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## Review Article

## Rhodiola plants: Chemistry and biological activity



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## ABSTRACT

*Rhodiola* is a genus of medicinal plants that originated in Asia and Europe and are used traditionally as adaptogens, antidepressants, and anti-inflammatory remedies. *Rhodiola* plants are rich in polyphenols, and salidroside and tyrosol are the primary bioactive marker compounds in the standardized extracts of *Rhodiola rosea*. This review article summarizes the bioactivities, including adaptogenic, antifatigue, antidepressant, antioxidant, anti-inflammatory, antinoception, and anticancer activities, and the modulation of immune function of *Rhodiola* plants and its two constituents, as well as their potential to prevent cardiovascular, neuronal, liver, and skin disorders.

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## 1. Introduction

The genus *Rhodiola* (Hong Jing Tian; Crassulaceae) consists of more than 200 species, of which approximately 20, including *Rhodiola rosea*, *Rhodiola alterna*, *Rhodiola brevipetiolata*, *Rhodiola crenulata*, *Rhodiola kirilowi*, *Rhodiola quadrifida*, *Rhodiola sachalinensis*, and *Rhodiola sacra*, are used as traditional medicines in Asia [1]. These plants grow mainly in the Himalayan belt, Tibet, China, and Mongolia, but are also cultivated in Europe and North America and are available on the market as dietary supplements [2,3]. *Rhodiola* plants extracts are traditionally used in tonics and adaptogen, antidepressant, and anti-inflammatory drugs [2,4]. The most widely known is *Rhodiola rosea*, which is also called the “golden root” or “roseroot.” The

pharmacological effects of *Rhodiola rosea*, including its role in increasing longevity, stimulating the central nervous system, and elevating work performance as well as its cardio-, neuro-, and hepatoprotective effects and immunotropic, antiviral, anti-inflammatory, and antibacterial activities, have been studied extensively [1,5]. *Rhodiola rosea* has been used for a long time in Eastern Europe and Asia to enhance physical and mental performance. It is also used in Eastern Europe and Asia as a traditional medicine to stimulate the nervous system, alleviate depression and fatigue, enhance work performance, and prevent high-altitude sickness, mountain malhypoxia, and anoxia [6], and in Russia and Mongolia for treating long-term illness and weakness caused by infection [7]. In addition, *Rhodiola rosea* has been proven to have cardiovascular protection effects [8,9]. In recent years, the root extracts of *Rhodiola rosea*

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have been used as drinks, food additives, and in commercial pharmaceutical preparations offered worldwide [10].

*Rhodiola* plants contain polyphenols such as flavonoids, proanthocyanidines, tyrosol, and cinnamyl alcohol, as well as glycosides, organic acids, essential oils, sugars, fats, alcohols, and proteins [5]. The polyphenol content of *Rhodiola rosea* is approximately  $41.4 \pm 3.41\%$  [11]. Rosavin (such as rosavin, rosarin, rhodionin, rhodiosin, and rosin), cinnamyl alcohol, salidroside (Fig. 1B), and tyrosol (Fig. 1A) are the major components of *Rhodiola* plants [12–18]. Salidroside and its aglycone, tyrosol, are the major compounds of *Rhodiola rosea*, and the content of the two compounds are often used as a criterion in evaluating the quality of crude drugs of *Rhodiola rosea* [19].

This review article presents an overview of the bioactivities of *Rhodiola* plants and their major components.

## 2. Adaptogenic and antifatigue activity

Adaptogens are substances that enable the normalization of physiologic responses to various stressors, enhances work performance, and increases the stress tolerance of the body [20,21]. Researchers have categorized *Rhodiola rosea* as an adaptogen because of its observed ability to increase resistance to various chemical, biological, and physical stressors [4,6,22,23] and its performance-enhancing effect in humans [24]. A study reported that repeated administration of *Rhodiola rosea* extract, SHR-5, exerts an antifatigue effect that increases mental performance, particularly the ability to concentrate, and reduces cortisol response to awakening stress in patients with burnout and fatigue syndrome [25]. The adaptogenic and central nervous system activities of *Rhodiola rosea* may be attributable to its influence on the levels and activity of monoamines and opioid peptides such as beta-endorphins [3].

Administering 100 mg/kg of an aqueous extract of *Rhodiola imbricata* provided maximum resistance to cold-hypoxia-restraint stress-induced hypothermia and quickened recovery from the stressor [26]. In addition, the aqueous extract of *Rhodiola imbricata* exhibited dose-dependent adaptogenic activity [27]. Research indicated that *Rhodiola* extracts have great

utility in treating asthenic conditions which develop after intense physical or intellectual strain, including a decline in work performance, sleep difficulties, poor appetite, irritability, hypertension, headaches, and fatigue [27].

Intense exercise increases oxygen consumption and causes oxidative stress as a result of increased reactive oxygen species (ROS) production [28]. Exogenous antioxidants may prevent oxidative damage because they scavenge ROS generated during exercise [29–32]. Salidroside was reported to elevate exercise tolerance and increase the liver glycogen levels of rats after exhaustive exercise such as swimming [29]. In addition, salidroside reduced malondialdehyde (MDA) levels and enhanced the activity of antioxidant enzymes [such as catalase, superoxide dismutase (SOD), and glutathione peroxidase] in the liver tissue of Sprague-Dawley (SD) rats [29].

The above mentioned studies suggested that *Rhodiola* plants elevate work performance and resistance to stress, and that salidroside is effective in preventing oxidative stress following exhaustive exercise.

