Chemical Components and Bioactivities of *Rhodiola rosea*

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**Abstract:** *Rhodiola rosea* is a perennial plant at high altitudes in the Arctic and mountainous regions throughout Europe and Asia. It contains various active compounds e.g. phenylpropanoids, phenylethanol derivatives, flavanoids, monoterpenes, triterpenes, phenolic acids, and essential oils. Salidroside and tyrosol are the major bioactive constituents in *Rhodiola rosea*. Traditionally, *Rhodiola rosea* is used for the treatment of various ailments like altitude sickness, fatigue, depression, anemia, impotence, infections gastrointestinal ailments, etc. The modern pharmacological studies and clinical trials have demonstrated that this plant possesses anti-fatigue, antioxidant, anti-hypoxic, anti-depressive, anti-anxiety, antimicrobial, antiviral, anti-inflammatory, anticancer, and immunomodulatory activities. This review summarizes current knowledge about chemical components and bioactivities of *Rhodiola rosea*.

**Keywords:** *Rhodiola rosea*; salidroside; tyrosol; anti-fatigue; antioxidant; anticancer.

1. Introduction

*Rhodiola rosea* belongs to the family Crassulaceae, sub-family Sedoideae, and genus Rhodiola,
is known by the common names Rhodiola, Roseroot, Rosenroot, Golden Root, Arctic Root, Orpin Rose, and Rhodiole Rougeâtre (Panossian et al., 2010). It is found at high altitudes in the Arctic and mountainous regions throughout Europe and Asia (Hung et al., 2011). *Rhodiola rosea* is a perennial plant that can reach a height of 12 to 30 in (70 cm) and produces yellow flowers, and owns a thick rhizome (Khanum et al., 2005).

*Rhodiola rosea* has a long history as a valuable traditional medicine in European, Asia and Russia for centuries. *Rhodiola rosea* was used as far back as by the Vikings to increase endurance and physical strength. It was also been prescribed for cancer and tuberculosis in Mongolia, given to newlyweds to boost fertility in Siberia (Ishaque et al., 2012). In traditional Chinese medicine, *Rhodiola rosea* have been used as a tonic, haemostatic for treatment of leucorrhea, contusion and improve cardiovascular function (Yu et al., 2014).

Last decade, *Rhodiola rosea* was intensively studied around the world. Its chemical components have been identified distinctly by different kinds of analysis methods, and many studies have demonstrated its biological activities like anti-fatigue, anti-aging, anti-hypoxic, anti-depressive, antioxidant, anti-inflammatory, anticancer, antimicrobial, and antiviral activities. The main objective of this review is to summarize the current knowledge about chemical components and bioactivities of *Rhodiola rosea*.

2. Chemical Components of *Rhodiola rosea*

*Rhodiola rosea* rhizome and root are the most medicinally valuable parts of *Rhodiola rosea* (Filion et al., 2008; Peschel et al., 2013). They contain various active compounds, e.g., phenolic compounds (tyrosol, salidroside, gallic acids), flavonoids (tricin-5-glucoside, tricin-7-glucoside, astragalin, kaempferol, rhodionin, rhodiosin, rhodiolgidin, rhodiolgin), cinnamic alcohol glucosides (rosin, rosarin, rosavin) (Perinskaya and Sakanyan, 2014).

The phytochemical characterization of different Rhodiola species usually exists differences. Yousef et al. (2006) compared phytochemical constituents between *Rhodiola rosea* and two other Rhodiola species (*R. heterodonta* and *R. semenovii*), chemical similarities among the three species were observed. However, each species displayed differences in phytochemical constituents. *R. heterodonta* contained a newly detected phenyl-ethanoid glycoside, heterodontoside. Both *R. heterodonta* and *R. rosea* contained phenylethanoid/propanoid that was not detected in *R. semenovii*. For *R. semenovii*, the cyanogenic glucosides rhodiocyanoside A and lotaustralin were detected. The variability of phytochemical characterization not only exists between varieties but also within species. Magsar et al. (2012) investigated intraspecific chemical variability of wild growing *Rhodiola rosea* from Southeastern Mongolian Altai. They compared the content of major chemical components in five
geographically distant populations, and the results showed significant differences between the populations in respect of the content of the compounds. The variability of chemical composition that exist in the same kind of *Rhodiola rosea* may be related to soil nutrient and plants age (Kolodziej and Sugier, 2013; Yan et al., 2004).

Early studies about the phytochemistry of *Rhodiola rosea* had confirmed the presence of many compounds and divided them into these classes, i.e., phenylpropanoids, phenylethanol derivatives, flavanoids, monoterpenes, triterpenes, and phenolic acids (Khanum et al., 2005). In addition, the recent studies found many new compounds, e.g., polysaccharides, tocopherols, and essential oils (Jin et al., 2013; Lei et al., 2003; Song et al., 2008).

2.1. Phenylpropanoids

Phenylpropanoids, which contain one or several C6-C3 fragments are widely distributed in nature, and can be treated as a large class of natural compounds (Kurkin, 2003). The phenypropanoids consisted in *Rhodiola rosea* mainly included phenylpropenoids rosin (cinnamyl-O-β-D-glucopyranoside) (1 in Fig. 1), rosarin (cinnamyl-(6-O-α-L-arabinofuranosyl)-O-β-D-glucopyranoside) (2 in Fig. 1) and rosavin (cinnamyl-(6-O-α-L-arabinopyranosyl)-O-β-D-glucopyranoside) (3 in Fig. 1), which are reported to be pharmacologically active as antioxidants and neurostimulants (Tolonen et al., 2003). Lignins are also complex phenylpropanoids, and 12 lignans were isolated from *Rhodiola crenulata* (Yang et al., 2012).

