Dietary polyphenols maintain homeostasis via regulating bile acid metabolism: A review of possible mechanisms

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Abstract

The synthesis and metabolism of bile acids (BAs) have been implicated in various metabolic diseases, including obesity and diabetes. Dietary polyphenols, as natural antioxidants, play a vital role in synthesizing and metabolizing bile acids. This paper reviews the mechanism of dietary polyphenols involved in bile acid (BA) synthesis and metabolism. The impact of different gut microorganisms on BA profiles is discussed in detail. The regulation of BA metabolism by dietary polyphenols can be divided into two modes: (1) Dietary polyphenols directly activate/inhibit farnesol X receptor (FXR) and Takeda G protein-coupled receptor (TGR5); (2) Dietary polyphenols regulate BA synthesis and metabolism through changes in intestinal microorganisms. Research on direct activation/inhibition of FXR and TGR5 by polyphenols should be ramped up. In addition, the effect of dietary polyphenols on intestinal microorganisms has been paid more and more attention and has become a target that cannot be ignored.

Keywords: dietary polyphenols, bile acid synthesis and metabolism, intestinal microorganisms, FXR and TGR5

1. Introduction

Bile acids (BAs) are a family of steroids that solubilize cholesterol, phospholipids, and other lipids. Many studies have shown that BAs are essential to connecting nutrients with intestinal microbiota and host metabolism.[1] BA disorders and impaired BA receptor transduction are associated with liver and intestinal diseases, such as steatohepatitis, hepatocellular carcinoma, enteritis, and colorectal cancer.[2] Two central BA-activated receptors, FXR and TGR5 (GP-BAR1 or M-BAR), are crucial in regulating physiological and pathological processes. These receptors are located at the intersection of multiple regulatory pathways.[1] FXR primarily functions to inhibit BA synthesis in the liver, regulate BA circulation in the intestine and liver tissue, and maintain a constant BA concentration in the body.[1] TGR5, on the other hand, exhibits potency dependence on BA hydrophobicity.[3] Activation of TGR5 by BA can increase energy consumption and reduce diet-induced obesity. In cases of excessive or insufficient BA production, FXR and TGR5 act as negative feedback regulators of BA metabolism.[1]

Polyphenols are a large class of organic compounds commonly found in natural products, with at least one aromatic ring with one or more hydroxyl functional groups.[4] They usually exist in the form of glycosides in food. Polyphenols have the ability to bind with various sugars such as glucose, galactose, rhamnose, and rutin and can exist as oligomers or high molecular weight polymers.[5] Based on their chemical structure, natural polyphenols can be classified into five categories: flavonoids, phenolic acids, lignans, stilbenes, and tannins.[6] Polyphenols have been shown to

have beneficial effects on various metabolic diseases.[5] Regular intake of polyphenols has been reported to reduce the risk of obesity, diabetes, insulin resistance, inflammation, liver failure, and brain diseases.[7] Previous studies have demonstrated that polyphenols can impact BA synthesis and metabolism, leading to increased BA excretion.[4] When polyphenols are ingested, they are not fully digested and can influence microbial populations in the large intestine. Consequently, most research focuses on how polyphenols regulate BA synthesis and metabolism by controlling intestinal microorganisms.[8] Additionally, polyphenols can directly act as exogenous activators or inhibitors of BA receptors, further participating in the regulation of BA metabolism.[9–11] However, the molecular mechanism underlying the effects of polyphenols on the regulation of BA metabolism remains unclear.

This review focuses on the key roles of BA-activated receptors FXR and TGR5. It provides the latest research results on the interaction between polyphenols and BA and clarifies the mechanism of polyphenols in BA synthesis and metabolism. Additionally, we summarize the gut microbes regulated by dietary polyphenols based on enzymes and genes capable of altering the BA profile. This has important implications for the precise intervention of dietary polyphenols in BA metabolism.

2. Synthesis and Metabolism of BAs

BAs are composed of a core structure consisting of 17 carbon atoms arranged in four "fused" rings: three six-membered cyclohexane rings (A-C ring) and one five-membered cyclopentane ring (D ring).[12] Additionally, BAs have a 5-8 carbon side chain terminating in a carboxylic acid, along

with several hydroxyl and methyl groups.[1] The structure of BAs exhibits both hydrophilic and hydrophobic characteristics, allowing them to act as surfactants.[1] BAs serve the purpose of emulsifying lipids and aiding in the absorption and utilization of cholesterol.[3] They can be categorized into primary and secondary BAs. The synthesis and transformation of BAs in the liver and intestines is illustrated in Fig.1. Primary BAs are synthesized in the liver through two pathways: the "classical" and the "alternative" pathway. In the "classical" pathway, cholesterol is converted to 7α-hydroxycholesterol by the enzyme CYP7A1, which is then further modified by sterol 12-α hydroxylase (CYP8B1) and sterol 27-hydroxylase (CYP27A1) to produce primary BAs like cholic acid (CA) and chenodeoxycholic acid (CDCA).[13] CYP7A1, the rate-limiting enzyme from BA formation, which is regulated by the negative feedback of the end product BAs.[1] The "alternative" pathway involves the hydroxylation of cholesterol by CYP27A1 followed by catalysis by CYP7B1, which mainly produces CDCA. In the liver, most primary BAs are conjugated with glycine(G) or taurine(T) to form conjugated BAs (CBAs).[14] The unconjugated BAs are then secreted into the bile in the intestine through a bile salt output pump (ABCB11 or BSEP).[4]

In the intestinal tract, bile saline hydrolase (BSH) produced by *Lactobacillus*, *Bifidobacterium*, *Enterococcus,* and *Clostridium* can uncouple CA and CDCA conjugated with glycine and taurine.[15] Then, *Clostridium* and *Eubacterium* produce α-dehydroxylase for 7α-dehydroxylation.[12] CDCA is converted to lithocholic acid (LCA), while CA is converted to deoxycholic acid (DCA).[16] Primary BAs (T-/G-

CA/CDCA) and secondary BAs (DCA and LCA) can be converted into oxycholic acid analogs by hydroxysteroid dehydrogenase (HSDH) produced by *Clostridium clusters XIVa IV* (*i.e.*, *C.scindens*, *C. hiranonis*, and *C. hylemonae*) and *XI.*[17–19] Secondary BAs also include secondary conjugated BAs and secondary unconjugated BAs.[20] Various secondary BAs can act as strong or weak agonists for FXR and TGR5, while some can inhibit their activity, such as taurocholic acid (in mice), an FXR antagonist.[21] The majority (95%) of secondary BAs in the intestine are reabsorbed by apical sodium-dependent BA transporter (ABST).[4] The conjugated BAs are actively reabsorbed in the ileum, and the unconjugated BAs are passively reabsorbed in the small intestine and large intestine.[1] The sodium/taurocholate co-transport peptide (NTCP) and organic anion transport peptide 1 (OATP1) were then ingested into the hepatocytes, and a small portion (5% LCA) was excreted through the feces.[12] The unconjugated BAs are reabsorbed into the liver and then synthesized into conjugated BAs with glycine and taurine, entering the intestinal-liver circulation once again.[12] Additionally, the liver MRP3, MRP4, and OSTα-OSTβ complexes provide an alternative pathway for BA excretion into the systemic circulation.[22] In the human body, the enterohepatic circulation of BAs occurs 6-12 times a day to metabolize dietary cholesterol. BA synthesis and metabolism are essential in maintaining body weight, glucose, and lipid tolerance.[23]

However, if the liver's ability to synthesize BA or lecithin decreases, excessive BA may be lost in the digestive tract, or the enterohepatic circulation of BAs may decrease, resulting in excessive excretion of

cholesterol into the bile (hypercholesterolemia). This imbalance in the ratio of BAs and lecithin to cholesterol can lead to the precipitation of cholesterol and the formation of gallstones.[13] Gallstones can cause cholestasis, and in cases of liver injury caused by cholestasis, it has been observed that BAs mediate the expression of inflammatory factors, leading to the recruitment of neutrophils in the liver and subsequent liver injury.[24] The study also discovered a correlation between changes in the BA pool and cardiac dysfunction, liver disease, and diabetes.[25] Microbial changes that impact the structure of BA can lead to inflammation, apoptosis, and cell death.[15] These findings highlight the crucial physiological role of regulating BA in preserving human health.

3. Key targets for controlling BA synthesis and metabolism: FXR and TGR5

BAs act as ligands for host cell receptors, namely FXR and TGR5, which are responsible for controlling the synthesis and metabolism of BAs.[3] In recent years, there has been significant interest in natural products that target FXR and TGR5, as they offer a new source of ligands with diverse chemical structures and biological activities.[1] Furthermore, the intestinal microbiota plays a role in modulating FXR and TGR5 through changes in microbial enzymes. Consequently, the impact of natural nutrients on the body's physiological functions through the intestinal microbiota has garnered public attention.[12]

3.1 FXR

FXR is a nuclear transcription factor that is primarily activated by endogenous BA.[26] It is mainly expressed in the liver and intestine, where it regulates gene expression involved in BA synthesis and transport. As a result, FXR serves as the primary regulator of BA homeostasis.[27] Moreover, FXR plays an important role in the

regulation of various metabolic pathways, including glucose, lipid, and sterol metabolism. FXR has been identified as a key target for the treatment of obesity, liver injury, cholestasis, and chronic inflammatory diseases.[3] Research has demonstrated that activation of intestinal FXR can effectively inhibit intestinal inflammation in LPS-induced mouse colitis models and human macrophages.[28] In the liver, FXR primarily functions to suppress BA synthesis, regulate the circulation of BAs in the liver-intestine axis, and maintain a constant BA content in the body.[29] Normal intestinal FXR plays a crucial role in maintaining the reflux of BAs to the portal vein, controlling the uptake of BA into intestinal cells, and limiting intracellular BA levels.[30] The most effective ligands that activate FXR are CDCA and CA, followed by LCA and DCA. FXR exerts its effects through direct binding of FXR/RXR heterodimers to the FXR response element (FXR-RE) in the promoter region of target genes.[1] Additionally, FXR can regulate other transcription factors, such as nuclear receptor small heterodimer partners (SHP) or hormones.[31] FXR binds to intestinal cells locally through BA, which leads to the expression of the regulatory hormone fibroblast growth factor 19 (FGF19, FGF15 is the mouse ortholog) in the intestinal tract, which then enters systemic circulation.[29] FGF15/19 interacts with the specific cell receptor liver fibroblast growth factor (FGFR4) in hepatocytes, inhibiting CYP7A1 activity and thereby regulating BA synthesis in the liver.[1] In summary, in the case of elevated intestinal BA levels, FXR is activated in the epithelial cells of the ileum and stimulates the transport of BA into the portal vein and back to the liver.[32] As a result, increased BA levels activate liver FXR, leading to a reduction in BA uptake from the blood and a decrease in BA synthesis. Furthermore, the study discovered that FXR can regulate the levels of lipid and glucose levels in the liver and serum, potentially impacting cardiovascular disease.[33] Obeticholic acid (OCA), an