## 3. Elongation of lifespan and anti-aging activity

*Rhodiola* markedly increased the lifespan of *Drosophila melanogaster*, possibly by increasing the resistance of organs to stress and alleviating oxidative stress [33]. Salidroside considerably reversed senescence-like phenotypes in an oxidant-challenged model, altering the morphology, cell cycle, SA-b-gal staining, and DNA damage as well as the expression of related molecules such as p53, p21, and p16 in the 2BS cell line (human fetal lung fibroblasts). Furthermore, the protection occurred in a dose-dependent manner [34]. In addition, salidroside blocked D-galactose-induced increases in serum advanced glycation endproduct levels in C57BL/6J mice [35]. It reversed D-galactose-induced aging effects in neural and immune systems, improved motor activity, increased memory latency time, and enhanced lymphocyte mitogenesis and interleukin-2 (IL-2) production [35]. Furthermore, salidroside reduced the elevated expression of glial fibrillary acidic protein and neurotrophin-3 in a mouse model of aging [35].

Accordingly, *Rhodiola* plant extracts and salidroside are potential agents for retarding aging and attenuating age-related diseases in humans and animals.

## 4. Antioxidative activity

ROS such as superoxide anions ( $O_2^-$ ), hydroxyl radicals ( $OH^\bullet$ ), and hydrogen peroxide ( $H_2O_2$ ) can cause oxidative stress in cellular DNA, protein, and lipids, resulting in numerous disorders and diseases, such as aging-related diseases, cancer, cardiovascular diseases, diabetes mellitus (DM), and various neurodegenerative diseases [32,36,37]. In addition, a *Rhodiola* plant extract exhibited antioxidant activity and reduced lipid peroxidation in SD rats [38]. *Rhodiola rosea* showed singlet oxygen scavenging,  $H_2O_2$  scavenging, hypochlorite scavenging, ferric reducing, ferrous chelating, and protein thiol protection activities [11]. *Rhodiola rosea* extract reduced glutathione levels, glyceraldehyde-3-phosphate

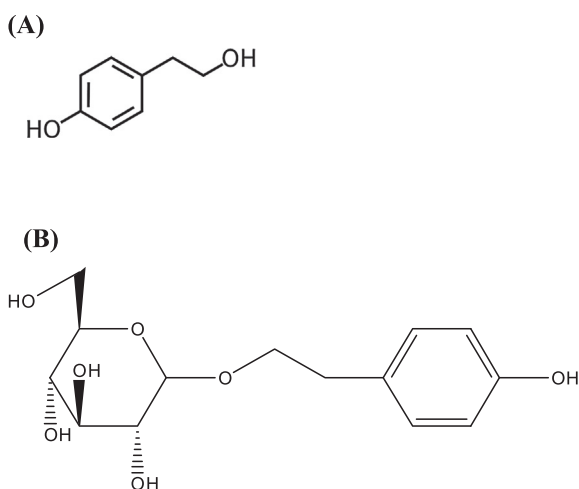


Fig. 1 – (A) The structure of tyrosol; (B) the structure of salidroside.

dehydrogenase activity, and thiobarbituric acid reactive substances levels in cultured human keratinocytes exposed to various oxidative insults such as  $\text{Fe}^{2+}$ /ascorbate,  $\text{Fe}^{2+}/\text{H}_2\text{O}_2$ , and tert-butyl-hydroperoxide insults [39]. In addition, *Rhodiola rosea* extract inhibited the production of intracellular ROS and increased the activity of antioxidant enzymes such as catalase, SOD, glutathione peroxidase, and glutathione reductase. *Rhodiola rosea* extract also increased in a time- and dose-dependent manner the activity of transplasma membrane oxidoreductase according to an indirect evaluation of the intracellular redox status in keratinocytes [39]. *Rhodiola rosea* extract and salidroside protected human cortical neurons from oxidative stress and prevented glutamate-induced cell apoptosis in a human cortical cell line (HCN 1-A) [40].

Aqueous and alcoholic extracts of *Rhodiola* rhizomes were observed to inhibit apoptosis and tert-butyl hydroperoxide (tert-BHP)-induced free radical production and to restore the antioxidant levels of U-937 human macrophages [41]. They also inhibited tert-BHP-induced decreases in mitochondrial transmembrane potential, significantly lowered the percentage of early and late apoptotic cells, and inhibited DNA single-strand breaks induced by tert-BHP [41].

*Rhodiola rosea* supplementation can protect human osteosarcoma-derived 143B cells or human fibroblast cell line IMR-90 from ultraviolet light, paraquat, and  $\text{H}_2\text{O}_2$  [42]. However, *Rhodiola rosea* did not alter the levels of the major antioxidant defenses, nor did it markedly activate the antioxidant response element or modulate heme-oxygenase-1 expression levels at relevant concentrations [42].

Water and methanol extracts of *Rhodiola sacra* exhibit active oxygen scavenging activities such as  $\text{O}_2^-$  radical scavenging [43]. Oligomeric proanthocyanidin from *Rhodiola rosea* (OPCRR) exhibited free-radical-scavenging activities such as the scavenging of 1,1-diphenyl-2-picrylhydrazyl (DPPH),  $\text{OH}^\bullet$ , and  $\text{O}_2^-$  [44]. In addition, OPCRR significantly enhanced the oxidative stress defense system, including SOD and glutathione peroxidase activities, and reduced the MDA content in the serum, heart, liver, and brain tissue of mice [44]. These results suggest that OPCRR has great potential to be a natural antioxidant because of its antioxidant activities *in vitro* and *in vivo* [44].

