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Rhodiola Rosea from the Selection of Traditional Applications to the Novel Phytotherapy for the Prevention and Treatment of Serious Diseases

By Dr. Rafie Hamidpour, Dr. Soheila Hamidpour, Dr. Mohsen Hamidpour,
Mrs. Mina Shahlari, Mrs. Mahnaz Sohraby, Ms. Nooshin Shahlari
& Ms. Roxanna Hamidpour

Shahid Beheshti University of Medical Sciences- Tehran-Iran, United States

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The studies on *Rhodiola rosea* have shown that the plant has anti-stress, anti-anxiety, anti-fatigue, and anti-depressant properties with no significant side effects. *Rhodiola rosea* has been considered in drug development because of its pharmacological activities throughout the world, especially in parts of Europe, Asia, and Russia. *Rhodiola Rosea* has shown more efficiency and safety than pharmaceutical drugs for anxiety and depression, which typically can have side effects, such as digestive upset, mood and sleep disorders.

Keywords: *antifatigue, antidepressant, alzheimer's disease, cancer and memory enhancement.*

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Rhodiola Rosea from the Selection of Traditional Applications to the Novel Phytotherapy for the Prevention and Treatment of Serious Diseases

Dr. Rafie Hamidpour ^α, Dr. Soheila Hamidpour ^ο, Dr. Mohsen Hamidpour ^ρ, Mrs. Mina Shahlari ^ω, Mrs. Mahnaz Sohraby [¥], Ms. Nooshin Shahlari [§] & Ms. Roxanna Hamidpour ^χ

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pharmaceutical drugs for anxiety and depression, which typically can have side effects, such as digestive upset, mood and sleep disorders.

This research paper, suggests that *Rhodiola rosea*, in addition to cure common disorders such as depression, binge eating, anorexia, generalized anxiety disorders, and physical and mental fatigue, might contribute to prevent, reduce and treat serious diseases such as Alzheimer's disease, Parkinson's disease, cardiovascular disease, diabetes, and cancer. The aim of our future research is to extract *Rhodiola rosea* into the filtration equipment and then, with purification and extended quality control, produce tablets for the animal trails.

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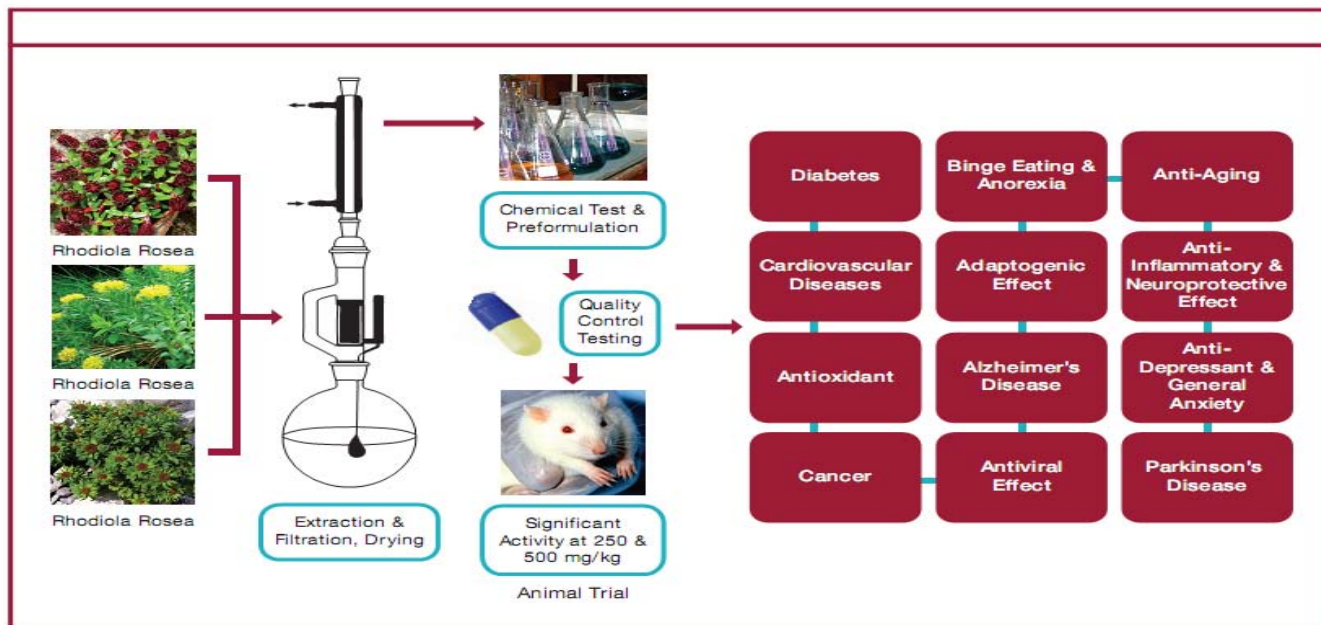


