Pakistan Veterinary Journal

ISSN: 0253-8318 (PRINT), 2074-7764 (ONLINE)
DOI: 10.29261/pakvetj/2026.203

REVIEW ARTICLE

Research Progress on the Treatment of Nonalcoholic Fatty Liver Disease with Polygonatum

Huijun Xiong[1#], Wenjuan Li[1#], Qiang Zhang[2*] and Hang He[1*]

[1]Chongqing Three Gorges Vocational College, Wanzhou, China; [2]Senior Veterinarian, Animal Husbandry Development Center of Anqiu City, Shandong Province, China. [#]These authors contributed equally to this work
*Corresponding author: 2003020011@cqsxzy.edu.cn (HH); qiangzhang1133@163.com (QZ)

ARTICLE HISTORY (26-851)

Received: June 11, 2026
Revised: July 20, 2026
Accepted: July 22, 2026
Published online: August 04, 2026

Key words:
Polygonatum
Nonalcoholic Fatty Liver Disease
Active ingredients
Pathogenesis
Clinical effects

ABSTRACT

This review summarizes recent studies on the treatment of nonalcoholic fatty liver disease (NAFLD) with Polygonatum. NAFLD is among the most common chronic metabolic liver diseases worldwide. With the widespread adoption of high-nutrient, high-energy feeding regimes and intensive farming practices, NAFLD has become a common lipid metabolism disorder in livestock, poultry and companion animals. Polygonatum is a traditional Chinese medicinal herb that is both a medicine and a food. Currently, many studies have confirmed that Polygonatum is rich in polysaccharides, saponins, flavonoids and plant sterols. Moreover, studies have confirmed that these compounds regulate glucose and lipid metabolism. These effects are achieved by reducing liver oxidative stress, alleviating inflammatory responses and balancing intestinal microbial flora homeostasis. Therefore, this review starts with the etiology of NAFLD and studies the therapeutic mechanisms of different active components in Polygonatum. It also assessed the limitations of studies on the target animal species, which include: an unclear dose-response relationship, as well as insufficient evaluation of safety, palatability and practical routes of administration in veterinary applications. It also summarizes the problems existing in current research, such as insufficient clinical evidence and inadequate quality control. These findings are expected to provide some ideas for subsequent research.

To Cite This Article: Xiong HJ, Li W, Zhang Q and He H, 2026. Research progress on the treatment of nonalcoholic fatty liver disease with polygonatum. Pak Vet J, 46(8): 1860-1871. http://dx.doi.org/10.29261/pakvetj/2026.203

INTRODUCTION

Pathogenesis and Current Treatment of NAFLD: Nonalcoholic fatty liver disease (NAFLD) is a common chronic metabolic liver disorder characterized by liver steatosis caused by the abnormal accumulation of lipids within liver cells. In the field of veterinary medicine, similar lipid metabolism disorders have also been observed in livestock, poultry, and companion animals. Examples include obesity-related fatty liver disease in dogs and cats, fatty liver and hemorrhagic syndrome in laying hens, and periparturient ketosis in dairy cows. These conditions share similar pathological characteristics with human NAFLD, making NAFLD highly relevant to veterinary clinical practice. This condition is diagnosed when chronic heavy alcohol consumption and other known causes of liver damage, such as viral hepatitis, drug-induced liver injury or malnutrition, are excluded. A liver fat content ≥5% is the primary diagnostic criterion for this condition (Rinella, 2015). NAFLD is typically classified into two types based on the stage of disease progression: simple nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). NASH can progress to liver fibrosis, cirrhosis or hepatocellular carcinoma. Since the diagnosis of NAFLD relies primarily on ruling out alcoholic liver disease and other causes of liver damage, this "diagnosis by exclusion" often makes it difficult in clinical practice to completely avoid interference from potential alcohol consumption or other factors causing liver damage, thereby affecting the accuracy of the diagnosis and the clarity of the disease definition to some extent. In veterinary clinical practice, the diagnosis of lipid metabolic liver disease relies primarily on the observation of clinical signs and the measurement of physiological and biochemical parameters, rather than on the exclusion of alcohol intake. Therefore, caution should be exercised when applying the concept of NAFLD to livestock, poultry, and other companion animals. Consequently, international academic organizations such as the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and the Latin American Association

for the Study of the Liver have proposed replacing the term NAFLD with metabolic dysfunction-associated fatty liver disease (MAFLD) (Eslam *et al*., 2020). The system employs clear positive diagnostic criteria, emphasizes the critical role of metabolic dysfunction in the onset and progression of the disease, and aids in clinical diagnosis and risk assessment (Younossi *et al*., 2024). However, the academic community is still in a transitional phase regarding the use of this term. Although the concept of MAFLD has gradually gained acceptance among researchers, relatively few studies have been published with this term as their central focus. Consequently, although the literature often uses MAFLD as a conceptual framework, the evidence cited in these studies stems primarily from research on NAFLD.

Pathophysiological characteristics of NAFLD: The pathophysiological mechanisms underlying NAFLD involve the multiple-hit hypothesis, with key components including insulin resistance (IR), dyslipidemia, oxidative stress, inflammatory responses and dysbiosis of the gut microbiota (Luo *et al*., 2024) (Table 1).

Insulin resistance and dyslipidemia: IR is the initiating factor and key driving force in the pathogenesis of NAFLD (Tanase *et al*., 2020; Qiu *et al*., 2023). When peripheral tissues, particularly skeletal muscle and adipose tissue, become less sensitive to insulin, compensatory hyperinsulinemia significantly upregulates the expression of fatty acid synthase (FAS), acetyl-CoA carboxylase (ACC) and other lipogenic genes. Moreover, studies have shown that insulin resistance inhibits the regulation of hormone-sensitive lipase (HSL), thereby increasing lipolysis in adipose tissue and leading to a large influx of free fatty acids (FFAs) into the liver (Smith and Kahn, 2016). The excessive influx of FFAs into hepatocytes, combined with limited mitochondrial β-oxidation capacity, ultimately leads to abnormal triglyceride (TG) accumulation within hepatocytes, resulting in hepatic steatosis (Ruppert and Kersten, 2024). Studies indicate that the proportion of fatty acids derived from de novo lipogenesis (DNL) in the livers of NAFLD patients can increase from 5% to more than 26% in normal individuals, and this metabolic reprogramming constitutes a key molecular basis for disease progression (Wallace and Metallo, 2020). Furthermore, high concentrations of FFAs directly lipotoxicize hepatic Kupffer cells (Li *et al*., 2018). This can promote the secretion of interleukin-1β (IL-1β) by activating the NLRP3 inflammasome and decreasing the release of adiponectin, thereby driving the progression from simple fatty liver disease to NASH (Li *et al*., 2021).

The pathogenesis of ketosis in periparturient dairy cows is also closely linked to IR. In high-producing dairy cows, lactation causes energy requirements to exceed the energy provided by feed, resulting in a negative energy balance. To compensate for this deficit, lipid breakdown in the liver and adipose tissue significantly increases, leading to elevated levels of non-esterified fatty acids (NEFAs) and β-hydroxybutyrate (BHBA) in circulation. In early lactation, to conserve glucose for milk synthesis, insulin concentrations in the cow's body decrease, while peripheral insulin sensitivity declines. However, excessive or prolonged IR exacerbates fat mobilization and the accumulation of NEFAs and triglycerides in the liver, thereby triggering ketosis in dairy cows (Sparks *et al*., 2026; Tan *et al*., 2026).

It is evident that, although the etiology of ketosis in dairy cows differs from that of human NAFLD, both conditions involve impaired insulin signaling. This cross-species etiology suggests that IR is not only a key driver of human NAFLD but also a major contributing factor to ketosis in dairy cows. Currently, research on human NAFLD is more extensive than in the veterinary field, which can provide insights for the precise nutritional regulation and pharmacological intervention of periparturient metabolic disorders in dairy cows.

Oxidative stress and mitochondrial dysfunction: Studies have shown that oxidative stress is a central mechanism underlying the pathological progression of NAFLD (Loomba *et al*., 2021). Excessive lipid accumulation within hepatocytes leads to compensatory enhancement of mitochondrial β-oxidation, exacerbating electron leakage from complexes I and III of the electron transport chain (ETC), and causes a sharp increase in reactive oxygen species (ROS) production (Rennert *et al*., 2020). Excessive ROS attack mitochondrial DNA (mtDNA), proteins, and membrane lipids, causing structural damage to the mitochondria and functional failure, thereby creating a vicious cycle. The level of malondialdehyde (MDA), the end product of lipid peroxidation, is significantly elevated in serum and liver tissue in NAFLD models, whereas the activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) decreases in response to compensatory or depletion-induced decreases (Rennert *et al*., 2020; Xu *et al*., 2025). Mitochondrial dysfunction can also trigger endoplasmic reticulum stress (ERS), which, through unfolded protein response (UPR) pathways such as PERK/eIF2α/ATF4 and IRE1α/XBP1, further exacerbates hepatocyte damage and inflammatory responses. The inhibition of the nuclear factor E2-related factor 2 (Nrf2)/antioxidant response element (ARE) signaling pathway leads to a comprehensive weakening of the liver's antioxidant defense capabilities (Henkel, 2018).

