Asian Journal of Agriculture and Biology
https://doi.org/10.35495/ajab.2025.238

Review Article

A review of the application potential of hyperoside in the regulation of glycolipid metabolism in livestock and poultry

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Received: 12 September 2025 / Revised: 13 December 2025 / Accepted: 19 December 2025 / Published Online: 29 January 2026

Abstract

Abnormalities in glycolipid metabolism are important health problems faced in livestock and poultry farming, which can lead to growth retardation, decreased production performance and multi-organ complications. Hyperoside (HYP) is a natural flavonoid compound found in various plants such as *Forsythia pinnata*, *Forsythia suspensa*, and *Cuscuta chinensis*. Medical studies have revealed that HYP exhibits a wide range of biological activities, including anticancer, anti-inflammatory, antibacterial, antiviral, antidepressant, and organ-protective effects. It is worth noting that HYP has demonstrated the intervention potential of multi-target and multi-pathway in the regulation of glycolipid metabolism. This paper systematically reviews its effects on glycolipid metabolism and related core molecular mechanisms by regulating carbohydrate absorption, improving insulin sensitivity, and protecting target organs such as the kidneys and liver. Additionally, this paper explores the potential of fibronectin type III domain-containing protein 5 (FNDC5) as a target for HYP to regulate glycolipid metabolism and thus influence meat quality, providing a theoretical basis for its development as a green feed additive and application in the livestock industry.

Keywords: Hyperoside, Glycolipid metabolism, Signaling pathway, Livestock production

How to cite this article:

Gao Y, Ye Y, Liu F, Li H, Luo L, Zhang H, Chamba Y and Shang P. A review of the application potential of hyperoside in the regulation of glycolipid metabolism in livestock and poultry. Asian J. Agric. Biol. 2026: e2025238. DOI: https://doi.org/10.35495/ajab.2025.238

Introduction

For a long time, abnormal glycolipid metabolism has been recognized as a metabolic disorder in livestock and poultry, characterized primarily by impaired glucose homeostasis. Under intensive farming regimens, the prevalence of this disorder has risen steadily year on year, particularly in large-scale pig, poultry, and dairy operations. Beyond retarding growth and reducing production performance in affected animals, this metabolic aberration also precipitates multi-organ complications, ultimately resulting in substantial economic losses for the farming industry (Huang et al., 2022; Jones, 2016; Song et al., 2024; Wen et al., 2024; Zhang et al., 2022). Traditional research has long centered on insulin secretion defects and functional impairments. In contrast, contemporary biomedical investigations have demonstrated that the pathogenesis of abnormal glycolipid metabolism is far more intricate. Chronic inflammation, oxidative stress, and metabolic network dysregulation interact synergistically to form a "pathological triad", which collectively drives the progression of this disorder (An et al., 2023; Yi et al., 2024).

It is worth noting that while obesity is closely correlated with abnormal glycolipid metabolism, the association between these two conditions is not unidirectional (Malone and Hansen, 2019; Perez-Torres et al., 2021). This phenomenon suggests that, beyond adipose tissue dysfunction, sphingolipids including diacylglycerol and ceramide can directly induce insulin resistance by impairing the phosphorylation of insulin receptor substrates, a mechanism that is partially independent of body fat content (Athyros et al., 2018; Petrenko et al., 2023; Xu et al., 2018).

From a molecular pathological standpoint, oxidative stress and chronic inflammation induced by hyperglycemia form a vicious cycle within the organism (Ma et al., 2018). Sustained hyperglycemia triggers the mitochondrial electron transport chain to overproduce reactive oxygen species (ROS), which in turn induces oxidative DNA damage and protein dysfunction. When the intracellular antioxidant system, including superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), fails to provide sufficient compensatory capacity, ROS activates the nuclear factor Kappa-B (NF-κB) signaling pathway, thereby promoting the excessive secretion of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). These cytokines not only suppress insulin receptor signal transduction but also induce apoptosis of pancreatic islet β-cells (Oguntibeju, 2019; Tsalamandris et al., 2019; Volpe et al., 2018).

Additionally, exosomes secreted by adipose tissue can shuttle miR-27a to hepatic and muscle tissues, thereby establishing a cross-organ inflammatory propagation network (Yu et al., 2018). This systemic disorder ultimately triggers multi-systemic pathologies such as hepatic steatosis, intestinal barrier dysfunction, and mammary tissue inflammation, severely affecting the health and production performance of livestock and poultry.

Hyperoside (HYP, molecular formula $C_{21}H_{20}O_{12}$) is a flavonoid glycoside widely present in plants, formed by the linkage of quercetin and galactose through a glycosidic bond, with a molecular weight of 464.39. Its chemical structure is shown in Figure 1 (Ferenczyova et al., 2020). Its chemical structure endows it with favorable water solubility and stability. Meanwhile, the preserved core active moieties of flavonoid compounds, including phenolic hydroxyl groups and conjugated double-bond systems, enable it to exert potent antioxidant effects via electron transfer or hydrogen atom donation mechanisms. Hyperoside (HYP) not only possesses a distinctive chemical structure but also exhibits a broad spectrum of biological activities, such as antibacterial, anti-inflammatory, antioxidant, hepatoprotective, and neuroprotective properties (Jang et al., 2018; Kwon et al., 2019; Lee et al., 2017; Orzelska-Gorka et al., 2019; Sun et al., 2021), holding broad prospects in the fields of drug development and clinical application.

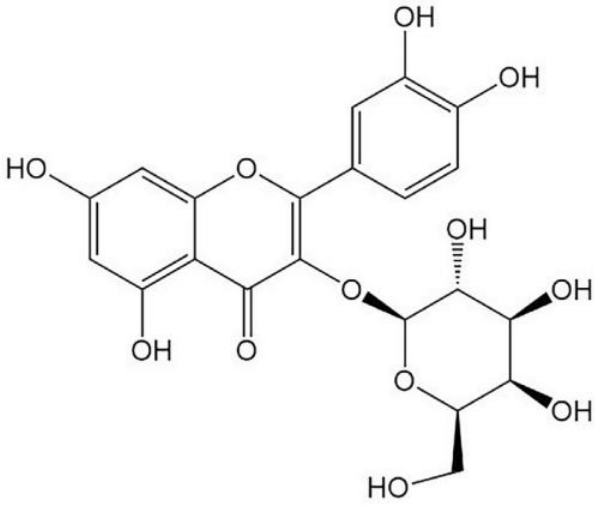

Figure-1. The chemical structure of HYP.

https://doi.org/10.35495/ajab.2025.238

HYP exists abundantly in medicinal plants such as Hypericum perforatum and Crataegus spp. Traditionally, these plants have been used for the treatment of inflammation, analgesia, and cardiovascular diseases (Chi et al., 2024; Yao et al., 2019). With the advancement of modern separation technologies, including macroporous resin adsorption and high-performance liquid chromatography (HPLC), the purification efficiency of HYP has been markedly enhanced. Meanwhile, the optimization of both chemical synthesis and biosynthesis approaches (e.g., microbial fermentation) has further facilitated its industrial-scale production. In recent years, progress in synthetic biology and medicinal chemistry has continuously refined the total synthesis, semisynthesis, and biosynthesis pathways of HYP, thereby laying a robust foundation for its large-scale manufacturing and in-depth investigation of pharmacological mechanisms (De Bruyn et al., 2015). Studies have shown that HYP has a wide range of biological activities. In terms of antibacterial effects, it inhibits pathogenic microorganisms such as Pseudomonas aeruginosa (Sun et al., 2017). In the fields of anti-inflammation and analgesia, animal experiments have demonstrated that HYP can reduce inflammatory responses in model animals (such as the rat wool ball implantation model) by inhibiting the release of inflammatory cytokines such as TNF-α and IL-6. It also exhibits analgesic effects in peripheral neuralgia models (Xie et al., 2022). Of further note are its prominent antioxidant and organ-protective properties: hyperoside (HYP) can efficiently scavenge free radicals, mitigate oxidative stress-induced damage, and exert marked cardioprotective effects in a mouse model of acute myocardial infarction. The underlying mechanism is likely associated with the modulation of the Nrf2/HO-1 signaling pathway (Huang et al., 2023).

