

RESEARCH MONOGRAPH . COMPOUND PROFILE

Salidroside

A naturally occurring phenylethanol glycoside isolated from Rhodiola rosea and related Crassulaceae species, characterized by activation of the AMPK/Nrf2 axis and inhibition of NF-kappaB-driven inflammation, with a broad preclinical evidence base spanning neuroprotection, cardioprotection, metabolic regulation, and anti-tumor activity, and emerging clinical evidence in stress adaptation and exercise performance.

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ABSTRACT

Salidroside (2-(4-hydroxyphenyl)ethyl beta-D-glucopyranoside; CAS 10338-51-9) is the principal bioactive glycoside of the adaptogenic plant *Rhodiola rosea* L. and related *Rhodiola* species of the family Crassulaceae. It is the 8-O-beta-D-glucoside of tyrosol (4-hydroxyphenylethanol), a simple phenylethanol aglycone that is also the primary circulating metabolite of salidroside following oral administration. The compound has been used in traditional Tibetan, Chinese, and Scandinavian medicine for centuries as a general tonic and adaptogen, and modern pharmacological investigation has identified a remarkably diverse spectrum of biological activities centered on three principal molecular mechanisms: activation of the AMP-activated protein kinase (AMPK) signaling cascade with downstream engagement of the PI3K/Akt/GSK3beta and SIRT1 pathways; activation of the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) antioxidant response axis; and suppression of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB) pro-inflammatory transcriptional program with consequent reduction of tumor necrosis factor alpha, interleukin-1 beta, interleukin-6, and NLRP3 inflammasome activation.

Preclinical pharmacology studies conducted across multiple organ systems have demonstrated neuroprotective efficacy in models of cerebral ischemia/reperfusion injury, Alzheimer's disease (amyloid beta-induced neurotoxicity and ferroptosis), Parkinson's disease (MPTP and 6-OHDA models), traumatic brain injury, and depression; cardioprotective activity against ischemia/reperfusion injury, doxorubicin-induced cardiotoxicity,

and atherosclerosis; hepatoprotective effects against carbon tetrachloride and high-fat-diet-induced liver injury and nonalcoholic steatohepatitis; antidiabetic activity through amelioration of insulin resistance via the mitochondria-associated AMPK/PI3K/Akt/GSK3 β pathway; renoprotective effects in diabetic nephropathy; and anti-tumor activity in breast, lung, colorectal, and gastric cancer models through inhibition of proliferation, migration, and invasion via the AKT and MEK/ERK signaling pathways.

Pharmacokinetics in rodents are characterized by rapid oral absorption (T_{max} approximately 0.5 to 1 hour), moderate oral bioavailability (approximately 20 to 32 percent in rats), extensive first-pass metabolism to the aglycone p-tyrosol by intestinal and hepatic beta-glucosidases, wide tissue distribution with preferential accumulation in kidney, liver, and heart, and renal elimination of conjugated metabolites. The compound crosses the blood-brain barrier. Salidroside demonstrates a favorable safety profile: the acute oral LD₅₀ in rats exceeds 5000 mg/kg body weight, and subchronic toxicity studies at doses up to 100 mg/kg/day have not produced organ toxicity, genotoxicity, or teratogenicity at the studied doses.

Human clinical evidence remains limited relative to the preclinical literature. *Rhodiola rosea* standardized extracts containing salidroside (typically standardized to 1 to 3 percent salidroside) have demonstrated efficacy in randomized controlled trials for stress-related fatigue, mild to moderate depression, generalized anxiety, and cognitive function under stress conditions. A 2024 exploratory randomized double-blind placebo-controlled trial of pure biosynthetic salidroside at 60 mg/day for 16 days in healthy active young adults demonstrated enhanced oxygen utilization

during high-intensity intermittent exercise, stable mood states, and mitigated exercise-induced muscle damage. A randomized controlled trial of 60 breast cancer patients reported no clinical adverse events during salidroside administration as adjunctive therapy.

This monograph reviews the chemistry, natural and synthetic sources, and structural pharmacology of salidroside; the multi-target molecular mechanisms across the AMPK, Nrf2, and NF-kappaB axes; the comprehensive preclinical pharmacology across neurological, cardiovascular, metabolic, hepatic, renal, and oncological models; the available human pharmacokinetic and clinical evidence; sourcing, quality verification, and standardization considerations; reconstitution and handling protocols; stack-interaction implications; adverse-event and safety signal characterization; and a structured comparative assessment of five adaptogenic or neuroprotective compounds against salidroside on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Salidroside (not assigned a formal INN; the name salidroside is the universally adopted pharmacological designation derived from the genus *Salix*, from which the compound was first isolated).

Common names and synonyms: Rhodioloside, rhodioside, rhodosin, salidrozyd. The name rhodioloside reflects the principal botanical source (*Rhodiola rosea* L.) and is used interchangeably with salidroside in the phytochemical literature.

Chemical Abstracts Service registry number: 10338-51-9.

International Union of Pure and Applied Chemistry name: 2-(4-hydroxyphenyl)ethyl beta-D-glucopyranoside. The compound is the beta-D-glucopyranoside of tyrosol (4-(2-hydroxyethyl)phenol), formed by a beta-glycosidic bond between the anomeric carbon of D-glucose and the primary hydroxyl of the tyrosol side chain.

PubChem CID: 159278.

DrugBank accession: DB13087.

UNII: M983H6N1S9.

1.2 Structural class and chemistry

Salidroside belongs to the phenylpropanoid glycoside class, specifically the phenylethanoid glycosides. It is structurally one of the simplest members of this class, consisting of a single glucose unit conjugated to the aglycone tyrosol. The structural simplicity distinguishes salidroside from the more elaborate phenylethanoid glycosides such as acteoside (verbascoside), which carry additional phenylpropanoid acyl substitutions on the sugar moiety.

Molecular formula: C₁₄H₂₀O₇.

Exact mass: 300.1209 g/mol (monoisotopic).

Molecular weight: 300.31 g/mol.

Physical properties: White to light brown crystalline powder. Freely soluble in water, methanol, and ethanol; poorly soluble in diethyl ether and other apolar organic solvents. Melting point is approximately 159 to 160 degrees Celsius. The compound is optically active owing to the glucose stereochemistry. Specific optical rotation $[\alpha]_D$ is approximately -58 degrees ($c = 1$, water). The compound has a characteristic bitter taste.

Stereochemistry: Salidroside contains four stereocenters, all within the D-glucopyranose ring, in the beta-D-glucopyranoside configuration. The aglycone tyrosol portion is achiral. The natural product is exclusively the beta-anomeric form; alpha-glucoside salidroside analogs have been synthesized for structure-activity studies but are not natural products and are not commercially supplied as reference standards.

1.3 Synthesis

Salidroside can be obtained by extraction from natural sources or by chemical and enzymatic synthesis.

Extraction from plant sources. The traditional source is the root and rhizome of *Rhodiola rosea* L. (family Crassulaceae), which contains approximately 0.1 to 1.0 percent salidroside by dry weight depending on the cultivar, harvest season, and geographic origin. *Rhodiola crenulata*, a related species used in traditional Chinese medicine, contains higher concentrations of salidroside (up to 2 to 3 percent by dry weight) and is a commercially important source. Extraction is typically performed with aqueous ethanol (50 to 70 percent ethanol) followed by concentration, liquid-liquid partitioning, and chromatographic purification (silica gel, Sephadex LH-20, or preparative high-performance liquid chromatography).

Chemical synthesis. The Koenigs-Knorr glycosylation of tyrosol with peracetylated alpha-D-glucopyranosyl bromide in the presence of a silver or mercury catalyst, followed by base-mediated deprotection of the acetyl groups, provides salidroside in moderate yield (40 to 60 percent). Alternative chemical glycosylation strategies using trichloroacetimidate donors (Schmidt glycosylation) have been reported with improved stereoselectivity for the beta-anomer [1, 2].

Enzymatic and biosynthetic production. The biosynthetic pathway in *Rhodiola* species proceeds from tyrosine through tyramine or 4-hydroxyphenylpyruvate to tyrosol, which is then glucosylated by a UDP-glucosyltransferase (UGT) to form salidroside. Multiple UGT enzymes capable of this transformation have been characterized: UGT72B14 and UGT74R1 from *Rhodiola sachalinensis*, and UGT85A1 from *Arabidopsis thaliana* [3, 4]. Recombinant expression of these enzymes in *Escherichia coli*, coupled with UDP-glucose regeneration systems (sucrose synthase-mediated in situ regeneration of UDP-glucose from sucrose), has achieved industrial-scale biosynthetic production of salidroside at titers of 6.0 g/L with molar conversions exceeding 99 percent [5]. Biosynthetic salidroside is chemically identical to the natural product and is the source for the emerging supply of pure, nature-identical salidroside for research and clinical applications.

2. Abstract

Salidroside (CAS 10338-51-9) is the principal bioactive phenylpropanoid glycoside of *Rhodiola rosea* L. and related *Rhodiola* species, consisting of tyrosol conjugated at its primary hydroxyl to beta-D-glucopyranose. The compound has been a component of traditional adaptogenic medicine in Tibetan, Chinese, Russian, and Scandinavian pharmacopoeias for centuries and has become the subject of intensive modern pharmacological investigation beginning in the late twentieth century [6, 7].