Figure 1

Author ^α: Ph.D., President, Pars Bioscience, Leawood, Kansas, United States. e-mail: rafie@parsbioscience.com

Author ^ο: M.D., School of Medicine, Departments of Pathology, University of Kansas City, Missouri, Kansas City, Missouri, United States. e-mail: soheila@parsbioscience.com

Author ^ρ: Ph.D., Department of Hematology and Blood banking- Faculty of Paramedical Sciences- Shahid Beheshti University of Medical Sciences- Tehran-Iran. e-mail: mohsen@parsbioscience.com

Author ^ω: BA in Biology, Pars Bioscience, Leawood, Kansas, United States. e-mail: mina@parsbioscience.com

Author [¥]: BA, Pars Bioscience, Leadwood, Kansas, United States. e-mail: mahnaz@parsbioscience.com

Author [§]: Summer Intern, Pars Bioscience, Leadwood, Kansas, United States.

Author ^χ: Summer Intern, Pars Bioscience, Leadwood, Kansas, United States.

I. INTRODUCTION

Rhodiola rosea, also known as golden root or *Lignum rhodium*, is a perennial herbaceous plant in the Crassulaceae family which has been used as a natural medicine from ancient times. This perennial plant reaches a height of 30-70 cm with a thick rhizome and yellow, fragrant flowers. It is a remarkable herb that is valued in traditional medicine in Eastern and Northern Europe, Asia, China, and Russia for its unique pharmacological activity.^[1] The plant has been categorized as an "adaptogen" by Russian researchers due to its ability to elevate body resistance to physical, chemical or biological stressors, treat fatigue, promote longevity, and support cognition and mood wellbeing.^[2] *Rhodiola rosea* (SHR-5 extract) has been indicated as an adaptogen in the situation of fatigue, poor mental performance and depression.^[3] *Rhodiola rosea* phytochemical extracts, are the source of important biological activities which is used widely in the treatment of a wide range of diseases like those of the nervous and cardiovascular systems, Alzheimer's and Parkinson's disease, cancer, and inflammatory diseases.^[4] The studies of pharmacological activities of *R. rosea* have revealed its hepato-protective and Monoamine oxidase A (MAO-A) inhibitory effects, in addition to the antiviral and antibacterial activities of this plant.^[5]

Phenylethanoid (salidroside, *p*-tyrosol), phenylpropanoid glycoside (rosarin, rosavin, rosin) and monoterpene (rosiridin) are responsible for the bioactivity of *R. rosea*. Salidroside, rosarin, rosavin, rosin, and *p*-tyrosol are the most critical plant constituents used for therapeutic activities. Salidroside and *p*-tyrosol have been found in all *Rhodiola* species but the other active glycosides: rosavin, rosin, and rosarin have not been detected in other genus of *Rhodiola* species. The compound rosavins (rosavin, rosin, and rosarin) are the compounds that contain the highest percent of *R. rosea*, which was not identified in other species. The compound salidroside is the most biologically active compound which shares many of its effects with rosavin.^[5,6] The absence of adverse drug interactions and side effects associated with *R. rosea* in the clinical trials make it possible to be used as a safe medication. *Rhodiola rosea* also can be applied as an adjuvant to enhance therapeutic effects of other medicines in a number of disorders such as chronic pneumonia, chronic tuberculosis, vascular dystonia, cancer (reduction of metastasis), and in reducing the debilitating effects of radiotherapy and chemotherapy.^[3,5]

II. COMMON NAMES

Rhodiola rosea has numerous common names. Some of the best known names include Arctic root,

Golden root, King's crown, Lignum rhodium, Orpin rose, Rose root, Sedum rhodiola, and SHR-5 extract. The term "arctic root" is used as a general name, however; arctic root is actually a trademark name for the specific commercial extract.

III. CHEMICAL COMPOSITION

The phytochemical analysis of the *Rhodiola* species has shown that the major beneficial components include salidroside and tyrosol, which are rich in the rhizomes.^[7] The dried rhizomes contained 0.05% essential oil. Terpenes and volatile compounds have been isolated from *Rhodiola rosea*. As shown in Table 1, Myrtenol (36.9%), trans-pinocarveol (16.1%), geraniol (12.7%), Cumin alcohol (12.1%), Linalool (2.7%), Perilla alcohol (1.7%) and dihydrocumin alcohols (12.1%) are the most abundant volatiles detected in the oil.^[8] Geraniol and Myrtenol are responsible for the rose like odor of the plant. A total number of 86 chemical compounds were identified in *R. rosea* roots. The principal components are phenylpropanoids (rosavin, rosin, and rosarin), Phenylethanoids (salidroside, *p*-tyrosol) and a monoterpene (rosiridin) which are responsible for the pharmacological effects of *R. rosea*.^[8,3] Rosiridin has attracted particular interest because of its effect in depression and senile dementia. Rhodioloside and salidroside active principles of the SHR-5 extract were found to have neuro-, cardio- and hepato- protective activities and can be effective in the prevention of a number of disorders related to neuro-endocrine and immune system. Three rosavin compounds (rosavin, rosin, and rosarin) which are unique to *R. rosea* (the most used species of *Rhodiola* genus) might be responsible for antidepressant, anticancer, neurotropic, and hepato- protective effects of this herb.^[3]

