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# *Salidroside: A Systematic Review on Sourcing Strategies, Structural Optimization, and Multitarget Therapeutic Applications*

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***Abstract.*** Glycosides are natural compounds formed by the linkage of a sugar moiety and an aglycone via a glycosidic bond, among which O-glycosides represent the most abundant category in medicinal plants. This article focuses on salidroside, a representative O-glycoside, and provides a systematic review of its sources, preparation methods, structural modifications, and biological activities. Salidroside is primarily derived from extraction from Rhodiola plants, chemical synthesis, and biosynthesis, with various preparation approaches alleviating the issue of raw material shortage. Pharmacologically, salidroside exerts antioxidant, antitumor, anti-inflammatory, and metabolic regulatory effects by modulating key signaling pathways such as PI3K/Akt, AMPK/mTOR, and NF-κ B, thereby achieving multi-organ protection. This review aims to lay a theoretical foundation for the development of novel glycoside-based drugs.

***Keywords:*** Salidroside, Structural modification, Anti-inflammatory, Anti-oxidation

## 1. Introduction

Glycosides in traditional Chinese medicine are compounds formed by the condensation between the hemiacetal hydroxyl group of a sugar and a hydroxyl or amino group of an aglycone, resulting in a glycosidic bond. A glycoside consists of a glycone (sugar moiety) and an aglycone (non-sugar moiety). The glycone primarily influences the water solubility of the glycoside, while the aglycone, which can be classified into numerous types such as flavonoids, steroids, and alkaloids, mainly determines the biological activity and pharmacological effects of the glycoside.

This review focuses on O-glycosides, the predominant glycoside family in medicinal plants characterized by a $C_1$-O-glycosidic bond between sugar and aglycone hydroxyl groups. Phenylethanoid glycosides, particularly salidroside (tyrosol-4'-O-β-D-glucopyranoside), have gained significant research interest due to their notable antioxidant and anti-stress bioactivities Salidroside(usal) is traditionally isolated from the dried roots/rhizomes or the entire herb of Rhodiola species and is chemically classified as a phenylpropanoid glycoside [1]. Sal is readily soluble in methanol and ethanol, which are therefore the solvents of choice for its extraction. However, the content of sal in planta is extremely low [2], and Rhodiola is a second-class nationally protected plant in China; over-harvesting has caused severe ecological degradation. Chemical

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synthesis offers an important resource-sparing alternative, yet the route is time- and energy-consuming, costly and potentially contaminated by heavy-metal residues. Biosynthetic methodsemploy microbial strains or enzymes to convert tyrosol into sal in vitro, but they suffer from narrow operational windows and other technical limitations. In addition, sal possesses numerous remarkable properties, including potent antioxidant, antitumor, anti-inflammatory, immunity-enhancing, blood glucose-regulating, neuroprotective, and cardiovascular function-improving effects. Therefore, this article will focus on sal as a representative glycoside of traditional Chinese medicine, highlighting its sources and preparation methods, structural modification, and biological activities.

## 2. Source and preparation methods of Sal

### 2.1. Source of Sal

Sal is a phenylethanoid glycoside compound with significant medicinal value. It is primarily derived from plants of the genus Rhodiola within the family Crassulaceae [3], particularly from Rhodiola rosea L. and Rhodiola crenulata, which serve as the main sources. These plants typically thrive in high-altitude regions characterized by harsh conditions such as extreme cold, low oxygen levels, and intense ultraviolet radiation, including the Qinghai-Tibet Plateau, the Tianshan Mountains in Xinjiang, and the Changbai Mountains in Northeast China. Research indicates that [4] to adapt to the adverse environments of cold and hypoxia, Rhodiola plants accumulate high concentrations of active compounds like Sal in their roots and rhizomes, which function as secondary metabolites to combat environmental stress.