![Figure 1. Chemical structures of (1) phenylpropenoids rosin, (2) rosarin and (3) rosavin.](image-url)
2.2. Phenylethanol Derivatives

Salidroside (4 in Fig. 2) and its aglycone tyrosol (5 in Fig. 2) are two major bioactive constituents in *Rhodiola rosea* (Chen et al., 2011). Concentration of these two components in *Rhodiola rosea* is one of the standard indexes to appraise the quality of *Rhodiola rosea* (Mao et al., 2007). Salidroside and tyrosol have many pharmacological properties, which include anti-anoxic, anti-cold, anti-fatigue, anti-microwave radiation, anti-virus and anti-tumour activities (Shi et al., 2013). The contents of salidroside and tyrosol were determined in the *Rhodiola rosea* samples gathered from various area in China through reversed-phase high performance liquid chromatographic method, and they were ranged over 1.3-11.1 mg/g and 0.3-2.2 mg/g, respectively (Linh et al., 2000).

![Figure 2. Chemical structures of (4) salidroside and (5) tyrosol.](image)

2.3. Flavanoids and Flavonol Glycosides

Kaempferol, rhodionin, and rhodiosin were several flavonol glycosides identified earlier in *Rhodiola rosea* (Du and Xie, 1995). According to the recent reports, more and more flavonoids were isolated from *Rhodiola rosea*, e.g., proanthocyanidins, rhodioloside, herbacetin, and gossypetin (Huang et al., 2008; Ismailov et al., 1999; Petsalo et al., 2006). Flavonoids have impacts on many aspects of human health, including anti-tumor, anti-oxidation, and anti-inflammation (Xu et al., 2013).

2.4. Monoterpenes

Rosiridol and its glucoside, rosiridin were two monoterpenoids which isolated from *Rhodiola rosea* earlier. Later study also discovered much monoterpenes and their glycosides in succession. Ma et al. (2006) isolated five monoterpene glycosides rhodiolosides A-E from the roots of *Rhodiola rosea*. A new monoterpene, sachalol and three new monoterpene glycosides, sachalosides VI, VII, VIII, were also isolated from the root of *Rhodiola sachalinensis* (Li et al., 2008).

2.5. Triterpenes

Daucosterol and β-sitosterol are triterpenes isolated from the roots of *Rhodiola rosea* in
Xinjiang through the column chromatography (Wang et al., 2011).

2.6. Phenolic Acids

High content of polyphenolics (0.971 ± 0.01 mg/100g of quercetin) was determined in hydro-alcoholic rhizome extract of *Rhodiola imbricate* native to the high-altitude Himalayas (Arora et al., 2005). Besides, *Rhodiola rosea* also contains caffeic acid, gallic acid and other phenolic acids (Ma et al., 1995).

2.7. Essential Oils

In recent years, many researchers identified chemical composition of the essential oil from *Rhodiola rosea*. For the different varieties and origins of *Rhodiola rosea*, their chemical compositions of essential oil are different (Evstatieva et al., 2010). Lei et al. (2003) analyzed essential oils from rhizomes of *Rhodiola crenulata* and *R. fastigiata* in eastern Tibet by using GC-MS. The major constituents were geraniol (53.3%), n-octanol (13.4%), 2-methyl-3-buten-2-ol (10.8%), citronellol (5.3%), 3-methyl-2-buten-1-ol (4.0%), myteol (3.0%) and linalool (2.4%) for *Rhodiola crenulata*, however, for *R. fastigiata*, the major constituents were geraniol (45.3%), n-octanol (12.3%), 2-methyl-3-buten-2-ol (8.0%), linalool (5.1%), isogeraniol (4.5%), citronellol (4.4%) and cis-sabinenehydrate (3.6%). Shatar et al. (2007) analyzed essential oils from rhizomes of *Rhodiola rosea* in Mongolia by using GC and GC/MS methods, and the main components were geraniol (32.3%), myrtenol (15.7%), octanol (13.7%), trans-pinocarveol (11.6%), trans-myrtanol (3.2%), isopinocamphone (2.8%) and piperitone (1.2%).

2.8. Other Chemical Components

Tocopherols, lotaustralin, polysaccharide and other chemical components were also isolated from *Rhodiola rosea* in recent years. Three types of tocopherols, α, β and γ-tocopherol were identified from *Rhodiola sachalinensis* by GC/MS (Jin et al., 2013). Lotaustralin was isolated as a mixture of two diastereoisomeric forms from the methanol extract of *Rhodiola rosea* roots by Akgul et al. (2004). Polysaccharides were isolated through hot water extracting and ethanol precipitating method (Song et al., 2008). The identification of these chemical components also helps explain that *Rhodiola rosea* has abundant biological activity.

