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REVIEW ARTICLE

The Research Mechanism of the Gut-Liver Axis in Non-Alcoholic Fatty Liver Disease

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ABSTRACT

Fatty liver haemorrhagic syndrome (FLHS) is a nutritionally induced metabolic disorder predominantly affecting laying hens, characterized by abnormal lipid deposition within hepatocytes and abdominal adipose tissue. Hepatic hemorrhages and liver function disorders are primary mortality drivers in caged commercial laying hens, particularly within intensive confinement systems where metabolic stressors are prevalent. They inflict substantial economic damage on the poultry sector through dual pathways: direct bird mortality and/or reduced egg output in infected flocks. Its pathogenesis is related to a variety of factors, including improper proportion of nutrients, lack of exercise, and the influence of estrogen. Bile acids, which are cholesterol-derived compounds synthesized in the liver, are crucial for fat metabolism. At present, a few studies on the direct relationship between bile acids and fatty liver syndrome are quite popular. Meanwhile, certain studies are also available indicating that the gut microbiota is closely related to the incidence of fatty liver. However, bile acids and gut microorganisms have an interactive relationship with each other. Therefore, this article aims to explore the interaction among bile acids, gut microbiota and fatty liver in laying hens, and to better understand the mechanism of the intestinal-liver axis research, in order to develop effective prevention and treatment methods for fatty liver in laying hens.

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INTRODUCTION

Fatty liver bleeding syndrome is a common non-infectious nutritional metabolic disease in high-yielding laying hens, which can lead to hepatic steatosis, bleeding, and decrease in egg production rate (Cheng *et al.*, 2024). The clinical features of this syndrome are obesity, reproductive impairment evidenced by decreased egg production, and characterized by pale combs (Zhang *et al.*, 2023). When fatty liver occurs, under normal circumstances, one can observe that the liver is enlarged, yellowish in color, has a brittle texture and a greasy feel, and there are bleeding spots on the liver surface (Liu *et al.*, 2018; Zhang *et al.*, 2024) along with yellowish thick fat accumulation within the abdominal cavity. The occurrence of the disease usually causes the egg production rate of chickens to drop from 45-85%, which seriously affects the efficiency of laying hens (He *et al.*, 2015; Anene *et al.*, 2023). The factors involved in its occurrence are improper availability of nutrients, lack of exercise and certain other toxic factors among which bile acid metabolism disorder is a very important factor (Yang *et al.*, 2024a; Xing *et al.*, 2024a).

Bile acid biosynthesis begins with the oxidation and transformation of cholesterol molecules, and its production and metabolism are related to lipid processing in the liver (Erdelyi *et al.*, 2018; Jian *et al.*, 2024). Studies have found that bile acid metabolism disorders are closely related to the composition and function of intestinal microbial community, and intestinal microorganisms can affect the metabolic process of bile acids through many ways (Dong *et al.*, 2019; Li *et al.*, 2024a) (Fig. 1). For example, certain intestinal bacteria can alter the structure and metabolic pathways of bile acids by generating enzymes such as bile salt hydrolase, thereby influencing their absorption and excretion in the intestine (Peng *et al.*, 2019; Chen *et al.*, 2023). In addition, the imbalance of intestinal microbial community may also trigger intestinal inflammation, which further aggravates bile acid metabolism disorders and intestinal dysfunction (Li *et al.*, 2022; Li, *et al.,* 2024a; Yan *et al.*, 2025).

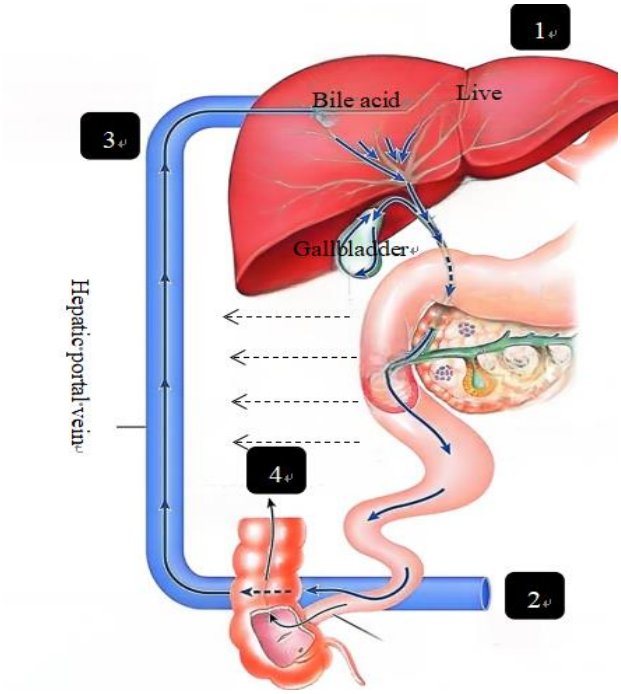

Fig. 1: The enterohepatic circulation of bile acids. 1: Total bile acids consist of 95% of circulating bile acids and 5% of newly synthesized bile acids.2: 95% of the bile acids are absorbed by the small intestine.3: The reabsorbed bile acids enter the enterohepatic circulation.4: 5% of bile salts are excreted in the feces.