FXR agonist, is currently the only designated drug being developed for the breakthrough treatment of nonalcoholic fatty liver disease (NAFLD).[34] The mechanism of action of OCA is attributed to its properties as a semi-synthetic hydrophobic BA analogue, which has activation potency similar to endogenous BA chenodeoxycholic acid but is 100 times more potent. Additionally, OCA induces the expression of gut-derived hormones, particularly FGF19.[35] In recent human trials, the administration of OCA to NAFLD and T2DM patients has been shown to increase insulin sensitivity.[36] However, some patients treated with OCA have reported itching, and the underlying mechanism for this side effect remains unclear.[37]

3.2 TGR5

TGR5 is a seven-transmembrane G-protein coupled secondary BAs receptor discovered in 2002.[38] The primary ligands for TGR5 are LCA and DCA, followed by CDCA and CA. The highest expression of this receptor was found in the ileum and colon (epithelial cells, endocrine cells, and intestinal neurons), bile duct tree (bile duct cells), gallbladder wall, placenta, and spleen.[12] Activation of the TGR5 signal regulates metabolic homeostasis, particularly in BAs and glucose metabolism. Studies have shown that fexaramine, an FXR agonist, has beneficial effects such as increasing energy consumption in brown adipose tissue (BAT), promoting browning of white adipose tissue (WAT), and altering BA composition. These effects have been attributed to the activation of TGR5 and can be reversed by TGR5 knockout models.[1] Furthermore, evidence suggests that FXR and TGR5 may be co-expressed in intestinal endocrine L cells. Activation of FXR in these cells promotes the transcription of the TGR5 gene through the FXR binding site in the TGR5 gene promoter.[39] FXR and TGR5 are also expressed in pancreatic β cells, and in humans, BA signals can promote insulin synthesis and secretion through these receptors.[29] This

mechanism may have potential implications for the treatment of diabetes mellitus type 2 (T2DM).[40,41] Additionally, the activation of TGR5 can trigger the release of various intestinal peptides, including intestinal motility peptideyy (PYY), which is involved in regulating immune signals.[42] The activation of TGR5 also promotes the production of the intestinal hormone glucagon-like peptide 1 (GLP-1), which promotes insulin secretion and appetite regulation. Moreover, it enhances energy consumption by converting thyroid hormone T4 into the active form T3.[42] While FXR agonists have been associated with side effects such as itching, recent studies suggest that TGR5 may not be involved in mediating pruritus in humans.[12] Consequently, the development of TGR5 agonists has emerged as a research focus, as they may potentially overcome the side effects associated with FXR agonists.

4. Mechanism of action mediated by polyphenols

As shown in Figure 2, dietary polyphenols generally are typically found in a bound form in food. Upon oral intake, these polyphenols are initially released into the stomach, a process facilitated by gastric digestive enzymes. Due to variations in structure and polymerization degree, different polyphenols exhibit varying levels of resistance to digestion.[43] The stomach absorbs polyphenols to a limited extent, after which they enter the duodenum through the pylorus. It is widely acknowledged that the small intestine serves as the primary site for absorption of most oral pharmaceutical preparations in the human body, allowing them to enter the blood circulation. Approximately 5-10% of the polyphenols in their free state are absorbed at this location.[44] Upon entering the blood stream, polyphenols accumulate in the liver and undergo methylation, glucuronidation, and sulfonation. However, due to the significant efflux of transporters, dietary polyphenols have low bioavailability in the intestinal mucosa.[4] Upon reaching the colon, the majority of unabsorbed polyphenols

are metabolized by the intestinal flora, resulting in the production and utilization of phenolic acid degradation products.[4] It is worth noting that different polyphenols can also influence the activities of the intestinal flora.

Many animal studies have evaluated the effects of polyphenols on the synthesis and metabolism of BAs and their mechanisms.[12,45,46] Ingestion of polyphenols has been found to increase cholesterol metabolism in the liver, decrease blood cholesterol levels, increase BA excretion in the intestine, and reduce BA accumulation.[12,45,46] Clinical studies have reported that polyphenol intervention can lead to a reduction in serum BAs in mice or humans.[47,48] However, there is currently no literature that summarizes and analyzes the specific mechanism by which polyphenols regulate BA synthesis and metabolism. Based on this, we propose that polyphenols can directly activate/inhibit BA receptors FXR and TGR5. Furthermore, the synthesis and metabolism of BAs can be regulated by indirectly activating/inhibiting FXR and TGR5 through their effects on intestinal microorganisms.

4.1 Polyphenols directly act on BA-activated receptors

Natural FXR and TGR5 ligands derived from plants serve as valuable templates for the development of novel FXR and TGR5 regulators. As shown in Table 1, polyphenols have been widely reported as activators and antagonists of FXR and TGR5. The effectiveness of these polyphenols has been confirmed through biological models, with some studies employing molecular model docking to illustrate their interaction with FXR pockets.[12]

Berberine is a kind of quinoline alkaloid that can be combined with statins to enhance the hypolipidemic effect and reduce the dose and side effects of statins. The double luciferase reporter gene assay showed that 2.5-50 mM berberine could enhance the luciferase activity of hFXR and hLXRα-activated OATP1B1 promoters in a

concentration-dependent manner in HepG2 cells, and the half effective concentration (EC50) was 12.19 ± 0.86 and 32.15 ± 2.32 mM, respectively.[10] In addition, after silencing FXR or LXRα with small interference RNA (siRNA), the expression of OATP1B1 induced by berberine was significantly decreased. Western blotting analysis of FXR and LXRα protein levels in cytoplasm and nucleus of berberine-treated HepG2 cells showed that berberine induced nuclear translocation and activation of FXR and LXRα. In HepG2 cells, 10 μM phytosterone (plant sterol guggulsterone, GS) promoted the expression of endogenous BSEP in the presence of FXR agonists such as chenodeoxycholate or GW4064. The maximum induction rate is 400-500% induced by FXR agonist alone, which reduces blood lipids in human primary hepatocytes and hepatoblastoma cells.[50] In addition, in the absence of FXR agonists, GS alone slightly increased the activation of the BSEP promoter.[50] The researchers found that polyphenols extracted from date palm fruit (containing hydroxycinnamic acid, proanthocyanidins, and lipophilic polyphenols) could also be used as co-agonist ligands for mouse FXR, and the ability to activate FXR with binding BA was stronger than that of BAs alone.[9] The extract activated PPARα chimera in a dose-dependent manner alone. It was also found that the combination of date palm fruit polyphenols and BA enhanced the expression of FGF19 in Caco-2 cells in a dose-dependent manner.[9]

Tetrahydroflavanone (Cryptochinones A-D) is a polyphenol isolated from the leaves of *cryptocarya chinensis*.[11] It was found that tetrahydroflavanone could transactivate FXR and regulate the promoter effect in a dose-dependent manner, including GAL4, SHP, CYP7A1, and PLTP promoters. As shown in Fig. 3BC, the molecular docking of cryptochinones A-D and FXR showed that flavanone showed similar activation to FXR as CDCA, thus reducing the mRNA expression of CYP7A1.[11,56] Kaempferol is

widely distributed in fruit and vegetables. It is an important ingredient in the traditional medicinal formula. Kaempferol reversed the decreasing trend in CDCA and 12α-hydroxylated BAs by increasing the CYP27A1 and sterol CYP8B1 expressions and upregulated FXR expression.[52] Importantly, molecular docking analysis revealed a direct interaction between kaempferol and FXR, the master regulator of BA signaling. Fig. 3D. shows the predicted binding position of kaempferol with mouse FXR. These results can prove that polyphenols can directly activate/inhibit FXR at the molecular level and verify our conclusions *in vitro.* *Passiflora leschenaultii* DC belongs to the family *Passifloraceae,* which possesses rich polyphenolic compounds with antioxidant, analgesic, anti-inflammatory, and antipyretic properties.[57] Leaf acetone extract (200/400 mg/kg) was given to paracetamol-induced Swiss albino male mice and Wistar albino rats for 14 days. It was found that acetone extract could significantly reduce the elevated levels of SGPT, SGOT, and ALP in serum.[53] The results of the docking study showed that there was a spatial interaction between the identified compounds and FXR to activate FXR. This indicates that the extract of *P. leschenaultii* leaves extract has a protective effect on liver injury induced by paracetamol. In addition, the molecular docking study of β-sitosterol in *Prosopis cineraria* L. (Druce) fruit extract with FXR receptor showed that they had an excellent binding conformation.[55] As a FXR agonist, β-sitosterol can reduce the levels of serum cholesterol, triglyceride, VLDL and LDL. At the 400 mg/kg dose, the result is almost the same as that of the standard drug simvastatin. It significantly reduces the hyperlipidemia of Sprague-Dawley rats induced by Triton.

EGCG is also considered to be an activator of FXR. It has been confirmed that EGCG can activate FXR in a specific and dose-dependent manner.[58] In addition, EGCG can induce the expression of FXR target genes *in vitro*. In the coactivator (SRC2)

recruitment experiment, the researchers found that EGCG did not recruit SRC2 to FXR, but it could inhibit GW6064's recruitment of SRC2 to FXR in a dose-dependent manner (IC50, 1μM).[58] GW6064 is an effective ligand for FXR synthesis.[59] EGCG can also inhibit FXR target gene expression induced by GW4064 or CDCA *in vitro*. mRNA expression of the FXR target factor set was induced in the intestinal tract of wild-type and FXR knockout mice treated with an acute dose of EGCG.[58] In another study, reporter gene analysis was used to study the regulatory effects of different extracts from Pu-er tea on transcription factors involved in lipid metabolism, such as FXR, liver X-activated receptor (LXR), and peroxisome proliferator-activated receptor (PPARγ and PPARδ).[54] It was found that the ethyl acetate extract of Pu-er tea had the strongest activating effect on FXR and PPARδ. Through column chromatography and UPLC-MS/MS technology, it was found that the main bioactive components in Pu-er tea were flavonoids.

Although there are many studies on the regulation of natural polyphenols on BA synthesis and metabolism, the studies on the direct effects of natural polyphenols on FXR and TGR5 still need to be completed. First, due to the limitations of *in vivo* studies, the current studies can only clarify the interaction between polyphenols and BAs from their physiological results. There are few or no details of the intermediate mechanism. Therefore, the *in vitro* study of molecular docking simulation is of great significance for elucidating the basic mechanism and determining the hypothesis of targeting *in vivo*. Second, the applicability of many animal models to the study of BAs is limited because the deviation in the distribution of BAs reduces the transferability to human mechanisms. For example, the BA pool in mice mainly comprises the hydrophilic BAs, muricholic, and cholic acids and thus differs markedly from the more hydrophobic BA pool in humans. Follow-up studies need to screen out more

natural polyphenols that directly act on the key targets of metabolic pathways and apply them to clinical medicine. Then, molecular docking and computer simulation explored the binding modes of different polyphenols and BA-activated receptors from various sources. Finally, developing an efficient targeted delivery system for functional substances is significant for developing drugs regulating natural metabolism.

