



Rhodiola rosea L.: A Critical Review on Biology, Medicinal Properties and Pharmacological Manifestations

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ABSTRACT

Potential of the medicinal plant *Rhodiola rosea* belonging to the angiosperm family Crassulaceae, has been used by mankind since time immemorial. However, scientific research documentation of this medicinal plant is gradually growing in literature throughout the world. *R. rosea* plant is known for its astonishing capacity in rejuvenation of life, cellular longevity, antioxidant capacity, and cardio-protective as well as neuroprotective nature; and over all, its central role as a powerful adaptogen, which is now being commercially exploited to prevent fatigues, illness, and even death in harsh climatic conditions. Its protective role in Cognitive Biology is pharmacologically proved. In this review paper, biology of the plant, medicinal properties, and pharmacological formulations have been structured. The cellular and molecular mechanisms, metabolic cross-talk, and regulation of gene expressions by plant formulations during prevention of human sufferings have also been reviewed.

1. Introduction

Rhodiola rosea L. (*R. rosea* L. synonym:- *Sedum Rhodiola* DC.) also known as golden root, rose root, or king's crown in the angiosperm dicot family Crassulaceae, is a perennial terrestrial flowering plant with a height of 2.0 to 15.7 inches, fleshy, and has several stems growing from a short, scaly rootstock. Leaves are simple, arranged alternately. Flowers are radially symmetrical showing four sepals and four petals, bright yellow to greenish yellow in color often tipped with red. It blooms during May to August, and the seeds ripe during July to August. The flowers are unisexual dioecious, pollinated by bees and flies. The genus *Rhodiola* possibly originated in Southwest China and the Himalayas and has its distribution from the Altai Mountains through Mongolia into many parts of Siberia (Russia). Different of its species displays a natural distribution in the mountainous regions of the Northern Hemisphere. It grows in arctic regions of the world, including Baffin Island to the mountains of North Carolina, parts of Europe, Scandinavia, Iceland, UK and Ireland. It generally grows on sea cliffs and on mountains at altitudes up to 2280 m, msl.

R. rosea is very recently discovered in Indian Western Himalayan region of Leh, the capital of Ladakh in Jammu and Kashmir State [1]. The plant has earned its reputation as an adaptogen due to its effectiveness in increasing physical endurance, longevity, tolerating high altitude sickness, and in the treatment of depression, fatigue, impotence, and respiratory infections. Due to extensive medicinal values, natural populations of *R. rosea* are endangered, and thus urgent conservation of this herb is needed [2, 3].

2. Phytochemical profiling

Occurrence of secondary metabolites and bioactive compounds is the novel features of *Rhodiola* sp. However, significant species-specific variation was observed in phytochemistry and pharmacology among different *Rhodiola* spp. Therefore, a cautious approach is necessary for consumers regarding the marketing product. The species composition of commercial *Rhodiola* products was recently supervised using DNA barcoding [4]. A *Rhodiola* dietary supplement DNA barcode database was successfully constructed using 82 voucher samples from 10 *Rhodiola* species. Based on the DNA barcoding standard operating procedure (SOP),

only 36 decoction piece sequences (40%) were authentic *R. crenulata* (recorded in Chinese Pharmacopeia), whereas 35 sequences (38.9%) were authenticated as *R. serrata*, only nine sequences (10%) were authenticated as *R. rosea* (documented in the United States Pharmacopeia), and the remaining samples were authenticated as other three *Rhodiola* species [4]. Root phytochemical profiling of *R. rosea* is unique to its own. It specifically contains three cinnamyl alcohol-vicianosides namely, rosin, rosarin and rosavin, as can be included in single term rosavins [5, 6]. Approximately, 140 chemical compounds have been analyzed in the subterranean portions of *R. rosea* which can be broadly classified as six distinct phytochemical groups [7-10]- (i) Phenylpropanoids: rosavin (2.1%), rosarin, and rosin; (ii) Phenylethanol derivatives: tyrosol and salidroside (rhodioloid); (iii) Flavanoids: acetylrodalgin, rodilin, rodionin, rodiosin, tricin, and tannins (16–18%); (iv) Phenolic acids: 15 chlorogenic and hydroxycinnamic, and gallic acids and essential oils; (v) Monoterpenes: kaempferol, rosiridol, and rosarinid; and (vi) Triterpenes: β -sitosterol and daucosterol.

Substantial variation in the chemical composition of the essential oil from *R. rosea* root is found in different countries. For example, *R. rosea* of Russian origin contains rosavins complex. Geraniol, cinnamic alcohol, and myrtenol are the main components of the essential oil from *Rhodiola* growing in Bulgaria. In Asian *R. rosea*, geraniol and 1-octanol are the main components in China, whereas in India the main component is phenylethilic alcohol [11]. Rosavins and the salidroside [2-(4-hydroxyphenyl)ethyl- β -D-glucopyranoside] or rhodioloid, as well as rodilin, rodionin, and roziridine are the principal bioactive medicinal components. The rosavins complex is specific only for *R. rosea*.

A large portion of the *Rhodiola* extracts (about 30% of the 70% acetone dry crude extract) is composed of proanthocyanidins [8]. These groups of oligomeric flavonoid compounds have significant bioactivities as antioxidant, anxiolytic, anti-inflammatory, anti-viral, anti-mutagenicity, anti-tumor, anti-allergic, and anti-aging functions [8, 12, 13]. Extract of *R. rosea* radix reduces the level of C-reactive protein and creatinine kinase in the blood [14].