Therefore, in-depth research on the interaction between gut microbiota and bile acid metabolism is crucial for elucidating the pathogenesis of fatty liver hemorrhagic syndrome in laying hens caused by bile acid disorders. This review may also provide new insights and directions for developing therapeutic strategies targeting other related diseases associated with bile acid metabolism dysregulation.

The pathogenesis of fatty liver syndrome in laying hens: At present, due to the complex etiology of FLHS, the pathogenesis of FLHS is still unclear, and it still exists in the stage of hypothesis. At present, "Two-hit" hypothesis and the "Multiple-hit" hypothesis are important theories to explain the pathogenesis of FLHS (Dansou *et al.*, 2024; Chu *et al.*, 2024) (Fig. 2). The “first hit” is due to insulin resistance and excessive free fatty acid produced by lipolysis in the body into the liver, which causes lipid metabolism disorder in the liver, a large amount of triglyceride deposition, and steatosis of hepatocytes (Yang *et al.*, 2024b). The “second hit” is that liver steatosis causes oxidative stress, mitochondrial dysfunction and liver injury, and produces a large number of inflammatory cytokines (Cui *et al.*, 2024; Wang *et al.*, 2024). Excessive inflammatory cytokines will aggravate hepatocyte steatosis, develop into more severe steatohepatitis, and even liver fibrosis and cirrhosis may eventually induce the occurrence of FLHS (Sharma *et al.*, 2018; Xing *et al.*, 2024b). On the basis of the "Two-hit" hypothesis, the "Multi-hit" hypothesis explains the process of the disease from fat deposition, insulin resistance, hormones secreted by adipose tissue, nutritional factors, inflammatory pathways, intestinal microbiota, and genetic and epigenetic factors, emphasizing the role of intestinal flora and adipokines secreted by adipose tissue (Trott *et al.*, 2014). It is believed that they may further trigger oxidative stress, lipotoxicity, and mitochondrial dysfunction through the "gut-liver axis", thereby aggravating FLHS (Sun *et al.*, 2023; Du X *et al.*, 2024).