4.2 Polyphenols regulate the synthesis and metabolism of BAs by changing intestinal microorganisms

BAs are synthesized in the liver, stored in the gallbladder, and then released into the intestines. The modification of primary and secondary BAs is controlled by intestinal microorganisms, which contribute uniquely to the diversity of BAs. These microorganisms produce bile salt hydrolase (BSH) and BAs inducible enzymes (BAI) that can modify BAs, resulting in the production of unconjugated BAs and secondary BAs, thereby promoting BA metabolism.[12] Cai et al. reviewed microorganisms with enzymes/genes that mediate biotransformation reactions.[12] BSH (E.C.3.5.1.24) is a microbial enzyme abundant in the intestinal microbiota, belonging to the protein NTN-hydrolase superfamily. Although all proteins in this large family hydrolyze amide bonds, they have different substrate specificities. The activity of BSH has been reported in various bacteria, including *Lactobacillus*, *Bifidobacterium*, *Enterococcus,* and *Clostridium*. Research has indicated that bacteria possessing BSH activity may also influence metabolic pathways, such as glucose and lipid metabolism, intestinal integrity, inflammation, and circadian rhythm.[60] Disruptions in the composition of gut microbiota can hinder BSH activity, leading to the accumulation of conjugated BAs in the colon.[1,12] Furthermore, certain secondary BAs, which are transformed by intestinal flora, may not be effectively reabsorbed and are excreted in feces.[3,4] This can

potentially stimulate increased BA biosynthesis in the liver, thereby resulting in enhanced cholesterol utilization and excretion. Consequently, any dietary component that influences the proliferation of bacteria that affect BSH activity in the intestinal tract can have an impact on BA's homeostasis and ultimately influence the cardiovascular health of the host. Additionally, unconjugated primary BAs that are not absorbed by intestinal cells enter the colon, where they are metabolized into secondary BAs by a small number of intestinal bacteria possessing enzymes encoded by BAI through the process of 7α-dehydroxylation. Due to the accessibility of hydroxyl groups, 7α-dehydroxylation can occur in primary BAs such as CDCA and CA, resulting in the production of DCA and LCA. The bacteria with 7α-dehydroxylation activity are known to belong to the *Clostridium* and *Eubacum*. These bacteria possess BA-induced genes (BAI). The intestinal microbiota has the ability to regulate BA metabolism by reducing taurocholic acid (TβMCA), which acts as a natural antagonist of the FXR receptor. Simultaneously, the antagonism of FXR can increase the expression of CYP7A1. Since the intestinal flora plays a central role in BA metabolism, any ruption in its balance can disturb BA homeostasis and impact the host's physiological processes. Several clinical studies conducted on patients and animal models with NAFLD or cholestasis have suggested that the protective effect on the liver may be attributed to changes in BA profile and the expression of BA-regulating genes.[28]

Recent studies have revealed that the intake of dietary polyphenols can lead to alterations in intestinal microorganisms, consequently impacting the synthesis of BAs.[60] Polyphenols, which are present in various foods like vegetables, fruits, and grains, have been recognized for their beneficial effects on human health. Fig. 4 illustrates the potential mechanism through which polyphenols regulate BA

metabolism by influencing intestinal microbes. Our findings suggest that polyphenols derived from different sources indirectly modulate the activation/inhibition of liver and intestinal FXR and TGR5 via intestinal microorganisms, as shown in Table 2.

4.2.1 Polyphenols regulate BA metabolism by affecting BSH enzyme-producing bacteria

Lactobacillaceae is a bacterium producing secondary BAs (LCA, DCA) in the colon.[85] Studies have found that an increase in *Lactobacillaceae* accompanies hepatic steatosis. Our study found that only xyloglucan compounded inulin could activate FXR and TGR5 in the liver and reduce the blood glucose level of ICR/KM mice induced by a high-fat diet.[85] *Lactobacillus* belongs to *Lactobacillaceae.* It is a kind of functional microorganism composed of Gram-positive and catalase-negative bacteria. Lactic acid produced by *Lactobacillus* is the main metabolic final product of carbohydrate fermentation. The most common types of *Lactobacillus* isolated from the gastrointestinal tract are *Levilactobacillus brevis*, *Lacticaseibacillus casei*, *Lactobacillus acidophilus*, *Lactiplantibacillus plantarum subsp. plantarum,* and *Ligilactobacillus salivarius*.[86] The genus *Lactobacillus* has been reported to be a microorganism expressing BSH in the gut.[87] BSH enzymes catalyze the deconjugation of bile salts by hydrolyzing the amide bond, thereby releasing the glycine/taurine moiety from the steroid core. Existing studies have found that *Lactobacillus acidophilus* can deconjugate taurocholic acid. Amino acids released by deconjugate can be further used as carbon and nitrogen sources for bacterial maintenance and survival. In addition, the bile salt hydrolase activity in the ileum content of mice was reduced by 86% without *Lactobacillus* and more than 98% without *Lactobacillus* and *Enterococci*.[87] Due to the detersive properties of BAs, certain BAs have antibacterial and inflammatory properties at high levels, including disruption of bacterial and host

cell membranes, protein denaturation, and iron and calcium chelation, which can cause oxidative damage to DNA.[88] Therefore, the tolerance of microorganisms to bile and BAs is important for their survival and persistence in the gastrointestinal tract. However, studies have found that *Lactobacillus* has an inherent resistance mechanism to deal with BAs.[88] Dihydromyricetin can increase the proportion of beneficial *Lactobacillus*, thereby increasing the unconjugated BAs in the gastrointestinal tract, including CDCA and LCA, enabling BAs to activate specific receptors, such as FXR and TGR5, and maintain intestinal integrity. This significantly improved colitis symptoms, intestinal barrier destruction, and colitis in DSS-treated mice.[67] Blueberry extract has been found to significantly increase BAT's energy consumption and improve liver fat metabolism in mice fed with a high-fat diet.[89] This is closely related to the expansion of *Lactobacillus* and the decrease of FXR inhibitors (TαMCA and TβMCA). The antibiotic treatment completely weakens this therapeutic effect. Studies have shown that intake of hesperetin-7-O-glucoside can accelerate the biosynthesis and excretion of BAs, thereby promoting digestion and reducing liver cholesterol and triglycerides.[88] Hesperetin-7-O-glucoside significantly increased the diversity of intestinal microbiota in mice, especially *Lactobacillus*, which is related to the secondary metabolism of BAs. Dietary supplements of polyphenol extract (quinoa and resveratrol) can effectively improve the level of *Lactobacillus* and promote the activity of the BSH enzyme. They indirectly activate FXR and TGR5, increase the transcriptional level of CYP7A1, and reduce the weight of mice. $_{L}$-Theanine is a bioactive component in tea, which has great potential to regulate lipid metabolism. It was found that $_{L}$-Theanine supplementation of 100mg/kg to Balb/c mice for 28 days decreased the activities of *Lactobacillus*, *Streptococcus*, *Bacteroides*, *Clostridium,* and *Enterobacter* associated with bile salt hydrolase, decreased the activity of bile salt

hydrolase, and increased the level of ileal binding BAs (such as glycocholic acid and LCA), thus inhibiting intestinal FGF15 signal pathway.[46] Inhibition of FXR-FGF15 signal transduction was accompanied by up-regulation of CYP7A1 gene and protein expression and increased liver production of CA, DCA, glycine cholic acid, and glycine ursodeoxycholic acid. Nuciferine has been found to alleviate alcoholic fatty liver in Sprague-Dawley rats fed with a high-fat diet, reduce the level of *Lactobacillus*, reduce BSH production, reduce 7α-dehydroxylation genus, and increase taurine metabolism-related genus.[76] In addition, *penthorum chinense* Pursh. extract (PCPE) was also found to improve the NAFLD of C57BL/6J mice by reducing the relative abundance of BSH-producing bacteria, especially *Lactobacillus*.[77] Theabrownin is one of the most active and abundant pigments in Pu-er tea. It has been found that supplementation of 450mg/kg/d theabrownin from Pu-erh tea to mice on a high-fat diet for 26 weeks can reduce the level of *Lactobacillus* in the intestine, increase the level of ileal conjugated BAs and then inhibit the intestinal FXR-FGF15 signal pathway, increasing liver production, BAs excretion, liver cholesterol, and fat production. The inhibition of intestinal FXR-FGF15 signal is accompanied by the increase of enzyme gene expression in the secondary BAs synthesis pathway, the production of chenodeoxycholic acid in the liver, and the activation of FXR in the liver. Reduced levels of *Lactobacillus* were also observed in the guts of mice supplemented with apple polyphenol extract, which reduces the activity of BSH.[45] Another interesting study found that supplementing mice fed a high-fat diet with 500 mg/kg/d of apple polyphenol extract for five weeks, restricting the mice's circadian rhythm, was able to reduce the F/B ratio in the gut and reduce ZT0. The levels of fecal total BA (TBA), secondary BAs, and unconjugated BAs significantly increased the expression of liver FXR at ZT0 and BSEP at ZT12. They inhibited the expression

of ileal FXR at ZT12. This work demonstrates that apple polyphenol extracts can regulate BA metabolism and prevent circadian rhythm disturbances in a clock-dependent manner.[61]

The action mechanism of *Bifidobacterium* and *Lactobacillus* is similar, which can change glucose metabolism or prevent protein misfolding.[88] It can counteract the harmful effects of bile salt in the intestine. *Bifidobacterium* can secrete BSH and modify primary BAs. In humans (n=20), drinking polyphenol-rich red wine (272 ml/d) was found to promote the growth of *Bifidobacterium*.[90] It has been found that resveratrol (RSV) can attenuate trimethylamine-N-oxide (TMAO)-induced atherosclerosis in ApoE$^{-/-}$ mice. RSV increased the activity of bile saline hydrolase by increasing the levels of *Lactobacillus* and *Bifidobacterium*, thus promoting the unwinding and excretion of BA in C57BL/6J and ApoE$^{-/-}$ mice.[91] This decreased the content of BAs in the ileum, inhibited FXR-FGF15, increased the expression of CYP7A1, and promoted the synthesis of BAs in the liver. The effect of FXR antagonists on the expression of FGF15 and CYP7A1 was the same as that of RSV, while FXR agonists could block the change of FGF15 and CYP7A1 expression induced by RSV.[91] In mice treated with antibiotics, RSV neither decreased TMAO levels nor increased liver BA synthesis. Antibiotics could significantly eliminate the inhibitory effect of RSV on AS induced by TMAO. The other four kinds of polyphenol extracts (blueberry extract, EGCG, grape extract, and quinoa) can increase the level of *Bifidobacterium*, regulate the activation/inhibition of FXR and TGR5, and reduce the body mass index of C57BL/6 mice.