3. Bioactivities of Rhodiola rosea

3.1. Anti-fatigue Effect and Enhancing Exercise Performance
In recent literature, *Rhodiola rosea* showed anti-fatigue effect and improvement of endurance exercise performance in people intervention trial and animal experiments (De Bock et al., 2004; Fintelmann and Gruenwald, 2007; Huang et al., 2009). A randomized, double-blind, placebo-controlled study was performed to assess the efficacy of the standardized extract SHR-5 of roots of *Rhodiola rosea* in the treatment of individuals suffering from stress-related fatigue, and the result showed that repeated administration of *Rhodiola rosea* extract SHR-5 exerted an anti-fatigue effect that increases mental performance, particularly the ability to concentrate, and decreases cortisol response to awakening stress in burnout patients with fatigue syndrome (Olsson et al., 2009). *Rhodiola rosea* can significantly enhance exercise performance, however the effect of acute dose of *Rhodiola rosea* and chronic *Rhodiola rosea* intake on endurance exercise performance are different. A randomized, double-blind, placebo-controlled study was performed to study the effects of an acute dose of *Rhodiola rosea* on endurance exercise performance, and the result showed that acute *Rhodiola rosea* ingestion decreases heart rate response to submaximal exercise and appears to improve endurance exercise performance by decreasing the perception of effort (Noreen et al., 2013). However, other study that investigated the effects of chronic *Rhodiola rosea* intake on physical performance of a group of competitive athletes showed chronic *Rhodiola rosea* ingestion can’t alter maximum heart rate but prolong the time of exhaustion (Parisi et al., 2009). There are several literature explore the mechanisms of the anti-fatigue effect, e.g., enhanced mitochondrial function, increased oxygen consumption and glycogen content, energy supply of lipogenic enzyme expressions and protective defense mechanisms, stimulating expression of Hsp70 and particularly with Hsp72 production (Abidov et al., 2003; Lee et al., 2009; Panossian et al., 2009; Zhang et al., 2009). Although much literature demonstrate that *Rhodiola rosea* has anti-fatigue effect and enhances exercise performance, there are several literature show the effect is not obvious (Punja et al., 2014; Shanely et al., 2014). The negative results may be due to the difference of population, dosage, and exercise mode.

3.2. Anti-hypoxic Effect

The anti-hypoxic action of *Rhodiola rosea* has been demonstrated strongly in animal experiment, and the mechanism has also been illuminated partly. A study on broiler chickens reared in Tibet Plateau was performed, and broiler chickens were allocated three groups i.e., blank control group, low-dose group and high-dose group. The three groups were implemented different dietary treatments i.e., basal diet, basal diet + 0.5% *Rhodiola rosea*, and basal diet + 1.5% *Rhodiola rosea*. The result showed low-dose group significantly reduced non-ascites induced mortality and total mortality compared with blank control group and high-dose group, and high-dose group significantly increased blood red blood cell counts and hemoglobin levels at 28d compared with other groups (Li et al., 2014).
Rhodiola rosea can also reduce hypoxic rats’ high altitude pulmonary edema and attenuate hypoxia-induced pulmonary injury by increasing lung tissue HIF-1αmRNA expression and alleviating the elevated ET-1 and VEGF levels to maintain the integrity of the alveolar-capillary barrier (Lee et al., 2013; Li, 2013). A in vivo and vitro study was performed to explore the effect and mechanism of Rhodiola crenulata extract (RCE) and its bioactive compounds (salidroside and tyrosol) on hypoxia-mediated Na, K-ATPase endocytosis. The result showed that RCE and its bioactive compounds significantly prevented the hypoxia-mediated endocytosis of Na, K-ATPase via inhibition of the ROS-AMPK-PKC zeta pathway in A549 cells. Furthermore, RCE also showed a comparable preventive effect on the reduction of Na, K-ATPase endocytosis and inhibition of AMPK-PKC xi pathway in the rodent model (Lee et al., 2013). In addition, Gupta et al. (2009) verified that Rhodiola rosea extract treatment in rats shifted anaerobic metabolism to aerobic metabolism during exposure to cold, hypoxia and restraint (C-H-R) stress induced hypothermia and post stress recovery. Although anti-hypoxic action of Rhodiola rosea had been demonstrated strongly in animal experiment, a randomized, double-blind, placebo-controlled, crossover crowd trial showed that Rhodiola crenulata extract was not effective in reducing the incidence and severity of acute mountain sickness as compared to placebo (Chiu et al., 2013). This conclusion conflicts with animal experiments and traditional view, which may be due to the Rhodiola species used in experiment are different. Therefore, the conclusion should be interpreted with caution.

3.3. Antioxidant Action

A series of in vitro experiments were performed by researchers to assess the antioxidant capacities of Rhodiola rosea, included DPPH radical scavenging, ABTS radical scavenging, and ferric reducing antioxidant power (FRAP) assays. All the experiments showed that Rhodiola rosea had antioxidant effect and free radical-scavenging activity (Chen et al., 2013; Senthilkumar et al., 2013). In addition, the studies indicated the antioxidant effect and free radical-scavenging activity were related to the contents of phenols, flavonoid, herbacetin glycosides and oligomeric proanthocyanidin, generally, higher contents showed stronger antioxidant effect and free radical-scavenging activity (Choe et al., 2012; Tayade et al., 2013; Zhou et al., 2014). Besides, there were several articles reported its cytoprotective effect as antioxidant. A study on effect of the Rhodiola rosea roots aqueous extract on human erythrocytes exposed to hypochlorous acid (HOCl)-oxidative stress showed that Rhodiola rosea presented a significant protection to human erythrocytes in presence of the oxidative agent, but, in the absence of any induced oxidative stress, the addition to erythrocyte of high doses of Rhodiola rosea extract caused severe alterations of the cell shape (Battistelli et al., 2005). Similar study in U-937 human macrophages and human keratinocytes demonstrated that Rhodiola rosea could protect U-937
human macrophages and human keratinocytes from oxidative injury (Calcabrini et al., 2010; Kanupriya et al., 2005). An animal study that investigated anti-oxidative effect of *Rhodiola imbricata* root extract in rats during cold, hypoxia and restraint (C-H-R) exposure and post-stress recovery also demonstrated that the root extract had anti-oxidant potential, and maintained cell membrane permeability (Gupta et al., 2010). Interestingly, Schriner et al. (2009) found that *Rhodiola rosea* supplementation could protect cultured cells against ultraviolet light, paraquat, and H$_2$O$_2$, but, it 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. They also found that *Rhodiola rosea* extract lowered mitochondrial superoxide levels and afforded elevated protection against the superoxide generator paraquat in *Drosophila melanogaster*, but the extract did not alter the activities of the major antioxidant enzymes, the superoxide dismutases or catalase, nor did it afford protection against H$_2$O$_2$ or soluble iron. These results showed that *Rhodiola rosea* was against oxidative stress without activation of antioxidant defenses. Hernandez-Santana et al. (2014) found that *Rhodiola rosea* root extract protected skeletal muscle cells against chemically induced oxidative stress by modulating heat shock protein 70 (HSP70) expression.