A similar mechanism has also been reported in fatty liver and hemorrhagic syndrome (FLHS) in laying hens. FLHS is a common nutritional metabolic disorder characterized by excessive fat accumulation in the liver and reduced egg-laying performance. In severe cases, it can lead to hemorrhagic liver disease and sudden death. Recent studies have shown that mitochondrial homeostasis is closely associated with the progression of FLHS. Furthermore, interventions aimed at restoring mitochondrial function in FLHS-affected laying hens can alleviate symptoms (Li *et al*., 2023; Zhou *et al*., 2025). In addition, current research suggests that lipid accumulation in the liver of cats is also associated with mitochondrial dysfunction and oxidative stress (Xu *et al*., 2026). However, research on hepatic lipid storage diseases in companion animals remains limited; most studies have focused solely on phenotypic analysis without further investigation into the underlying mechanisms. However, it cannot be denied that these findings indicate a close link between the mechanisms underlying NAFLD and lipid metabolic liver disease in veterinary medicine.

Table 1: Pathophysiological mechanisms underlying NAFLD

Pathophysiological mechanism	Key molecular and cellular events	Key molecules and signaling pathways	Pathological consequences	References
Insulin resistance and dyslipidaemia	IR in peripheral tissues induces compensatory hyperinsulinaemia, upregulating lipogenic genes and inhibiting HSL-mediated lipolysis regulation; enhanced adipose lipolysis causes massive hepatic FFA influx; limited mitochondrial β-oxidation capacity leads to abnormal TG accumulation	FAS, ACC, HSL, FFAs, TG; de novo lipogenesis (DNL); inflammasome, cells	Hepatic steatosis; DNL proportion increases from 5% to NLRP3>26%; lipotoxicity to Kupffer cells; IL-1β, promotes IL-1β secretion and Kupffer adiponectin downregulation, driving progression from simple steatosis to NASH	(Qiu *et al*., 2023; Tanase *et al*., 2020; Smith and Kahn, 2016; Ruppert and Kersten, 2024; Wallace and Metallo, 2020; Li *et al*., 2018, 2021)
Oxidative stress and mitochondrial dysfunction	Excessive lipid accumulation enhances mitochondrial β-oxidation and exacerbates electron leakage from ETC complexes I and III, causing ROS overproduction; ROS attacks mtDNA, proteins, and membrane lipids, creating a vicious cycle of mitochondrial damage; mitochondrial dysfunction triggers ERS via UPR pathways	ROS, mtDNA, MDA; antioxidant enzymes (SOD, CAT, GSH-Px); ERS, UPR (PERK/eIF2α/ATF4, IRE1α/XBP1); Nrf2/ARE signaling	Mitochondrial structural damage and functional failure; significantly elevated MDA with compensatory or depletion-induced decreases in antioxidant enzyme activity; exacerbated hepatocyte damage and inflammatory responses; comprehensive weakening of hepatic antioxidant defense	(Loomba *et al*., 2021; Rennert *et al*., 2020; Xu *et al*., 2025; Henkel, 2018)
Chronic low-grade inflammation and cytokine networks	Steatotic hepatocytes release DAMPs, activating Kupffer cells and inducing M1 polarization; massive release of pro-inflammatory cytokines synergistically activates NF-κB; IRS-1 serine phosphorylation exacerbates IR; NLRP3 inflammasome activation requires dual signaling (NF-κB-mediated transcriptional priming and mitochondrial ROS/lysosomal damage); adipokine imbalance from adipose tissue dysfunction	DAMPs, Kupffer cells (M1 phenotype); TNF-α, IL-1β, IL-6; NF-κB; IRS-1; NLRP3 inflammasome; adiponectin, resistin, leptin	Chronic low-grade inflammatory state; aggravated insulin resistance; amplified hepatic inflammatory response driving progression from NAFLD to NASH and hepatic fibrosis	(Fang *et al*., 2018; Petrescu *et al*., 2022; Xu *et al*., 2023; Utzschneider and Kahn, 2006)
Gut microbiota dysbiosis and gut-liver axis dysfunction	High-fat diet alters Firmicutes/Bacteroides ratio, reduces beneficial SCFA-producing bacteria, and increases opportunistic pathogens; impaired intestinal barrier function with downregulated tight junction proteins and increased intestinal permeability; LPS enters the liver via portal vein; reduced SCFA production affects GPR41/43-mediated metabolic regulation; altered bile acid metabolism disrupts FXR and TGR5 signaling	Firmicutes, Bacteroides; Bifidobacterium, Lactobacillus; Enterobacteriaceae; SCFAs; ZO-1, Occludin; LPS; TLR4/NF-κB; GPR41/43; FXR, TGR5	Compromised intestinal barrier integrity; activation of hepatic inflammatory signaling pathways; disrupted homeostasis of hepatic lipid and glucose metabolism; gut-liver axis as an emerging potential intervention target	(Qiu *et al*., 2025; Shi *et al*., 2021; Zhang *et al*., 2025; Ma *et al*., 2021; Xi and Li, 2020)

Note: ACC, acetyl-CoA carboxylase; CAT, catalase; DAMPs, damage-associated molecular patterns; DNL, de novo lipogenesis; ERS, endoplasmic reticulum stress; ETC, electron transport chain; FAS, fatty acid synthase; FFAs, free fatty acids; FXR, farnesoid X receptor; GSH-Px, glutathione peroxidase; HSL, hormone-sensitive lipase; IL, interleukin; IR, insulin resistance; LPS, lipopolysaccharide; MDA, malondialdehyde; mtDNA, mitochondrial DNA; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NF-κB, nuclear factor-κB; NLRP3, NOD-like receptor family pyrin domain containing 3; Nrf2, nuclear factor E2-related factor 2; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; SOD, superoxide dismutase; TGR5, G protein-coupled bile acid receptor 1; TG, triglyceride; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-α; UPR, unfolded protein response.

Chronic low-grade inflammation and cytokine networks: The inflammatory features of NAFLD manifest as a chronic, low-grade inflammatory state involving an imbalance in the regulation of a complex cytokine network (Fang *et al*., 2018). Hepatocyte steatosis releases damage-associated molecular patterns (DAMPs), which activate Kupffer cells and induce their polarization toward the proinflammatory M1 phenotype, leading to the massive release of tumor necrosis factor-α (TNF-α), IL-1β and interleukin-6 (IL-6) (Petrescu *et al*., 2022; Xu *et al*., 2023). These inflammatory mediators exert synergistic effects by activating the nuclear factor-κB (NF-κB) signaling pathway. Additionally, they induce serine phosphorylation of insulin receptor substrate-1 (IRS-1), exacerbating insulin resistance (Utzschneider and Kahn, 2006). The assembly and activation of the NLRP3 inflammasome represent a central hub in the regulation of NAFLD inflammation, and its activation requires dual signaling triggers. The first signaling pathway involves NF-κB-mediated transcriptional upregulation of NLRP3 and pro-IL-1β, whereas the second signaling pathway depends on mitochondrial ROS or lysosomal damage. Furthermore, adipokine imbalance resulting from adipose tissue dysfunction leads to decreased levels of adiponectin and increased levels of resistin and leptin. This imbalance in cytokine levels further amplifies the hepatic inflammatory response, driving the progression of NAFLD to NASH and liver fibrosis (Petrescu *et al*., 2022).

Dysbiosis of the Gut Microbiota and Abnormalities in the Gut-Liver Axis: Dysfunction of the gut–liver axis is considered one of the key mechanisms underlying the development and progression of NAFLD (Shi *et al*., 2021; Qiu *et al*., 2025; Cheng et al., 2025). Factors such as a high-fat diet can induce an imbalance in the gut microbiota, manifested by changes in the Firmicutes/Bacteroides ratio, a relative decrease in beneficial bacteria, such as Bifidobacterium and Lactobacillus, that produce short-chain fatty acids (SCFAs), and an increase in the abundance of certain opportunistic pathogens, such as Enterobacteriaceae (Zhang *et al*., 2025). Microbiota dysbiosis is closely associated with impaired intestinal barrier function, often accompanied by the downregulation of the expression of tight junction proteins such as ZO-1 and Occludin and increased intestinal permeability. This facilitates the entry of lipopolysaccharide (LPS) into the liver via the portal vein, thereby activating inflammatory signaling pathways such as the Toll-like receptor 4 (TLR4)/NF-κB pathway (Ma *et al*., 2021). Consistently, natural polysaccharide interventions have been shown to improve antioxidant capacity and intestinal integrity, alleviate inflammatory responses, and beneficially modulate the gut microbiota (Meng et al., 2024).

In addition, reduced SCFA production may affect metabolic regulation mediated by G protein-coupled receptors (GPR41/43), while alterations in bile acid metabolism involving the gut microbiota may also disrupt signaling pathways such as the farnesoid X receptor

(FXR) and TGR5, thereby influencing the homeostasis of hepatic lipid and glucose metabolism to some extent (Xi and Li, 2020). Overall, gut dysbiosis contributes to the pathophysiology of NAFLD by affecting intestinal barrier integrity, inflammatory responses, and metabolic signaling, making the gut-liver axis an emerging potential target for intervention.