Bacteroides are among the most common and abundant bacterial genera in the human distal gut. *Bacteroides* species are generally "friendly" commensal organisms in the gut, are major vitamin K synthesizers, and play an essential role in the

immunoregulation of the human immune system. The study found that *Bacteroides* dominated the gut microbiota of Italian children, while *Prevotella* dominated that of African children, and that different diets may be a driving factor in the formation of gut microbiota.[92] *Bacteroides* can degrade a variety of complex carbohydrates and interact with host immune cells.[92] Danielle E. reports that *Bacteroides BV01*, a prominent human gut symbiont *Bacteroides* vulgaris, alters the transcriptome of its host.[93] This alteration occurs through phage-induced repression of a tryptophan-rich sensory protein (TspO) and inhibition of BA decoagulation. Microbially modified BAs are important signals for mammalian hosts, a mechanism by which *Bacteroides* affect mammalian phenotypes. Apple polyphenol extract can decrease the level of hyodeoxycholic acid and increase β-muricholic acid by increasing *Bacteroides*, prevent colon shortening and mucosal damage, and significantly improve DSS-induced ulcerative colitis in C57BL/6.[94] Our investigation found that multiple polyphenol extracts (Chokeberry, dihydromyricetin, EGCG, lignin-Rich insoluble residue of Brewer's spent grain, xyloglucan compounded inulin) can increase the level of *Bacteroides* in the intestine, act as indirect activators of FXR and TGR5, alleviate DSS-induced colonic inflammation, and reduce obesity levels in mice fed a high-fat diet. In another study, mice were fed a diet supplemented with $_{L}$-Theanine for 100/300mg/kg for 28 days and found that BSH activity decreased. It increases the level of ileal binding BAs, such as glycine cholic acid (GCA) and taurine cholic acid (TCA), thus inhibiting the intestinal FXR-FGF15 signal pathway.[46] In humans, TCA in jejunum has been reported to lower blood sugar and activate the release of satiety hormones such as GLP-1 and PYY.[95] In addition, after ingestion of 300 g raspberry, the ileum metabolites detected by LC-MC showed that triterpenoids increased, and TCA and GCA increased by 100 times that before ingestion.[96] The upregulation of

CYP7A1 mRNA and protein expression and the increased secretion of CA, DCA, GCA, glycine cholic acid, and glycine ursodeoxycholic acid in the liver accompanies the inhibition of the FXR-FGF15 signal pathway. At the same time, increasing hepatic uncoupled BAs upregulated the expression of (HMG)-CoA reductase mRNA and protein and down-regulated the expression of stearoyl-CoA desaturase-1, hepatic low-density lipoprotein receptor and type B scavenger receptor mRNA and protein. This indicates that $_{L}$-Theanine can be used as an indirect inhibitor of FXR to reduce the levels of serum cholesterol and triglycerides. In short, polyphenols significantly regulate *Bacteroides*, indirectly regulating the activation/inhibition of FXR and TGR5. Future studies will reveal the physiological and metabolic details of little-known *Bacteroides* strains and their interactions.

Enterococcus can produce BSH enzyme with high activity and has unique allosteric catalysis for BA.[97] Curcumin can increase the concentration of primary and secondary BAs metabolites (CDCA and LCA) by increasing *Enterococcus*, reverse the synthesis of FXR and TGR5 induced by lipopolysaccharide, increase interleukin 22 (IL-22) produced by ILC3, and improve the imbalance of intestinal environment Dihydromyricetin[67] and resveratrol[91] supplementation can increase *Enterococcus* in mice and regulate BA synthesis and metabolism as an indirect agonist/inhibitor of FXR and TGR5.

In summary, the intake of dietary polyphenols (Dihydromyricetin, esperetin-7-O-glucoside, RSV, Curcumin, etc.) can significantly increase the gut microbes that produce BSH enzyme (*Lactobacillus*, *Bifidobacterium*, *Bacteroides*, *Enterococcus*, etc.), which may affect the accumulation of conjugated BAs in the colon and lead to the increase of secondary BA affection, thereby affecting the BA profile and regulating the activation and inhibition of FXR and TGR5 in the intestine and liver,

thus affecting metabolic diseases.

4.2.2 Polyphenols regulate BA metabolism by affecting bacteria with BAI genes

Clostridium is a kind of anaerobic, Gram-positive, spore-forming bacteria that is the main cause of gastroenteritis in hospitals. It has been found that *Clostridium* is a BA 7α-dehydroxy intestinal bacteria that can bioconvert primary BAs into secondary BAs. The study found that adding 1% grape extract to a high-fat diet could induce BAT thermogenesis in obese mice.[72] The intake of grape extract increased the abundance of *Clostridium*, which was negatively correlated with the concentration of TαMCA and TβMCA, and positively correlated with DCA. The change of BA promotes the expression of TGR5 in BAT, thus promoting heat production. The survey found that hesperetin-7-O-glucoside[85] and lignin-rich insoluble residue of Brewer's spent grain[74] can improve the level of *Clostridium* and play an exciting role in FXR or TGR5. It can promote the transcription of CYP7A1 and reduce the body weight of mice fed a high-fat diet. *Clostridium* increases the level of secondary BAs through 7α-dehydroxylation, which further promotes its resistance. On the other hand, a 1% proanthocyanidin-rich extract of grape polyphenols was supplemented in the diet of diabetic rats for four weeks. It was found that the relative abundance of intestinal bacteria related to secondary BAs decreased, especially *Clostridia*, and the levels of serum secondary BAs THDCA, ω-muricholic acid (ωMCA), and tauro-ω-muricholic acid (TωMCA) decreased. The serum primary BAs (PBA) level increased, consistent with PBA synthase CYP7A1 gene expression.[98] The expression of FXR-responsive genes SHP, FGF15, and *Fabp6* decreased in the ileum and liver, negatively regulating the synthesis of PBA and promoting glucose regulation. In addition, a variety of polyphenol extracts ($_{L}$-theanine[46], nuciferine[76], *Penthorum chinense* Pursh. extract[77]) decreased the level of *Clostridium* in the intestines of C57BL/6 mice and Sprague-

Dawley rats induced by a high-fat diet. It promoted the transcription of CYP7A1 or CYP27A1 as an inhibitor of intestinal FXR, thus reducing obesity.

Blautia is a genus of anaerobic bacteria with probiotic properties widely found in the feces and gut of mammals. Recently, much research has focused on the probiotic effects of this genus, such as biotransformation and its ability to regulate host health and alleviate metabolic syndrome. It has been found that certain *Blautia* can perform 7α-dehydroxylation of primary BAs and convert them into secondary BAs, such as lithocholic acid and deoxycholic acid.[76] It shows that this genus may have a significant impact on BA metabolism. Polyphenols can regulate the ratio and spectrum of primary and secondary BAs by controlling the number of *Blautia*, thereby playing the role of BA receptor activators. Oat (*Avena sativa* L.), as a well-known functional food, has been widely reported to have cholesterol-lowering effects because it is rich in β-glucan, phytic acid, phenolic substances, and *Avena sativa* L., as well as some unique components soluble biologically active compounds. It was found that flavonoids from whole-grain oats (FO) supplemented with 50mg/kg could significantly improve the serum lipid distribution and reduce body weight and lipid deposition in C57BL/6N mice fed a high-fat diet.[71] 16s rRNA sequencing showed that FO significantly increased *Akkermansia* and decreased *Lachnoclostridium*, *Blautia, Colidextribacter,* and *Desulfovibrio*. This leads to a decrease in the production of secondary BAs, which up-regulates the expression of PPAR α, CPT-1, CYP7A1, FXR, TGR5, NTCP, and BSTP, and down-regulates the expression of SREBP-1c, FAS, and ASBT. FO inhibits adipogenesis, promotes fat decomposition and BA synthesis, and is excreted through the FXR pathway into feces. A decrease in *Blautia* was also found in HFD-fed mice fed with 2g/d quinoa.[79] However, the difference is that quinoa upregulates the expression of TGR5 in the colon and brain and GLP-1 in the colon,

liver, and brain. At the same time, down-regulate the expression of TLR4 in the colon and liver and the markers of ER stress and oxidative stress in the liver and serum. In addition, tight junctions in the colon and brain are also increased by quinoa. This is due to the stimulating effect of TGR5. In another study, adding a 1% proanthocyanidin-rich extract of grape polyphenols to a high-fat diet caused an increase in the proportion of *Blautia*.[98] This may be related to the decrease in the relative abundance of other intestinal bacteria associated with secondary BAs, such as *Clostridium* and *Lachnospiraceae*. Thus, as an inhibitor of intestinal FXR, it changes the BAs-FXR signal pathway and promotes glucose regulation. In addition, dihydromyricetin supplementation to IBD mice can increase intestinal *Blautia* and restore the metabolism of intestinal microorganisms and BAs in the gastrointestinal tract.[67] This is related to increased levels of unconjugated BAs in the gastrointestinal tract containing CDCA and LCA, enabling BAs to activate specific receptors, such as FXR and TGR5, and maintain intestinal integrity, alleviating colitis induced by DSS in mice.

In brief, the intake of grape extract, hespertin-7-o-Glucoside, lignin-rich insoluble, proanthocyanidin-rich extract, $_{L}$-theanine, nuciferine, *Penthorum chinense* Pursh. extract, FO, and dihydromyricetin affect the synthesis of secondary BAs (DCA and LCA) by changing the amount of *Clostridium* and *Blautia*, which have BAI genes, then regulate the activation of FXR and TGR5, and affect the expression of genes related to BA metabolism.

4.2.3 Polyphenols regulate BA metabolism by influencing other gut microbes

Firmicutes and *Bacteroidetes* are the two most important bacterial phyla in the gastrointestinal tract, which have received extensive attention recently. *Firmicutes* include gram-positive bacteria with rigid or semi-rigid cell walls, mainly from the

genera *Bacillus*, *Clostridium*, *Enterococcus*, *Lactobacillus*, and *Retrogastrococcu*. *Bacteroidetes* include approximately 7,000 different species of Gram-negative bacteria, mainly from the genera *Bacteroides*, *aliistipes*, *Parabacterium*, and *Prevotella*. It can be seen that *Firmicutes* and *Bacteroidetes* contain many BSH enzyme-producing bacteria and 7α-dehydroxyl active bacteria, so the ratio of F/B can have a significant impact on BA synthesis and metabolism. In addition, the *Firmicutes/Bacteroidetes* ratio is widely recognized to be important in maintaining normal intestinal homeostasis. Dysbiosis is considered to be an elevated or decreased F/B ratio, the former typically presenting with obesity and the latter presenting with inflammatory bowel disease (IBD). Although some studies have pointed out that F/B cannot be used as a marker of obesity.[62] In another study, researchers put obese subjects on a fat-restricted, low-calorie diet for one year. They found that it decreased the F/B ratio, suggesting that the reduction in bile excretion reversed the F/B ratio to the normal range. In addition, the study found that in the non-alcoholic fatty liver rats model, the decrease in CA level correlated with the *Firmicutes* level. This causes gut dysbiosis and lipid accumulation in the liver, resulting in altered BA levels in rat serum, liver, and cecum.[99] Decreased F/B ratios in the gut and serum, liver, and most secondary BAs were also found in mice taking antibiotics (vancomycin+imipenem and cephalosporin+neomycin).[100] Combining the two antibiotics significantly increased the mRNA of hepatic BAs uptake transporters (*Ntcp* and *Oatp1b2*) and tubular BAs efflux transporters (BSEP and *Mrp2*), decreased the mRNA of hepatic BAs synthase CYP8B1, and increased enterohepatic circulation of BAs. This suggests a link between gut bacteria and host BAs metabolism. Hesperetin-7-O-glucoside is a typical flavonoid monoglycoside produced by hydrolysis by hesperidin removing rhamnose. Intake of hesperetin-7-O-glucoside can accelerate the biosynthesis and

