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Research on the regulatory effect of berberine on fatty liver

Abstract: *The liver, as the metabolic hub of the body, plays a pivotal role in lipid transformation processes. Excessive intake of a high-fat diet disrupts this equilibrium mechanism, leading to a significant increase in lipid deposition within hepatocytes. Studies have revealed that when dietary fat consumption exceeds the liver's metabolic capacity, it not only activates sterol regulatory element-binding protein 1c (SREBP-1c) to promote lipogenesis but also suppresses the PPARα-mediated lipid oxidation pathway. Research on the pharmacological effects of berberine demonstrates its remarkable therapeutic potential in metabolic syndromes such as non-alcoholic fatty liver disease (NAFLD) and obesity. This review primarily focuses on elucidating berberine's mechanisms in addressing oxidative stress, steatosis, and fatty liver diseases, providing valuable references for subsequent research on lipid accumulation-related pathologies.*

Keywords: *Berberine, Steatosis, Oxidative stress, Non alcoholic steatohepatitis, Liver metabolism*

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1. Introduction

Berberine (BBR), also known as berberine hydrochloride, is a quaternary ammonium alkaloid and the primary active ingredient of the traditional Chinese medicine Coptis chinensis. It possesses various pharmacological effects including anti-inflammatory, anti-infective, anti-tumor, anti-arrhythmic, and lipid- and glucose-regulating properties. Recent studies in livestock farming have also indicated that berberine exhibits anti-coccidial, antibacterial, anti-oxidative stress, anti-mycotoxin, and fat-reducing effects. As the core antibacterial component of Coptis chinensis, berberine exerts broad-spectrum antibacterial activity against pathogens such as Staphylococcus aureus by inhibiting bacterial DNA gyrase and topoisomerase activities.

2. Regulatory Effects of Berberine on Animal Liver Metabolic Disorders and Pathological Progression

Berberine exhibits multi-target synergistic effects on regulating liver metabolic disorders and pathological progression in animals. During the initial stage of metabolic imbalance induced by a high-fat diet, excessive lipid accumulation triggers oxidative stress through reactive oxygen species (ROS) produced by mitochondria, leading to the inhibition of the nuclear factor E2-related factor 2 (Nrf2) signaling pathway and a 40%-50% decrease in liver superoxide dismutase (SOD) activity. In the progression of non-alcoholic steatohepatitis (NASH), oxidative stress products synergistically activate the nuclear factor-κB (NF-κB) pathway with free fatty acids, causing a 3-5 fold increase in the secretion of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which induce hepatocyte pathology and inflammatory infiltration. This forms a virtuous cycle of "inhibiting lipogenesis, enhancing oxidative metabolism, repairing the gut-liver barrier, and promoting lipid transport". This multi-dimensional regulatory property offers new avenues for the intervention of metabolic liver diseases.

2.1 Effects of Berberine on Oxidative Stress

Oxidative stress refers to the oxidative damage caused by substances produced by redox-sensitive mechanisms when an individual is stimulated by various stressors or pathogens. Liver oxidative stress occurs in various liver diseases, not only in chronic liver diseases such as non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) but also in acute liver injury. In livestock farming, oxidative stress is a common physiological phenomenon that can harm the growth, health, and performance characteristics of livestock and poultry.

Berberine can alleviate stress by inhibiting the PERK/eIF2α pathway in diabetic rats. Yue Wu et al. proposed that berberine reduces endoplasmic reticulum stress induced by thapsigargin in Ht22/Amyloid

precursor protein cells. In terms of inflammatory factors, berberine can inhibit the stress response caused by cerebral hypoxia-reoxygenation. By regulating the NF-κB/MAPK signaling pathway in piglets challenged with deoxynivalenol, berberine improves intestinal barrier function and reduces inflammation, immunosuppression, and oxidative stress. Supplementing the diet with 2 g/d or 4 g/d berberine can enhance the antioxidant capacity and immune function of peripartum goats, improving postpartum production performance and having a beneficial effect on alleviating oxidative stress and inflammation in peripartum goats. In 2020, Shen Yan et al. suggested that berberine regulates stress phenomena by activating the caspase-12/calpain I apoptosis signaling pathway.