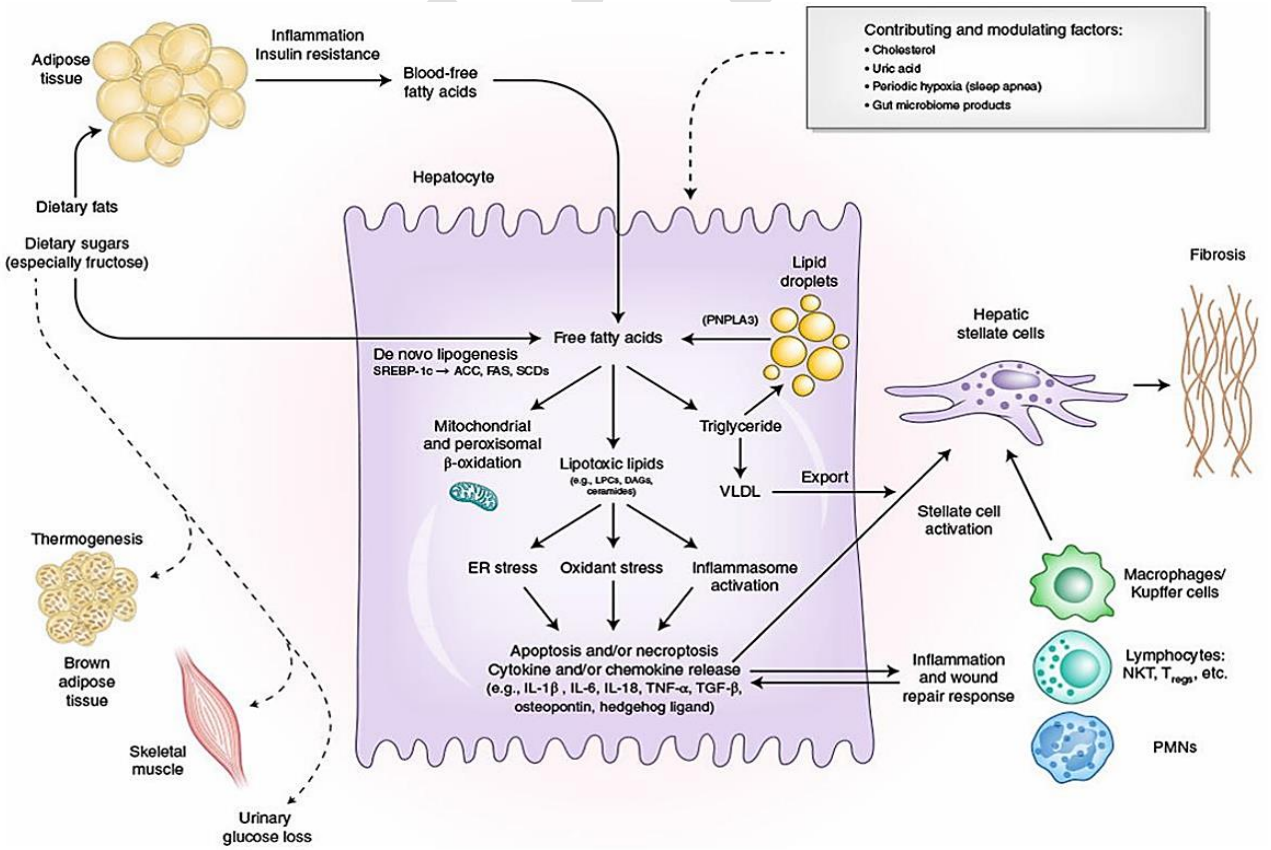

Fig. 2: The pathogenesis of FLHS.

Factors influencing the occurrence of FLHS

Nutritional factors: Different sources of energy and protein in the diet are the main causes of FLHS in laying hens (Yin *et al.*, 2023; Xiao *et al.*, 2025). When hens are at their peak laying period, it would lead to excessive feeding of laying hens, resulting in excessive fat and energy accumulation in the body (Choi *et al.*, 2014; Li *et al.*, 2023). If the produced fat exceeds the liver transport capacity, it leads to excessive fat deposition in liver cells, thereby causing hepatic steatosis (Yang *et al.*, 2021). Excessive energy and insufficient protein in the diet would cause the synthesized fat in the liver to be unable to be effectively exported due to the lack of apolipoproteins, resulting in the decrease of the liver's transport capacity for fat, and the accumulation in the liver leading to hepatocyte degeneration and necrosis, ultimately inducing FLHS (Yang *et al.*, 2023a). When dietary intake of vitamins and mineral elements is insufficient, the level of free radicals in laying hens increases, triggering oxidative stress and disrupting the dynamic balance between free radicals and antioxidants. This series of reactions induces lipid peroxidation in the liver, disrupts the dynamic balance of lipid metabolism, and ultimately leads to FLHS (Wang *et al.*, 2022; Lv *et al.*, 2024).

Environmental factors: FLHS frequently occurs at higher rates during hot and humid summer months (Liu *et al.*, 2019; Hu *et al.*, 2024). High-temperature environments typically induce heat stress, which elevates the body's metabolic rate ultimately leading to metabolic dysregulation. Exogenous corticosteroids and glucocorticoids released during stress can promote gluconeogenesis, accelerate lipid synthesis, and may lead to lipid deposition (Yang *et al.*, 2017). In high-temperature environments, chickens reduce their energy requirements, and the rate of fatty acid breakdown decreases (He *et al.*, 2023; Lv *et al.*, 2025). Concurrently, the high-temperature conditions stimulate fatty acid synthesis, ultimately leading to excessive fat deposition in the body, which can induce FLHS (Zhang *et al.*, 2025). The metabolism of the diseased chicken is vigorous in the high temperature environment, and the blood vessels may be fully dilated, which is easy to cause liver rupture and bleeding, and may cause the death of the chicken (Shini *et al.*, 2019). High temperatures can also lead to a decrease in the secretion of thyroid hormones in laying hens and inhibit their production performance (Wu *et al.*, 2023). Furthermore, under conditions of shorter photoperiods or irregular lighting, the production of melatonin synthetase decreases, thereby disrupting the balance of the circadian rhythm regulation in laying hens (Yang *et al.*, 2023b). This may lead to an increase in metabolic rate and elevated cortisol levels, which intensifies the metabolic burden on the liver, thereby increasing the risk of FLHS.