629 excretion of BAs in C57BL/6J mice, thus promoting digestion and reducing liver
630 cholesterol and triglycerides.[88] 16S rRNA gene sequencing showed that hesperetin-7-
631 O-glucoside significantly increased the diversity of intestinal microbiota and
632 decreased the ratio of F/B, especially the bacteria related to the secondary metabolism
633 of BAs. Continuous administration of *Penthorum chinense* Pursh. extract with
634 2/4/8g/kg body weight for eight weeks can effectively improve NAFLD caused by
635 HFD in mice and reduce dyslipidemia and insulin resistance.[77] *Penthorum chinense*
636 Pursh. extract treatment reduced intestinal biological imbalance, especially decreased
637 the relative abundance of BSH-producing bacteria, significantly increased the level of
638 taurine-conjugated BAs in feces, such as taurine-β-rhamnic acid (TβMCA), taurine
639 ursodeoxycholic acid (TUDCA) and taurine chenodeoxycholic acid (TCDCA), and
640 increased the content of CDCA in the liver. TUDCA supplementation has been shown
641 to increase insulin sensitivity in the liver and muscles in humans.[101] The protein and
642 mRNA expression of FXR and FGF15 decreased. At the same time, the increase of
643 taurine-conjugated BAs inhibited the intestinal signaling pathway, which was related
644 to the increased expression of enzyme genes in the alternative BAs synthesis pathway,
645 thus reducing cholesterol levels. The increase of CDCA produced by the secondary
646 BAs synthesis pathway promotes the activation of FXR and the excretion of BAs in
647 the liver. Resveratrol decreased the percentage of F/B in the intestine and the level of
648 BA, including CDCA in the feces of mice fed with a high-fat diet, while CDCA
649 stimulated FXR, NF-κB, and SR-B1 in Caco-2 cells. Studies have shown that the
650 intestinal microbiome is the main target of resveratrol. It improves lipid balance, at
651 least in part, by inhibiting the increase of intestinal SR-B1 stimulated by CDCA.[66] In
652 our investigation, it was found that cranberry extract[66] and quinoa[79] can reduce the
653 F/B ratio in the intestine. They act as agonists of FXR/TGR5 and limit body weight

654 gain in high-fat diet-induced C57BL/6 mice. Blackberry (*Aronia melanocarpa* L.) is
655 rich in polyphenols, and chokeberry is extracted from the blackberry. Chokeberry
656 treatment was found to prevent high-fat-induced obesity, hepatic steatosis, and
657 dyslipidemia in rats fed a high-fat diet at a dose of 1000 mg/kg for 40 days.[64]
658 Chokeberry regulates the composition of intestinal flora and reduces the F/B ratio
659 with the prolongation of treatment time. The total BA pool was gradually reduced,
660 especially when the relative content of CA and DCA was decreased and the relative
661 content of CDCA was increased. This conclusion was confirmed by the experimental
662 results of fecal microbiota transplantation (FMT). However, supplementation of 1%
663 grape extract in a high-fat diet can increase the F/B ratio, regulate changes in BAs,
664 and promote TGR5 in BAT. Promotes thermogenesis and reduces body weight in
665 mice.[72] Another study found that curcumin at 300 mg/kg for 21 days could inhibit the
666 LPS-induced decrease in the F/B ratio in the chicken intestine, remodel the cecal
667 microbial community, and activate FXR to maintain BA's metabolism.[65] Curcumin
668 helps regulate intestinal mucosal immunity by promoting anti-inflammatory
669 (interleukin-10, IL-10) cytokines and increasing concentrations of BA primary and
670 secondary metabolites. This suggests that curcumin can target the gut microbiome to
671 regulate BAs metabolism and ILC3s, improving the function of LPS-induced
672 intestinal homeostasis in chickens. In addition, changes in *Firmicutes* or *Bacteroidetes*
673 were also found in apple polyphenol extract,[61,94] EGCG,[68] grape seed
674 proanthocyanidin,[73] and xyloglucan compounded inulin[85]-fed mice. This change
675 affects BA synthesis and metabolism, thereby restoring homeostasis. This change can
676 affect BA synthesis and metabolism and restore body homeostasis. Overall,
677 polyphenols can significantly affect F/B, thereby modulating the ratio of BAs, but the
678 interrelationship between changes in F/B and BA synthesis and metabolism needs to

be further explored.

Akkermansia muciniphila is an intestinal bacterium isolated from human fecal samples ten years ago. Its expertise in mucin degradation makes it a key organism at the mucosal interface between the lumen and host cells. It is considered the next generation of beneficial microorganisms that show many metabolic benefits. It is reported that there is a strong correlation between the abundance of *Akkermansia* and the level of BA uncoupling.[102] Although there is no direct evidence that *Akkermansia* produces BSH, studies have found that its abundance is related to the plasma BA pool.[89] Significantly, decreased *Akkermansia* levels were observed in obese people with inflammatory bowel disease and metabolic disorders. EGCG supplemented with 100mg/kg significantly increased the number of *Akkermansia* in mice fed a high-fat diet, decreased the intestinal FXR agonist CDCA, and increased the concentration and regulatory signals of FXR and TGR5 agonists in the liver.[69] This effectively reduces increased dietary obesity, visceral fat, and insulin resistance. In another study, EGCG significantly reversed the decreased population of serum primary cholic acid and β-muricholic acid as well as the increased population of taurine-conjugated cholic acid, β-muricholic acid, and deoxy-cholic acid in high-fat diet-fed mice.[103] The study found that adding 1% matcha green tea to a high-fat diet could improve obesity, fat accumulation, and liver steatosis in rats.[75] The results showed that matcha green tea could reverse the decline of *Akkermansia* caused by a high-fat diet, restore the composition of intestinal microorganisms, and thus restore the BA spectrum of feces. In addition, it was found that apple polyphenols extract,[45,61,94] blueberry extract,[89] cranberry extract,[66] quinoa,[79] flavonoids from whole-grain oat,[71] and xyloglucan compounded inulin[85] could increase the level of *Akkermansia* and act as an indirect agonist of FXR or TGR5. It reduces the expression level of CYP7A1, regulates BA

synthesis and metabolism, and reduces the body weight level of C57BL/6 mice. This association was further confirmed by adding chokeberry (*Aronia melanocarpa* L.)[64] to the Wistar rats fed on a high-fat diet. At present, only one study found that proanthocyanidin-rich extract of grape polyphenols[78] can increase the level of *Akkermansia* as an indirect inhibitor of intestinal FXR. It increases the expression level of liver CYP7A1. *Akkermansia* can be used as a medium for polyphenols to regulate BA metabolism, although the relationship mechanism is unclear. The possible mechanism is that *Akkermansia* affects the growth of BSH-producing microorganisms in the intestinal tract, which regulates BA metabolism.

Prevotella has been found to improve glucose homeostasis by enhancing BA synthesis and metabolism and FXR signal transduction, which is a promising intervention for new T2DM. 1000 mg/kg/d chokeberry (*Aronia melanocarpa* L.) can prevent obesity and liver steatosis and improve dyslipidemia in rats fed with a high-fat diet.[64] Chokeberry supplementation decreased the relative content of CA and DCA and increased the relative content of CDCA. These changes were positively correlated with *Bacteroides* and *Prevotella* and negatively correlated with *Clostridium*, *Eubacteria,* and *Ruminococcaceae*. In our study, we also found that quinoa[79] and total phenolic extracts of *Citrus aurantium* L[83] can increase the level of *Prevotella* in the intestinal tract of C57BL/6 mice and male Wistar rats, thus helping to activate FXR and TGR5.

It is reported that *Desulfovibrio* can promote the formation of secondary BAs, produce endotoxins such as LPS, and participate in the pathogenesis of intestinal inflammatory diseases.[104] EGCG,[68,70] flavonoids from whole-grain oat,[71] and chokeberry (*Aronia melanocarpa* L.)[64] decreased the level of *Desulfovibrio* in the intestinal tract of high-fat-fed mice, which was beneficial to the activation of FXR and

TGR5.

In addition, the supplement of polyphenols from different sources increased the number of beneficial bacteria such as *Faecalibaculum*, *Allobaculum*, *Eubacterium*, *Ruminococcaceae*, and *Turicibacter* in the intestinal tract. It decreased the number of harmful bacteria such as *Lachnoclostridium* and *Streptococcus*. Although there is a lack of studies on the effects of these bacteria on BA synthesis and metabolism, they may become an essential medium for polyphenols to affect BA synthesis and metabolism indirectly.

In conclusion, as important bioactive compounds, polyphenols may represent a natural complement and integrative therapy. They have the ability to influence the transformation and modification of primary and secondary BAs by gut microbes, regulate the effects of endogenous activators/inhibitors (BAs) on FXR and TGR5, and control metabolic diseases such as obesity and inflammation. Furthermore, plays a significant role in this process. The presence of polyphenols in the intestinal lumen can lead to changes in one or multiple microorganisms, ultimately affecting the entire intestinal microbial system. Further research is needed to explore the interrelationships between these microorganisms. Future studies should focus on investigating how polyphenols or their catabolism modulate host pathways and determining whether there is a causal link between changes in gut microbiota and host metabolic parameters. Given the complexity of the intestinal environment, the analysis of polyphenol metabolites' structure and function is still in its early stages. Therefore, it is crucial to conduct more omics analysis of intestinal microbial metabolites and identify metabolites that exhibit biological activity.

