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Research Article

Beneficial effects of dietary herbs on high-fat diet-induced obesity linking with modulation of gut microbiota

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Abstract: Obesity, a pervasive global public health challenge, impacts human well-being, and there is a growing interest in the potential of herbs for their anti-obesity effects. However, the specific herbs that possess these properties are not well understood. This study aims to identify and characterize herbs that promote weight loss and to elucidate the mechanisms involved. We employed a high-fat diet (HFD)-induced obesity mouse model to assess the efficacy of various herbs in weight reduction and to explore how these herbs interact with the gut microbiota. By leveraging the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP), we identified active ingredients present in the herbs and analyzed their regulatory effects on the gut microbiota. Among the 65 herbs, inulin, mori follum, corn silk, maydis seigma, crataegus, taraxacum, portulacae herba, rhizoma gastrodiae, rose rugosae flos, thalluslaminariae were found to significantly reduce body weight and restore the gut microbiota dysbiosis associated with HFD-induced obesity. We found that *Blautia*, which was enriched by the anti-obesity herbs, was inversely related to triglyceride (TG) levels. Conversely, *Desulfovibrio*, reduced by the anti-obesity herbs, was a positively linked to weight and weight gain. Furthermore, we discovered that arachidonic acid, shared by three anti-obesity herbs, was associated with beneficial bacteria such as *Blautia*. Our study identified 10 herbs with anti-obesity properties, detailing their active constituents and their influence on the gut microbiota. Our finding not only identified nearly 10 herbs that significantly reduce body weight, but also contribute to improving the understanding of the regulatory network between herbs and the gut microbiota.

Keywords: herbs; gut microbiota; obesity; *Blautia*; arachidonic acid

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1 Introduction

Obesity has emerged as an urgent global public health concern, increasing the risk of chronic conditions such as cardiovascular disease, diabetes, and certain types of cancers[1,2]. This condition, characterized by the chronic body fat accumulation and disruptions in lipid, glucose, and protein metabolism, poses a significant threat to human health[3,4]. In recent years, diet-induced obesity has become increasingly prevalent due to lifestyle. Given the severe side effects associated with synthetic weight-loss drugs, there is an imperative to explore safe and efficacious biochemical alternatives for obesity treatment[5], which is why edible and medicinal plants have become a promising area of research for preventing and managing obesity. This study aims to explore the anti-obesity effects of various edible and medicinal plants, and to shed light on the mechanism behind their effectiveness by examining a range of herbs.

Edible and medicinal herbs have emerged as promising candidates for obesity prevention and management. For example, *Portulaca oleracea* L., commonly known as purslane[6,7], alkaloids, and flavonoids[8], that have shown potential in modulating metabolic pathway related to obesity and diabetes[8-11]. Similarly, extracts from corn silk and lemon balm have been demonstrated lipid metabolism-protective properties through activating sterol regulatory element-binding protein1 couples (SREBP-1c), emphasizing the need to explore the mechanisms behind these

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natural remedies[12]. Recent research underscores the close relationship between herbs, gut microbiota, and host metabolism[13-16]. Herbs have the potential to regulate metabolism by influencing the gut microbiome's composition and activity, thereby improving gut health[17-19]. The dysbiosis of gut microbiota and their related metabolites, including bile acids, trimethylamine, and short-chain fatty acids (SCFAs), have been confirmed to modulate the gut microbiota and contribute to participate in the relieving obesity. The gut microbiota's dysbiosis and its metabolisms, such as bile acids and short-chain fatty acids (SCFAs), are implicated in obesity progression, highlighting the microbiota's modulatory role[20]. It has been suggested that herbs are particularly effective in altering the gut microbiota to confer health benefits. Edible and medicinal herbs was reported to improve metabolic syndrome by modulating the gut microbiota and regulating metabolites including SCFA and bile acids[21, 22]. However, the specific active ingredients in herbs that are effectively alleviate obesity and their interaction with the gut microbiota are not yet fully understood. Therefore, it is necessary to conduct further research to gain a deeper understanding of this relationship.

In this study, we establish an HFD-induced obese mice model in order to investigate the obesity-ameliorating effects of various herbs. We identified herbs that alleviate obesity and metabolic syndrome and found that their beneficial effects are associated with the restoration of gut microbiota balance. Specifically, we found that these herbs increase the abundance of the beneficial bacteria like *Blautia*, which is negatively correlated with triglyceride (TG) levels, and decrease harmful bacteria, such as *Desulfovibrio*, which is positively associated with weight gain. Additionally, we highlight that arachidonic acid as a shared active ingredient in three anti-obesity beneficial herbs, associated with beneficial bacteria.

By exploring the intricate relationship between herbs, gut microbiota, and host metabolism, this study aims to enhance our understanding of herbal mechanism in obesity management and contribute to the development of safe and effective therapeutic agents.

2 Materials and methods

2.1 Experimental model and subject details

C57BL/6 WT male mice were purchased from Shanghai Model Organisms and were maintained under specific pathogen-free conditions. At 4-week-old of age, the mice were randomized into groups and fed one of three diets: a grain-based rodent chow (referred to as "chow"), a high-fat diet (HFD) or herb-supplemented HFD group. The chow diet contained 5% fat by weight (equivalent to 10%–15% of calories) and 15%–25% fiber, while the HFD was 35% fat by weight (contributing to 60% of calories) with 5% cellulose as a fiber source (Trophic Animal Feed High-tech Co., Ltd., China).

