Gut Microbiota: Therapeutic Targets of Ginseng Against Multiple Disorders and Ginsenoside Transformation

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Panax ginseng, as the king of Chinese herb, has significant therapeutic effects on obesity, type 2 diabetes mellitus, fatty liver disease, colitis, diarrhea, and many other diseases. This review systematically summarized recent findings, which show that ginseng plays its role by regulating gut microbiota diversity, and gut microbiota could also regulate the transformation of ginsenosides. We conclude the characteristics of ginseng in regulating gut microbiota, as the potential targets to prevent and treat metabolic diseases, colitis, neurological diseases, cancer, and other diseases. Ginseng treatment can increase some probiotics such as Bifidobacterium, Bacteroides, Verrucomicrobia, Akkermansia, and reduce pathogenic bacteria such as Deferribracters, Lactobacillus, Helicobacter against various diseases. Meanwhile, Bacteroides, Eubacterium, and Bifidobacterium were found to be the key bacteria for ginsenoside transformation in vivo. Overall, ginseng can regulate gut microbiome diversity, further affect the synthesis of secondary metabolites, as well as promote the transformation of ginsenosides for improving the absorptivity of ginsenosides. This review can provide better insight into the interaction of ginseng with gut microbiota in multiple disorders and ginsenoside transformation.

Keywords: ginseng (Panax ginseng C.A. Meyer), gut microbiota, multiple disorders, gisenoside transformation, ginsenoside

INTRODUCTION

Panax ginseng C. A. Meyer (ginseng), called the king of herbs, has become one of the most popular Chinese herbal medicines in the world. It is widely used to treat various diseases (Ratan et al., 2021) and regulate human health (Fan et al., 2020). Moreover, ginseng also has high production value. According to statistics in 2016, China’s Ginseng output reached 28,900 tons, creating an output value of $7.5 billion for
the ginseng industry in Jilin Province, ranking the first position (Li et al., 2019). In recent years, a variety of active ingredients have been isolated and identified from ginseng, mainly ginsenoside, polysaccharide, volatile oil, amino acid, polyacetylene, alkaloid, as well as a small amount of salicylic acid amine, organic acid, nonsaponin water-soluble glucoside, maltol and its derivative glucoside (Liu et al., 2020). Polysaccharides, as one of the main components of ginseng, have the functions of immunomodulation, anti-tumor and anti-diabetes (Zhao et al., 2019). Amino acids in ginseng can enhance immunity, promote cell growth, proliferation and angiogenesis (Sah et al., 2021). Polyacetylene can significantly inhibit the proliferation of cancer cells and lipid peroxidation, improve memory (Al-Hazmi et al., 2015) and anti-inflammatory (Jin et al., 2021). Alkaloids have the functions of radiation protection, anti-diabetic (Chen et al., 2019) and anti-tumor (Ajeblı, 2021; Xu et al., 2021). The volatile oil in ginseng has the effects of antioxidation and liver protection (Bak et al., 2012). Ginsenoside is the most extensively studied active ingredient at this stage and has been considered as the main components of pharmacological action (Guo et al., 2021), such as anti-tumor (Kim et al., 2016), anti-inflammatory (Han and Kim, 2020), antioxidant, inhibition of apoptosis (Zheng et al., 2018). There are other trace components in ginseng, but they are not the main active components.

At present, it has been found that ginseng contains a variety of non-widespread initial ginsenosides, however, it does not have good biological activity, but after the processing and transformation of gut microbiota, it is found that there are 289 kinds of ginsenosides (including free ginsenoside) and their biological activities were significantly improved (Li et al., 2022). Although ginseng has many biological effects, the mechanisms of the pharmacological effect and its metabolic process in vivo have not been fully explained. In recent years, multiple studies have shown that the effect of ginseng is closely related to the role of gut microbiota (Pan et al., 2019; Santangelo et al., 2019), and gut microbiota is also the main tool for ginsenoside transformation (Kim, 2018).

Human microbial community is a complex ecosystem, in which the microbial community in the intestine has the largest scale and the most species (Tan et al., 2020). There are as many as 100 trillion microorganisms in human intestine, which are composed of at least 1,500 genera and 50 different phyla (Robles-Alonso and Guarner, 2013). In the long process of evolution of gut microbiota, through individual adaptation and natural selection, the microbiota of different species, microbiota and host, microbiota and host environment are always in a state of dynamic balance, forming an interdependent system. More and more evidences show that gut microbiota plays a key role not only in the metabolism of nutrients and drugs and the absorption of fat in the diet, but also in the regulation of immunity, physiology, metabolism, and health maintenance (Xi et al., 2021; Zhang et al., 2021). Besides, intestinal microorganisms could affect multiple tissues and organs, such as intestinal cells, liver, adipose tissue, brain, and muscle. These extensive studies about intestinal microbiota have made great progress in both humans and animals. As an example, specific changes in microbiota composition are associated with various diseases (Cani et al., 2021). For example, the ratio of Firmicutes to Bacteroidetes is increased in obese patients, while it is decreased in enteritis patients (Stojanov et al., 2020). Meanwhile, many treatments have targeted gut microbiota, which have found that probiotics are a potential treatment option for different diseases, such as Alzheimer's disease (Ji and Shen, 2021). Therefore, gut microbiota has been considered as potential targets for the prevention and treatment of various diseases.

Currently, there are a few reviews for summarizing the regulation of ginseng on gut microbiota in a series of diseases and the biotransformation of ginsenosides by gut microbiota. In our review, we searched and summarized the recent publications that ginseng could treat various diseases through the regulation of gut microbiota, including obesity, type 2 diabetes mellitus (T2DM), liver diseases, diarrhea, colitis, and others. Moreover, we summarized the gut microbiota affected by ginseng in the treatment process, and the transformation process of ginsenosides under the action of gut microbiota. By the relevant reports on ginseng and gut microbiota, it reveals new potential targets, intestinal microbiota for ginseng in the prevention and treatment of a variety of diseases and provides new insights into the future research direction, intestinal microorganisms as potential targets of ginseng.