### 3.4. Effect on the Central Nervous System

The effect of *Rhodiola rosea* on central nervous system can be classified into neuroprotective effect, anxiolytic effect, anti-stress, anti-depression and the improvement of withdrawal symptoms.

#### 3.4.1. Neuroprotective effect

In brain neurons injury model induced by different harmful substances, *Rhodiola rosea* showed neuroprotective effect (Lee et al., 2013; Qu et al., 2009). Qu et al. (2012) built a rat model of Alzheimer's disease (AD) induced by intracerebroventricular injection of streptozotocin (STZ), and given the rat pretreatment with the *Rhodiola crenulata* extract. They found that the extract significantly improved the impaired neurogenesis and reduced the oxidative stress in the hippocampus of AD rats. Besides, they further explored the mechanism, and found that *Rhodiola crenulata* extract improved the impaired hippocampal neurogenesis through protecting neural stem cells by its main ingredient salidroside which scavenged intracellular ROS. Another study was performed by using transgenic *caenorhabditis elegans* that showed neuronal death and behavioral dysfunction mediated by polyglutamine (polyQ) toxicity, and the result suggested that salidroside was able to reduce neuronal death and behavioral dysfunction mediated by polyglutamine. Moreover, the result demonstrated that salidroside exerted its neuroprotective function against polyQ toxicity via oxidative stress pathways (Xiao et al., 2014). A study was performed to explore the effect of *Rhodiola rosea* extract (RrE) on
oxidative stressor hydrogen peroxide (H$_2$O$_2$) and glutamate (GLU)-induced cell apoptosis in a human cortical cell line (HCN 1-A) maintained in culture. The results showed the pre-treatment with RrE or salidroside significantly increased cell survival and prevented the plasma membrane damage and the morphological disruption caused by GLU or H$_2$O$_2$. In addition, RrE or salidroside significantly reduced H$_2$O$_2$ or GLU-induced elevation of intracellular free Ca$^{2+}$ concentration. These findings indicated that RrE or salidroside had a neuroprotective effect in cortical neurons through reduction in the accumulation of intracellular calcium (Palumbo et al., 2012). Rhodiola rosea extract also improved learning and memory function of rats with scopolamine-impaired memory, but the mechanism of action was non-specific (Getova and Mihaylova, 2013).

3.4.2. Anti-stress effect

Rhodiola rosea is a kind of anti-stress plant in European and Asiatic traditional medicine. In recent studies, Rhodiola rosea was proved to have anti-stress effect in animal experiments and clinical trials. Exposure to both physical and psychological stress can reduce feeding in rodents, therefore, researchers can investigate the anti-stress effect of Rhodiola rosea by establishing a model of anorexia. Mattioli and Perfumi (2007) established a rat model of anorexia induced by (1) physical stress due to 60 min immobilization, and (2) intracerebroventricular injection of corticotrophin-releasing factor (CRF, 0.2 µg/rat), the major mediator of stress responses in mammals. Hydroalcoholic Rhodiola rosea extract standardized in 3% rosavin and 1% salidroside was administered acutely by gavage to male Wistar rats 1h before the experiment. The result found that the extract reversed the anorectic effects induced both by immobilization and by intracerebroventricular CRF injection. Other study was performed to determine whether chronic treatment with hydroalcoholic Rhodiola rosea extract (RHO) can prevent alterations in female rats following 6 weeks of chronic mild stress procedure. The study used behavioral and physiological parameters of consumption of 1% sucrose solution, locomotive and exploratory activities, body weight gain and oestrous cycle length as indicators. Decreased sucrose intake, reduced moving behavior, minimized weight gain and dysregulation of oestrous cycle were presented in the blank group rats, however, treatment with RHO completely reverted all of these changes (Mattioli et al., 2009). The anti-stress effect was demonstrated in animal experiments, and the study from crowd also showed that Rhodiola rosea extract had anti-stress effect. A multicentre, non-randomized, open-label, single-arm trial was performed to investigate whether a 4 week treatment with Rhodiola rosea extract can improve life-stress symptoms of subjects. The result showed that Rhodiola rosea extract at a dose of 200 mg twice daily for 4weeks was safe and effective in improving life-stress symptoms to a clinically relevant degree (Edwards et al., 2012).
3.4.3. Anxiolytic effect

*Rhodiola rosea* was proved to have anxiolytic effect in clinical study and animal experiments. Bystritsky et al. (2008) conducted a pilot clinical study to evaluate whether *Rhodiola rosea* was effective in reducing symptoms of generalized anxiety disorder (GAD). Ten participants with a DSM-IV diagnosis of generalized anxiety disorder (GAD) were enrolled in this study. The participants received a total daily dose of 340 mg *Rhodiola rosea* extract for 10 weeks. The result showed that the GAD symptoms of participants were improved by giving the pretreatment of *Rhodiola rosea*, and the adverse events were generally mild or moderate in severity. The anxiolytic effect was also presented in animal experiments, and Cayer et al. (2013) further explored the mechanism, although the mechanism was not elucidated clearly, they excluded the GABA(A)-benzodiazepine site of the GABA(A) receptor.