Limitations of current treatment strategies:

Adherence challenges in lifestyle interventions: Currently, lifestyle interventions, including dietary control, weight management, and regular exercise, are still considered the cornerstone of NAFLD treatment (Kucher *et al*., 2025). Previous studies have shown that weight loss of approximately 7 to 10% typically improves hepatic steatosis, whereas weight loss exceeding 10% is associated with improvements in histological markers of NASH in some patients. However, long-term adherence to such interventions is relatively limited; most studies have shown that only a small proportion of patients are able to maintain effective long-term weight control, and weight regain is relatively common (van Baak and Mariman, 2025). These limitations are not confined to human diseases; similar constraints exist in veterinary clinical practice as well. For companion animals suffering from metabolic disorders associated with hepatic lipid deposition, treatment adherence depends entirely on the pet owner. Factors such as the owner's level of cooperation and feeding habits can all influence treatment outcomes. In this regard, humans and companion animals share similar characteristics. Furthermore, the proportion of patients with lean NAFLD is on the rise; this population has a normal or near-normal body mass index, and the benefits of relying solely on weight loss strategies are relatively limited (Han and Lee, 2023). For patients who have progressed to NASH with moderate to severe fibrosis, lifestyle interventions alone often fail to achieve significant histological reversal and typically require comprehensive interventions, such as medication (Shi and Fan, 2022). Similarly, in livestock and poultry, it is difficult to control lipid metabolism disorders in the liver through management measures alone. To meet human productivity demands, the use of high-energy feed and intensive farming practices are unavoidable.

Bottlenecks in the efficacy and safety of Western medicine treatments: Currently, the U.S. Food and Drug Administration (FDA) has approved a drug specifically for the treatment of NAFLD/ NASH, the thyroid hormone receptor-β (THR-β) agonist resmetirom, for the treatment of adult patients with non-cirrhotic NASH/MASH accompanied by moderate to advanced fibrosis, in conjunction with diet and exercise therapy. Drugs currently in clinical development include obeticholic acid (an FXR agonist), for which phase III clinical trials have demonstrated antifibrotic effects but with a pruritus incidence as high as 51% and an increase in LDL-C (Fiorucci *et al*., 2025). Resmetirom (a THR-β agonist), which demonstrated dual benefits of NASH remission and fibrosis improvement in the MAESTRO-NASH trial, but its clinical application is currently mainly focused on selected adult patients with fibrotic MASH, and long-term outcome data remain under accumulation (Harrison *et al*., 2024). Vitamin E is recommended only for nondiabetic NASH patients; long-term high-dose use may increase the risk of prostate cancer and hemorrhagic stroke (Pacana and Sanyal, 2012). A common limitation of these drugs is that their single-target mechanism of action does not fully match involves the multifactorial pathological network underlying NAFLD and adverse reactions significantly impact patient tolerability. More importantly, the development of these drugs is focused solely on human medicine. For livestock, poultry, and companion animals, differences in metabolism, drug safety, cost-effectiveness, and routes of administration across species make it impossible to directly adapt human medications for veterinary use. Therefore, the development of safe, low-cost, and multi-targeted drug interventions holds greater significance for veterinarians.

Advantages and prospects of multitarget interventions using traditional Chinese medicine: Traditional Chinese medicine (TCM) has a solid theoretical foundation and a wealth of practical experience in the prevention and treatment of NAFLD. TCMs and their active components typically exhibit multicomponent, multitarget and multipathways synergistic effects (Yang *et al*., 2024). To a certain extent, they can simultaneously influence multiple pathological processes, including lipid metabolism disorders, insulin resistance, oxidative stress, inflammatory responses, and gut microbiota imbalance, which aligns well with the complex pathogenesis of NAFLD (Li *et al*., 2025). This approach is also one of the strategies commonly used by veterinarians today to treat liver disorders involving lipid metabolism, such as those related to nutrition, production stress, and obesity (Xu et al., 2025).

Polygonatum (*Polygonatum sibiricum* Delar. ex Redouté) has received extensive attention because of its dual medicinal and edible properties (Liu *et al*., 2022). According to TCM theory, Polygonatum is generally described as having the functions of tonifying qi, nourishing yin, strengthening the spleen and lungs, and replenishing kidney essence. In recent years, increasing attention has been given to its chemical composition and pharmacological effects. Research has shown that Polygonatum is rich in polysaccharides, steroid saponins and flavonoids. These components are involved in the regulation of glucose and lipid metabolism and may help reduce oxidative stress and inflammatory responses, thereby showing good effects in metabolic diseases (Shi *et al*., 2023; Liu *et al*., 2024). In studies related to animal feed, Polygonatum polysaccharides have been used to improve the production performance of broiler chickens and enhance their antioxidant capacity (Yang *et al*., 2024). These studies suggest that Polygonatum has potential for use as a functional feed additive. Current research suggests that it holds potential application value in improving metabolism-related abnormalities; however, the underlying mechanisms of action and clinical evidence still require further systematic research for validation (Lin *et al*., 2024). Therefore, Polygonatum and its active components can serve as candidate natural products for NAFLD intervention studies, providing a reference for supplementation with existing treatment strategies and for the development of safe, multitarget interventions for hepatic lipid metabolic disorders in companion animals and livestock.

Theoretical basis for the treatment of NAFLD with Polygonatum:

Chemical composition and pharmacological effects of Polygonatum: Polygonatum is a perennial herb in the Liliaceae family. The 2020 edition of the *Chinese Pharmacopoeia* lists the following species as medicinal Polygonatum: Yunnan Polygonatum (*P. kingianum* Coll. et Hemsl.), Siberian Polygonatum (*P. sibiricum* Red.), and many-flowered Polygonatum (*P. cyrtonema* Hua) (Hong-Min *et al*., 2020). Moreover, *P. sibiricum* Red. is found mainly in North China, Northeast China and Northwest China; its rhizome is nodular and curved-cylindrical in shape and is commonly known as "chicken-head Polygonatum". *P. cyrtonema* Hua is widely distributed in Central and South China, East China and the Southwest; its rhizome is beaded or tuberous in shape and is commonly known as "ginger-shaped Polygonatum". *P. kingianum* Coll. et Hemsl. is primarily found in southwestern regions such as Yunnan, Guizhou and Sichuan; its rhizome is thick, tuberous or beaded and is commonly known as "large Polygonatum". There are significant differences in the chemical compositions of these three species, which directly influence their pharmacological activity and clinical applications (Table 2; Table 3).

Table 2: Comparison of the content of major bioactive compounds in three standardized Polygonatum species

Polygonatum Species	Polysaccharide content (mg/g)	Saponin content (mg/g)	Flavonoid content (mg/g)	Key Structural Features
P. sibiricum	40.68-123.58	0.289-2.017	0.018-0.035	Predominantly neutral polysaccharides, fructan type.
P. kingianum	31.24-140.94	1.303-2.845	0.015-0.030	The contains a high proportion of polysaccharides and a wide variety of saponins.
P. cyrtonema	22.34-140.94	0.030-8.920	0.004-0.034	Sulfated polysaccharides are rich in uronic acids, and saponins exhibit the greatest variation.

Molecular weight distribution and Glycosidic bond configuration of Polygonatum polysaccharides: Polysaccharides from Polygonatum (PPs) are the most abundant and extensively studied bioactive components in Polygonatum, accounting for 10 to 20% of the dry weight of the herbal material. They are also the only components designated as quality control indicators in the 2020 edition of the Chinese Pharmacopoeia, which stipulates that their content must not be less than 7.0% (Liu *et al*., 2022). PPs belong to the fructan class of polysaccharides, characterized by a backbone composed of fructose residues linked by β-(2→1) glycosidic bonds, with a degree of polymerization (DP) primarily ranging between 5 and 10, forming an oligo-fructan structure; some varieties contain an α-D-glucose-initiating residue and β-(2→6) branching bonds (Yang *et al*., 2023). The monosaccharide composition includes fructose, glucose, mannose, galactose, arabinose, rhamnose, and small amounts of glucuronic acid and xylose.

Studies on molecular weight distribution indicate that PPs have a wide range of weight-average molecular weights (Mws), varying from several thousand to several hundred thousand daltons. PPs of different molecular weight ranges exhibit different biological activities: high-molecular-weight components (>100 kDa) stand out in the regulation of immunity (Wang *et al*., 2020). The medium- and low-molecular-weight fragments (10–50 kDa) are more readily fermented by the intestinal microbiota, generating oligosaccharide products with direct metabolic regulatory activities (Wei *et al*., 2022; Hu *et al*., 2024; Li *et al*., 2025a).

Specifically, the polysaccharide structures of different Polygonatum species significantly differ. The polysaccharides of *P. kingianum* are primarily composed of fructose, glucose, and galactose, whose molecular weight distribution ranges from 2 to 100 kDa (Yu *et al*., 2022). The backbone of many-flowed Polygonatum polysaccharides consists of →1)-β-D-fructofuranose-(2→ and →1,6)-β-D-fructofuranose-(2→, with side chains of β-D-fructofuranose (2→) linked to the C6 position of the main chain (Liu *et al*., 2022a); *P. sibiricum* polysaccharides, on the other hand, consist primarily of fructose and glucose monomers, and after fermentation modification, the antiaging activity of the low-molecular-weight fractions (10-50 kDa) is significantly enhanced (Yang *et al*., 2023).

Aglycone types and Glycosidic modifications of Steroidal saponins: Polygonatum steroidal saponins (PSSs) are a class of important bioactive compounds found in plants of the genus Polygonatum, comprising mainly spirostanol, isospirostanol and furostanol saponins, whose structural diversity primarily arises from differences in the steroid aglycone skeleton and the composition of the sugar chains. Previous studies have reported a variety of steroidal saponin compounds in Polygonatum species, whose aglycone structures are predominantly related to diosgenin, trillenogenin, kryptogenin and their derivatives (Luo *et al*., 2022; Xu *et al*., 2023a). Zheng *et al*. employed UPLC–QTOF–MS technology to conduct a systematic analysis of saponin constituents in four Polygonatum species, identifying a total of 30 saponin compounds, including 11 spiro-saponins, 10 iso-saponins and 9 furo-saponins, further revealing the relatively rich structural diversity of saponins in Polygonatum species (Zheng *et al*., 2026).