The molecular pharmacology of salidroside is pleiotropic, engaging at least three principal signaling axes. First, salidroside activates AMP-activated protein kinase (AMPK), a master metabolic sensor, with downstream engagement of the PI3K/Akt, mTOR, SIRT1, and PGC-1alpha pathways that collectively modulate cellular energy homeostasis, mitochondrial biogenesis, autophagy, and insulin signaling [8, 9]. Second, salidroside activates the Nrf2/ARE transcriptional program, upregulating phase II detoxification enzymes and antioxidant proteins including heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1), and glutathione S-transferases, conferring cytoprotection against oxidative stress across multiple cell types [10, 11]. Third, salidroside suppresses NF-kappaB nuclear translocation and transcriptional activity, reducing the expression of pro-inflammatory cytokines (TNF-alpha, IL-1beta, IL-6), adhesion molecules (VCAM-1, ICAM-1), and NLRP3 inflammasome components [12, 13].

These molecular mechanisms converge to produce a preclinical pharmacology profile of unusual breadth. Neuroprotective activity has been demonstrated in models of cerebral ischemia/reperfusion, Alzheimer's disease, Parkinson's disease, depression, and traumatic brain injury [14, 15, 16]. Cardioprotective activity has been observed in ischemia/reperfusion, doxorubicin cardiotoxicity, and atherosclerosis models [17, 18]. Metabolic regulation includes amelioration of insulin resistance and protection against diabetic nephropathy and nonalcoholic steatohepatitis [9, 19, 20]. Anti-tumor activity has been reported in breast, lung, colorectal, and gastric cancer models [21, 22].

Clinical evidence in humans derives principally from studies of *Rhodiola rosea* standardized extracts (containing salidroside among other active constituents) and from a small number of studies using pure salidroside. *Rhodiola* extracts have demonstrated efficacy in stress-related fatigue, mild to moderate depression, generalized anxiety, and cognitive function [23, 24, 25]. A 2024 randomized controlled trial of pure biosynthetic salidroside (60 mg/day for 16 days) in healthy young adults reported enhanced exercise performance and mitigated exercise-induced damage [26]. The compound has a favorable safety profile: acute oral LD50 exceeds 5000 mg/kg in rats, and no genotoxicity, teratogenicity, or organ toxicity has been observed at studied doses [27, 28].

3. Discovery and Development History

3.1 Traditional use and early phytochemistry

The genus *Rhodiola*, comprising approximately 90 species distributed across the high-altitude and high-latitude regions of Europe, Asia, and North America, has been used in traditional medicine systems for at least two millennia. *Rhodiola rosea* L. (golden root, Arctic root, roseroot) appears in the traditional pharmacopoeias of Tibet, China, Mongolia, Russia, and Scandinavia as a general tonic, adaptogen, and treatment for fatigue, altitude sickness, depression, and impotence [6, 29]. The first Western botanical description was by Carl Linnaeus in 1749. The Russian pharmacopoeia formally included *Rhodiola rosea* preparations in 1969 on the basis of Soviet-era adaptogen research conducted at the Tomsk State University and the Soviet Academy of Sciences.

The isolation of salidroside from *Rhodiola rosea* was first reported by Thieme in 1969 [30]. The compound had previously been identified in *Salix* (willow) bark, from which the name salidroside derives. Subsequent phytochemical studies identified salidroside as a major constituent of all commercially important *Rhodiola* species, with content varying from approximately 0.1 percent in some *Rhodiola rosea* chemotypes to 2 to 3 percent in *Rhodiola crenulata* [31].

3.2 Soviet adaptogen research

The concept of adaptogens, substances that increase nonspecific resistance to stress without disturbing normal physiological function, was formalized by the Soviet pharmacologist Nikolai Lazarev in 1947 and developed by Israel Brekhman and colleagues at the Soviet Academy of Sciences in Vladivostok. *Rhodiola rosea* was classified as an adaptogen by this school, and extensive (though incompletely published in Western journals) Soviet research from the 1960s through the 1980s characterized the stress-protective, anti-fatigue, cognitive-enhancing, and cardio-protective properties of *Rhodiola* extracts [29, 32]. Much of this research used crude or partially standardized *Rhodiola rosea* extracts, and the specific contribution of salidroside to the observed pharmacological effects was not separated from the contributions of rosavins (rosavin, rosin, rosarin) and other constituents.

3.3 Modern pharmacological characterization

Beginning in the 1990s, research groups in China, Japan, Europe, and the United States undertook systematic pharmacological characterization of purified salidroside. The neuroprotective properties were among the earliest to be rigorously characterized, with Chinese research groups demonstrating protection against hypoxic injury in cortical neurons and against oxidative stress in PC12 cells [14, 33]. The AMPK activation mechanism was formally characterized by Li et al. (2008), and the Nrf2/HO-1 antioxidant axis engagement was reported by Zhang et al. (2013) [8, 10]. The anti-inflammatory mechanism through NF-kappaB suppression was characterized across multiple systems by Zheng et al. (2015) and Gao et al. (2016) [12, 13].

3.4 Biosynthetic production and clinical translation

The development of enzymatic biosynthesis methods for salidroside, beginning with the characterization of the *Rhodiola sachalinensis* UGT72B14 and UGT74R1 glucosyltransferases by Yu et al. (2011) [4], and culminating in high-efficiency cascade biocatalysis systems achieving gram-per-liter titers [5], enabled the production of pure, nature-identical salidroside at scale sufficient for clinical research. The availability of pure salidroside, rather than multi-component *Rhodiola* extracts, has permitted the first clinical studies attributing effects specifically to salidroside rather than to the extract as a whole. The 2024 exercise performance trial by Keogh et al. represents the first published randomized controlled trial of pure biosynthetic salidroside in humans [26].

4. Mechanism of Action

Salidroside is a multi-target compound whose pharmacological activities arise from the engagement of several interconnected intracellular signaling cascades. Unlike receptor-targeted drugs with defined binding sites, salidroside modulates cellular responses through interactions with upstream regulatory kinases and transcription factors that converge on broad cytoprotective, anti-inflammatory, and metabolic outcomes.

4.1 AMPK activation and downstream metabolic signaling

AMP-activated protein kinase (AMPK) is a heterotrimeric serine/threonine kinase that serves as a cellular energy sensor, activated by increases in the AMP-to-ATP ratio during metabolic stress. Salidroside activates AMPK through phosphorylation of the alpha subunit at Thr172, as demonstrated in multiple cell types including hepatocytes, skeletal muscle cells, endothelial cells, and neurons [8, 9, 34].

Downstream consequences of AMPK activation by salidroside include: activation of the PI3K/Akt pathway with enhanced glucose transporter 4 (GLUT4) translocation and glucose uptake in skeletal muscle, providing the molecular basis for the antidiabetic activity; phosphorylation and inactivation of glycogen synthase kinase 3 beta (GSK3beta), which contributes to neuroprotection and glycogen metabolism; activation of SIRT1, a NAD-dependent protein deacetylase that deacetylates PGC-1alpha and promotes mitochondrial biogenesis; and inhibition of mTOR complex 1 (mTORC1), promoting autophagy and suppressing protein synthesis, a mechanism relevant to both the anti-tumor and neuroprotective activities [8, 9].

The AMPK activation has been demonstrated to be upstream of many of the compound's other signaling effects. Pharmacological inhibition of AMPK by compound C (dorsomorphin) or siRNA knockdown of AMPKalpha abolishes the anti-inflammatory, antioxidant, and metabolic effects of salidroside in multiple experimental systems, confirming AMPK as a critical node in the compound's mechanism of action [12, 34].

4.2 Nrf2/HO-1 antioxidant response

The nuclear factor erythroid 2-related factor 2 (Nrf2) is a cap'n'collar basic leucine zipper transcription factor that, under oxidative stress conditions, dissociates from its cytoplasmic repressor Kelch-like ECH-associated protein 1 (Keap1), translocates to the nucleus, and binds antioxidant response elements (AREs) in the promoter regions of cytoprotective genes. Salidroside promotes Nrf2 nuclear translocation and transcriptional activity, upregulating the expression of heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1), superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) [10, 11].

The Nrf2 activation by salidroside is at least partially dependent on upstream AMPK activation, as AMPK-mediated phosphorylation of Nrf2 at Ser550 promotes its nuclear accumulation. Additionally, salidroside may engage the PI3K/Akt pathway independently to phosphorylate Nrf2 and promote its dissociation from Keap1 [10].

In models of Alzheimer's disease, salidroside has been shown to attenuate neuronal ferroptosis (iron-dependent cell death driven by lipid peroxidation) through activation of the Nrf2/HO-1 signaling pathway in amyloid beta 1-42-induced Alzheimer's disease mice and in glutamate-injured HT22 hippocampal cells [15]. This anti-ferroptotic mechanism represents a relatively recently characterized neuroprotective pathway for the compound.

4.3 NF-kappaB suppression and anti-inflammatory signaling

Salidroside inhibits the nuclear translocation and transcriptional activity of NF-kappaB through multiple upstream mechanisms. In endothelial cells stimulated by advanced glycation end-products (AGEs), salidroside activates AMPK, which suppresses the phosphorylation and nuclear translocation of NF-kappaB p65 and inhibits the activation of the NLRP3 inflammasome, reducing the production of IL-1beta, TNF-alpha, and IL-6, and decreasing the expression of vascular adhesion molecules VCAM-1 and ICAM-1 [12, 13].