An herb-supplemented HFD group was also included, with herb added at a precise concentration calculated based on based on human-to-mouse equivalent dosages, following guidelines from the *Chinese Pharmacopoeia* (2010 edition). The detailed dosage information is provided in Table S1. In this study, each group consisted of six mice, ensuring adequate sample size and statistical power. Mice received herbs through their diet daily. After an 8-week experimental period, feces and blood were collected prior to euthanasia, followed by the collection of organs-including liver, spleen, kidney, and adipose tissue-for weight measurement and subsequent analysis (Fig. 1A). This study was approved by the BGI Animal Center Animal Ethics Committee (19058J).

2.2 Glucose measurement

Glucose tolerance testing was performed using Amplex Red Glucose/Glucose Oxidase Assay kit (Invitrogen, USA), following the manufacturer's instructions. Briefly, blood samples were collected from the mice, which were placed in a clean cage, provided with water, but fasted overnight (12 h). The collected blood sample were centrifuged at 3,000 r/min for 10 min to obtain serum. Serum glucose levels were measured using a colorimetric assay based on the glucose oxidase-peroxidase reaction. In brief, 10 μL of serum was added to 990 μL of the reagent mixture containing glucose oxidase, peroxidase, and 4-aminoantipyrine. The mixture was incubated at 37 °C for 20 min, and absorbance was measured at 540 nm using a Nova Max plus Glucose meter (Nova Biomedical, USA). A standard curve was generated using known concentrations of glucose ranging from 0 mmol/L to 20 mmol/L. Glucose concentration in the samples was determined by interpolation from the standard curve. All measurements were performed in triplicate, and the average value was used for statistical analysis. The coefficient of variation for intra-assay precision was less than 5%. Mice administered glucose, 2 mg/g body weight, and blood glucose levels measured 30, 60, and 90 min later. Data are expressed as mg/dL blood.

2.3 Assays for cholesterol, TG

Cholesterol and TG levels in serum were measured using kits (Shanghai Kehua Bio-engineering, China) according to the manufacturer's instructions. Briefly, serum samples were collected from participants after an overnight fast and centrifuged at 3,000 r/min for 10 min to obtain clear serum. A 10 μL volume of serum was added to a reaction mixture containing cholesterol oxidase, peroxidase, and 4-aminoantipyrine. The mixture was then incubated at 37 °C for 10 min. The absorbance was measured at 500 nm using a microplate reader (Bio-Rad, USA). A standard curve was generated using known concentrations of cholesterol ranging from 0 mg/dL to 20 mg/dL.

The cholesterol/TG concentration in the samples was determined by interpolation from the standard curve. All measurements were performed in triplicate, and the average value was used for statistical analysis.

The leptin concentration in the samples was determined using the ELISA kit (ML-G11308) according to the assay procedure.

2.4 16S rRNA gene sequence analysis

16S rRNA gene amplification and sequencing were conducted as described. Briefly, DNA was extracted from feces of C57BL/6 mice, which was collected at 10-week post diet initiation, using a PowerSoil-HTP kit (QIAGEN, USA). The region V4 of 16S rRNA genes was amplified by the primers listed in Table S1; The PCR product of each sample was combined and purified with Ampure magnetic purification beads (Beckman Coulter, USA). Products were then quantified using a Quant-iT PicoGreen dsDNA Assay Kit (Life Technologies, USA). The pooled products were quantified and sequenced by using an Illumina Miseq sequencer at BGI (Beijing Genomics Institute, BGI, Shenzhen, China). The sequences were demultiplexed, quality filtered using the Quantitative Insights into Microbial Ecology (QIIME 2, version