## GINSENG TREATS VARIOUS DISEASES BY REGULATING GUT MICROBIOTA

### Obesity

Obesity is a global health problem (Safaei et al., 2021). Many chronic diseases associated with obesity, such as diabetes, cardiovascular disease and non-alcoholic fatty liver disease which are the main causes of human death (Hu et al., 2017). At present, the studies have found that gut microbiota is a necessary condition for the progress of obesity. Transplanting the microbiota of obese mice into healthy mice can induce obesity in healthy mice. At the same time, the activation and accumulation of fat by gut microbiota have been gradually revealed (Crowesy et al., 2020; Liu et al., 2021). Ginseng extract could also induce Enterococcus faecalis to produce unsaturated long-chain fatty acids and myristic acid has good effect on activating brown fat, promoting the production of beige fat, and reducing the body weight of obese mice (Quan et al., 2020). Firmicutes can promote energy absorption and fat accumulation (Orbe-Orihuela et al., 2018), and Bacteroides can regulate bile acid metabolism, reduce the level of inflammation, and inhibit fat accumulation in obese hosts. The ratio of Firmicutes to Bacteroidetes also plays an important role in the process of obesity (Gibiino et al., 2018). At present, ginseng extract, red ginseng extract, and the combination of ginsenoside Rb1 with salvianolic acid B have been proved to reduce weight and lipid by decreasing the ratio of Firmicutes to Bacteroidetes (Zhou et al., 2020; Bai et al., 2021; Lee et al., 2021). Meanwhile, ginseng treatment for 28 days can also up-regulate Bacteroides, Parabacteroides, and
Lactobacillus probiotics to reduce the abundance of bacteria that can induce obesity, such as Firmicutes, Deferribactera, Helicobacter in obese hosts. Monascus fermented ginseng can reduce the ratio of Firmicutes to Bacteroides in the intestinal tract of HFD rats, further to decrease the relative levels of sterol regulatory element binding protein-2 (SREBP-2) and hydroxymethylglutaryl-CoA (HMG-CoA) reductase, and increase the expression of CYP7A1 to improve lipid level of total cholesterol (TC) in blood and liver against metabolic disorder (Zhao et al., 2021). The microbiota structure in obese hosts might be the pathogenic factor, but ginseng can help the body return to the normal metabolic level and lose weight by improving this unbalanced microbiota structure. In obesity animal models, Firmicutes, Bacteroidetes, Lactobacillus, and Helicobacter may be potential targets for ginseng in the treatment of obesity (Table 1). Meanwhile, relative studies have found ginseng could reduce the body weight, blood lipid, blood glucose, and inflammatory level, as well as can significantly improve the structure of gut microbiota in obese patients (Table 2) (Song et al., 2014; Seong et al., 2021).

**Type 2 Diabetes Mellitus (T2DM)**

T2DM is a complex disease, which is characterized by hyperglycemia and its complications mainly caused by insulin resistance (Del Prato and Chilton, 2018; Himanshu et al., 2020). In recent years, it has been found that the disorder of gut microbiota is an important factor in the occurrence and development of T2DM (Canfora et al., 2019). For example, the ratio of Firmicutes and Bacteroidetes is generally relatively high in the T2DM hosts (Perry et al., 2016). Current results have confirmed that ginseng plays a role in improving blood glucose level and insulin sensitivity in patients with T2DM (Gui et al., 2016). It proved that the treatment with ginsenoside T19 in C57BL/6 mice model induced by high-fat diet combined with streptozotocin could exert therapeutic effect for treating T2DM by reducing the relative abundance of pathogenic bacteria such as Coprobacillus and decreasing the ratio of Firmicutes and Bacteroidetes, as well as enhancing the relative abundance of probiotics such as Bacteroidetes (Xu et al., 2020). Ginsenoside Rg5 can also reverse the disordered gut microbiota, alleviate metabolic endotoxemia, repair intestinal barrier, inhibit nuclear factor kappaB (NF-κB) and other related inflammatory pathways to improve T2DM of Db/Db mice (Wei et al., 2020). Besides these ginsenosides, the combination of red ginseng, Aronia, Shiitake mushroom, and Nattokinase and Buzhong Tongluo decoction including Astragalus membranaceus, Dioscorea hemsleyi, Salvia miltiorrhiza, Scrophularia ningpoensis, Ophiopogon japonicus, Panax ginseng, Fritillariae cirrhosae, and Whitmania pigra Whitman have been proved to be able to up-regulate Bacteroides, Lactobacillus, Akkermansia probiotics, reduce the abundance of bacteria causing hyperglycemia, such as Helicobacter, Flavonifractor, and reduce the ratio of Firmicutes and Bacteroidetes, thus play their hypoglycemic effects (Yang et al., 2018; Zheng et al., 2020). In another disorder, metabolic syndrome, the powder from Korean red ginseng (KRG) has a good therapeutic effect, and its mechanism might be related to the improvement of the disorder of lipid metabolism (the reductions of TC and low-density lipoprotein, LDL) by increasing the relative abundance of Bacteroides and reducing the relative abundance of Firmicutes and Proteobacteria (Seong et al., 2021). Most studies show that ginseng can correct the abnormal metabolic level in the body by reversing the ratio of Firmicutes and Bacteroidetes. However, in the experiment of T2DM rat model treated with ginseng polysaccharide combined with Rb1, the ratio of Firmicutes and Bacteroidetes were increased after the treatment, which finally reduced the blood glucose level and increased β-glucosidase activity (Li et al., 2018). As same as most medical treatment, the ratio of Firmicutes and Bacteroidetes could be decreased, verse originally elevated in the pathological model. This change of gut microbiota could reduce the body's energy intake and improve the level of glucose and lipid metabolism. However, this ratio was increased after treatment with polysaccharide and Rb1 in the above research. The original author did not make a targeted explanation. We speculate that it may be related to the state of the model, but the specific reason remains to be further revealed.

Therefore, the disordered gut microbiota is the inducer of T2DM, but ginseng can reverse the structures of disordered gut microbiota to restore the glucose metabolism and improve the disorder of glucose and lipid metabolism, ultimately inhibit the development of T2DM (Table 1).

