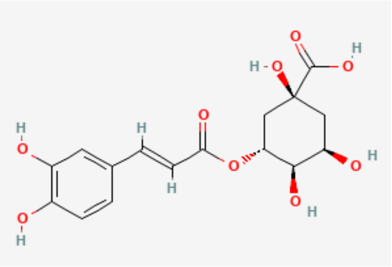

Figure 2: 2D structure of Chlorogenic acid (PubChem Compound Summary for CID 1794427, Chlorogenic Acid, 2024)

Aging is an irreversible and unavoidable phenomenon for human beings. Aging is reflected not only in physical appearance but also in changes in the gut microbiome. Kim stated that aging could deteriorate the relationship between the gut microbiota and the host, provoking pro-inflammation and other diseases (Kim et al., 2018). However, chlorogenic acid (CGA) in Matcha tea has the benefit of ameliorating gut aging.

In Wei's study, his lab team worked on D-galactose - an aging model that induced gut aging can be ameliorated by CGA and EGCG alone or in combination (Wei et al., 2023). After eight weeks of treatment, the CGA alone and EGCG alone improved the colon structure damaged by D-galactose due to the protection of the gut barrier of mice. The combination of the CGA and EGCG group can potentially decrease the gut permeability to normal levels compared to the D-galactose-induced group (Wei et al., 2023).

Even though the CGA and EGCG alone group could not suppress the levels of TNFα and IL-6, the CGA plus EGCG group reduced the levels of TNFα and IL-6. The combination therapy reduced colon inflammation very well. Furthermore, the combination therapy decreased the IFN-γ level to 2308.8 ± 802.4 pg mg −1 prot ($p < 0.01$), which is approximately 1,600 pg mg −1 prot smaller than the D-galactose group. Fortunately, CGA alone, EGCG alone, and combination therapy can decrease the secretion of 1L-1β (Wei et al., 2023). The D-galactose group decreases 29% of total antioxidant capacity. However, the combination of CGA and EGCG mice had higher levels of total antioxidant capacity and lower levels of malondialdehyde. This proves that combination therapy decreases colon oxidative stress in D-galactose-induced mice (Wei et al., 2023).

From the gut microbiome analysis, the D-galactose has a lower alpha diversity. Under the combination therapy, the Shannon index was strengthened. At the same time, the community abundance was recovered to the control group level using the CGA and EGCG combination group. From the phylum and family levels analysis, the abundance of Firmicutes, Deferribacter, Actinobacteria, and Proteobacteria increased, but the abundance of Bacteroidota, Desulfobacte, and Campylobacter decreased in the D-galactose group. This gut dysbiosis can be ameliorated by using CGA alone and combination therapy (Wei et al., 2023).

In a rats study, CGA has demonstrated beneficial effects on post infections IBS (PI-IBS). After taking CGA, the elevated levels of proinflammatory cytokines (IL-1β, IL-6, TNF-α) and increased intestinal permeability suggest alterations in intestinal barrier function and inflammatory responses that contribute to developing IBS rats (Zheng et al., 2023). At the phylum level, PI-IBS rats showed a higher abundance of Firmicute and a lower abundance of Bacteroidetes and Proteobacteria compared to the control group. In addition, Muribaculaceae, Parasutterella, Prevotellaceae, and Alistipe decreased, but increased in Staphylococcus. However, after CGA-fecal microbiota transplantation, the symptoms of PI-IBS were improved, and gut microbiomes were also changed. The abundance of Firmicutes and Proteobacteria increased again. The abundance of Muribaculaceae was decreased and the increased levels of Eubacterium and Candidatus Saccharimonas. Moreover, CGA treatment contribute to disease modulation by increased levels of B.acidifaciens compared to PI-IBS rats (Zheng et al., 2023).

Some studies found that chlorogenic acid had the potential to alter microbiota composition to improve diabetes (Yan et al., 2022; Zhou et al., 2023;. In Yan’s study, Firmicutes, Proteobacteria, and Bacteroidetes were the most abundant, with lower Bacteroidetes and higher Proteobacteria abundance observed in the diabetes mice. Certain metabolites produced by the gut microbiota, such as short-chain fatty acids, can alleviate obesity and insulin resistance induced by diet (Yan et al., 2022; Jiao et al., 2020).