3. Medicinal properties

3.1 Ethnomedicinal Uses

3.1.1 India

Locally known as 'solo', the discovery of *R. rosea* in harsh climate of Ladakh, India, has surprised India's leading scientists to guess whether or

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not the herb is the end to the search for “sanjeevani”, the mythical herb that renewed the life to Lakshman, Lord Ram’s brother in the epic Ramayana. Plant leaves are usually used as vegetable by local Ladakhi tribes. Its therapeutic values are now being explored by researchers of the Leh-based Defense Institute of High Altitude Research (DIHAR), DRDO (Defense Research and Development Organization) in India. Primary reports suggested that the herb has significant therapeutic and functional values for the troops posted in high altitude mountainous terrain such as the 5,400 m (msl) high of the Siachen glacier [1].

3.1.2 China and Mid Asia

R. rosea has been used in traditional Chinese medicine to combat high-altitude sickness. In Mongolia physicians prescribed it for tuberculosis and cancer. In the Amchi system of medicine (Tibetan system) the herb has been used as anti-stress, radio-protective, anticancer, anti-inflammatory, and adaptogenic agent. Tea prepared from its leaves is found the most effective treatment for cold and flu during severe Mid-Asian winters. *Rhodiola* tea is taken as a weight loss aid, immune system supporter, stress reliever, mood lifter, energy enhancer and memory booster. The effects of this herbal tea are mainly from the adaptogenic properties of *R. rosea* extract. Drinking this herbal beverage every day is said to prevent colds and flues and also to restore skin tone and maintain a youthful looks.

3.1.3 Europe, Russia and North America

Throughout centuries, *R. rosea* has been used as an herbal medicine in Russia and Scandinavia. Various medicinal applications of *R. rosea* were published in the scientific literature of Sweden, Norway, France, Germany, the erstwhile Soviet Union, and Iceland in between 1725 and 1960. *R. rosea* was famed as an astringent and for the treatment of hernia, headache, hysteria, and leucorrhoea by Linneaus [7]. Russian athletes and cosmonauts were tested for its impact. In Siberian mountain villages, a bouquet of roots is considered auspicious to pre-marriage couples to enhance fertility and assure the birth of healthy children [15]. After the Cold War era, the secret of this ‘magic’ herb was openly published. In Russia, *R. rosea* has been used to treat SAD (Seasonal Affective Disorder), sometimes known as the ‘Winter Blues’ - which has much influence in the country due to the long, and dark winters, which detrimentally influence productivity during this time. Medieval Vikings used this herb to improve their physical endurance. Pedanius Dioscorides included *R. rosea* in “De Materia Medica” written in 77 A.D. Medicinal values of the herb are also described in the Swedish Pharmacopoeia published in 1755; and since 1969, it has been included in the official Russian medicine [7]. In Germany, the use of *R. rosea* was beneficial in treatment of headache, depression, pain, scurvy, hemorrhoids, and also used as a stimulant and an anti-inflammatory. Its traditional use particularly in managing fatigue and improving endurance is the foundation of modern clinical and pharmacological implication of this medicinal herb. The indigenous Inuit people of Nunavik and Nunatsiavut, Eastern Canada, use *R. rosea* as a mental and physical rejuvenating agent [12].

3.2 Modern Clinical and Pharmacological Implications

Studies on isolated organs, tissues, cells and enzymes have revealed that *R. rosea* preparations contain phenolic and/or cyanogenic glycosides which exhibit adaptogenic effect, neuroprotective, cardioprotective, anti-fatigue, antidepressive, anxiolytic, nootropic, life-span increasing, and Central Nervous System (CNS) stimulating effects. Interactions with the hypothalamic-pituitary-adrenal (HPA)-system (Cortisol-Reducing), protein kinase p-JNK, nitric oxide, and defense mechanism proteins [e.g. heat shock proteins (Hsp) 70, and the FoxO/Daf-16 family of transcription factors] are some of the possible mechanisms [10] of pharmacological effects of *R. rosea*. Pharmacological formulations of *R. rosea* are now available in different forms [16].

3.2.1 *R. Rosea*: Antioxidant Properties, Oxidative Stress Influences and Longevity-Promoting Effects

Generation of free radicals is an inevitable event in aerobic organisms [17-19]. Excess generation of free radicals in the form of reactive oxygen species (ROS) may cause severe oxidative stress through redox imbalance between ROS and antioxidants. Polyphenols in plants are excellent natural antioxidants [20]. The antioxidant activity of oligomeric proanthocyanidin from *R. rosea* L. was investigated in vivo. Results suggested higher free radical-scavenging activities of plant extracts than vitamin C and proanthocyanidin significantly enhanced the SOD and GSH-Px activities, and reduced the MDA content in mice [21]. The SHR-5, a formulation of *R. rosea* extract from the Swedish Herbal Institute (SHI), Gothenburg, Sweden could extend both mean (24% in both sexes) and maximum (16% in males and 31% in females) life span in *Drosophila melanogaster* in