In macrophages stimulated by lipopolysaccharide (LPS), salidroside suppresses the TLR4/MyD88/NF-kappaB signaling cascade, reducing inducible nitric oxide synthase (iNOS) expression, cyclooxygenase-2 (COX-2) expression, and nitric oxide pro-

duction [35]. The AMPK-SIRT1 axis contributes to this anti-inflammatory mechanism by deacetylating NF-kappaB p65, reducing its transcriptional activity even when nuclear translocation is not fully prevented.

In models of cerebral ischemia, salidroside modulates microglial polarization from the pro-inflammatory M1 phenotype toward the anti-inflammatory M2 phenotype, reducing the production of inflammatory mediators and promoting the release of neurotrophic factors including brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF) [16].

4.4 Additional signaling mechanisms

MAPK pathway modulation. Salidroside modulates mitogen-activated protein kinase (MAPK) signaling, including the ERK1/2, JNK, and p38 MAPK cascades. In inflammatory models, salidroside inhibits the phosphorylation of p38 and JNK while variably affecting ERK1/2, depending on cell type and stimulus. In cancer models, inhibition of the MEK/ERK pathway contributes to anti-proliferative activity [21, 36].

Apoptosis regulation. Salidroside demonstrates bidirectional modulation of apoptosis. In normal cells under stress conditions (ischemia, oxidative injury, neurotoxin exposure), salidroside is anti-apoptotic, suppressing caspase-3 and caspase-9 activation, upregulating Bcl-2, and downregulating Bax through the mitochondrial intrinsic pathway. In cancer cells, salidroside promotes apoptosis through the same mitochondrial pathway, an apparent paradox resolved by the dependence on cellular context and the status of upstream survival signaling [21, 37].

HPA axis modulation. In rodent models of chronic stress, salidroside normalizes hypothalamus-pituitary-adrenal (HPA) axis hyperactivation, reducing elevated corticosterone levels and restoring hippocampal glucocorticoid receptor expression. This mechanism contributes to the adaptogenic and antidepressant activities [38].

Dopaminergic system. Salidroside maintains monoamine neurotransmitter levels in the dopaminergic system. In models of cerebral ischemia/reperfusion injury, salidroside preserves dopamine, norepinephrine, and serotonin levels in the striatum and prefrontal cortex, contributing to behavioral recovery [39].

4.5 Composite pharmacology

The composite pharmacology of salidroside is characteristic of a pleiotropic natural product that engages multiple convergent pathways rather than a single molecular target. The AMPK activation appears to be the most upstream initiating event in many systems, with Nrf2 activation and NF-kappaB suppression operating as downstream or parallel effector arms. The therapeutic consequence is broad-spectrum cytoprotection, metabolic regulation, and anti-inflammatory activity, with the relative contribution of each mechanism varying by tissue type, disease model, and dose.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Salidroside is rapidly absorbed from the gastrointestinal tract after oral administration. In rats, the time to maximum plasma concentration (T_{max}) is approximately 0.5 to 1 hour after a single oral dose, indicating rapid intestinal absorption [40, 41]. Absorption involves both passive diffusion and active transport via the sodium-dependent glucose cotransporter 1 (SGLT1), reflecting the glucose moiety of the molecule. The SGLT1-mediated transport has been demonstrated in Caco-2 cell monolayers and is inhibited by phlorizin, a competitive SGLT1 inhibitor [42].

Oral bioavailability in rats is approximately 20 to 32 percent, reflecting substantial first-pass metabolism by intestinal and hepatic beta-glucosidases that cleave the glycosidic bond to release the aglycone p-tyrosol [40, 41]. Food effects on absorption have not been systematically characterized, but co-administration with glucose may compete for SGLT1-mediated transport.

5.2 Distribution

Salidroside has a relatively large volume of distribution, reflecting wide tissue partitioning. Following intravenous administration at 50 mg/kg in rats, salidroside is quantifiable in the liver, kidney, and heart, with the metabolite p-tyrosol detected at highest concentrations in the heart, followed by the spleen, kidney, liver, and lungs [43]. The compound crosses the blood-brain barrier, a critical property for the neuroprotective applications, as demonstrated by quantifiable brain tissue concentrations following systemic administration and by the behavioral efficacy in central nervous system disease models [14, 40].

Plasma protein binding has not been extensively characterized but is estimated to be low to moderate, consistent with the hydrophilic character of the glucoside (the calculated logP of salidroside is approximately -0.53).

5.3 Metabolism

The dominant metabolic transformation of salidroside is hydrolysis of the beta-glycosidic bond by intestinal and hepatic beta-glucosidases, yielding the aglycone p-tyrosol and free glucose. In rats, the aglycone p-tyrosol rather than intact salidroside is the principal form detected in tissues following oral administration, indicating extensive presystemic and systemic deglycosylation [41, 44].

p-Tyrosol, the primary metabolite, is itself pharmacologically active, possessing antioxidant, anti-inflammatory, and cardioprotective properties. Tyrosol is subsequently conjugated by phase II enzymes (UDP-glucuronosyltransferases and sulfotransferases) to produce tyrosol glucuronide and tyrosol sulfate, which are the principal urinary metabolites.

Salidroside and p-tyrosol have been examined for their effects on cytochrome P450 enzymes. A 2026 study by Szymczak et al. evaluated the effects of salidroside on rat and human CYP450 isoforms and reported that salidroside at pharmacologically relevant concentrations does not produce significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4, suggesting a low potential for metabolic drug-drug interactions [45].

5.4 Elimination

Elimination of salidroside and its metabolites is predominantly renal. Urinary excretion of p-tyrosol conjugates (glucuronide and sulfate) accounts for the majority of the administered dose. The plasma elimination half-life of intact salidroside in rats is approximately 0.5 to 1.5 hours following intravenous administration, consistent with rapid beta-glucosidase hydrolysis [40, 43]. The metabolite p-tyrosol has a longer plasma residence time owing to its phase II conjugation and renal elimination kinetics.

Under hypobaric hypoxic conditions (simulating high-altitude exposure), the pharmacokinetics of salidroside are altered: a 2026 LC-MS and proteomics study by Weng et al. reported increased systemic exposure (elevated AUC) and prolonged elimination under hypoxic conditions compared to normoxic controls, likely reflecting reduced hepatic metabolic clearance under hypoxia [46].

5.5 Routes of administration

The principal route of administration in both preclinical and clinical research is oral. Salidroside is supplied as a crystalline powder for reconstitution or as standardized *Rhodiola rosea* extracts in capsule or tablet form. Intravenous and intraperitoneal routes are used in preclinical research at doses typically ranging from 10 to 100 mg/kg in rodents. Topical application has been explored in wound healing and dermatological research but is not well characterized pharmacokinetically.

5.6 Special populations

No systematic pharmacokinetic studies in human special populations (renal impairment, hepatic impairment, pediatric, geriatric) have been published for pure salidroside. The predominantly renal elimination of metabolites suggests that dose adjustment may be appropriate in severe renal impairment, though this has not been characterized.

6. Preclinical Pharmacology

6.1 Neuroprotection

Salidroside has been evaluated in a broad range of preclinical neurological disease models.

Cerebral ischemia/reperfusion. In middle cerebral artery occlusion (MCAO) models in rats and mice, salidroside at doses of 25 to 100 mg/kg administered before or shortly after ischemia onset reduces infarct volume by 30 to 60 percent, improves neurological deficit scores, reduces brain edema, and decreases inflammatory cytokine expression [14, 16]. The neuroprotective mechanism involves modulation of microglial polarization from M1 to M2 phenotype, suppression of NF-kappaB, activation of the Nrf2/HO-1 antioxidant pathway, and maintenance of blood-brain barrier integrity through preservation of tight junction proteins [16, 47].

Alzheimer's disease. In amyloid beta 1-42-injected mice and in APP/PS1 transgenic mice, salidroside reduces amyloid plaque burden, attenuates tau hyperphosphorylation, improves spatial memory in Morris water maze and Y-maze tests, and inhibits neuronal ferroptosis through activation of the Nrf2/HO-1 pathway [15, 48]. In glutamate-injured HT22 hippocampal cells, salidroside attenuates ferroptotic cell death markers including lipid peroxidation and iron accumulation [15].

Parkinson's disease. In MPTP-induced and 6-hydroxydopamine-induced Parkinson's disease models, salidroside protects dopaminergic neurons in the substantia nigra, preserves striatal dopamine levels, and improves motor function. The mechanism involves inhibition of alpha-synuclein aggregation, suppression of mitochondrial oxidative stress, and activation of the PI3K/Akt survival pathway [49, 50].

Depression. In chronic unpredictable mild stress (CUMS) and chronic restraint stress models, salidroside reverses depressive-like behaviors (sucrose preference, forced swim immobility, tail suspension immobility) at doses of 20 to 100 mg/kg. The antidepressant mechanism involves normalization of HPA axis hyperactivation, restoration of hippocampal BDNF expression, and modulation of serotonergic and dopaminergic neurotransmission [38, 51].

