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SHORT COMMUNICATION

Green tea catechin epigallocatechin gallate alleviates high-fat diet-induced obesity in mice by regulating the gut–brain axis

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Abstract

Plant polyphenols have gained attention in recent years because of their potential to alleviate obesity and metabolic syndrome, protect neurological function, and maintain intestinal function. Here, we evaluated the effect of green tea catechin epigallocatechin gallate (EGCG) to suppress obesity, alleviate intestinal inflammation, and regulate hypothalamic neurotransmitters in high-fat diet mice. Obese male C57BL/6J mice were gavaged with 25, 50, or 100 mg/kg·body weight (bw) of EGCG or water per day for 6 weeks. The results demonstrated that EGCG significantly reduced bw, fat accumulation, and liver steatosis. EGCG also modulated hypothalamic neurotransmitters such as dopamine and 5-HTP. Besides, EGCG attenuated the expression of colonic inflammatory factors and barrier damage, increased the gut microbial abundance such as genus *Alloprevotella*, reduced short-chain fatty acids, and downregulated the transcription factors. The results suggest that EGCG may alleviate obesity and related metabolic disorders through gut–brain interaction.

KEYWORDS
central nervous system, gut microbiota, neurotransmitters, obese mice, short-chain fatty acids, tea polyphenols

1 | INTRODUCTION

With the increasing number of obese people, related metabolism disorders have become one of the most challenging public health problems worldwide (James, 2008). Obesity is caused by an imbalance between energy intake and expenditure, resulting in abnormal or excessive accumulation of body fat, leading to type 2 diabetes mellitus, cardiovascular disease, hypertension, hyperlipidemia, nonalcoholic fatty liver disease (NAFLD), and other related metabolic syndromes (Blancas-Velazquez et al., 2017; Jiang et al., 2019; Kopelman, 2000). It is generally believed that obesity is formed by a combination of genetics, lifestyle, social environment, emotions, and other factors. Because of its complex causes and the associated multiple metabolic syndromes, it is not fully treatable by drugs or surgery at present and may cause a series of side effects (Apovian et al., 2015; Eslam et al., 2018). Therefore, there is a worldwide demand for lifestyle interventions to prevent or alleviate obesity and the use of plant-derived functional food supplements for daily health maintenance, and disease prevention has received increasing attention.

Obesity was considered to be a systemic chronic low-grade inflammation (Hotamisligil, 2017), and inflammatory responses generated by inflammatory factors including tumor necrosis factor-α (TNF-α), interleukin-6, and so forth were considered to be key triggers of obesity-related complications (Hummasti & Hotamisligil, 2010). The gut is one of the key organs for the synthesis of inflammatory factors (Rohm et al., 2021). Studies have shown that the levels of

inflammatory factors in the intestine of mice under a high-fat diet (HFD) were significantly elevated (Ma et al., 2021; Nerurkar et al., 2019). It is also worth noting that the pro-inflammatory response in the intestine preceded the rise in relevant indicators in plasma and the increase in body weight (bw) (Ding et al., 2010), suggesting that intestinal inflammation can serve as a signal for the onset of metabolic disorders in the early stages of obesity.

The central nervous system (CNS), especially the hypothalamus, plays a decisive role in maintaining the body's energy regulation and metabolic homeostasis (Raji et al., 2009; Schwartz et al., 2000). Inflammatory cytokines can cross the blood–brain barrier through the gut barrier or affect gut nerve cells on the vagal pathway (Agirman et al., 2021), which in turn affects brain neurotransmitter metabolism, neuroendocrine function, synaptic plasticity, emotion-regulating neural circuits, and motor neuron transmission, leading to inflammatory responses and dysfunction of the CNS (Braniste et al., 2014). Studies have shown that the microbe–gut–brain (MGB) regulation could interact bidirectionally through immune, neurological, and endocrine pathways to jointly regulate the body's metabolism (Mayer, 2011; Parker et al., 2020). This regulation is called the gut–brain axis (Dalile et al., 2019), but the detailed mechanisms have not yet been fully investigated.

In recent years, polyphenol phytochemicals have been reported to have positive effects on gut microbial homeostasis (P. Zhou et al., 2022; Zhu et al., 2020) that can inhibit organismal pathologies through gut–brain axis (Kim et al., 2022; Syeda et al., 2021). Green tea is a natural health food with a long history of production and a large consumer base, and the polyphenolic compound catechins in it have prominent roles in the prevention and alleviation of obesity (Juhel et al., 2000; Yang et al., 2001). (−) -Epigallocatechin-3-gallate (EGCG) is the most abundant, physiologically active and widely studied catechin in green tea (Kao et al., 2006; Rains et al., 2011), which has been proven to take effect through inhibiting intestinal energy absorption (Grove et al., 2012), affecting lipid synthesis and metabolism (Liu et al., 2006), and regulating the balance of intestinal flora (Dey et al., 2020). In addition, EGCG has also been found to affect brain protein signaling and some neuroactive substances, thereby preventing obesogenic diet-induced cognitive deficits (Ettcheto et al., 2020). Our previous study also found that EGCG could effectively prevent obesity by affecting the CNS to inhibit neuroinflammation and activating brown fat thermogenesis (J. Zhou et al., 2018). However, current studies mainly focused on the independent role of the brain or peripheral tissues.

Given the scarcity of research exploring the anti-obesity effect of green tea catechin EGCG through the synergy of multiple tissues and organs, the present study revolved around the interactions between the CNS and other organs to investigate the effects of EGCG to reduce intestinal inflammation and improve gut microbial structure in HFD mice as well as affect the contents of neurotransmitters in the hypothalamus. This study aimed to present new evidence for EGCG as an effective nutritional strategy to mitigate obesity-related metabolic disorders through the gut–brain axis and provide new insights into the comprehensive utilization of green tea catechin.

2 | MATERIALS AND METHODS

2.1 | Animals and experiments

All animal experiments have been approved by the Animal Care and Use Committee at Zhejiang University (ethic approval code: ZJU20210199) and conformed to the guidelines, following the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. Twenty-five 4-week-old C57BL/6 male mice were obtained from Shanghai SLAC Laboratory Animal Co., Ltd. (Shanghai, China). All mice were housed in controlled conditions of temperature (21–23∘C), humidity (40%–60%), and a 12 h light/dark cycle. Feed and water were provided ad libitum during the experimental period. All mice underwent an acclimation period of one week before using them in experiments.