4.3 Polyphenols can activate/inhibit FXR and TGR5, but the mechanism is not elucidated

754 Many studies have shown that other polyphenols also can regulate the synthesis and
755 metabolism of BAs, thereby regulating the health of the body. Table S1 summarizes
756 these polyphenol extracts. Curcumin is a natural polyphenol beneficial to patients
757 with NAFLD. It has been proved that curcumin of 50/100 mg/kg can be used as an
758 activator of FXR to increase the transcription of CYP7A1 in C57BL/6 mice.[109] From
759 the classical way to promote the transformation of cholesterol to BA, it plays a
760 significant role in alleviating NAFLD induced by a high-fat and high-fructose diet.
761 Feeding *Rhizoma Coptidis* alkaloids at 140 mg/kg for 35 days reduced body weight
762 gain and serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein
763 cholesterol (LDL-C), total BA (TBA), and lipopolysaccharide[129]. Another study found
764 that grape seed proanthocyanidins extract enhanced FXR activity in a dose-dependent
765 manner in the presence of CDCA.[118] Intragastric administration of grape seed
766 proanthocyanidins could reduce triglyceridemia in wild-type mice but not in FXR
767 deletion mice. This shows that FXR is an important mediator of the TG-lowering
768 effect of procyanidins *in vivo.* In addition, the researchers found that grape seed
769 proanthocyanidins increased histone acetylation, decreased HDAC1 activity *in vivo,*
770 and inhibited recombinant HDAC2 and three activities in a dose-dependent manner *in*
771 *vitro.* At this time, the expression of the PPARα gene and phosphorylated protein
772 increased, and the target genes involved in fatty acid catabolism also increased. With
773 the increase of serum fibroblast growth factor 21 (*Fgf21*), the level of TG decreased
774 by 28%.[117] Resveratrol was fed to *M. amblycephala* juveniles on a high-carbohydrate
775 diet and was found to act as an inhibitor of FXR in the hindgut.[128] However, it can be
776 used as a TGR5 agonist to up-regulate CYP7A1 and down-regulate *mrp2*, *oatp1,* and
777 *oatp4* in the hindgut to increase BAs synthesis and bile excretion, thereby reducing
778 cholesterol accumulation. Furthermore, in mouse liver, enzymatically modified

779 isoquercitrin promoted the phosphorylation of acetyl-CoA carboxylase and increased
780 the expression of PPARα, constitutive androstane receptor, and FXR.[115]
781 Although these studies found that polyphenols from different sources can exert
782 activating/inhibiting effects on BA-activated receptors, the mechanism of action still
783 needs to be investigated. Complementary molecular docking and cellular models may
784 be the current preferred means to understand polyphenols' detailed mechanism of
785 action. In addition, these polyphenols may be more inclined to play a regulatory role
786 by regulating gut microbes on BAs, so exploring the interaction mechanism between
787 polyphenols and gut microbes is essential.
788 In summary, dietary polyphenol-rich extracts have demonstrated effectiveness in
789 humans in regulating BA synthesis and metabolism. These polyphenols achieve
790 cholesterol excretion through multiple pathways. We propose two mechanisms by
791 which dietary polyphenols regulate BA metabolism: (1) Direct interaction with BA-
792 activated receptors (FXR and TGR5). (2) Modulation of BA synthesis and
793 metabolism by influencing the gut microbiome. However, there are several areas in
794 current research that require improvement. Firstly, many of the studies lack
795 identification of the active compounds and their concentrations. Polyphenols, being
796 natural compounds, exhibit variations in distribution and concentration across source
797 materials, thereby impacting their effectiveness. Secondly, the research on
798 polyphenol-mediated regulation of BA metabolism through gut microbes has mainly
799 been correlational, and the underlying mechanisms remain undiscovered. Lastly, the
800 majority of the research has been conducted on animals, and clinical studies provide
801 limited and conflicting data. Future research should prioritize the following aspects:
802 (1) *In vivo* studies must be validated through targeted *in vitro* experiments such as
803 cellular and molecular simulations. (2) Targeting polyphenols and their metabolites to

specific microorganisms should be better understood. (3) More microbes that can modify BAs should be found. (4) Addressing the significant limitation of poor bioavailability in using polyphenols. This can be achieved by exploring alternative routes of delivery or administration, which is crucial for translational studies of polyphenols. (5) Evaluating the side effects of certain polyphenols, including carcinogenicity, pruritus-causing effects, toxicity, increased cholesterol and LDL-c levels, and decreased high-density lipoprotein cholesterol (HDL-c). Additionally, it is important to assess the effects of dosage and the sources of polyphenols. (6) Conducting clinical trials to develop drugs that regulate BA metabolism.

Author contribution statement

Yongyong Liu: Writing - original draft, Investigation. Kai Huang: Writing - review & editing. Yu Zhang: Writing – editing, Formal analysis, Conceptualization. Hongwei Cao: Software, Validation. Xiao Guan: Funding acquisition, Supervision.

Interest conflict

The authors declare that there are no conflicts of interest.

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Fig. 1. Synthesis and transformation pathway of BAs in the liver and intestine.

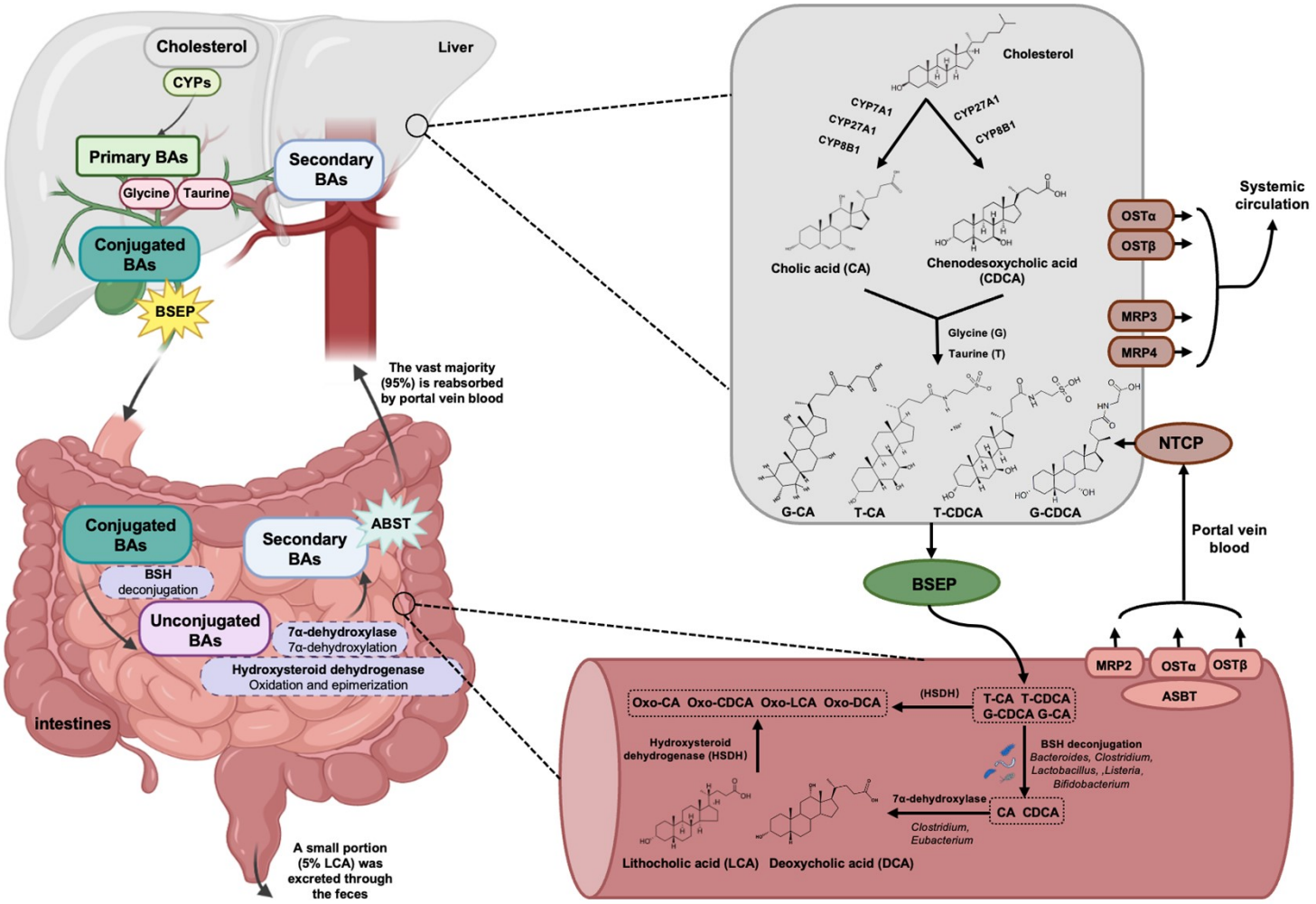

Fig. 2. Bioavailability of dietary polyphenols *in vivo*.

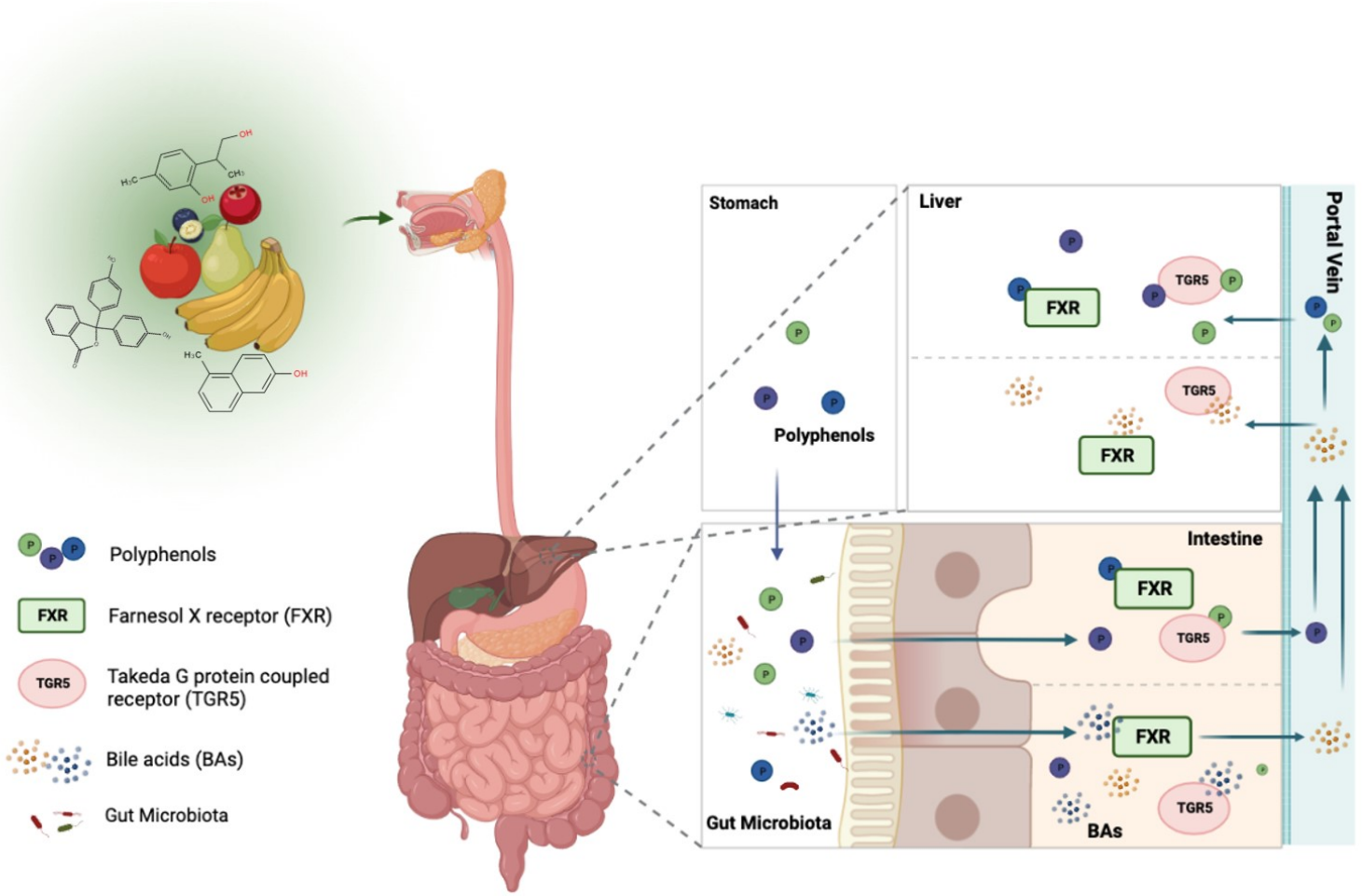

Fig. 3. (A) FXR structure; (B) Binding model of cryptochinone C in FXR ligand binding pocket. (C) Hydrophilic interactive binding mode of cryptochinone C in FXR ligand binding pocket. The oxygen atom is red and the hydrogen atom is white in color. The green line indicates the hydrogen bond interaction.[16] (D) The predicted binding position of kaempferol with mouse FXR.[18]