Berberine can increase the activity of AMP-activated protein kinase (AMPK) by targeting mitochondria, thereby increasing the mass and activity of brown adipose tissue. Jian-Hua Ming et al. experimentally demonstrated that berberine can activate the AMPK signaling pathway, regulate the expression, production, and transport genes of lipolysis, thus promoting lipid metabolism, enhancing antioxidant capacity, and reducing excessive lipid deposition. Simultaneously, berberine may improve lipid metabolism abnormalities in alcoholic fatty liver disease through the AMPK/SIRT1 pathway. In 2023, it was proposed that berberine can reduce liver injury through the AMPK/mTOR pathway. Berberine has a dual inhibitory effect on intestinal cholesterol and fatty acid absorption, significantly controlling the expression of sterol O-acyltransferase 2 (SOAT2). The intestinal-specific deletion of SOAT2 can effectively regulate intestinal cholesterol absorption, thereby reducing problems arising from abnormal lipid metabolism. Berberine can downregulate the expression of C/EBP homologous protein (CHOP) and c-Jun N-terminal kinase (JNK) in the livers of diabetic rats, improving inflammation and hepatocyte injury.

Through extensive research, berberine can effectively alleviate oxidative stress issues in animals by acting on pathways such as PERK/eIF2α, NF-κB/MAPK, and caspase-12/calpain I apoptosis, thereby improving liver diseases caused by lipid deposition.

2.2 Effects of Berberine on Steatosis

The liver is a crucial site for fat transformation and metabolism. Increased blood lipids lead to the accumulation of large amounts of lipids within liver cells, causing phenomena such as hepatocyte steatosis, which increases inflammation and may even trigger oxidative stress damage and hepatocyte injury. Abnormal lipid increase can lead to progressive liver fibrosis, ultimately resulting in liver cancer or other liver system diseases.

Berberine can effectively reduce hepatic steatosis by decreasing the methylation of the microsomal triglyceride transfer protein (MTTP) promoter, DNA demethylation, and histone acetylation, and regulating the function of L-pyruvate kinase. XinXia Chang et al. also experimentally proposed that berberine upregulates hepatic MTTP expression, enhancing MTTP function and reducing the incidence of steatosis. Berberine can help improve hepatic lipidosis by increasing the endocrine capacity of the gut microbiota. SREBP-1c, carbohydrate-responsive element-binding protein (CHREBP), fatty acid synthase (FAS), and CCAAT/enhancer-binding protein β (C/EBPβ) are important regulators of fatty acid synthesis. Berberine can significantly downregulate the mRNA levels of SREBP-1c, CHREBP, FAS, and C/EBPβ in mice, providing a protective effect against hepatic steatosis. Hossein Rafiei et al. established a cell culture model and found that berberine reduces inflammatory cytokines and chemokines induced by several activating mixtures, such as MIP-1α, MIP-1β, MCP-1, and IL-7, suggesting that berberine can play a role in the initial stage of steatosis by preventing inflammatory cell infiltration into the liver. Ma ChunYan et al. proposed that berberine downregulates proprotein convertase subtilisin/kexin type 9 (PCSK9) through the ERK1/2 pathway, alleviating hepatic steatosis. Hong MeiYan et al. concluded through multiple clinical trials that berberine acts preferentially on the liver, significantly improving hepatic steatosis in patients with NAFLD. In 2018, it was found that berberine inactivates the AKT-S6 kinase pathway related to hepatocyte steatosis by inducing the expression of miR-373 in hepatocytes.

Research shows that berberine can effectively improve hepatic steatosis by regulating gene expression and downregulating inflammatory factors.

2.3 Effects of Berberine on Non-alcoholic Steatohepatitis

There is a close relationship between obesity and non-alcoholic fatty liver disease (NAFLD). In the initial stages of NAFLD, immune cells in the liver produce pro-inflammatory factors, leading to further development of inflammatory cells and more severe inflammation, which can trigger irreversible non-alcoholic steatohepatitis (NASH).