This paper reviews the regulatory mechanisms of hyperin on glycolipid metabolism, which not only provides a solid scientific basis for developing hyperin-derived hypoglycemic functional feed additives but also serves as an important reference for the application of natural compounds in the livestock sector.

The mechanism of HYP in regulating glycolipid metabolism

Regulation of carbohydrate absorption and metabolism

As a key digestive enzyme located in the brush border of the small intestine, the activity of α-glucosidase directly affects the digestion efficiency of complex carbohydrates such as starch and oligosaccharides, thereby influencing the absorption rate of glucose. The stronger its activity, the faster the postprandial blood glucose rises (Sun et al., 2024). Using HPLC, researchers identified HYP from Myrica rubra and confirmed it as one of the key active components in Myrica rubra. α-glucosidase inhibition experiments showed that HYP has a significant effect on regulating glucose metabolism in mice (Chang et al., 2022). It can effectively inhibit the activity of α-glucosidase in the intestine, delaying the process of carbohydrate decomposition into glucose, thereby reducing the postprandial blood glucose peak. Its mechanism of action is similar to that of acarbose. This characteristic helps to optimize the glucose metabolism process in livestock and poultry, and is of great significance for maintaining the healthy growth of livestock and poultry and improving the breeding efficiency (Verma et al., 2013).

During *in vivo* experiments, it was found that HYP extracted from *Rosa davurica* fruits gradually enhanced the scavenging capacity of DPPH and ABTS free radicals during the gastrointestinal digestion process in mice. At the end of the simulated digestion, the inhibition rate of α-glucosidase can reach 89.17%. This not only helps improve the glucose metabolism status of mice but also enhances their antioxidant capacity (Du, 2023). Studies have also shown that HYP extracted from black mulberries can reverse the harmful effects of excessive glucose in mice by inhibiting α-glucosidase and lipase, enhance their stress resistance, prevent the accumulation of lipofuscin, and reduce ROS production (Nunez et al., 2025). Moreover, HYP extracted from the Myrcia multiflora leaves not only exhibits antioxidant activity against DPPH and ABTS free radicals, but also possesses α-glucosidase inhibitory activity and in vitro glycation activity (Oliveira et al., 2021).

Overall, α-glucosidase inhibitory activity is the core common mechanism by which HYP from different plant sources regulates glucose metabolism, but variations exist among HYP from various sources in functional expansion (e.g., antioxidant, lipid-lowering, anti-stress effects), activity intensity (e.g., HYP from *Rosa davurica* Pall. exhibits an enzyme inhibition rate of 89.17%), and application orientation

(only HYP from Myrica rubra links to livestock and poultry scenarios). Current research has obvious gaps: insufficient cross-species validation, with most studies focusing on mouse models and unclear adaptability to livestock and poultry; lack of in-depth analysis of structure-activity relationships and the synergistic mechanism of "glucose-lowering-antioxidant-lipid-lowering"; and absence of research on application technologies such as feed addition dosage and activity retention. These gaps limit the application of HYP in livestock and poultry farming. However, its multi-effectiveness aligns well with the needs of healthy livestock and poultry farming. Future studies should focus on cross-species validation, structure-activity relationship analysis, and application optimization to promote the large-scale application of HYP as a green feed additive.

Improve insulin sensitivity

Insulin, a hormone secreted by the pancreas, primarily functions to regulate blood glucose levels by facilitating glucose uptake into cells for subsequent energy production or storage. Insulin sensitivity reflects the responsiveness of target tissues to insulin, namely the efficiency with which insulin drives glucose uptake and utilization. As a key determinant of maintaining normoglycemia in livestock and poultry, insulin sensitivity exerts a pivotal role in glucose homeostasis. Indeed, any factor that alters insulin sensitivity, including genetic predispositions, nutritional status, pathogenic conditions, and environmental stimuli, can profoundly impact glucose metabolism in these animals, thereby compromising their growth, development, and overall health (Baruselli et al., 2016; Burdick et al., 2016; Du et al., 2023; Ji et al., 2020).

Researchers established an animal model of obesity with insulin resistance by feeding mice a high-fat diet, simulating in vivo states of hyperglycemia, hyperlipidemia, and insulin resistance, to observe the effects of HYP on mouse metabolism. The results showed that HYP could improve the insulin resistance state in high - fat diet - induced obese mice by regulating AMPK and lipid metabolism - related genes SREBP1c, ACC and FAS (Yang et al., 2023). Studies have shown that HYP can reduce the activation level of the AMPK/SIRT1 pathway and increase the expression of p62 protein in mice with abnormal glucose metabolism, suggesting that the reduction of autophagic level by HYP may be a relevant mechanism for improving insulin resistance in these mice.(Wang et al., 2023) Additionally, studies have found that the autophagy activator rapamycin can alleviate HYP's inhibitory effect on the activation of the AMPK/SIRT1 pathway, leading to increased levels of hepatic autophagy and apoptosis in mice, exacerbation of liver tissue lesions and insulin resistance, and reduced body weight. This further suggests that the mechanism by which HYP improves insulin resistance in mice with abnormal glucose metabolism may be related to the inhibition of autophagic pathways mediated by the AMPK/SIRT1 pathway. Meanwhile, HYP supplementation can also restore the activity of pancreatic antioxidant enzymes. In the culture experiment of MIN6 cells that produce and secrete insulin, the HYP-treated group reduced intracellular calcium concentration and restored insulin secretion function by inhibiting the expression of TXNIP (Zhang et al., 2021).

Overall, the core mechanisms by which HYP improves insulin resistance and regulates glucose metabolism focus on autophagy regulation mediated by the AMPK/SIRT1 pathway and pancreatic function protection, with relevant studies providing evidence at the pathway, molecular target, and cell/animal model levels. However, obvious limitations exist: the crosstalk between different pathways and the regulatory differences across various tissues remain unclear; research models are concentrated on mice and MIN6 cells, lacking validation in livestock and poultry scenarios and analysis of cross-species applicability; data on dose-effect relationships, synergistic effects with other nutrients, and practical application effects in livestock and poultry diets are insufficient. Insulin sensitivity is crucial for the glucose metabolic homeostasis of livestock and poultry, and the multi-dimensional regulatory properties of HYP align with the needs of healthy farming. Future studies should conduct in-depth analysis of pathway crosstalk, validation in livestock and poultry models, and optimization of application dosages to provide scientific support for the translational application of HYP as a green feed additive in farming.