Table 1. Chemical Composition of oil of *Rhodiola rosea*

Compound	Percentage
Linalool	2.7
Octanol	13.6
6,6-dimethyl-bicyclo[3,1,1] hept-2-ene-2-carboxaldehyde	1.0
Trans-pinocarveol	16.1
Myrtenol	36.9
Geraniol	12.7
Myrtenol	1.0
Perilla alcohol	1.7
Dihydrocumin alcohol	2.1
Cumin alcohol	12.1

Ref: [8] *J Essen Oil Res* 2005; 17(6):628-9.

a) Antioxidative effect

The imbalance between reactive oxygen species (ROS) generation and antioxidant defense mechanism causes oxidative damage to the proteins, membrane lipids and nucleic acids in the cells. The increased generation of ROS damages the mitochondria, the power house of the body, which account for reducing the ability of maintaining energy at the cellular level and results in muscular atrophy and

muscle fatigue, leading to the decreased performance of an individual.^[9]

Antioxidants are natural substances that prevent or delay some type of cell damages and protect the body against the oxidative stress and free radicals. Various *Rhodiola* species have shown significant antioxidant activities. Among the 28 different compounds identified in *R. rosea*, P-tyrosol, salidroside, and five salidroside-like glycoside (Rhodiolin, rosiridin, rosarin, rosavin, and rosin), possess strong antioxidant activities.^[10]

Polyphenols in *R. rosea* neutralize oxidative reactions, which are induced by free radicals since they are excellent donors of protons and electrons. In addition, polyphenols, due to their metal chelating properties, are able to decrease oxidative stresses, induced by transition metals.^[12]

Salidroside (SDS), a major component extracted from *Rhodiola rosea*, is a glucoside of tyrosol which possess a broad spectrum of pharmacological properties including strong antioxidant activity. Salidroside induces its antioxidant effects to the cells by preventing collection of intracellular ROS, restoring the impaired mitochondria function and mitigating oxidative-stress-induced apoptosis.^[11]

Production and detoxification of Reactive Oxygen Species (ROS) are of major importance in regulation of erythropoiesis (formation of red blood cells). Salidroside plays an essential role in maintaining normal erythropoiesis through the up-regulation of antioxidant defense mechanism. Salidroside could mediate its effect as blood tonic supplement and adaptogen. Patients with anemia and malhypoxia can take advantage of SDS as an adjuvant for erythropoietin (EPO) or other erythropoiesis-stimulating agents. This compound also defends erythroblasts against oxidative stress through up-regulating the expression of antioxidant molecules, glutathione peroxidase, and thioredoxin, and it also nullifies ischemia-induced cardiomyocyte death through suppressing ROS overgeneration.^[11,13]

b) Effect on cancer cells

Cancer is a class of diseases characterized by out-of-control cell growth. Complete eradication of cancer without damage to the rest of the body is the goal of the treatment. Some plant extracts that indicate potential as an anticancer agent have shown to be useful for the treatment or prevention of the cancer with minimal toxicity, and they act synergistically with cytostatic to reduce their toxicity. The study showed that the use of *R. rosea* extract in combination with the antitumor agent cyclophosphamide increased the anti-tumor and antimetastatic efficacy of the drug.^[14]

The results of investigation *in vivo* show that *R. rosea* extract has cytotoxic effect on tumor cell line through its major component, polyphenols. The

cytotoxicity effect of polyphenols on tumor cells are induced by reaction oxygen species (ROS) mediated mechanisms. Polyphenols including tannins and gallic acids, induce apoptosis in tumor cells by increasing intracellular peroxides.^[15,16] The results show that salidroside, a component isolated from plants that belong to the *Rhodiola* genus, causes growth inhibition in several human cancer cell line in concentration between 1 μ g/ml and 32 μ g/ml dose dependently by induction of G1-phase and/or G2-phase arrest. A number of studies have investigated the inhibitory effect of salidroside on the growth of stomach adenocarcinoma cells, leukemia cells, and parotid carcinoma cells *in vitro*. In a few studies performed in China, was found that Salidroside could inhibit tumor-induced angiogenesis in mice.^[17]