3.4.4. Anti-depression effect

*Rhodiola rosea* had been proved to have anti-depression effect in clinical trials and animal experiments, and the mechanism of anti-depression effect was further explored. Darbinyan et al. (2007) conducted the phase III clinical trial to assess the efficacy and safety of *Rhodiola rosea* extract in patients suffering from a current episode of mild/moderate depression, and the well-designed clinical trial is a randomized double-blind placebo-controlled study with parallel groups over 6 weeks. The result showed that *Rhodiola rosea* extract had anti-depressive potency in patients with mild to moderate depression when administered in dosages of either 340 or 680 mg/day over a 6-week period compared with the placebo group; moreover, no serious side-effects were reported. In animal experiments, the Porsolt behavioural despair assay was performed to assess the anti-depression effect of *Rhodiola rosea* extract. The result demonstrated that *Rhodiola rosea* extract had strong anti-depression effect, and exhibited a stronger anti-depressant type effect than imipramine (at 30 mg/kg) when administered at 20 mg/kg of the extract. Moreover, rhodioloside and tyrosol were proved to be the main active principles (Panossian et al., 2008). Several articles that explored the antidepressant mechanism of *Rhodiola rosea* suggested that the antidepressant effect may be through monoamine oxidase inhibition, increase of 5-HT content in hippocampus and repairmen of the injured neurons at hippocampus (Chen et al., 2009; Mannucci et al., 2012; van Diermen et al., 2009).

3.4.5. Improvement of the withdrawal symptoms

*Rhodiola rosea* can improve the withdrawal symptoms and drug dependence effectively in animal models. The recent literature reported that *Rhodiola rosea* was able to improve nicotine withdrawal and reduce morphine tolerance and dependence in animal experiments (Mattioli and
Perfumi, 2011a & b). Besides, *Rhodiola rosea* also attenuated the acquisition and expression of cocaine-induced Conditioned Place Preference (Titomanlio et al., 2013). Moreover, Titomanlio et al. (2014) evidenced that salidroside was the important active constituent in improving the withdrawal symptoms and drug dependence.

3.5. Effect on the Cardiovascular System

*Rhodiola rosea* had been proved to have protective effect on the cardiovascular system in animal experiments and clinical trials. A study was performed to evaluate the cardiovascular protective effect of *Rhodiola sacra* radix in propofol anesthetized Sprague-Dawley rats. The result showed that systemic administration of the water-soluble fraction of *Rhodiola sacra* radix had a potent hypotensive effect through the withdrawal of sympathetic vasomotor tone and interaction with the circulatory angiotensin system, and had inotropic and chronotropic effects on the heart. Moreover, a direct vagal inhibition on the heart was considered as the mechanism of positive inotropic and chronotropic effects (Shih et al., 2008). *Rhodiola rosea* may also induce release of β-endorphin to lower systolic blood pressure in spontaneously hypertensive rats (Lee et al., 2013). Cheng et al. (2012) constructed a diabetic rat model with heart failure by injection of streptozotocin, and exerted treatment of *Rhodiola rosea* on the diabetic rats. The result indicated that the ethanol extract of *Rhodiola rosea* increased the cardiac output in diabetic rats with heart failure, and the action of Rodiola-ethanol extract resulted from increase of PPAR-delta.

*Rhodiola rosea* had also a positive effect in treating ischemic heart disease (IHD). Yu et al. (2014b) developed a meta-analysis of randomized controlled trials to evaluate the efficacy and safety of *Rhodiola rosea* formulations in treating ischemic heart disease either as a sole agent or in combination with routine western medicine (RWM). The result showed that *Rhodiola rosea* formulations might have a positive effect on treating IHD alone and in combination with RWM. Besides, Sun et al. (2012) found that salidroside and tyrosol from *Rhodiola rosea* protected H9c2 cells from ischemia/reperfusion-induced apoptosis, and certified that the key mechanism of protective effect was inhibition of the JNK signaling pathway.

3.6. Antibacterial and Antiviral Effects

3.6.1. Antibacterial effect

Several animal experiments were performed to investigate the antibacterial effect of *Rhodiola rosea* extract, and all the animal experiments built mice model infected by *Pseudomonas aeruginosa*. These experiment results showed that the infection intensity of *Rhodiola rosea* feeding group was
highly significantly lower than the control group (Bany et al., 2009; Siwicki et al., 2012; Skopinska-Rozewska et al., 2012). However, the mechanism of antibacterial activity was not studied.