relation to control by lowering mitochondrial superoxide levels, and provided elevated protection against the superoxide generator paraquat in both sexes [22]. Despite *R. rosea* is very rich in phenolic compounds and antioxidant properties, conflicting reports are available regarding stimulating effects of the herb through stimulation of body’s antioxidant defense system. *R. rosea* root extract successfully prevented onset of oxidative damage in cultured human keratinocytes (NCTC 2544) by modulating reduced glutathione (GSH), activity of the trans plasma membrane nicotinamide adenine dinucleotide-oxido reductase (NAD⁺/NADH) and glyceraldehyde-3-phosphate dehydrogenase, and enhancing antioxidant defense enzymes like catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and glutathione reductase (GR) activities. This consequently reduced membrane lipid peroxidation and protected NCTC 2544 induced by oxidative stress of Fe(II)/ascorbate, Fe(II)/H₂O₂, and tert-butyl-hydroperoxide [23]. In contrast, plant extracts protected cultured human cell exposed to ultraviolet light, paraquat, and H₂O₂ without stimulating antioxidant defense [22]. Effect and mechanism of herbal formulations of *R. rosea* were evaluated on 90 minutes swimming-induced oxidative stress in male Wistar rats which were fed with three elevated doses (5, 25, 125 mg/day/rat) of plant extracts in drinking water [24]. The treatment of 4 weeks of plant extracts containing major ingredients (salidroside and rosavins) significantly inhibited swimming exercise-enhanced O₂⁽⁻⁾ production in the blood, liver and skeletal muscle and plasma malonaldehyde (MDA) concentration by scavenging O₂⁽⁻⁾, H₂O₂, and hypochlorous acid (HOCl) in a dose-dependent manner. It also substantially enhanced Mn-SOD, Cu/Zn-SOD, and CAT expressions in livers at 125 mg/day/rat and consequently increased swimming performance [24]. In Vitro human erythrocytes exposed to HOCl triggered oxidative damages like modifications in membrane proteins and lipids, transformation of the discocyte shape to the echinocyte one, and lysis. Roots aqueous extracts of *R. rosea* reversed the stress induced oxidative damage in erythrocytes, but red blood cells (RBC) exposed to high concentrations of extracts without any stress may lose its normal shape [25, 26].

Increased oxidative stress plays an important role in the etiology and pathogenesis of diabetes mellitus and its complications [27, 28]. Pretreatment of the human umbilical vein endothelial cells (HUVECs) with salidroside significantly reduced the cytotoxicity brought by H₂O₂ and rescued the endothelium-dependent relaxation and reduced superoxide anion (O₂⁽⁻⁾) as well as nitric oxide production induced by H₂O₂ by inhibiting H₂O₂-induced activation of endothelial nitric oxide synthase (eNOS), adenosine monophosphate-activated protein kinase (AMPK), and Akt, as well as the redox sensitive transcription factor, NF-kappa B (NF-κB), and by increasing mitochondrial biogenesis, peroxisome proliferator-activated receptor gamma-coactivator-1alpha (PGC-1α), and mitochondrial transcription factor A (TFAM) in the endothelial cells [29]. Both *R. rosea* and *R. crenulata* water extract were found effective for the inhibition of alpha-amylase, alpha-glucosidase and angiotensin converting enzyme (ACE) inhibitory activity and thereby could manage type II diabetes and hypertension [30]. *R. rosea* (200 mg/kg/day) treated diabetic in C57BL/Ks db/db mice groups in 12 weeks of treatment significantly ameliorated type II diabetes related complications through decreased blood glucose, increased levels of GSH and the activities of antioxidant enzymes like GR, glutathione S-transferase (GSTs), glutathione peroxidases (GSH-Px), CAT and SOD in the liver. Extract treatment also significantly decreased lipid peroxidation, thus preventing oxidative damage to liver [31]. *Rhodiola*-water extract dose-dependently lowered the plasma glucose in STZ-diabetic rats by increasing plasma β-endorphin, and increased expression of glucose transporter subtype 4 (GLUT 4) in skeletal muscle and a marked reduction of phosphoenolpyruvate carboxykinase (PEPCK) expression in liver [32]. Intense exercise increases oxygen consumption and may produce oxidative imbalance. Effects of *R. rosea* derived salidroside (25, 50 and 100 mg/kg as low, moderate and high doses, respectively) were evaluated on intense exercise-induced oxidative stress in rats forced under an exhaustive swimming exercise [33]. Salidroside was able to increase the liver glycogen levels and reduce MDA (a membrane lipid peroxidation product) levels. Activities of SOD, CAT and GSH-Px were also increased in the liver tissues to confer exercise tolerance of the rats [33]. Further studies indicate that *R. rosea* extract (*Rhodioli*) protects murine skeletal muscle cells (C2 C12 myotubes) against peroxide-induced oxidative stress through the modulation of the molecular chaperone HSP70 [34].