Table 3: Structural characteristics and pharmacological effects of major bioactive components in Polygonatum

Species	Geographical distribution	Rhizome morphology	Common name	Distinctive chemical characteristics	References
P. kingianum	Southwestern China (Yunnan, Guizhou, Sichuan)	Thick, tuberous or beaded	Large Polygonatum	Polysaccharides composed mainly of fructose, glucose, and galactose; Mw 2–100 kDa	(Hong-Min *et al*., 2020; Yu *et al*., 2022)
P. sibiricum	North, Northeast, and Northwest China	Nodular, curved-cylindrical	Chicken-head Polygonatum	Polysaccharides composed primarily of fructose and glucose monomers; relatively stable saponin content with anti-inflammatory and metabolic regulatory activities	(Hong-Min *et al*., 2020; Yang *et al*., 2023; Lin *et al*., 2024; Luo *et al*., 2022)
P. cyrtonema	Central, South, East, and Southwest China	Beaded or tuberous	Ginger-shaped Polygonatum	Polysaccharide backbone consists of →1)-β-D-fructofuranose-(2→ and →1,6)-β-D-fructofuranose-(2→, with side chains of β-D-fructofuranose-(2→) linked to the C6 position of the main chain; saponin content peaks in 3-year-old rhizomes	(Hong-Min *et al*., 2020; Liu *et al*., 2022a; Li *et al*., 2022)

From a structural perspective, the glycan moiety of Polygonatum steroidal saponins typically consists of monosaccharides such as glucose, galactose, xylose, rhamnose and fucose linked to the steroidal aglycone via glycosidic bonds. The type of sugar, the linkage pattern and the length of the glycan chain may influence the physicochemical properties and biological activity of the saponins (Xu *et al*., 2023a). Generally, the structure of the glycan chain influences the lipophilicity, membrane interactions and absorption characteristics of a saponin in vivo; relatively short or structurally simple glycan chains may enhance the membrane permeability of certain saponins, but their specific activity must still be assessed in conjunction with the structure, experimental models and target sites of action of the compound; therefore, it is inappropriate to simply generalize that shorter glycan chains result in greater activity.

Methyl protodioscin (MPD) is among the representative steroidal saponins reported in plants such as Polygonatum. Previous studies have shown that MPD can alleviate inflammatory responses in the intestinal mucosa in models of intestinal inflammation induced by DSS, and these effects may be associated with the regulation of intestinal immune responses, the promotion of intestinal epithelial repair, and the improvement of barrier function (Zhang *et al*., 2015). Furthermore, MPD derived from *Asparagus cochinchinensis* roots can inhibit the production of inflammatory factors such as IL-6, IL-8 and TNF-α in IL-1β-stimulated A549 cells, an effect that may be related to the inhibition of JNK/c-Jun signaling activation (Lee *et al*., 2015). Therefore, MPD and related steroidal saponins have some research value in terms of anti-inflammatory effects and mucosal barrier regulation; however, their direct role and mechanisms in NAFLD require further experimental validation.

Comparative phytochemical analysis has demonstrated that different Polygonatum species exhibit substantial variability in steroidal saponin content. A notable example is *P. multiflorum*, whose degree of variation in the accumulation of saponins is considerable. These findings suggest that this species may be an important source of steroidal saponins. These interspecific differences may be related to factors such as genetic background, growth conditions, and developmental stage, all of which collectively influence the biosynthesis of secondary metabolites (Li *et al*., 2025b).

P. sibiricum is characterized by its relatively stable saponin content; this species also exhibits pharmacological activities, such as anti-inflammatory and metabolic regulatory effects, which have attracted significant attention from researchers (Luo *et al*., 2022; Lin *et al*., 2024). In contrast, researchers reported that the saponin content of *P. cyrtonema* fluctuates dynamically across different growth stages. Typically, the greatest accumulation of saponins occurs in three-year-old rhizomes (Li *et al*., 2022). Studies have shown that *P. multiflorum* possesses a relatively diverse range of steroidal saponin structures, including various spiro- and furo-saponins. These findings indicate that *P. multiflorum* exhibits greater structural diversity, which may confer broader functional potential (Gvazava *et al*., 2019).

Although many species of the Polygonatum genus serve as sources of steroidal saponins, *P. cyrtonema* is characterized by significant chemical diversity. In contrast, *P. sibiricum* and *P. cyrtonema* are more suitable for standardized pharmaceutical production because of their relatively stable chemical composition.

Synergistic chemical basis of Flavonoids, Alkaloids and Volatile compounds: In addition to polysaccharides and steroidal saponins, Polygonatum contains a variety of other chemical compounds, such as flavonoids, alkaloids, isoflavonoids, lignans, phytosterols, and volatile compounds. The medicinal effects of Polygonatum are attributed to the synergistic interactions among these components (Xu *et al*., 2023a, 2023b). Studies have shown that flavonoids possess significant antioxidant and anti-inflammatory properties (Li *et al*., 2016; Panche *et al*., 2016). Although their concentrations are relatively low, alkaloids have been identified in several species of the genus Polygonatum. These compounds may exert their biological activity through neuroprotective and immunomodulatory effects. However, compared with those of other components, the specific mechanisms of action of these alkaloids have not yet been fully elucidated (Wink, 2015). Numerous studies have shown that isoflavones and lignans possess antioxidant and metabolic-regulating properties. These properties are expected to enhance the biological effects of flavonoids and saponins (Teponno *et al*., 2016). In addition, volatile compounds extracted from the rhizomes of Polygonatum, including aldehydes, alcohols, ketones, and terpenoids, have been shown to possess antibacterial and anti-inflammatory properties. However, further research is needed to elucidate the extent to which these compounds contribute to the drug's systemic pharmacological effects (Sun *et al*., 2022). The results of this study revealed that the samples analyzed contained plant sterols such as β-sitosterol. Numerous studies have shown that plant sterols are associated with lipid metabolism and anti-inflammatory responses (Racette *et al*., 2010).

Taken together, these compounds may exhibit synergistic effects that contribute to the overall pharmacological properties of Polygonatum. However, the specific mechanisms underlying these interactions require further mechanistic and systems-level study.

Therapeutic strategies for the treatment of NAFLD using Polygonatum:

Therapeutic efficacy of animal experiments

Monotherapy: After 14 weeks of treatment with *P. kingianum*, rats fed a high-fat diet (HFD) exhibited dose-dependent improvements in liver function and a reduction in hepatic steatosis. Specifically, serum alanine aminotransferase (ALT) levels decreased from 120 to 65 U/L ($P<0.01$), aspartate aminotransferase (AST) levels decreased from 150 to 80 U/L ($P<0.01$) and liver TG levels decreased from 180 to 100 mg/g ($P<0.05$). The mechanism involves multitarget mitochondrial protection: UPLC–MS/MS metabolomics revealed that *P. kingianum* restored the levels of biomarkers related to mitochondrial riboflavin metabolism and increased the activity of mitochondrial complexes I and II ($P<0.05$), as well as adenosine triphosphate *s*ynthesis (Yang *et al*., 2019). Moreover, it upregulated carnitine acyl transferase I (CPT-1) mRNA expression ($P<0.01$), thereby promoting

fatty acid β-oxidation; downregulated uncoupling protein 2 (UCP-2) mRNA expression, reducing energy wastage; and inhibited the release of mitochondrial cytochrome c as well as the caspase cascade, thereby alleviating hepatocyte apoptosis. At the histological level, the liver tissue inflammation score decreased ($P<0.05$) and the fibrosis score decreased ($P<0.05$) (Yang *et al*., 2019a).

In mice with NAFLD treated with *P. multiflorum* polysaccharide PCP1 for 8 weeks, PCP1 reduced triglyceride (TG) levels in the liver ($P<0.05$) and alleviated steatosis by activating the AMPK/SIRT1 pathway and inhibiting fatty acid synthase (FAS) activity. The area of Oil Red O-positive lesions decreased from 35 to 15% ($P<0.01$). Additionally, the serum adiponectin concentration increased from 5 to 12 μg/mL ($P<0.05$). Furthermore, PCP1 improved the lipid profile; specifically, serum total cholesterol (TC) decreased from 5.5 to 3.8 mmol/L ($P<0.01$). Low-density lipoprotein cholesterol (LDL-C) concentration decreased from 3.2 to 2.0 mmol/L ($P<0.01$). High-density lipoprotein cholesterol (HDL-C) increased from 1.0 to 1.5 mmol/L ($P<0.05$) (Liu *et al*., 2022). Polysaccharides from Polygonatum can alleviate oxidative stress damage by increasing SOD and GSH-Px activity in liver tissue and reducing MDA levels (Yang *et al*., 2019).

After 8 weeks of treatment with Polygonatum water extract (PSRwe) in HFD-fed mice, it exerted a protective effect on the gut–liver axis by reshaping the gut microbiota: the abundance of *Akkermansia muciniphila* in the gut increased from 0.2 to 1.8% ($P<0.05$). The bacterium degrades the intestinal mucus layer, thereby reducing LPS entry into the bloodstream, simultaneously promoting the production of short-chain fatty acids (SCFAs) ($P<0.01$) and inhibiting liver inflammation via the activation of GPR43/GPR41 receptors. Pharmacologically, the body weight of the mice decreased ($P<0.05$) and the hepatic fat content decreased ($P<0.01$), indicating that orlistat was superior (Ou *et al*., 2024).