Salidroside reduced hydrogen-peroxide-induced intracellular ROS production in human erythrocytes. In addition, salidroside increased cell survival significantly and prevented human erythrocytes from undergoing eryptosis or erythroptosis mediated by  $\text{H}_2\text{O}_2$  [45]. The protection activity of salidroside may rise in a dose-dependent manner through its antioxidative activity and the inhibition of caspase-3 activation and stress-induced intracellular  $\text{Ca}^{2+}$  production [45]. Salidroside is a protective agent against oxidative stress in human erythrocytes and may be a suitable adaptogen for enhancing the resistance of the body to stress and fatigue.

Like salidroside, *Rhodiola rosea*'s aglycone, tyrosol, has various biological properties, including antioxidative, cancer preventive, and anti-inflammatory properties [46]. Tyrosol exhibits antioxidant activity, scavenges DPPH free radicals, and has an  $\text{IC}_{50}$  of 4.7  $\mu\text{g}/\text{mL}$  [47].

*Rhodiola* extract, salidroside, and tyrosol may prevent oxidative-stress-related disorders.

## 5. Anti-inflammatory activity

Studies have reported that the tincture extract of *Rhodiola rosea* exhibits anti-inflammatory activity. In the plethysmometer test, orally administering *Rhodiola rosea* extract (50 mg/kg body weight and 100 mg/kg body weight) significantly reduced carrageenan-induced paw edema in Wistar rats [48]. The extract (250 mg/kg body weight) inhibited carrageenan-induced paw edema, formaldehyde-induced arthritis, and nystatin-induced paw edema in a rat model in a dose-dependent manner [1].

*Rhodiola* aqueous extract treatment of human peripheral blood mononuclear cells (PBMCs) increased the production of IL-6 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) through phosphorylated I $\kappa$ B and the transcription factor NF- $\kappa$ B, showing that this treatment has immunostimulatory potential [49]. The treatment also increased the synergistic production of nitric oxide (NO) and lipopolysaccharide (LPS) in RAW 264.7 cells. *Rhodiola* extract at 250  $\mu\text{g}/\text{mL}$  increased p-I $\kappa$ B expression and activated the nuclear translocation of NF- $\kappa$ B in human PBMCs. The results of the mentioned study suggest that *Rhodiola* activated proinflammatory mediators through the phosphorylation of inhibitory  $\kappa$ B and the transcription factor NF- $\kappa$ B [49].

The tincture extract from *Rhodiola rosea* inhibited the activities of enzymes relating to inflammation, including cyclooxygenase-1 (COX-1), COX-2, and phospholipase A2 (PLA2) in an *in vitro* study [1]. The inhibition of nystatin-induced edema and PLA2 suggested that membrane stabilization is the most probable mechanism of the extract's anti-inflammatory action [1].

A *Rhodiola rosea* extract inhibited inflammatory C-reactive protein and creatinine kinase expression in the blood levels of healthy untrained volunteers after exhausting exercise [50], indicating that the extract has an anti-inflammatory effect and protects muscle tissue during exercise.

*Rhodiola crenulata* increased the survival rates of adult flies and the expression of antimicrobial peptide genes after pathogen or toxic compound ingestion. Moreover, decreased levels of ROS and epithelial cell death were associated with improvements in intestinal morphology in *Drosophila melanogaster* [51]. *Rhodiola crenulata* extract may prevent inflammatory diseases of the intestine [51].

Salidroside attenuated D-galactosamine (700 mg/kg)-induced and LPS (10 mg/kg)-induced increases in the levels of TNF- $\alpha$  and serum nitric oxide in mouse liver tissue in a dose-dependent manner [52]. Salidroside significantly attenuated TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 production in serum from mice challenged with LPS [53]. In a murine model of endotoxemia, mice were treated with salidroside before or after LPS challenge, and salidroside significantly increased the likelihood of survival [53]. Salidroside downregulated LPS-induced nuclear transcription factor-B (NF-B) DNA-binding activation and extracellular signal-related kinase (ERK)/Mitogen-activated protein kinases (MAPK) signal transduction pathway production in RAW 264.7 macrophages [53]. The results of this study indicated that salidroside modulated early cytokine responses by blocking NF-B and ERK/MAPK activation and increased mouse survival. These effects of salidroside may be useful in treating inflammation-mediated endotoxemia [53]. In

addition, salidroside protected LPS-induced acute lung injury in mice [54]. Pretreatment with a single 120 mg/kg dose of salidroside prior to the administration of intratracheal LPS induced mouse myeloperoxidase activity in lung tissue and reduced the protein concentration and the total number of cells, neutrophils, and macrophages in the bronchoalveolar lavage fluid in BALB/c mice [54].

Salidroside administered 1 hour before LPS infusion significantly attenuated inflammatory cell infiltration, reduced the activity of myeloperoxidase in mammary tissue, and reduced the concentration of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 in a dose-dependent manner [55]. Salidroside also inhibited the production of several inflammatory cytokines, including TNF- $\alpha$ , IL-6, and IL-1 $\beta$ , and NF- $\kappa$ B DNA-binding activation after LPS challenge [54]. These results indicated that salidroside exerts a protective effect on LPS-induced acute lung injury in mice. Another study reported that salidroside downregulated the phosphorylation of LPS-induced NF- $\kappa$ B p65 and an inhibitor of NF- $\kappa$ B  $\alpha$  (I $\kappa$ B $\alpha$ ) in the NF- $\kappa$ B signal pathway and suppressed the phosphorylation of p38, ERK, and c-jun NH(2)-terminal kinase (JNK) in MAPK signaling pathways [55,56]. Salidroside is an effective suppressor of inflammation and may be a candidate for the prophylaxis of mastitis.