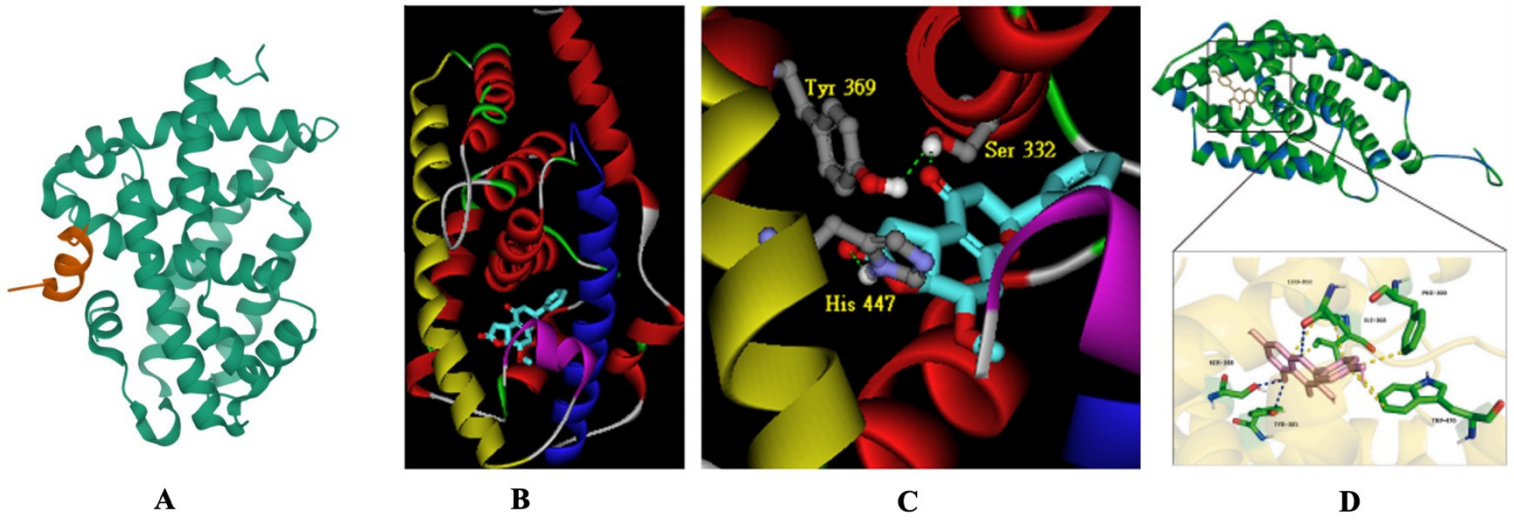

Fig. 4. Dietary polyphenols can regulate the composition of intestinal microorganisms, especially BSH enzyme producing bacteria (*Lactobacillus*, *Bifidobacterium*, *Enterococcus*, and *Clostridium*) and 7-dehydroxy active bacteria (*Clostridium* and *Eubacum*). Regulate intestinal FXR-FGF19 by regulating the ratio and type of endogenous primary and secondary BAs activators/inhibitors, and finally affect the synthesis of primary BAs in the liver. In addition, the activation/inhibition of TGR5 by polyphenols can regulate the expression of GLP-1 and PYY, and then regulate blood glucose.

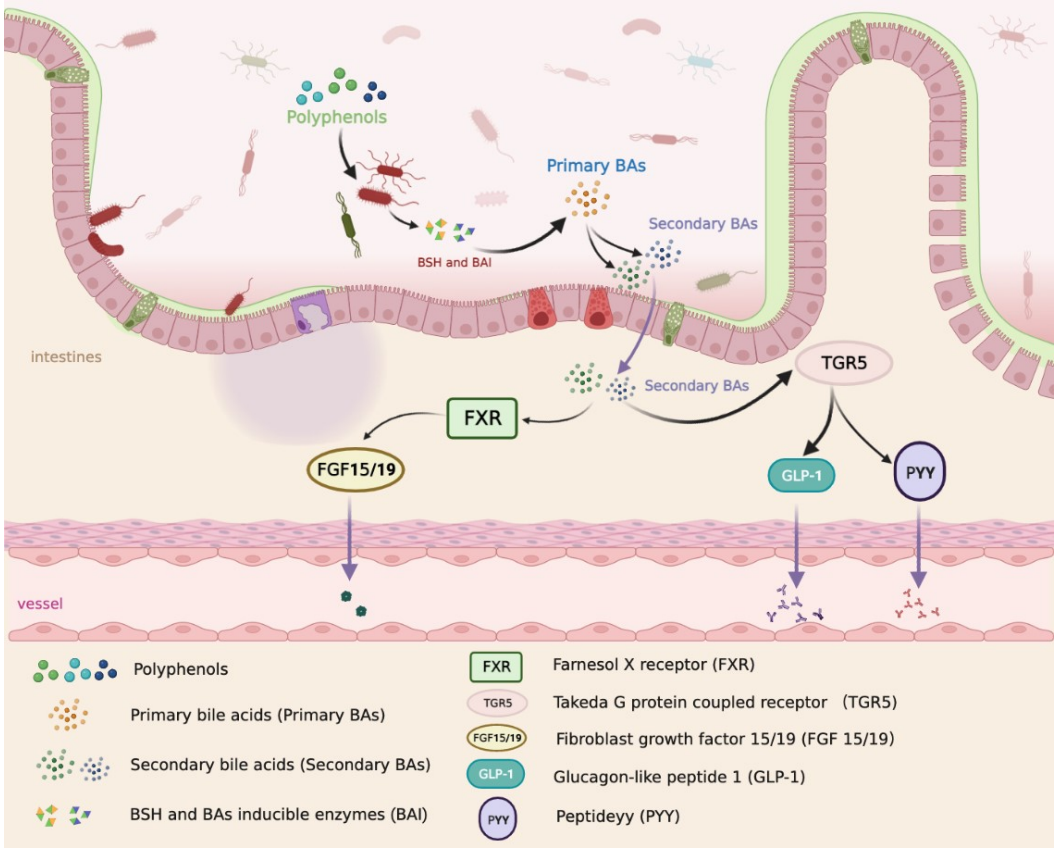

Table 1. Dietary polyphenols directly activate/inhibit FXR and TGR5 in the liver and intestine

Source of polyphenols	Dose	Model	time	With receptor action form	Metabolic or Functional Effects	Refs
Berberine	2.5-50 mM	HepG2 cell	24 hours	FXR agonist	OATP1B1, BSEP, PLTP, CYP7A1 ⬆; NTCP ⬇	10
Cryptochinones from *Cryptocarya chinensis*	1 mM	HepG-2 cell; Docking models	/	FXR agonist	SHP, PPARγ ⬆; CYP7A1 ⬇	11
Date palm extract (including hydroxycinnamic acids, proanthocyanidins, and lipohilic polyphenols)	100 mg/L	Caco-2 cells, Dulbecco's Modified Eagles medium (DMEM) supplemented with 20% FBS, 1% L-glutamine	12 hours	FXR agonist	PPARα, fibroblast growth factor 19(FGF19), *Ostα*; IBABP, *OSTβ* ⬇	9
Epigallocatechin-3-gallate (EGCG)	100 mg/kg	C57BL/6J FXR-knockout KO male mice	2 days	Intestinal FXR agonist	intestine FXR ⬆; FXR target gene expression induced by either GW4064 or chenodeoxycholic acid in vitro⬇	49
Guggulsterone	10 μM	Human Primary Hepatocyte and Hepatoma Cell	30 hours	FXR inhibitor	BSEP ⬆	50
		HepG-2 cell	24 hours	FXR inhibitor	BSEP, SHP ⬆	51
Kaempferol	50/100 mg/kg	$Apc^{Min/+}$ mice carry an impaired tumor suppress gene, molecular docking	6 weeks	FXR agonist	Ki67, LGR5 ⬇; CYP27A1, CYP8B1, BSEP ⬆	52
Polyphenols rich *Passiflora leschenaultii* leaves	200/400 mg/kg	Swiss albino male mice and Wistar albino rat paracetamol-induced, molecular docking	14 days	FXR agonist	SGPT, SGOT, ALP ⬇	53
Pu-erh tea extract	10/30/ 50 μg/mL	Cell model PPARδ, PPARγ, FXR and LXR	/	FXR agonist	FXR ⬆	54

Prosopis cineraria L(Druce) Fruit Extract	400/600 mg/kg	Triton-induced Sprague Dawley rats, molecular docking	24 hours	FXR agonist	serum cholesterol, triglyceride, VLDL, LDL, atherogenic index ⬇	55

Table 2. Dietary polyphenols indirectly activate/inhibit liver and intestinal FXR and TGR5 through gut microbes

Polyphenol	Dose	Animal Model	time	microbiome profiles	With receptor action form	Metabolic or Functional Effects	Refs
Apple Polyphenol Extract	125/500 mg/(kg·bw·day)	Male C57BL/6J mice fed a high-fat diet	12 weeks	*Akkermansia* ⬆; *Lactobacillus* ⬇	Liver FXR agonist	CYP7A1, CYP27A1, LRH-1⬇; MAFG, *Lxr, Abca1, Abcg1, Abcg5, Abcg8, Sar1b*⬆	45
	500 mg/(kg·bw·day)	Regulating the circadian rhythms in daytime-restricted high-fat diet feeding C57BL/6 male mice	5 weeks	*Firmicutes/Bacteroidetes, Lactobacillus* ⬇; *Akkermansia* ⬆	Liver FXR agonists, Ileal FXR inhibitor	BSEP ⬆; CYP7A1, ASBT ⬇; restored the rhythms of *Clock*, *Cry1* and *Cry2* in the ileum, restored the rhythm of *shp*	61
	100 mg/kg	C57BL/6 is processed with DSS	3 weeks	*Bacteroides, Akkermansia* ⬆; *Bacterodetes* ⬇	FXR and TGR5 agonist	NF-κB, p65, IKKβ, p-p65, p65, Il-6, CYP7A1, Lrh-1 ⬇; TGR5, Occludin, SHP, Fgf15, β-klotho ⬆	62
Blueberry Extract	5 gL^{-1} BE in drinking water	Male C57BL/6J mice fed a high-fat diet	14 weeks	*Akkermansia, Bifidobacterium, Lactobacillus, Desulfovibrio. Bifidobacterium Lactobacillus* ⬆	FXR and TGR5 agonist	FXR, SHP, SREBP-1c, ChREBP, ACC-1, PPARγ1, PPARγ 2, CD36, FAS, GPAT, FABP4, ATG4b, ATG5, ATG7, CPT-I, PPARα, ACS, CYP7A1, D2, UCP1, PRDM16, PGC-1α⬆; TαMCA, TβMCA ⬇	63
Chokeberry (*Aronia melanocarpa* L.)	1000 mg/kg	Male Wistar rats fed a high-fat diet	40 days	*Firmicutes/Bacteroidetes, Desulfovibrio, Lachnoclostridium, Lachnospiraceae_NK4A13_group* ⬇; *Bacteroides, Prevotella, Akkermansia, Bacteroides, Prevotella* ⬆	FXR and TGR5 agonist	PPARγ, UCP1, PGC-1α, ACC1, SREBP-1c, UCP1⬆	64
Curcumin	300 mg/kg	The chickens injected with LPS	21 days	*Butyricicoccus, Enterococcus, Firmicutes/Bacteroidota* ⬆	FXR agonist	IL-10, IL-22, *sirtuin 1, sirtuin 5, GPRC5A, GPRC5B* ⬆	65
Cranberry extract	200 mg/kg	C57BL/6J mice fed high Fat-High Sucrose (HFHS) diet	13 weeks	*Firmicutes/Bacteroidetes* ⬇; *Akkermansia muciniphila, Barnesiella spp* ⬆	FXR agonist	PPARg, LXRa/b ⬆; COX2, TNFa, NF-kB, IkB ⬇	66