### 2.2. Plant extraction method

#### 2.2.1. Traditional solvent extraction method

Sal exhibits high solubility in both hot water and organic solvents (e.g., methanol/ethanol), with industrial extraction primarily utilizing two traditional methods. Water extraction, the earliest approach, employs heated decoction with water as solvent. Optimal conditions involve boiling medicinal materials with 8× (v/w) water for three 2-hour cycles to maximize Sal extraction [5]. Alcohol extraction utilizes ethanol's solvation properties, with studies demonstrating optimal parameters as 6× (v/w) 80% ethanol in two 2-hour extraction cycles, achieving maximal yields of Sal and tyrosol [6].

#### 2.2.2. Improvement methods

Wang et al. [7] optimized the extraction method of Sal by employing water extraction and alcohol precipitation. The optimal extraction conditions were as follows: decoction was performed three times, each time with 8 times the amount of water, and extraction lasted for 2 hours. During the alcohol precipitation process, the liquid concentration was 0.4 g/mL, and the ethanol concentration in the liquid was 70%. This method is simple, practical, resource-efficient, and cost-effective. To further enhance the extraction yield of Sal, Wang [8] optimized an ultrasound-assisted extraction protocol, achieving efficient preparation of sal. Under optimized conditions (70% ethanol as solvent, solid/liquid ratio of 1:19 g/mL, pH 8, 73°C extraction temperature, and 70 min processing time), a maximum extraction yield of 2.4% was attained, with the resulting product purity reaching 98%. Separately, Yu et al. [9] employed microwave-assisted extraction (MAE), reporting a relative

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standard deviation (RSD) of <7.5% and enhancement of recovery rates from 94.4% to 123%. Qian et al. [10] proposed a novel strategy using deep eutectic solvent as both the extraction solvent and dispersion liquid, with zinc oxide nanoparticles serving as the adsorbent. This approach reduces sample and solvent consumption and can serve as an alternative to traditional extraction techniques.

### 2.2.3. Comparison of advantages and disadvantages

Traditional water extraction offers simple operation and low cost, but suffers from limited extraction efficiency. Ethanol extraction can improve yield and purity by adjusting parameters such as ethanol concentration, yet it requires additional recovery equipment and incurs higher costs. The water extraction and ethanol precipitation method combines the advantages of both, ensuring low cost while improving purity, making it highly feasible for industrial applications. Ultrasound/microwave-assisted techniques significantly reduce processing time and enhance extraction yield; however, scaling up production remains challenging, limiting their suitability to small-batch, high-purity preparation. Emerging methods such as deep eutectic solvents show potential for being green and low-consumption alternatives, though the technology is not yet mature and remains largely confined to laboratory-scale research.

## 2.3. Chemical synthesis

### 2.3.1. Classical route - direct glucosylation method

The classical method for the chemical synthesis of Sal involves direct glycosylation of tyrosol. In 1969, Soviet scholar Troshenko A.T. was the first to apply the Koenigs-Knorr glycosylation reaction to the synthesis of sal, providing a reproducible synthetic route. The process involves an O-glycosylation reaction between p-hydroxy phenethyl alcohol and bromo-tetraacetylglucose, followed by saponification to remove the acetyl groups, yielding Sal and its analogs. The experimental procedure is illustrated in Figure 1 [11].

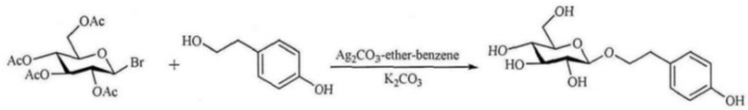


Figure 1. Synthesis of Sal from tyrosol [11]