Salidroside pretreatment reduced the ratio of concanavalin-A-induced aspartate transaminase to alanine transaminase (also called the aspartate-aminotransferase-to-alanine-aminotransferase ratio) markedly and suppressed the secretion of proinflammatory cytokines by downregulating the activity of NF- $\kappa$ B [57]. Salidroside altered the distribution of CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes in the liver and spleen by regulating CXCL-10 and reduced the severity of liver injuries [57].

## 6. Antinociceptive effect

Studies have reported that *Rhodiola* extract exhibits analgesic activity. The antinociceptive effect of *Rhodiola* extract was evaluated using the hot-plate test, Randall-Selitto test, and formalin test in male Wistar rats. In the hot-plate test, orally administering *Rhodiola rosea* at 50 mg/kg and 100 mg/kg body weight increased the latency reaction [48]. In the Randall-Selitto test, *Rhodiola rosea* caused a significant increase in pressure reaction at 50 mg/kg [48]. In the formalin test, *Rhodiola rosea* significantly reduced the paw-licking time during the first phase at 100 mg/kg [48]. The studies indicated that *Rhodiola rosea* extract exhibited significant analgesic activity in different pain models, inhibiting thermal pain, mechanical hyperalgesia, and formalin-induced pain behavior.

## 7. Immune system

*Rhodiola* aqueous extract significantly enhanced tetanus toxoid-specific immunoglobulin levels in rats [58] and the level of ovalbumin-induced antibody responses. Tetanus toxoid and ovalbumin in combination with complete Freund's adjuvant or *Rhodiola* aqueous extract were observed to evoke a significant delayed-type hypersensitivity response [58]. *Rhodiola* aqueous extract did not suppress the swelling response

in an adjuvant-induced arthritis model [58]. *Rhodiola* aqueous extract exhibits adjuvant and immunopotentiating activity.

*Rhodiola imbricata* rhizome extract inhibited the proliferation of the human T-cell lymphoma cell line EL-4 and erythroleukemic cell line HL-60 [59]. Furthermore, treating human peripheral blood mononuclear cells (hPBMCs) with LPS and *Rhodiola imbricata* extract suppressed regulated upon activation, normal T cell expressed and secreted production [59]. However, the number of TNF- $\alpha$  spots in *Rhodiola imbricata*-rhizome-extract-treated hPBMCs increased. *Rhodiola imbricata* extract upregulated TLR-4 mRNA expression in the splenocytes of rats [59].

Aqueous and 50% hydroalcoholic extracts of *Rhodiola quadrifida* stimulated granulocyte activity *in vitro* and increased the response of lymphocytes to mitogens in mice and rats [60]. The ability of parental strain mouse lymphocytes to induce a local cutaneous graft-versus-host reaction in F1 hybrids was stimulated by the 50% hydroalcoholic extract [60].

*In vitro* aqueous and 50% hydroalcoholic *Rhodiola kirilowii* extracts stimulated granulocyte activity and increased lymphocyte response to mitogens, and, *in vivo*, they enhanced the ability of lymphocytes derived from parental strain mice fed *Rhodiola kirilowii* aqueous and hydroalcoholic extracts to induce a local cutaneous graft-versus-host reaction in F1 hybrids [61]. The results of this study suggested that *Rhodiola kirilowii* extract enhances cellular immunity [61].

In another study, the dietary intake of salidroside increased the total number of T cells (CD3<sup>+</sup>) and T helper cells (CD4<sup>+</sup>) in aged Wistar male rats (21 months old), and salidroside supplementation significantly increased the delayed-type hypersensitivity response in aged rats and substantially increased the production of anti-keyhole limpet hemocyanin (anti-KLH) IgG, anti-KLH IgG 1, and anti-KLH IgG 2  $\alpha$  in aged rats without disturbing immune homeostasis [62].

Intraperitoneally administering salidroside before an ovalbumin challenge resulted in the significant inhibition of asthmatic reactions [63]. Moreover, ovalbumin significantly increased the activation of NF $\kappa$ B and p38 in lung tissue, whereas salidroside markedly suppressed NF- $\kappa$ B translocation and reduced the phosphorylation of p38 [63]. Salidroside attenuated the expression of intercellular adhesion molecule 1 and IL-6 by modulating the activities of p38 and NF- $\kappa$ B in BEAS-2B cells stimulated by proinflammatory cytokines [63].

These results indicate that *Rhodiola* plant extracts influence immune modulation and salidroside prevents ovalbumin-induced airway inflammation and airway hyper responsiveness, at least in part by downregulating NF- $\kappa$ B and p38 activities [63].

## 8. Antidepressant

Extracts of SHR-5 from *Rhodiola rosea* rhizomes alleviated depressive symptoms in patients with mild or moderate depression, yielding no severe side effects [20]. Orally administering salidroside (20 mg/kg and 40 mg/kg) for 2 weeks notably alleviated olfactory-bulbectomy-induced hyperactivity in an open-field test and reduced immobility time in a forced swimming test [64]. Chronic treatment with salidroside greatly reduced TNF- $\alpha$  and IL-1 $\beta$  levels in the hippocampus

[64]. Salidroside increased glucocorticoid receptor and brain-derived neurotrophic factor expression in the hippocampus of rats. In addition, salidroside attenuated corticotropin-releasing hormone expression in the hypothalamus and the levels of serum corticosterone [64]. Salidroside significantly reduced depression-like behavior in olfactory bulbectomized rats; the mechanisms of this reduction might be associated with the anti-inflammatory effects of and regulation of hypothalamic–pituitary–adrenal axis activity by salidroside.