Molecular and pharmacomolecular mechanisms involved in extension of life span by *R. rosea* are still being debated. Schriener et al. [35] recently tested that *R. rosea* might act through a pathway related to dietary restriction (DR) that can extend lifespan in a range of model organisms (flies, worms, and yeast). While the mechanism of DR itself is not known, three molecular pathways have been proposed to be associated with it: i)

the silent information regulator 2 (SIR2) proteins, ii) insulin and insulin-like growth factor signaling (IIS), and iii) the target of rapamycin (TOR). In this experiment, dietary yeast content was reduced to implement DR in flies. The results revealed that *R. rosea* extract extended lifespan in both sexes independent of the yeast content in the diet and the extract also extended lifespan when the SIR2, IIS, or TOR pathways were genetically attenuated [35]. In female flies, the expression levels of glycolytic genes, and dSir2 were down-regulated, and NADH levels were decreased; whereas, no protection was given to male flies against heat stress. The plant extract had no effect on the major heat shock protein HSP70 and actually down-regulated the mitochondrial HSP22 in males, suggesting some sex-specific differences in response to *R. rosea* [35]. Gospodaryov et al. [36] evaluated the effects of rhizome powder on lifespan and age-related physiological functions of *Drosophila melanogaster*. The study suggested that flies which were fed with food supplemented with 5.0 mg/mL and 10.0 mg/mL of *R. rosea* rhizome powder had a 14% to 17% higher median lifespan whereas at 30.0 mg/mL, fly lifespan was decreased by 9% to 12%, - without any reduction in fly fecundity. However, a fair life-span extension depended on diet compositions with protein-to-carbohydrate ratios less than one, and a long-term dietary supplementation with *R. rosea* rhizome is recommended to increase life span with decreasing food consumption and age-related functional decline [36]. In mice model, salidroside - the phenylpropanoid glycoside from *R. rosea* - prevented the loss of hematopoietic stem cells (HSCs) due to oxidative stress [37]. Although salidroside did not prevent the ROS production it reduced H₂O₂-induced DNA-strand breaks in bone marrow cells enriched for HSCs. Poly (ADP-ribose) polymerase-1 (PARP-1) is a component of the DNA base excision repair pathway which was activated by salidroside in mouse bone marrow HSCs as well as primary fibroblasts and human lymphoblasts, affecting HSCs homeostasis and its function [37]. *R. rosea* aqueous extract at low concentration extended yeast chronological lifespan, by preventing protein oxidation under H₂O₂-induced oxidative stress and consequently, increased oxidative stress resistance of stationary-phase cells in exponentially growing cultures. At high concentrations, *R. rosea* extract sensitized yeast cells to stresses and shortened yeast lifespan, indicating biphasic concentration-responses [38]. Potential involvement of Msn2/Msn4 and Yap1 regulatory proteins in realization of *R. rosea* beneficial effects is suggested under the same study.

3.2.2 Immunomodulatory Effects, Neuroprotections and Cognitive Biology

Initial clinical and pharmacological formulations revealed stimulating effects of small and medium doses of plant extracts by lengthening of swimming time and remaining on vertical perches to the limit of the abilities of mice. Small doses increased the bioelectrical activity of the brain, attributable to the direct effects on the brainstem ascending and descending reticular formation [7]. Medium range doses enhanced the development of conditioned avoidance reflexes and facilitated learning based on emotionally positive reinforcement in rats. In contrast, more sedative effects were noticed in larger doses. Actually, in small and medium doses, *R. rosea* stimulated the effects of neurotransmitters like norepinephrine (NE), dopamine (DA), serotonin (5-HT), and nicotinic cholinergic on the CNS by increasing the permeability of the blood brain barrier to precursors of DA and 5-HT. Release of NE, 5-HT, and DA in ascending pathways activates the cerebral cortex and the limbic system. Consequently, the five cognitive (thinking, analyzing, evaluating, calculating, and planning) functions of the cerebral cortex and the attention, learning, and memory functions along with other aspects of memory as encoding, sorting, storage, and retrieval of the prefrontal and frontal cortex are enhanced. The neurotransmitter acetylcholine (ACh) in cholinergic system contributes to memory function via pathways ascending from the memory storage systems of the limbic system to various areas of the cerebral cortex (memory retrieval). Acetylcholine esterase suppresses ACh activity and interferes with memory. *R. rosea* reverses this blockade and alleviates some age-related neuronal dysfunction [7]. Expression of iNOS, pro-inflammatory cytokines in BV2 cells, IL-1 β , and TNF- α in the kidney and prefrontal cortex of brain in mice was suppressed by the constituents of *R. rosea* in a concentration-dependent manner. Regarding neuroprotective activity, the L-glutamate-induced neurotoxicity was suppressed by the treatment with rosin but not by rosin. The increased level of phosphorylated MAPK, pJNK, and pp38 due to L-glutamate treatment was reversed by rosin and salidroside treatment [39].

Certain medicinal plants exhibited remarkable capacity to restore and enhance cognitive memory functions [40, 41]. *R. rosea* may also exert stimulating effects on cognitive memory through resistance to mental and physical stress [16]. Stress impedes memory functions and, in course of time, deteriorates memory systems in a complex pathway that involves

generation of excess ROS and disruption of ROS-homeostasis which is delicately balanced in an aerobic cell [17-20, 42, 43]. *R. rosea* protects the nervous system from free radical-induced oxidative damage [16], as exhibited by cognitive stimulation and emotional calming [44].