Regulate renal glycolipid metabolism

The kidneys possess a robust capacity for glucose reabsorption. As blood passes through the glomerulus, water, inorganic salts, glucose, and urea in the plasma with the exception of blood cells and macromolecular proteins are filtered into the capsular space of the kidney to form primary urine. Under physiological conditions, glucose in the primary urine is almost

entirely reabsorbed back into the circulation in the renal tubules. This process is primarily mediated by sodium-glucose cotransporters (SGLTs) localized on the brush border membrane of renal tubular epithelial cells. Specifically, sodium-glucose cotransporter-2 (SGLT2) is responsible for reabsorbing most of the filtered glucose, whereas sodium-glucose cotransporter-1 (SGLT1) mediates the reabsorption of the remaining small fraction. This highly efficient reabsorption mechanism plays a critical role in maintaining blood glucose homeostasis and preventing excessive urinary glucose loss (Ghezzi et al., 2018; List and Whaley, 2011; Mathew et al., 2024).

The kidney is one of the important organs for gluconeogenesis in the body. During situations such as hunger or prolonged exercise, blood glucose levels in the body decrease. At this time, the kidneys utilize non-carbohydrate substances such as amino acids, lactic acid, and glycerol to synthesize glucose through the gluconeogenesis pathway, thereby maintaining relatively stable blood glucose levels. Gluconeogenesis in the kidneys can partially compensate for the insufficient gluconeogenic capacity of the liver, especially when liver function is impaired or the body's demand for glucose increases drastically, the role of renal gluconeogenesis becomes more prominent. The kidney is one of the main sites for insulin degradation, with approximately 20%-30% of insulin being degraded in the kidney. When renal function is impaired, the degradation of insulin decreases, which may lead to an increase in insulin levels in the body and further affect blood glucose regulation. Angiotensin II can indirectly regulate glucose metabolism by affecting insulin signal transduction and other pathways (Liu, 2007; Pereira-Moreira and Muscelli, 2020). Meanwhile, the kidneys indirectly affect glucose metabolism by regulating acid-base balance. During the process of glucose metabolism, some acidic metabolites are produced, such as lactic acid and ketone bodies. The kidneys maintain acid-base balance in the body by secreting hydrogen ions and reabsorbing bicarbonate ions. When renal function is impaired, it may lead to acid-base imbalance, thereby affecting the normal process of glucose metabolism (Chen et al., 2019; Stancu et al., 2018).

Diabetic nephropathy (DN), a common microvascular complication of abnormal glucose and lipid metabolism, is the most common cause of end-stage renal disease. It is characterized by adverse manifestations such as glomerular hyperfiltration and renal hypertrophy. In the terminal stage, it can lead to renal failure, seriously endangering life and health (Gaddy et al., 2025). Currently, the treatment of DN mainly uses medications such as SGLT2 inhibitors, selective endothelin A receptor antagonists (ERAs), and selective non-steroidal mineralocorticoid receptor antagonists (MRAs). However, their use is limited by strong side effects.(Sawaf et al., 2022) Existing studies have shown that HYP regulates abnormal renal glucose and lipid metabolism through multi-target and multi-pathway mechanisms (Figure 2).

Zhang et al. (2016) reported that HYP can improve glomerulosclerosis in DN by downregulating miR-21 and thus increasing the expression of its target matrix metalloproteinase-9 (MMP-9). This significantly alleviates glomerulosclerosis in DN mice and maintains normal renal function, Zhou et al. (2021) demonstrated that HYP can significantly relieve glomerular filtration dysfunction, renal damage, and early nephropathy symptoms associated with abnormal glucose and lipid metabolism in DN rats by targeting miR-499-5p/APC. The study further indicated that HYP holds potential as a novel therapeutic agent for DN. However, limited research has been conducted on its effects on renal epithelial-mesenchymal transition (EMT) in DN rats. Renal fibrosis is a major pathological feature of DN and is closely associated with renal function impairment. Data indicate that renal EMT is one of the initial links in renal fibrosis. Activation of the transforming growth factor β-1 (TGFβ-1)/smad pathway is closely related to the progression of DN and the occurrence of renal EMT.(Lan, 2011) Studies have shown that HYP can reduce renal fibrosis and inhibit the EMT process in DN rats, which may be related to the inhibition of the TGF-β1/smad pathway.(Wang et al., 2021) By establishing models with low-dose HYP gavage group, high-dose HYP gavage group and control group, HYP can reduce the phosphorylation level of IRS-1, activate the PI3K/Akt pathway, and alleviate the pathological damage of renal tissues in DN rats (Zhang et al., 2023).

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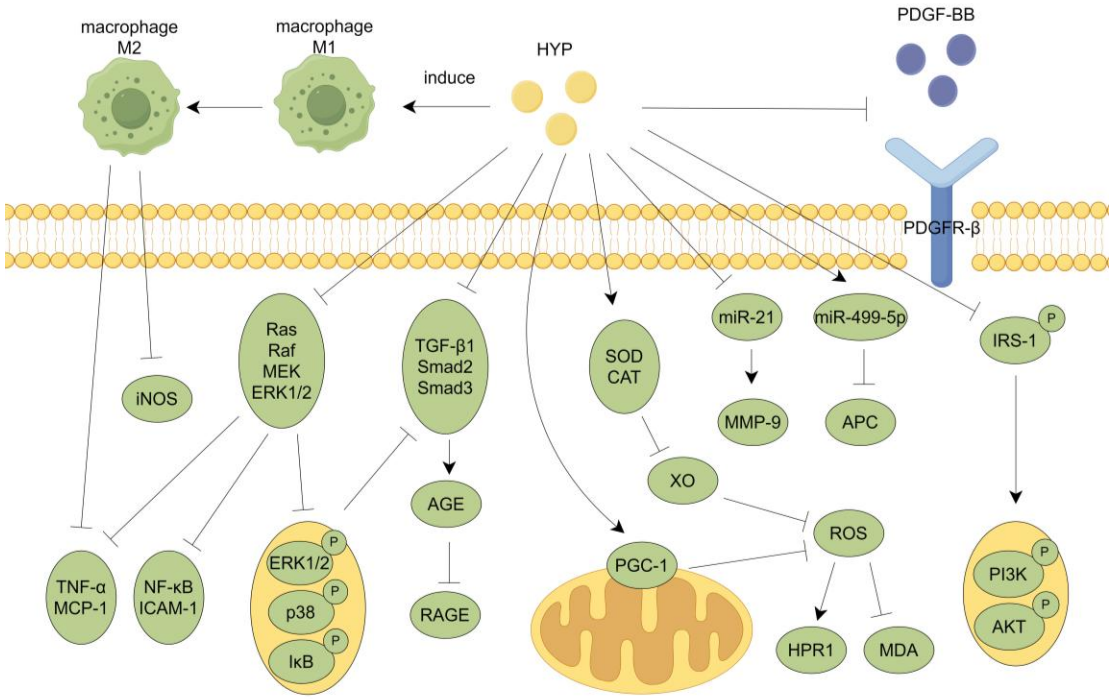

Figure-2. Molecular mechanisms of HYP in regulating renal glucose and lipid metabolism. The pointed arrow represents the promoting effect, and the flat arrow represents the inhibiting effect. Phosphorylated protein labeled with ' P ' in the upper right corner.