### 2.3.2. Glycosylation after phenolic hydroxy protection

(1)Guo et al. [12] used benzyl protection for the phenolic hydroxyl group of tyrosol: First, the phenolic hydroxyl group of p-hydroxyphenyl ethanol was protected with a benzoyl group, followed by a glycosylation reaction with D-glucose pentaacetate in a mixture of ethyl ether, dichloromethane, and boron trifluoride. Finally, hydrogenation reduction was performed to obtain Sal. Guo et al. [13] used benzoyl protection for the phenolic hydroxyl group of tyrosol: First, benzoyl chloride was reacted with p-hydroxyphenyl ethanol to produce 2-(4-benzoyloxyphenyl)-ethanol. Then, the hydroxyl groups of glucose were protected by reacting it with pyridine and isobutyryl chloride. Subsequently, 2-(4-benzoyloxyphenyl)-ethanol was reacted with 1,2,3,4,6-O-pentaisobutyryl glucose to form 1-[2-(4-benzoyloxyphenyl) ethyl]-2,3,4,6-O-tetraisobutyryl-β-D-glucopyranoside. Finally, alcoholysis was carried out in a sodium methoxide methanol solution to obtain Sal. Deng et al. [14] used acylating reagents to protect the phenolic hydroxyl group of tyrosol: First, the phenolic hydroxyl and alcohol hydroxyl groups of p-hydroxyphenyl ethanol were

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acetylated. Then, a glycosylation reaction was catalyzed by silver carbonate with bromotetraacetyl glucose. Finally, saponification was performed in a sodium methoxide methanol solution to obtain Sal.

#### 2.3.3. Comparison of advantages and disadvantages

Although the direct glycosylation of tyrosol offers a concise synthetic route with low production costs, the parallel reactivity of phenolic and alcoholic hydroxyl groups leads to substantial byproduct formation, challenging product isolation and yielding inferior purity. In contrast, phenol hydroxyl protection via benzylation or benzoylation enhances selectivity and purity. However, the benzyl approach involves cumbersome steps that increase cost and operational complexity, while the benzoyl method—despite effective protection and minimal side reactions—requires toxic reagents such as benzoyl chloride or isobutyryl chloride. Alternatively, phenolic hydroxyl protection through acylation effectively safeguards the phenol group and ensures high product purity. Nevertheless, this approach suffers from practical limitations including costly/unstable silver carbonate catalysts, intricate preparation of brominated sugar donors, and reliance on time-consuming column chromatography for purification, thus impeding industrial-scale implementation.

### 2.4. Biosynthesis method

#### 2.4.1. Enzyme catalysis method

In the study of Sal biosynthesis via enzymatic methods, the core reaction mechanism involves the glycosylation reaction between the substrate tyrosol and glucose molecules under the catalysis of specific enzymes. This process forms specific glycosidic bonds to ultimately produce the target compound, Sal. The academic community currently recognizes two primary mechanisms for glycoside synthesis reactions [15]: (1) Direct Glycosylation Reaction: Under the direct and specific catalysis of β-glucosidase, the reaction system utilizes monosaccharide molecules as glycosyl donors and nucleophilic alcohols as glycosyl acceptors. These two components directly undergo glycosylation to form glycosides. For example, Yang et al. [16] developed a fermentation-based conversion method for Sal production. They constructed an enzymatic catalysis system by fermenting recombinant E. coli to produce glucosyltransferase. Using glucose and tyrosol as substrates, they achieved Sal production with a maximum yield of 9206.0 mg/L and a tyrosol conversion rate exceeding 80.0%. (2) Transglycosylation involves the enzyme-catalyzed transfer of a glycosyl unit from sugar donors to nucleophilic alcohol acceptors, enabling directional glycoside synthesis. Diverse saccharides—including disaccharides and oligosaccharides—commonly serve as glycosyl donors in such systems. Torrens-Spence et al. [17] first identified 4-hydroxyphenylacetaldehyde synthase (Rr4HPAAS) from Rhodiola rosea, then heterologously co-expressed 34 glycosyltransferase candidate genes in Saccharomyces cerevisiae engineered for Rr4HPAAS production. Screening revealed three alcohol hydroxyl-specific glycosyltransferases (RrUGT29, RrUGT32, RrUGT33) from R. rosea capable of catalyzing sal biosynthesis in both S. cerevisiae and Nicotiana benthamiana.