3.6.2. Antiviral effect

*Rhodiola rosea* had potential antiviral effect against multiple viruses, e.g. hepatitis C virus, influenza virus, coxsackievirus B3 and dengue virus. However, the active ingredients and mechanism of action are different for different types of viruses. *Rhodiola rosea* possessed potential anti-HCV effect because four (-)-epicatechin derivatives of *Rhodiola rosea* had inhibitory activity against HCV NS3 serine protease (Zuo et al., 2007). Jeong et al. (2009) found that five flavonols isolated from *Rhodiola rosea* showed neuraminidase inhibitory activities, and further evaluated their anti-influenza viral activities in vitro. The result showed that all the flavonols had anti-influenza viral activities, and kaempferol exhibited the highest activity against influenza viruses. Wang et al. (2009) found that salidroside exhibited obvious antiviral effects against coxsackievirus B3 both in vitro and vivo experiments. In vivo experiments, salidroside was also found to modulate the mRNA expression of interferon-gamma (IFN-gamma), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-alpha), and interleukin-2 (IL-2) in hearts of infected BALB/c mice. Diwaker et al. (2014) found that Rhodiola could inhibit dengue virus multiplication by enhancing the innate immune response in human monocytes. They also certified the enhancing immune response effect because Rhodiola treatment promoted interferon-stimulated gene (ISG), acid-inducible gene (RIG) I, melanoma differentiation-associated protein (MDA)5 gene expression and increased the number of NK cells in dengue-virus-infected human PBMCs.

3.7. Immunomodulatory Effect

3.7.1. In vitro immunomodulatory effect

*Rhodiola rosea* had been proved to have positive immunomodulatory activity in vitro. Aqueous and hydro-alcoholic extracts of underground parts of *Rhodiola quadrifida* or *Rhodiola kirilowii* in concentration up to 10 μg/mL stimulated granulocyte potential killing (PKA) and respiratory burst (RBA) activity in blood leukocyte cultures of pigs (Wojcik et al., 2008 & 2009). Mishra et al. (2006) found that aqueous extract of *Rhodiola imbricata* rhizome stimulated production of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) in human peripheral blood mononuclear cells (PBMCs) as well as mouse macrophage cell line RAW 264.7. They also found that aqueous extract of *Rhodiola imbricata* rhizome at 250 μg/mL increased the phosphorylated I kappa B expression and activated the nuclear translocation of nuclear factor-kappa B in human PBMCs. Therefore, they suggested that Rhodiola most likely activated proinflammatory mediators via phosphorylated
inhibitory kappa B and transcription factor NF-kappa B. Mishra et al. (2009) found that aqueous extract of *Rhodiola imbricata* rhizome induced Toll-like receptor-4 expression and intracellular granzyme-B in treated splenocytes, which indicated that *Rhodiola imbricata* had potent immunostimulatory activity.

### 3.7.2 In vivo immunomodulatory effect

An in vivo experiment was developed to evaluate the effect of *Rhodiola quadrifida* extracts on the metabolic activity of blood granulocytes in mice. The metabolic activity of blood phagocytosing cells was determined through measurement of their chemiluminescent activity in scintillation counter. The result presented that aqueous and 50% hydro-alcoholic extracts of *Rhodiola quadrifida* rhizomes stimulated granulocytes activity in 400 μg doses, but only hydro-alcoholic extract was effective in lower dose (200 μg) (Skopinska-Rozewska et al., 2008). Besides, Skopinska-Rozewska et al. (2008) found that 50% hydro-alcoholic extracts of *Rhodiola quadrifida* enhanced the ability of lymphocytes derived from parental strain mice fed the extract, to induce local cutaneous graft-versus-host reaction (GVH) in F1 hybrids. However, there was no evidence indicated that the number of blood granulocytes increased in mice fed the extracts. Even, Zdanowski et al. (2014) found that the number of blood granulocytes was diminished in Balb/c mice fed *Rhodiola rosea* hydro-alcoholic extract. In addition to stimulate granulocytes activity, *Rhodiola rosea* have a adjuvant effect in terms of humoral and cell-mediated immune response against strong antigen like tetanus toxoid (TT) and weak antigen like ovalbumin, e.g. increasing higher TT specific immunoglobulin levels, evoking stronger delayed type hypersensitivity (DTH) response (Mishra et al., 2010). Moreover, Guan et al. (2011) found only salidroside played an adjuvant role on the immune responses to ovalbumin in mice.

### 3.8 Anti-inflammatory Activity

A study was performed by Pooja et al. (2009) to evaluate the anti-inflammatory efficacy of the tincture extract of *Rhodiola rosea* roots. They constructed an inflammatory model of rats. The result showed that the tincture extract exhibited inhibitory effect against acute and subacute inflammation at a dose of 250 mg/kg body weight. They further developed in vitro experiments to evaluate the anti-inflammatory effect of the tincture extract against the enzymes relating to inflammation, and the results showed that the tincture extract exhibited inhibitory effect against cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2) and Phospholipase A(2) (PLA(2)). Besides, other researchers have also explored the anti-inflammatory activity of certain component of *Rhodiola rosea*, e.g. Jung et al. (2008) found that caffeic acid phenethyl ester (CAPE) extracted from *Rhodiola sacra* reduced the magnitude of inflammatory process triggered by endotoxin shock and the production
of inflammatory mediators. Kaempferol extracted from *Rhodiola sachalinensis* A. Bor also exhibited anti-inflammatory activity (Choe et al., 2012).

### 3.9. Antitumor Activity

Multiple studies demonstrated that *Rhodiola rosea* had antitumor activity. The antitumor activity of *Rhodiola rosea* was verified from two aspects, that is direct action on tumor cells and reduce angiogenesis.