Studies have confirmed that the Ras/Raf/MEK/ERK1/2 signaling pathway is involved in the renal fibrosis process of mice with abnormal glucose and lipid metabolism. This pathway is associated with the regulation of ureteral bud branching, differentiation of nephrogenic mesenchymal cells, and is linked to multiple diseases in the mature kidney, such as polycystic kidney disease, glomerulonephritis, nephropathy with abnormal glucose and lipid metabolism, and unilateral ureteral obstruction. When upstream signaling molecules are activated, tyrosine kinases become phosphorylated. Meanwhile, nucleotide exchange factors (Sos) act on membrane complexes, enabling the upstream factor Ras protein of the signaling pathway to complete modification and localization on the cell membrane. This promotes energy conversion by guanosine nucleotides (GTP), further inducing the downstream factor Raf protein to phosphorylate downstream substrates, thereby phosphorylating ERK1/2 and activating downstream inflammatory factors. Multiple studies have shown that the ERK1/2 signaling pathway is involved in abnormal biological signal transduction caused by inflammatory mediators, stress stimuli etc., and the activation of the ERK1/2 pathway is closely associated with inflammatory responses (Fu et al., 2022; Guo et al., 2021; Li et al., 2023; Lucas et al., 2022; Mandal et al., 2016; Rizwan et al., 2020; Sabnam and Pal, 2019; Song et al., 2023). According to the results of network pharmacology studies, it is speculated that the ERK1/2 signaling pathway may be one of the main pathways for HYP intervention in DN. Subsequent animal experiments also showed that HYP protects the kidneys, improves renal function, and delays the occurrence and development of DN by inhibiting the activation of Ras/Raf/MEK/ERK1/2, further suppressing the expression of downstream inflammatory factors NF-κB, TNF-α, MCP-1, and ICAM-1 (Sun et al., 2025).

Long-term hyperglycemia can lead to changes in renal hemodynamics, increasing intraglomerular pressure. Meanwhile, it causes thickening of the glomerular basement membrane, expansion of the mesangial area, and accumulation of extracellular matrix (ECM) (Czajka and Malik, 2016). In addition, hyperglycemia can activate various cytokines and signaling pathways, further exacerbating glomerular damage. Glomerular

https://doi.org/10.35495/ajab.2025.238

lesions lead to impaired renal function, affecting the excretion of metabolic waste products in the body and causing their accumulation, which further exacerbates disorders of glucose and lipid metabolism (MacDonald and Rorsman, 2023).

Through the in vivo test, it was found that HYP significantly reduced the proteinuria and mesangial matrix expansion caused by abnormal glucose and lipid metabolism, and significantly improved the fasting blood glucose level, hyperlipidemia and body weight of mice (Dwivedi and Sikarwar, 2025; Infante et al., 2022; Liu et al., 2021). HYP can inhibit the accumulation of ECM and mesangial proliferation in the glomeruli of SDT rats by suppressing the interaction between PDGF-BB and PDGFR-β. It improves the occurrence and development of complications of abnormal glucose and lipid metabolism, and can be used for the treatment of early-stage renal insufficiency due to abnormal glucose and lipid metabolism (Sohn et al., 2018).

In vitro experiments have shown that HYP may inhibit adriamycin (ADR)-induced mitochondrial dysfunction and glomerular mesangial cell (GMCs) injury by suppressing mitochondrial fission (Chen et al., 2017). Meanwhile, it was also found that HYP may attenuate AGE/RAGE binding and TGF-β1 expression by downregulating phosphorylated extracellular signal-regulated kinase 1/2 (pERK1/2), phosphorylated p38 mitogen-activated protein kinase (p38MAPK), and IκB phosphorylation in GMCs under abnormal glucose and lipid metabolism conditions, and delay the progression of abnormal glucose and lipid metabolism (Kim et al., 2016).

Additionally, it has been found that HYP pretreatment may prevent and treat renal injury and GMCs apoptosis, as well as reduce albuminuria excretion in early DN, by inhibiting the increased expression of caspase-3 and caspase-8 induced by advanced glycation end products (AGE) (Zhou et al., 2012). In addition, experiments have demonstrated that HYP prevents the development of proteinuria and glomerular basement membrane damage in DM mice by reducing heparinase expression in GMCs.

Additionally, studies have shown that HYP can significantly reverse the protein expression levels of α-SMA, Fibronectin, Collagen I, and Collagen III in renal tissues of UUO mice and TGF-β1-induced NRK-52E cells. Meanwhile, it significantly reduces the levels of serum creatinine (Cr) and blood urea nitrogen (BUN) in UUO mice, and markedly improves renal tissue pathological changes and renal interstitial collagen deposition, HYP can significantly inhibit the protein expression levels of YAP and CTGF in TGF-β1-induced NRK-52E cells both in vivo and in vitro, and it has a similar effect to verteporfin. Both can significantly improve TGF-β1-induced fibrosis in NRK-52E cells (An et al., 2017).

Overall, the kidneys maintain glucose metabolic homeostasis through pathways such as glucose reabsorption, gluconeogenesis, and insulin degradation. DN, a severe microvascular complication of abnormal glucose and lipid metabolism, has limitations in current drug therapy, while HYP exhibits multi-target intervention advantages: it can improve glomerulosclerosis by regulating miRNA targets, inhibit pathways including TGF-β1/Smad and Ras/Raf/MEK/ERK1/2 to alleviate renal fibrosis, EMT processes, and inflammatory responses, target AGE/RAGE, mitochondrial fission, and other links to protect glomerular mesangial cells, as well as improve symptoms such as proteinuria and hyperlipidemia. However, obvious gaps exist in current research: the crosstalk mechanism among the multiple pathways through which HYP regulates renal glucose metabolism and improves DN remains unclear; studies are concentrated on rodent models, lacking validation in nephropathy models of agricultural animals such as livestock and poultry, making it difficult to address renal damage caused by glucose metabolic disorders in breeding; the dose-effect relationship, administration methods, and synergistic effects with other substances have not been systematically explored, and there is insufficient direct evidence for its role in renal gluconeogenesis and insulin degradation. Renal glucose metabolic imbalance is a core inducement for the development of DN, and HYP's multi-target characteristics align with the needs of preventing and treating renal diseases related to glucose metabolic disorders. Future studies should strengthen the analysis of pathway crosstalk mechanisms, cross-species validation, and optimization of application schemes to provide scientific support for its transformation into a green additive for regulating glucose metabolism and preventing/treating nephropathy in livestock and poultry.

Regulate hepatic glycolipid metabolism

As a core organ for carbohydrate, lipid, and protein metabolism, the liver plays a pivotal role in the physiological processes of glucose metabolism. Abnormalities in glucose and lipid metabolism are

characterized by insulin resistance (IR) and/or insufficient insulin secretion, leading to hepatic metabolic disorders, including: Insulin resistance inhibits hepatic glycogen synthesis while enhancing gluconeogenesis, exacerbating fasting hyperglycemia; IR promotes the transfer of free fatty acids (FFAs) to the liver, leading to triglyceride (TG) deposition and the formation of fatty liver; Hyperglycemia activates pro-inflammatory pathways through mitochondrial dysfunction and ROS accumulation, accelerating hepatocyte damage (He et al., 2025; Roumans et al., 2020; Yao et al., 2023; Wang et al., 2025). HYP regulates hepatic metabolism by improving insulin resistance through anti-autophagy, anti-apoptosis, and anti-oxidative stress, inhibiting fat synthesis, promoting fat breakdown, and treating liver fibrosis (Figure 3).