## 9. Skin care and skin whitening

Studies have reported the potential for using *Rhodiola rosea* extract in skin care and wound healing, and that *Rhodiola rosea* extract modulates skin melanogenesis. *Rhodiola rosea* extract/L-carnosine-associated compound (RCAC) treatment for sensitive skin reduced transepidermal water loss in humans, thereby improving skin barrier function [65]. RCAC treatment also exhibited a positive subjective response in patients with sensitive skin, promoted the release of proopiomelanocortin peptides, and returned to normal levels the increased number of neuropeptides and cytokines produced by keratinocytes exposed to ultraviolet radiation [65].

*Rhodiola imbricata*-treated wounds healed more rapidly than control group, and the plant extract promoted cellular proliferation and collagen synthesis at the wound site in SD rats [38]. *Rhodiola imbricata* extract increased DNA, protein, hydroxyproline, and hexosamine expression in granulation cells more than providone–iodine ointment [38]. The extract also exhibited antioxidant activity and reduced lipid peroxidation. Thus, it exhibits wound healing activity.

*Propionibacterium acnes*, a Gram-positive bacterium, is critical in the pathogenesis of acne vulgaris [66]. *Propionibacterium acnes* is capable of biofilm formation, and the decreased antimicrobial susceptibility of biofilm-associated cells may hamper the effective treatment of *Propionibacterium acnes* infection. *Rhodiola crenulata* extract exhibited antibiofilm activity against *Propionibacterium acnes* [66].

Melanin is responsible for skin color and plays a major role in the defense against harmful external factors such as ultraviolet irradiation [67–70]. Tyrosinase is the rate-limiting step of tyrosine hydroxylation and is responsible for the critical steps of melanogenesis [70,71]. The mechanisms of the action of skin hypopigmenting agents are thought to be based on the ability of an agent to inhibit the activity of tyrosinase and, thus, down-regulate melanin synthesis [70,72,73]. Studies have shown that the acetone extract of *Rhodiola rosea* exhibits antityrosinase activity [74] and that the hydroalcoholic extract of *Rhodiola rosea* extract and its hydrolysate inhibited melanin synthesis and tyrosinase activity in B16F0 cells (mouse melanoma cells) [75]. *Rhodiola rosea* extract also inhibited the gene and protein expression of melanocortin 1 receptor (MC1R), inhibited c-AMP response element binding protein phosphorylation, suppressed the activation of AKT and glycogen synthase kinase-3 beta (GSK3b), and inhibited the expression of microphthalmia-associated transcription factor and tyrosinase-related protein 1 (TRP-1) [70,76,77]. The hydrolysate of *Rhodiola rosea* inhibited the phosphorylation of CREB, activation of AKT and GSK3 $\beta$ , and expression of MITF and tyrosinase.

In one study, tyrosol and its glycoside, salidroside, exhibited antimelanogenesis activity [78]. Treating B16F0 cells with tyrosol and salidroside reduced melanin content and the inhibition of tyrosinase activity and its expression [78]. Tyrosol suppressed  $\alpha$ -MSH-induced MC1R and TRP-1 expression, but salidroside did not. Neither tyrosol nor salidroside affected MITF or TRP-2 expression. The compounds exhibited metal-coordinating interactions with copper ions in molecular docking with tyrosinase [78]. Salidroside significantly inhibited tyrosinase activity in B16F0 cells at 1000  $\mu$ M and melanin content at 100–1000  $\mu$ M in a dose-dependent manner [79]. Salidroside inhibited UVB-induced hyperpigmentation in brown guinea pig skin by reducing the number of DOPA-positive melanocytes in the basal layer of the epidermis and reducing tyrosinase activity and melanin synthesis in melanocytes [79]. *Rhodiola rosea* extract, salidroside, and tyrosol may be effective skin-whitening agents; Table 1 summarizes their effects on skin.

## 10. Protection against neuron and central neuron system disorders

A titolated extract from *Rhodiola rosea* and salidroside protected human cortical cells (HCN 1-A) from oxidative stressors such as H<sub>2</sub>O<sub>2</sub> and glutamate-induced cell apoptosis [40]. Pretreatment with *Rhodiola rosea* extract significantly increased cell survival and prevented plasma membrane damage and morphological disruption caused by glutamate or H<sub>2</sub>O<sub>2</sub>, indicating that *Rhodiola rosea* extract protects neurons from oxidative-stress-induced disorders [40]. In addition, *Rhodiola rosea* extract significantly reduced oxidative-stress-induced elevation of intracellular free Ca<sup>2+</sup> concentrations [40].

Significant improvement in long-term memory was observed after 10 days of treatment with 0.1 mL of *Rhodiola rosea* extract [6]. However, in another study, *Rhodiola rosea* exhibited cytotoxic effects at 100  $\mu$ g/mL in cultured primary cortical neurons [80]. *Rhodiola rosea* extracts exhibited antioxidant capacity but did not exhibit neuroprotective effects in primary cortical neurons [80].