**Fatty Liver Diseases**

Non-alcoholic fatty liver disease (NAFLD), a gradually serious health problem worldwide, is a chronic and multi-factorial cause of liver disease (Younossi et al., 2016), which is often observed in patients with obesity, dyslipidemia and diabetes, and manifesting as hepatic steatosis (Polyzos et al., 2019). Pathogenic causes of fatty liver diseases include insulin resistance, hepatic lipid metabolism disorder, inflammation, genetics, and other factors (Friedman et al., 2018). In addition, the studies have found that the gut microbiota is able to influence hepatic lipid metabolism as well as the balance of pro-inflammatory and anti-inflammatory factors in the liver. Therefore, the gut microbiota has been a potential target for the prevention and treatment of NAFLD (Kolodziejczyk et al., 2019). Ginseng is widely used in metabolic diseases and also has a significant effect on the improvement of NAFLD (Roh et al., 2020; Yoon et al., 2021; Gu et al., 2021). Another study of ginseng extract treatment for fatty liver mice induced by high-fat diet demonstrated that ginseng could reverse the structure of disturbed gut microbiota to inhibit the levels of sterol regulatory element binding protein-1c (SREBP-1c), fatty acid synthetase (FAS), and acetyl-coenzyme a carboxylase 1 (ACC-1), and increase carnitine palmityl transferase 1A (CPT-1a) expression to alleviate hepatic lipid accumulation and suppress NF-κB/I-kappa-B (IκB) inflammasome pathway (Liang et al., 2021). Alcoholic fatty liver disease is also a highly harmful chronic liver disease. And its occurrence is confirmed to be associated with the gut microbiota (Liu et al., 2018). The researches have proved that fermented ginseng can up-regulate probiotics such as Bifidobacterium, Lactobacillus, Akkermansia and down-regulate pathogenic bacteria such as Peptostreptococcaceae, Colibacillus that lead to metabolic disorders, which can...
### TABLE 1 | Summary of anti-obesity activities of ginseng by regulating gut microbiota and related pathways.

| Conditions          | Compounds/Extracts | Dose/Period | Models               | Gut microbiota | Mechanisms                                                                 | Refs.          |
|---------------------|--------------------|-------------|----------------------|----------------|-----------------------------------------------------------------------------|----------------|
| Obesity             | Ginseng extract    | 10 mg/kg; 56 days | db/db mice           | Efa            | Increases myristoleic acid, brown adipose tissue activation and beige fat formation to reduce adiposity. | (Quan et al., 2020) |
| Obesity             | Water extract of red and white ginseng | 5.5 ml/kg; 70 days | HFD-induced BALB/c mice | Lac, Bac, Para | Increases UCP1 and LCFA levels to decrease body weight, LPS, IFN-γ, IL-1β, IL-6, IL-10. | (Zhou et al., 2020) |
| Obesity             | KRG extract        | 235 mg/kg; 28 days | HFD-induced C57BL/6 mice | Ver, Pro, Def, Lac, Hel, Bar, All, Osc | Up-regulates insulin and leptin levels to down-regulate body weight, fat, GLU, Insulin resistance, GOT, GPT. | (Lee et al., 2021) |
| Obesity             | Rb1 and salvianolic acid B | 200-400 mg/kg/d 28 days | HFD-induced SD rats | Bac, Fr, Mur | Decreases the relative expression levels of SREBP-2 and HMG-CoA reductase, TC contents in blood and liver, increases the expression level of CYP7A1 to improve lipid levels in blood and lipid metabolism disorders. | (Zhao et al., 2021) |
| T2DM                | Ginsenoside T19    | 10-60 mg/kg; 42 days | HFD-induced SD rats | Pro, Bac, Fr, Cop, Str, Rum, Ana, Ros, Sci | Decreases the levels of GLU, OGGTT, ITT, TC, TG and LDL by increasing the expressions of GLUT4, P3K, AKT, GSK3β and AMPK. | (Ku et al., 2020) |
| T2DM                | Ginsenoside Rg5    | 1.0 mg/mL; 28 days | db/db mice           | Bac, Fr, Clo, Hel, Fla, Pse, Dor, Ace, Bil, Ros, Sci | Inhibits the NF-κB pathway to decrease IL-6, IL-1β levels of serum, decreases the expression of TLR4 and increases the expression of Occludin, ZO-1, IκB-α, to decrease liver index, Glu. | (Wei et al., 2020) |
| T2DM                | Red ginseng, Aronia, shiitake mushroom, nattokinase | 0.5-1 g/kg; 84 days | HFD-induced SD rats | Bac, Fr, Clo, Ery | Decreases GLU and insulin resistance by inhibiting islet B cell apoptosis and increasing bone mineral density. | (Yang et al., 2019) |
| T2DM                | BuZangTongLuo decoction | 5 g/kg/day; 21 days | HFD-induced C57BL/6J mice | Bac, Fr, Pro, Ver, Bif, Akk | Reduces the Water and food intake to control GLU. | (Zheng et al., 2020) |
| T2DM                | Ginseng polysaccharides + Rb | 160 mg/kg; 30 days | HFD-induced Wistar rats | Bur, Eys, Kie | Increases β-glucosidase activity to lower blood sugar levels. | (Li et al., 2018) |

**Notes:**
- **Bif:** Bifidobacterium; **Fae:** Faecalibacterium; **Blu:** Blautia; **Ela:** Eteacallosa; **Lac:** Lactobacillus; **Fr:** Firmicutes; **Bac:** Bacteroidetes; **Para:** Parabacteroides; **Ver:** Verrucomicrobia; **Akk:** Akkermansia; **Muc:** Mucispirillum; **Pro:** Proteobacteria; **Def:** Delftiaaspira; **Hel:** Helicobacter; **Bar:** Barnesiella; **All:** Allistipes; **Osc:** Oscillibacter; **Cor:** Coriobacteriaceae; **Adl:** Adlercreutzia; **Dor:** Doritilunibacter; **Cop:** Coprothermobacter; **Par:** Parasutterella; **Clo:** Clostridium; **Fla:** Flavonifractor; **Pse:** Pseudonitroreductus; **Ace:** Acetatifactor; **Bl:** Blipholia; **Ros:** Roseburia; **Sci:** Scillibacter; **Str:** Streptococcus; **Rum:** Ruminococcus; **Ana:** Anaerotruncus; **Ros:** Roseburia; **Aci:** Acidobacteria; **Des:** Desulfovibrio; **Ery:** Erysipelothrix; **Ver:** Verrucomicrobia; **Bla:** Blautia; **Wei:** Weissella; **Esc:** Escherichia; **Shi:** Shigella; **Kur:** Kurthia; **STZ:** streptococci.