According to the process shown in Figure S1, the 25 mice were randomly assigned to five groups ($n = 5$). One group was fed with a normal chow diet (NCD) and the other four groups with an HFD diet. The NCD (10% energy from fat, #D12450J) and HFD (60% energy from fat, #D12492) diets were purchased from Research Diets, Inc. Co., Ltd. (New Brunswick, NJ, USA). The feed composition referred to our previous study (J. Zhou et al., 2018). During this modeling stage, bw and food intake were measured every week. After 10 weeks, the four groups were already induced to obesity.

Next, all groups were continuously fed as the same as the modeling stage and under the daily gavage administration: (1) the control group receiving a daily water administration (NCD); (2) a group of HFD receiving a daily water administration (HFD); and (3) three groups of HFD gavaged with 0.1 mL dose of 25 mg/kg·bw (HEL), 50 mg/kg·bw (HEM) and 100 mg/kg·bw (HEH) of EGCG per day. ECGC doses used in the study were based on the pre-experiment and previous literature (Jhang et al., 2016). The EGCG was purchased from Huzhou Rongkai Foliage Extract Co., Ltd. (Huzhou, Zhejiang, China). Feed and water were available ad libitum. Body weight and food consumption were recorded weekly.

After six weeks of the experiment, the mice were euthanized under isoflurane anesthesia. The fecal samples were collected and frozen at −80∘C.

2.2 | Collection of serum and tissue samples

Blood samples were harvested from the 12-h fasted mice. The liver and adipose tissue samples were harvested and weighed. The intestine with the colon part and its contents were also collected. Tissues isolated for histological analysis were washed in phosphate buffered saline (PBS)

and fixed in 4% formalin. Tissues isolated for subsequent experiments were immediately frozen in liquid nitrogen and stored at −80∘C.

2.3 | Serum biochemical analysis

The serum biochemical analysis included the level of serum glucose (Glu), total triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL), using the TBA-40FR automatic biochemical analyzer (Toshiba Medical, Tokyo, Japan).

2.4 | Histological analysis

Liver, colon, and adipose tissues were mounted in paraffin blocks, sliced at 5 μm, and stained with hematoxylin and eosin (H&E) after the prior fixation for 24 h. The stained samples were detected with a microscope (Zeiss, Oberkochen, Baden-Württemberg, Germany).

2.5 | Quantitative real-time polymerase chain reaction analysis

Total ribonucleic acid (RNA) of intestinal tissues was extracted using the Trizol reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions and our previous study (Y. Wang et al., 2022). The RNA was reversely transcribed using a high-capacity complementary DNA (cDNA) reverse transcription kit (Invitrogen). Synthetic cDNA was amplified using the SYBR Green PCR Master Mix (Applied Biosystems, Foster City, CA, USA) on the LightCycler480 real-time system (Roche, Basel, Switzerland). The sequences of the primers in this study are listed in Table S1.

2.6 | 16S ribosomal DNA high-throughput sequencing

The gut microbial genomic DNA was extracted from the colonic contents using TruSeq® DNA PCR-Free Sample Preparation Kit (Illumina, San Diego, CA, USA). The V3-V4 region of the 16S rRNA gene was amplified by PCR using the primers 343F (5-TACGGRAGGCAGCAG-3) and 798R (5AGGGTATCTAATCCT-3) and then fully sequenced on the NovaSeq PE250 platform (Illumina) from the Wuhan Metware Biotechnology Co, Ltd. (Wuhan, Hubei, China). After being quality-filtered, the paired-end reads were turned into the tags which were assigned to operational taxonomic units (OTUs) with a cut-off value of 97%. Taxonomic assignment was based on the SILVA_138 database. The alpha-diversity (Chao1 index) and beta-diversity (principal coordinates analysis (PCoA) index) analyses were conducted with the Qiime 2 software (QIIME 2 Workshop Fort, Collins, Co., USA) and displayed with the R software (R Foundation for Statistical Computing, Vienna, Austria). Stool microbial characterization was subjected to linear discriminant analysis (LDA) effect size (LEfSe). The Spearman's correlation analysis between lipid-related traits and the key intestinal microbial phylotypes was calculated by psych package and visualized by heatmap package.

2.7 | Short-chain fatty acids and hypothalamic neurotransmitter quantification

After pretreatment of the intestinal contents and hypothalamic tissues, the target metabolites were analyzed qualitatively by the Ultra Performance Liquid Chromatography-Electrospray Ionization-Tandem Mass Spectrometry (UPLC-ESI-MS/MS) system. Metabolite quantification was performed using triple quadrupole mass spectrometry with multiple reaction detection (MRM) modes. Each MRM transition was automatically identified and integrated using the SCIEX OS-MQ software (Sciex, Redwood City, CA, USA), and the concentration of each target transmitter was obtained by data statistics, analysis, and processing.

2.8 | Statistical analysis

All figures were plotted by GraphPad Prism Software version 9.0 (GraphPad Software Inc., San Diego, CA, USA), statistical analyses were performed by SPSS 20.0 (IBM Corporation, Armonk, NY, USA), and quantitative analysis of tissue staining was performed by ImageJ 1.53a (National Institute of Mental Health, Bethesda, MD, USA). Data and results were expressed as mean ± standard error of the mean (SEM). The statistical significance was indicated by the one-way analysis of variance followed by Tukey's multiple comparison test. Differences were considered statistically significant when $p < 0.05$ and indicated with different superscripts.

3 | RESULT

3.1 | EGCG alleviated HFD-induced obesity

As shown in Figure 1A, the HFD significantly increased the bw after the first 10 weeks, indicating that the high-fat modeling was successful. After 6 weeks of intervention, the weight of the HEH group was significantly lower than the HFD group, which was close to the level of the NCD group. The energy intake (food intake multiplied by feed calories) of the NCD group was lower than that of those high-fat diet groups, and there was some difference in energy intake among the HFD groups but did not reach a significant level (Figure 1B). The serum biochemical parameters (Figure 1C) showed that the HFD group had higher levels of Glu, TG, TC, and LDL/HDL ratio compared with the NCD group, while the EGCG administration groups showed reduced levels of Glu, TG, TC, and LDL/HDL ratio, suggesting that EGCG has the potential to alleviate blood glucose and blood lipids.