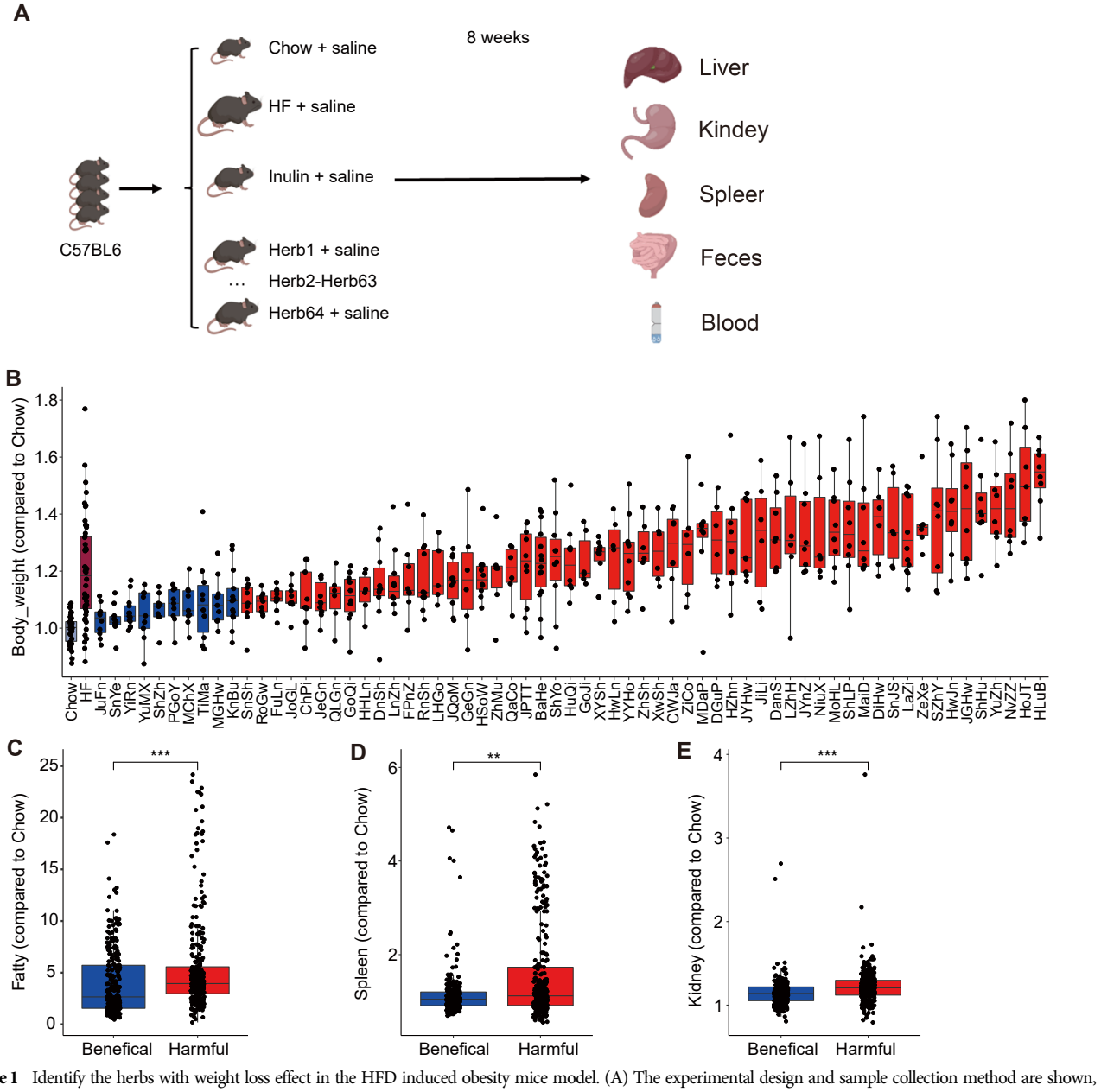

Figure 1 Identify the herbs with weight loss effect in the HFD induced obesity mice model. (A) The experimental design and sample collection method are shown, (B) Body weight for individual mouse in Chow group, HFD group, each herb group, (C-E) Fatty, spleen and kidney weights of the mice in the two group at the end of treatment.

2019.10) software package before analysis as previously described[23].

2.5 Statistical analysis

Statistical analyses were performed in R platform (version 4.0.1). To minimize the batch variation, we normalized the data to chow group within each batch and then compared the impact of each herb on weight loss and gut microbiota. The Shannon index was employed to compute the diversity of microbial communities in the samples. The Wilcoxon rank sum test was performed on alpha diversity index between groups to obtain the difference between different groups. Community composition dissimilarity is based on the Bray-Curtis dissimilarity metric. To further explore the microbial differences between the two groups, we applied the linear discriminant analysis effect size (LEfSe) method and found a total of 22 genus were significantly differentially enriched (linear discriminant analysis (LDA) score > 3.0, $P < 0.05$). 16 bacterial species were enriched in beneficial group and six bacterial species were enriched in harmful group. LEfSe analysis was performed using the LEfSe software (http://huttenhower.sph.harvard.edu/lefse/), and the default LDA score threshold was set to 3. Spearman's rank-based correlation test was performed on the herbs and gut microbiota, microbial species with clinical data. Heatmaps were generated using the pheatmap function of pheatmap R package. The Venn diagram was printed by UpSetR in R packages (version 1.4.0).

3 Results

3.1 Identifying herbs with weight-reducing effect

The diet induced obese (DIO) mice model is a widely used approach to evaluate the efficacy of anti-obesity compounds and therapies[5, 24-26]. In our study, we induced obesity in C57BL/6 mice

by feeding them a HFD for 4 weeks to evaluate the weight loss effects of various herbs. Prior to analyzing the weight loss effects of the herbs, we confirmed the success of the HFD mice model by examining obesity markers (Fig. S1). Mice fed an HFD displayed metabolic syndrome characteristics, such as increased body weight, fatty mass, and total cholesterol (TC) (Figs. S1A-S1C). Additionally, the gut microbial community of the HFD mice was altered (Figs. S1D-S1F). The alpha diversity of microbiota, calculated with the Shannon index, appeared to increase in HFD groups, although there was no significant difference (Fig. S1D). Using the Bray-Curtis dissimilarity metric, we measured the dissimilarity in bacterial community composition, findings greater dissimilarity between the Chow and HFD groups than within groups (Fig. S1E), suggesting that HFD's impact on gut microbiota composition. LEfSe analysis revealed that *Sutterella*, *Akkermansia*, and *Streptococcus* were significantly more abundant in the HFD group, while *Bacteroides*, AF12, and *Allobaculum* are more abundant in the Chow group (Fig. S1F), suggesting a negative correlation with obesity[27-31]. We conducted a comparative study between HFD-fed mice and those supplemented with herbal supplements to examine the weight loss effects of each herb. Among the 65 herbs screened, inulin demonstrated the strongest weight reduction effect (Fig. 1B). The herbs were categorized into beneficial and harmful groups based on their impact on weight loss. The 10 beneficial herbs significantly reduced body weight in HFD mice (Fig. 1B), while the harmful group showed a significant increase in fatty content, spleen weight, and kidney weight ($P < 0.05$, Figs. 1C-1E). No significant difference was observed in liver, heart, pancreas weight, or the peripheral blood index (Fig. S2). Collectively, these results indicate that 10 out of 65 tested herbs effectively reduced body weight and improved metabolic phenotypes in HFD mice, suggesting their potential for weight loss assistance.