The psychostimulant effects of plant extracts were investigated in healthy as well as in patients suffering from with neuroses and asthenic syndromes. Patients with reduced work capacity, fatigue, loss of appetite, irritability, and headaches responded favorably to 50 mg of plant extract thrice daily. *R. rosea* ameliorated irritability, distractibility, fatigue, headache, weakness and other vegetative symptoms in 64% of 128 patients aged between 17 and 55 years. Improvement was assessed by psychological testing and work productivity [7]. *R. rosea* enhanced intellectual capacity to a greater extent than an extract of Siberian ginseng (*Eleutherococcus senticosus* Rupr. et Max., Araliaceae). In a double-blind 20 days study of medical students during a stressful exam period, the use of 100 mg/day of *R. rosea* extract led to significant improvements in quality of their final examinations over placebo [45]. The effects of extract of *R. rosea* on learning and memory processes on rats were evaluated by passive avoidance test in step-down and step-through processes [46]. Naïve rats treated with the extract showed the prolongation of latency of reaction of both passive avoidances compared to the control, and also the scopolamine groups - probably by non-specific mechanisms on cholinergic neurons - showing the plant extract can be a preventive agent against dementia [46]. *R. rosea* extract protects human cortical neurons against glutamate and hydrogen peroxide-induced cell death through reduction in the accumulation of intracellular calcium [47].

'Fatigue index' which is an overall level of measurement of mental fatigue involving complex cognitive functions (associative thinking, calculation, concentration, speed of audio-visual perception) was found significantly enhanced in physicians on long night duty without any side effects [48].

Compromise in functionality of the dopaminergic nerves in the basal ganglia leads to patients develop a constellation of "Parkinsonian" symptoms, which includes tremors, stiffness, bradykinesia (slowed movements) among many others. Alarming, antipsychotic medicines used in high doses over a long period to treat schizophrenic patients may affect the dopaminergic nerves as side effect. *R. rosea* was found effective in schizophrenic patients whose anticholinergic medications had failed to relieve Parkinsonian symptoms [7]. A patent has been granted for phytonutraceutical synergistic composition for Parkinson's disease (US 7553503 B2) comprising of a specific combination of herbal extracts and nutraceuticals based on energy, bio-intelligence, and organization. The patent claimed 32 mg of *Rhodiola rosea*, along with other herbal extracts, co-enzymes, Vitamins B1 and E21 and pharmaceutically acceptable excipients that can alleviate said disease [49]. DIHAR researchers have found that the anti-aging potential of *R. rosea* is related to tissue regeneration, protecting neurons in low oxygen level, and cognitive improvement [1]. Mechanistic details are awaited.

3.2.3 Radioprotection

Nuclear and radiological emergencies, either due to energy release resulting from a nuclear chain reaction, nuclear reactor accident or from the radioactive decay as happened in many countries suggest that any inadvertent or intentional lapse may lead to the radiation exposure [50]. During biochemical warfare, the herb can nullify the effects of gamma radiation. While aqueous extracts (up to 100 mg/mL) exhibited pro-oxidant activity, methanolic extracts showed marked antioxidant activity up to 250 mg/mL, contributing to its radioprotective efficacy. The aquo-methanolic fraction showed concentration-dependant cytotoxicity (up to 250 μ g/mL) but cytoprotection activity at 1000 μ m/mL. Whereas the conversion of Fe(III) to Fe(II) and Cu(II) to Cu(I) due to the presence of certain bioactive constituents (served as electron donors at lower concentrations) of plants favors pro-oxidant activity, certain other active constituents involved in metal ion chelation contributed to the overall antioxidant and radioprotective activity of the plant extracts [50].

3.2.4 Adaptogenic Capability, Anti-Fatigue Effects and Depression Treatment

An adaptogen is a non-specific agent which can help body to adapt with hard and exhaustive workload without causing minimal disturbance of the normal physiological functions. In contrast to classical stimulants which stimulate the initial increase in work-capacity followed by its decline, adaptogens have the capacity to maintain work despite fatigue (endurance). Plant adaptogens cause our physiology to begin the adaptation process under stress [51, 52]. In a stressful situation, adaptogens generate a degree of generalized adaptation (or non-specific resistance) that allows our physiology to handle the stressful situation in a more resourceful manner [53]. While continuous use of CNS stimulants

depletes brain catecholamines and decreases conditioned reflexes, *R. rosea* extracts, in contrast, always maintain working capacity of brain to the above average. Athletes given *R. rosea* had statistically significant increased shooting accuracy due to less arm tremor and better coordination. *R. rosea* improved recovery time, strength, endurance, cardiovascular measures, and coordination. Adaptogenic qualities of *R. rosea* can help the soldiers in adjusting to the low pressure-low oxygen environment through its anti-depressant and appetizer properties [1, 54]. Possible biochemical mechanisms involved are: increased cellular energy metabolisms through enhanced ATP, ribonucleic acid (RNA), protein, and amino acid biosynthesis, increased creatine phosphate (or phosphocreatine) in the muscle and brain mitochondria, and enhanced ammonia re-assimilation, during heavy muscular workloads [16, 54]. *R. rosea* boosts the body energy by stimulating the release of fats from adipose tissue. Root extracts in combination with daily exercises is an effective procedure of weight management which consequently helps toning mood, behavior and adaptability to new work and environment. An adaptogen ADAPT-232 comprising of *R. rosea* root extracts along with other plant extracts (Eleutherococcus senticosus root and Schisandra chinensis berry) reduced the cyclic Adenosine MonoPhosphate (cAMP) level in human neuroglial cell line T98G cells by down-regulating adenylate cyclase gene ADC2Y and up-regulating of phosphodiesterase gene PDE4D. This synergy is essential for energy homeostasis and for switching from catabolic to anabolic states and vice versa. Down-regulation of cAMP by adaptogens may decrease cAMP-dependent protein kinase A activity in various cells. This has led to inhibition of stress-induced catabolic transformations and energy saving for many ATP-dependant metabolic systems. Besides, up-regulations of the PLCB1 gene, encoding phosphoinositide-specific phospholipase C (PLC) and phosphatidylinositol 3-kinases (PI3Ks) for the regulation of NF- κ B-mediated defense responses, up-regulation of heat shock protein Hsp70 as well as serpin peptidase inhibitor (neuroserpin), and down-regulation of genes encoding ER α estrogen receptor, cholesterol ester transfer protein and 5-HT₃ receptor of serotonin are targets of adaptogen. The results suggested influence of adaptogen on regulation at transcriptional levels and at the level of the whole organism [55]. However, fermented *R. rosea* extract was found to be superior to non-fermented extract, significantly increasing swimming time, hepatic superoxide dismutase content, and serum lactate dehydrogenase in mice, while decreasing serum blood urea nitrogen content [56].