Genetic factors: Throughout the production cycle, genetic factors play a significant role, leading to considerable variation in the incidence of FLHS among different chicken breeds. Due to differences in their inherent physiological environments across breeds and even individuals, the underlying molecular pathways are affected. Consequently, variations in hepato-epigenetic characteristics also contribute to varying susceptibilities to FLHS (Ren *et al.*, 2021). Few studies have found that white Leghorn are more likely to develop FLHS than other layers due to higher enzyme activity in liver tissue and higher liver fat content (Tan *et al.*, 2021). UCD-003 laying hens are more susceptible to FLHS due to liver dysfunction than other breeds of same-aged laying hens (Zhu *et al.*, 2020). A FLHS model of laying hens was established by exogenous factors, and it was found that Rhode Island red hens were more likely to induce FLHS than white Leggers (Rozenboim *et al.*, 2016).

Poisoning factors: The intake of mycotoxins is recognized as a key environmental factor inducing and exacerbating this disease, with disruption of lipid metabolism being the core mechanism. Mycotoxins cause fat accumulation in hepatocytes by interfering with key enzymes and transcription factors involved in hepatic lipid synthesis, export, and oxidation (Adugna *et al.*, 2024). Mycotoxins, including aflatoxin B1, have been demonstrated to upregulate the expression of sterol regulatory element-binding protein-1c (SREBP-1c), a key regulator of lipid metabolism pathways associated with toxicological responses. Its upregulation activates downstream enzymes including acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), leading to a substantial increase in fatty acid synthesis. Mycotoxins (e.g., aflatoxins and ochratoxins) damage hepatocyte organelles such as the endoplasmic reticulum and mitochondria. They also inhibit the synthesis of apolipoprotein B100 (ApoB100), resulting in impaired assembly and secretion of Very Low-Density Lipoprotein (VLDL) (Wang *et al.*, 2024). Consequently, fats cannot be efficiently transported out of the liver. Secondly, during mycotoxin metabolism in the liver, large amounts of reactive oxygen species (ROS) are generated, disrupting the balance between oxidation and antioxidation. Excessive ROS triggers a depletion of antioxidant substances (e.g., GSH, SOD and CAT), thereby initiating lipid peroxidation. This ultimately damages cell membrane structures, proteins, and DNA, causing hepatocyte injury, necrosis, and even apoptosis (Yegani *et al.*, 2006). Furthermore, mycotoxins induce an inflammatory response. Oxidative stress and hepatocyte damage release danger signals, which activate the nuclear factor kappa B (NF-κB) signaling pathway. Subsequently, the activated NF-κB translocates into the nucleus and initiates the transcription of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, leading to persistent hepatic inflammation. This inflammation further exacerbates hepatocyte dysfunction and lipid metabolism disorders, creating a vicious cycle (Cheng *et al.*, 2022). These three mechanisms act synergistically: 1) Enhanced lipogenesis (via SREBP-1c), 2) Impaired lipid export (via VLDL disruption), and 3) Hepatocyte damage (via oxidative stress and inflammation). This synergy ultimately leads to hepatocyte swelling, degeneration, necrosis, and hemorrhage, thereby defining the pathological features of mycotoxin-aggravated hemorrhagic fatty liver syndrome (HFLS) in laying hens (Tu *et al.*, 2023).

The impact of bile acid deficiency on fatty liver

The physiological functions of bile acids: Bile acid is an important component of bile, which is converted from

cholesterol in the liver and plays an important role in fat metabolism and absorption. Bile acids are mainly present in the enterohepatic circulation system and play a protective role through recycling (Neijat *et al.*, 2017). Bile acid synthesis primarily occurs through two pathways: the classic pathway and the alternative pathway. The classic pathway, mediated and catalyzed by cholesterol 7α-hydroxylase (CYP7A1), determines the bile acid content in the liver (Li *et al.*, 2024b) (Fig. 3). The canonical pathway is mediated by sterol 7α-hydroxylase (CYP7A1), which determines the content of bile acids in the liver. The key enzymes in the alternative pathway are sterol 27α-hydroxylase (CYP27A1) and oxosterol 7α-hydroxylase (CYP7B1), which mainly synthesize chenodeoxycholic acid (CDCA) (Li *et al.,* 2024a). After synthesis in the liver, bile acids enter the intestines via the bile ducts. Upon binding to bile acid receptors, bile acid can inhibit liver lipid synthesis through SREBP-1c, promote hepatic lipid breakdown via PPARα and lipoprotein lipase, **f**acilitate extrahepatic lipid transport through VLDL secretion, and play a vital role in the absorption of dietary lipids and fat-soluble vitamins.