Breast cancer is the most common cancer diagnosed in women in the United States. It develops by the mammary cell proliferation induced by estrogen. Resistance of estrogen receptor negative (ER⁻) tumors to anti-hormone therapy is the main concern in breast cancer treatment. Investigations of the effects of salidroside on the breast cancer showed its inhibitory properties on human breast cancer MDA-MB-231 cells. The result indicated that salidroside in concentration between 5 μ m and 80 μ m dose dependently induced cell-cycle arrest and apoptosis cell death in ER-negative and ER-positive tumors in human breast cancer.^[18]

Thyroid cancer is the most frequent endocrine neoplasia and accounts for about 2% of cancer-related deaths. Management options for thyroid cancer include total or near total thyroidectomy, radioiodine therapy and pharmacotherapy. These patients may have neuropsychological concerns such as depressive moods or developed cardiovascular problems such as hypertension, electrocardiogram abnormalities, and diastolic dysfunction. In numerous studies, *R. rosea* has demonstrated CNS stimulating, neuro-, cardio-protective and antidepressant effects. Since most of these symptoms are in fact the clinical aspect of hypothyroidism, *Rhodiola rosea* is recognized to aid in patient preparation during the hormone withdrawal period. Oxidative stress increases when thyroid hormones are missing during hypothyroidism. Studies in rats reveal that supplementation with *R. rosea* extract can protect cells from oxidative injuries in dose-dependent manner. This finding has also been replicated in human. *Rhodiola rosea* have potentially additional benefits as an adaptogen that tends to be a regulator, having normalizing effects on the organism. Hypothyroidism can be considered as a stressor and then *R. rosea* as an adaptogen that could help the organism's responding.^[19]

c) Alzheimer's Disease

Alzheimer's disease (AD) is a progressive brain disorder characterized by the memory and

cognitive impairments. Neuropathologically, AD is defined by the accumulation of amyloid plaques and neurofibrillary tangles in certain region of the brain which are important in memory and can cause the loss of synaptic connection between cells. One of the most important parts of unraveling the AD mystery is discovering what causes the disease. It has been suggested that oxidative stress and dysfunction of neurogenesis play important roles in pathogenesis of AD.^[20] Beta-amyloid (A β) peptide, the hallmark of Alzheimer disease induces an oxidative damage to neurons and finally causes neurons death. Reduced levels of anti-oxidative activity have been observed in the specific regions of the central nervous system of AD patients.

Now researchers are paying great efforts to find potent natural antioxidant with neuroprotective potentials. Salidroside, an active compound occurring naturally in *Rhodiola rosea* L. is protective against (A β)-induced oxidative stress by the induction of antioxidant enzymes, thioredoxin (Trx), heme oxygenase-1 (HO-1), and peroxiredoxin-1 (Prxl); the down regulation of pro-apoptotic protein Bax and the up regulation of anti-apoptotic Bcl-X1. Pathophysiology of neurodegenerative diseases such as AD has shown that A β is associated with ROS generation which leads to mitochondrial dysfunction, lipid peroxidation and apoptosis. Exposure to ROS also inhibits neurogenesis, which is the onset of cognitive impairments and memory deficits. Salidroside could decrease the intracellular ROS level and restore the abnormal mitochondrial membrane potential (MMP). The neuroprotective effect of Salidroside may offer long-term protection in the pathogenesis of AD.^[20,21]

d) *Adaptogenic and antifatigue effects*

Adaptogens are unique group of herbal ingredients which help strengthen the body's response to stress, enhance its ability to cope with anxiety, and fight fatigue. They have the unique ability to adapt their function according to the body's specific needs and do not disturb bodily functions at normal levels. *Rhodiola rosea* is known as a plant's adaptogens because it possesses anti-fatigue and anti-stress activities that can increase mental and physical working performance against a background of fatigue or stress.^[22] The phenylpropanoid glycoside called salidroside, flavonoids, Phenolic, polyphenolic, and flavolignans are thought to be the main components of stress-protective and adaptogens of *Rhodiola rosea*. Other constituents isolated from *R. rosea*, including rhodioniside, rhodioloside A-E, rhodiolin, rosin, rosavin, rosarin, rosiridin, rosiridol, rhodalgin, acetyl rhodalgin, and lotaustralin, might also be responsible for *R. rosea*'s stimulant or adaptogenic effects. Such compounds can play an active role in increasing energy, stamina, strength and mental

capacity required in fight to fight situation to help the body to adapt and resist physical, chemical, and environmental stresses.^[22,23]

Clinical efficacy of adaptogens in behavioral and mental disorder has been reviewed. It is now accepted that adaptogens have shown anti-fatigue, anti-depressant, anxiolytic, nootropic, and CNS stimulating effects. Adaptogens do not possess any side effects of conventional drugs such as addiction, tolerance and abuse potentials, or impair mental function, neither do they cause psychotic symptoms with long term use.^[24]