### TABLE 2 | Summary of ginseng regulating gut microbiota in human models.

| Conditions          | Compounds/Extracts | Dose/Period | Models | Gut microbiota | Mechanisms                                                                 | Refs.          |
|---------------------|--------------------|-------------|--------|----------------|-----------------------------------------------------------------------------|----------------|
| Obesity             | Ginseng extract    | 4g; 56 days | Obesity middle-aged Korean women patients with metabolic syndrome | Bif, Fae, Bla | Reduces the BW, BMI and GLU, TC, TG of the serum. | (Song et al., 2014) |
| Metabolic syndrome  | Korean red ginseng powder | 6000 mg/ day; 56 days | Patients with metabolic syndrome | Bac | Improves metabolic syndrome by reducing systolic blood pressure, serum lipid metabolism markers TC and LDL levels and insulin resistance. | (Seong et al., 2021) |
| NAFLD               | KRG powder capsules (including Rg1, Rb1, Rg3) | 4.5 mg/g; 2 g/day; 28 days | Patients with nonalcoholic steatohepatitis | Bif, Esc, Eub, Erys, Kie | Reduces AST, ALT, TC, TG, γ-GT levels in the liver. | (Hong et al., 2021) |
alleviate the level of inflammation and improve the situation of alcoholic liver injury (Fan et al., 2019). The further deterioration of non-alcoholic fatty liver disease and alcoholic fatty liver disease could lead to hepatitis and even liver cancer (Ocker, 2020). In a dimethylnitrosamine induced-cancer mice, ginsenoside Rg3 combined with Fe@Fe3O4 nanoparticles can reduce the number of cancerous cells and prolong the survival time of mice with liver cancer by elevating the ratio of Firmicutes and Bacteroidetes or reversing the pathogenic gut microbiota structure (Ren et al., 2020). In summary, ginseng can treat the animal liver diseases models by reversing the imbalanced gut microbiota, improving liver metabolism, and restoring host homeostasis (Table 3). Moreover, in NAFLD patients, KRG could decrease the ratio of Firmicutes and Bacteroidetes to improve liver lipid metabolism, decrease serum TC and total triglyceride (TG) (Table 2) (Hong et al., 2021).

**Diarrhea**

Diarrhea is one of the leading diseases with the highest morbidity and mortality worldwide which is characterized by acute and infectious (Shankar and Rosenbaum, 2020). Prolonged diarrhea can lead to the consequences such as hypovolemia, electrolyte imbalance, malnutrition, and skin damage (Reintam Blaser et al., 2015). There are many causes of diarrhea, and commonly there are the disorders of bile acid metabolism (Hughes et al., 2021), viruses (Becker-Dreps et al., 2020), and *Escherichia coli* infection (Ahmed et al., 2013). Furthermore, recent studies have found that gut microbiota is an important pathogenic factor leading to diarrhea (Fan and Pedersen, 2021). While the occurrence of diarrhea could be prevented and improved by restoring the structures of disorganized gut microbiota (Gallo et al., 2016). Ginseng can alleviate diarrheal symptoms by modulating the gut microbiota structure. In the Kunming mice induced by 5-fluorouracil, a combination of total ginsenoside and volatiles of *Atractylodes Macrophala* can decrease the abundances of Bacteroides, Proteobacteria and other bacteria and increase the abundances of Firmicutes and Lactobacillus to restore gut microbiota homeostasis for the improvement of diarrheal situation (Wang et al., 2019a). Moreover, the combination of ginseng polysaccharides and volatilized oil from *Atractylodes Macrophala* could reduce the diarrhea index and ameliorate colonic lesions by restoring the structures of gut microbiota in the disease state (Wang et al., 2019b). In addition, fermented ginseng and ginseng polysaccharides have also been proved to have therapeutic effects on diarrhea by up-regulating Firmicutes, Lactobacillus, the ratio of Firmicutes and Bacteroidetes, and down-regulating Proteobacteria, and Bacteroidetes (Qi et al., 2019; Qu et al., 2021). Taken together, the active components from ginseng can restore intestinal homeostatic balance and improve water and salt metabolism to alleviate diarrhea (Table 4).

**Colitis**

Colitis is a chronic and persistent inflammatory environment leading to colon cancer, which is the third deadliest cancer of the world (Bocchetti et al., 2021). There are many factors leading to colitis, but the most fundamental is the gut microbiota. The changes in the composition and diversity of gut microbiota could lead to the damage of intestinal barrier and the immune function, and increase high levels of pro-inflammatory cytokines in the intestine and the incidence of erosion and ulcer (Hering et al., 2012). Studies have shown that probiotics supplementation can regulate bile acid metabolism and alleviate enteritis symptoms in mice (Liu and Wang, 2021). Probiotics can also restore unbalanced gut microbiota, enhance intestinal mucosal barrier function, improve intestinal immunity, and reduce gastrointestinal infection (Shen et al., 2018). Therefore, restoring the structure of gut microbiota is an important mechanism for the treatment of colitis. Ginseng has an anti-inflammatory and analgesic effects (Lee et al., 2019) and it could prevent the colitis and related cancer induced by dextran sodium sulfate (Shin et al., 2020). In the studies of dextran sodium sulfate (DSS)-induced SD rats, ginseng polysaccharides can significantly up-regulate the relative abundance of probiotics, reduce the relative abundance of pathogenic bacteria, and inhibit a variety of inflammatory signal pathways (Shen et al., 2018; Wang et al., 2021). Ginsenoside Rk3 can increase the abundance of probiotics

### Table 3 | Summary of anti-liver diseases activities of ginseng by regulating gut microbiota and related pathways.

| Conditions     | Compounds/Extracts | Dose/Period | Models | Gut microbiota | Mechanisms | Refs. |
|----------------|--------------------|------------|--------|----------------|------------|-------|
| NAFLD          | Ginseng extract    | 200 mg/kg  | HFD-induced C57BL/6j male mice | Bac, Eps, Ver | Inhibits the NF-kB pathway, and increases the expression of TNF-α, IL-1β, IL-6, FAS, VDR, and ZO-1 | Liang et al., 2021 |
| Alcoholic liver injury | Fermented ginseng | 300 mg/kg/day; 56 days | Alcohol feeding C57BL/6N | Bif, Lac, Akk, Rum, Eub, Bil, Deh, Sat, All, Osc, Dor, Bac, Ver, Rum, Akk, Bar | Reduces the TNF-α, IL-6, LPS, ALT, AST levels of serum to decrease the liver index. | Fan et al., 2019 |
| Liver cancer   | conjugate Fe@Fe₃O₄ nanoparticles with ginsenoside Rg3 (NpRg3) | 70 mg/kg; 490 days | Dimethylnitrinosamine-induced C57BL/6 mice | Bac, Eps, Ver, Rik | Increases the lifetime and alleviates the pathological state of liver by inhibiting the proliferation of tumor cells. | Shen et al., 2020 |

Eub, Eubacterium; Erys, Erysipelotrichaceae; Kle, Klebsiella; Meg, Megamonas; Dia, Dialister; Eps, Epsilonbacteraeota; Act, Actinobacteria; Deh, Dehalobacterium; Sut, Suterella; All, Allobaculum; Osc, Oscillospora; Pep, Peptostreptococcaceae; Col, Colibacillus; Ent, Enterococcus; Lach, Lachnospiraceae; Rik, Rikenella.
such as *Bacteroides* and *Lactobacillaceae* and reduce the abundance of pathogenic bacteria that can promote the production of inflammatory factors such as *Proteobacteria*, *Helicobacteraceae*. At the same time, ginseng can decrease the ratio of *Firmicutes* and *Bacteroidetes*, increase the expressions of tight junction protein 1 (ZO-1) and occludin, improve the ratio of *Firmicutes* and *Bacteroidetes*, and increase the relative abundance of probiotics and reducing the abundance of pathogenic bacteria (Bai et al., 2021; Chen et al., 2021).