In terms of tissue steatosis, the HFD significantly increased the liver weight and adipose tissue weight, while the administration of

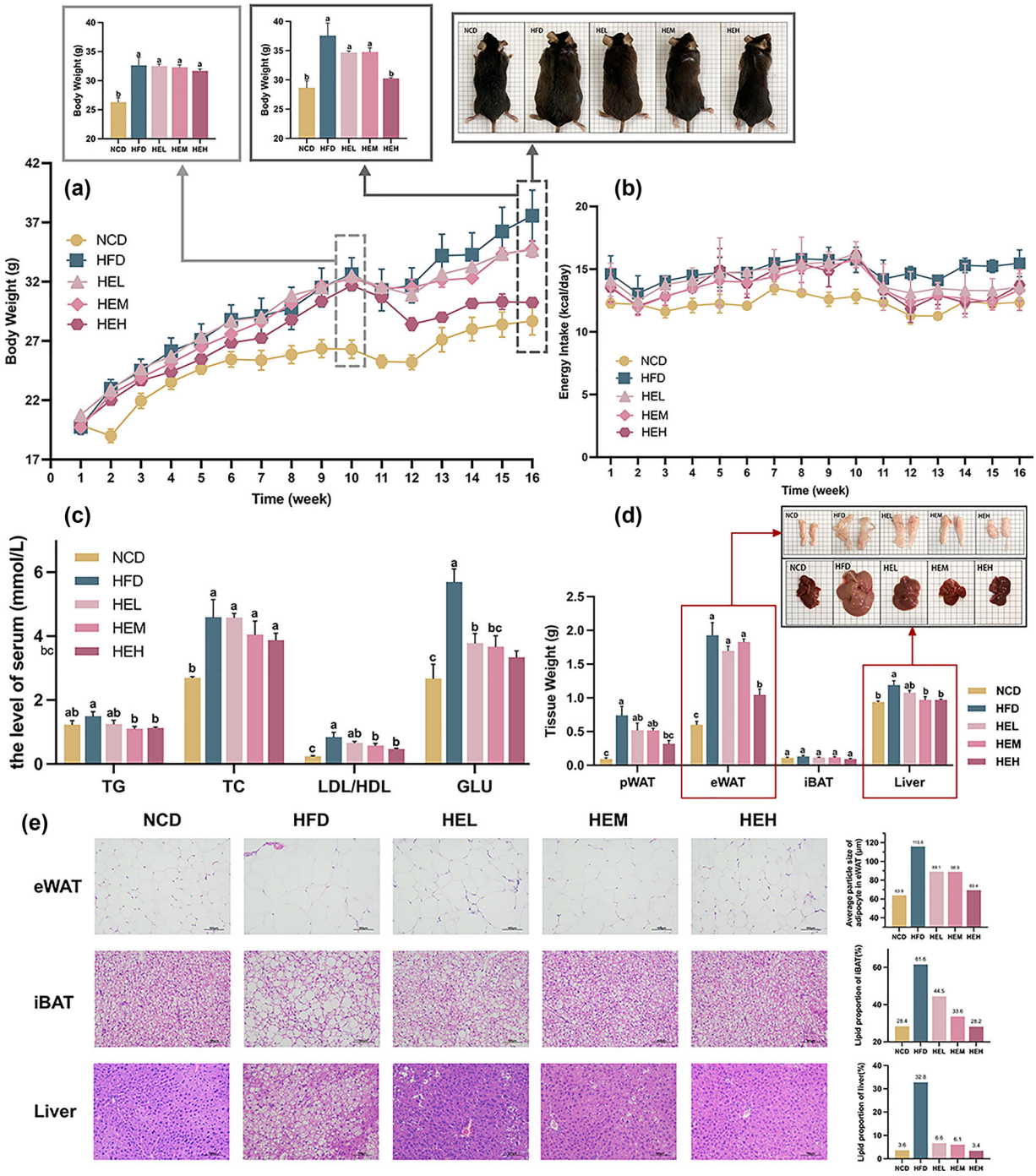

FIGURE 1 Effects of (−) -epigallocatechin-3-gallate (EGCG) on high-fat diet (HFD)-induced obesity. (A) Weight gain in 16 weeks. (B) Energy intake. (C) Serum biochemical parameters. (D) Tissue weight. (E) Hematoxylin-eosin staining of the adipose tissue and liver. Data are expressed as means ± SEM ($n = 5$). Means with different letters (a–d) were considered significantly different at $p < 0.05$ according to Tukey's test. Normal chow diet (NCD), mice on a normal chow diet with a daily water gavage; HFD, mice on a high-fat diet with a daily water gavage; HEL, mice on a high-fat diet with a daily EGCG gavage at the dose of 25 mg/kg; HEM, mice on a high-fat diet with a daily EGCG gavage at the dose of 50 mg/kg; HEH, mice on a high-fat diet with a daily EGCG gavage at the dose of 100 mg/kg; eWAT, epididymal adipose tissue; pWAT, perirenal adipose tissue; iBAT, interscapular brown adipose tissue. In the body diagram in (A) and the tissue diagram in (D), the length of each small cell is 0.5 cm.