Neuro-degenerative disorders characterized by the progressive loss of structure or function of neurons in the brain region involved in learning and memory. *Rhodiola rosea* as an adaptogen could induce a positive effect in neuro-degenerative disorders due to their inhibitory effects on the formation of p-SAPK (phosphorylated stress-activated protein kinase). Related data may be considered to add further support to the hypothesis that adaptogens have beneficial effect on mental performance and cognitive function.^[22] The key point of action of adaptogens on stress appears to be related to the regulation of homeostasis via hypothalamic-pituitary-adrenal axis and regulation of molecular chaperones, stress-activated c-Jun, N-terminal protein kinase, forkhead box O transcription factor DAF-16, cortisol, nitric oxide (NO) and beta-endorphin.^[24] The optimal corticosteroid level is required for efficient cognitive function. Significant changes (up or down) in circulating levels of corticosteroids have been accepted as the reason for cognitive impairment. Regulatory effects of *R. rosea* on the basal level of salivary cortisol results in an improvement in cognitive function.^[3]

Rhodiola rosea combines well with other adaptogens and tonics in appropriate dosages. The herbal drug ADAPT-232 is based on the synergistic effect of the three most efficient adaptogen plants, *Rhodiola rosea*, *Schisandra Chinensis* and *Eleutherococcus senticosus* in a fix combination. Administration of single and repeated doses of ADAPT-232 has been shown to increase physical energy as well as mental performance and cognitive function.^[25] ADAPT-232 significantly increases secretion and release of stress hormones, neuropeptide Y (NPY) and Heat Shock Protein 72 (Hsp 72) which increase tolerance and adaptation to stress. These pathways contribute to the anti fatigue effect of ADPAT, increase the attention and improve the cognitive function.^[24]

Furthermore, a number of studies have investigated the effects of ADAP-232 on pneumonia patients. Clearly, adjuvant therapy on pneumonia patients with ADAPT-232 has a positive effect on the recovery of the patients, by decreasing the duration of the acute phase of the illness, increasing mental

performance of the patients during the rehabilitation period and by improving their quality of life.^[25]

e) *Anti-depressant and general anxiety*

Depression is a severe despondency and sadness accompanied by a feeling of desperation and inadequacy. The mechanism of depression is complex. The therapeutic effects of anti-depressants such as Tricyclic antidepressants (TCAs), Monoamine oxidase inhibitors (MAOIs) and Selective serotonin reuptake inhibitors (SSRIs) come with a number of side effects like psychomotor impairment and dependence liability.^[26] The use of Alternative Medicine especially natural products for the treatment of mental disorders have been increased in the U.S and worldwide. The most common reason for people to use complementary therapies is that they want to avoid the common side-effects of prescription antidepressant drugs. A few natural psychotropics have been more extensively examined in well-designed, placebo-controlled, double-blind studies. *Rhodiola rosea* is one of these second-tier natural products for mood disorders.^[27] The standardized extract SHR-5 (3% rosavin and 0.8% salidroside) from *R. rosea* have a significant antidepressant activity in mild to moderate depression. The symptoms evaluated were emotional instability, decreased motivation, cognitive complaints and susceptibility to stress.^[28] Significant improvement in the overall symptom of depression and mood deficiencies was observed in a 6-week monitoring study in Sweden, which *R. rosea* was given daily with a dosage of two tablets a day, each containing 170mg of the extract.^[28] The role of serotonin, a monoamine neurotransmitter, is usually known and associated with depression, however, serotonin also has some cognitive functions, including the enhancement of memory and learning. Regulation of serotonin at synapses is a major mechanism of action possibly contributing to pharmacological antidepressants. Central and peripheral serotonin levels decreases in patients with depression. Monoamine oxidase type A has an important role in degradation of biogenic amines such as epinephrine, norepinephrine, and serotonin. Monoamine oxidase inhibitors (MAOIs) prevent the breakdown of monoamine neurotransmitters including serotonin and therefore increases the concentrations of neurotransmitter in the brain. MAOIs therapy with synthetic drugs are known to interact negatively with other medications and even with food. MAOIs can cause death if they are taken in overdose extent. There is evidence that *R. rosea* acts as monoamine oxidase inhibitors and influences the level and activity of biogenic monoamines such as serotonin, norepinephrine, and dopamine in the nerve terminal. *Rhodiola rosea* inhibits the activity of the enzymes responsible for monoamine degradation (monoamine oxidase and catechol-O methyl

transferase).^[4,3] General anxiety disorder (GAD) is a common disorder that involves chronic worrying, nervousness and tension. There are different types of medication for GAD, including antidepressants, Benzodiazepines, and serotonin reuptake inhibitors. Patients who do not respond to conventional treatment often experience adverse side effects that may interfere with their consistency. *Rhodiola rosea* is safe and tolerable alternative medicine. Administration of *R. rosea* in dosages of 2-3 capsules each containing 100-170 milligrams daily approximates to the perfect dose to gain beneficial effects.^[29]