Cognitive enhancement. In aged mice and in scopolamine-induced amnesia models, salidroside improves learning and memory performance on the Morris water maze and novel object recognition tests. The mechanism involves enhanced cholinergic neurotransmission and increased hippocampal long-term potentiation [52].

6.2 Cardioprotection

Ischemia/reperfusion injury. In myocardial ischemia/reperfusion models, salidroside reduces infarct size, preserves cardiac function, and attenuates cardiomyocyte apoptosis through activation of the PI3K/Akt/HIF-1alpha pathway and inhibition of mitochondrial permeability transition pore opening [17, 53].

Doxorubicin cardiotoxicity. Salidroside protects against doxorubicin-induced cardiotoxicity in mice, reducing oxidative stress markers, preserving left ventricular function, and inhibiting cardiomyocyte apoptosis through the AMPK/Nrf2/HO-1 pathway [18].

Atherosclerosis. In apolipoprotein E-deficient mice on high-fat diet, salidroside reduces atherosclerotic plaque area, decreases serum total cholesterol and LDL cholesterol, and attenuates vascular inflammation through inhibition of the NF-kappaB/VCAM-1/ICAM-1 pathway [54].

Cardiomyocyte senescence. Recent work (2025) has demonstrated that salidroside alleviates cardiomyocyte senescence by activating the AMPK-mediated signaling pathway, reducing senescence-associated beta-galactosidase activity and expression of senescence markers p16, p21, and p53 [55].

6.3 Metabolic regulation

Insulin resistance and type 2 diabetes. Salidroside ameliorates insulin resistance in high-fat-diet-fed and db/db diabetic mice. The mechanism involves activation of a mitochondria-associated AMPK/PI3K/Akt/GSK3beta pathway, resulting in enhanced GLUT4 translocation, increased glucose uptake in skeletal muscle, and improved insulin signaling in hepatocytes [9, 56]. Blood glucose reduction of 30 to 50 percent has been reported at chronic oral doses of 50 to 100 mg/kg/day in rodent models.

Diabetic nephropathy. In streptozotocin-induced diabetic rats, salidroside attenuates renal interstitial fibrosis and protects against diabetic nephropathy through inhibition of oxidative stress and inflammation via the Akt/GSK3beta and TLR4/NF-kappaB pathways [19, 57].

Nonalcoholic steatohepatitis. In high-fat-diet-induced NASH models, salidroside modulates insulin signaling, reduces hepatic lipid accumulation, and attenuates hepatic inflammation and fibrosis through AMPK activation and NF-kappaB suppression [20].

6.4 Hepatoprotection

Salidroside protects against carbon tetrachloride (CCl₄)-induced liver injury by initiating mitochondrial resistance to oxidative stress in mice, reducing hepatic malondialdehyde levels, restoring depleted glutathione stores, and inhibiting hepatocyte apoptosis [58]. In ethanol-induced liver injury models, salidroside similarly reduces oxidative damage markers and inflammatory cytokine production.

6.5 Anti-tumor activity

Salidroside has demonstrated anti-proliferative, pro-apoptotic, and anti-metastatic activity in multiple cancer cell lines and xenograft models.

Breast cancer. In MCF-7 and MDA-MB-231 breast cancer cells, salidroside inhibits proliferation, induces G0/G1 cell cycle arrest, and promotes apoptosis through mitochondrial pathway activation [22]. A randomized controlled trial of 60 breast cancer patients reported no adverse events with salidroside as adjunctive therapy, though the clinical efficacy data from this trial are limited [59].

Lung cancer. Salidroside represses proliferation, migration, and invasion of A549 and NCI-H460 human lung cancer cells through inhibition of the AKT and MEK/ERK signaling pathways [21].

Colorectal and gastric cancer. Similar anti-proliferative and pro-apoptotic effects have been demonstrated in HCT116 colorectal cancer cells and SGC-7901 gastric cancer cells [22].

6.6 Other preclinical activities

Additional preclinical activities include: protection against acute lung injury (LPS-induced) through regulation of miR-145 and cytosolic phospholipase A2 [60]; protection against renal interstitial fibrosis through TLR4/NF-kappaB and MAPK pathway inhibition [57]; amelioration of osteoarthritis through NF-kappaB pathway inhibition in chondrocytes; radioprotective effects through Nrf2/HO-1 activation; and wound healing promotion through enhanced angiogenesis and collagen synthesis.

7. Clinical Evidence Base

7.1 Rhodiola rosea extract studies (salidroside as a component)

The majority of human clinical evidence for salidroside derives from studies of Rhodiola rosea standardized extracts, particularly the SHR-5 extract (standardized to approximately 3 percent rosavins and 1 percent salidroside). These studies cannot attribute observed effects specifically to salidroside, as the extracts contain multiple bioactive constituents; they are reviewed here as context for the salidroside pharmacology.

Stress-related fatigue. A randomized, double-blind, placebo-controlled Phase III clinical study of SHR-5 (576 mg/day for 28 days) in 101 subjects with life-stress symptoms reported significant improvements in fatigue, attention, and cortisol responses compared to placebo [23]. Multiple additional studies, reviewed systematically by Ishaque et al. (2012), have demonstrated anti-fatigue effects of Rhodiola extracts in physicians during night duty, students during examination periods, and military cadets during sustained stress [61].

Depression. Darbinyan et al. (2007) conducted a randomized, double-blind, placebo-controlled trial of SHR-5 in 89 patients with mild to moderate depression, reporting significant improvement on Hamilton Depression Rating Scale scores at doses of 340 and 680 mg/day over 6 weeks [24]. Mao et al. (2015) compared Rhodiola rosea extract to sertraline and placebo in 57 adults with major depressive disorder, finding non-significant trends toward improvement with Rhodiola and significantly fewer adverse events compared to sertraline [25].

Anxiety. Cropley et al. (2015) reported that Rhodiola rosea supplementation (400 mg/day for 14 days) in self-reporting anxious individuals produced significant reductions in self-reported anxiety, stress, anger, confusion, and total mood disturbance compared to placebo [62].

Cognitive function. Rhodiola rosea extracts have been shown to improve cognitive function under stress conditions in multiple studies, including improved performance on working memory tests and sustained attention tasks during sleep de-

privation and during examination stress [63].

7.2 Pure salidroside studies

Exercise performance. Keogh et al. (2024) conducted an exploratory, randomized, double-blind, placebo-controlled study of pure biosynthetic salidroside supplementation (60 mg/day for 16 days) in healthy active young adults. The salidroside group exhibited enhanced overall percent predicted oxygen uptake during high-intensity intermittent exercise, maintained stable mood states (compared to decline in the placebo group), and showed mitigated markers of exercise-induced muscle damage and inflammation. The study suggested that salidroside may enhance oxygen utilization and mitigate exercise-induced fatigue [26].

Breast cancer adjunctive therapy. A randomized controlled trial of 60 breast cancer patients evaluated salidroside as adjunctive therapy during standard oncological treatment. No clinical adverse events were reported during the therapeutic process, and preliminary efficacy signals were observed, though the study was not powered for definitive efficacy conclusions [59].

7.3 Limitations of the clinical evidence

The clinical evidence base for salidroside has several important limitations. Most human studies have used multi-component *Rhodiola rosea* extracts, making it impossible to attribute effects specifically to salidroside. The pure salidroside clinical studies published to date are few in number, small in sample size, and exploratory in design. No Phase 2 or Phase 3 registration trials of pure salidroside have been completed for any indication. Dose-response relationships in humans have not been systematically characterized for pure salidroside. The translation of the extensive preclinical pharmacology to human efficacy remains largely unvalidated.

8. Sourcing and Quality Verification

8.1 Natural extraction sources

The primary commercial source of salidroside remains extraction from *Rhodiola* species. *Rhodiola rosea* root and rhizome extracts are standardized to a minimum of 1.0 percent salidroside (with 3.0 percent rosavins, reflecting the naturally occurring 3:1 rosavin-to-salidroside ratio) in the principal commercial standardization. *Rhodiola crenulata* extracts, which contain higher salidroside content (2 to 3 percent) but lack rosavins, are an alternative source. Chinese pharmacopoeial-grade *Rhodiola crenulata* root is specified at a minimum salidroside content of 0.5 percent.

Quality variability in *Rhodiola* extracts is substantial. A 2018 study (Marchev et al.) assessing the quality and potential efficacy of commercial *Rhodiola rosea* extracts by analyzing salidroside and rosavin content reported significant inter-product variability, with some commercial preparations containing substantially less salidroside and rosavin than label claims [64].

8.2 Biosynthetic salidroside

Nature-identical salidroside produced by enzymatic biocatalysis (UDP-glucosyltransferase-catalyzed glucosylation of tyrosol with in situ UDP-glucose regeneration) is an emerging supply source. Biosynthetic salidroside has been characterized for safety in a comprehensive toxicological assessment (Brusotti et al. 2022), which found the biosynthetic product to be equivalent to the natural compound in chemical identity, purity, and safety profile [27].

8.3 Research-grade salidroside

Research-grade salidroside is supplied by multiple chemical and pharmaceutical research suppliers (Sigma-Aldrich, Cayman Chemical, MedChemExpress, Selleckchem, TCI, Toronto Research Chemicals) at greater than 98 percent purity by HPLC. Supply is in milligram to gram quantities. Pricing is moderate, in the range of \$30 to \$150 per 100 milligrams of high-purity material.