The treatment of red ginseng and coix seed in the trinitrobenzene sulfonic acid-induced colitis rats is achieved by increasing the abundance of probiotics and reducing the abundance of pathogenic bacteria (Lee et al., 2015). Collectively, ginseng can inhibit the inflammation and improve colitis by reducing the relative abundance of pathogenic bacteria, such as *Helicobacter*, and increasing the relative abundance of *Lactobacillus* and *Bacteroides* probiotics (Table 4).

### Other Diseases

Importantly, many studies have proved that ginseng, ginsenosides, and ginseng polysaccharides play potential effects on other diseases. For male Wister rats with spleen deficiency syndrome, the combination of ginseng and wild jujube could up-regulate the relative abundance of *Firmicutes*, *Bacteroidetes*, *Lactobacillus*, and *Bifidobacterium*, reduce the relative abundances of *Actinobacteria*, *Proteobacteria*, *Streptococcus*, *Escherichia*, *Shigella*, *Veillonella*, and *Enterococcus*, reverse the pathological state of the gut microbiota imbalance of the spleen.
deficiency syndrome, and improve the spleen deficiency syndrome (Li et al., 2020). For the fatigue, two studies showed that the extracts of ginseng and fermented ginseng leaf can recover from exercise-induced fatigue by improving the structure of gut microbiota and reducing the level of inflammation (Zheng et al., 2021; Zhou et al., 2021). For neurological diseases, ginseng extract, ginsenoside or the formula containing ginseng can regulate gut microbiota to play neuroprotective effect and improve memory impairment. In the rat ischemia/reperfusion model, ginsenoside Rb1 can increase the relative abundance of Lactobacillus and gamma-aminobutyric acid receptors to reduce the proinflammatory cytokines for the improvement of neuroprotection (Chen et al., 2020). In the rats induced by D-galactose, ginseng decoction called Dushen Tang showed good curative ability for memory impairment by up-regulating Bacteroidetes and down-regulating Lactobacillus (Wang et al., 2021). In the mice with Parkinson’s disease, the treatment with the extract from KRG can improve neuronal function and alleviate Parkinson’s symptoms by up-regulating the relative abundance of Eubacterium and down-regulating the relative abundances of Verrucomicrobia and Ruminococcus (Jeon et al., 2020). For Alzheimer’s disease, a formula named Qisheng Wan containing ginseng and ginsenoside Rg1 can restore the structures of disordered gut microbiota and reduce the levels of inflammatory factors to reduce the symptoms of Alzheimer’s disease (Wang et al., 2020; Xiong et al., 2022). In the ApcMin/+ mice during the development of colorectal cancer, ginsenoside Rb3 and Rd can promote the growth of beneficial bacteria (Bifidobacterium spp., Lactobacillus spp., Bacteroides acidifaciens, and Bacteroides xylanisolvens) and lower the abundance of cancer cachexia-related bacteria (Dysgonomonas spp., Helicobacter spp.) to reinstatement mucosal architecture and improve mucosal immunity (Huang et al., 2017). Moreover, ginsenosides can facilitate the therapeutic effect of cyclophosphamide in the mice with mammary carcinoma, which may be related with the increases of anti-tumor cytokines and the production of gut probiotics (Aktermansia, Bifidobacterium, and Lactobacillus) (Zhu et al., 2021). In addition, ginseng polysaccharides at 200 mg/kg can potentiate anti-tumor effect of anti-programmed cell death 1/programmed cell death ligand 1 immunotherapy in non-small lung cancer by regulating the relative abundance of bacteria such as Escherichia, Rikenella, Parabacteroides distasonis, and Bacteroides vulgatus (Huang et al., 2021).

The products of red ginseng, including its water extract, 50% ethanol extract and bifidobacterial-fermentation of ethanol extract were compared to explore their mechanisms against ovalbumin-induced allergic rhinitis. It found that bifidobacteria-fermented extract of red ginseng can reduce the levels of IL-4, IL-5, and IL-13 in the colon and restore the populations of gut microbiota (Bacteroidetes, Actinobacteria, and Firmicutes) (Kim et al., 2019). Furthermore, the same research group reported that bifidobacteria-fermented extract of red ginseng and its main constituent, ginsenoside Rd, protopanaxatriol can ameliorate gut dysbiosis (Bacteroidetes and Proteobacteria populations) to mitigate anxiety/depression (Han et al., 2020). Additionally, the intake of ginseng extract for 34 weeks can decrease the abundance of Bifidobacteriaceae and Lactobacillaceae, and increase the abundance of Proteobacteria, Methylobacteriaceae, and Parabacteroides, Sutterella, which suggest that it regulate the host-gut metabolism in the normal rats (Sun et al., 2018). Collectively, ginseng can up-regulate the relative abundance of probiotics, reduce the relative abundance of pathogenic bacteria, or restore the structure of unbalanced gut microbiota to prevent and treat various diseases, including fatigue, neurological diseases, cancer, allergic rhinitis, and depression (Table 5).

In summary, ginseng has significant therapeutic effects on a series of diseases, including obesity, T2DM, liver diseases, colitis, diarrhea, exercise-induced fatigue, Alzheimer’s disease, and cancer by regulation gut microbiota. Recent studies demonstrate that ginseng can further inhibits NF-κB and other inflammatory pathways to reduce the levels of proinflammatory factors (TNF-α and IL-1β) and increases the expressions of key proteins such as TLR4, ZO-1, and Occludin by regulating the species diversity and relative abundance of intestinal flora, thus maintaining the intestinal mucosal barrier homeostasis. The flora regulated by ginseng mainly includes Bacteroides, Bifidobacterium, Parabacteroides, Akkermani, Helicobacter, Lactobacillus, and Proteobacteria during the process of different diseases. The detailed information for the compositions of gut microbiota and regulated signaling pathways in the therapeutic effect of ginseng against various diseases has been shown in Figure 1.