Dihydromyricetin	100 mg/kg	Male C57BL/6J mice fed administering 3% (w/v) DSS in drinking water	7 days	*Lactobacillus, Akkermansia, Romboutsia, Turicibacter, Lachnoclostridium, Bacteroides, Blautia, Streptococcus, Enterococcus* ⬆	FXR and TGR5 agonist	LCA, CDCA ⬆	67
	40 mg/kg EGCG and 20 mg/kg caffeine	Sprague Dawley (SD) male rats fed a high-fat diet	10 weeks	*Bifidobacterium, Alloprevotella, Allobaculum, Faecalibaculum, Turicibacter* ⬆; *Firmicutes, Actinobacteria* ⬇	Liver TGR5 agonist, intestinal FXR inhibitor	CYP7A1 ⬆; FGF15 ⬇	68
Epigallocatechin-3-gallate (EGCG)	100 mg/kg	C57BL/6 mice fed a Western diet (21% fat, 34% sucrose, and 0.2% cholesterol, w/w)	12 weeks	*Akkermansia muciniphila, Verrucomicrobiaceae, Enterococcaceae* ⬆*; Lachnospiraceae, Desulfovibrionaceae, Bacteroidaceae, Prevotellaceae, Rikenellaceae, Deferribacteraceae* ⬇	Liver FXR and TGR5 agonist	CD36, PPAR-γ, SREBP-1C, FASN, *Scd1, Scd2, Cyp7a1, Cyp8b1*⬇; *Cyp4a10* ⬆	69
	0.32% of the diet	Male C57BL/6N mice fed a high-fat diet	8 weeks	*Adlercreutzia, Akkermansia, Allobaculum, f_Coriobacteriaceae, g_Adlercreutzia* ⬆; Desulfovibrionacea,g_Unclassified ⬇	FXR agonist	serum primary cholic acid, β-muricholic acid ⬆; taurine-conjugated cholic acid, β-muricholic acid and deoxy-cholic acid ⬇	70
Flavonoids from Whole-Grain Oat	50/100 mg/kg	Male C57BL/6N mice fed a high-fat diet	4 weeks	*Akkermansia* ⬆; *Lachnoclostridium, Blautia, Colidextribacter, and Desulfovibrio* ⬇	FXR agonist	PPARα, CPT-1, CYP7A1, FXR, TGR5, NTCP, BSTP ⬆; SREBP-1c, FAS ⬇	71
Grape Extract	1% of the diet	Male C57BL/6Cnc mice fed a high-fat and high-fructose diet	13 weeks	*Bifidobacterium, Clostridia, Firmicutes/Bacteroidetes*⬆	TGR5 agonist	PRDM16, UCP1, DCA ⬆	72
Grape Seed Proanthocyanidin	250 mg/kg	LPS and antibiotic gavage male C57BL/6J mice	20 days	*Bacteroidetes, Ruminococcaceae, and Ruminococcus* ⬆; *Actinobacteria* ⬇	FXR agonist	LCA, CDCA, CYP27A1, CYP7B1 ⬆; CYP8B1 ⬇	73
Hesperetin-7-O-glucoside	0.05% of the diet	C57BL/6J mice	9 weeks	Firmicutes/Bacteroidetes ⬇, *Clostridium, Muribaculaceae, Lactobacillus, Eubacterum, Ruminococcus, Lachnoclostridium, Turicibacter, Colidextribacter, Coriobacteriaceae, Desulfovibrio*, and *Rikenellaceae* ⬆	TGR5 agonist	taurine, phosphocholine, creatine, and lactate ⬇; BCAAs, phenylalanine, and tyrosine, Cyp7a1, Fgf15, Tgr5 ⬆	73
Lignin-Rich Insoluble Residue of Brewer's Spent Grain	20% of the diet	Male C57BL/6 mice fed a high-fat diet	14 weeks	*Clostridium leptum, Bacteriodes* ⬆	FXR agonist	*Srebp2, Hmgcr, Ldlr, Cyp7a1, Pparα, Fxr,* and *Pxr* ⬆	74

L-Theanine	100/300 mg/kg	Balb/c mice	28 days	*Lactobacillus, Streptococcus, Bacteroides, Clostridium*, *Enterorhabdus* ⬇	FXR inhibitor	CYP27A1, 3-hydroxy-3-methylglutaryl-CoA, SREBP-1c, HMGCR ⬆; BSH, FASN, FGF15, stearoyl-CoA desaturase-1, liver low-density lipoprotein receptor, type B scavenger receptor ⬇	46
Matcha green tea	1% of the diet	Male C57BL/6 mice fed a high-fat diet	8 weeks	*Faecalibaculum, Alloprevotella, Romboutsia, Akkermansia, Alistipes* ⬆	FXR agonist	C/ebp-α, CD36, Fatp, Fas, Acat2 ⬇	75
Nuciferine	10/25 mg/kg	Sprague-Dawley rats fed a high-fat diet	8 weeks	*Lactobacillus, Clostridium*, *Enterococcus, Clostridium, Eubacterium* ⬇; *Bilophila, Escherichia* ⬆	intestinal FXR inhibitors, hepatic FXR/SHP agonist	FXR, FGF15, FGFR4, ASBT, *Cyp8b1, Ibabp, Ostα/β* ⬇; CYP7A1, CYP27A1, Cyp7b1 ⬆	76
Penthorum chinense Pursh. extract	2/4/8 g/kg	Male C57BL/6J mice fed a high-fat diet	8 weeks	*Firmicutes/Bacteroidetes, Clostridium_IV, Clostridium_XIVb, Lactobacillus, Clostridium, Lactobacillus* ⬇	intestinal FXR inhibitors, hepatic FXR/SHP agonist	FGF15, BSH, CYP7A1 ⬇; CYP27A1, CYP7B1, BSEP ⬆	77
Polyphenol-rich extract from chokeberry (*Aronia melanocarpa* L.)	1000 mg/kg	Male wistar ratsfed high fat diet	40 days	*Firmicutes/Bacteroidete*s, Desulfovibrio, *Lachnoclostridium, Lachnospiraceae_NK4A136_group* ⬇; *Bacteroides, Prevotella, Akkermansia* ⬆	FXR and TGR5 agonist	PPARγ(iBAT), UCP1(iBAT), PGC-1α (iBAT), SHP, FGF15, FGFR4, BSEP, TGR5 ⬆; SREBP-1c, C/EBPα, ACC1, PPARγ, FAS, CYP7A1 ⬇	64
Proanthocyanidin-rich extract of grape polyphenols	1% of the diet	Male C57BL/6J mice fed a high-fat diet	10 weeks	*Akkermansia, Blautia, Clostridium, S24-7* ⬆; *Clostridiales, Ruminococcaceae, Lachnospiraceae families, Clostridium genus* ⬇	Intestinal FXR inhibitor	*Shp, Fgf15, Fabp6, Smpd3, Sptlc2, Cers4, Fxr, Tgr5* ⬇; *Cyp7a1*⬆	78
Quinoa	2 g/d	Male C57BL/6 mice fed a high-fat diet	8 weeks	*Firmicutes/Bacteroidetes, Blautia* ⬇; *Akkermansia, Bifidobacterium, Atopobium, Lactobacillus, Prevotellaceae* ⬆	TGR5 agonist	GLP-1 ⬆, TLR4 ⬇	79
Resveratrol	400 mg/kg	ApoE$^{-/-}$ mice with a C57BL/6 genetic background	8 weeks	*Lactobacillus, Enterococcus faecalis, Bacteroidetes/Firmicutes, Bifidobacterium* ⬆	FXR inhibitor	CYP7A1, BSH, FMO3, FMO ⬆; FGF15, TEM ⬇	80

	0.4% of the diet	*db/db* mice	10 weeks	*Firmicutes, Lactobacillaceae, Bacteroidates_S24_7_group, Lachnospiraceae* ⬇; *Bacteroidaceae, Porphyromonadaceae, Alcaligenaceae* ⬆	TGR5 agonist	UCP1, PGC1a, SIRT1, BAT ⬆	[81]
	500 mg/kg	Male C57BL/6J mice fed a high-fat diet	12 weeks	*Bacteroidetes/Firmicutes, Eubacterium_nodatum*_group, Bacteroides ⬆, *Eubacterium_brachy*_group, *Erythrobacter*, *Streptomyces* ⬇	FXR inhibitor	jejunal SR-B1, CDCA ⬇; Cpt1a, Acadm ⬆	[82]
Total phenolic extracts of *Citrus aurantium* L.	8.7 g/kg	Antibiotics-Induced male C57BL6 mice	4 weeks	*Firmicutes, Ruminococcaceae, Prevotellaceae, Lactobacillaceae* ⬆	FXR agonist	ZO-1, Occludin proteins, FGF15, BSEP, NTCP, OATPs ⬆; serum endotoxin, CYP7A1 ⬇	[83]
Theabrownin from Pu-erh tea	450 mg/kg	Male C57BL/6 mice fed a high-fat diet	26 weeks	*Lactobacillus, Bacillus, Streptococcus, and Lactococcus* ⬇	intestinal FXR inhibitors, hepatic FXR agonists	SHP (liver), TCDCA, TUDCA ⬆; FGF15, FGFR4 ⬇	[84]
Xyloglucan compounded inulin	4 % of the diet	Male ICR/KM mice fed a high-fat diet	8 weeks	*Allobaculum, Lachnospiraceae NK4A136, Bifidobacterium, Lachnospiraceae_UCG_001, Lachnospiraceae, Bacteroides, Akkermansia* ⬆; *Firmicutes, Helicobacter, Faecalibaculum* ⬇	FXR and TGR5 agonist	Glut4, Occludin ⬆; OGTT, G6Pase, CYP7A1, TNF-α, Il1-β ⬇	[85]

Graphical Abstract