3.2 The herbs restore the HFD-induced microbiota

Our study investigates the capacity of herbs to restore the gut microbiota altered by HFD in obesity and metabolic syndrome, which have been reported to be linked to alterations in intestinal microbiota composition in both mice and humans[32]. Ingestion of certain herbs was observed to significantly influence the abundance of various bacteria types, including those that produce beneficial anti-inflammatory and SCFA, as well as those that are proinflammatory and pathogenic[33-37]. In assessing the intestinal microbiota composition in both beneficial and harmful group, we calculated alpha diversity, a measure of richness and diversity within a microbial community and found that the bacterial alpha diversity of the beneficial group is significantly higher than that of the harmful group ($P < 0.01$) (Fig. 2A). This increase in alpha diversity indicates a healthier gut microbiota. Furthermore, we calculated the Bray-Curtis dissimilarity for all community distance matrices between groups and revealed that the beneficial herbs' microbiota community structure was more closely related to the chow group, serving as a healthy control, than that of the harmful herbs (Fig. 2B). This suggests that the beneficial herbs effectively counteracted the HFD-induced dysbiosis, restoring microbial diversity and community structure. In this study, taxonomic associations have been identified that distinguish bacteria enriched in either a beneficial group or harmful group. *Sutterella*, *Helicobacter*, *Slackia*, and *Clostridium* were significantly associated with beneficial individuals while *Streptococcus*, *Dorea*, *Erwinia*, and *Desulfovibrio* were linked to the harmful individuals (Fig. 2C). Notably, the HFD-induced obesity mice model showed increased relative abundance of both *Streptococcus* and *Sutterella*; however, beneficial herbs restored the relative abundance of *Streptococcus* while having no significant effect on *Sutterella*. In order to further investigate the bacterial clusters that are impacted by different types of herbs and clustered them using heatmap (Fig. 2D). We found distinct separations between three clearly defined clusters of bacteria, which were either positively or negatively correlated with obesity-related indicators. The beneficial group showed enrichment of *Oscillospira*, *Helicobacter*, *Sutterella*, *Blautia*, and *Ruminococcus*, while the harmful group was characterized by *Desulfovibrio*, *Streptococcus*, and *Dorea*[38]. The presence of *Blautia* and the absence of *Desulfovibrio* among the beneficial bacteria are particularly noteworthy, as they are associated with positive and negative impacts on weight loss, respectively. Additionally, Ruminococcus, negatively associated with weight gain in mice, which has been in the study[39]. These results underscore the potential of beneficial herbs to modulate the gut microbiota in ways that could mitigate obesity.

3.3 Distinct microbial signatures discriminate between beneficial and harmful herbs associated with obesity

In this study, we investigated the impact of herbal treatment on gut microbiota composition and their effect on obesity-relevant indicators. The gut microbiota functions as a metabolic organ, fermenting dietary substances and transforming host metabolites, such as bile acids and SCFAs, which are integral to the regulation of obesity. For instance, an inulin-supplemental diet has been shown to promote weight loss and decrease diastolic blood pressure, aspartate aminotransferase (AST) and insulinemia by decreasing Desulfovibrio and Clostridium level[40]. To explore the potential relationship between host obesity phenotypes and alterations in gut microbiota induced by herbal consumption, we performed a Spearman's rank-based correlation test on the intestinal microbes and clinical parameters. We observed numerous associations between changes in gut bacteria and biological variables, identifying two distinct cluster of bacteria positively or negatively correlated with indicators of obesity (Fig. 3A). Our results have shown that certain beneficial bacteria, such as *Blautia,* are negatively associated with the level of TG in the body. On the other hand, harmful bacteria, such as *Desulfovibrio*, have been found to be positively associated with weight and weight gain. The enrichment of *Streptococcus* in the harmful group was positively correlated with body weight gain and TC (Figs. 3B and 3C). *Streptococcus*, as the main oral genus, has been reported to have adverse effect in the gut. It carries the *vanB* antibiotic gene and can spread in the gut microbiota[41]. This bacterium was notably more abundant in the gut of the non-healthy aging cohort compared to the healthy aging cohort[42]. Conversely, several beneficial bacteria were negatively correlated with obesity indicators. For instance, *Sutterella*, was negatively correlated with fat mass (Fig. 3D), and *Rikenella* are negatively correlated with TC (Fig. 3E). *Rikenella* is found to be the dominant bacterium in the colon and cecum[43]. These findings are consistent with previous studies[39, 44], which also found a negative correlation between *Rikenella* and *Sutterella* with obesity. Additionally, we displayed the blood glucose level as "OGTT_AUC", an index closely correlated with the abundance of multiple species, as shown in Fig. 3A. Additionally, we compared the values of OGTT_AUC between the beneficial group and the harmful group. However, no significant differences were observed in this index between the two groups. Overall, these data