5.3 Ferulic Acid

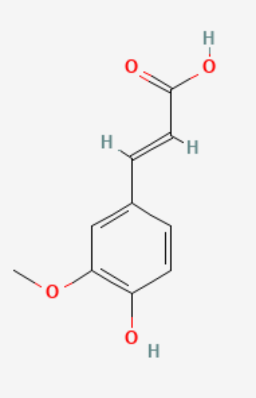

Figure 3: 2D structure of Ferulic acid (PubChem Compound Summary for CID 445858, Ferulic acid, 2024)

Devkota’s group reported that Ferulic acid (FA) in 80% MeOH extract of Matcha tea powder sample is approximately 45.5-289.0 μg/g (Devkota et al., 2021). FA is an effective component in Chinese medicine herbs such as *Angelica sinensis, Cimicifuga heracleifolia and Lignsticum chuangxiong* (Ou&Kwok, 2004). The research found that FA can increase intestinal Lactobacillus to improve cardiovascular diseases because the abundance of Lactobacillus had a negative relationship with cardiac-hypertrophy indices (Liu et al., 2019).

FA has been reported to improve the symptoms of diabetes as well. The PCoA results demonstrated that FA altered the microbiota distribution away from the diabetes group but did not reach the control group, which means FA could impact gut microbiota but not heal diabetes rates. Besides, FA increased the SCFAs and improved the growth of *Blautia* (Song et al., 2020).

The experiment demonstrated that Matcha tea improved the symptoms of high-fat diet (HFD) induced non-alcoholic fatty liver disease (NAFLD) (Zhou et al., 2021). NAFLD is a liver problem in which too much fat builds up in the liver that affecting people who drink little to no alcohol and significantly overweight or obese people (Mayoclinic, 2024; NIH, 2024). There is no clear pathogenesis of NAFLD; the most accepted mechanism of action is that GM disruption and intestinal barrier dysfunction lead to the translocation of bacteria to trigger liver inflammation (Tilg et al., 2020; Wang et al., 2022a). There is no drug to be approved to treat impaired intestinal barrier. FA, a natural phenolic acid in food, has improved intestinal barrier function (Chen et al., 2022).

In Fu's study, one group of mice was treated with HFD and FA for eight weeks. The α-diversity did not change, meaning the microbiome amounts are the same after FA supplementation (Fu et al., 2023). However, PCA analysis showed that gut microbiomes dramatically changed. Compared with the HFD group, Deferribacterota and Campilobacterota were decreased in the HFD+FA group, and the abundance of Proteobacteria was increased (Fu et al., 2023). Moreover, FA supplementation significantly increased the abundance of some SCFAs-producing bacteria, such as the genus Prevotella, Alloprevotella, and Faecalibacterium ($P < 0.05$) (Fu et al., 2023).

Fu's group proved that FA could enhance the colonic intestinal barrier, indicated by the up-regulated mRNA levels of Zo-1, Occludin, and Claudin-1 in the distal colon (30

Fu et al., 2023). Besides, the concentration of SCFA levels was increased, especially acetic and butyric acid. Interestingly, compared with HFD mice, the lower expression of pro-inflammatory cytokines Il-1β, Il-6, and Tnf-α suggested a potential anti-inflammatory effect on FA supplementation (Fu et al., 2023). Overall, FA supplementation effectively mitigated hepatic lipid accumulation and inflammation. This was achieved by modulating the gut microbiota-liver axis, specifically restoring both the proximal and distal intestinal barriers. FA supplementation also reduced circulating LPS levels, inhibiting the hepatic TLR4 signaling pathway (Fu et al., 2023).

5.4 Sinapic Acid

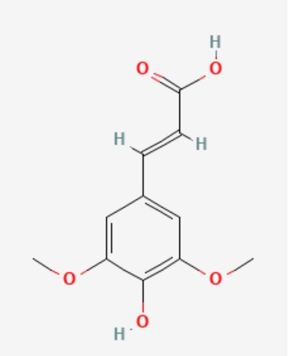

Figure 4: 2D structure of Sinapic acid (PubChem Compound Summary for CID 637775, Sinapinic acid, 2024)

Sinapic acid (SA) has proven its antioxidant, anti-inflammatory, anti-cancer, hepatoprotective, cardioprotective, renoprotective, neuroprotective, anti-diabetic, anxiolytic, and anti-bacterial activities (Pandi & Kalappan, 2021). The possible anti-inflammatory mechanism of SA involves modulating NF-kB activity in macrophages, which leads to the suppression of iNOS, COX-2, and pro-inflammatory cytokine production. The two methoxyl groups and hydroxyl groups of SA presented anti-bacterial action and the minimum inhibitory concentration was 2.2 mM, 2.0 mM and 1.9 mM (Pandi & Kalappan, 2021). Jang demonstrated that SA can alleviate IBD and improve intestinal microbiota (Jang et al., 2023). In this study, after taking SA, the colon of the DSS-induced mice was longed for, and the inflammatory cytokines were produced. The damaged colon tissue was also recovered after SA supplementation. The interesting thing was the increased abundance of Ligilactobacillus and Limosilactobacillus after SA treatment. The characteristic of Limosilactobacillus is its anti-inflammatory effects, and it can prevent E.coli and Helicobacter, these infected bacteria. These results suggest that SA can act as a probiotic agent for beneficial gut microbiomes (Jang et al., 2023).