f) *Anti-inflammatory and neuroprotective effect*

In general, inflammation is a localized reaction of the body tissues to infections, irritation, injuries, or disorders of the immune system which produce redness, warmth, swelling, and pain. As we age, the level of inflammatory immune cytokines increases and we get vulnerable to a number of inflammation-linked diseases, such as cancer, arthritis, muscle weakness, fatigue, sleep disorder, Alzheimer's and Parkinson's disease. An enormous amount of research has demonstrated the link between chronic low-level brain inflammation and elevated brain glutamate levels, which are a neurotransmitter normally involved in learning and memory. In some cases, glutamate can be an excitotoxin that is involved in nerve-cell death in various neurodegenerative disorders including Alzheimer's and Lou Gehrig's disease. Glutamate not only influence amyloid β production (the cause of Alzheimer's disease), but also amyloid β can change the levels of glutamate in the brain which increase the vulnerability of cortical neurons to glutamate cytotoxicity. It has been shown in several studies that *R. rosea* could improve inflammation and neurotoxicity in cortical neuronal cells. *Rhodiola rosea* modulates the neuronal over action and endogenous anti-inflammatory.^[30]

Microglia, a type of glial cell, acts as the first and main form of active immune defense in the central nervous system (CNS), and thus plays a key role in the inflammatory reaction. Inflammatory process, in the central nervous system leads to neuronal cell death, and inflammatory response is mediated by the activated microglia, which remove the damaged cell by phagocytosis. The chronic activation of microglia may in turn cause neuronal damage through the secretion of cytotoxic molecules such as proinflammatory cytokines (interleukin-1 β (IL-1), IL-6 and TNF- α), proteases, and reactive oxygen species (ROS), and nitric oxide (NO). Therefore, suppression of microglia-mediated inflammation can appear to be the most promising option in neurodegenerative disease therapy. Since overproduction of NO plays an important role in neuroinflammatory disease, the effect of the *R. rosea* on nitric oxide production was investigated in lipopolysaccharide (LPS)-induced microglia cells.

Rhodiola rosea has shown to strongly inhibit NO production and the expression of Inducible nitric oxide synthase (iNOS), the key enzyme for NO in LPS-stimulated microglia cells.^[30]

g) Antiviral activity

The influenza is an acute infectious disease caused by an RNA virus of the family orthomyxovirus. Influenza virus infects the epithelial cells of respiratory tract that causes acute pulmonary diseases. Influenza outbreak usually occurs in winter, killing numerous people in pandemic years. The epidemic outbreaks of influenza are associated with influenza virus type A and B. Type C virus is associated with minor symptoms. Two neuraminidase inhibitors have been approved by FDA (zanamivir and oseltamivir) to treat influenza virus infection. Both of these inhibitors are active against influenza virus A and B, however, they have several toxic effects in the digestive and autonomic nervous system. The flavonols Kaempferol, Herbacetin, Rhodiolinin, Rhodionon and Rhodiosin were isolated from *Rhodiola rosea*. The compounds showed neuraminidase inhibitory and anti-influenza virus activities. The *in vitro* anti-influenza virus activities of flavonoids were evaluated using two influenza viral strains, H1N1 and H9N2, testing their ability to reduce virus-induced cytopathic effect (CPE) in MDCK, Madin-Darby Canine Kidney Cells (virus tissue culture). Anti-influenza activity depends on the position and the number of hydroxyl groups on the flavonoids backbone. Kaempferol showed the highest activity against two influenza viruses, H1N1 and H9N2 with the half maximal effective concentration (EC₅₀) values of 30.2 and 18.5 μM.^[9]

Coxsackievirus B3 (CVB3) is important human pathogen that belongs to picornavirus family. CVB3 is the most common cause of viral myocarditis, a serious disease that can further lead to dilated cardiomyopathy and cardiac failure and also often induce pancreatitis and aseptic meningitis. Although a few vaccines have been reported to be effective in a murine CVB3-induced myocarditis model, there are no effective therapeutic agents against CVB3 for the clinic up to now. Salidroside (p-hydroxyphenethyl-β-D-glucoside) which is extracted from *R. rosea* demonstrated antiviral activity while not affecting the normal physiological function of the host cells. Salidroside exhibited obvious antiviral activity *in vitro* and protected myocardial cells against CVB3 infection. The antiviral activities of salidroside against CVB3 may be related to modulating serum superoxide dismutase (SOD), serum nitric oxide (NO), serum catalase (CAT), and serum Malondialdehyde (MDA) activities to protect heart muscle against the harmful effect of free radicals. Also salidroside has the ability to increase the hemoglobin capacity to carry oxygen, which provides protection for the myocardial cells