#### 3.9.1. Direct action on tumor cells

Majewska et al. (2006) found that the extract of *Rhodiola rosea* rhizomes inhibited division of HL-60 cells and induced apoptosis and necrosis of HL-60 cells, and HL-60 cells entered apoptosis from phase G2/M of the cell cycle. Mishra et al. (2008) investigated the anti-proliferative effects of Rhodiola aqueous extract (RAE) in human erythroleukemic cell line K-562 using MTT cell proliferation assay. The result showed that Rhodiola aqueous extract arrested cell cycle progression in G2/M phase and induced intracellular reactive oxygen species (ROS) in K-562 cells at 200 µg/mL, this leaded to apoptosis and necrosis of HL-60 cells. Gauger et al. (2010) found that *Rhodiola crenulata* could block several features associated with mammary epithelial cancer stem cell behavior, including migration, invasion, resistance to anoikis and tumorsphere formation. They also found that the mRNA expression levels of Id (Inhibitor of differentiation or Inhibitor of DNA-binding) proteins were regulated by *Rhodiola crenulata*. Besides, *Rhodiola rosea* extracts and salidroside were found to decrease the growth of bladder cancer cell lines through inhibition of the mTOR pathway and induction of autophagy (Liu et al., 2012). Lu et al. (2011) found the division of MCF-7 Cells was also inhibited by *Rhodiola algida* Var. Tangutica, and they identified the main active ingredients as salidroside and tyrosol. Polysaccharides extracted from *Rhodiola rosea* also had antitumor activity, in vitro experiment, the polysaccharides exerted a direct cytotoxic effect on Sarcoma 180(S-180) cells, and in vivo experiment, the polysaccharides could also inhibit tumor growth of S-180 tumor transplanted in mice (Cai et al., 2012).

#### 3.9.2. Reduce angiogenesis

*Rhodiola rosea* was proved to have antiangiogenic properties in mice. Skopinska-Rozewska et al. (2008) developed a study to investigate the antiangiogenic effect of aqueous and 50% hydroalcoholic extracts of *Rhodiola rosea* roots, and constructed a neovascular reaction model in the skin of Balb/c mice after grafting of L-1 sarcoma cells. The mice were fed extracts in daily dose 50, 100, 200 and 400 µg. After 72 hours, they identified and counted all newly formed blood vessels in
mice by dissection microscope. They found both extracts in 100-400 µg daily doses significantly decreased neovascular reaction. Besides, they found that the pure compound of rosavin administered orally also decreased neovascular reaction. A similar study was developed, 50% hydro-alcoholic extract from rhizomes of *Rhodiola quadrifida* and the pure compound of salidroside also significantly decreased neovascular reaction in the skin of Balb/c mice after grafting of syngeneic L-1 sarcoma cells (Skopinska-Rozewska et al., 2008). Antiangiogenic effects of aqueous and hydro-alcoholic *Rhodiola kirilowii* extracts were compared, and the results showed that hydro-alcoholic *Rhodiola kirilowii* extracts administered orally significantly decreased neovascular reaction in the skin of Balb/c mice after grafting sarcoma L-I syngeneic tumor cells, but *Rhodiola kirilowii* aqueous extracts had no influence on cutaneous angiogenesis reaction (Zdanowski et al., 2012).

### 3.10. Antihyperglycemic and Antidiabetic Effects

In vitro and vivo experiments had been conducted to evaluate the antihyperglycemic and antidiabetic effect of *Rhodiola rosea*. The results showed that *Rhodiola rosea* had antihyperglycemic and antidiabetic effect. A study was performed to evaluate the antidiabetic effect of *Rhodiola sachalinensis* root extract (RS) in streptozotocin-induced diabetic rats. The streptozotocin-induced diabetic rats were fed RS in daily dose 200 mg/kg, 400 mg/kg. After 40 days, the results showed that RS treatment significantly lowered blood glucose, serum total cholesterol and triglycerides, and increased serum insulin levels. Furthermore, RS treatment decreased malondialdehyde levels, while increased superoxide dismutase, catalase and glutathione peroxidase activities in the liver and kidney of diabetic rats (Gao et al., 2009). Another study was performed to evaluate the effect of *Rhodiola crenulata* root (RCR) on glucose and lipid metabolism in the metabolic syndrome and type 2 diabetes models. Metabolic syndrome and type 2 diabetes models were constructed by using the Zucker diabetic fatty (ZDF) rats, and the rats were fed RCR powder in daily dose 100 mg/kg, 500 mg/kg for 4 weeks. The results showed that the increased plasma insulin and triglyceride concentrations at baseline, the index of the homeostasis model assessment of insulin resistance (HOMA-IR) and excessive hepatic triglyceride accumulation were decreased by RCR treatment. The abnormal increases in plasma glucose and insulin concentrations were also inhibited by RCR treatment during oral glucose tolerance test. Furthermore, the increased adipose insulin resistance index and the accelerated decline of plasma concentrations of non-esterified fatty acids were reversed by RCR treatment after exogenous glucose stimulation. These results demonstrated that RCR treatment could improve metabolic derangements in ZDF rats (Wang et al., 2012).

The mechanisms of antihyperglycemic effect of *Rhodiola rosea* were also studied. Niu et al. (2014) found that rhodiola-water extract improved hyperglycemia via an increase of β-endorphin
secretion from adrenal gland to activate opioid mu-receptors in streptozotocin-induced diabetic rats. α-Glucosidase inhibitory constituents of *Rhodiola rosea* were also conducive to explain hypoglycemic activity of *Rhodiola rosea*. Chu et al. (2014) isolated four α-glucosidase inhibitors from *Rhodiola crenulata*, i.e. epicatechin (EC), epicatechin-(4β,8)-epicatechin gallate (B2-3’-O-gallate), epicatechin gallate (ECG) and 2-(4-hydroxyphenyl) ethyl 3,4,5-trihydroxybenzoate (HETB). The B2-3’-O-gallate, ECG and HETB presented a stronger α-glucosidase-inhibitory effect compared to a known α-glucosidase inhibitor quercetin.