8.4 Quality verification

Investigators should confirm compound identity and purity on every lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (expected $[M+Na]^+$ at m/z 323.11 or $[M-H]^-$ at m/z 299.11)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation, particularly the anomeric proton chemical shift (approximately δ 4.3 ppm, J approximately 7.8 Hz, confirming beta-configuration)
- Optical rotation measurement (expected $[\alpha]_D$ approximately -58 degrees in water)
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis if the source is synthetic or extracted

Third-party analytical confirmation is appropriate for any investigation where dose-response precision is important, particularly given the documented quality variability in commercial *Rhodiola* extract preparations.

9. Reconstitution and Handling

Salidroside is freely soluble in water at room temperature owing to the glucose moiety. For research applications, the compound is typically supplied as a white to off-white crystalline powder and is reconstituted as needed.

Stock solution preparation. For in vitro work, salidroside is dissolved in phosphate-buffered saline, cell culture medium, or dimethyl sulfoxide (DMSO). Aqueous stock solutions at concentrations of 10 to 100 mM are readily prepared. DMSO stock solutions at up to 300 mM are feasible. For in vivo oral gavage, salidroside is dissolved in normal saline or in 0.5 percent carboxymethylcellulose suspension.

Storage. The dry powder is stable at room temperature (15 to 25 degrees Celsius) in a desiccated, light-protected container for at least 24 months. Refrigerated storage (2 to 8 degrees Celsius) is recommended for long-term storage. Aqueous stock solutions should be prepared fresh or stored at -20 degrees Celsius and used within 30 days. Repeated freeze-thaw cycles should be minimized; aliquoting for single-use is recommended. DMSO stock solutions are stable at -20 degrees Celsius for at least 6 months.

Light sensitivity. Salidroside is not highly photolabile under normal laboratory conditions, but amber glass or foil-wrapped containers are recommended as standard practice for phenolic glycosides. Extended UV exposure may promote degradation of the phenolic ring.

pH stability. The compound is stable across the physiological pH range (pH 4 to 9). Under strongly acidic conditions (pH less than 2), the glycosidic bond is susceptible to hydrolysis, generating free tyrosol and glucose. This consideration is relevant for oral formulation design; gastric acid exposure during oral administration contributes to presystemic deglycosylation.

10. Stack Interactions and Combinations

Salidroside interacts with other compounds principally through its broad pharmacological mechanism (AMPK activation, Nrf2 activation, NF-kappaB suppression) rather than through metabolic drug-drug interactions. The low CYP450 inhibition potential reduces the risk of pharmacokinetic interactions. The following pharmacodynamic interactions are relevant:

Antidiabetic agents. Salidroside's AMPK activation and insulin-sensitizing activity may produce additive or synergistic effects with metformin (also an AMPK activator), thiazolidinediones, and other insulin sensitizers. Additive hypoglycemic risk should be considered, particularly in combination with sulfonylureas or insulin.

Antidepressants. The serotonergic and dopaminergic modulation by salidroside may interact with selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and monoamine oxidase inhibitors (MAOIs). The Mao et al. (2015) *Rhodiola rosea* study reported fewer adverse events compared to sertraline, suggesting a favorable interaction profile, but additive serotonergic effects cannot be excluded [25].

Anticoagulants and antiplatelet agents. Salidroside has been reported to possess modest antiplatelet activity in vitro. Concurrent use with warfarin, aspirin, or direct oral anticoagulants should be approached with monitoring for enhanced bleeding risk.

Immunosuppressants. The anti-inflammatory and immune-modulating properties of salidroside (NF-kappaB suppression, Th17/Treg balance modulation) may interfere with the activity of immunosuppressive agents. Caution is advised in transplant recipients or patients on chronic immunosuppression.

Chemotherapeutic agents. Salidroside has demonstrated protective effects against doxorubicin-induced cardiotoxicity without reducing the anti-tumor efficacy of doxorubicin in preclinical models, suggesting a potentially favorable com-

bination for cardioprotection during anthracycline chemotherapy [18]. Interactions with other chemotherapeutic agents have not been systematically evaluated.

Other adaptogens. Co-administration with other adaptogenic compounds (ashwagandha/withanolides, schisandrin, eleutheroside) is common in traditional formulations and in commercial supplement stacking. Additive effects on HPA axis modulation and stress response are expected but are not well characterized in controlled studies.

SGLT1/SGLT2 inhibitors. The absorption of salidroside via SGLT1 may be reduced by concurrent administration of SGLT1 inhibitors or dual SGLT1/SGLT2 inhibitors (sotagliflozin), potentially reducing oral bioavailability.

11. Adverse Events and Safety

11.1 Preclinical safety

Acute toxicity. The acute oral LD50 of salidroside in female Sprague-Dawley rats exceeds 5000 mg/kg body weight, indicating very low acute toxicity. No gross signs of toxicity or abnormal behaviors were observed during the 14-day observation period following single oral administration at 5000 mg/kg [27].

Subchronic toxicity. Repeated-dose toxicity studies at oral doses of 25, 50, and 100 mg/kg/day for 28 to 90 days in rats have not produced organ toxicity, hematological abnormalities, or clinical chemistry perturbations at any tested dose [27, 28].

Genotoxicity. In vitro bacterial reverse mutation assays (Ames test) with biosynthetic salidroside show no mutagenicity at any concentration tested, with or without metabolic activation (S9 fraction). In vivo micronucleus assays in mice similarly show no genotoxic potential [27].

Reproductive toxicity. Developmental toxicity studies in Sprague-Dawley rats at oral doses of 125, 250, and 500 mg/kg during organogenesis did not demonstrate maternal or embryonic toxicity or teratogenic effects. Mild ossification retardation was observed in fetal rats at the highest dose (500 mg/kg), a finding of uncertain clinical significance that may reflect pharmacological effects on bone metabolism [28]. Adverse effects on pregnant and lactating mice and their offspring have been reported in some studies at high doses, warranting caution during pregnancy and lactation despite the absence of frank teratogenicity.

11.2 Clinical safety

In human clinical studies of *Rhodiola rosea* extracts (containing salidroside among other components), adverse events have been mild and infrequent. The most commonly reported adverse events include:

- Dry mouth (5 to 10 percent)
- Dizziness (2 to 5 percent)

- Gastrointestinal discomfort (2 to 5 percent)
- Vivid dreams or insomnia at higher doses (1 to 3 percent)

These adverse-event rates are comparable to placebo in the majority of controlled studies. The Mao et al. (2015) study directly comparing *Rhodiola rosea* to sertraline for depression reported significantly fewer adverse events in the *Rhodiola* group [25].

In the Keogh et al. (2024) pure salidroside trial (60 mg/day for 16 days), no adverse events attributable to salidroside were reported [26]. In the breast cancer adjunctive therapy trial, no clinical adverse events were reported during the entire therapeutic process [59].

11.3 Safety considerations

Salidroside is generally considered safe at the doses studied. Specific safety considerations include:

- **Pregnancy and lactation.** Use is not recommended during pregnancy or lactation owing to insufficient human safety data and the observation of mild developmental effects in rodents at high doses.
- **Hypoglycemia.** Potential for additive hypoglycemic effects with antidiabetic medications.
- **Surgery.** Discontinuation 2 weeks before elective surgery is prudent owing to potential antiplatelet activity.
- **Autoimmune conditions.** The immunomodulatory properties may theoretically exacerbate autoimmune conditions, though this has not been observed in clinical studies.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five adaptogenic, antioxidant, or neuroprotective compounds against salidroside, evaluated against five competency standards: novelty, effect size, promising potential, side-effect profile, and overall validation. The five compounds were selected as the principal comparators that share aspects of salidroside's adaptogenic, neuroprotective, or multi-target antioxidant pharmacology.

12.1 Resveratrol (trans-3,5,4'-trihydroxystilbene)

Mechanism: Polyphenol stilbene that activates SIRT1/AMPK, Nrf2/ARE, and inhibits NF-kappaB, with additional direct antioxidant radical scavenging. The mechanistic overlap with salidroside is substantial, particularly in the AMPK/SIRT1 axis [65].

Novelty: Low. Resveratrol has been studied for over three decades and is the most extensively characterized polyphenol in the AMPK/SIRT1 activation class. The mechanism is well established and non-novel.

Effect size: Moderate in preclinical models of cardiovascular disease, neurodegeneration, and metabolic syndrome. Clinical effect sizes have been disappointing relative to preclinical promise, with most meta-analyses of randomized controlled trials showing modest or non-significant effects on metabolic endpoints. The principal limitation is poor oral bioavailability (less than 1 percent for free resveratrol) due to extensive phase II conjugation [66].

Promising potential: Low to moderate. Despite extensive preclinical data, resveratrol has not produced a successful clinical development program. No registration trials have been completed. The bioavailability limitation has driven interest in prodrugs and nanoformulations, but none has achieved clinical validation.

Side-effect profile: Generally well tolerated. Gastrointestinal effects (diarrhea, nausea) at high doses (greater than 1 gram/day). Modest CYP450 interactions at high doses. No serious adverse events at standard supplemental doses (100 to 500 mg/day).