Salidroside suppressed the LPS-induced expression of iNOS and cytokines in BV2 cells in a concentration-dependent manner [81]. Orally administering *Rhodiola rosea* crude extract (500 mg/kg) suppressed the expression of the proinflammatory factors iNOS, IL-1 $\beta$ , and TNF- $\alpha$  in the kidney and prefrontal cortex of the brain in mice [81]. L-Glutamate treatment increased the levels of phosphorylated MAPK, p-JNK, and p-p38 [81]. These results indicate that *Rhodiola rosea* may have therapeutic potential for treating inflammation and neurodegenerative disease [81].

Oxidative stress plays a crucial role in Parkinson's disease and other neurodegenerative disorders. Salidroside has a neuroprotective effect in cortical neurons because of its antioxidant activity and ability to stabilize cellular Ca<sup>2+</sup> homeostasis [40]. Incubating PC12 cells with salidroside prior to MPP<sup>+</sup> exposure significantly reduced cell apoptosis and attenuated the collapse of the mitochondrial membrane potential [82]. Furthermore, salidroside inhibited MPP<sup>+</sup>-induced NO increases, the overexpression of nNOS and iNOS, and the accumulation of ROS and intracellular free Ca<sup>2+</sup> [82]. Salidroside inhibited ROS and NO production, protecting PC12 cells

**Table 1 – The activities of *Rhodiola* plants and its active constituents on skin disorders.**

Plants/constituents	Models	Results	References
<i>Rhodiola rosea</i>	B16F0 cells	1 Suppressed melanin synthesis and tyrosinase activity 2 Inhibited TRP-1 and tyrosinase expression 3 Inhibited MC1R/ CREB/ GSK3 $\beta$ /MITF	[74,75]
<i>Rhodiola rosea</i> extract/ L-carnosine-associated compound	Human skin	1 Reduced transepidermal water loss (TEWL) 2 Elevated the skin barrier function 3 Positive subjective response	[65]
<i>Rhodiola rosea</i> extract/ L-carnosine-associated compound	Keratinocytes	1 Promoted the release of proopiomelanocortin peptides 2 Restored to normal the increased levels of neuropeptides and cytokines	[65]
<i>Rhodiola imbricata</i>	SD rats	1 Promoted wound healing 2 Promoted cellular proliferation 3 Increased collagen synthesis 4 Increased the DNA, protein, hydroxyprolin, and hexosamine in granulation cells 5 Antioxidant and decrease lipid peroxidation	[38]
<i>Rhodiola crenulata</i> extract	Propionibacterium acnes	antibiofilm activity against <i>Propionibacterium acnes</i>	[66]
Salidroside	B16F0 cells	Suppressed melanin synthesis and tyrosinase activity, but no effect on the expression of MC1R, MITF, TRP-1, or TRP-2	[74,78,79]
Tyrosol	B16F0 cells	1 Suppression of melanin synthesis and tyrosinase activity 2 Suppressed the expression of MC1R and TRP-1, but not TRP-2 and MITF	[78]

from oxidative stress. The protective effects of salidroside on PC12 cells are mediated by the inhibition of ROS generation and the NO pathway [82]. In addition, salidroside pretreatment protected dopaminergic neurons against MPTP/MPP<sup>+</sup>-induced toxicity in a dose-dependent manner [83]. The mechanisms of this protection included salidroside reducing the production of ROS and NO, regulating the ratio of Bcl-2/Bax, reducing cytochrome-c and Smac release, inhibiting caspase-3, caspase-6, and caspase-9 activation, and reducing  $\alpha$ -synuclein aggregation [83].

Pretreatment with salidroside markedly attenuated H<sub>2</sub>O<sub>2</sub>-induced cell viability loss and apoptotic cell death in a dose-dependent manner in human neuroblastoma SH-SY5Y cells [84]. Salidroside protected neuron cells from oxidative stress by inducing several antioxidant enzymes such as thioredoxin, heme oxygenase-1, and peroxiredoxin-I and downregulating the proapoptotic gene Bax and upregulating the antiapoptotic genes Bcl-2 and Bcl-X<sub>L</sub> [84]. Furthermore, salidroside dose-dependently restored H<sub>2</sub>O<sub>2</sub>-induced loss of mitochondrial membrane potential and elevated intracellular calcium levels [84]. Salidroside alleviated hydroxyl-peroxide-induced cell viability loss and apoptotic cell death in a dose-dependent manner in cultured nerve-growth-factor-differentiated PC12 cells [85]. The neuroprotective effects of salidroside might be modulated by the ERK signaling pathway, particularly at the level of or upstream from caspase-3 [85]. In addition, salidroside (100  $\mu$ M) significantly reduced hydroxyl-peroxide-induced apoptosis and necrosis and markedly attenuated oxidative insult caused by hydroxyl peroxide exposure in cultured rat cortical neurons [86]. Salidroside prevented cerebral ischemic injury induced by middle cerebral artery occlusion and reperfusion in SD rats. Furthermore, there were more normal neurons and cells in the hippocampus after salidroside treatment [86]. These results suggest that salidroside has protective

effects against oxidative-stress-induced cell apoptosis and is thus a potential therapeutic agent for treating or preventing neurodegenerative diseases involving oxidative stress.

Salidroside reduced neuronal death and behavioral dysfunction mediated by polyglutamine expressed in ASH neurons in transgenic *Caenorhabditis elegans* [87]. Salidroside's antioxidative capability, but not its direct inhibition of polyglutamine aggregation, may contribute to neuron protection [87].