#### 2.4.2. Synthesis via genetic engineering

The terminal reaction in sal biosynthesis—tyrosol glycosylation—is catalyzed by uridine diphosphate glucosyltransferase (UGT) [18]. Given the genetic diversity of Rhodiola UGTs and their differential impact on sal accumulation, cloning UGT genes proves essential for screening

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high-activity UDP-glucosyltransferases and subsequent sal synthesis. Xue et al. [19]achieved high-yield expression of codon-optimized UGT72B14 in E coli, enabling efficient sal production via fed-batch fermentation. Concurrently, Zeng et al. engineered an E. coli platform for de novo sal biosynthesis by modifying the ARO10 and ADH6 genes for tyrosol precursor synthesis, introducing heterologous glucosyltransferase UGT85A1, and overexpressing endogenous pgm and galU. This optimized strain produced 16.8 g/L sal with a productivity of 0.4 g/L·h in a 5-L bioreactor.

#### 2.4.3. Comparison of advantages and disadvantages

The enzymatic synthesis of Sal offers advantages such as high specificity, high product purity, mild reaction conditions, simple equipment requirements, and energy efficiency. However, its application is constrained by the high cost of enzyme purification and the poor stability of certain enzymes, which leads to inactivation and reduced synthesis efficiency. In contrast, genetic engineering approaches enable autonomous synthesis through engineered microorganisms without requiring precursor compounds, while also allowing genetic modifications to enhance yield and quality. Nevertheless, these methods face challenges including high technical complexity, potential instability of engineered strains, and increased purification costs due to fermentation byproducts.

## 3. Biological activities of Sal

### 3.1. Antioxidation

Oxidative stress refers to a pathological state characterized by an imbalance between the production and clearance of oxidative substances, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to the accumulation of oxidative damage. Studies have found that Sal can effectively counteract damage caused by oxidative stress in multiple organs. Regarding the heart, Chen et al. [20] discovered that Sal significantly alleviates LPS-induced myocardial injury by inhibiting the ROS-mediated PI3K/Akt/mTOR pathway. In the liver, Yang et al. [21] confirmed that Sal reduces oxidative stress in rats with Non-Alcoholic Fatty Liver Disease (NAFLD). Further research demonstrates its protective effects on pulmonary vessels. Lei et al. [22] investigated the protective role of Sal in pulmonary arterial endothelial cells, finding that it safeguards these cells against hypoxia-induced apoptosis via the AhR/NF-κB and Nrf2/HO-1 pathways. Additionally, Sal shows potential in kidney protection. Its mechanism involves regulating iron transport-related proteins and ferroptosis-related proteins, significantly reducing renal lipid peroxidation levels, thereby delaying renal aging and inhibiting glomerular fibrosis [23]. In summary, multiple studies consistently indicate that Sal is an effective inhibitor of multi-organ oxidative stress damage and exhibits protective effects on vital organs such as the heart, liver, lungs, and kidneys.

### 3.2. Antitumor effects

Studies indicate that Sal exerts broad antitumor effects primarily by inducing tumor cell apoptosis, inhibiting proliferation, metastasis, and invasion, through multi-target mechanisms. For instance, in lung cancer research, Ben et al. [24] found that Sal downregulates the activity of the PI3K/Akt/mTOR signaling pathway, promotes autophagy in the A549 lung cancer cell line, thereby significantly inhibiting cell proliferation and inducing apoptosis. In research on urological tumors, Chen et al. [25] confirmed that Sal effectively inhibits the proliferation, migration, and invasion of renal cell carcinoma (RCC, ACHN andA498 cell lines) and induces apoptosis. More importantly, it also demonstrated significant in vivo antitumor effects and good safety in nude mouse xenograft

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models. In studies on female reproductive system tumors, Bai et al. [26] observed that Sal markedly alters the morphology and growth state of ovarian cancer SKOV3 cells, inhibits proliferation, and promotes apoptosis. Its mechanism of action may involve upregulating the expression levels of tumor suppressor genes ARID1A, PTEN, and FHIT. Additionally, it is noteworthy that Sal shows potential in cancer adjuvant therapy. As an example of a radioprotective agent, research shows that Salcan protect salivary glands from radiation-induced damage by mitigating radiotherapy-induced mitochondrial oxidative stress [27], suggesting its potential value in improving the side effects of radiotherapy in cancer patients.