**TRANSFORMATION AND MODIFICATION OF GINSENSOIDS BY GUT MICROBIOTA**

Microbiota is an important core to host metabolism, could regulate the expression and function of enzymes involved in drug metabolism (Xu et al., 2017), it can also participate in the regulation of ginsenoside transformation by producing nitrate reductase and glucuronidase to hydrolyze glycosidic bonds (Yang et al., 2020). Besides, many important components such as folate, indole, gamma-aminobutyric acid, and short chain fatty acids (SCFAs) are produced by the metabolism of ingested ingredients by microbiota. These metabolites also are the raw materials for the synthesis of above-mentioned molecules. Therefore, gut microbiota plays an vital role in the pharmacokinetics and pharmacodynamics of natural products (Pan et al., 2019).

The oral utilization of ginsenosides is very low, and the activity of some ginsenosides is not good, hence they need to be transformed to improve their activity. Ginsenoside compound K (CK) is a kind of ginsenoside with good activity, which is transformed from a variety of ginsenosides through different processing. A large number of studies have found that ginsenoside CK has many pharmacological effects that it can induce apoptosis of colon cancer cells (Pak et al., 2020), treat lung cancer (Jin et al., 2018), and reduce the formation of atherosclerotic plaque (Zhou et al., 2016). Together, most studies have proved that CK has a significant therapeutic effect.
### Summary of anti-other diseases activities of ginseng by regulating gut microbiota and related pathways.

| Conditions                      | Compounds/Extracts                  | Dose/Period | Models                     | Gut microbiota | Mechanisms                                                                 | Refs.                  |
|---------------------------------|-------------------------------------|-------------|----------------------------|----------------|-----------------------------------------------------------------------------|------------------------|
| Spleen deficiency syndrome      | Ginseng and Jujube seeds            | 0.4 mg/mL   | Wistar rats                | Fi, Bac, Lac, Bif, Act, Pro, Str, Esc, Shi, Ent, Vei | Reverse carbohydrate metabolism, signal transduction, and amino acid metabolism. | (Li et al., 2020)      |
| Exercise-induced fatigue        | Fermented ginseng leaf              | 50 mg/kg/d 28 days | SD rats | Bac, Ver, Def, Fi, Pro, Act | Decreases hypoxanthine and isoprostane, increases protein expression of Pdx7 and MycD1, decreases gene expression of MyHC-1 and MyHC-2lb, ameliorates the levels of acetic acid, propionic acid, total short chain fatty acids, TNF-α and IL-10. | (Zheng et al., 2021) |
| Sports fatigue                  | Ginseng extract                     | 1.42 g/kg; 14 days | Exercise-induced fatigue SD rats | Bac, Lac, Bif, Str, Oio, Cop | Decreases the levels of IL-1β, LA, CP, LDH, BUN and GLU by inhibiting the expression levels of TACDA, TCDCA, UDCA3, CDCA3 and TGR5, further regulating the metabolism of butyric acid and tryptophan. | (Zhou et al., 2021)   |
| Neuroprotection                 | Ginsenoside Rb1                      | 50 mg/kg; 13 days | PGF-SD rats | Lac | Increases the levels of A subunit and B subunit in GABA and IL-1β, IL-6, TNF-α to reduce neurological deficit and cerebral infarct area. | (Chen et al., 2020) |
| Memory impairment               | Dushen Tang                          | 0.3 g/kg/d; 49days | D-gal-induced SD rats | Bac | Inhibits nerve damage and exerts antiaging effects by activating the cAMP signaling pathway. | (Wang et al., 2021)   |
| Parkinson’s disease             | Korean red ginseng extract           | 100 mg/kg   | MPTP-induced PD mice | Eub | Prevents MPTP-induced dopaminergic neuronal death, activation of microglia and astrocytes, and accumulation of α-synuclein in the SN, and the regulation of inflammation-related factors in the colon. | (Jeon et al., 2020)   |
| Alzheimer’s disease             | Qishen Wan formula (contain ginseng) | 5.6-22.4 g/kg | SD rats | Akk, Lac, Bif, Ali, Lach | Inhibits the expression of Tau in hippocampus and cortex to improve learning and memory. | (Xiong et al., 2022)   |
| Alzheimer’s disease             | Ginsenoside Rg1 formula              | 7.5-30 mg/kg; 56 days | Conventional tree shrews | Pro, Ent, Esc, Fi, Str, Lac, Pas, Clo | Increases the levels of A subunit and B subunit in GABA and IL-1β, IL-6, TNF-α to reduce pathological damage of hippocampus. | (Wang et al., 2020)   |
| Colon cancer                    | Ginsenoside Rb3 and Rd               | 20 mg/kg; 56 days | Apc Min/+ mice | Lac, Bif, Rum, Bif, Pre, Pse, Acid, Cio, Hel, But, Fae, Pre, Str, Bif, Lach | Decreases the expression levels of iNOS, N-cadherin, FOXP3, CXCL10, and increases the expression levels of arginase-1 and TREm-2 to reduce serum IL-1β, IL-6, IL-12, IL-17 and IL-23 size and number. | (Huang et al., 2017) |
| Breast cancer                   | Ginsenoside and Cyclophosphamide    | 2.205 g ginsenosides extract/6000 g ginseng crude drug, 1 h | ICR mice | Bif, Akk, Ver, Str, Lach, Bac, Pre, Odo, Vei, Lach | Reduces the NF-kB pathway, promotes the expression of Caspase-3, Nlr2 and tight junction protein to reduce tumor volume and improve the pathological status of small intestine. | (Zhu et al., 2021)   |
| Non-small cell lung cancers     | Ginseng polysaccharides              | 200 mg/kg   | PD-1 knock-in mice | Mur, Ery, Bif, Pre, Esc, Lac, Rik, Ach | Reduces tumor weight, increases the levels of IFN-γ, TNF-α, GZMB and the expression of CLCA3, TFF3, AGR2, Zg16, Pza2g10, Guca2a. | (Huang et al., 2021) |
| Allergic rhinitis                | Fermented red ginseng and ginsenoside Rd | 20 mg/kg; 30 days | BALB/c mice | Bac, Act | Promotes the expression of IgE and inhibits the myeloperoxidase activity to reduce eosinophils. | (Kim et al., 2019)   |
| Anxiety and depression          | Bifidobacterium fermented red ginseng and ginsenoside Rd | 10-25 mg/kg/ day; 5 days | 2,4, 6-TNBS-induced C57BL/6 mice | Bac, Pro, Str, Bac, Parap, Mur, Al, Bac, Lach, Rum, Col, Tm7 | Promotes the expression of IgE and inhibits the myeloperoxidase activity to reduce eosinophils. | (Han et al., 2020) |
| Metabolism and gut microbial influence | Ginseng extract                     | 100 mg/kg; 238 days | Wistar Rats | Bif, Lac, Meth, Para | Reduces the levels of IL-2, IL-6, IgG and IgM proinflammatory factors and increases the levels of IL-4, IL-10 and IgA anti-inflammatory factors by improving the immune system. | (Sun et al., 2018) |