from hypoxemia. Since salidroside also has shown antiviral activities against CVB3 *in vitro*, the findings have significant implications for a potential therapeutic agent for treatment of viral myocarditis and influenza virus infections which is worthy of further future researches.^[32]

h) Antidiabetic

The anti-diabetic effects of dietary administration of *Rhodiola*-water extract on streptozotocin (STZ)-induced diabetes rat model were investigated. STZ is a toxin with the ability to damage pancreatic beta cells, resulting in hypoinsulinemia and hyperglycemia. The study used STZ mice as a model because it is considered an appropriate model to assess mechanisms of diabetes and evaluate potential therapies. Three days administration of *Rhodiola*-water extract in STZ-diabetic rats resulted in an increase of glucose transporter subtype 4 (GLUT 4) in skeletal muscle and a reduction of phosphoenolpyruvate carboxykinase in liver. It has been reported that *Rhodiola*-water extract have a long-term blood glucose level control effect and improves hyperglycemia by an increase of beta-endorphin secretion from adrenal gland to activate opioid μ-receptors to achieve the higher of GLUT 4 gene expression in STZ rats model.^[33]

Evidence in both experimental and clinical studies shows that increased oxidative stress is the common pathogenic factor causing diabetic mellitus and its complication. Diabetes is a chronic metabolic disorder characterized by hyperglycemia and the inability of tissues to utilize glucose. Hyperglycemia and fluctuation in blood glucose generate oxidative stress through overproduction of reactive oxygen species. Dietary *R. rosea* supplementation results in a significant reduction on blood glucose and lipid peroxide, increased levels of glutathione, glutathione peroxide, catalase, and superoxide dismutase (SOD) in the liver. *Rhodiola rosea* extracts may be effective for correcting hyperglycemia and preventing diabetic complications.^[34] Managing diabetes without any side effect is still a challenge. Therefore, it is worth more investigation in the antidiabetic activity of natural products such as *R. rosea* on humans in the future.

i) Lifespan increasing effects

Recent studies on *Drosophila melanogaster* and *Caenorhabditis elegans* have shown that bioactive components of *R. rosea*, particularly salidroside and/or rosavins, may have an effect on lifespan and improve health spans. The plant adaptogens can induce their effects by different routes. Adaptogens can extend the lifespan by increasing an organism's resistance against the damaging effects of different stress conditions. The plants adaptogens such as *R. rosea* interfere with the localization of DAF-16, a forkhead/winged-helix transcription factor. The *Caenorhabditis elegans* DAF-16 transcription factor is

critical for diverse biological processes specifically longevity and stress resistance. *Rhodiola rosea* induce translocation of the DNF-16 transcription factor from the cytoplasm into the nucleus. DAF-16 in the nucleus reprograms the transcriptional activities favoring the transcription of a large number of genes involved in stress resistance and longevity.^[35]

Moreover dietary conditions are another hypothesis for anti aging effect of *Rhodiola rosea*. The effect of *R. rosea* supplement on the lifespan of fruit fly depends on diet composition particularly on the protein-to-carbonate ratio. Dietary compositions with the protein-to-carbohydrate ratio less than 1 extends the lifespan by 15% to 21%, but diets with high protein-to-carbohydrate ratio or high calorificity do not support the beneficial action of *R. rosea* on longevity.^[36] Hormesis is favorable biological responses to a low dose stress-induced stimulation resulting in biologically beneficial effects on growth, reproduction and longevity. Hormesis activates defense systems of the body and the defense process repair the damage caused by the toxin and also protect body against any additional stress. It can be hypothesized that the plants adaptogen like *R. rosea* act as a mild stressor leading to activate an adaptive response which protects the cells from stressful environments and increase the life span. In this way, it can be mentioned that adaptogen acts as hormetic agents. The findings of a study support the view that low doses of *R. rosea* extract (10-25µg/ml) works in a deliberate and systematic way in order to increase the stress resistance and lifespan of *C. elegans* between 10 and 20%, whereas the higher doses tested (250µg/ml) of *Rhodiola* showed a life span shortening of 15 to 25 percent.^[35]

j) *Cardioprotective effects*

Hyperhomocysteinemia (high homocysteine level in the blood) is a major risk factor of cardiovascular disease. An abnormal accumulation of homocysteine, an amino acid that is produced by human body due to consuming meat, is related to various cardiovascular diseases such as coronary heart disease, stroke and peripheral vascular disease (fatty deposits in peripheral arteries). Homocysteine exert its adverse effect on endothelial function by increasing superoxide production and decreasing the activity of nitric oxide synthase. Homocysteine could be a starting point for the development of atherosclerosis by disturbing vascular permeability, damaging the inner lining of the arteries and promoting blood clots. Slidroside extracted from *Rhodiola* protect rats aortas against homocysteine-induced impairment of endothelium by inhibiting NOX2-dependent ROS overproduction. These results suggest that salidroside significantly inhibit ROS overproduction associated with vascular dysfunction, a common pathological process in hypertension and diabetes.^[11]