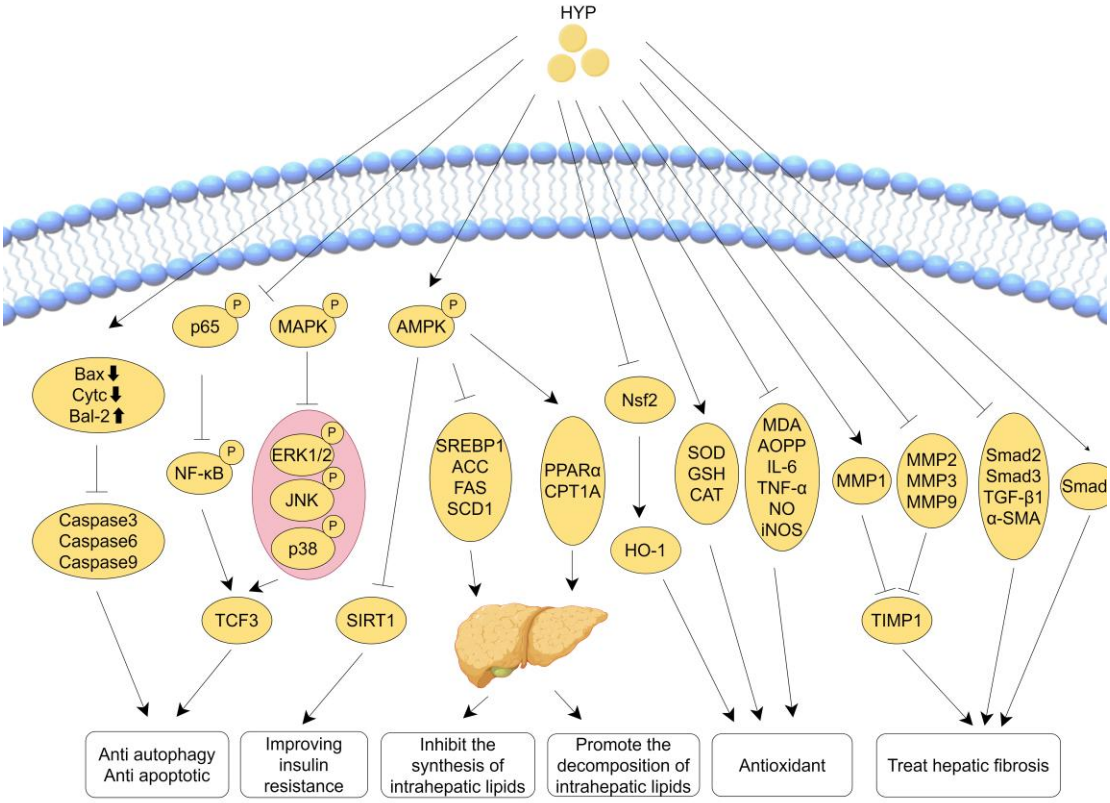

Figure-3. Molecular mechanisms of HYP in regulating hepatic glucose and lipid metabolism. The pointed arrow represents the promoting effect, and the flat arrow represents the inhibiting effect. Phosphorylated protein labeled with ' P ' in the upper right corner.

The study found that in metabolic dysfunction mice, body weight and hepatic p62 protein expression were decreased, while fasting blood glucose (FBG), fasting insulin (FINS) levels, HOMA-IR, the proportion of hepatic Beclin1-positive cells, and protein expression levels of p-AMPK/AMPK, SIRT1, LC3-II/LC3-I, Bax, and caspase-6 were increased. Liver tissues showed irregular cell morphology, incomplete structure, accompanied by vacuolation, edema, and necrosis. After HYP treatment, all the above phenomena were improved. The conclusion is that HYP may improve insulin resistance in mice by inhibiting the AMPK/SIRT1 pathway-mediated autophagic pathway.

Additionally, HYP can treat abnormal glucose and lipid metabolism by inhibiting the phosphorylation of p65/NF-κB and MAPK (including p38, JNK, and ERK1/2) in hepatocytes, activating the protein expression of TCF3, and suppressing the expression of Bax, Cytc, caspase-9, and caspase-3 in the liver tissues of mice with abnormal glucose metabolism (Zhang et al., 2018).

https://doi.org/10.35495/ajab.2025.238

Non-alcoholic fatty liver disease (NAFLD) is the most common liver complication in abnormal glucose and lipid metabolism. Its pathogenesis is closely related to IR, lipotoxicity, and adipose tissue dysfunction (Tang et al., 2025; Wang et al., 2021). HYP may inhibit hepatic lipid synthesis and promote lipid breakdown by regulating the adenosine monophosphate-activated protein kinase (AMPK) pathway, suggesting that HYP could be a potential drug for the treatment of NAFLD (Zhi et al., 2023).

The liver is the primary site for cholesterol synthesis, and abnormalities in total cholesterol levels are closely associated with liver diseases. When liver function is impaired, such as in hepatitis or cirrhosis, the liver's capacity to synthesize, metabolize, and transport cholesterol decreases, potentially leading to reduced total cholesterol levels in the blood. Conversely, certain liver diseases can also cause cholesterol metabolic disorders, increasing blood total cholesterol levels. For example, hyperlipidemia increases the liver's burden, which can induce hepatic steatosis and trigger conditions like NAFLD over time (Huang et al., 2023; Lu et al., 2023; Wu et al., 2016).

Studies have shown that HYP may promote the uptake of plasma LDL-C by mouse liver tissue by increasing the abundance of LDLR (low-density lipoprotein receptor), thereby reducing plasma cholesterol levels in mice (Tong et al., 2025). Some scholars have found that after feeding HYP, the number of hepatic fat vacuoles, lipid accumulation, liver weight, and TAG content in mice, as well as the levels of ALT, AST, and TAG in serum, were significantly reduced compared with the model group. Meanwhile, the protein expression level of PPARα in liver tissues was significantly increased, and the pathological and morphological changes of NAFLD were alleviated. Lipidomics analysis revealed that HYP can reduce the relative levels of lipid metabolites such as triacylglycerol and diacylglycerol in the liver. Compared with the model group, lipid accumulation and triacylglycerol content in cells of both low and high HYP concentration groups were significantly reduced. It is concluded that HYP may effectively improve high-fat diet-induced NAFLD in mice by activating PPARα to regulate hepatic lipid synthesis (Long et al., 2025).

Intracellular lipid accumulation in hepatocytes (hepatic fat content >5%) can progress to non-alcoholic steatohepatitis (NASH) (Geng et al., 2021). Studies have shown that after intragastric administration of HYP to obese mice with insulin resistance induced by a high-fat diet, lipid deposition in the liver was reduced compared with the high-fat group, while adiponectin and leptin levels were significantly higher than those in the high-fat group (Guan et al., 2022). A metabolic-associated fatty liver disease model was induced in mice through a high-fat diet. The results showed that HYP could reduce liver cell vacuolization and inflammatory infiltration in model mice; significantly improve lipid deposition; significantly reduce serum levels of LDL-C, AST, and ALT; significantly decrease hepatic MDA, IL-6, and TNF-α levels; and significantly increase hepatic SOD and GSH-Px levels (Yang et al., 2023).