In addition, the antioxidant activity of the processed Polygonatum extract significantly increased after treatment with black soybean juice, with an IC_{50} value of 0.25 mg/mL for ABTS radical scavenging activity, which was superior to that of raw Polygonatum (Zhang *et al*., 2023).

Combination therapy: After 4 weeks of treatment with Polygonatum multiflorum ethanol extract (PCE) in combination with simvastatin in HFD-fed mice, the serum TC concentration decreased from 5.5 to 3.0 mmol/L ($P<0.01$) and the hepatic fat content decreased from 25 to 8% ($P<0.01$), demonstrating superior efficacy compared with that of either drug alone. The underlying mechanism of this synergistic effect is that Polygonatum, by modulating mitochondrial function and the gut microbiota, combines with the inhibitory effect of simvastatin on cholesterol synthesis to produce a dual-targeted intervention on lipid metabolism. Furthermore, studies have shown that Polygonatum extract (PCE) can reduce the levels of TNF-α and IL-6 in liver tissue in a dose-dependent manner by inhibiting the NF-κB pathway (Chen *et al*., 2025).

In a recent study, rats with type 2 diabetes (T2DM) received an 8-week combination therapy of Polygonatum polysaccharides and metformin to treat NAFLD. The results revealed a significant reduction in the homeostatic model assessment of insulin resistance (HOMA-IR) score ($P<0.01$) and a significant reduction in liver fibrosis score ($P<0.05$). The treatment regimen involved the concurrent use of Polygonatum and metformin (Yang *et al*., 2021).

After 8 weeks of treatment with Polygonatum polysaccharides combined with Bifidobacterium bifidum in mice with NAFLD, the levels of SCFAs in the gut increased ($P<0.01$) and liver inflammation scores decreased significantly ($P<0.01$), demonstrating a synergistic effect of the microbiota (Liu *et al*., 2022).

Clinical studies: Currently, there are no large-scale clinical trials on the use of Polygonatum as a monotherapy for NAFLD; however, studies on compound formulations and extracts have yielded preliminary evidence. A randomized controlled trial (RCT) involving 50 NAFLD patients revealed that after 12 weeks of treatment with "Qinggan San", a compound formulation containing Polygonatum promoted fatty acid oxidation by inhibiting the nuclear translocation of sterol regulatory element-binding protein-1 (SREBP-1) and upregulating peroxisome proliferator-activated receptor alpha (PPARα) and CPT-1 levels. The serum ALT concentration decreased from 85 to 55 U/L ($P<0.01$), the AST concentration decreased from 75 to 45 U/L ($P<0.01$), the TC concentration decreased from 5.2 to 3.8 mmol/L ($P<0.01$), the TG concentration decreased from 2.8 to 1.5 mmol/L ($P<0.01$), the MRI-PDFF decreased significantly ($P<0.05$) and hepatic steatosis improved markedly. This compound also reduced the hepatic hydroxyproline content ($P<0.01$) and the fibrosis-4 (FIB-4) index ($P<0.05$) (Yang *et al*., 2021).

In terms of inflammation control, Polygonatum can reduce serum TNF-α ($P<0.01$) and IL-6 ($P<0.05$) levels in patients with NAFLD (Chen *et al*., 2025).

Methods for evaluating efficacy: Imaging techniques provide objective, quantitative evidence for evaluating the efficacy of Polygonatum in treating NAFLD. Among these, magnetic resonance imaging-proton density fat fraction (MRI-PDFF) can be used to quantitatively assess liver fat content. Studies have shown that following treatment with Polygonatum, liver fat content in HFD-fed rats decreases from 25 to 10% ($P<0.01$) (Yang *et al*., 2019). In addition, ultrasound elastography can be used to assess the degree of liver fibrosis, and liver stiffness measurements (LSMs) were significantly reduced ($P<0.05$) following intervention with PSRwe (Ou *et al*., 2024). Computed tomography (CT) can also reflect the degree of steatosis by measuring the liver-to-spleen density ratio. Studies have shown that this index increased from 0.8 to 1.0 ($P<0.05$), suggesting an improvement in hepatic fat deposition (López López *et al*., 2023). Furthermore, long-term ultrasound follow-up results indicated that after 24 weeks of intervention, the hepatorenal index (HRI) decreased from 1.5 to 1.2 ($P<0.01$), further supporting the sustained beneficial effect of Polygonatum on hepatic steatosis (Yang *et al*., 2019).

Metabolomics can reveal the potential mechanisms by which Polygonatum affects NAFLD at the molecular level. Studies using UPLC–Q–TOF/MS have indicated that Polygonatum can modulate 25 differentially expressed metabolites in the serum of NAFLD rats,

primarily involving pathways such as tyrosine metabolism and glycerophospholipid metabolism. Among these, key metabolic markers, such as L-tyrosine, phosphatidylcholine, and leukotriene B4 (LTB4), tended to improve following intervention, suggesting that Polygonatum may participate in the disease improvement process by regulating amino acid metabolism, lipid metabolism, and inflammation-related metabolic networks and providing evidence at the metabolic phenotype level for studies on its mechanisms of action and potential precision interventions (Li *et al*., 2025b) (Fig. 1).

Controversies and challenges in the treatment of NAFLD with Polygonatum

Safety concerns regarding the use of Polygonatum in the treatment of Nonalcoholic fatty liver disease: Polygonatum has a good safety profile, with no significant toxic reactions observed in animal studies. After 14 weeks of HFD-fed rats were treated with 4g/kg *P. kingianum*, no abnormalities in liver or kidney histopathology were observed (Yang *et al*., 2019). After 8 weeks of HFD-fed mice were treated with 7.5mg/kg PSRwe, serum creatinine and blood urea nitrogen levels (Ou *et al*., 2024) did not significantly change. Although Polygonatum shows promising prospects for the treatment of NAFLD, its clinical translation still requires attention to certain issues regarding rational drug use. Studies have confirmed that raw Polygonatum contains a certain amount of mucilage and potentially irritating components. Direct consumption without standardized steaming or processing may irritate the gastrointestinal mucosa, thereby triggering adverse reactions such as bloating and diarrhea. This underscores the significance of TCM. Furthermore, although numerous studies have demonstrated that Polygonatum has a favorable therapeutic effect on nonalcoholic fatty liver disease at high doses, some studies have indicated that high concentrations of Polygonatum can lead to hypoglycemia. These findings not only confirm the pharmacological effects of Polygonatum in regulating glucose and lipid metabolism but also verify that it is at risk of causing hypoglycemia. This suggests that for patients with diabetes or those receiving hypoglycemic treatment, the dosage of Polygonatum should be adjusted.

Standardization issues in the treatment of NAFLD with Polygonatum: As demonstrated by the present experiments and clinical applications, Polygonatum odoratum has been shown to be advantageous for multitarget regulation in the treatment of NAFLD. However, the plant sources are not uniform. This problem has a significant impact on the quality control of medicinal materials. The Polygonatum odoratum species complex is frequently utilized in clinical diagnosis and treatment, as well as in scientific research. Notable examples include *P. sibiricum*, *P. multiflorum*, and *P. cyrtonema*, among others. There are significant differences among them in terms of polysaccharide composition, monosaccharide composition, and the types and contents of secondary metabolites. With respect to the variety and active components, the monosaccharide with the highest content in *P. multiflorum* is fructose, while the main monosaccharide in *P. cyrtonema* is glucose. These structural differences in components alter their roles in regulating immunity and altering metabolism, leading to differences in the therapeutic effects of different sources of Polygonatum odoratum in the treatment of NAFLD. Furthermore, notably, the extraction methods employed can result in significant differences in the chemical components that are extracted. However, there are currently no standardized guidelines for extraction parameters, solvent systems, or process conditions. Consequently, in the absence of a uniform set of standards, comparisons between the findings of disparate studies are challenging, thereby impeding the development of a stable and controllable agent system.