Depression is an emerging and life threatening disease worldwide [48]. By 2020, it is feared to be the second-leading cause of disability. Depression typically is represented as lowered mood, difficulty in thinking, loss of interest, and physical complaints such as headache, disturbed sleep, loss of energy, and changes in sex drive. The biochemical alterations in the brain cells are thought to be the primary cause of depression. Although pharmaceutical prescription, including selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), and monoamine oxidase inhibitors (MAOI), is shown to be effective in the treatment of depression, the treatments are not devoid of adverse side-effects like gastrointestinal disturbances including nausea and constipation, anticholinergic effects, orthostatic hypotension, arrhythmias, weight gain, and sexual dysfunction. Use of herbal therapy in this background is proven to be the most effective method. Extract of *R. rosea* administered together with tricyclic anti-depressants markedly reduced the side-effects of the drugs and exhibited a positive effect on psychopathological symptoms in patients with psychogenic depression [54, 57]. However, in a pioneering randomized clinical study with double-blind and placebo-controlled conditions, direct anti-depressive effect of SHR-5 (a standardized extract of *R. rosea* rhizome) in patients suffering from mild to moderate depression was investigated over six weeks [48]. There were significant improvements in HAM-D (Hamilton Rating Scale for Depression) scores in active groups. No improvement was found in the placebo group. Symptoms of depression, lack of emotional stability, and insomnia were markedly improved in both groups without any side effects as reported in medical and placebo groups [48]. Another work was related to investigate the influence of *R. rosea* roots on mood disorders, testing extracts against monoamine oxidases (MAOs A and B) in a microtitre plate bioassay. This investigation demonstrates potent anti-depressant activity of *R. rosea* plant extract [58].

R. rosea plant extract influences neurotransmitters monoamine (NE, DA, 5-HT) levels in nerve tracts and regulates mood, anxiety, and emotion in the amygdala, hippocampus, hypothalamus, and midbrain underlining a complicated complex of psychotropic activity (stimulating, tranquilizing, anti-stress, and antidepressant). Oral administration of a water extract to rats for 10 days modulated biogenic monoamines in the cerebral cortex, brain stem, and hypothalamus. Whereas levels of nor-epinephrine and dopamine decreased, serotonin level increased significantly in the cerebral cortex and brain stem. On the other hand, norepinephrine and

dopamine increased by about three-fold, and serotonin levels exhibited reducing trend in the hypothalamus. These changes in monoamine levels are mainly due to *R. rosea* induced inhibition of monoamine degrading enzymes like monoamine oxidase and Catechol-O-Methyl Transferase (COMT) which coupled with enhanced transport of neurotransmitters prevent both catecholamine release and subsequent cAMP elevation in the myocardium facilitating symptoms of stress relieve [45, 53, 54, 59].

In higher animals and humans, nonspecific resistance may also be enhanced by improvements in the neurological mechanisms of dealing with stress. One of the significant abilities of *R. rosea* to help the body adapt to stress may be attributed to its ability to enhance the level of serotonin, dopamine and other brain neurotransmitters. The serotonin system is necessary for the stress response reaction, adaptation to new environmental conditions, and tolerance of hypoxia [7]. Numerous stressors decrease serotonin in the hypothalamus. Serotonin and dopamine are normally broken down by the enzyme, COMT. Active constituents from *R. rosea* extracts have shown to inhibit the COMT activity. Clinical trials have proved that *R. rosea* roots can increase the level of neurotransmitters by 30% and decrease COMT activity by 60% [15]. Additionally, *R. rosea* can reduce the activation of components of the stress response system. It moderately increased serum beta-endorphins which protected rats against subsequent stress-induced excess endorphin elevation and controlled the release of stress-responsive opioid peptides in the pituitary adrenal axis, generating shield against sudden increase in opioid and catecholamine (NE and DA) levels. Over accumulation of NE and DA interferes with normal brain functions and can lead to heart damage. However, a moderate release stimulates stress tolerance without damaging the CNS or the cardiovascular system. Also, by reducing the secretion of corticotrophin releasing factor (CRF) during stress, *R. rosea* extracts protect the brain and heart [7, 43, 48, 54, 57].