Long-term hyperglycemia and IR activate hepatic stellate cells (HSCs), promote collagen deposition, and lead to fibrosis (Paradis et al., 2001). Studies have shown that HYP may have anti-fibrotic effects and can be used for the prevention and treatment of liver fibrosis. It can significantly restore liver structure and antioxidant balance, reduce collagen deposition in the liver, and improve liver function. The liver-protective mechanism is based on HSC inhibition, reduction of oxidative stress and liver injury, downregulation of the TGF-β1/Smad signaling pathway, and rebalancing of matrix metalloproteinases (MMPs)/tissue inhibitors of metalloproteinases (TIMP) (Balta et al., 2023). Abnormalities in glucose and lipid metabolism are independent risk factors for hepatocellular carcinoma (HCC), with mechanisms including: chronic inflammation and oxidative stress promoting DNA damage; hyperinsulinemia stimulating hepatocyte proliferation through the IGF-1 pathway; and gut microbiota dysregulation potentially participating in carcinogenesis through the gut-liver axis (Cheng et al., 2024; Li et al., 2017; Wang et al., 2025). Additionally, research indicates that HYP protects the liver by influencing core targets such as Caspase-3, TNF, ESR1, MAPK3, CAT, and PTGS2, collectively intervening in apoptotic signaling pathways, TNF signaling pathways, and cancer signaling pathways (Zhang et al., 2022).

Overall, the liver, as a core metabolic organ, abnormal glucose and lipid metabolism (centered on insulin resistance) can easily lead to complications such as fatty liver, liver fibrosis, and even liver cancer. HYP exerts liver-protective effects through multiple pathways and targets - it inhibits autophagy mediated by the AMPK/SIRT1 pathway, regulates the p65/NF-κB and MAPK pathways to improve insulin resistance and hepatocyte apoptosis, activates the AMPK and PPARα pathways to regulate lipid metabolism, down-

regulates the TGF-β1/Smad pathway and balances MMPs/TIMPs to improve liver fibrosis, and also has antioxidant, anti-inflammatory and cholesterol metabolism regulatory effects. It has shown significant effects in NAFLD and liver fibrosis disease models. However, current research has obvious limitations: the cross-regulation network of multiple pathways has not been systematically analyzed, the association of core targets is unclear, studies are mainly focused on rodents and lack validation in livestock and poultry models, and there is a lack of application data such as the appropriate dosage and administration methods of HYP in livestock and poultry diets. Moreover, the research on the specific mechanisms of different liver diseases is insufficient. The metabolic homeostasis of the liver is crucial for the health and growth of livestock and poultry. The multi-dimensional protective characteristics of HYP are in line with the needs of animal husbandry. In the future, it is necessary to analyze the cross-regulation network of pathways, conduct validation in livestock and poultry models and optimize dosages, and clarify the application schemes in diets to provide scientific support for its transformation into a green additive for liver metabolic regulation in livestock and poultry.

Core molecular mechanisms and functions

According to network pharmacology and experimental studies, the treatment of abnormal glucose and lipid metabolism by HYP mainly involves the following molecular targets and pathways (Table 1). HYP improves insulin sensitivity by activating core energy metabolism pathways. In the AMPK/SIRT1 pathway, it activates downstream autophagy-related proteins (such as LC3-II and Beclin-1) through phosphorylating AMPK (p-AMPK), while upregulating SIRT1 expression to promote glucose uptake in adipocytes and lipid oxidation in hepatocytes. For example, in an osteoporosis rat model, HYP reverses bone metabolism disorders through this pathway, manifested as increased bone mineral density (BMD) and improved trabecular bone structure (Wang et al., 2023). HYP inhibits the inflammatory cascade through a dual mechanism. On one hand, it suppresses the NF-κB pathway, reducing nuclear translocation of the p65 subunit and release of pro-inflammatory factors (TNF-α, IL-6), such as alleviating hepatic inflammatory infiltration in high-fat diet-fed ApoE$^{-/-}$ mice. On the other hand, it activates the Nrf2/HO-1 antioxidant pathway, promoting the expression of antioxidant enzymes (SOD, GSH-Px) and reducing levels of malondialdehyde (MDA) and ROS (Guan et al., 2022). In the high-glucose-induced MIN6 pancreatic islet β-cell model, HYP inhibits cell apoptosis through Nrf2 nuclear translocation, leading to a reduction of over 30% in Cleaved-caspase3 expression (Zhang et al., 2021). HYP alleviates renal fibrosis by inhibiting the TGF-β1/Smad pathway, downregulating the expression of α-SMA, fibronectin, and Collagen I, while upregulating Smad7 (Zhang et al., 2016; Wang et al., 2025). In in vitro models, it inhibits mesangial cell proliferation by blocking the ERK/CREB/miRNA-34a pathway and reverses the pro-fibrotic effects mediated by miRNA-34a.(Zhang et al., 2020) For NAFLD,HYP activates the AMPK/mTOR/ULK1 pathway to promote hepatocyte autophagy and reduce lipid droplet deposition; meanwhile, it inhibits the Ras/Raf/MEK/ERK1/2 pathway to decrease the levels of inflammatory factors in liver tissue (Sun et al., 2025). It protects pancreatic islet β-cells through the Nrf2/HO-1/ARE pathway, significantly improving cell viability and restoring insulin secretion function in RIN-m5F cells, with mechanisms related to inhibiting TXNIP expression and intracellular calcium overload (Liu et al., 2024). In terms of microRNA (miRNA) regulation, it upregulates miR-499-5p to target and inhibit the APC gene, improving podocyte injury; it downregulates miR-199a to inhibit alveolar epithelial cell apoptosis and alleviate pulmonary inflammatory responses (Zhou et al., 2021).

https://doi.org/10.35495/ajab.2025.238

Table-1. Core molecular mechanisms, pathways and functions. ↑ represents an increase, ↓ represents a decrease.