*Rhodiola* plant extracts and salidroside prevented neural disorders such as Parkinson's disease and other neurodegenerative disorders. Table 2 lists studies of the effects of these agents on neurons.

## 11. Liver protection

The methanolic extract from the roots of *Rhodiola sachalinensis* exhibited a protective effect on D-galactosamine-induced cytotoxicity in primary cultured mouse hepatocytes [88]. In addition, the principal constituents, sachalosides III and IV, rhodiosin, and transcaffeic acid, exhibited hepatoprotective effects [88].

Salidroside attenuated D-galactosamine- and LPS-induced acute increases in serum aspartate aminotransferase and alanine aminotransferase activities and in levels of TNF- $\alpha$  and serum NO in a dose-dependent manner [52]. It restored depleted hepatic glutathione, SOD, catalase, and glutathione peroxidase activities, reduced MDA levels, and considerably reduced histopathological changes in liver tissue [52]. In addition, salidroside reduced the size of necrotic regions, caspase-3 expression, and hypoxia-inducible factor (HIF)-1 $\alpha$  in liver tissue in mice [52]. The hepatoprotective mechanism of salidroside may be related to antioxidant activity and the

**Table 2 – The activities of *Rhodiola* plants and its active constituents on neuron system.**

Plants/ constituents	Models	Results	References
<i>Rhodiola rosea</i>	Human cortical cell line (HCN 1-A)	1 Against oxidative stressor 2 Increased cell survival 3 Prevented the plasma membrane damage	[40]
<i>Rhodiola rosea</i>	Rats	improvement of the long-term memory	[6]
Salidroside	Transgenic <i>Caenorhabditis elegans</i> models	1 Decreased ROS levels 2 Decreased paraquat-induced mortality 3 Increased antioxidant enzyme activities 4 Reduced lipid peroxidation 5 Reduced neuronal death and behavioral dysfunction mediated by polyQ expressed in ASH neurons	[87]
Salidroside	PC12 cells	1 Protected PC12 cells against MPP <sup>+</sup> -induced apoptosis 2 Rescued MPP <sup>+</sup> -induced changes in nuclear morphology 3 Attenuated the MPP <sup>+</sup> -induced decrease in mitochondrial membrane potential 4 Inhibited MPP <sup>+</sup> -induced NO increase	[82]
Salidroside	PC12 cells	1 Protected NGF-differentiated PC12 cells against H <sub>2</sub> O <sub>2</sub> -induced neurotoxicity and apoptosis 2 Activated ERK phosphorylation 3 Antagonized H <sub>2</sub> O <sub>2</sub> -induced increase in cleaved caspase-3 protein expression in a dose-dependent manner	[85]
Salidroside	PC12 cells C57BL/6 mice	1 Exerted a protective effect against MPP <sup>+</sup> -induced cytotoxicity in PC12 cells 2 Reduced the MPP <sup>+</sup> -induced rate of apoptosis in PC12 cells 3 Counteracted the decrease in the Bcl-2/Bax ratio and the expression of the proteins induced by MPP <sup>+</sup> in a dose-dependent manner in PC12 cells 4 Decreased the expression of Bcl-2, Bax, Cyt-c, Smac, caspase-3, caspase-6, and caspase-9 in C57BL/6 mice	[83]
Salidroside	Human neuroblastoma SH-SY5Y cells	1 Prevented SH-SY5Y cells against H <sub>2</sub> O <sub>2</sub> -induced cytotoxicity 2 Increased thioredoxin, heme oxygenase-1 and peroxiredoxin-I mRNA expression decreased by H <sub>2</sub> O <sub>2</sub> 3 Protected SH-SY5Y cells against H <sub>2</sub> O <sub>2</sub> -induced apoptosis 4 Prevented H <sub>2</sub> O <sub>2</sub> -induced reduction of the mitochondrial membrane potential 5 Inhibited H <sub>2</sub> O <sub>2</sub> -induced Ca <sup>2+</sup> influx increase	[84]

inhibition of HIF-1 $\alpha$  [52]. *Rhodiola sachalinensis* and salidroside protected liver tissue from oxidative-stress-induced damage.

## 12. Cardiovascular disease

*Rhodiola rosea* was observed to prevent stress-induced cardiac damage [9]. The cardioprotective effects of *Rhodiola rosea*, including a pronounced antiarrhythmic effect [9], the prevention of reduced coronary flow, and an increase in contractility in the postischemic period, were observed in animals [89]. *Rhodiola rosea* was ascertained to prevent both stress-induced catecholamine release and elevation of cAMP levels in the myocardium [9]. Moreover, it lowered blood pressure [90] and prevented stress-induced cardiac damage, indicating its critical role as a cardioprotective agent in animals [8].

The rhizome of *Rhodiola kirilowii* significantly increased the expression of von Willebrand factor in the infarct border zone and noninfarct zone in the myocardium of rats [91]. The expression of HIF-1 $\alpha$ , HIF-1 $\beta$ , and vascular endothelial growth factor (VEGF) mRNAs as well as HIF-1 $\alpha$  and VEGF proteins was significantly increased in a *Rhodiola kirilowii* group [91].

Salidroside exhibited activity similar to that of *Rhodiola kirilowii*, increasing the expression of HIF-1 $\alpha$ , HIF-1 $\beta$ , and VEGF during ischemia and hypoxia [91]. In addition, salidroside

protected human endothelial cells (EVC-304) from H<sub>2</sub>O<sub>2</sub>-induced oxidative damage in a dose-dependent manner [92]. Salidroside inhibited the activation of caspase-3, caspase-9, cleavage of poly(ADP-ribose)polymerase, and Bax induced by endogenous H<sub>2</sub>O<sub>2</sub> [92].