Another study proved that the concentration of SA up to 1400 μg/g can alleviate oxidative stress by impacting gut microbiomes in HFD rats (Yang et al., 2019). Especially combined SA with resveratrol, a compound with anti-inflammatory and anti-obesity compounds, can have a notable effect on HFD rats (Yang et al., 2019). From the analysis of α-diversity, high-fat mice (HF) with resveratrol supplementation group (HFR) and high-fat mice with SA supplementation group (HFS) had more OTUs (Yang et al., 2019). The Chao 1 and ACE indexes demonstrated that HFS significantly increased by 1.25 to 1.3 times abundance richness compared to the HF group (Yang et al., 2019). Thus, SA supplementation can improve the gut microbiome compositions. Furthermore, the ratio of Firmicutes to Bacteroidetes (F/B ratio) was increased in the

HFR group compared to the HF group (Yang et al., 2019). Since the decreased F/B ratio was demonstrated to be related to obesity phenotype, resveratrol did have beneficial effects on the HFD rats (Sun et al., 2016). Tenericutes and Actinobacteria phyla abundance was low in the HFS group (Yang et al., 2019). Besides, Coriobacteriia and Erysipelotrichi Bacilli Gammaproteobacteria classes had rich abundance in the HFS group (Yang et al., 2019). SA supplementation could not reverse the weight gain in HFD rats, but it can alleviate oxidative stress in the liver and colon (Yang et al., 2019). SA and resveratrol both increased the proportions of Blautia ($p<0.05$) and Dorea ($p<0.01$) within the Lachaospiraceae family while inhibiting the growth of bacterial species associated with diseases and inflammation, such as Bacteroides ($p<0.05$) and Desulfovibrionaceaesp ($p<0.01$) (Yang et al., 2019). SA

5.5 Ellagic Acid

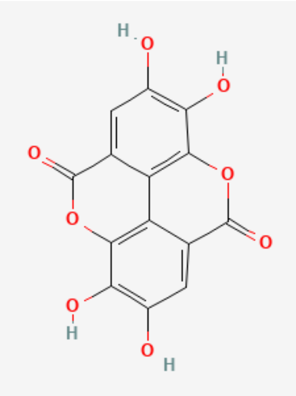

Figure 5: 2D structure of Ellagic acid (PubChem Compound Summary for CID 5281855, Ellagic Acid, 2024)

Some studies documented that ellagic acid (EA) demonstrates antioxidant, anti-inflammatory, and anticancer pharmacological properties (Devipriya et al., 2007; Shukla et al., 2008; Aggarwal et al., 2006). In Kim's study, ellagic acid could prevent inflammatory bowel disease (IBD) and liver and brain injury through regulation of the gut microbiome (Kim et al., 2023). IBD referred to conditions characterized by persistent inflammation of the tissues lining the digestive tract over an extended period, including Ulcerative colitis and Crohn's disease (Mayo Clinic, 2024). Kim's lab aimed to investigate the effects of EA (60 mg/kg/day) on inflammation and oxidative stress in an acute colitis mouse model induced by 5% DSS over seven days (Kim et al., 2023). The disease activity index was notably higher in the DSS group but slightly reduced in the DSS +EA group (Kim et al., 2023). Levels of oxidative stress markers NO and ROS and pro-inflammatory cytokines TNF and IL-1β increased in the DSS group (Kim et al., 2023). However, they significantly decreased with EA treatment, indicating EA's dual anti-inflammatory and antioxidant effects in DSS-induced colitis mice (Kim et al., 2023).

Gut microbiome sequencing showed changes in phylum composition, with increased Verrucoicrobia and decreased Bacteroidetes in colitis (Kim et al., 2023). The abundance of Lactobacillus decreased with DSS but was restored with DSS + EA group, while Bacteroides exhibited the opposite trend. DSS-induced colitis increased E.coli abundance, significantly reduced by DSS + EA treatment, indicating EA's potential to modulate harmful gut bacteria and fungi (Kim et al., 2023).