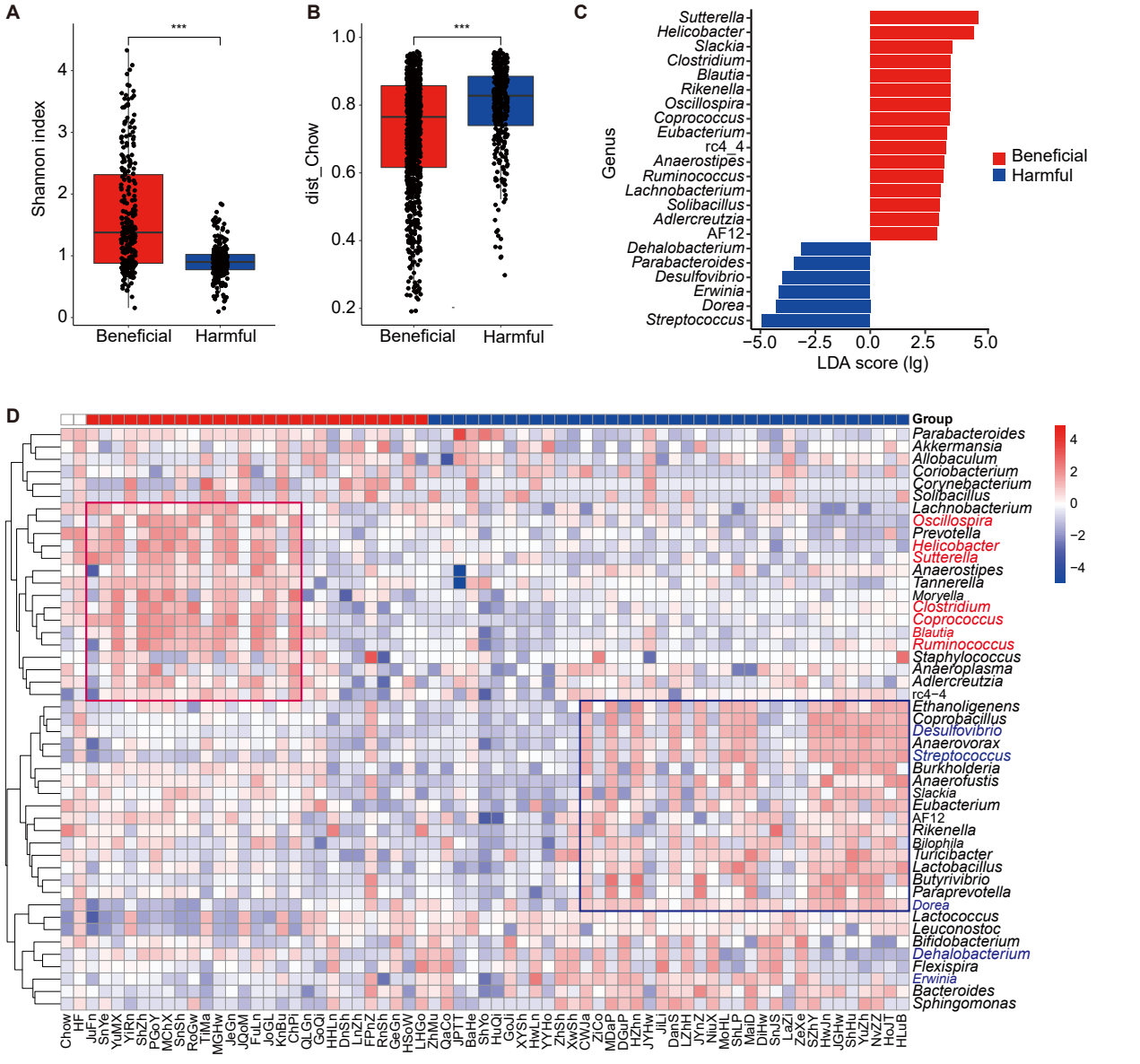

Figure 2 (A) Boxplot shows that Shannon index between different groups. The points indicate the microbiota of each sample, and the red box represent beneficial groups while blue box represents harmful groups, (B) Boxplot shows that the dissimilarity calculated by Bray-Curtis's distance between different groups. The points indicate the microbiota of each sample, and the dissimilarity was calculated by Bray-Curtis's distance, (C) LEfSe identify the bacteria that are significantly enriched in beneficial and harmful group, (D) Heatmap displays the abundance of bacteria in each herb's treatment experiment, with the rows that are scaled and clustered using Euclidean distance measurement. The color of the space ranges from red to blue. Redder spaces indicate a greater lg value of the relative abundance of bacteria in the group, indicating that the bacteria are more enriched in this herb's treatment group.

collectively demonstrate that herbal-induced alterations in the gut microbiota have distinct implications for obesity.

3.4 The active ingredients target the gut microbiota

Elucidating the bioactive ingredients of herbs is crucial for understanding their therapeutic effects. To link these components with the modulation of gut microbiota, a comprehensive analysis of the bioactive ingredients in herbs was conducted using Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP). Additionally, we performed a meta-analysis of the regulatory effects of herbs on intestinal microbiota, as reported in previous studies.

Based on our findings, only 10 out of 65 herbal medicines are found to be effective in reducing HFD-induced obesity. Given the intricate composition of herbal medicines, pinpointing specific bioactive ingredients is crucial for enhancing their therapeutic potential and applicability. We compiled data on 48 herbs out of 65 tested herbs in this study, identifying 4,685 pieces of ingredients information. We then screened these ingredients for oral bioavailability (OB, which is greater than 30%) and drug-likeness (DL, which is greater than 0.18), resulting in 715 pieces of information from 47 herbs. Utilizing a Venn diagram, we identified the common and unique components among the beneficial group and harmful groups (Figs. 4A-4B). While herbs predominantly contain unique active ingredients, arachidonic acid was shared by three beneficial herbs: Thalluslaminariae, Portulacae Herba, and Mori Follum. Additionally, quercetin, β-carotene, and β-sitosterol were shared by Portulacae Herba, Rose Rugosae Flos, and Mori Follum (Fig. 4A). In contrast, only β-sitosterol was the only common ingredient in the harmful group (Fig. 4B), highlighting its dual presence in both beneficial and harmful herbs.