Berberine exhibits 多元性 in its targets for participating in NASH, intervening in NASH through various pathways. It can regulate the phenotypic changes of macrophages in liver tissue, downregulating the production of pro-inflammatory cytokines and upregulating the production of anti-inflammatory cytokines, thereby controlling the occurrence of NAFLD. Berberine can also reduce fatty acid uptake and lipid formation

in the liver by downregulating genes such as CD36, FABP, SCD1, and PPARγ related to fatty acid metabolism, thereby mitigating hepatic fat accumulation and improving NASH symptoms. Berberine effectively reduces factors that promote liver fibrosis, highlighting its potential benefits in NASH/NAFLD. Dongya Chen proposed in 2023 that berberine can reduce fat accumulation and improve glucose metabolism by altering the concentrations of Atopobiaceae and Bacteroides in the gut, thereby decreasing the incidence of NASH.
By intervening in multiple targets of NASH, berberine reduces fat accumulation in the body and lowers the incidence of NASH.

2.4 Regulatory Effects of Berberine on Animal Liver Metabolism

Fatty liver syndrome (FLS), also known as fatty liver hemorrhage syndrome, commonly occurs in pigs, cattle, sheep, chickens, fish, and other animals. The main symptoms may vary among different livestock and poultry. Laying hens in the late laying period exhibit high fat accumulation, leading to lipid metabolism disorders and oxidative damage, which can easily trigger metabolic diseases such as fatty liver hemorrhage syndrome. Insufficient energy during the peripartum period of dairy cows can lead to reduced feed intake, resulting in increased free fatty acids. In animal farming, animals consuming high-energy, high-fat feeds for extended periods ingest excessive energy and fat, leading to overeating, nutritional excess, and lipid metabolism imbalance, which can form fatty liver.

Research has shown that treating bovine hepatocytes with 10 or 20 μmol/L berberine can improve mitochondrial respiratory chain function and insulin signaling impaired by non-esterified fatty acids (NEFA), providing a new approach for the prevention and treatment of fatty liver in dairy cows. Treating pig adipocytes with 20 or 40 μmol/L berberine can activate the AMPK signaling pathway, inducing lipolysis in pig adipocytes. Additionally, 0.1 μg/mL berberine can promote lipid metabolism and improve the in vitro maturation of pig oocytes by activating the expression of miR-192. Berberine regulates the metabolic signaling pathways of lipid synthesis and oxidative decomposition in the livers of laying hens, reducing fat deposition in the liver and preventing fatty liver hemorrhage syndrome. Supplementing the diet with 50 mg/kg berberine can regulate the expression of fat generation and fat decomposition genes in black seabream, thereby enhancing liver fat metabolism. Berberine can also increase muscle fat content, contributing to the deliciousness of black seabream meat and providing new ideas for the development of aquaculture. Berberine reduces liver metabolic burden by inhibiting fat synthesis and promoting fat decomposition, increasing fat uptake by peripheral tissues. Research has found that berberine can effectively alleviate liver cell damage caused by lipid metabolism issues in zebrafish.

Studies have shown that berberine can regulate fat cell metabolism, inhibit fat synthesis, and enhance fat decomposition in animals, thereby reducing liver damage caused by lipid metabolism issues.

3. Conclusion

In summary, berberine regulates issues such as oxidative stress, steatosis, and liver metabolism in organisms through certain signaling pathways and inflammatory factors. Berberine acts on fat through multiple pathways, and with accumulation, it can effectively improve liver diseases. Research has shown that berberine's pharmacological effects prioritize the liver, capable of preventing and treating diseases caused by abnormal fat accumulation.

Currently, there are more in vitro experimental studies on large livestock but fewer on poultry. Therefore, we can conduct various experimental studies on small poultry using berberine. The low bioavailability of berberine affects its permeability in adipose tissue. The design and development of drug delivery systems provide new ideas for our next steps in research. Based on the biological characteristics of berberine, its application as an effective feed additive in animal production can not only improve animal growth performance but also prevent and treat animal diseases such as inflammation, oxidative stress, and abnormal fat accumulation, contributing to the production and development of the livestock and poultry industry.

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