Model types	Type of action	Key Signaling pathways	Mechanism description	Key molecules and changes	Final effects	Reference
High-fat diet mice (vivo)	Improve insulin resistance	AMPK/SIRT1	Activate AMPK phosphorylation and SIRT1 expression, and promote adipocyte autophagy and glucose uptake	p-AMPK/AMPK↑, SIRT1↑, LC3-II/LC3-I↑, p62↓	FBG↓, HbA1c↓, insulin resistance↑	(Wang et al., 2023)
STZ-induced diabetic rats (vivo)	Kidney Protection	TGF-β1/Smad	Inhibit TGF-β1-induced Smad2/3 phosphorylation and block EMT	α-SMA↓, Fibronectin↓, Smad7↑, E-cadherin↑	Urinary protein↓, kidney fibrosis area↓, kidney function improved	(Wang et al., 2021)
High-glucose HK-2 cells (vitro)	Anti-apoptosis	Akt/GSK-3β	Activate Akt phosphorylation, inhibit GSK-3β activity, and block the mitochondrial apoptotic pathway	p-Akt↑, p-GSK-3β↑, Bcl-2/Bax↑, Cleaved-caspase3↓	Cell apoptosis rate↓, oxidative stress injury alleviated	(Wu et al., 2023)
Diabetic retinopathy rats (vivo)	Retinal protection	TGF-β1/miR-200b/VEGF	Downregulate the expression of TGF-β1 and VEGF, and upregulate miR-200b to inhibit angiogenesis	TGF-β1↓, miR-200b↑, VEGF↓, Retinal endothelial cell proliferation↓	Retinal vasculopathy alleviated, visual function improved	(Yu et al., 2025)
High-glucose MIN6 cells (vitro)	Pancreatic protection	Nrf2/HO-1/ARE	Promote nuclear translocation of Nrf2, activate HO-1 and antioxidant enzyme activities, and inhibit oxidative stress-induced β-cell apoptosis	Nrf2 nuclear translocation ↑, HO-1 ↑, SOD ↑, MDA ↓, insulin secretion ↑	Islet β-cell survival rate↑, insulin resistance improved.	(Liu et al., 2024)
High-fat diet $ApoE^{-/-}$ mice (vivo)	Anti-inflammation	p65/TNF-α	Inhibit nuclear translocation of p65 and downstream inflammatory cytokine expression, and reduce M1 macrophage infiltration	p65 nuclear translocation ↓, TNF-α ↓, IL-6 ↓, M2 macrophage polarization ↑	Liver inflammation Infiltration ↓, lipid peroxidation ↓	(Guan et al., 2022)
High-glucose mesangial cells (vitro)	Inhibit proliferation	ERK/CREB/miRNA-34a	Block ERK phosphorylation and CREB transcription factor activation, and downregulate pro-proliferative miRNA-34a	p-ERK ↓, CREB phosphorylation ↓, miRNA-34a ↓, cyclin D1 ↓	Mesangial cell proliferation rate ↓, extracellular matrix deposition decreased	(Zhang et al., 2020)
AGEs-induced podocytes (vitro)	Anti-fibrosis	miR-499-5p/APC	Upregulate miR-499-5p to target and inhibit APC gene expression, reducing podocyte apoptosis and basement membrane damage	miR-499-5p↑, APC↓, Cleaved-caspase3,↓nephrin↑	Proteinuria ↓, glomerular basement membrane thickness ↓	(Zhou et al., 2021)

https://doi.org/10.35495/ajab.2025.238

The application prospects of HYP in livestock and poultry production

Since HYP was first extracted from Rumex in 1955 (Horhammer and Volz, 1955), its role in regulating energy metabolism has garnered extensive attention from researchers in life sciences and medicine. It is widely recognized as having enormous potential in the prevention and treatment of obesity and related metabolic diseases in humans, with accumulating evidence supporting its ability to modulate core metabolic pathways, such as glucose uptake, insulin sensitivity, and lipid homeostasis, that are conserved across vertebrate species.

Notably, while direct research on HYP in livestock and poultry production remains scarce, and critical questions regarding its application protocols, efficacy, optimal dosage, and cost-effectiveness remain unanswered, existing studies have shed light on the translational value of metabolic regulation mechanisms. For instance, transcriptomic and metabolomic analyses have revealed that glucose metabolism-related signaling pathways, including fructose and mannose metabolism, amino acid biosynthesis, nucleotide sugar metabolism, and glucagon signaling, can effectively regulate fat deposition and meat quality in pig breeds (Kumar et al., 2024). These pathways are functionally analogous to those targeted by HYP in human metabolic disease research, highlighting the potential cross-species applicability of HYP's regulatory effects.

Building on this mechanistic commonality, HYP holds considerable promise for application in certain areas of livestock and poultry research and production. By leveraging its ability to regulate glucose metabolic homeostasis, an evolutionarily conserved biological process, it may help improve animal health, mitigate metabolic disorders, and ultimately enhance breeding efficiency in the livestock and poultry industry.

Potential regulation of livestock and poultry meat quality by HYP

Muscle fiber development and intramuscular fat deposition are two independent yet interrelated biological processes during muscle growth, jointly influencing the meat quality of livestock and poultry. The composition of muscle fiber types directly affects meat quality traits such as muscle color, tenderness, pH, water-holding capacity, intramuscular fat content, and flavor/taste, highlighting its importance in regulating livestock and poultry meat quality.

Studies have shown that peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) is involved in regulating skeletal muscle development and metabolism, serving as a key regulatory factor for promoting skeletal muscle fiber type transformation (particularly the generation of oxidative muscle fibers) (Lin et al., 2002). Its main physiological functions include improving motor function, alleviating muscle atrophy, reducing age-related muscle loss, repairing mitochondrial function, promoting glycogen synthesis and fatty acid oxidation, and enhancing insulin sensitivity (Svensson and Handschin, 2014). PGC-1α has become a critical target for intervening in and treating related metabolic diseases. Additionally, research has demonstrated that HYP treats glucose-lipid metabolic diseases by upregulating the protein expression of p-AMPK/AMPK and PGC-1α in the liver, reducing PPARα levels, and decreasing mitochondrial fragmentation (Li et al., 2025). This provides a theoretical basis for understanding the association between the HYP-PGC-1α pathway and oxidative muscle fiber generation. Moreover, increased mitochondrial content is also an important marker of oxidative muscle fiber formation. These findings suggest that the HYP pathway may be significantly correlated with skeletal muscle fiber type transformation, though the mechanism by which it directly regulates the expression of genes related to oxidative muscle fiber generation requires further investigation. Given the interconnection between PGC-1α and oxidative muscle fiber generation, it is bound to play a key role in regulating the biological characteristics of livestock and poultry muscle.

Research indicates that PGC-1α is an upstream regulator of fibronectin type III domain-containing protein 5 (FNDC5) and can upregulate FNDC5 expression. Under exercise or other stimulating factors, increased PGC-1α expression in livestock and poultry promotes FNDC5 expression, which acts on target cells (e.g., white adipocytes), induces their browning, and enhances fat decomposition and energy expenditure.(Bostrom et al., 2012) On the other hand, FNDC5 is associated with lipid distribution and carotid atherosclerosis susceptibility in type 2 diabetes patients (Yang et al., 2022). Since HYP has glucose-lipid metabolism regulatory functions and nutrients such as omega-3 fatty acids, retinoic acid, raspberry polyphenols, and Green cardamom can induce FNDC5 expression and secretion (Amengual et al., 2018; Daneshi-Maskooni et al., 2019; Vaughan et al., 2012;

Xing et al., 2018), this offers the possibility of using nutritional interventions to influence FNDC5 expression and thereby regulate livestock/poultry health and meat quality. Although studies on HYP-mediated direct regulation of meat quality via FNDC5 have not been reported, research on the nutritional regulation of PGC-1α (the upstream regulator of FNDC5) can provide relevant references.