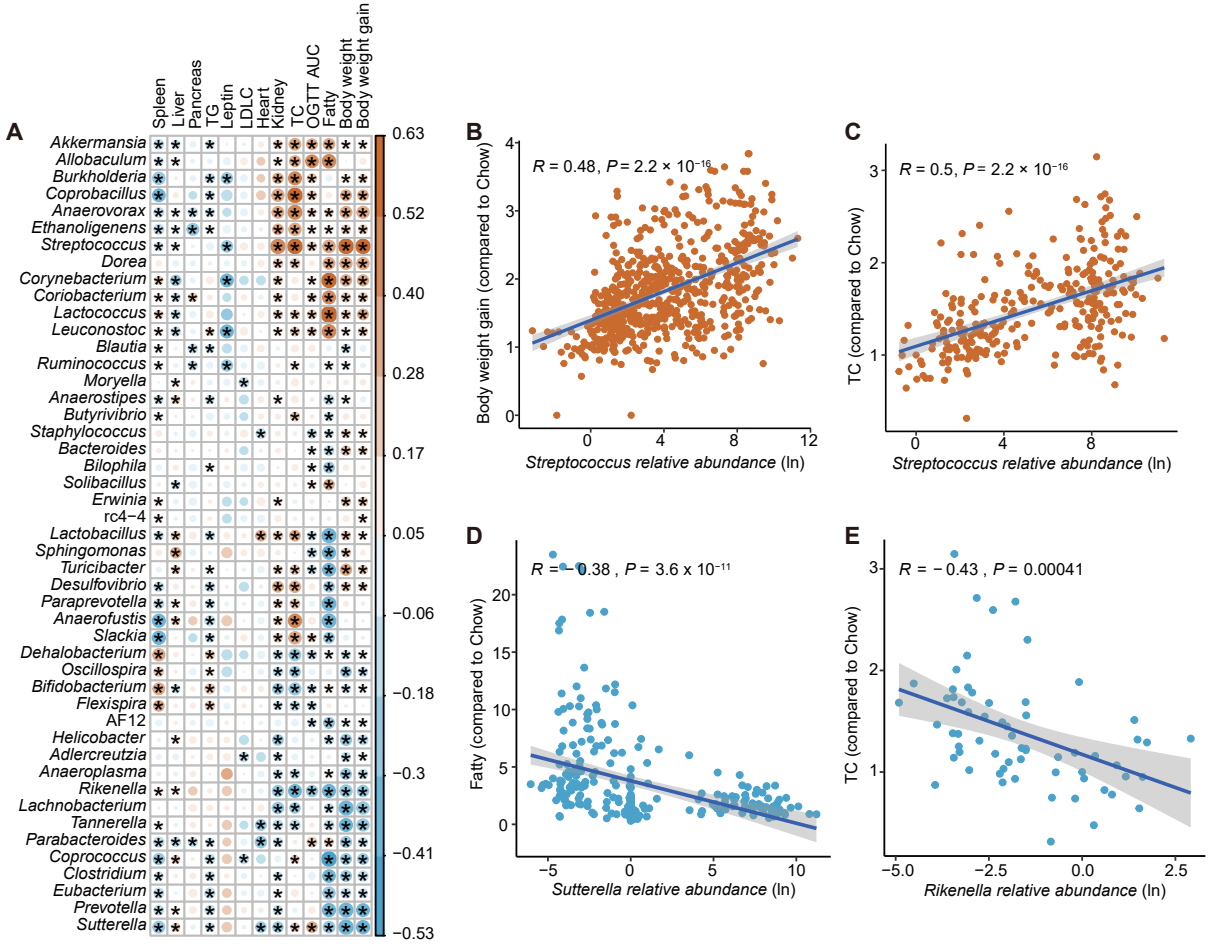

Figure 3 (A) The heat map shows the Spearman correlation between microbial species with clinical data. Orange values indicate species were positively correlated with clinical data, while blue ones indicate the species were negatively correlated with clinical data. Significant associations (adjusted $P < 0.05$) are indicated by asterisk, (B) Spearman's test showed that the relative abundance (lg) of *Streptococcus* was positively correlated with body weight gain, (C) Spearman's test showed that the relative abundance (lg) of *Streptococcus* was positively correlated with the level of TC, (D) Spearman's test showed that the relative abundance (lg) of *Sutterella* was negatively correlated with the content of fatty in the mice model, (E) Spearman's test showed that the relative abundance (lg) of *Rikenella* was negatively with the level of TC.

Despite advances in network pharmacology elucidating the targeting mechanisms of bioactive ingredients, their regulatory relationship with the gut microbiota remains largely unexplored. To bridge this knowledge gap, we reviewed 85 studies examining interactions between 303 different bacteria and 96 herbs, constructing a network that delineates these regulatory relationships. Our study reveals that various herbs regulate multiple genera of bacteria, with beneficial herbs promoting the growth of beneficial bacteria like *Blautia*, positively regulated by Panax Ginseng (RnSh) and Radix Puerariae (GeGn), while harmful herbs increase the abundance of detrimental bacteria such as *Streptococcus*, negatively regulated by Hedysarum Multijugum Maxim (HuQi) and Rehmanniae Radix Praeparata (DiHw) (Fig. 4C).

Together, our data not only identify the bioactive ingredients in beneficial herbs but also suggest their modulatory role on the gut microbiota, providing a foundation for further research based on both database information and published studies.

4 Discussion

In this study, we identified 10 herbs from a pool of 65 that effectively reduced body weight in an HFD-induced obesity mouse model. These beneficial herbs not only induced body weight loss but also decreased fat content and organ weights, suggesting an improvement in metabolic health. The beneficial herbs increased gut microbial diversity within the beneficial group aligns with the notion that a diverse gut microbiota is crucial for a stable and functional ecosystem. This finding is particularly significant given the established link between herbs, overall health, and gut microbiota.