*Rhodiola rosea* could not only lower blood sugar and improve the metabolic derangements but also have a protective effect on diabetic nephropathy. A study was performed to investigate the therapeutical effects of *Rhodiola rosea* extract on rats with type 2 diabetic nephropathy (DN). The result showed that *Rhodiola rosea* extract treatment significantly reduced 24-h urinary albumin, the ratio of kidney mass/body weight and glomerular area. Meanwhile, the transforming growth factor (TGF)-beta 1 expression in renal tissues was also significantly decreased. Therefore, the decrease of renal expression of TGF-beta 1 might be a mechanism of protective effect of the extract on early nephropathy in diabetic rats (Wang et al., 2013). In vitro experiments, salidroside was found to inhibit high glucose-induced mesangial cell proliferation, which might be related to suppressing TGF-beta 1 production and ERK1/2 phosphorylation (Yin et al., 2009).

### 3.11. Anti-aging Effect

Jafari et al. (2007) developed a study to investigate the anti-aging effect of *Rhodiola rosea*. They found that *Rhodiola rosea* supplied every other day at 30 mg/mL significantly extended the lifespan of *Drosophila melanogaster*. Schriner et al. (2013) further explored the mechanism of anti-aging effect, although their findings didn’t elucidate specific mechanisms, their findings largely ruled out two possible mechanisms, i.e. an elevated general resistance to stress and dietary restriction-related pathways. Mao et al. (2010) investigated the anti-aging effect of salidroside. They constructed human fetal lung diploid fibroblasts premature senescence model induced by H2O2. The result showed that salidroside significantly reversed senescence-like phenotypes, including alterations of morphology, cell cycle, SA-beta-gal staining, DNA damage, and related molecules expression such as p53, p21 and p16. Furthermore, they inferred that modulating oxidative status played part of role.

### 3.12. Other Bioactivities

#### 3.12.1. Hepatoprotective effect

A study was performed to investigate the hepatoprotective effect of *Rhodiola sachalinensis*, and the result showed that the methanolic extract of *Rhodiola sachalinensis* weakened D-
galactosamine-induced cytotoxicity in primary cultured mouse hepatocytes. And, sachalosides III and IV, rhodosin, and trans-cafeic acid were identified to play a major role (Nakamura et al., 2007). Senthilkumar et al. (2014) developed a study to estimate the hepatoprotective activity of *Rhodiola imbricata* rhizome acetone extract. They constructed a hepatic damage model in Wistar rats by administering paracetamol, and then implemented *Rhodiola imbricata* rhizome acetone extract treatment. The results showed that *Rhodiola imbricata* treatment considerably protected the hepatic cells from damage. Moreover, compared to the control groups, the hematological and biochemical parameters of *Rhodiola imbricata* treatment group recovered normal.

### 3.12.2. Hypopigmenting effect

Melanin is responsible for skin color; some in vitro and in vivo factors can stimulate melanogenesis to produce excessive melanin. Tyrosinase is responsible for the critical steps of melanogenesis, including the rate-limiting step of tyrosine hydroxylation. Therefore, inhibiting the activity of tyrosinase can reduce melanin synthesis (Wen et al., 2013). Salidroside was found to inhibit tyrosinase activity and reduce melanin synthesis in mouse B16F10 melanoma cells (Peng et al., 2013). P-coumaric acid which existed in *Rhodiola sachalinensis* was also found to inhibit tyrosinase activity and reduce melanin synthesis in mouse B16F10 melanoma cells (Park et al., 2008). Chiang et al. (2014) further explored the mechanisms of inhibitory effect, and found that the hydroalcoholic extract of *Rhodiola rosea* and its hydrolysate inhibited melanin synthesis and tyrosinase activity in mouse melanoma cells (B16F0 cells). Besides, the gene and protein expression of melanocortin 1 receptor (MC1R), c-AMP response element binding protein (CREB) phosphorylation, the activation of ART and glycogen synthase kinase-3 beta (GSK3 beta), the expression of microphthalmia-associated transcription factor (MITF) and tyrosinase-related protein 1 (TRP-1) were also inhibited by the extract. Therefore, the inhibitory effect of *Rhodiola rosea* hydroalcoholic extract was associated with the CREB/MITF/tyrosinase pathway.

### 3.12.3. Radioprotective effect

The radioprotective effect of *Rhodiola imbricata* was investigated, and the aqueous (RD-I) and aqua-alcoholic (RD-II) extracts of *Rhodiola imbricata* were found to reduce whole-body lethal gamma irradiation (10 Gy)-induced mortality in Swiss albino strain "A" mice. In the observation period of more than 30 days, pre-irradiation administration of RD-I produced > 90% survival rate, RD-II produced > 83% survival rate (Goel et al., 2006).

### 4. Conclusions and Prospects
Rhodiola rosea is an important medicinal plant with immense pharmacological potential, such as anti-fatigue, antioxidant, anti-hypoxic, anti-depressive, anti-anxiety, antimicrobial, antiviral, anti-inflammatory, and anticancer activities. Salidroside and tyrosol are the major bioactive constituents in Rhodiola rosea. Although its biological activities are clearly proved by abundant studies, mechanisms of action are not very clear. Further research, more clinical trials and product development are needed to make full use of Rhodiola rosea for the public health.

References


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