**Flora (Vei, Veillonella; Meth, Methylobacteriaceae; Pse, Pasteurellaceae; Lep, Lepoturn; Odo, Odoribacter Parap, Paraprevotella; Ali, Alistipes; Pse, Pseudomonas; Acid, Acidoides; But, Butyricimonas; Cam, Campylobacter; Dys, Dysgonomonas;)**
on inflammation and cancer. Structurally, CK has less Arabinofuranose (Araf), arabopyranose (Arap), and glucose (Glc) than the initial ginsenoside. Ginsenoside Rc can be transformed into Mb and Mc by removing Glc at C-3 under the action of Bacteroides and Fusobacterium, and then into CK by removing Araf at C-20 through Bacteroides, Eubacterium and Bifidobacterium (Choi et al., 2018). Ginsenoside Rb2 can first remove the Glc at C-3 through Bacteroides and Eubacterium, then remove the Araf at C-20 under the action of Bacteroides and Fusobacterium and convert it into F2, and finally transformed into CK under the action of Bacteroides and Fusobacterium (Kim et al., 2018). Ginsenoside Rb1 has only three more molecules of Glc than CK, which is transformed into CK under the action of Eubacterium, Lactobacillus and Bacteroides (Quan et al., 2013). In addition, Ginsenoside Rd and F2 are transferring states for CK transformation. Ginsenoside Rd is usually transformed from Rb1, Rb2 and Rc by removing redundant Araf and Glc under the action of Eubacterium and Bifidobacterium, while F2 is transformed from Mb, Co and Rd by removing Araf or Glc under the action of Eubacterium, Fusobacterium and Bacteroides (Zhang et al., 2021). Meanwhile, it found that ginsenoside which have Arap and Araf at C-20 preferentially removed Glc at C-3 during transformation. Bacteroides tends to preferentially remove the Glc at C-3. In addition, in the whole process of CK transformation, the enzymatic hydrolysis of Araf group mainly depends on Bifidobacterium, Bacteroides mainly guides the enzymatic

**FIGURE 1** | Ginseng shows its potential therapeutic effects on a variety of diseases through the regulation of gut microbiota in animal models.
FIGURE 2 | The metabolism of ginsenosides under the action of gut microbiota.
hydrolysis of Glc, and the enzymatic hydrolysis of Arap is mainly mediated by *Fusobacterium* (Figure 2A).

Proto-ginsenoside of ginsenosidol type (PPD) has also been shown to have a significant inhibitory effect on breast cancer (Zhang et al., 2018), uterine cancer (Jo et al., 2021), prostate cancer (Cao et al., 2014), and metastasis of cancer cells (Lu et al., 2020). Although PPD has good pharmacological activity, it cannot be directly extracted from ginseng, it needs to be processed and transformed under the action of gut microbiota in vivo. Most of PPD is transformed from CK by removing the Glc at C-20 under the action of *Bacteroides*, Eubacterium and *Bifidobacterium*, and the other part is transformed from ginsenoside Rg3 by removing the two molecules of Glc at C-3 under the action of *Bacteroides*, Eubacterium and *Bifidobacterium* (Figure 2A). Proto-ginsenoside of ginsentriol type (PPT) is also a saponin with good activity, which has pharmacological effects such as reducing memory and cognitive impairment, improving Alzheimer’s disease (Lu et al., 2018), inhibiting septic shock and peritonitis (Jiang et al., 2020), improving cellular inflammation (Kim et al., 2015). PPT is not an initial saponin, which is transformed from a variety of ginsenoside under the action of gut microbiota in the intestine. In the whole transformation process of PPT, ginsenosides Re and Rf are the initial ginsenoside and ginsenoside Rh1 is the key secondary ginsenoside. During the transformation, ginsenoside Re can remove Glc or rhamnose (Rha) under the action of *Fusobacterium*, *Bacteroides* and *Eubacterium*, and then convert to F1, Rg1 and Rg2 (Bi et al., 2019). Ginsenoside Rh1, as a transferring style for PPT transformation, can be transformed from Rg1, Rg2, Rf by removing Glc, Rha and Glc under the action of *Bacteroides*, Eubacterium and *Bifidobacterium*, respectively. Under Bacteroides-mediated enzymatic hydrolysis, ginsenoside F1 and Rh1 can remove Glc at C-6 or C-20 to finally transformed into PPT (Chen et al., 2007). In addition, ginsenoside Rg1 can remove Glc, Rha at C-6 and then convert into F1 under the action of *Fusobacterium* and *Bacteroides* (Kim et al., 2011).

Summarily, we found that ginsenoside containing Rha such as Re, Rg2 could preferentially remove Rha when converted into PPT, and then hydrolyze other sugar groups. The hydrolysis of Rha for ginsenosides mainly depends on *Eubacterium* (Figure 2B). Besides, we concluded that *Bacteroides*, *Bifidobacterium* and *Eubacterium* are intestinal bacteria mainly involved in the transformation of ginsenoside. Among them, *Bacteroides* that degrade polysaccharides are most important bacteria. It has been found that *Bacteroidetes* could regulate thousands of enzymes, which can regulate specific carbohydrate degrading according to the structural information of the target glycan (Lapebie et al., 2019). As shown in Figure 3, we found that *Bacteroides* could induce the hydrolysis of glycosidic bonds at all possible positions. Besides, *Bifidobacterium* prefer to hydrolyze the glycosidic bond at position C-20, which mainly depends on its own glucosidase and glucanase, including β-glucan (Fernandez-Julia et al., 2021). Nowadays, it also has been approved that the hydrolysis by *Eubacterium* is closely related to β-glucosidase, but the further mechanism of ginsenoside transformation is unclear (Yang et al., 1995). According to the available evidence, *Lactobacillus* prefers to hydrolyze the glycosidic bond at position C-3, and the glycosidic bonds hydrolyzated by *Microbacterium* and *Rhodanobacterium* are more tended located at position C-20 (Figure 3). Collectively, *Bifidobacterium* and *Bacteroides* are the most beneficial bacteria and participate in the transformation process of ginsenosides in vivo. The therapeutic effect of ginseng depends on the further processing and modification of a variety of ginsenoside by the gut microbiota to enhance the absorption and the activity of ginsenoside in the body. At present, most researches of gut microbiota regulating ginsenoside transformation were still at an initial level, just showed the relationship between microbiota and transformation, but the internal mechanism and details need to be further clarified.