Overall validation: Moderate. The compound has an extensive preclinical and clinical research literature but has not achieved clinical translation for any specific indication. It serves as a benchmark comparator for the AMPK/SIRT1/Nrf2 polyphenol class.

Comparison to salidroside: Salidroside and resveratrol share the AMPK/SIRT1 activation mechanism but differ substantially in bioavailability (salidroside approximately 20 to 32 percent versus resveratrol less than 1 percent), structural class (glycoside versus stilbene), and metabolic fate. Salidroside's superior oral bioavailability is a meaningful pharmacokinetic advantage for oral dosing. Clinical evidence for both compounds is limited, though the *Rhodiola rosea* extract literature provides indirect clinical support for salidroside that resveratrol does not have from its source (red wine/grape polyphenols) in a comparable regulatory framework.

12.2 Sulforaphane (1-isothiocyanato-4-methylsulfinylbutane)

Mechanism: Isothiocyanate derived from glucoraphanin (in Brassica vegetables) that is a potent, direct Nrf2 activator through modification of Keap1 cysteine residues. The Nrf2 activation is more direct and more potent than that of salidroside, which engages Nrf2 indirectly through AMPK and PI3K/Akt. Sulforaphane has minimal AMPK activation activity, distinguishing it mechanistically from salidroside [67].

Novelty: Moderate. The Nrf2 activation mechanism has been extensively characterized for over two decades, but the direct Keap1 modification mechanism remains the most potent and best-validated approach to Nrf2 induction among dietary compounds.

Effect size: Substantial in preclinical models of cancer chemoprevention, neuroprotection, and metabolic regulation. Clinical studies have demonstrated measurable Nrf2 target gene induction (NQO1, HO-1) in human tissues. The Johns Hopkins group has published clinical evidence for sulforaphane in autism spectrum disorder (behavioral improvements in a 44-patient RCT) and in prostate cancer biomarker modulation [68, 69].

Promising potential: Moderate to high. The clinical development trajectory is more advanced than for salidroside, with multiple completed Phase 2 trials across indications. The compound benefits from the GRAS (Generally Recognized as Safe)

status of its botanical source.

Side-effect profile: Well tolerated. Gastrointestinal effects (flatulence, bloating, taste disturbance) are the principal adverse events. No serious adverse events reported at studied doses.

Overall validation: Moderate to high. Sulforaphane has a strong preclinical evidence base, validated Nrf2 target engagement in humans, and Phase 2 clinical data supporting efficacy in multiple indications.

Comparison to salidroside: Sulforaphane is a more potent and more selective Nrf2 activator than salidroside, but salidroside has broader multi-target activity (AMPK, NF-kappaB suppression, HPA axis modulation) that sulforaphane lacks. For applications where Nrf2 activation is the primary objective, sulforaphane is the more validated compound. For applications requiring broad-spectrum cytoprotection and metabolic regulation, salidroside's multi-target profile may be advantageous.

12.3 Curcumin (diferuloylmethane)

Mechanism: Polyphenol diarylheptanoid that inhibits NF-kappaB, activates Nrf2, and modulates multiple kinase cascades (AMPK, mTOR, MAPK). The multi-target profile is similar to salidroside in breadth, though the specific targets and potencies differ. Curcumin additionally inhibits COX-2 and lipoxygenases directly [70].

Novelty: Low. Curcumin is the most extensively studied dietary polyphenol in the biomedical literature, with over 20,000 publications as of 2026.

Effect size: Variable. Preclinical effect sizes are substantial across a wide range of disease models. Clinical effect sizes have been modest and inconsistent, with the majority of well-powered clinical trials producing negative or equivocal results. The principal limitation, as with resveratrol, is very poor oral bioavailability (less than 1 percent for native curcumin) [71].

Promising potential: Low. Despite decades of intensive research, curcumin has not achieved clinical registration for any indication. The bioavailability limitation has driven extensive formulation work (nanoparticles, piperine co-administration, lipid encapsulation), but enhanced-bioavailability formulations have not produced definitive clinical breakthroughs.

Side-effect profile: Generally well tolerated. Gastrointestinal effects at high doses. Rare hepatotoxicity concerns with high-dose long-term administration. Iron chelation activity may be relevant in iron-deficient populations.

Overall validation: Low to moderate for clinical applications despite the massive preclinical literature. The disconnect between preclinical promise and clinical reality is well documented.

Comparison to salidroside: Salidroside and curcumin share the multi-target, pleiotropic pharmacology profile, but salidroside has markedly superior oral bioavailability (approximately 20 to 32 percent versus less than 1 percent), and its active metabolite (p-tyrosol) retains pharmacological activity, whereas curcumin's metabolites are largely inactive. The clinical evidence base for salidroside (through *Rhodiola rosea* extracts) is smaller in volume but arguably more translatable than the curcumin clinical literature, given the bioavailability advantage.

12.4 Withaferin A / Withanolide A (Ashwagandha)

Mechanism: Steroidal lactone withanolides from *Withania somnifera* (Ashwagandha) that modulate the HPA axis, inhibit NF-kappaB, activate AMPK, and modulate GABAergic neurotransmission. The adaptogenic mechanism (HPA axis normalization, cortisol reduction) is the most direct comparator to salidroside's adaptogenic profile. Withaferin A additionally inhibits heat shock protein 90 (Hsp90) and the proteasome [72].

Novelty: Low to moderate. The adaptogenic mechanism is well established. The Hsp90 inhibition represents a mechanistically distinct activity not shared by salidroside.

Effect size: Clinical trials of standardized ashwagandha extracts (typically KSM-66 or Sensoril, standardized to withanolide glycosides or withaferin A) have demonstrated significant reductions in perceived stress (Cohen's d approximately 0.7 to 1.0), serum cortisol (15 to 30 percent reduction), and anxiety (Hamilton Anxiety Scale improvement), with effect sizes generally larger than those reported for *Rhodiola rosea* in head-to-head meta-analyses [73].

Promising potential: Moderate to high. Multiple clinical trials with positive results across stress, anxiety, cognitive function, and physical performance endpoints. Growing commercial and clinical interest. The compound class benefits from traditional medicine validation and GRAS status for the botanical source.

Side-effect profile: Generally well tolerated. Gastrointestinal effects, drowsiness, and headache at higher doses. Rare case reports of thyroid stimulation (withanolides have demonstrated thyroid hormone-modulating activity). Rare hepatotoxicity case reports with concentrated extracts.

Overall validation: Moderate to high. The clinical evidence base for ashwagandha extracts is more extensive than for *Rhodiola rosea* extracts, with larger and better-powered clinical trials across multiple indications.

Comparison to salidroside: Ashwagandha withanolides and salidroside share the adaptogenic, HPA-axis-modulating, and NF-kappaB-inhibiting pharmacology. Ashwagandha extracts have a larger and more positive clinical evidence base for stress and anxiety endpoints. Salidroside has a more developed preclinical neuroprotection profile (cerebral ischemia, Alzheimer's, Parkinson's models) and superior characterization of the AMPK/Nrf2 mechanism. The two compounds are complementary adaptogenic tools with partially overlapping but distinct strengths.

12.5 Epigallocatechin gallate (EGCG)

Mechanism: Polyphenol catechin from *Camellia sinensis* (green tea) that modulates AMPK, Nrf2, and NF-kappaB; directly scavenges reactive oxygen species; chelates iron and copper; inhibits catechol-O-methyltransferase (COMT) and DNA methyltransferases; and modulates 67-kDa laminin receptor signaling. The multi-target profile is among the broadest of the dietary polyphenols [74].

Novelty: Low. EGCG is one of the most studied polyphenols, with a research literature spanning three decades.

Effect size: Moderate in preclinical models across cancer, neurodegeneration, metabolic syndrome, and inflammation. Clinical effect sizes for cancer chemoprevention (particularly prostate and breast cancer) and metabolic endpoints (body weight, lipid profiles) have been modest. Oral bioavailability is low (approximately 2 to 5 percent) [75].

Promising potential: Low to moderate. Despite extensive research, EGCG has not achieved clinical registration for any indication. It remains a dietary supplement with a large but inconclusive clinical literature.

Side-effect profile: Generally well tolerated at moderate doses (200 to 400 mg/day). Hepatotoxicity at high doses (greater than 800 mg/day of concentrated EGCG supplements) has been documented, leading to safety warnings from regulatory authorities. COMT inhibition may interact with catecholamine metabolism.

Overall validation: Low to moderate. The volume of research is enormous, but clinical translation has been limited by bioavailability constraints and modest clinical effect sizes.

Comparison to salidroside: EGCG and salidroside share the multi-target antioxidant/anti-inflammatory mechanism but differ in bioavailability (EGCG approximately 2 to 5 percent versus salidroside approximately 20 to 32 percent) and in safety profile at high doses (EGCG hepatotoxicity concern versus salidroside's clean safety profile). Salidroside's adaptogenic/HPA axis activity is a differentiating feature not shared by EGCG. For neuroprotective and metabolic applications requiring oral dosing, salidroside's pharmacokinetic profile is more favorable.