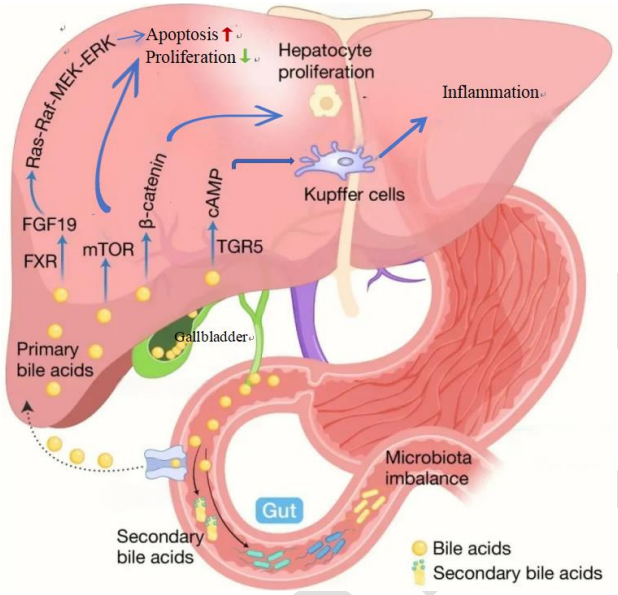

Fig. 3: Bile acid physiology.

Bile acids play an irreplaceable role in the emulsification of fat, can activate lipase and enhance the activity of lipase (Li *et al.*, 2025). During the absorption of fats, fatty acids must combine with bile acids to form complexes in order to be recognized by small intestinal epithelial cells and complete the fat absorption process (Zhang *et al.*, 2022). In case of fatty liver disease, the liver secretes insufficient bile acids to meet physiological demands. This not only disrupts gut microbiota metabolism but also exacerbates fatty liver symptoms, thereby forming a vicious cycle (Li, et al., 2024b).

Bile acid FXR receptor: FXR receptor serves as the endogenous ligand for bile acids, as well as their primary receptor and biosensor. It is predominantly expressed in the liver and small intestine. Upon binding to the ligand-dependent transcriptional activation domain at its carboxyl terminus, bile acids trigger FXR to form heterodimers. These heterodimers then bind to specific DNA response elements of downstream target genes, thereby modulating their expression. This process regulates the synthesis, secretion, and reabsorption of bile acids, and maintains the homeostasis of both bile acids and cholesterol, thereby playing a critical regulatory role in the bile acid metabolic pathway (Sharma *et al.*, 2018). In recent years, some new functions of FXR have been gradually revealed. At present, it is believed that FXR is not only a bile acid receptor, but also a biological signaling molecule. It is essential for lipid metabolism, glucose metabolism, energy balance, and even immune response, and is closely related to nutritional metabolism, inflammation, cancer and other diseases (Zhang *et al.*, 2024).

Metabolic role of FXR in glucose: As a metabolism-related signaling molecule, the role of FXR in glucose metabolism has attracted more attention. Glucose could down-regulate FXR and CYP7A1 gene expression, while insulin could up-regulate them (Liu *et al.*, 2022a). This indicates that there is a close relationship between bile acid metabolism and glucose metabolism. In the pancreas, FXR modulates glucose homeostasis by inducing insulin secretion from pancreatic β cells via cAMP-mediated mechanisms. It also stimulates intestinal L-cell production through induction of lithocholic acid (LCA) generation through gut microbiota, thereby promoting secretion of glucagon-like peptide-1 (GLP-1) (Wang *et al.*, 2024). It acts as incretin hormone to lower blood glucose concentrations in order to regulate glucose metabolism. A few studies have shown that FXR gene knockout in mice leads to decreased expression of a variety of gluconeogenesis-related genes, impaired glucose tolerance and insulin resistance, and the addition of FXR agonist GW4064 to the diet of diabetic mice can reduce blood glucose levels (Gong *et al.*, 2022). In the liver, FXR also suppresses gluconeogenic gene expression through the transcription factor SHP and inducing intestinal secretion of Fgf19. Circulation to the liver acts on fibroblast growth factor receptor-4 (FGFR4) or KLB (klotho β) to activate hepatic glycogen synthase and increase hepatic glycogen synthesis (Qiao *et al.*, 2025) .