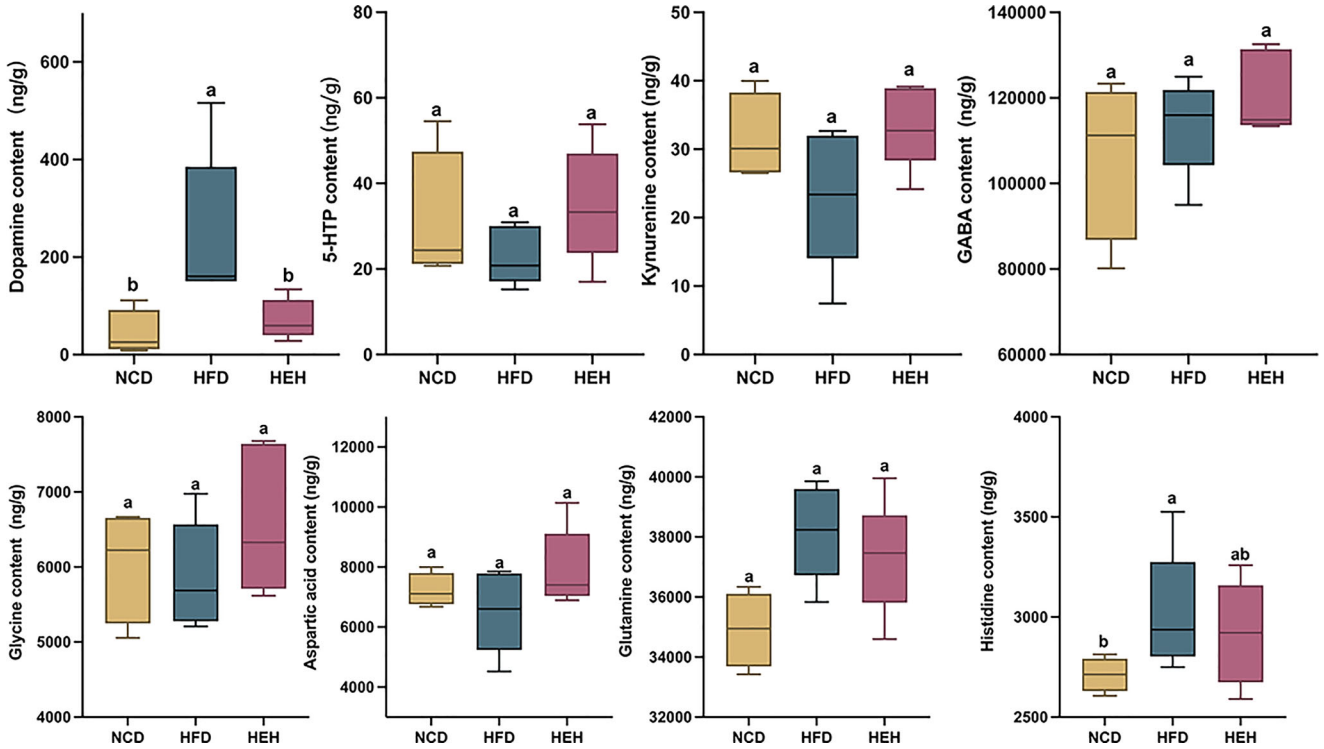

FIGURE 2 Effects of (−) -epigallocatechin-3-gallate (EGCG) on hypothalamic neurotransmitters. Data are expressed as means ± SEM ($n = 5$). Means with different letters (a and b) were considered significantly different at $p < 0.05$ according to Tukey's test.

EGCG reduced the fat accumulation and alleviated the liver steatosis related to obesity (Figure 1D). Histological staining showed that the size of adipocytes of epididymis white adipose tissue, liver, and the lipid droplets deposition of intrascapular brown adipose tissue in the HFD group was much larger than that in the NCD group, which notably decreased in varying degrees with the change of EGCG administration concentration (Figure 1E).

These results indicate that EGCG effectively alleviated HFD-induced weight gain and lipid accumulation in a dose-dependent manner.

3.2 | Effects of EGCG on hypothalamic neurotransmitters

As shown in Figure 2, the content of dopamine in the hypothalamus of HFD group mice was significantly higher than that in the NCD group, while EGCG administration significantly reduced the content of dopamine, which was close to that in the NCD mice. The content of 5-hydroxytryptophan (5-HTP) in HFD group mice was downregulated compared with NCD mice. After EGCG administration, the content of 5-HTP was increased close to that of the NCD group. In the HFD group, the content of kynurenine was downregulated, while EGCG administration inhibited the downregulation. EGCG administration also affected the content of the gamma-amino butyric acid (GABA) to some extent but $p > 0.05$. The HFD also decreased the contents of aspartic acid and glycine and increased the contents of histidine and glutamate, while EGCG administration inhibited the change trends of them.

The above results showed that EGCG administration affected the content of dopamine, 5-HTP, kynurenine, and some amino acid in the hypothalamus of HFD mice.

3.3 | Effects of EGCG on intestinal inflammation

A gut histological staining (Figure 3A) showed that the colon villi of NCD mice were orderly arranged, the crypts and mucosa structure were complete, and the thickness of the muscle layer was moderate. However, the colon villi of HFD group mice were irregularly arranged, the crypts were damaged, the muscle layer was thin, and the inflammatory infiltration was obvious. After EGCG administration, the intestinal inflammatory infiltration was improved, and the structure of villi, mucosa, and crypt was restored. The therapeutic effect was better with the increase of EGCG concentration that HEH group basically returned to the normal intestinal state compared with the NCD group. Therefore, the HEH group that had the best therapeutic effect was selected to detect the expression of intestinal inflammatory factors (Figure 3B). The results showed that an HFD significantly changed the expression of inflammatory factors, while EGCG administration effectively downregulated the expression of *Tnf-α*, *Il-1β* and *Il-6* and upregulated the expression of *Il-10*.

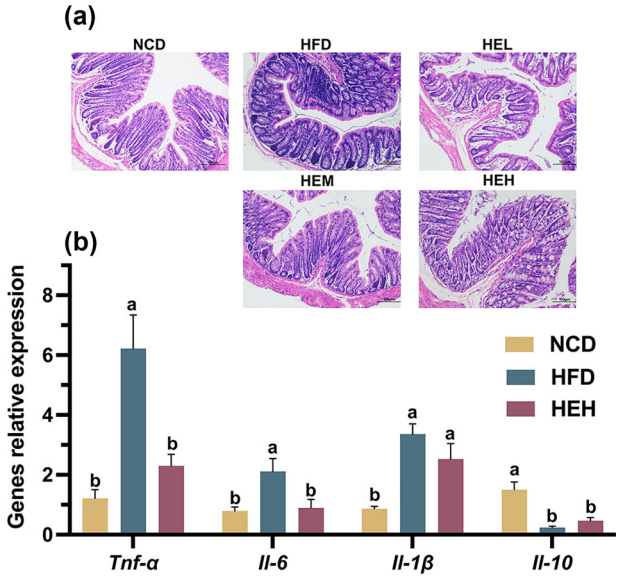

FIGURE 3 Effects of (−) -epigallocatechin-3-gallate (EGCG) on intestinal inflammation. (A) Hematoxylin-eosin (H&E) staining of the colon. (B) mRNA relative expressions of Tnf-α, Il-6, Il-1β, and Il-10 in the colon. Data are expressed as means ± SEM ($n = 5$). Means with different letters (a–b) were considered significantly different at $p < 0.05$ according to Tukey's test.

The results suggested that EGCG administration alleviated HFD-induced intestinal inflammation and restored the structural integrity of the gut.

3.4 | Effects of EGCG on gut microbiota, short-chain fatty acids, and key genes of MGB regulation

The 16S rRNA gene-based analysis of fecal DNA samples mined a total of 1,706,281 original sequences. After sequence processing, 1590142 effective 16S rRNA tags (93.2% of the original sequence) were obtained with an average length of 417 bp. These sequences were grouped into temporary clusters as OTUs. Compared with the standard database (Silva 138 database), these OTUs were divided into 19 phyla, 30 classes, 84 orders, 143 families, and 273 genera. As seen in the gradually flattening rarefaction curves (Figure S2A), the overwhelming majority of microbial diversity in all fecal samples was captured. Wayne diagram (Figure S2B) showed that there were 1110 core OTUs overlapping among different groups. Compared with NCD (1270) and HFD (363), the unique OTU in the HFD group was reduced. Compared with NCD&HEH (539) and NCD&HFD (190), HEH had the same OTUs with NCD more than HFD group, showing that EGCG alleviated intestinal dysbacteriosis. PCoA was performed to figure out the whole compositional differences of the gut microbiota among groups (Figure 4A). Samples from the same group gathered together at the OTU level and microbial composition was apparently changed under the EGCG administration. Microbial community richness of NCD and HFD groups showed significant differences as indicated by estimators such as Chao and Shannon (Figure S2C,D), which was not distinctively restored by the EGCG administration. The EGCG administration caused the structure change of gut microbiota in HFD mice, making it close to the microbiota structure of NCD group (Figure S2E).