CONCLUSION AND FUTURE PERSPECTIVE

In our review, we summarized the findings of many studies, which showed that ginseng can play a role in the prevention and treatment of obesity, diabetes, fatty liver, colitis, diarrhea, cancer, and other diseases by regulating the host microbiota. At the same time, microbiota is also the key medium of ginsenoside transformation in vivo. The pharmacological functions of ginseng against various diseases might be related with the abundance and the structure of gut microbiota, including increase the relative abundance of probiotics (*Bacteroides*, *Lactobacillus*, *Bifidobacterium*, *Akkermansia*) and reduce the relative abundance of pathogenic bacteria (*Firmicutes*, *Helicobacter*, *Clostridium Proteobacteria*). Ginsenosides could be transformed into CK, PPD or PPT for better activities under the actions of probiotics, including *Bacteroides*, *Eubacterium*, *Bifidobacterium* and *Fusobacterium*. Therefore, we can use probiotics combined with ginseng to improve the pharmacodynamic value of ginseng to fully play its pharmacological effect in future. Based on the current findings, the network relationship of ginseng extract, formula containing ginseng, ginsenosides, and polysaccharides with different microbiota have summarized and shown in Figure 4.

The following aspects and suggestions about ginseng and gut microbiota should be considered, according to the research status: (1) The number of human experiments is relatively small, and most experiments use animal models, very few the studies were performed in human. (2) The detection methods for gut microbiota are mostly limited to 16S rDNA sequencing, and the changes of microbiota are not revealed deeply and specifically enough. (3) Most of the current research results only find the changes of microbiota, but there are few reports on the regulation mechanism of microbiota. (4) The detection method is single, only one detection method is used, the method of multi-omics combination is not used. (5) The ginseng used in the current studies lacks standardized and unified standards. Researchers rarely report the quality control results of ginseng, which cannot ensure the repeatability and stability of the experiment. Therefore, we suggest that future researches...
FIGURE 3 | The summary of gut microbiota participates regulating ginsenoside transform. The left row is the gut microbiota involved in ginsenoside transformation. The middle part shows branched chain position of glycosidic bond hydrolysis, the removed sugar group, and the remaining functional groups respectively. The corresponding ginsenosides transformed are listed on the right row.
should focus on the species, types, and strain of gut microbiota, their metabolites, and related signaling pathways regulated by ginseng. This review can provide better insight into the interaction of ginseng with gut microbiota in multiple disorders and ginsenoside transformation.

**AUTHOR CONTRIBUTIONS**

ZC and ZZ collected, analyzed, and reviewed the literature, wrote the main manuscript. JQL, HQ, QH, and JL assembled figures/tables. JQL, HQ, JL, JC, and QL added and checked references. ZZ, JM, and XL designed and supervised the manuscript. JM and XL revised the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

**FUNDING**

This study was supported by the National Natural Science Foundation of China (U19A2013, 81804013), National Key Research and Development Program of China (2017YFC1702103), the Science and Technology Development Plan Project of Jilin Province (20200404057YY, 2020YFC0845000, 202002053JC, 202012228JC).

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## Glossary

| Abbreviation | Full Form |
|--------------|-----------|
| T2DM         | type 2 diabetes mellitus |
| FLR         | fatty liver disease |
| NF-κB       | nuclear factor kappaB |
| NAFLD       | Nonalcoholic fatty liver disease |
| TC          | total cholesterol |
| TG          | total triglyceride |
| SREBP-1c    | sterol regulatory element binding protein-1c |
| FAS         | fatty acid synthetase |
| ACC-1       | acetyl-coenzyme A carboxylase 1 |
| OPT-1a      | carnitine palmitoyl transferase 1A |
| IκB         | I-kappa-B |
| ZO-1        | tight junction protein 1 |
| TLR4        | toll-like receptor 4 |
| IL          | interleukin |
| TNF-α       | tumor necrosis factor-α |
| PPD         | Proto-ginsenoside of ginsenoside type |
| PPT         | Proto-ginsenoside of ginsenoside type |
| Bif         | Bifidobacterium |
| Fae         | Faecalibacterium |
| Bla         | Blautia |
| Ela         | Efalacis |
| Lac         | Lactobacillus |
| Fir         | Firmicutes |
| Bac         | Bacteroidetes |
| Para        | Parabacteroides |
| Ver         | Verrucomicrobia |
| Ack         | Akkermansia |
| Muc         | Mucispirillum |
| Pro         | Proteobacteria |
| Def         | Deferribacteres |
| Hel         | Helcocacter |
| Bar         | Barnesiella |
| All         | Allistipes |
| Osc         | Oscillibacter |
| Cor         | Coriobacteriacea |
| Adl         | Adlercreutzia |
| Dor         | Dorea |
| Cop         | Coprobacter |
| Par         | Parasutterella |
| Clo         | Clostridium |
| Fls         | Flavonifractor |
| Pse         | Pseudoflavonifractor |
| Ace         | Acetatifactor |
| Bil         | Bilophila |
| Ros         | Roseburia |
| Sci         | Scillibacter |
| Str         | Streptococcus |
| Rum         | Ruminococcus |
| Ana         | Anaerotruncus |
| Ros         | Roseburia |
| Aci         | Acidobacteria |
| Des         | Desulfovibrio |
| Ery         | Erysipelotrix |
| Ver         | Verrucomicrobia |
| Bla         | Blautia |
| Wei         | Weissella |
| Esc         | Escherichia |
| Shi         | Shigella |
| Kur         | Kurthia |
| STZ         | streptozocin |
| Eub         | Eubacterium |
| Erys        | Erysipelotrichaceae |

(Continued)