3.2.5 Effects on Endocrine, Reproductive and Cardiovascular Systems

R. rosea enhanced thyroid function by helping thymus glands work better without causing hyperthyroidism in animal studies, thus preventing age-related involution. Plant extract helped adrenal glands which functioned with better reserve without hypertrophy, enhanced egg maturation in rats by reducing the resting period from 3.8 days (control) to 2.2 days (treated), elevated the relative number of estrus days from 29% to 56%, and prevented amenorrhea (loss of menstrual cycles) [16].

Prevention of stress-induced cardiac damage, reduction of myocardial catecholamines as well as cAMP levels, and decrease of adrenal catecholamine release are some of the cardioprotective effects of *R. rosea* extracts [16]. Also, activation of muopiate receptors by the plant prevented reperfusion arrhythmias in animal heart muscle [16]. The sympathetic and the parasympathetic nerves comprise autonomic nervous system. While the sympathetic nervous system operates as “fight-or-flight” system, helping the organism to respond stress by increasing pulse as well as respiratory rate, and muscle tone, the parasympathetic nervous system conserves and restores energy by slowing the heart and respiratory rate together with metabolism. *R. rosea* can stimulate both the systems, enabling the organism to put out more energy under stress without depleting the energy reserves. Rhodiolside and salidroside – two active principles of the plant- are used to administer as neuro-cardio-and hepato-protective activity, mitigating stress-induced impairments and neuro-endocrine and immune systems disorders. The mechanisms involved behind these effects have been reviewed [55]. Some other notable mechanisms involved are (i) prevention of ROS-mediated oxidative damage, (ii) restoration of functions of hematopoietic cells of the bone marrow depressed anemia, (iii) blockage in H₂O₂-induced apoptosis, (iv) protection of cardiomyocytes, (v) stimulation of glucose uptake, (vi) improvement of CNS functional rate, etc. [55]. Xing et al. [60] recently discovered that salidroside improves endothelial function and alleviates atherosclerosis by activating a mitochondria-related AMPK/PI3K/Akt/eNOS pathway. In another study, salidroside treatment markedly improved cell viability, decreased lactate dehydrogenase (LDH) release, reduced cell apoptosis, significantly improved cardiomyocytes glucose uptake by 1.7-fold and increased O-GlcNAc levels by 1.6-fold, as well as reducing cytosolic Ca²⁺ concentration compared to untreated cells following ischemia/reperfusion [61]. The modification of proteins with O-linked N-acetylglucosamine (O-GlcNAc) is increasingly recognized as an important posttranslational modification that modulates cellular function and this augmentation of O-GlcNAc levels increase cell survival following stress [61].

Effects of *R. rosea* on adipocyte differentiation and metabolism were studied through anti-adipogenic and lipolytic activity of two extracts of *R. rosea*, containing 3% salidroside (RS) or 1% salidroside and 3% rosavines (RR) on primary human visceral adipocytes [62]. While salidroside extract significantly induced higher apoptosis and lipolysis, rosavines extract

significantly reduced triglyceride incorporation during maturation. Differentiation of pre-adipocytes in the presence of salidroside and rosavines extracts showed a significant decrease in Expression of genes involved in adipocyte function such as SLC2A4 and the adipogenic factor FGF2 and genes involved in inhibition of adipogenesis, such as GATA3, WNT3A, WNT10B were found up-regulated. The rosavines extract significantly down-regulates PPAR γ , the master regulator of adipogenesis and FABP4 [62].

3.2.6 Effects on Tumor Progression and Carcinogenesis

R. rosea has potent anti-tumor and anti-cancer properties. Supplementation with plant extract inhibited the growth of solid Ehrlich adenocarcinoma and metastasizing rat Pliss lymphosarcoma tumor types. Plant extract can also decrease metastasis to the liver, and extended survival times. Pharmacological formulation also directly suppressed the growth and the extent of metastasis from transplanted Lewis lung carcinomas and in combination with the antitumor agent cyclophosphamide enhanced the antitumor and antimetastatic efficacy of drug treatment [53]. In another study [63], extracted and purified salidroside from *R. rosea* at 20 μ g/mL reportedly reduced the viability and the growth of human glioma cells U251 by arresting them at G0/G1 checkpoint during the cell cycle (in vitro study). A possible inhibition of the growth of human glioma tissue in nude mice in vivo study was accompanied with sustainability of body weight compared to quick decreasing body weight in control group. The treatment of salidroside inhibited overgrowth of astrocytes due to the onset of oxidative stress in the brain cortex [63]. As a potent antioxidant, purified salidroside can decline strain rate, ROS accumulation, normalize ecocardiograph, and can provide a protective effect on epirubicin (breast cancer drug)-induced early left ventricular regional systolic dysfunction in patients having breast cancer [63]. *R. rosea* suppresses thymus T-lymphocyte apoptosis by downregulating tumor necrosis factor- α -induced protein 8-like-2 in septic rats [64]. Furthermore, the extract and one of its bioactive components, salidroside, has the ability to inhibit the growth of human bladder cancer cell lines with a minimal effect on nonmalignant bladder epithelial cells TEU-2, indicating selective ability of the extract to inhibit the growth of malignant cells. The plant extract and salidroside treatment of UMUC3 cells resulted in an increase of AMP-activated protein kinase (AMPK)- α phosphorylation and a decrease of 4E-BP1 phosphorylation, resulting in increased binding of 4E-BP1 to m7 GTP, suggesting the fact that the *R. rosea* extract and salidroside inhibit translation initiation. Also, both the plant extract and salidroside treatment of UMUC3 cells caused a significant percentage of cells undergoing autophagy, thereby preventing growth of bladder cancer cell lines [65].