Alcoholic-associated liver disease (ALD) is caused by overconsumption of alcohol, and the primary diseases include alcoholic steatohepatitis (ASH), acute hepatitis, and cirrhosis (Hopkins Medicine, 2024). Some new evidence suggests that alcohol consumption can lead to gut dysbiosis, which plays a crucial role in the development of ASH (Woodhouse et al., 2018). In Zhao's study, mice treated with alcohol (M), low-dose EA (EL), and high-dose EA (EH) for four weeks (Zhao et al., 2021). The phylum results demonstrated that compared with the control group, alcohol consumption increased the abundance of Firmicutes, Verrucomicrobia, and Actinobacteria and decreased the abundance of firmakkerdetes and Proteobacteria (Zhao et al., 2021). Compared with the M group, the EH group highly decreased the abundance of actinobacteria and slightly decreased the abundance of Verrucomicrobia, which means EA supplementation can restore the alcohol-lost microbiomes. M group showed decreased *norank_f__Muribaculaceae* and *Bacteroides*, partially restored by EA treatment (Zhao et al., 2021). In addition, Bacteroides increased while Lachnospiraceae_Nk4A136_group decreased in the EH group compared to the control group (Zhao et al., 2021). EA also boosted the abundance of Bifidobacterium, highlighting its significant impact on GM composition (Zhao et al., 2021).

5.6 Caffeic Acid

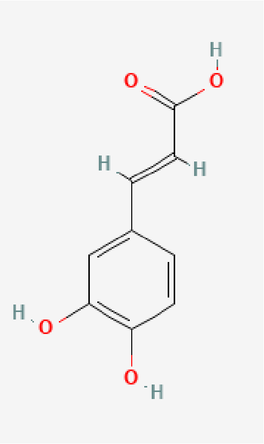

Figure 6: 2D structure of Caffeic acid (PubChem Compound Summary for CID 689043, Caffeic Acid, 2024)

In recent studies, caffeic acid (CA) has been demonstrated to alleviate colonic inflammation and oxidative stress by improving gut microbiota (Wan et al., 2021). In Wan's study, female ICR mice were induced with DSS and DSS+CA (CA) in separate groups. The results showed that the colon length of DSS (≈8 cm) was shortened comparing the control group (CON) (≈ 9.2 cm). CA inhibited the shortened colon length administered by DSS, approximately 9.0 cm ($p < 0.05$), which means CA supplements had the colitis symptoms alleviation functions. According to the Hematoxylin and Eosin (H&E) staining image, the intestinal permeability of DSS was increased. Meanwhile, the number of goblet cells was notably decreased in the mucosa, which means the protective mucus blanket was not synthesized and secreted. Fortunately, CA improved the colon damage under the H&E and histologic score. Moreover, CA supplementation decreased the FITC-Dextran concentration to improve gut barrier function. In addition, compared with the DSS group, CA decreased ROS and LPS production to inhibit the secretion of inflammatory cytokines, such as IL-1β, IL-6, TNF-α, and IL-10 (Wan et al., 2021).

CA modulated colon microbiome compositions as well. PCoA analyzed that Con had significant differences from DSS and CA ($p<0.01$), even though DSS and CA presented different trends. DSS had a high abundance of Bacteroides and Turicibacter. However, CA showed a relatively lower abundance of these genus-level bacteria. In other studies, Bacteroides and Turicibater positively correlated with colon inflammation (Shang et al., 2021). Compared with the DSS group, CA presented a significantly high abundance of Alistipes, Dubosiella, and Akkermansia. Alistipes and canisa showed the benefits of treating or alleviating IBD (Yang, Y. et al., 2022; Fan et al., 2021). Akkermanisa can still repair epithelial damage by strengthening the mucosal barrier and protecting against colitis (Bian et al., 2019; Zhai et al., 2019). However, the mechanism of Dubosiella was not found (Wan et al., 2021).

From the data shown, CA supplementation influenced short-chain fatty acids as well. Acetic acid gradually increased from the control and DSS groups to the CA groups. Propionic acid had a slightly higher concentration in the CA group. Butyric acid significantly decreased in the DSS group but improved back in CA. However, it did not reach CON concentration. Furthermore, the results indicated that Akkermansia abundance positively correlated with butyric acid concentration ($r=0.457$, $p=0.009$). In controversy, the abundance of Turicibacter presented a negative correlation with propionic acid (r=-0.392, p=0.027) and butyric acid concentration (r=-0.507, p=0.005) (Wan et al., 2021).

5. Conclusion

Phenolic acids in Matcha tea bring multiple therapeutic effects on gut-related diseases by impacting or modulating gut microbiomes. Especially on the IBD, IBS, Colitis, and NAFLD. Further human clinical trials are needed to explore more benefits and mechanisms of action on gut-related diseases.

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