The HFD-induced obesity mouse model used in our study is well-established for its ability to mimic the metabolic disruptions associated with human obesity. We employed this model to screen herbs for weight loss properties and found that the beneficial herbs counteracted the HFD-induced dysbiosis, potentially by modulating the composition of gut microbiota and gene expression, which are known to influence lipid absorption and metabolism[45]. This disruption causes more fat to enter the terminal ileum, which inhibits the lipid absorption of epithelial cells through the CD36-mediated[46]. Obesity is not simply defined by an excess of adipose tissue, but also by an increase in the masses of other organs and tissues that are closely related to metaboli[47]. It is a low-inflammatory metabolic disease that poses a risk factor for chronic kidney disease[48]. The spleen, an important organ for lipid metabolism and immune cell selection, also plays a role in obesity. Spleen-derived interleukin (IL)-10 is present in

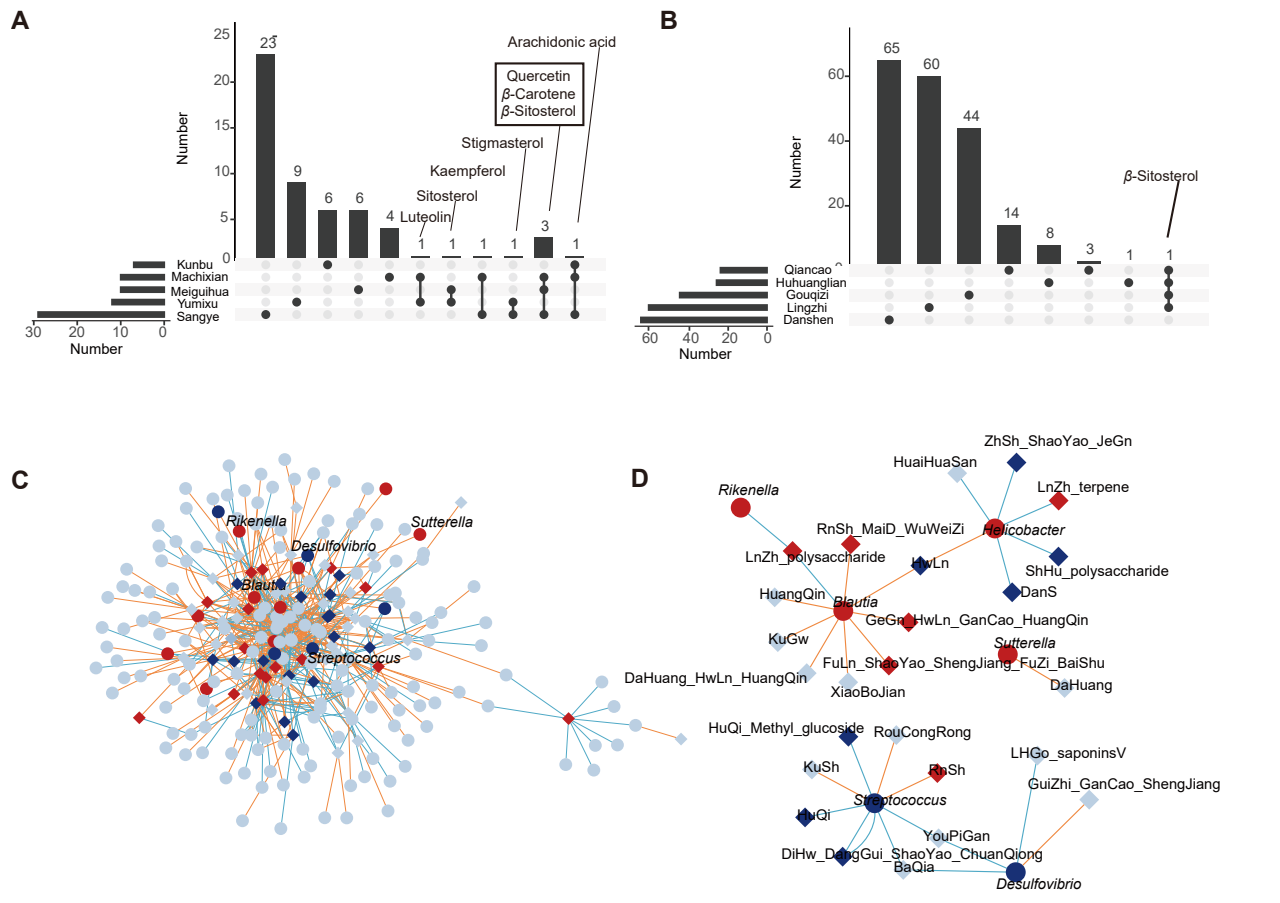

Figure 4 (A-B) Venn diagram for the components of these herbal medicine from beneficial group and harmful group, (C-D) The association between herb and bacteria microbiota. The circle represents the microbiota, the diamond represents the herb; the dark blue represents the harmful group, and the red represents the beneficial group; the orange line represents the positive correlation, and the blue represents the negative correlation.

obesity and reduces other cytokines in the spleen, which counteracts obesity-induced hypo-inflammation[49]. Our data show that spleen weight was increased in the HFD-induced obesity mice model.