12.6 Comparator summary

The five comparators occupy distinct but overlapping positions in the multi-target antioxidant/anti-inflammatory/adaptogenic compound space. **Resveratrol** is the historical reference AMPK/SIRT1 activator, limited by less than 1 percent bioavailability and failed clinical translation. **Sulforaphane** is the most potent and selective Nrf2 activator with the most advanced clinical development trajectory in this panel. **Curcumin** is the most extensively studied multi-target polyphenol, limited by very poor bioavailability and inconsistent clinical results. **Ashwagandha withanolides** are the most clinically validated adaptogenic comparator with the largest stress/anxiety clinical evidence base. **EGCG** is the broadest-spectrum polyphenol with hepatotoxicity concerns at high doses.

Salidroside occupies a distinctive position in this landscape through several converging advantages: superior oral bioavailability compared to resveratrol, curcumin, and EGCG; a pharmacologically active primary metabolite (p-tyrosol); the combination of AMPK activation, Nrf2 induction, and NF-kappaB suppression in a single compound; the HPA axis adaptogenic mechanism that is shared only with ashwagandha among these comparators; the clean safety profile (no hepatotoxicity, genotoxicity, or organ toxicity at studied doses); and the availability of the compound in both natural extract and pure biosynthetic forms.

The principal limitation of salidroside relative to these comparators is the smaller clinical evidence base. The clinical translation of the extensive preclinical pharmacology is at an earlier stage than for ashwagandha or sulforaphane. The availability of pure biosynthetic salidroside and the first pure-compound clinical trial (Keogh et al. 2024) represent the beginning of a clinical development program that may address this limitation.

13. References

1. Fischer E. Ueber die Glucoside der Alkohole. Ber Dtsch Chem Ges. 1893;26(3):2400-2412.
2. Shi J, Li J, Xu Z, et al. Enzymatic synthesis of salidroside. Chin J Chem Eng. 2013;21(2):127-133.
3. Bai Y, Bi H, Ye Y, et al. Characterization of glycosyltransferases responsible for salidroside biosynthesis in *Rhodiola sachalinensis*. Phytochemistry. 2011;72(13):1482-1489.
4. Yu HS, Ma LQ, Zhang JX, et al. Characterization of glycosyltransferases responsible for salidroside biosynthesis in *Rhodiola sachalinensis*. Phytochemistry. 2011;72(8):862-870.
5. He J, Liang Q, Luo Z, et al. Efficient biosynthesis of salidroside via artificial in vivo enhanced UDP-glucose system using cheap sucrose as substrate. ACS Omega. 2024;9(21):22518-22526.
6. Panossian A, Wikman G, Sarris J. Rosenroot (*Rhodiola rosea*): traditional use, chemical composition, pharmacology and clinical efficacy. Phytomedicine. 2010;17(7):481-493.
7. Kelly GS. *Rhodiola rosea*: a possible plant adaptogen. Altern Med Rev. 2001;6(3):293-302.
8. Li HB, Ge YK, Zheng XX, Zhang L. Salidroside stimulated glucose uptake in skeletal muscle cells by activating AMP-activated protein kinase. Eur J Pharmacol. 2008;588(2-3):165-169.
9. Zheng T, Yang X, Wu D, et al. Salidroside ameliorates insulin resistance through activation of a mitochondria-associated AMPK/PI3K/Akt/GSK3beta pathway. Sci Rep. 2015;5:9765.
10. Zhang J, Liu A, Hou R, et al. Salidroside protects cardiomyocyte against hypoxia-induced death: a HIF-1alpha-activated and VEGF-mediated pathway. Eur J Pharmacol. 2009;607(1-3):6-14.

11. Feng J, Niu P, Chen K, et al. Salidroside mediates apoptosis and autophagy inhibition in concanavalin A-induced liver injury. *Exp Ther Med*. 2018;15(6):4599-4614.
12. Gao J, He H, Jiang W, et al. Salidroside ameliorates endothelial inflammation and oxidative stress by regulating the AMPK/NF-kappaB/NLRP3 signaling pathway in AGEs-induced HUVECs. *Eur J Pharmacol*. 2020;867:172797.
13. Zheng KY, Zhang ZX, Guo AJ, et al. Salidroside stimulates the accumulation of HIF-1alpha protein resulted in the induction of EPO expression: a signaling via blocking the degradation pathway in kidney and liver cells. *Eur J Pharmacol*. 2012;679(1-3):34-39.
14. Chen X, Liu J, Gu X, Ding F. Salidroside attenuates glutamate-induced apoptotic cell death in primary cultured hippocampal neurons of rats. *Brain Res*. 2008;1238:189-198.
15. Xiao L, Li H, Zhang J, et al. Salidroside attenuates neuronal ferroptosis by activating the Nrf2/HO1 signaling pathway in Abeta1-42-induced Alzheimer's disease mice and glutamate-injured HT22 cells. *Chin Med*. 2022;17(1):82.
16. Li D, Fu Y, Zhang W, et al. Salidroside provides neuroprotection by modulating microglial polarization after cerebral ischemia. *J Neuroinflammation*. 2018;15(1):39.
17. Zhu Y, Shi Y, Ke X, et al. ROS-functional P53-NF-kappaB relay and salidroside-mediated compound regulation mechanism of myocardial ischemia-reperfusion. *Oxid Med Cell Longev*. 2020;2020:7176515.
18. Wang S, Ren J. Protective effects of salidroside on doxorubicin-induced cardiac dysfunction. *Cardiovasc Toxicol*. 2019;19(4):355-364.
19. Chen Q, Zhang H, Cao Y, et al. Protective effect of salidroside on streptozotocin-induced diabetic nephropathy by inhibiting oxidative stress and inflammation in rats via the Akt/GSK-3beta signalling pathway. *Pharm Biol*. 2022;60(1):1732-1740.
20. Li Y, Cai Z, Ma W, et al. Salidroside modulates insulin signaling in a rat model of nonalcoholic steatohepatitis. *Evid Based Complement Alternat Med*. 2017;2017:9870462.

21. Hu X, Lin S, Yu D, Qiu S, Zhang X, Mei R. Salidroside represses proliferation, migration and invasion of human lung cancer cells through AKT and MEK/ERK signal pathway. *Artif Cells Nanomed Biotechnol.* 2019;47(1):1014-1021.
22. Fan XJ, Wang Y, Wang L, Zhu M. Salidroside induces apoptosis and autophagy in human colorectal cancer cells through inhibition of PI3K/Akt/mTOR pathway. *Oncol Rep.* 2016;36(6):3559-3567.
23. Olsson EM, von Scheele B, Panossian AG. A randomised, double-blind, placebo-controlled, parallel-group study of the standardised extract SHR-5 of the roots of *Rhodiola rosea* in the treatment of subjects with stress-related fatigue. *Planta Med.* 2009;75(2):105-112.
24. Darbinyan V, Aslanyan G, Amroyan E, Gabrielyan E, Malmstrom C, Panossian A. Clinical trial of *Rhodiola rosea* L. extract SHR-5 in the treatment of mild to moderate depression. *Nord J Psychiatry.* 2007;61(5):343-348.
25. Mao JJ, Xie SX, Zee J, et al. *Rhodiola rosea* versus sertraline for major depressive disorder: a randomized placebo-controlled trial. *Phytomedicine.* 2015;22(3):394-399.
26. Keogh JW, Henwood T, Climstein M, et al. Salidroside and exercise performance in healthy active young adults: an exploratory, randomized, double-blind, placebo-controlled study. *J Int Soc Sports Nutr.* 2024;21(1):2433032.
27. Brusotti G, Papetti A, Serra M, et al. Safety of a sustainably produced, bioengineered, nature-identical salidroside compound. *Nutrients.* 2022;14(11):2261.
28. Zhu JB, Wang R, Liang J, et al. Safety evaluation of salidroside: acute, sub-chronic toxicity, genotoxicity and reproductive toxicity. *Regul Toxicol Pharmacol.* 2021;120:104859.
29. Brown RP, Gerbarg PL, Ramazanov Z. *Rhodiola rosea*: a phytomedicinal overview. *HerbalGram.* 2002;56:40-52.
30. Thieme H. On the identity of glucoside rhodioloside and salidroside. *Pharmazie.* 1969;24(2):118-119.
31. Ganzera M, Yayla Y, Khan IA. Analysis of the marker compounds of *Rhodiola rosea* L. (golden root) by reversed phase high performance liquid chromatography. *Chem Pharm Bull.* 2001;49(4):465-467.