Furthermore, we analyzed the relative abundance of the dominant taxa to evaluate specific changes in three groups (Figure 4B,C). At the phylum level (Figure 4B), EGCG administration drastically changed the gut microbial structure and increased Firmicutes/Bacteroidetes ratio from 0.96 in HFD group to 3.79 in HEH. To further define the differences and dominant microbes at the genus level, LEfSe analysis was performed based on relative abundance. According to the LDA scores shown in Figure 4D, EGCG administration affected the gut microbiota by distinctively enriching the genera *Alloprevotella*, *Muribaculaceae*, and *Bacteroides* and suppressed the genera *Blautia*, *Mucispirillum*, and *Colidextribacter*.

The content of short-chain fatty acids (SCFAs) in intestinal contents was determined, and the results showed that the EGCG administration notably reduced the content of acetic acid, butyric acid, propionic acid, pentanoic acid, isobutyric acid, and isovaleric acid which were increased in the HFD group (Figure 4E). Furthermore, the relative expression levels of *Nf-κb*, *Stat-3*, and *Ppar-γ* in colonic tissue (Figure 4F) were examined, and the results showed that the expression of *Nf-κb* and *Ppar-γ* was suppressed by EGCG administration. There was no significant difference in *Stat3* expression level between the HFD and HEH groups. Suggested that it might not be the key factor for EGCG to take effect. The above results suggested that EGCG could alter the content and proportion of SCFAs in the intestinal contents of HFD mice and may be involved in MGB regulation by affecting key genes *Nf-κb* and *Ppar-γ*.

Together, we developed a correlation analysis of the various elements involved in the MGB regulation of obesity. In Spearman's correlation analysis (Figure 5A), a variety of microflora enriched in HFD group mice exhibited positive significance with obesity and related parameters such as *Blautia*. Enriched by the addition of EGCG administration, *Muribaculaceae* and *Alloprevotella* showed a significant negative correlation with obesity-related parameters. Network construction (Figure 5B) showed that PPAR-γ, NF-κB, and TNF-α had a strong correlation with HFD-induced obesity. Furthermore, dopamine also played a role in the gut–brain axis network analysis.

4 | DISCUSSIONS

Green tea is a widely recognized natural health food with several health benefits. EGCG is a kind of green tea catechin with an outstanding activity which has been reported to have positive effects in preventing obesity with its induced metabolic syndrome (F. Li et al., 2018; J. Zhou et al., 2018). However, the limitation of the current studies of green tea is that most of them focus on a single metabolic system, and there are few studies on how peripheral organs and CNS work in combination. CNS plays an important role in the steady-state regulation of energy metabolism. The hypothalamus receives nutritional,