Obesity has become a significant global health concern, resulting from overnutrition and excess body weight[50]. Research has shown that the dysbiosis of gut microbiota plays a critical role in the development of diet-induced obesity[51,52]. Shifts in the gut microbiota are associated with HFD-induced obesity, which can affect the development and progression of chronic metabolic diseases through altering circulating metabolites and hormones[53-56]. The metabolic health of the host is influenced by the gut microbiota through the production and transformation of various metabolites and molecules. These metabolites and molecules include SCFA, bile acids, endogenous cannabinoids, trimethylamine N-oxide (TMAO), lipopolysaccharides (LPS), and other pathogen-related molecular patterns, as well as bacterial proteins such as Amuc_1100, 12-HETE, along with fructose lysine and imidazole propionic acid. These molecules interact with different host cell receptors, including Toll-like receptors (TLRs), PPARα/γ, aryl hydrocarbon receptor (AhR), G protein-coupled receptors (GPR) (such as GPR41/43/119 and the G-protein-coupled bile acid receptor (TGR5)), and endogenous cannabinoid receptors. Through this interaction, they can regulate host signaling pathways and impact physiological functions such as intestinal environment, intestinal barrier, and intestinal hormone secretion[57-59]. The microbiota exhibits a high degree of plasticity and is considered a crucial variable factor in the development of obesity and diabetes. Modulating the gut microbiota has been shown to target pathways involved in the pathogenesis of diet-induced obesity[56]. Studies have indicated that several *Blautia* species were linked to obesity, insulin resistance, and fecal levels of inflammatory cytokines[60]. In addition to *Blautia*, recent studies have shown that *Parasutterella* sp. also play a significant role in the development of type 2 diabetes and obesity through involving the dietary carbohydrate-microbiota-host metabolic axis. Specifically, the metabolism of *L*-cysteine may be linked to the development of type 2 diabetes, while the connection to the fatty acid biosynthesis pathway is associated with weight gain from a carbohydrate-rich diet in the development of obesity[61]. These two genera were found to be enriched in the beneficial group in our study, which were consistent with these previous reports. In addition, some other genera were significantly associated with obesity. For example, *Akkermansia*, *Oscillibacter*, *Intestinimonas*, and *Alistipes* bacteria were significantly reduced in obesity; while *Faecalibacterium prausnitzii* bacteria, which has anti-inflammatory functions, was also greatly reduced in obese people[62]. Recent studies have shown that the metabolites produced by the gut microbiota can have an impact on host metabolism and obesity. For example, Shulman and his team have observed that acetate, a SCFA, stimulates insulin secretion in obesity mice models. Additionally, the researchers compared the effects of acetate to other SCFAs and found that a higher level of acetate was in rodents fed a HFD. They also noted that the infusion of acetic acid stimulated insulin secretion from β cells in the pancreas[63]. Despite this finding, the precise mechanism

responsible for this effect requires further investigation.

The popularity of dietary supplements underscores the demand for non-pharmacological obesity intervention. Recent studies have shown that certain herbs have been found to play a crucial role in reducing the absorption of lipids and carbohydrates by inhibiting digestive enzymes, such as lipase, α-amylase, and α-glucosidase, thereby leading to weight loss. These findings suggest that herbs could show promise as potential candidates for obesity reduction. However, it is important to note that the weight loss effects of different herbs may vary due to their various compositions. Therefore, we examined 65 herbs and screened 10 out of 65 showed significant potential in reducing body weight in mice with HFD-induced obesity in this study. There findings suggest that these 10 herbs could be promising candidates for weight loss. Various herbal bioactive ingredients, such as polysaccharides[34, 64, 65], polyphenols[24, 26] and saponins[66], have been found to possess anti-obesity functions[65, 66]. Resveratrol (RSV), a natural polyphenol, has also been found to have anti-obesity effects by regulating the composition and metabolic function of the gut microbiota. Specifically, RSV increase the abundance of *Blautia* while decreasing the abundance of *Desulfovibrio* and Lachnospiraceae_NK4A136_group. In addition, the gut microbiota metabolizes RSV into 4-hydroxyphenylacetic acid (4-HPA) and 3-hydroxyphenylpropionic acid (3-HPP)[38], which contribute to improving lipid metabolism and are associated with the intestinal oxidative state. In this study, we identified that arachidonic acid is shared by three beneficial herbs: *Thalluslaminariae*, *Portulacae Herba*, and *Mori Follum*. In fact, recent studies have reported that arachidonic acid collaborates with T cell-derived interferon (IFN-γ) to induce immunogenic ferroptosis in tumors which sheds light on the roles of AA in novel mechanism of $CD8^+$ T cell-mediated tumor killing and the induction of ferroptosis in tumor cells[67, 68]. Interestingly, the arachidonic acid metabolism was changed by HFD in the obesity mice model through the gut microbiota[69]. Thus, we can assume that the lipid-lowering effects of beneficial herbs may be attributed, at least partially, to the bioactive ingredient, arachidonic acid metabolism pathway, which appears to be mediated by intestinal microbiota, such as *Blautia* and Ruminococcaceae_UCG-005. Gut microbiota is crucial in the converting various herbal compounds, such as carbohydrates, proteins, lipids, and non-nutritive small chemical compounds, into metabolites that can have either beneficial or harmful effects on human health[14, 70]. Reciprocally, herbs have a significant impact on the composition of the gut microbiota[21]. Both changed in microbiota and the use of transformed herbs may contribute to alleviate obesity. Research has shown that *Blautia* and Ruminococcaceae are mostly associated with obesity. Further detailed analyses have indicated that the abundance of potentially beneficial and harmful bacteria can be differentially affected by the ingestion of different herbs[34, 37]. Recent studies have shown that a variety of herbal components can influence microbial abundance and diversity, which is closely related to the efficacy of herbs. For example, polysaccharides purified from *Ganoderma lucidum* and *Hirsutella sinensis* mycelium significantly reduced obesity[33, 34]. Mulberry fruit polysaccharides also influenced obesity and modulated gut microbiota[64]. Further research is needed to confirm the effect of beneficial bioactive ingredient on the weight loss, which can be used as prebiotics in the clinics.

5 Conclusion

In conclusion, our study provides evidence that select herbs can modulate the gut microbiota and reduce body weight in HFD-induced obesity mice. The beneficial herbs not only reduced body weight but also restored the gut microbiota, suggesting a potential therapeutic role in obesity management. The identification of bioactive ingredients and their impact on the gut microbiota offers a foundation for further research and the development of novel obesity treatment strategies.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

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