## 3.3. Anti-inflammatory and immunomodulatory effects

### 3.3.1. Neuroinflammatory diseases

Neuroinflammation is a crucial defense mechanism mediated by glial cells (especially microglia) within the central nervous system. However, its excessive or chronic activation becomes a common pathological feature of various neurological diseases, leading to neurodegeneration. Research shows that Sal can effectively modulate the neuroinflammatory process and exert neuroprotective effects, which are closely related to its regulation of microglial state and autophagic flux. Xiao et al. [28] first confirmed this effect: in a mouse model of septic encephalopathy, Sal exerted neuroprotective effects by activating the silent information regulator 1(Sirt1) pathway to promote autophagy. Similarly, in the field of spinal cord functional recovery, Wang et al. [29] found that Sal significantly improved functional recovery after spinal cord injury in rats. The core mechanism involves stimulating autophagic flux via the AMPK/mTOR signaling pathway, thereby regulating the polarization of microglia toward a beneficial phenotype. Extending further to neurodegenerative diseases, Gao et al. [30] showed that Sal also has positive effects in a rat model of Alzheimer's disease, suggesting its broad applicability. Notably, microglia-driven chronic neuroinflammation is also considered a key pathological factor in depression. Fan et al. [31] specifically focused on this point, finding that Sal significantly improved chronic stress-induced depressive symptoms by effectively inhibiting the activation of pathological microglia, highlighting its great application value in neurological immunomodulation.

### 3.3.2. Colitis

Colitis is an inflammatory bowel disease characterized by diarrhea, abdominal pain, weight loss, and rectal bleeding. Liu et al. [32] established two colitis models with different causes of intestinal mucosal damage: acute colitis induced by dextran sulfate sodium (DSS) and an obese mouse model induced by a high-fat diet (HFD). Studies showed that Sal has therapeutic effects on both models. It reduces intestinal mucosal barrier permeability by enhancing the physical and immune barriers, exerting pharmacological effects against acute and chronic colitis. Nitric oxide (NO), an important inflammatory mediator produced mainly by inducible nitric oxide synthase (iNOS), is involved in the pathogenesis of ulcerative colitis. Guo et al. [33] investigated the treatment of UC mice with Sal combined with iNOS small hairpin RNA (shRNA). The results indicated that the combined use effectively treated DSS-induced ulcerative colitis. Li et al. [34] found that Sal could alleviate the inflammatory response in DSS-induced colitis mice by regulating the Sirt1/FoxO3a pathway. The above evidence indicates the great application potential of Sal in treating colitis.

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#### 3.3.3. Osteoarthritis (OA)

Osteoarthritis is a degenerative joint disorder, involves pathological mechanisms including inflammation, metabolic dysregulation, and cellular senescence. Emerging evidence demonstrates sal therapeutic potential through multi-target modulation. Meng et al. [35] identified sal ferroptosis-regulating capacity in lipopolysaccharide-induced OA models, showing chondroprotective effects without cytotoxicity in ATDC5 cells. Chen et al. [36] elucidated sal dual inhibition of TLR4/NF-κ B and HIF pathways, effectively suppressing inflammation and apoptosis. Complementary in vivo studies by Cai et al. [37] revealed sal ability to reduce joint swelling and enhance cartilage repair in monoiodoacetate-induced OA rats, mediated through NF-κ B pathway suppression. Collectively, these findings establish Sal as a multi-mechanistic agent targeting OA progression via anti-inflammatory, anti-apoptotic, and tissue-repair regulatory actions.