Salidroside and tyrosol dose-dependently inhibited nuclear condensation in H9c2 cells [93]. Furthermore, salidroside and tyrosol, separately and in combination, significantly reduced caspase-3 activity, cytochrome c release, and JNK activation. The antiapoptotic effect of the combination was markedly higher than that of salidroside and tyrosol alone [93]. The inhibition of the JNK-signaling pathway is the key mechanism for the cytoprotective effects of salidroside and tyrosol in ischemia-reperfusion-induced apoptosis in H9c2 cells [93]. *Rhodiola* plants, salidroside, and tyrosol may facilitate preventing and treating oxidative stress in cardiovascular and cerebrovascular diseases.

## 13. DM

DM is associated with increased oxidative stress. Rats with streptozotocin (STZ)-induced DM experienced heart failure caused by increased PPAR $\delta$  expression. The ethanol extract of *Rhodiola* increased PPAR $\delta$  expression and cardiac output in

STZ-diabetic rats [94]. Salidroside administered to mice daily (50 mg/kg, 100 mg/kg, and 200 mg/kg for 28 days) was demonstrated to cause hypoglycemic activity and have protective effects against DM-induced oxidative stress, including significantly reduced fasting blood glucose, total cholesterol, triglyceride, and MDA levels [95]. In addition, it increased serum insulin, SOD, and glutathione peroxidase levels as well as catalase activity in the liver in mice [95]. Therefore, *Rhodiola* extracts and salidroside should be considered for use in treating DM [95].

#### 14. Obesity and hyperlipidemia

*Rhodiola rosea* inhibited the activity of lipase in isolated mouse plasma *in vitro* and in the mouse gastrointestinal tube *in vivo* and can be used in treating or preventing lifestyle-related diseases such as hyperlipidemia and exogenous obesity [14]. *Rhodiola* extracts dose-dependently increased SOD activity, resulting in a reduced ROS level during adipogenesis [96]. Treatment with *Rhodiola* extract inhibited the activities of proline dehydrogenase (PDH) and glucose-6-phosphate dehydrogenase (G6PDH) as well as lipid accumulation and ROS production in 3T3-L1 preadipocytes [96]. In addition, SOD activity in cells treated with *Rhodiola* extract increased significantly during the differentiation of 3T3-L1 preadipocytes [96]. The inhibition of PDH and G6PDH prevented the proline oxidation required for critical ATP generation that is coupled with the antioxidant enzyme response via the proline-mediated pentose phosphate pathway, leading to the inhibition of adipogenesis [96]. The antiadipogenic effects of *Rhodiola* extract may disrupt proline-mediated energy generation and antioxidant enzyme response via the proline-mediated pentose phosphate pathway, resulting in the suppression of adipogenesis and lipid accumulation [96].

Tyrosol at 1.0 mg/mL significantly increased SOD activity during the differentiation of 3T3-L1 preadipocytes [96]. In addition, tyrosol inhibited the activities of PDH and G6PDH and lipid accumulation [96]. *Rhodiola* extract and tyrosol may be used to prevent obesity.

#### 15. Anticancer

Incubation with *Rhodiola imbricata* aqueous extract at 100 mg/mL and 200 mg/mL for 72 hours significantly reduced the proliferation of K-562 human erythroleukemic cells in a dose-dependent manner but not the proliferation of normal human peripheral blood lymphocytes or RAW-264.7 mouse macrophage cells [97]. In addition, *Rhodiola imbricata* aqueous extract was observed to induce intracellular ROS in K-562 cells at 200 mg/mL and, thus, induce apoptosis [97]. *Rhodiola imbricata* aqueous extract arrested the cell cycle progression of K562 and NK cells in the G2/M phase in early and late periods of exposure [97].

Salidroside significantly reduced the proliferation of A549 human alveolar adenocarcinoma cells, inhibited cell cycle arrest in the G0/G1 phase, and induced apoptosis in A549 cells by reducing pp38 protein expression [98]. Salidroside inhibited transforming growth factor- $\beta$ -induced tumor invasion and

suppressed protein expression [98]. Salidroside inhibited intracellular ROS formation in a dose-dependent manner in A549 cells [98]. Another study reported that salidroside significantly reduced tumor-induced angiogenesis in mice [2].

#### 16. Antivirus activity

Salidroside provided protection against coxsackievirus B3, which causes viral myocarditis, in both *in vitro* and *in vivo* experiments [99]. The IC<sub>50</sub> of salidroside for coxsackievirus B3 is 39.0  $\pm$  1.2 mg/L. Salidroside can modulate the mRNA expression of interferon-g, IL-10, TNF- $\alpha$ , and IL-2 in coxsackievirus B3. Salidroside increased lactic dehydrogenase, aspartate transaminase, and creatine kinase activities in infected BALB/c mouse serum [100]. Salidroside is a potential agent for treating viral myocarditis [99].

#### 17. Conclusion

*Rhodiola* plants are commonly used in traditional medicines in Asia and Europe. Studies have shown that the plants and their two major constituents, salidroside and tyrosol, exhibit adaptogenic, antifatigue, antidepressant, antioxidant, anti-inflammatory, antinociception, and anticancer bioactivities, modulate immune function, and prevent cardiovascular, neuronal, liver, and skin disorders.

#### Conflicts of interest

The authors declare that they have no conflicts of interest related to this work.

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