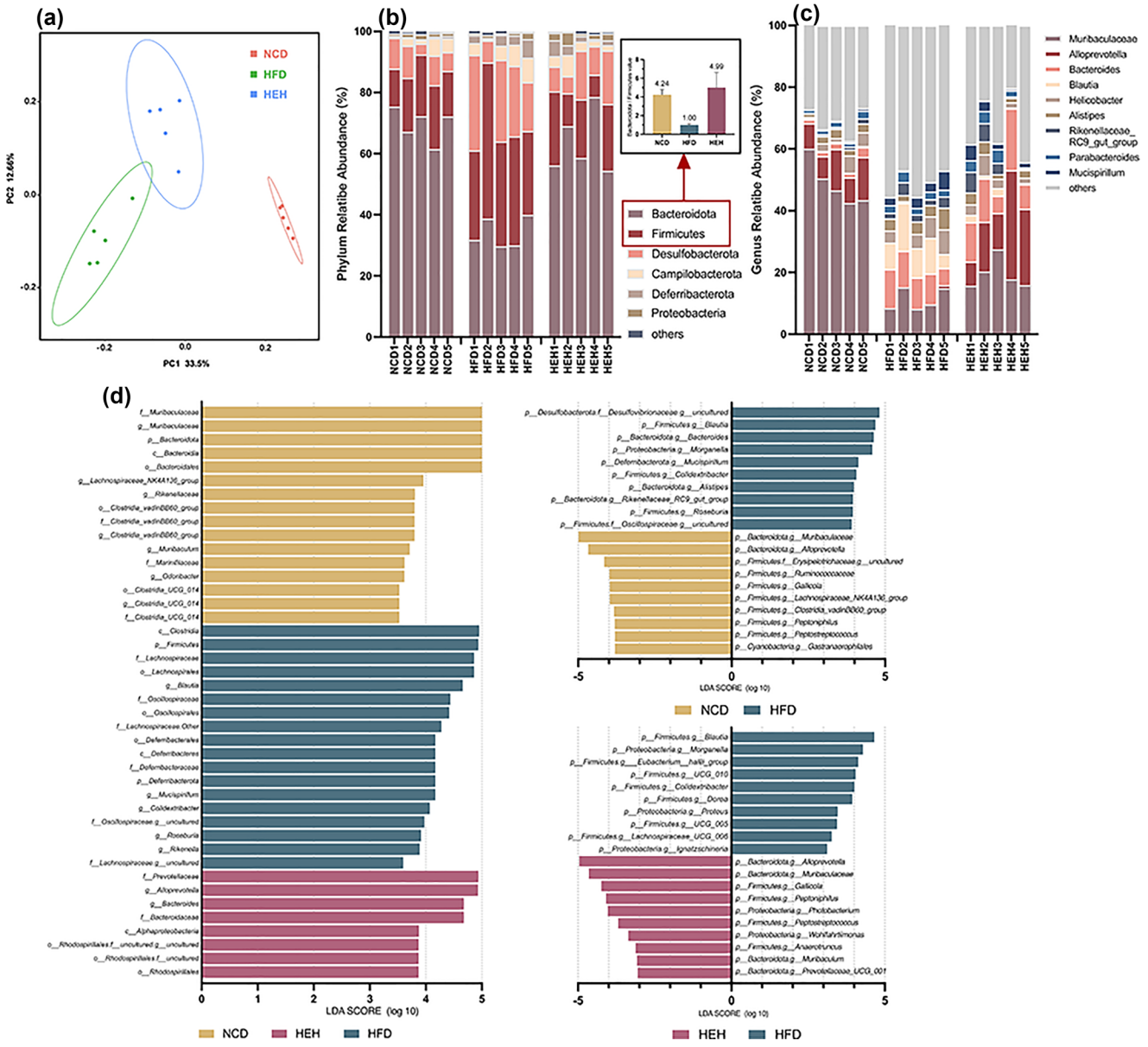

FIGURE 4 Effects of (−) -epigallocatechin-3-gallate (EGCG) on gut microbiota, short-chain fatty acids (SCFAs) contents, and genes relative expressions. (A) Beta diversity (PCoA). (B) Phylum relative abundance. (C) Genus relative abundance. (D) Linear discriminant analysis (LDA) to estimate the impact of abundance of each component (genus) under different treatment classifications. (E) The contents of SCFAs in gut. (F) The relative expressions of Nf-κb, Stat-3, and Ppar-γ. The LDA scores of the significantly contributing microbial taxa in the different groups were counted, and the lengths of the bar graphs represent the effect sizes of the significantly different microbes. Microbes exhibiting LDA scores are statistically different. Means with different letters (a–d) were considered significantly different at $p < 0.05$ according to Tukey's test.

hormonal, and neural information about the metabolic status from the body to coordinate the adaptive changes of food intake and energy consumption. This change signal may be transmitted to the peripheral nerve through neurotransmitters (López, 2017). In this study, we investigated the contents of neurotransmitters in the hypothalamus of mice and speculated that the therapeutic effects of EGCG on obesity may be achieved through dopamine, 5-HTP, kynurenine, and some amino acid metabolic pathways. The synthesis and metabolism of dopamine in animals are complex. Research has shown that an HFD could cause hedonic overeating in mice during resting periods, leading to food-borne obesity, which required the involvement of dopamine signaling (Grippo et al., 2020). 5-HTP is an important neurotransmitter and an important precursor of the 5-HT, which can regulate energy balance in the body and control appetite (He et al., 2021). Meanwhile, dopamine and 5-HT in the CNS have been reported to be correlated with intestinal damage and microbial disorders (El Aidy et al., 2017; Hartstra et al., 2020). Kynurenine is closely related to physiological activities such as gut microbiota, immune cell response, and neuronal excitation (Dadvar et al., 2018). GABA in the brain is known to synergize with 5-HT circuits to regulate obesity and control appetite (Xia et al., 2021), and GABA

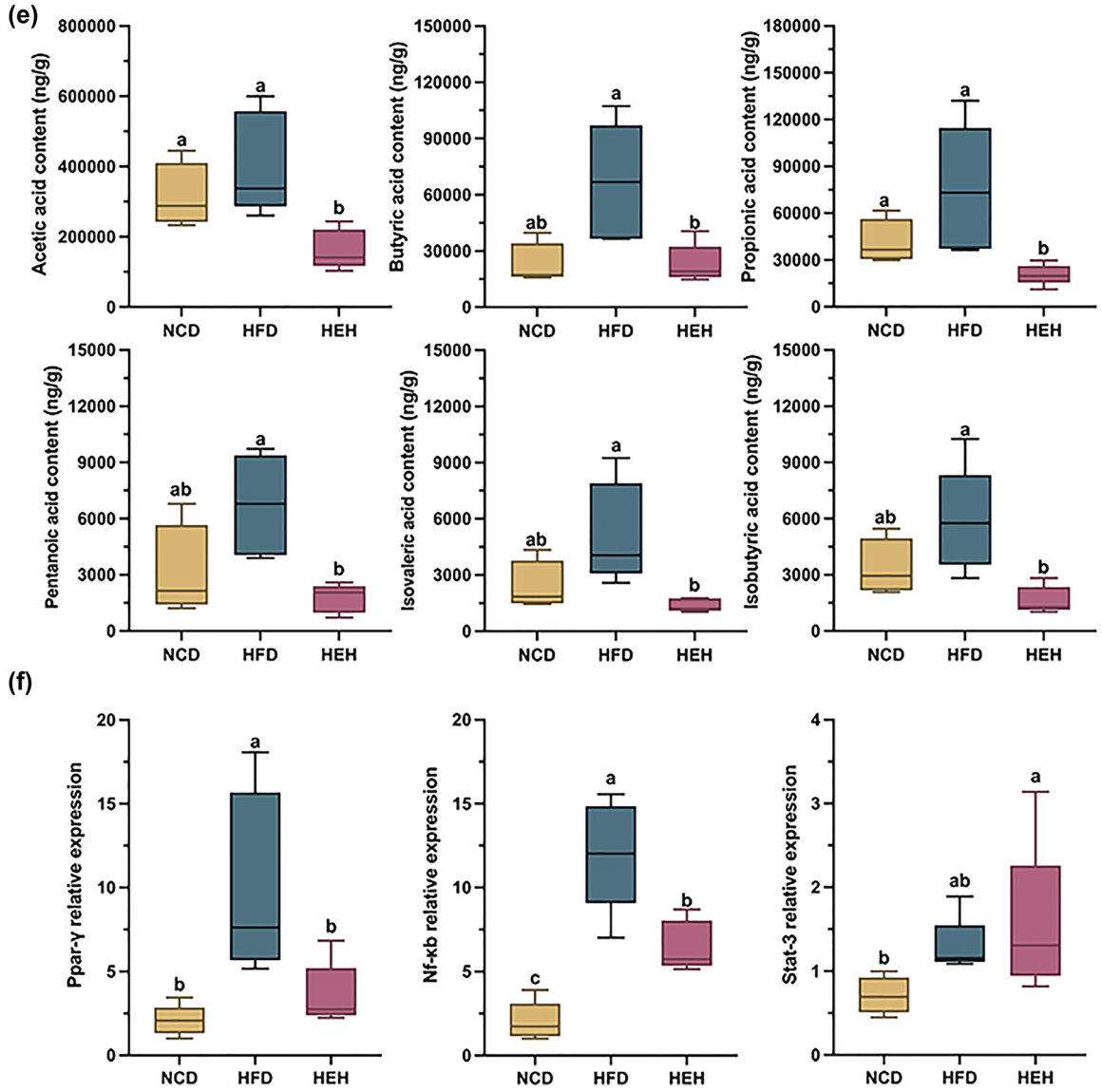

FIGURE 4 Continued

has also been reported to be associated with gut microbes under some neurological disorders (Zheng et al., 2019). This part of the experiment demonstrated that EGCG was related to the regulation of neurotransmitters associated with obesity and its complications in the hypothalamus. Besides, some plant polyphenols are known to maintain gut function and gut microbiota by modulating these neurotransmitters. For example, resveratrol has been reported to activate protein signaling between the gut and brain via the 5-HT signaling pathway, thereby resisting depression and abnormal bowel function (Yu et al., 2019).