Role of FXR in lipid metabolism: Research has found that FXR is actively involved in bile acid metabolism, lipid metabolism, cholesterol metabolism, and energy balance. In terms of lipid metabolism, FXR reduces blood triglyceride level mainly by inhibiting triglyceride synthesis and promoting triglyceride decomposition. FXR can inhibit the synthesis of triglyceride by down-regulating sterol regulatory element binding protein SREBP1c through SHP (Yegani *et al*., 2006). In addition, it can also stimulate intestinal transepithelial cholesterol secretion through its downstream target gene 'FGF19' to reduce intestinal cholesterol absorption. Studies have found that FXR deficient mice have higher plasma and hepatobiliary cholesterol and triglyceride levels(Adugna, *et al*., 2024; Wang, *et al*., 2024) . This is due to the reduced expression of bile acid transporters caused by FXR deficiency, resulting in reduced total bile acid in the gallbladder. FXR knockout mice have increased plasma high-density lipoprotein cholesterol (HDL-C) and significantly reduced HDL-C clearance. Plasma concentrations of apolipoprotein

B are elevated, and absorption of intestinal cholesterol is increased. Activation of FXR in mice increases LDLR expression and reduces plasma low-density lipoprotein levels. Additionally, activated FXR inhibits cholesterol regulatory element-binding protein 1c (SREBP-1c) to suppress hepatic lipogenesis (Kulcsar *et al.*, 2024).

FXR regulates bile acid transporters: The bile salt export pump (BSEP) and multidrug resistance-associated protein 2 (MRP2) transport bile acids, which are synthesized in the liver, into the bile tubules. Following food intake, the gallbladder contracts under cholecystokinin (CCK) stimulation, leading to biliary secretion of bile acids into the duodenum (Zhang *et al.*, 2025). Conjugated bile acids are received by the bile acid transporter ASBT in the ileum to reach the intestinal epithelial cells, bound to the ileal bile acid binding protein IBABP, transported to the basolateral membrane, and exported into the portal vein through the organic solute α/β heterodimer (Ostα /β) (Jiang *et al.*, 2021). Under the mediation of sodium taurocholate co-transporting peptide (NTCP) and organic anion transporting peptide (OATP), bile acids are reabsorbed by hepatocytes. After reabsorption, the bile acids are converted into conjugated bile acids and re-secreted into the bile canaliculi to participate in bile formation, a process known as the enterohepatic circulation of bile acids (Fig. 4). Numerous studies have shown that in cases of liver disease or cholestasis, most bile acid transporters are inhibited or downregulated. Activated FXR can promote the transcription of bile acid-binding protein genes, as well as enhance the transcription of organic solute transporter genes, thereby facilitating the transport of bile acids from the ileum to the portal venous system.

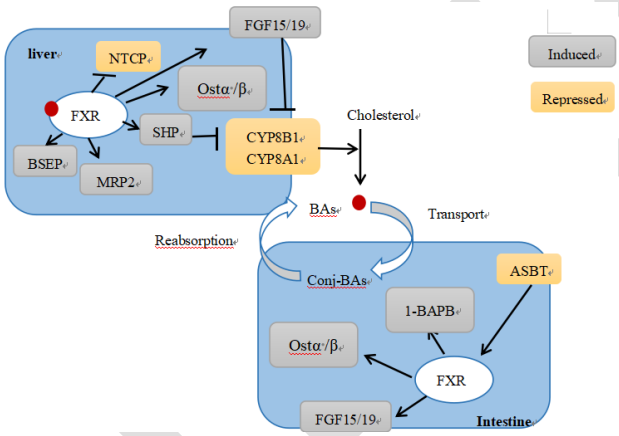

Fig. 4: The mutual conversion of bile salts regulated by FXR.

The role of intestinal microorganisms in FHLS: Intestinal microbial imbalance has been proven to be one of the important pathological factors causing abnormal lipid metabolism in laying hens (Fig. 5). Relevant studies have shown that intestinal microorganisms play a central role in the pathogenesis of metabolic diseases such as NAFLD and non-alcoholic steatohepatitis (NASH). For example, *Bacteroides fragilis* (*B. fragilis*) has the dual functions of reshaping the intestinal microbiota structure and regulating lipid metabolism. Supplementing mice with *B. fragilis* would interfere with their blood sugar balance, upregulate the expression of lipid metabolism-related genes in the liver, simultaneously alter the abundance of the intestinal microbial community, increase the abundance of the *Desulfobulbaceae* (pathogenic bacteria) community, induce liver dysfunction, aggravate liver tissue damage and accelerate the process of fatty degeneration (Liu, *et al.*, 2022a). On the contrary, *Akkermansia muciniphila* has been proven to alleviate symptoms such as liver lipid deposition, fatty degeneration and chronic inflammation (Cheng, *et al.*, 2022). Studies have shown that treatment with *A. muciniphila* can effectively alleviate liver inflammation in mice with fatty liver disease, improve oxidative stress-induced cell apoptosis, and enhance lipid metabolism and intestinal health (Liu *et al.*, 2022b). The regulation of lipid metabolism and cholesterol homeostasis mainly depends on bile acids, and this regulatory process directly or indirectly affects the development of FLHS diseases. Bile acids are the end products of cholesterol metabolism and play a key role in emulsifying fats (Meng *et al.*, 2021), effectively accelerating the digestion and absorption of fat-soluble substances. They hold a central position in lipid metabolism (Meng, *et al.*, 2021).