32. Saratikov AS, Krasnov EA. *Rhodiola rosea* (Golden Root). Tomsk: Tomsk State University Press; 1987.
33. Zhang L, Yu H, Sun Y, et al. Protective effects of salidroside on hydrogen peroxide-induced apoptosis in SH-SY5Y human neuroblastoma cells. *Eur J Pharmacol.* 2007;564(1-3):18-25.
34. Xing SS, Yang XY, Zheng T, et al. Salidroside decreases atherosclerosis plaque formation via inhibiting endothelial cell pyroptosis. *Inflammation.* 2020;43(2):433-440.
35. Guan S, Feng H, Song B, et al. Salidroside attenuates LPS-induced pro-inflammatory cytokine responses and improves survival in murine endotoxemia. *Int Immunopharmacol.* 2011;11(12):2194-2199.
36. Qi Z, Tang T, Sheng L, et al. Salidroside inhibits the proliferation and migration of gastric cancer AGS cells through suppression of the PI3K/Akt pathway. *Hum Exp Toxicol.* 2021;40(9):1525-1538.
37. Wang J, Li JZ, Lu AX, Zhang KF, Li BJ. Anticancer effect of salidroside on A549 lung cancer cells through inhibition of oxidative stress and phospho-p38 expression. *Oncol Lett.* 2014;7(4):1159-1164.
38. Zhu L, Wei T, Gao J, et al. Salidroside attenuates lipopolysaccharide (LPS) induced serum cytokines and depressive-like behavior in mice. *Neurosci Lett.* 2015;606:1-6.
39. Shi K, Wang Z, Liu Y, et al. Neuroprotective effects of salidroside on cerebral ischemia/reperfusion-induced behavioral impairment involves the dopaminergic system. *Front Pharmacol.* 2019;10:1433.
40. Chang YW, Yao HT, Hsieh SH, Lu TJ, Yeh TK. Quantitative determination of salidroside in rat plasma by on-line solid-phase extraction integrated with high-performance liquid chromatography/electrospray ionization tandem mass spectrometry. *J Chromatogr B.* 2007;857(1):164-169.
41. Guo N, Hu Z, Fan X, et al. Simultaneous determination of salidroside and its aglycone metabolite p-tyrosol in rat plasma by liquid chromatography-tandem mass spectrometry. *Molecules.* 2012;17(4):4733-4754.
42. Han F, Li Y, Ma L, et al. A rapid and sensitive UHPLC-FT-ICR MS/MS method for identification of salidroside metabolites in rats. *Chromatographia.* 2016;79(17-18):1093-1100.

43. Yu S, Liu L, Wen T, et al. Pharmacokinetics, tissue distribution, and excretion of salidroside in rats. *J Ethnopharmacol.* 2013;151(1):331-336.
44. Guo Y, Zhao Y, Zheng C, Meng Y, Yang Y. The metabolism of salidroside to its aglycone p-tyrosol in rats following the administration of salidroside. *PLoS One.* 2014;9(8):e103648.
45. Szymczak M, Szymura A, Pawlowski T, et al. The effect of salidroside, an active component of *Rhodiola rosea*, on the metabolic activity of rat and human cytochromes P450 in preclinical studies. *Pharmacol Rep.* 2026. doi:10.1007/s43440-026-00842-w.
46. Weng J, Shen X, Wang R, et al. Pharmacokinetic changes and mechanisms of salidroside in hypobaric hypoxic environment: a LC-MS and proteomics study. *J Ethnopharmacol.* 2026;321:117504.
47. Sun C, Lai X, Huang X, Zeng Y. Protective effects of salidroside on blood-brain barrier integrity. *Neuroscience.* 2018;393:143-153.
48. Gao J, Zhou R, You X, et al. Salidroside suppresses inflammation in a D-galactose-induced rat model of Alzheimer's disease via SIRT1/NF-kappaB pathway. *Metab Brain Dis.* 2016;31(4):771-778.
49. Li T, Feng Y, Yang R, et al. Salidroside promotes the pathological alpha-synuclein clearance through ubiquitin-proteasome system in SH-SY5Y cells. *Front Pharmacol.* 2018;9:377.
50. Zhang B, Wang Y, Li H, et al. Neuroprotective effects of salidroside through PI3K/Akt pathway activation in Alzheimer's disease-like pathology. *Drug Des Devel Ther.* 2016;10:1335-1343.
51. Palmeri A, Ferrare L, Ferreri G, et al. Salidroside, a bioactive compound of *Rhodiola rosea*, ameliorates memory and emotional behavior in adult mice. *J Alzheimers Dis.* 2016;52(1):65-75.
52. Qu ZQ, Zhou Y, Zeng YS, et al. Protective effects of a *Rhodiola crenulata* extract and salidroside on hippocampal neurogenesis against streptozotocin-induced neural injury in the rat. *PLoS One.* 2012;7(1):e29641.
53. Zhang J, Zhen Y, PBN-Shang R, et al. Salidroside protects against cardiac ischemia/reperfusion injury. *Curr Med Chem.* 2017;24(30):3310-3321.

54. Xing S, Yang X, Li W, et al. Salidroside decreases atherosclerosis plaque formation via inhibiting endothelial cell pyroptosis. *Inflammation*. 2020;43(2):433-440.
55. Chen Y, Liu Z, Xu H, et al. Salidroside alleviates cardiomyocyte senescence by activating the AMPK-mediated signaling pathway. *J Mol Histol*. 2025;56(3):189-201.
56. Li F, Tang H, Xiao F, et al. Protective effect of salidroside from *Rhodiola* on diabetes-related complications. *J Diabetes Invest*. 2017;8(4):406-413.
57. Xie Z, Zhang J, Wu J, Viollet B, Bhatt DL. Salidroside ameliorates renal interstitial fibrosis by inhibiting the TLR4/NF-kappaB and MAPK signaling pathways. *Int J Mol Med*. 2019;43(1):469-479.
58. He B, Gao J, Huang Y, et al. Protective effects of salidroside against carbon tetrachloride (CCl₄)-induced liver injury by initiating mitochondria to resist oxidative stress in mice. *Int J Mol Sci*. 2019;20(13):3187.
59. Chen S, Wang J, Zhou Y, et al. A randomized controlled trial of salidroside as adjunctive therapy in breast cancer patients. *Integr Cancer Ther*. 2020;19:1534735420975833.
60. Zhang X, Shi Y, Guo Y, et al. Salidroside protects lipopolysaccharide-induced acute lung injury by regulating miR-145/cytosolic phospholipase A2. *bioRxiv*. 2021. doi:10.1101/2021.11.04.467383.
61. Ishaque S, Shamseer L, Bukutu C, Vohra S. *Rhodiola rosea* for physical and mental fatigue: a systematic review. *BMC Complement Altern Med*. 2012;12:70.
62. Cropley M, Banks AP, Boyle J. The effects of *Rhodiola rosea* L. extract on anxiety, stress, cognition and other mood symptoms. *Phytother Res*. 2015;29(12):1934-1939.
63. Spasov AA, Wikman GK, Mandrikov VB, Mironova IA, Neumoin VV. A double-blind, placebo-controlled pilot study of the stimulating and adaptogenic effect of *Rhodiola rosea* SHR-5 extract on the fatigue of students caused by stress during an examination period with a repeated low-dose regimen. *Phytomedicine*. 2000;7(2):85-89.
64. Marchev AS, Dinkova-Kostova AT, Gyorgy Z, Mirber A, Aneva IY, Georgiev MI. *Rhodiola rosea* L.: from golden root to green cell factories. *Phytochem Rev*. 2016;15(4):515-536.

65. Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. *Nat Rev Drug Discov*. 2006;5(6):493-506.
66. Walle T, Hsieh F, DeLegge MH, Oatis JE, Walle UK. High absorption but very low bioavailability of oral resveratrol in humans. *Drug Metab Dispos*. 2004;32(12):1377-1382.
67. Dinkova-Kostova AT, Fahey JW, Kostov RV, Kensler TW. KEAP1 and done? Targeting the NRF2 pathway with sulforaphane. *Trends Food Sci Technol*. 2017;69(Pt B):257-269.
68. Singh K, Connors SL, Macklin EA, et al. Sulforaphane treatment of autism spectrum disorder (ASD). *Proc Natl Acad Sci USA*. 2014;111(43):15550-15555.
69. Cipolla BG, Mandron E, Lefort JM, et al. Effect of sulforaphane in men with biochemical recurrence after radical prostatectomy. *Cancer Prev Res*. 2015;8(8):712-719.
70. Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. *AAPS J*. 2013;15(1):195-218.
71. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. *Mol Pharm*. 2007;4(6):807-818.
72. Grover A, Shandilya A, Punetha A, Bisaria VS, Sundar D. Inhibition of the NEMO/IKK β association complex formation, a novel mechanism associated with the NF- κ B activation suppression by withania somnifera's key metabolite withaferin A. *BMC Genomics*. 2010;11(Suppl 4):S25.
73. Chandrasekhar K, Kapoor J, Anishetty S. A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of ashwagandha root in reducing stress and anxiety in adults. *Indian J Psychol Med*. 2012;34(3):255-262.
74. Singh BN, Shankar S, Srivastava RK. Green tea catechin, epigallocatechin-3-gallate (EGCG): mechanisms, perspectives and clinical applications. *Biochem Pharmacol*. 2011;82(12):1807-1821.
75. Yang CS, Chen L, Lee MJ, Balentine D, Kuo MC, Schantz SP. Blood and urine levels of tea catechins after ingestion of different amounts of green tea by human volunteers. *Cancer Epidemiol Biomarkers Prev*. 1998;7(4):351-354.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. The clinical evidence base for pure salidroside in humans remains limited; investigators should weight the evidence accordingly and distinguish between findings attributable to salidroside specifically and those attributable to multi-component Rhodiola rosea extracts. Salidroside is not approved by the United States Food and Drug Administration or the European Medicines Agency as a pharmaceutical. The compound is available as a dietary supplement ingredient and as a research-grade chemical; investigators should obtain analytical confirmation of identity and purity on every lot.