### 3.4. Metabolic regulation

#### 3.4.1. Fatty liver disease

The core pathogenesis of NAFLD involves the interaction of multiple pathways: disordered hepatic lipid metabolism, oxidative stress, sustained activation of inflammatory signals, gut microbiota-liver axis dysfunction, and imbalance in apoptosis/autophagy. Research shows that Sal ameliorates these pathological processes by synergistically regulating multiple targets: it not only reduces hepatic lipid deposition (inhibiting disordered lipid metabolism) [38] by activating the AMPK-dependent pathway to downregulate TXNIP/NLRP3 inflammasome activity , but also alleviates liver injury and steatosis [21] by inhibiting key mediators of oxidative stress—reducing the activity of CYP2E1 enzyme and Nox2, thereby decreasing free radical production; at the level of inflammation regulation, Sal effectively inhibits NF-κ B signaling (blocking the inflammatory cascade) [39] by downregulating the phosphorylation levels of Iκ B kinase β (Ikkβ) and the NF-κ B p65 subunit, while enhancing IκBα stability ; furthermore, Sal remodels the gut microbiota-bile acid metabolism axis and activates the farnesoid X receptor (FXR), improving pathological changes [40] in NAFLD induced by a high-fat diet; notably, supplementation with the natural product Sal can antagonize concanavalin A (ConA)-induced hepatocyte apoptosis (regulating cell death pathways) [41] by activating the PI3K/Akt pathway, suggesting that Sal may share similar anti-apoptotic mechanisms, collectively forming a multi-dimensional therapeutic strategy for intervening in NAFLD.

#### 3.4.2. Diabetes

Diabetes is a metabolic disorder characterized primarily by elevated blood glucose levels due to insufficient insulin secretion or reduced tissue sensitivity to insulin. Insulin resistance, a metabolic state where insulin cannot effectively regulate tissue and cellular uptake and utilization of glucose, is a key mechanism in the pathogenesis of type 2 diabetes. Bai et al. [42] found that Sal could improve insulin resistance in skeletal muscle cells of mice by activating the AMPK/Sirt1 signaling pathway and inhibiting mitochondrial ROS production. The cause of type 1 diabetes is a rapid, massive decrease in pancreatic β-cell numbers due to autoimmunity. Pancreatic and duodenal homeobox 1 (PDX1) is an essential transcription factor for maintaining β-cell function and survival, while forkhead box transcription factor O1 (FoxO1), a negative regulator of PDX1 function, mediates β-cell dysfunction and apoptosis. Ju et al. [43] found that in diabetic db/db and high-fat diet-induced mice, Sal inhibited FoxO1 by activating AMPK/Akt, thereby restoring PDX1 nuclear localization to

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alleviate high glucose-mediated oxidative stress and improve pancreatic β-cell survival. Additionally, Sal intervention reversed the loss of retinal ganglion cells in streptozotocin (STZ)-induced diabetic rats, preventing diabetic retinopathy (DR), possibly by regulating the PI3K/Akt/GSK-3β/NF-κ B signaling pathway [44] .

## 4. Conclusion

Glycosides from traditional Chinese medicine are key bioactive molecules, with structural and functional properties determined by glycone solubility and aglycone efficacy. This review focuses on sal, a representative O-glycoside, summarizing its sources, preparation strategies, structural modifications, and biological functions. Key findings include: ① Preparation Bottlenecks and Advances: Traditional plant extraction is constrained by resource scarcity; chemical synthesis faces high pollution and cost issues; biosynthesis offers an eco-friendly alternative but requires improvements in enzyme stability and engineered strain optimization. ② Multifaceted Biological Effects: Salidroside exhibits multi-target therapeutic potential, including antioxidant, antitumor, anti-inflammatory, and metabolic regulation via pathways like PI3K/Akt, AMPK/mTOR, and NF-κB. Current shortcomings involve unbalanced preparation efficiency, cost, and sustainability; toxic reagents in synthesis; instability in biosynthesis; lab-stage modifications; and incomplete elucidation of molecular mechanisms hindering clinical translation. Future research should prioritize green, scalable production technologies and novel glycoside derivatives to accelerate drug development.

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