FXR, as a specific receptor for bile acids, is known as the "bile acid sensor" and exerts metabolic regulatory functions by activating downstream signaling pathways (Clifford *et al.*, 2021; Wang *et al.*, 2024). The activation of FXR can induce the activities of fibroblast growth factor 15/19 and CYP7A1, thereby achieving precise regulation of bile acid biosynthesis (Chiang and Ferrell, 2020). Moreover, the activation of FXR can also increase the expression of VLDL receptors, accelerate the clearance of lipoproteins in plasma, and help reduce lipid levels. The findings provide evidence that in FLHS egg-laying hens, the components and abundances of bile acids are significantly different from those of normal egg-laying hens, and the transcriptional levels of key regulatory factors FXR, CYP7A1, and FGF19 for bile acids are significantly inhibited (Li *et al.*, 2024). Simultaneously, research has indicated that by supplementing cholic acid from geese in the diet of egg-laying hens, it can significantly inhibit the synthesis of TG and fatty acids in the liver of FLHS egg-laying hens, accelerate the transport of cholesterol in the liver and the conversion of bile acids, thereby effectively reducing liver fat deposition.

FXR interacts with gut microbes: Upon entering the intestine, primary bile acids are deconjugated and dehydroxylated by gut microbiota, transforming into secondary bile acids, thereby changing the chemical structure and physiological activity of metabolic enzymes such as bile saline lyase (BSH) expressed by intestinal microorganisms can hydrolyze the binding of bile acids to amino acids during bile acid transformation (Li, *et al.*, 2024b). When intestinal microbes are dysregulated, they can lead to bile acid metabolism disorders, which in turn affect lipid metabolism, hepatobiliary function and intestinal health. Similarly, changes in bile acids also affect the gut microbiota. For instance, high concentrations of bile acids can alter membrane lipid composition and even dissolve cell membranes, thereby inhibiting the growth of intestinal microorganisms (Huang *et al.*, 2015; Adorini and Trauner, 2023).The results show that by activating the FXR receptor, bile acids can indirectly regulate the composition of the gut microbiota. Thus, bile acids and their receptor FXR play a crucial role in maintaining intestinal microbial balance (Yang, *et al.*, 2023a).

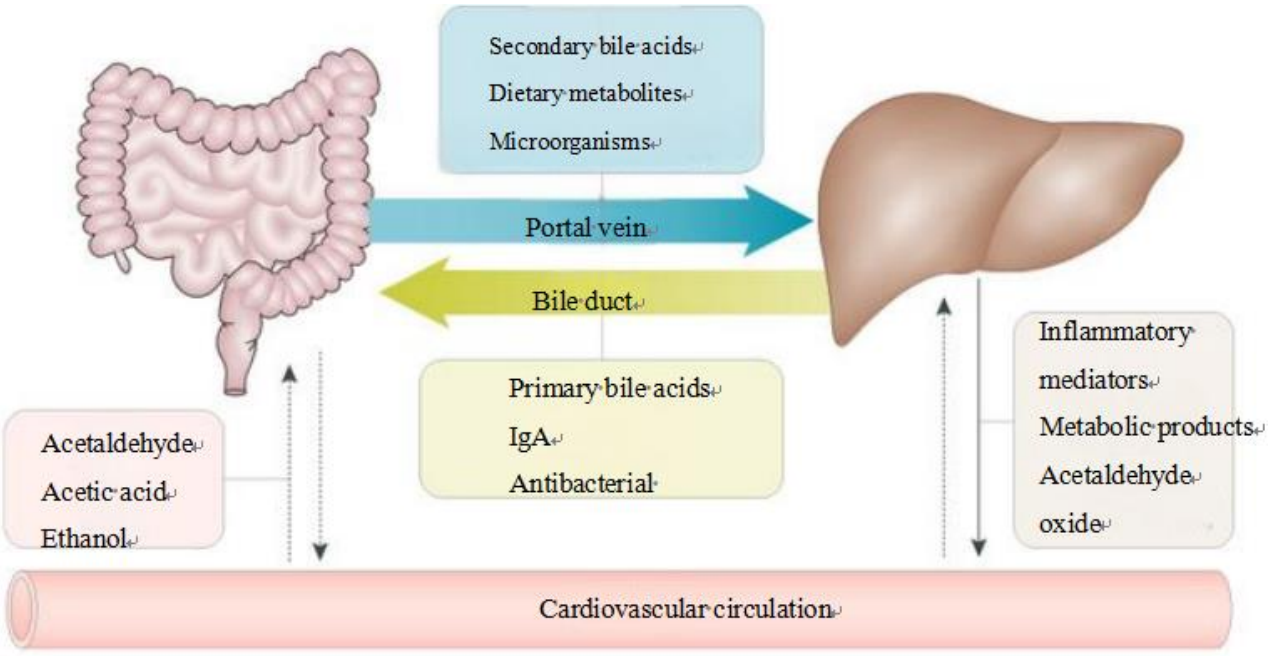

Fig. 5: Liver-gut interaction relationship.

Association of gut microbiota with FXR receptors and NAFLD: Intestinal microecology plays an important role in regulating energy metabolism, and the imbalance of the intestinal microecology is essential for pathogenesis of NAFLD and the metabolism of bile acids. Researches reveal that the content of intestinal bile acids in mice fed with high-fat diet increases significantly, followed by significant changes in intestinal microflora (Miao *et al.*, 2021). Feeding bile acids combined with normal diet can produce similar changes in intestinal microflora as high-fat diet, while inhibiting bile acid synthesis can correct the changes in intestinal microflora induced by high-fat diet, indicating that bile acids are an important factor regulating intestinal microflora (Guo *et al.*, 2024). Studies have found that obeticholic acid can regulate the intestinal flora of NAFLD mice, significantly increase the abundance of *Blautia* bacteria, and reduce the content of taurine binding bile acids in the liver, suggesting that obeticholic acid can treat NAFLD by regulating intestinal flora and bile acid metabolism (Nakayama and Narita, 1977). Additionally, it has been discovered that metabolites of intestinal bacteria such as bile acids and short-chain fatty acids can also enter the circulation system through the intestinal barrier and activate or inhibit the activity of FXR (farnesoid X receptor) by binding to it on liver cells, thereby exerting biological effects (Xing *et al.*, 2020). FXR can regulate glucose and lipid metabolism and inflammation in the liver, which is an important therapeutic target for NAFLD (Meng, *et al*., 2021). This forms the "gut microbia-bile acid-FXR" axis (Fig. 6), which is of great significance in the pathogenesis of NAFLD. Therefore, improving the "gut microbia-bile acid-FXR" axis is an important treatment strategy for NAFLD (Liu, *et al*., 2022b).

Conclusions: In conclusion, the transport of bile acids in the body occurs mainly through the gut-liver axis circulation system, so the homeostasis of gut-liver axis function determines the balance of bile acids in the body. In the process of maintaining the homeostasis of gut-liver axis, the homeostasis of liver and gut microbiota plays a decisive role. Therefore, it is of great significance to pay attention to the metabolism of bile acids in the gut-liver axis circulation and the influence of intestinal microorganisms on bile acids in the prevention and treatment of diseases.

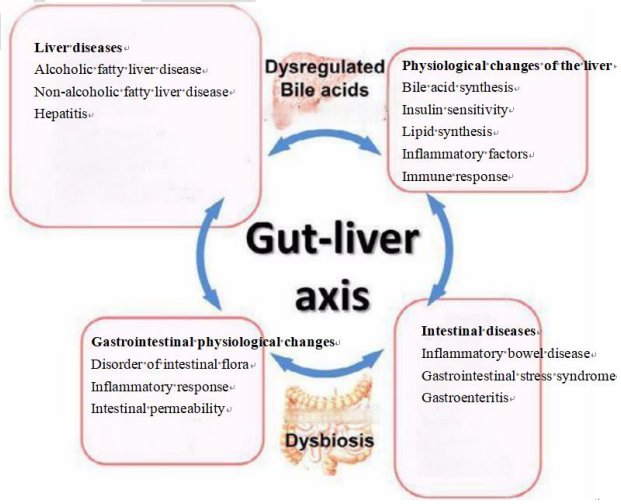

Fig. 6: Gut-Liver Axis: Interconnected Health, Influencing Well-being.

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Cheng, who also performed the analysis of sera and tissue samples. Xin Liu and Ping Liu were responsible for data analysis. In addition, all authors collectively interpreted the data, provided critical feedback on the manuscript, and approved the final version.

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