Additionally, meat tenderness and juiciness primarily depend on intramuscular fat content. Therefore, how to increase intramuscular fat content while maintaining lean meat percentage and reducing peripheral fat deposition has become another research hotspot in improving livestock and poultry meat quality. In porcine primary adipocytes, FNDC5 promotes cell proliferation and differentiation, and enhances the expression of brown adipocyte marker genes (Cai et al., 2017). In $MSTN^{-/-}$ Meishan pigs, skeletal muscle mass and muscle FNDC5 expression are increased, and subcutaneous white adipose tissue browning is induced via PGC-1α activation. Since HYP also plays an important role in lipid metabolism regulation, fully exploiting its effects of inhibiting de novo white fat synthesis and promoting brown adipogenesis in preadipocytes may be one of the key pathways for regulating intramuscular fat development in livestock and poultry (Cheng et al., 2023).

Potential amelioration of fatty liver degeneration in poultry by HYP

Poultry fatty liver syndrome is a nutritional and metabolic disorder characterized by hepatic steatosis, which predominantly occurs in laying hens during their peak egg-laying period. Its pathogenic mechanisms involve multiple biological processes, including lipid metabolism regulation, antioxidant stress response, anti-inflammatory activity, and liver injury repair. Moreover, this syndrome can also impair breast meat quality, alter its lipid composition and flavor in broilers, thereby directly compromising the production efficiency of the poultry industry (Zhang et al., 2024; Zhang, 2019). Based on the above discussion, HYP inhibits fat synthesis and promotes fatty acid oxidation. As a green feed additive, it represents a novel approach for preventing and treating hepatic steatosis in poultry. In summary, HYP has the potential to ameliorate lipid metabolism disorder-induced hepatic steatosis in poultry, reducing or eliminating the negative effects of fatty liver and related diseases on poultry industry productivity.

Conclusions and Future Prospects

Core biological functions of HYP

As a natural flavonoid compound, HYP exhibits multi-dimensional potential in regulating glucose metabolism, improving reproductive performance, and exerting antioxidant and anti-inflammatory effects in livestock and poultry. Its glucose metabolism regulatory mechanisms involve multiple key links: inhibiting the activities of intestinal α-glucosidase and α-amylase to delay carbohydrate absorption; activating insulin signaling pathways such as PI3K/Akt to enhance cellular glucose uptake and utilization, improve insulin resistance, and promote glucose conversion into glycogen for storage; regulating hepatic gluconeogenesis and glycogen synthesis to maintain stable blood glucose levels. Additionally, HYP can scavenge free radicals (e.g., superoxide anion radicals and hydroxyl radicals) in the body, increase the activity of antioxidant enzymes such as SOD and GSH-Px, and protect pancreatic islet β cells to maintain normal insulin secretion. It also inhibits the release of inflammatory factors including TNF-α and MCP-1, regulates the NF-κB signaling pathway, and alleviates systemic inflammatory responses, thereby reducing the risk of metabolic diseases caused by glucose metabolism disorders. Furthermore, its regulatory effect on lipid metabolism helps decrease the incidence of reproductive system diseases induced by abnormal glucose and lipid metabolism.

With the development of metabolomics, the role of HYP in reprogramming reproductive metabolism of livestock and poultry has gradually attracted attention. It may participate in metabolic reprogramming of the reproductive system and regulation of the reproductive microenvironment by modulating oxidative phosphorylation and lipid metabolism. Based on existing studies, it is hypothesized that HYP exerts regulatory effects on glucose and lipid metabolism by upregulating the hepatic expression of PGC-1α. PGC-1α can further upregulate the expression of FNDC5 to promote fat decomposition. Therefore, FNDC5 is expected to be a potential target through which HYP regulates glucose-lipid metabolism and influences fat deposition and meat quality in pigs, providing a theoretical basis for its application as a green feed additive.

https://doi.org/10.35495/ajab.2025.238

Key challenges in current research and application

Despite its significant potential, the translational application of HYP faces multiple obstacles: Firstly, limited research objects, most existing studies focus on mice, with scarce research conducted on mainstream livestock and poultry. In particular, studies on HYP influencing fat deposition and meat quality in pigs by regulating glucose metabolism signaling pathways remain relatively insufficient. Secondly, lagging applied research, current research is mostly confined to basic stages such as cell experiments and animal trials, lacking large-scale, high-quality applied studies in commercial farms. Its safety and effectiveness in livestock and poultry production have not yet been fully verified. Thirdly, production and quality control dilemmas, as a natural compound, the content and purity of HYP vary significantly among plants from different sources. Extraction and preparation techniques also affect its quality stability, restricting standardized production and application.

Future research and application directions

To address the aforementioned challenges, future efforts can promote the research and application of HYP from multiple dimensions: At the mechanism research level, modern technologies such as high-throughput sequencing, proteomics, and metabolomics can be utilized to deeply explore potential regulatory targets and signaling pathways, for example, analyzing changes in protein expression in livestock and poultry germ cells after HYP treatment via proteomics. In terms of drug delivery system development, nanotechnology, microsphere technology, and other novel methods can improve the solubility, stability, and targeting of HYP. The application of cell membrane-camouflaged nanocarriers, reproductive organ-targeted delivery systems, and pH/temperature-sensitive controlled-release mechanisms enables precise drug delivery and enhances bioavailability. Existing studies have confirmed that composite nanoparticles prepared by combining HYP with specific biomaterials significantly improve its bioavailability (Shi et al., 2023a; Wang et al., 2021a; Wu et al., 2022), bringing new prospects for healthy livestock and poultry farming. At the applied research level, more rigorously designed farm trials with scientific evaluation indicators are needed to fully verify the safety and effectiveness of HYP in regulating glucose metabolism and improving reproductive performance in livestock and poultry, providing reliable evidence for its practical application. In production and quality control, microbial production systems (e.g., Escherichia coli or yeast) can be optimized through metabolic engineering, combined with technologies such as deep eutectic solvent-assisted extraction and microwave-assisted separation to achieve large-scale, environmentally friendly, and low-cost production. Advanced analytical techniques including HPLC-MS and NMR can establish a comprehensive quality control standard to ensure stable and consistent product quality.

In the future, with the integration of cross-disciplinary technologies such as multi-omics integrated analysis and synthetic biology, HYP is expected to play an important role in glucose metabolism management of livestock and poultry as an independent regulator or a key component of combined regulation. Through interdisciplinary integration and continuous exploration and innovation, HYP holds broad application prospects in livestock and poultry production and health management and will also provide important references for the development of natural compounds in the animal husbandry industry.

Acknowledgment

This work was financially supported by the Science and Technology Projects of Xizang Autonomous Region, China（XZ202501ZY0147）; National key research and development project of China (2022YFD1600900); Xizang agriculture and Animal Husbandry University Doctoral Program in forestry (Phase I) (533325001).

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: This research work was funded by the Science and Technology Projects of Xizang Autonomous Region, China（XZ202501ZY0147）; National key research and development project of China (2022YFD1600900); Xizang agriculture and Animal Husbandry University Doctoral Program in forestry (Phase I) (533325001).

Declaration on Use of Generative AI Tools

Authors declare that GenAI tools were used to improve the language of this manuscript and they take full responsibility for the contents of this article.

Contribution of Authors

Gao Y: Conceptualization, data analysis, writing and reviewing the manuscript.
Ye Y: Performed the experiments, collected data and wrote the manuscript.
Liu F, Li H and Luo L: Were responsible for data validation.
Zhang H: Contributed to conceptualization, supervision and revised the manuscript.
Chamba Y and Shang P: Contributed to the conceptualization and funding acquisition of the study

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