k) *Effect on Binge eating and Anorexia*

Binge eating (BE) and Anorexia Nervosa are official eating disorders. Binge eating appears to be characterized by extreme overeating without subsequent purging episodes, usually secretive, and filled with shame.^[37] Topiramate or sibutramine are medications that have been suggested to reduce BE. However, their uses are associated with a variety of adverse side effects which causes serious problems, such as cardiovascular disorder and stroke. As a result they have been withdrawn from the market in many European countries. Since stress is a key factor in BE, a reduction of stress response might show an effective mechanism for the treatment of BE. Therefore, due to its anti-stress properties, the effect of Slidroside, an active principle of the dry extract of *R. rosea*, was evaluated for treatment of BE. Studies have shown that Salidroside abolishes BE by suppressing the activation of hypothalamic-pituitary- adrenal (HPA) axis, leading to a reduction of serum corticosterone flowing chronic treatment.^[1]

Furthermore, new evidence shows that *R. rosea* may cancel out the anorexia (out of control dieting), another troubling manifestation of stress.

Eating disorders are associated with stress responses depending on the intensity of stress itself; moderate stressors stimulate eating while acute stressors, which cause high levels of CRF (corticotrophin-releasing factors), induce anorexia. In particular, considerable evidence suggests a role for endogenous brain CRF system in appetite regulation and the cause of eating disorder. At doses of 15 and 20mg/kg, *Rhodiola* extract significantly inhibits the anorexia effects of stress within 60 minutes after a single oral administration of *R. rosea* extract.^[38] Therefore, the different effects evoked by *R. rosea* on eating behavior could be attributed to its ability to modulate the activation of several components of stress-response system rather than a direct effect on orexigenic or anorexigenic mechanisms.^[1]

l) *Effect on Parkinson's Disease*

Parkinson's disease (PD) is a chronic and progressive disorder of the nervous system that affects movements of the body and the symptoms continue and worsen over the time. Parkinson's primarily affects neurons in the area of the brain called substantia nigra. Cells within the substantia produce and release dopamine, a neurotransmitter that controls the movement and balance. In patients suffering from Parkinson's, the amount of dopamine produced in the brain decreases. The shaking or tremor may begin to interfere with the daily activities of the PD patients. As these symptoms become more pronounced, patients may have difficulty walking, talking or performing other simple tasks. Although

there is no cure, there are treatment options such as medication and surgery to control the symptoms.^[39]

The new plant preparation Phytomix-40(PM-40) is developed for the treatment of Parkinson's disease. Phytomix (PM-40) is a mixture of natural extracts of 40 medical plants, including extracts of *R. rosea*, *Eleutherococcus*, ginseng, and other adaptogens with neuroprotective properties. Animal experiments demonstrated that PM-40 had a low toxicity. The neuroprotective plant adaptogen can be used in complex therapy for the Parkinson's disease for improving its efficacy. Oral administration of 10% solution of Phytomix-40 to mice with MPTP-induced Parkinson's syndrome reduces the severity of rigidity and increase motor activity. The preparation normalized immunobiological parameters in PD patients and relieved the clinical symptom of the disease. The mechanism of action of PM-40 contributes to the recovery of the dopamine synthesis by healing of damaged neurons. PM-40 can be used with the combination of other standard antiparkinsonian drugs in order to improve their clinical effects and minimize side effects of Parkinson's medication.^[39]

m) Overview of toxicological and safety data

Through the doses administered in clinical trials, there is no report of serious side effects that could be attributed to the extract of *Rhodiola rosea*. The normal usage of *R. rosea* is safe, however, it is important to consider that *R. rosea*, a strong adaptogenic and tonic herb, might have an addictive effect with other substances exhibiting stimulant properties (such as caffeine).^[40]

Continuous daily use of *R. rosea* for days and months is followed by an interval with no supplementation (three weeks "on" and one week "off"). This clinical recommendation helps avoid possible side effects at higher dosages such as insomnia, irritability, dizziness, dry mouth, and allergy (unspecified).^[29]

The most commonly used standardized extract has a minimum of 3% rosavin and 1% salidroside. The typical daily dose for chronic administration extracts range from 100-170 mg per day when standardized for 2.6% rosavin. Evidence on the safety and appropriateness of *R. rosea* supplementation during pregnancy and lactation has not been established.^[14]

IV. CONCLUSIONS

Rhodiola rosea, which is also known as the golden root, is one of the most studied *Rhodiola* species. As an adaptogen, many health benefits are related to *Rhodiola* drug extracts due to their balancing and regulatory effects. