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Anti-inflammatory Activities of Berberine in the Treatment of Metabolic Disorders by Regulating the Gut Microbiota*

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Abstract The gut microbiota is closely related to the energy metabolism, and the disorder of its composition and metabolism can lead to insulin resistance, obesity and type 2 diabetes (T2DM) through multiple pathways. Berberine is used as an adjuvant treatment for metabolic diseases, such as obesity, T2DM, and nonalcoholic fatty liver disease, due to its effects on weight loss, hypoglycemia, lipid regulation, and other physiological parameters. Recent studies have shown that berberine can regulate the composition and metabolism of the gut microbiota, improve the gut micro-ecological environment, thereby ameliorating insulin resistance and metabolism. This review clarifies how the gut microbiota induces systemic low-grade inflammation and the development of metabolic diseases. It also explores berberine intervention in metabolic diseases, affecting the intestinal microbiota-inflammation axis, in order to find new therapeutic strategies for the treatment of such diseases and to provide important guidance for in-depth research in this field.

Key words berberine, gut microbiota, inflammation, metabolic diseases
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Berberine is an isoquinoline alkaloid isolated from several herbal substances[1]. Owning to its low toxicity and high safety, berberine has been used for the treatment of infectious diarrhea for thousands of years in China[2]. However, in recent years, berberine has been widely used in the adjuvant treatment of metabolic diseases, such as obesity, type 2 diabetes mellitus(T2DM) and nonalcoholic fatty liver disease (NAFLD), due to its multiple pharmacological effects, including having antibacterial properties, improving glucogenesis and lipid metabolism.

Traditionally, herbal medicine is consumed in the form of decoctions. The functional components of the decoction, such as small RNAs, are absorbed into the body and play pharmacological roles[3]. However, drug metabolism and pharmacokinetic studies have shown that the bioavailability of berberine in the human body is extremely low. Berberine is basically excreted in the form of the original drug, with an intestinal absorption rate of only 5%-10%, which means it may not exert pharmacological effects after absorption into the blood[1]. It is worth noting in recent studies that the gut microbiota participates in

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host energy and is closely related to obesity, insulin resistance, T2DM and related metabolic diseases, suggesting that the pharmacological target of berberine may be the gut microbiota[4]. After entry into the gut and exposure to the gut micro-ecological environment, berberine can alleviate systemic inflammation and improve energy metabolism and insulin resistance by promoting or inhibiting the growth and proliferation of certain microorganisms, and by reshaping the structure and improving the metabolism of the gut microbiota[5]. In turn, the gut microbiota can affect berberine metabolism. Bacterial nitroreductase of the gut microbiota can convert berberine into dihydroberberine, thereby increasing the absorption of berberine in the gut and modify its clinical effects[6-7]. Based on these bi-directional effects, understanding the anti-inflammatory activity of berberine based on intestinal flora in metabolic diseases is expected to provide new ideas for the precise treatment of metabolic diseases. Therefore, we review below the relationship between gut microbiota and metabolic diseases, and the use of berberine in the prevention and treatment of obesity and related metabolic diseases through the gut microbiota-inflammation axis (Figure 1, Table 1).

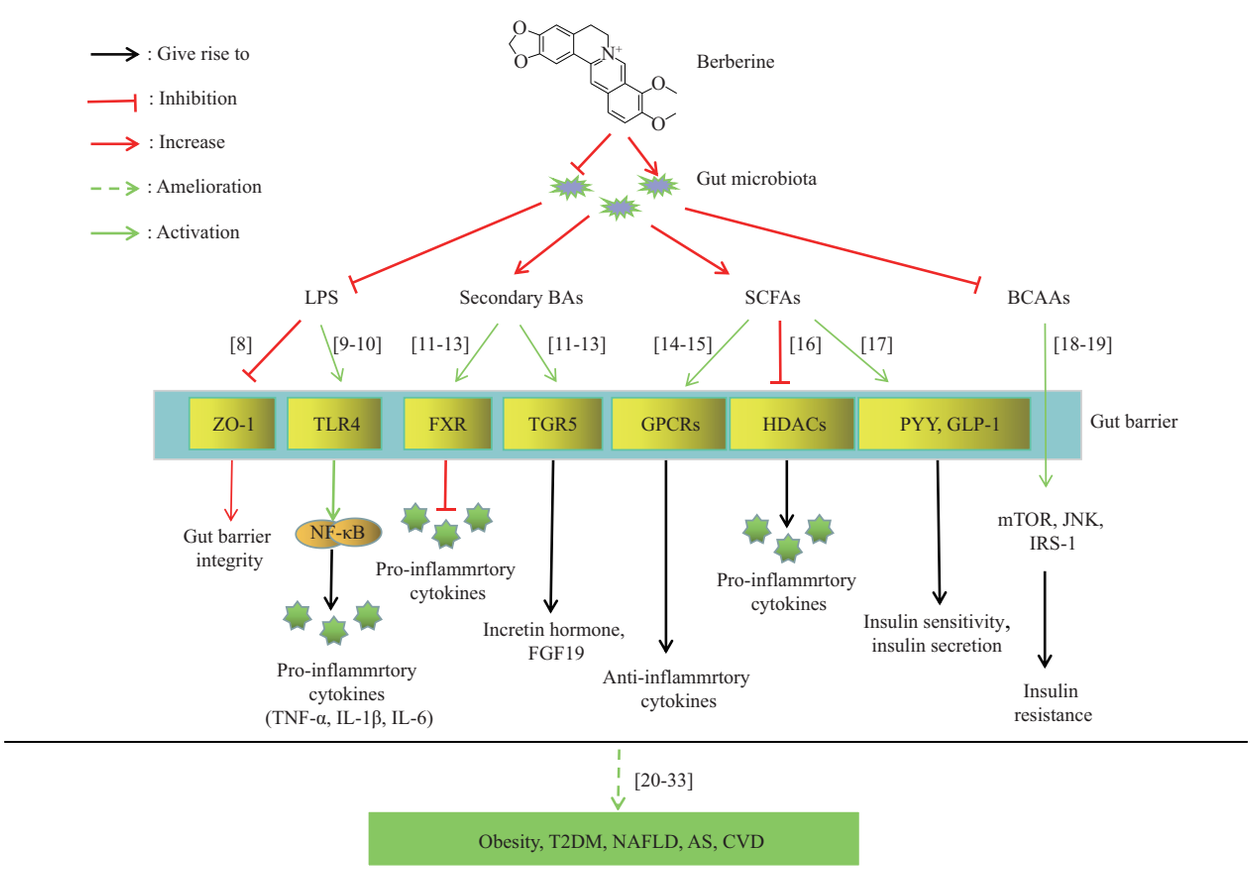

Fig. 1 The possible mechanism of berberine in the treatment of metabolic diseases *via* the gut microbiota−inflammation pathway

Table 1　Berberine treats metabolic diseases *via* regulating gut microbiota

Metabolic disease	Animals models/Patients	Regulation of intestinal microbiota	Ref.
Obesity	C57BL/6J mice	*Firmicutes*/*Bacteroidetes* ↓	[20]
	Wistar rats	*Allobaculum*， *Bacteriodes*， *Blautia*， *Butyricoccus* and Phascolarctobacterium ↑ the diversity of gut microbiota ↓	[21]
	SD rats	*Fusobacteria* and *Proteobacteria* ↑ *Firmicutes* and *Actinobacteria* ↓	[22]
T2DM	Wistar rats	*Blautia* and *Allobaculum* ↑	[23]
	DB/DB mice	*Butyricimonas*， *Coprococcus*， *Ruminococcus*， *Lactobacillus* and *Akkermansia*） ↑	[24]
	Wistar rats	*Bifidobacterium* ↑ *Escherichia coli* ↓	[25]
	SD rats	*Bacteroidetes*， *Clostridia*， *Lactobacillales*， *Prevotellaceae* and *Alloprevotella* ↑ *Bacteroidales*， *Lachnospiraceae*， *Rikenellaceae*， and *Desulfovibrio* ↓	[26]
	C57BL/6J mice	*Clostridiales*， *Streptococcaceae*， *Clostridiaceae*， *Prevotellaceae*， *Streptococcus* and *Prevotella* ↓	[27]
	SD rats	*Bacteroidetes*/ *Firmicutes* ↑	[28]
NAFLD	Wistar rats	*Bacteroides*， *Blautia* ↑ *Escherichia* ↓	[29]
	BALB/C Mice	*Bifidobacteria* and *Bacteroidetes*/ *Firmicutes* ↑	[30]
	SD rats	*Bacteroides* ↑ *Faecalibacterium prausnitzii* ↓	[31]
AS	Apoe(-/-) mice	*Akkermansia spp* and *Bacteroides* ↑	[32]
	Apoe(-/-) mice	*Firmicutes* and *Verrucomicrobia* ↑ *Bacteroidetes* and *Proteobacteria* ↓	[33]

1　Gut microbiota and metabolic diseases

In recent years, with the establishment of high-throughput sequencing technologies, a large number of studies have shown that gut microbiota-host interactions are closely related to disease and health. The gut microbiota is referred to as the "second genome" of the organism, forming a dynamically balanced micro-ecological environment in the gut and associating with the host in a symbiotic manner under normal physiological conditions. The gut microbiota obtains nutrients from the host gut, digests complex nutrients, regulates and balances metabolism and inflammation in the host, and plays an important role in safeguarding host health[34-35]. Previous studies have revealed structural and metabolic disorders of the gut microbiota in obesity, T2DM and other metabolic diseases, mainly manifested by a reduction in beneficial bacteria, and an increase in potential pathogenic bacteria and inflammatory cytokines[36-37]. Dysregulation of the gut microbiota can cause host metabolic disorders, systemic low-grade inflammation and insulin resistance through gut microbiota metabolites, especially endotoxin, short-chain fatty acids (SCFAs) and bile acids (BAs). Studies of fecal microbial transplantation have further revealed the pathogenic role of the gut microbiota in metabolic diseases, suggesting the gut microbiota is a potential target for drugs.

1.1　Gut microbiota and endotoxemia，low-grade inflammation

Low-grade inflammation is a common feature of metabolic diseases such as obesity, T2DM, and NAFLD[38-39]. Lipopolysaccharide (LPS) is a key signaling molecule that induces low-grade inflammation, which is closely related to energy metabolism disorders and insulin resistance[14]. The levels of LPS and inflammatory cytokines in the intestines and plasma of individuals with metabolic diseases, such as obesity, insulin resistance and T2DM, are significantly increased. First, LPS can activate the nuclear transcription factor, NF-κB, and promote the expression of various inflammatory cytokines (including tumor necrosis factor α(TNF-α)

and interleukin 6(IL-6) by forming a complex with LPS binding protein and CD14, and acts on the cell surface transmembrane receptor, toll-like receptor 4 (TLR4) [9-10]. What is more, LPS can destroy the integrity of the gut mucosal barrier and increase its permeability by reducing expression levels of intestinal tight junction proteins, including claudin-1, claudin-2 and zonula occludens-1[8]. In brief, the gut mucosal barrier is the key mediator when the gut microbiota interacts with the host; once its integrity is destroyed, the gut microbiota, together with LPS translocation, will aggravate the inflammatory response.

1.2 Gut microbiota and SCFAs

In addition to providing energy to intestinal epithelial cells, SCFAs can also modulate host energy metabolism, which mainly include acetate, propionate, and butyrate. SCFAs can promote the oxidative metabolism of fatty acids in liver and adipose tissue by decreasing peroxisome proliferator-activated receptor-γ(PPARγ) expression and activity, and subsequently improve insulin resistance and metabolic abnormalities in mice[40]. In addition, as anti-inflammatory factors, SCFAs can promote the repair of the intestinal mucosal barrier, inhibit gut microbiota and intestinal toxins (such as LPS), and reduce inflammation induced by endotoxemia[41]. Furthermore, SCFAs can down-regulate NF-κB by activating G-protein-coupled receptors signaling pathways and inhibiting histone deacetylase signaling pathways, therefore regulating immunity, reducing inflammation, and ameliorating insulin resistance and energy metabolism[14-16]. It was also reported that the SCFAs-mediated activation of G-protein coupled receptor 43 also promotes insulin secretion and reduces insulin resistance by up-regulating the expression of PYY and glucagon-like peptide-1 (GLP-1) [17]. Previous studies have found that levels of SCFAs-producing bacteria and SCFAs in feces are significantly reduced in obese, insulin-resistant, and TD2M patients, and are closely related to energy metabolism disorders, low-grade inflammation, and insulin resistance.

1.3 Gut microbiota and BAs

BAs are produced by cholesterol in the liver through a series of enzymatic reactions and then secreted into the gut. *Clostridium entericus* enables bile acid transformation by 7α dehydroxylation, whereby primary BAs synthesized by the liver are dehydroxylated into secondary BAs[42]. As a signaling molecule, secondary BAs bind the farnesoid X receptor (FXR) and G-protein-coupled bile acid receptor 5, and regulate the synthesis and secretion of incretin hormone and fibroblast growth factor 19[11-12]. Meanwhile, activated FXR can inhibit excessive proliferation of the gut microbiota, and maintain gut micro-environmental stability and gut mucosal barrier integrity. Furthermore, activated FXR can alleviate inflammatory bowel disease by reducing the expression of pro-inflammatory cytokines[13]. In addition to directly acting on the gut, the gut microbiota can also regulate the synthesis and secretion of primary bile acids in the liver by activating bile acid synthesis by cholesterol 7 alpha-hydroxylase, CYPA1[43]. Therefore, any reduction of gut microbiota involved in BAs metabolism can lead to disorders in BAs metabolism, destruction of the intestinal mucosal barrier, insulin resistance, and the release of inflammatory factors that can promote energy metabolism disorders, obesity, insulin resistance, and related metabolic diseases.

1.4 Gut microbiota and branched chain amino acids （BCAAs）

BCAAs include leucine, isoleucine, and valine, which are mainly derived from the diet or synthesized by gut microbiota. BCAAs are closely related to metabolic diseases because they can mediate obesity and insulin resistance. The increase in BCAAs in insulin-resistant individuals is associated with the gut microbiota, the imbalance of gut microbiota can increase BCAAs levels in the plasma partially by stimulating de novo synthesis, slowing catabolism, or by increasing intestinal permeability. Furthermore, BCAAs can induce insulin resistance by fatty acid oxidation via mammalian target of rapamycin, c-Jun NH_2-terminal kinase and insulin receptor substrate-1 pathways[18-19].

Animal studies have revealed that the selective supplementation of beneficial bacteria, such as *Bifidobacteria, Lactobacillus* and *Akkermansia muciniphila*, can improve energy metabolism and insulin resistance in mice by repairing the intestinal mucosal barrier and reducing the expression of inflammatory factors[44-46]. In summary, the gut microbiota-inflammation axis is closely related to the occurrence of metabolic diseases such as obesity and

insulin resistance; such correlations are inseparable from the intestinal mucosal barrier. Therefore, restoring the dynamic balance of the intestinal microbiota opens up a new direction for the treatment of metabolic diseases.

2 Treatment of metabolic diseases with berberine *via* the gut microbiota–inflammation pathway

2.1 Obesity

Obesity is an independent risk factor for a variety of chronic metabolic diseases, including TD2M, NAFLD, and cardiovascular disease. Studies have shown that berberine can reduce the accumulation of lipids in adipose tissue and thereby reduce body weight, but its specific mechanism of action is not yet clear. In recent years, many studies shown that the anti-obesity effects of berberine may be mediated in part by intestinal microbes. As a type of traditional Chinese medicine(TCM) with an antibacterial effect, berberine not only inhibits various pathogenic bacteria, but also affects the structure of the gut microbiota. Berberine significantly reduced the proportions of fecal *Firmicutes* and *Bacteroidetes* in high fat diet (HFD) mice, and increased the expression of fasting-induced adipose factor (FIAF, a key protein negatively regulated by gut microbes, which is related to energy metabolism) in gut and visceral adipose tissue[20]. Berberine alleviated HFD-induced structural changes of the gut microbiota by significantly decreasing its diversity and selectively enriching SCFA-producing bacteria, including *Allobaculum*, *Bacteriodes*, *Blautia*, *Butyricoccus,* and *Phascolarctobacterium*; this was closely related to improvements in metabolism [21]. Berberine reduced levels of inflammation and oxidative stress markers, and mRNA expression levels of markers of macrophage infiltration in visceral adipose tissue by increasing numbers of *Fusobacteria* and *Proteobacteria*, and decreasing *Firmicutes* and *Actinobacteria*. Berberine also inhibited the inflammatory response by decreasing intestinal permeability and increasing the expression of tight junction proteins. Furthermore, berberine restored levels of gut hormones in portal vein plasma, such as glucagon-like peptide-1, peptide YY, glucose-dependent insulinotropic polypeptides, and pancreatic polypeptides[22]. Current studies indicate berberine can induce weight loss and improve insulin resistance by regulating the structure and metabolism of the gut microbiota, restoring the intestinal mucosal barrier, and alleviating metabolic endotoxemia and systemic inflammation.

2.2 T2DM

T2DM is a metabolic disease characterized by hyperglycemia and is caused by insulin deficiency due to insulin resistance and the destruction of β-cell islet function. Many reports exist on the clinical use of berberine in the treatment of T2DM. Interestingly, recent studies showed that berberine can exert its effects on T2DM by regulating the gut microbiota. Berberine increased the number of SCFAs-producing bacteria (including *Butyricimonas*, *Coprococcus*, *Ruminococcus, Blautia* and *Allobaculum*) and other probiotics (e. g., *Lactobacillus* and *Akkermansia*), decreased serum LPS levels, reduced intestinal inflammation and repaired the intestinal barrier[23-24]. HFD altered the composition of the gut microbiota by decreasing protective bacteria, such as *Bifidobacteria*, and increasing Gram-negative bacteria, such as *Escherichia coli*, which led to an increase in LPS release into plasma. Berberine increased the expression of insulin receptor and insulin receptor substrate-1 in the liver, inhibited the activation of LPS-induced TLR4/TNF- α and reversed the effects of HFD[25]. Administration of berberine significantly improved the energy metabolism of rats with T2DM, increased the number of *Bacteroidetes*, *Clostridia*, *Lactobacillales*, *Prevotellaceae* and *Alloprevotella*, and reduced the number of *Bacteroidales*, *Lachnospiraceae*, *Rikenellaceae* and *Desulfovibrio*. Furthermore, it was found that berberine reduced inflammation, inhibited the overexpression of TLR4 and p-JNK, and increased the expression of phosphoinositide 3-kinase, glucose transporter 2, and other proteins that are closely related to oxidative stress, thereby promoting glucose metabolism[26]. Berberine improved insulin resistance by affecting the metabolism of BCAAs, which was not only associated with a decrease in BCAAs biosynthesis due to changes in the gut microbiota, but was also associated with enhanced BCAAs decomposition in the liver and adipose tissue. Berberine significantly reduced the number of BCAAs-producing bacteria, including the *Clostridiales* order, *Streptococcaceae*, *Clostridiaceae*, and *Prevotellaceae* families, and *Streptococcus* and *Prevotella* genera[27]. In addition, berberine promoted

GLP-1 expression in L cells, elevated GLP-1R and neuropeptide Y expression in the brain by increasing the *Bacteroidetes/Firmicutes* ratio and SCFA-producing bacteria, and therefore improving energy metabolism through a microbiota-gut-brain axis[28]. In conclusion, current studies indicated that the efficacy of berberine in T2DM is partially mediated through the gut microbiota-inflammation axis.

2.3 NAFLD

NAFLD is a chronic metabolic liver disease closely related to obesity, lipid metabolism disorders, insulin resistance, and genetic susceptibility. The evolution of the disease spectrum includes simple fatty liver, nonalcoholic steatohepatitis, cirrhosis, and hepatocellular carcinoma[47]. Studies have found that berberine is beneficial for obesity, however, the specific mechanisms of berberine in the treatment of NAFLD are still controversial. Recently, several studies have found that gut microbiota was involved in the treatment of NAFLD with berberine[29-31,48]. Serum lipids were significantly decreased, and serum pyruvic acid and glycogenic amino acids increased in rats after berberine treatment without obvious adverse side effects. Berberine treatment also caused an increase in *Bacteroides* and a reduction in *Escherichia*[29]. Berberine treatment restored the relative levels of *Bifidobacteria* and the proportion of *Bacteroidetes/Firmicutes* compared to the control group. The alteration of the gut microbiota resulted in a significant decrease in body weight, serum lipid and glucose levels, insulin resistance, and expression levels of CD14, interleukin (IL)-1, IL-6 and TNF-α in serum[30]. The effects of berberine in NAFLD were also related to the recovery of intestinal mucosal barrier function. Berberine treatment significantly mitigated HFD-induced hepatic steatosis and intestinal mucosal histopathological changes; and reduced the expression levels of endotoxin, intestinal fatty acid binding protein, and TNF-α. Berberine also significantly elevated the level of *Bacteroides* and decreased the level of *Faecalibacterium prausnitzii*[31]. In addition, the therapeutic effects of berberine in NAFLD were related to bile acid metabolism in the gut and subsequent FXR signaling pathways. Berberine inhibited bile salt hydrolase activity in the gut microbiota and increased levels of tauro-conjugated bile acids, particularly taurocholic acid in the gut, which can activate the intestinal FXR pathway and reduce the expression of liver CD36[48]. The above results showed that berberine improved NAFLD and reduced damage to organs caused by abnormal lipid metabolism by acting on the gut microbiota and regulating its metabolism.

2.4 Atherosclerosis

Atherosclerosis is associated with disorders of lipid metabolism and inflammation of the arterial wall, which is the main cause of coronary heart disease, cerebral infarction, and peripheral vascular disease. Although statins are widely used to reduce lipids and prevent cardiovascular and cerebrovascular diseases, the global burden of such diseases is still very heavy. Berberine is used for adjuvant treatment of atherosclerosis due to its effects against inflammation, as well as its ability to regulate lipids and inhibit the proliferation of vascular smooth muscle cells. In recent years, studies have found that berberine can dilate blood vessels, improve blood flow, prevent platelet aggregation, lower blood pressure, and interfere with the formation of atherosclerosis by regulating the intestinal microbiota. Berberine treatment significantly reduced atherosclerosis, and increased the number of *Akkermansia spp.* and *Bacteroides* in HFD-fed mice. Meanwhile, the thickness of the tight junction protein and mucus layer in the gut was markedly increased, which was related to the recovery of intestinal barrier integrity. In addition, berberine treatment also reduced HFD-induced metabolic endotoxemia and decreased expression levels of pro-inflammatory cytokines and chemokines in the arteries and intestines, which helped reduce inflammation and insulin resistance, and delay the development of atherosclerosis[32]. The inhibition of the development of atherosclerosis and the expression of inflammatory cytokines of BBR-treated HFD-fed mice was induced through increased *Firmicutes* and *Verrucomicrobia*[33]. The above results indicated that the effects of berberine on arteriosclerosis are also related to the gut microbiota.

3 Perspectives

Metabolic diseases result from the interaction of multiple risk factors; however, the underlying mechanisms of their onset remain unexplored. Recently, many studies have shown that gut microbiota was closely related to the energy metabolism of the host. Structural and metabolic disorders induce low-grade inflammation and energy

metabolism disorders through various pathways, leading to obesity, insulin resistance and T2DM. Therefore, the gut microbiota can be used as a new target for the prevention and treatment of obesity and related metabolic diseases.

Berberine has a significant therapeutic effect on metabolic diseases, and recent studies have found the effects were achieved by a gut microbiota-inflammation axis. Berberine can reduce the low-level inflammatory response caused by gut microbiota disorders by promoting the proliferation of beneficial bacteria in the gut and by improving the metabolism of the gut microbiota, such as SCFAs, BAs, and endotoxin. In addition, the gut microbiota can affect the clinical efficacy and toxicity of berberine by affecting its biotransformation and metabolism. Based on these bi-directional effects, in-depth studies of the pharmacological actions of berberine *via* the gut microbiota-inflammation axis in metabolic diseases will enrich the theory of TCM, and lead to the development of TCM preparations that target the gut microbiota and guide the rational use of such drugs in the clinic. With the development of precision medicine, research on the treatment of metabolic diseases through the gut microbiota-inflammation axis should be extended to other TCM. If these effects shown to be safe and effective, TCM intervention in energy metabolism through the gut microbiota-inflammation axis will be expected to be a new pathway for the treatment of metabolic diseases.

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基于肠道微生态探讨黄连素在代谢性疾病中的抗炎作用*

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摘要　肠道菌群与能量代谢密切相关，其组成和代谢紊乱可通过多种途径导致胰岛素抵抗、肥胖和2型糖尿病. 黄连素因具有减重、降糖、调脂等作用被广泛用于肥胖、2型糖尿病及非酒精性脂肪性肝病等代谢性疾病的辅助治疗. 研究表明，黄连素可调节肠道菌群的组成和代谢，改善肠道微生态环境，从而改善胰岛素抵抗和代谢. 本文综述了黄连素通过肠道菌群-炎症轴在干预代谢性疾病的研究进展，以期为代谢性疾病的治疗寻找新的策略，并为今后该领域的深入研究提供指导意义.

关键词　黄连素，肠道菌群，炎症，代谢性疾病
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