Obesity is a systemic chronic low-grade inflammatory disease (Gregor & Hotamisligil, 2011; Rocha & Libby, 2009), and the release of intestinal inflammatory factors induced by HFD-induced obesity can cause intestinal dysfunction and damage to the intestinal wall (Birchenough et al., 2017; Rohm et al., 2021). Impaired intestinal barrier and immune homeostasis in HFD-induced obese mice trigger a series of alterations, such as the expression of inflammatory factors, related to lipid metabolism and inflammatory immunity, which can be seen as an early signal of obesity (Ding et al., 2010; Ghezzal et al., 2020). Meanwhile, inflammatory signals can be transmitted bidirectionally between the gut and CNS through multiple pathways, including blood, immune, and neural pathways (Agirman et al., 2021). Here, we found that EGCG may restore barrier damage and intestinal inflammation by inhibiting the expression of *Tnf-α*, *Il-1β*, and *Il-6* inflammatory factors and promoting the expression of *Il-10* cytokines in HFD mice.

Recent studies suggest that the correlation and synergy between CNS and gut may be achieved through the MGB regulation (Mayer, 2011), and SCFAs that are the products of microbial metabolism can target the brain directly through vagal stimulation or indirectly through immune-neuroendocrine mechanisms, thereby modulating central appetite and food reward signals (Dalile et al., 2019). Besides, research proved that compounds with high biological activity, such as polyphenols, can help modulate gut microbiota dysbiosis and

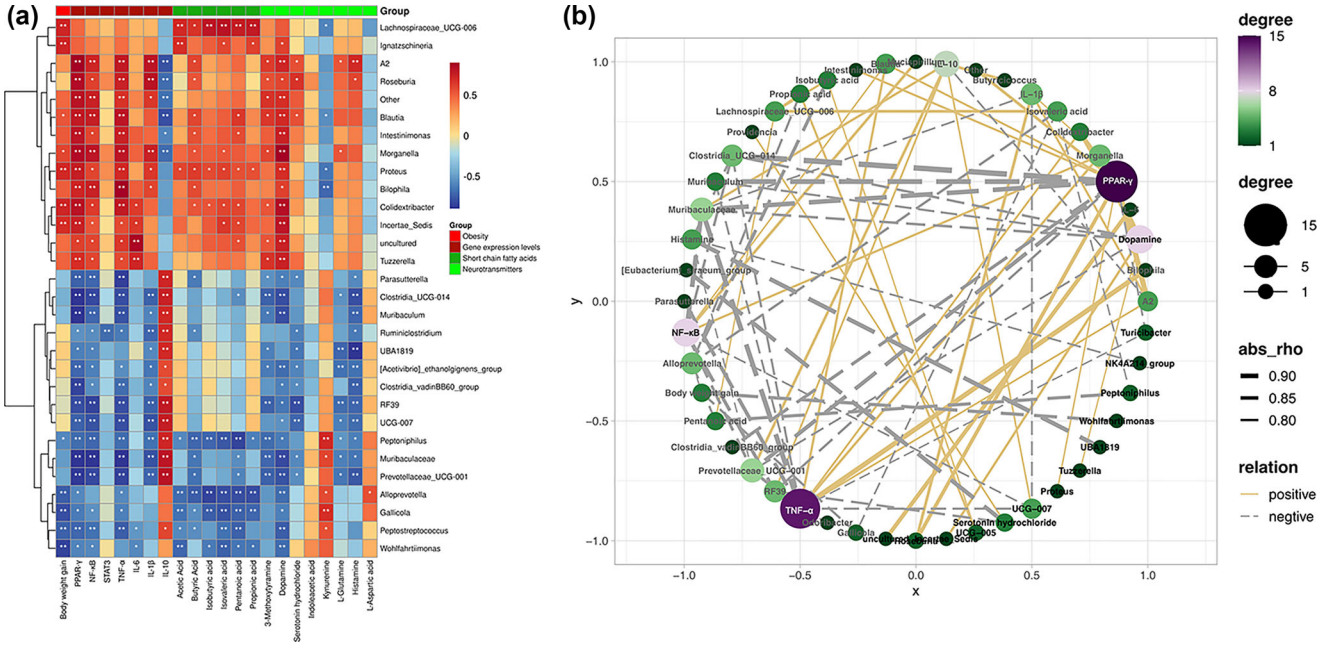

FIGURE 5 Correlation analysis (A) Spearman's correlation analysis of the top 30 abundance gut microbiota at the genus level with obesity traits, inflammatory factors, short-chain fatty acids (SCFAs), hypothalamic neurotransmitters, and transcription factors. The degree of red indicates that the relationship between them tends to be positively correlated. In contrast, the blue degree indicates that the relationship between them tends to be negatively correlated. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. (B) Network construction. The larger the area of the circle and the more purple the color, the more significant it is.

intervene the obesity (Choudhuri et al., 2022; Masumoto et al., 2016). For example, hesperidin was able to modulate gut microbiota in HFD mice to reduce intestinal inflammation and alleviate obesity (Lu et al., 2020), which implied EGCG might have a similar effect in gut microbial homeostasis. Gene sequencing results showed that EGCG gavage administration shaped the gut microbiota of mice by affecting both its diversity and composition. EGCG administration increased the ratio of Bacteroidetes and Firmicutes (B/F in the gut, which is thought to be drastically lower in obese individuals (Xu et al., 2012). *Alloprevotella*, which was the producer of SCFAs and the probiotics to resist inflammation and obesity (Guo et al., 2018; S. Li et al., 2021), remarkably enriched in EGCG administration mice. *Muribaculaceae* and *Bacteroides* that negatively correlated with obesity (Ye et al., 2021) were increased under the EGCG administration. According to the results of correlation analysis, *Blautia* is a momentous production of acetic and butyric acids (Aoki et al., 2021), which was found to have a positive correlation with most of the lipid metabolism-related parameters in mice induced by HFD (Chen et al., 2022; Lv et al., 2021) that might be the key microbe to increase SCFAs in our research. Genera such as *Muribaculaceae* and *Alloprevotella* mentioned above, showed a significant negative correlation with obesity-related parameters that suggest gut microbes may be crucial regulators and mediators in the gut–brain axis pathway to regulate the improvement of obesity and intestinal inflammation.