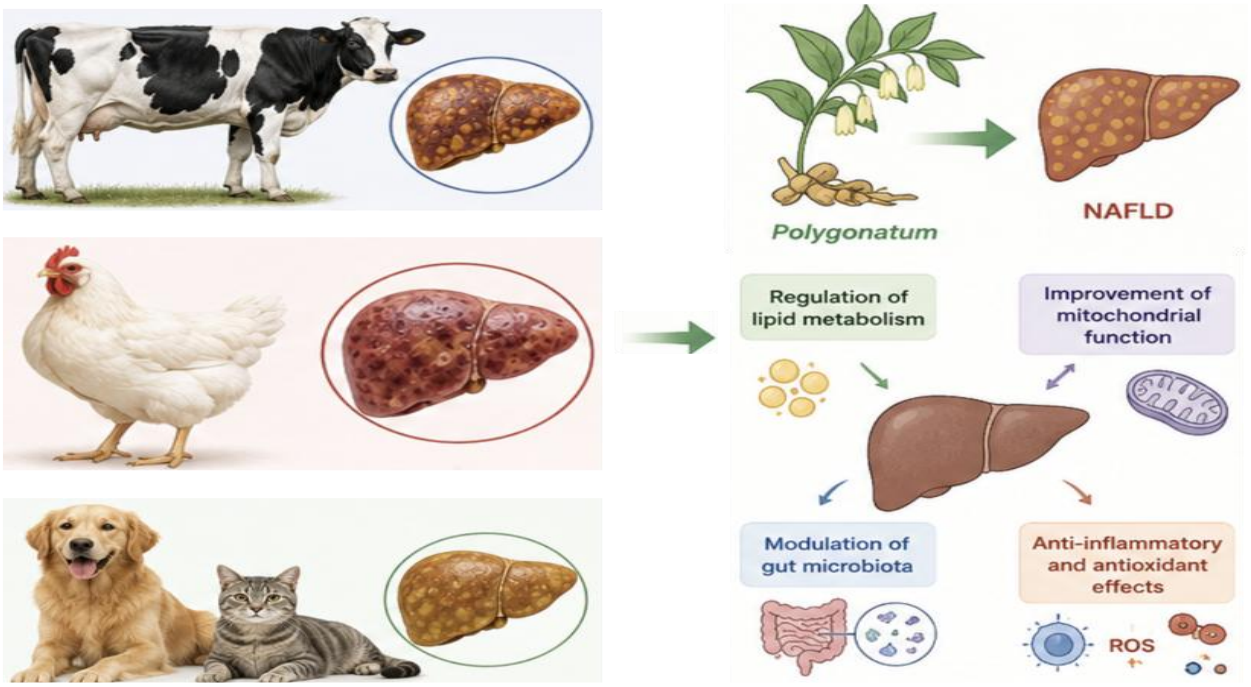

Fig. 1: Strategies for the treatment of NAFLD with Polygonatum.

Moreover, the prevailing pharmacopoeia merely establishes a threshold for the presence of polysaccharides, serving as an indicator of quality. Nevertheless, no systematic quantitative control methods have been established for potential bioactive components such as saponins and flavonoids (Zhao *et al*., 2020). The evaluation method based on a single indicator is inadequate for accurately reflecting the complex chemical composition and overall pharmacological effect of Polygonatum odoratum. Consequently, its application as a functional natural medicine for treating NAFLD is also limited. Consequently, to improve quality control, a set of quality markers (Q-markers) based on the synergistic effect of multiple components should be established to improve the control level of the quality of Polygonatum odoratum.

From the perspective of the extraction process, the absence of standardized processing procedures also hinders the wide promotion and application of Polygonatum (Yang *et al*., 2021). Studies have confirmed that the polysaccharide content of Polygonatum increases after nine cycles of steaming and drying (Zhu *et al*., 2022). However, at present, there is no unified standard for the number of steaming cycles, the duration of each cycle, or the selection of auxiliary materials. This absence of standardization is likely to result in substantial variations in the quality of Polygonatum products.

The outlook:

Development of nanoscale delivery systems and targeted formulations: The present study investigates the recent surge of interest in the field of nanomedicine within the academic community, which has been prompted by the advantages offered by nanomedicine delivery systems, including low toxicity, low dosage, high targeting accuracy, and high bioavailability. When it is administered orally, the bioavailability of active components such as polysaccharides and saponins in Polygonatum is relatively low. Specifically, the ability of polysaccharides to cross the intestinal barrier is limited, and the solubility and membrane permeability of certain saponins do not meet the required standards. The introduction of a nanodelivery system is expected to optimize the in vivo delivery of these active components. Specifically, this manifests as improving the stability of the components, enhancing the specificity of tissue distribution, and weakening the influence of the gastric acid environment on the structure of polysaccharides within a certain range to better regulate the intestinal flora. In the field of veterinary medicine, such administration strategies also help improve the feasibility of administering medications to companion animals and livestock, thereby addressing clinical challenges such as poor palatability, low compliance among pet owners and livestock farmers, and significant variations in gastrointestinal degradation and species-specific absorption. The combination of this type of nanodelivery system with a delivery system modified by liver-targeting ligands has the potential to further increase the accumulation of active components in liver tissue, thereby improving the therapeutic effect and reducing the potential risks of off-target distribution. Similarly, in animal models of liver lipid metabolism disorders, strategies that directly target the liver are promising. They not only improve treatment efficacy but also reduce systemic drug exposure. For metabolic disorders requiring long-term treatment, this represents an excellent option.

Multicenter clinical trial design: During the clinical translation stage, the execution and refinement of randomized controlled trials can facilitate a systematic evaluation of the efficacy and safety of Polygonatum luteum in the treatment of patients with NAFLD. The design of the trial should comply with internationally recognized standards, with liver histological examination or validated noninvasive alternative markers set as the primary outcome indicators. Research subjects should include a sample group with diverse metabolic characteristics and different demographic features, with the aim of enhancing the general applicability of the research results.

Compared to current research on laboratory animals, future veterinary research should focus more on natural clinical cases. For companion animals and livestock suffering from spontaneous or production-related liver lipid metabolism disorders, studies should include serum biochemical markers, liver ultrasound examinations, metabolomic biomarkers, indicators of inflammation and oxidative stress, production performance, feed intake, body condition scores, and, where ethically permissible, liver histopathological examinations. Such evidence will be more directly applicable to veterinary clinical practice and the development of functional feed additives.

Utilization of Polygonatum resources and standardized cultivation: As the market demand for Polygonatum continues to grow, concerns about the stability of its supply and the quality assurance of its products have gradually emerged. Therefore, in the future, the focus of work should be on evaluating germplasm resources and cultivating superior varieties. Moreover, conducting relevant research on species identification and quality control using molecular marker technology can ensure the consistency of the quality of medicinal materials.

Conclusions: In traditional Chinese medicine, Polygonatum is an important plant with both medicinal and edible properties. Current research has confirmed that it can exert therapeutic effects on NAFLD by regulating lipid metabolism, restoring mitochondrial function, and balancing the intestinal microbiota. These mechanisms also apply to metabolic liver disorders in livestock, poultry, and companion animals, suggesting that Polygonatum has the potential to prevent and treat obesity-related liver dysfunction in companion animals, as well as nutrition- or production-related fatty liver disease in livestock and poultry. However, some issues still need to be addressed urgently. For instance, long-term clinical data are lacking, and no established sets of standards for processing methods exist. Therefore, in the future, more clinical trials should be conducted to formulate quality standards. The veterinary field will also further clarify the dosages for target animals and the safety of drug residues in food-producing animals and will further integrate these considerations into the feed processing system. A review

of the research on Polygonatum is expected to help researchers gain a deeper understanding of the current development trends.

Authors Contribution: Huijun Xiong: Conceptualization, Literature search, Writing-original draft, Writing-review & editing. Wenjuan Li: Literature search, Data curation, Writing – original draft, Visualization. Qiang Zhang: Conceptualization, Supervision, Writing-review & editing. Hang He: Literature search, Writing-review & editing.

Funding: This article was supported by Chongqing Municipal Education Commission Research Project: A Novel Veterinary Drug Study on the Structure-Activity Relationship of Active Components from Rhizoma Polygonati Radix in Northeastern Chongqing for Regulating Animal Immunity (KJZD-M202503501) and Chongqing Municipal Education Commission Research Project (KJQN202503523).

Generative AI Statement: The author declares that no generative AI tools were used in the writing of this manuscript.

Declaration of competing interests: The authors declare that they have no conflicts of interest.

REFERENCES

Chen D, Shen Y, Huang F, *et al*., 2025. Ethanol extract of polygonatum cyrtonema hua mitigates non-alcoholic steatohepatitis in mice. Frontiers in Pharmacology 15: 1487738. https://doi.org/10.3389/fphar.2024.1487738.

Cheng S, Liu X, Cheng S, *et al*., 2025. The research mechanism of the gut-liver axis in non-alcoholic fatty liver disease. Pakistan Veterinary Journal 45(4):1524-1531. https://doi.org/10.29261/pakvetj/2025.300

Eslam M, Newsome PN, Sarin SK, *et al.,* 2020. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. Journal of Hepatology 73(1):202-209. https://doi.org/10.1016/j.jhep.2020.03.039.

Fang Y, Chen H, Wang C, *et al.,* 2018. Pathogenesis of non-alcoholic fatty liver disease in children and adolescence: from "two hit theory" to "multiple hit model". World Journal of Gastroenterology 24(27):2974-2983. https://doi.org/10.3748/wjg.v24.i27.2974.

Fiorucci S, Urbani G, Distrutti E, *et al.,* 2025. Obeticholic acid and other farnesoid-x-receptor (FXR) agonists in the treatment of liver disorders. Pharmaceuticals 18(9):1424. https://doi.org/10.3390/ph18091424.

Gvazava L, Nebieridze V, Ganzera M, *et al.,* 2019. New furostanol glycosides from *Polygonatum multiflorum* Natural Product Research 33(1):9-16. https://doi.org/10.1080/14786419.2018.1431628.

Han E and Lee Y, 2023. Lean or non-obese nonalcoholic fatty liver disease patients: are they really lean? Clinical and Molecular Hepatology 29(4):980-983. https://doi.org/10.3350/cmh.2023.0250.

Harrison SA, Bedossa P, Guy CD, *et al.,* 2024. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. The New England Journal of Medicine 390(6):497-509. https://doi.org/10.1056/NEJMoa2309000.

Henkel AS, 2018. Unfolded protein response sensors in hepatic lipid metabolism and nonalcoholic fatty liver disease. Seminars in Liver Disease 38(4):320-332. https://doi.org/10.1055/s-0038-1670677.

Hong-Min R, Ya-Ling D, Jin-Lian Z, *et al.,* 2020. Research progress on processing history evolution, chemical components and pharmacological effects of *Polygonati rhizoma*. Journal of Chinese Materia Medica 45(17):4163-4182. https://doi.org/10.19540/j.cnki.cjcmm.20200522.601.

Hu Y, Tang Y, Zhang J, *et al*., 2024. *In-vitro* digestion and fermentation of polysaccharides from nine common polygonatum spp. and their impact on human gut microbiota. International Journal of Biological MacromoleculesInternational Journal of Biological Macromolecules 280(Pt 4):136052. https://doi.org/10.1016/j.ijbiomac.2024.136052.

Kucher SV, Mudra UO, Tkachuk VV, *et al*., 2025. Impact of lifestyle modification interventions on metabolic syndrome and obesity in adults. Wiadomosci Lekarskie (Warsaw, Poland: 1960) 78(9):1857-1865. https://doi.org/10.36740/WLek/212515.

Lee JH, Lim HJ, Lee CW, *et al*., 2015. Methyl protodioscin from the roots of asparagus cochinchinensis attenuates airway inflammation by inhibiting cytokine production. Evidence-Based Complementary and Alternative Medicine 2015:640846. https://doi.org/10.1155/2015/640846.

Li D, Wang Q, Chen S, *et al*., 2022. De novo assembly and analysis of polygonatum cyrtonema hua and identification of genes involved in polysaccharide and saponin biosynthesis. BMC Genomics 23(1):195. https://doi.org/10.1186/s12864-022-08421-y.

Li H, Wu Y, Zhou Q, *et al*., 2025. Polysaccharide from steamed polygonatum sibiricum ameliorates ulcerative colitis by protecting the intestinal mucosal barrier and regulating gut microbiota. International Journal of Biological MacromoleculesInternational Journal of Biological Macromolecules 301:140343. https://doi.org/10.1016/j.ijbiomac.2025.140343.

Li J, Wang X, Mei K, *et al*., 2021. Lateral size of graphene oxide determines differential cellular uptake and cell death pathways in kupffer cells, LSECs, and hepatocytes. Nano Today 37:101061. https://doi.org/10.1016/j.nantod.2020.101061.

Li L, Wang Y, Wang H, *et al*., 2023. Protective effects of genistein on the production performance and lipid metabolism disorders in laying hens with fatty liver hemorrhagic syndrome by activation of the GPER–AMPK signaling pathways. Journal of Animal Science 101. https://doi.org/10.1093/jas/skad197.

Li L, Liu M and Dai H, 2025a. *Houttuynia cordata* Thunb. extract in pig production: a multifaceted alternative to antibiotics with antimicrobial, antioxidant and health-promoting properties. Animal Diseases 5:48. https://doi.org/10.1186/s44149-025-00203-9

Li M, Xu C, Shi J, *et al*., 2018. Fatty acids promote fatty liver disease via the dysregulation of 3-mercaptopyruvate sulfurtransferase/hydrogen sulfide pathway. Gut 67(12):2169-2180. https://doi.org/10.1136/gutjnl-2017-313778.

Li X, Cui F, Tang S, *et al*., 2025b. Untargeted metabolomic study on the mechanism of polygonatum sibiricum in non-alcoholic fatty liver disease in rats using UPLC-q-TOF/MS. Biomedical Chromatography 39(12):e70269. https://doi.org/10.1002/bmc.70269.

Li Y, Yao J, Han C, *et al*., 2016. Quercetin, inflammation and immunity. Nutrients 8(3):167. https://doi.org/10.3390/nu8030167.

Li Z, Hu Z, Zhao Y, *et al*., 2025c. Geographical variations in polygonatum polysaccharides and saponins biosynthesis in polygonatum species. Industrial Crops and Products 227:120814. https://doi.org/10.1016/j.indcrop.2025.120814.

Lin H, Wang W, Peng M, *et al*., 2024. Pharmacological properties of polygonatum and its active ingredients for the prevention and treatment of cardiovascular diseases. Chinese Medicine 19(1):1. https://doi.org/10.1186/s13020-023-00871-0.

Liu R, Zhang X, Cai Y, *et al*., 2024. Research progress on medicinal components and pharmacological activities of *Polygonatum sibiricum*. Journal of Ethnopharmacology 328:118024. https://doi.org/10.1016/j.jep.2024.118024.

Liu S, Jia Q, Peng Y, *et al*., 2022. Advances in mechanism research on polygonatum in prevention and treatment of diabetes. Frontiers in Pharmacology 13:758501. https://doi.org/10.3389/fphar.2022.758501.

Liu W, Shao T, Tian L, *et al*., 2022a. Structural elucidation and anti-nonalcoholic fatty liver disease activity of *Polygonatum cyrtonema* hua polysaccharide. Food & Function 13(24):12883-12895. https://doi.org/10.1039/d2fo03384d.

Loomba R, Friedman SL and Shulman GI, 2021. Mechanisms and disease consequences of nonalcoholic fatty liver disease. Cell 184(10):2537-2564. https://doi.org/10.1016/j.cell.2021.04.015.

López López AP, Tuli S, Lauze M, *et al*., 2023. Changes in hepatic fat content by CT 1 year after sleeve gastrectomy in adolescents and young adults with obesity. The Journal of Clinical Endocrinology and Metabolism 108(12):e1489-e1495. https://doi.org/10.1210/clinem/dgad390.

Luo L, Qiu Y, Gong L, *et al*., 2022. A review of polygonatum mill. Genus: its taxonomy, chemical constituents, and pharmacological effect due to processing changes. Molecules 27(15):4821. https://doi.org/10.3390/molecules27154821.

Luo X, Guo J, Deng H, *et al*., 2024. Unveiling the role of disulfidptosis-related genes in the pathogenesis of non-alcoholic fatty liver disease. Frontiers in Immunology 15:1386905. https://doi.org/10.3389/fimmu.2024.1386905.

Ma J, Piao X, Mahfuz S, *et al*., 2021. The interaction among gut microbes, the intestinal barrier and short chain fatty acids. Animal Nutrition 9:159-174. https://doi.org/10.1016/j.aninu.2021.09.012.

Meng A, Zhang X, Pubu P, *et al*., 2024. Protective effect of lentinan against LPS-induced injury in mice via influencing antioxidant enzyme activity, inflammatory pathways and gut microbiota. Pakistan Veterinary Journal 44(3):647-656. https://doi.org/10.29261/pakvetj/2024.225.

Ou X, Chen J, Li B, *et al*., 2024. Multiomics reveals the ameliorating effect and underlying mechanism of aqueous extracts of polygonatum sibiricum rhizome on obesity and liver fat accumulation in high-fat diet-fed mice. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology 132:155843. https://doi.org/10.1016/j.phymed.2024.155843.

Pacana T and Sanyal AJ, 2012. Vitamin e and nonalcoholic fatty liver disease. Current Opinion in Clinical Nutrition and Metabolic Care 15(6):641-648. https://doi.org/10.1097/MCO.0b013e328357f747.

Panche AN, Diwan AD and Chandra SR, 2016. Flavonoids: an overview. Journal of Nutritional Science 5:e47. https://doi.org/10.1017/jns.2016.41.

Petrescu M, Vlaicu SI, Ciumărnean L, *et al*., 2022. Chronic inflammation-a link between nonalcoholic fatty liver disease (NAFLD) and dysfunctional adipose tissue. Medicina 58(5):641. https://doi.org/10.3390/medicina58050641.

Qiu H, Wen Y, Luo Y, *et al*., 2025. Gut microbiota regulates serum metabolites in mice with nonalcoholic fatty liver disease via gut metabolites: mechanisms involving branched-chain amino acids and unsaturated fatty acids. Frontiers in Endocrinology 16:1606669. https://doi.org/10.3389/fendo.2025.1606669.

Qiu Y, Zhang J, Zeng F, *et al*., 2023. Roles of the peroxisome proliferator-activated receptors (PPARs) in the pathogenesis of nonalcoholic fatty liver disease (NAFLD). Pharmacological Research 192: 106786. https://doi.org/10.1016/j.phrs.2023.106786.

Racette SB, Lin X, Lefevre M, *et al*., 2010. Dose effects of dietary phytosterols on cholesterol metabolism: a controlled feeding study. The American Journal of Clinical Nutrition 91(1):32-38. https://doi.org/10.3945/ajcn.2009.28070.

Rennert C, Heil T, Schicht G, *et al*., 2020. Prolonged lipid accumulation in cultured primary human hepatocytes rather leads to ER stress than oxidative stress. International Journal of Molecular Sciences 21(19):7097. https://doi.org/10.3390/ijms21197097.

Rinella ME, 2015. Nonalcoholic fatty liver disease: a systematic review. JAMA 313(22):2263-2273. https://doi.org/10.1001/JAMA.2015.5370.

Ruppert PMM and Kersten S, 2024. Mechanisms of hepatic fatty acid oxidation and ketogenesis during fasting. Trends in Endocrinology and Metabolism 35(2):107-124. https://doi.org/10.1016/j.tem.2023.10.002.

Shi Y and Fan J, 2022. Current status and challenges in the drug treatment for fibrotic nonalcoholic steatohepatitis. Acta Pharmacologica Sinica 43(5):1191-1199. https://doi.org/10.1038/s41401-021-00822-1.

Shi Y, Si D, Chen D, *et al*., 2023. Bioactive compounds from polygonatum genus as anti-diabetic agents with future perspectives. Food Chemistry 408:135183. https://doi.org/10.1016/j.foodchem.2022.135183.

Shi Z, Lei H, Chen G, *et al*., 2021. Impaired intestinal akkermansia muciniphila and aryl hydrocarbon receptor ligands contribute to nonalcoholic fatty liver disease in mice. MSystems 6(1):e00920-e00985. https://doi.org/10.1128/mSystems.00985-20.

Smith U and Kahn BB, 2016. Adipose tissue regulates insulin sensitivity: role of adipogenesis, de novo lipogenesis and novel lipids. Journal of Internal Medicine 280(5):465-475. https://doi.org/10.1111/joim.12540.

Sparks BB, Lima AFS, Osorio JS, *et al*., 2026. Effects of the periparturient period and parity on local innervation markers in subcutaneous adipose tissue of dairy cows. Journal of Dairy Science 109:7601-7617. https://doi.org/10.3168/jds.2025-27515.

Sun J, Sun P, Kang C, *et al*., 2022. Chemical composition and biological activities of essential oils from six lamiaceae folk medicinal plants. Frontiers in Plant Science 13:919294https://doi.org/10.3389/fpls.2022.919294.

Tan J, Wang Y, Niu H, *et al*., 2026. Hesperidin alleviates systemic inflammation and oxidative stress by remodeling adipose tissue lipid metabolism in periparturient dairy cows. Journal of Animal Science and Biotechnology 17(1):58. https://doi.org/10.1186/s40104-026-01372-4.

Tanase DM, Gosav EM, Costea CF, *et al*., 2020. The intricate relationship between type 2 diabetes mellitus (t2DM), insulin resistance (IR), and nonalcoholic fatty liver disease (NAFLD). Journal of Diabetes Research 2020:3920196. https://doi.org/10.1155/2020/3920196.

Teponno RB, Kusari S and Spiteller M, 2016. Recent advances in research on lignans and neolignans. Natural Product Reports 33(9):1044-1092. https://doi.org/10.1039/c6np00021e.

Utzschneider KM and Kahn SE, 2006. Review: the role of insulin resistance in nonalcoholic fatty liver disease. Journal of Clinical Endocrinology and Metabolism 91(12):4753-4761. https://doi.org/10.1210/jc.2006-0587.

van Baak MA and Mariman ECM, 2025. Physiology of weight regain after weight loss: latest insights. Current Obesity Reports 14(1):28. https://doi.org/10.1007/s13679-025-00619-x.

Wallace M and Metallo CM, 2020. Tracing insights into de novo lipogenesis in liver and adipose tissues. Seminars in Cell and Developmental Biology 108:65-71. https://doi.org/10.1016/j.semcdb.2020.02.012.

Wang Y, Liu N, Xue X, *et al*., 2020. Purification, structural characterization and *in-vivo* immunoregulatory activity of a novel polysaccharide from polygonatum sibiricum. International Journal of Biological Macromolecules 160:688-694. https://doi.org/10.1016/j.ijbiomac.2020.05.245.

Wei C, Yao L, Zhang L, *et al*., 2022. *In-vitro* digestion and fecal fermentation of peach gum polysaccharides with different molecular weights and their impacts on gut microbiota. Foods 11(24):3970. https://doi.org/10.3390/foods11243970.

Wink M, 2015. Modes of action of herbal medicines and plant secondary metabolites. Medicines (Basel, Switzerland) 2(3):251-286. https://doi.org/10.3390/medicines2030251.

Xi Y and Li H, 2020. Role of farnesoid x receptor in hepatic steatosis in nonalcoholic fatty liver disease. Biomedicine and Pharmacotherapy 121:109609. https://doi.org/10.1016/j.biopha.2019.109609.

Xu C, Xia B, Zhang Z, *et al*., 2023. Research progress in steroidal saponins from the genus polygonatum: chemical components, biosynthetic pathways and pharmacological effects. Phytochemistry 213:113731. https://doi.org/10.1016/j.phytochem.2023.113731.

Xu J, Sui J, Luo Y, *et al*., 2025. The protective and therapeutic effects of herbal medicines on hepatic disorders in animals. Pakistan Veterinary Journal 45(4):1491-1502. https://doi.org/10.29261/pakvetj/2025.324.

Xu R, Yang Y, Bu F, *et al*., 2026. Preliminary metabolic characterization of hepatic lipidosis in cats using liquid chromatography-mass spectrometry and gas chromatography-mass spectrometry: pathway insights and candidate biomarkers. Journal of Veterinary Internal Medicine 40(1):aalaf091. https://doi.org/10.1093/jvimsj/aalaf091.

Xu X, Pang Y and Fan X, 2025. Mitochondria in oxidative stress, inflammation and aging: from mechanisms to therapeutic advances. Signal Transduction and Targeted Therapy 10(1):190. https://doi.org/10.1038/s41392-025-02253-4.

Xu Z, Xi F, Deng X, *et al*., 2023. Osteopontin promotes macrophage m1 polarization by activation of the JAK1/STAT1/HMGB1 signaling pathway in nonalcoholic fatty liver disease. Journal of Clinical and Translational Hepatology 11(2):273-283. https://doi.org/10.14218/JCTH.2021.00474.

Yang B, Li X, Mesalam NM, *et al*., 2024. The impact of dietary supplementation of polysaccharide derived from polygonatum sibiricum on growth, antioxidant capacity, meat quality, digestive physiology, and gut microbiota in broiler chickens. Poultry Science 103(6):103675. https://doi.org/10.1016/j.psj.2024.103675.

Yang B, Sun J, Liang S, *et al*., 2021. Prediction of srebp-1 as a key target of qing gan san against MAFLD in rats via RNA-sequencing profile analysis. Frontiers in Pharmacology 12:680081. https://doi.org/10.3389/fphar.2021.680081.

Yang J, Zhang X, Dai J, *et al*., 2023. Effect of fermentation modification on the physicochemical characteristics and anti-aging related activities of polygonatum kingianum polysaccharides. International Journal of Biological Macromolecules 235:123661. https://doi.org/10.1016/j.ijbiomac.2023.123661.

Yang X, Wang X, Shi T, *et al*., 2019. Mitochondrial dysfunction in high-fat diet-induced nonalcoholic fatty liver disease: the alleviating effect and its mechanism of polygonatum kingianum. Biomedicine and Pharmacotherapy 117:109083. https://doi.org/10.1016/j.biopha.2019.109083.

Yang X, Wei J, Mu J, *et al*., 2019a. Mitochondrial metabolomic profiling for elucidating the alleviating potential of polygonatum kingianum against high-fat diet-induced nonalcoholic fatty liver disease. World Journal of Gastroenterology 25(43):6404-6415. https://doi.org/10.3748/wjg.v25.i43.6404.

Yang Y, Zhao Y, Zhang Q, *et al*., 2024. Advances in research on the efficacy of traditional chinese herbal medicine in combating african swine fever. Animal Diseases 4(1):19. https://doi.org/10.1186/s44149-024-00122-1.

Younossi ZM, Alqahtani SA, Alswat K, *et al*., 2024. Global survey of stigma among physicians and patients with nonalcoholic fatty liver disease. Journal of Hepatology 80(3):419-430. https://doi.org/10.1016/j.jhep.2023.11.004.

Yu M, Yang M, Yang T, *et al*., 2022. Relative molecular mass distribution and monosaccharide composition of polysaccharides in polygonatum kingianum var.grandifolium. Zhongguo China Journal of Chinese Materia Medica 47(13):3439-3446. https://doi.org/10.19540/j.cnki.cjcmm.20220412.101.

Zhang J, Wang J, Yang L, *et al*., 2023. Comprehensive quality evaluation of polygonatum cyrtonema and its processed product: chemical fingerprinting, determination and bioactivity. Molecules 28(11):4341. https://doi.org/10.3390/molecules28114341.

Zhang R, Gilbert S, Yao X, *et al*., 2015. Natural compound methyl protodioscin protects against intestinal inflammation through modulation of intestinal immune responses. Pharmacology Research & Perspectives 3(2):e00118. https://doi.org/10.1002/prp2.118.

Zhang Y, Sun J, Zhang X, *et al*., 2025. Structural characterisation of hawthorn polysaccharide and its mechanisms of action against non-alcoholic fatty liver disease. International Journal of Biological Macromolecules 319(Pt 4):145713. https://doi.org/10.1016/j.ijbiomac.2025.145713.

Zhao P, Li X, Wang Y, *et al*., 2020. Characterisation and saccharide mapping of polysaccharides from four common polygonatum spp. Carbohydrate Polymers 233:115836. https://doi.org/10.1016/j.carbpol.2020.115836.

Zheng Y, Liu B, Wang X, *et al*., 2026. Recognition of bioactive saponins from polygonatum based on UPLC-QTOF/MS and molecular docking. Talanta 297(Pt A):128485. https://doi.org/10.1016/j.talanta.2025.128485.

Zhou Y, Yang G, Liu H, *et al*., 2025. *Polygonatum sibiricum* polysaccharides combat fatty liver haemorrhage syndrome in hens via regulation of lipid metabolism, oxidative stress and inflammatory response. British Poultry Science 67(2):179-190. https://doi.org/10.1080/00071668.2025.2536340.

Zhu S, Liu P, Wu W, *et al*., 2022. Multi-constituents variation in medicinal crops processing: investigation of nine cycles of steam-sun drying as the processing method for the rhizome of polygonatum cyrtonema. Journal of Pharmaceutical and Biomedical Analysis 209:114497. https://doi.org/10.1016/j.jpba.2021.114497.