Roles of salidroside in cell proliferation, the cell cycle, apoptosis, invasion and epithelial-mesenchymal transition (EMT) were also studied in A549 lung cancer cells. Salidroside significantly reduced the proliferation of A549 cells, inhibited cell cycle arrest in the G0/G1 phase and expression of phospho-p38, ROS-formation and induced apoptosis [66].

3.2.7 *R. rosea* in Skin Care and as an Anti-Allergic

As an ingredient in organic skincare, *Rhodiola* acts as an adaptogen, helping the skin to cope with environmental stresses and consequent oxidative stress caused by sun exposure. By improving oxygen consumption in the skin, it can boost vitality and respiration in the cells and promptly adjust subtle environmental changes. Several certified organic skincare products have been commissioned in Europe using bioactive ingredients from root extracts of *R. rosea*. Notable among of these are (i) Skincare Neutralise Cleanser– a gentle non-foaming cleanser to soothe and reduce redness, and particularly useful in sensitive/normal to combo/oily skins; (ii) Skincare Balance Fluid– an anti-ageing moisturiser which is perfect for normal to oily and sensitive skins, and for a balanced, matte finish; (iii) Skincare Restore Cream– this anti-ageing moisturizer boosts hydration levels, soothes inflammation and reduces wrinkles in normal to dry sensitive skin [23]. Arctic bioactive compounds of the plant are the main constituent of these skin care formulations.

Molecular mechanisms of *R. rosea* extract as a skin whitening agent has recently been studied [67]. *R. rosea* extract and its hydrolysate inhibited melanin synthesis and tyrosinase activity in mouse melanoma cells (B16F0 cells) by inhibiting gene and protein expression of melanocortin 1 receptor (MC1R), c-AMP response element binding protein (CREB) phosphorylation, suppressing the activation of AKT and glycogen synthase kinase-3 beta (GSK3 β), and inhibiting the expression of microphthalmia-associated transcription factor (MITF) and tyrosinase-related protein 1 (TRP-1). The results suggest that *R. rosea* extract is a novel tyrosinase inhibitor and it regulated the CREB/MITF/tyrosinase pathway in B16F0 during inhibition of melanogenesis and can act as a skin whitening agent [67, 68].

The anti-allergic effects of *R. rosea* extracts were also studied. Ovalbumin-sensitized/challenged mice showed airway hyperresponsiveness (AHR) to inhaled methacholine and have an increased amount of T-helper2 type cytokines [interleukin (IL)-4, IL-5, and IL-13] and eosinophils in their bronchoalveolar lavage fluids and lung tissues. Intraperitoneal administrations of salidroside before the last OVA-challenge significantly inhibited asthmatic reactions and markedly suppressed NF- κ B translocation and reduced phosphorylation of p38 MAP Kinase [69]. Furthermore, salidroside attenuates the expression of intercellular adhesion molecule 1 and IL-6 through modulating the activities of p38 MAPK and NF- κ B in the BEAS-2B cells stimulated by proinflammatory cytokines [69].

3.2.8 *R. rosea*: Toxicity and Risk Factors

Low level of toxicity with very few side effects has been reported in some pharmacological preparation of *R. rosea*. The LD50 (lethal dose at which 50% of animals die) was calculated as 28.6 mL/kg in rat toxicity assessment which is 235 g equivalent dosage in a 70 kg man, suggesting a huge margin of safety in usual clinical doses of 200-600 mg/day. However, in particular anxious individuals, it can cause people agitated and hyperactive. In that case, lower doses are recommended [7]. An early hour use of the plant product is prescribed to prevent interference with sleep. Associated people suffering from bipolar spectrum disorder and who are vulnerable to anxiety should be barred from using this herbal drug due to its activating antidepressant effect [7].

Although *R. rosea* is unique by its reported ability to promote cognitive improvements, the energizing components may also promote anxiety in anxiety sufferers. Some to suspect risks of negative interactions of *R. rosea* with anxiety are through i) stimulated β Waves – caused by high doses of *R. rosea* in the brain which with varying frequencies signal anxiety, and ii) stimulated processing of fatty acids- The rosavin –induced processing of fatty acids in people already suffering from anxiety may run the risk of further stimulation and resultant anxiety attacks. Simultaneous stimulation of brain serotonin may sometimes offset this type of stimulation.

4. Conclusion

Despite its rising popularity, public education about biological implications of *R. rosea* is still in its infancy. Substitution from other species of *Rhodiola* and adulteration may deprive the consumers from the desired benefits of this medicinal herb. Given the popular proverb that "an ounce of prevention is worth a pound of cure," professionals and retailers alike may be confused by conflicting feedbacks by patients. Therefore, a holistic and comprehensive strategy should be formulated to iron out the difficulties faced by research related to commercial applications of this medicinal plant as a common man drug. A strict toxicological assessment and consumer safety protocol should be laid down by concerned authority. Present review encompasses a vast area of research on *R. rosea* and will be useful for academicians, military, disaster management workers, and industry personnel for prudent use of products obtained from this miracle medicinal herb.

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