Furthermore, we focused on how EGCG affected the signaling communication between the gut microbiota and the CNS. SCFAs are important products of gut microbial metabolism, with the function of maintaining the integrity of the intestinal wall barrier and preventing intestinal inflammation, which are thought to mediate in the MGB interactions (Dalile et al., 2019). It has been shown that an increase in the ratio of Firmicutes and Bacteroides, the two main SCFA-producing microbial phyla in the HFD mice model, affects the concentration and ratio of acetic, propionic, and butyric acids in the gut; for example, HFD-induced obese mice may have significantly elevated levels of acetic acid in the body due to metabolic disturbances (Perry et al., 2016). Numerous studies have shown that plant polyphenols are able to influence the levels of SCFAs in the intestine and feces, such as capsaicin and quercetin (Freitas et al., 2022). Here, we found that EGCG administration changed the structure and abundance of gut microbiota to reduce the rise of total SCFAs in the gut of HFD-induced obese mice. We also examined the expression of several transcription factors in the gut. SCFAs in the gut are activators of several transcription factors (den Besten et al., 2015; Oh et al., 2019). The NF-κB signaling pathway is a major component of the human inflammatory and immune response and has been reported to be activated and produce inflammatory effects in the presence of excessive lipid accumulation (Chen et al., 2021). The PPAR-γ nuclear transcription factor is a major regulator of adipocytes and has been reported to be involved in adipocyte differentiation, lipid metabolism, and regulation of cellular inflammatory factors (Kurosaki et al., 2003; Marimuthu et al., 2022). In this study, EGCG ameliorated HFD-induced intestinal inflammation by inhibiting NF-κB and PPAR-γ activation through alteration of SCFAs. These two transcription factors have been shown to access the CNS via the circulation system, thus enabling signals and regulation between the gut–brain axis. As we speculated, in the subsequent correlation analysis we found that PPAR-γ might be a key transcription factor in the

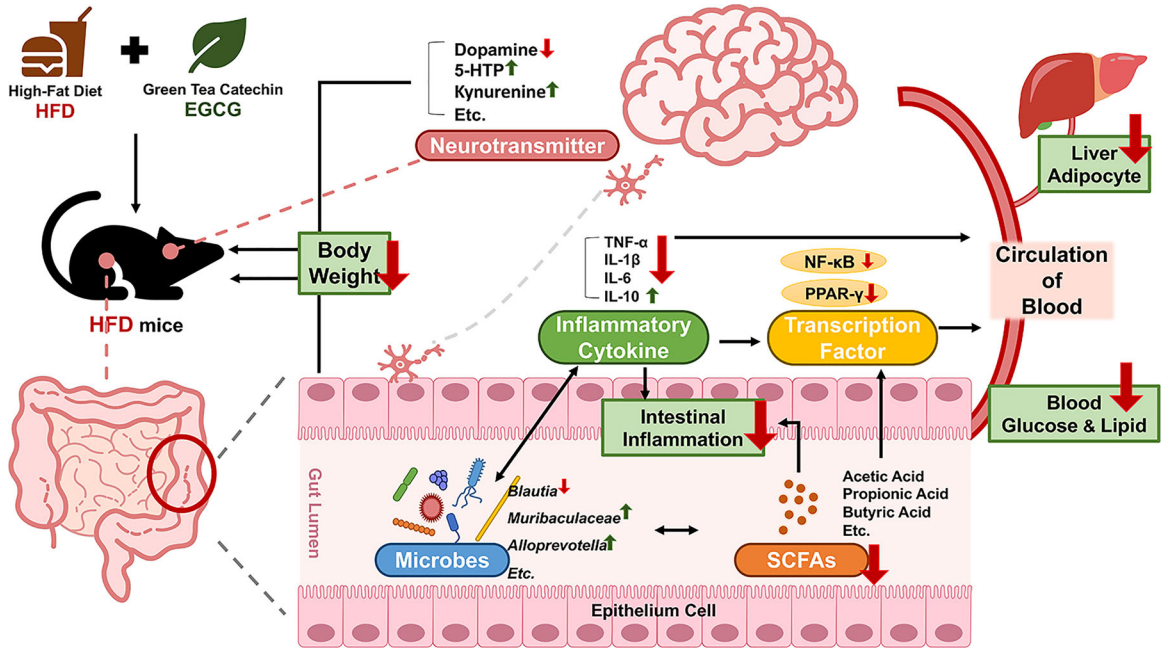

FIGURE 6 Schematic diagram showing the possible mechanisms of green tea catechin (−) -epigallocatechin-3-gallate (EGCG) alleviating high-fat diet (HFD)-induced obesity through the gut–brain axis.

gut–brain axis, and NF-κB with its activator TNF-α (Webb et al., 2016) also showed a strong correlation. These demonstrated that EGCG intervention in gut microbiota could reduce intestinal inflammation while achieving communication between the gut–brain axis through the release and delivery of relevant factors. Furthermore, dopamine played a role in the gut–brain axis pathway, which effectively confirmed our suspicion that EGCG could ameliorate HFD-induced obesity by affecting gut microbiota that transmitted signals to the CNS, based on existing studies that dopamine has an important function in obesity-related metabolism (Grippo et al., 2020; G.-J. Wang et al., 2001). The above analysis results provided evidence for how EGCG was involved in MGB regulation to achieve the anti-obesity effect.

5 | CONCLUSION

To summarize, in this study, the improvement in obesity-related parameters was strongly correlated with the abundance and structure of key gut microbiota, the level and proportion of gut SCFAs, the expression levels of inflammatory and transcription factors, and alterations in hypothalamic neurotransmitters, suggesting that gut–brain axis is a potential regulatory pathway for green tea EGCG in improving obesity and its induced inflammatory response, as shown in Figure 6. Upregulations of transcription factors PPAR-γ and NF-κB, expression levels of the neurotransmitter dopamine, and inflammatory factor TNF-α were considered to play a key role in the MGB regulation. Meanwhile, EGCG decreased the total amount of SCFAs, which might take a part in multiple regulatory pathways. The enrichment of *Alloprevotella* and *Muribaculaceae* and the decrease of *Blautia* provide favorable information for the mining of functional probiotics with the ability to improve intestinal inflammation and thus treat obesity. This study provided new evidence that green tea catechin EGCG could be used to combat obesity and improve gut health via the gut–brain axis, which revealed the positive role of green tea as a natural food and food supplement in alleviating obesity.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

ETHICS STATEMENT

All animal experiments have been approved by the Animal Care and Use Committee at Zhejiang University (ethic approval code: ZJU20210199) and conformed to the guidelines, following the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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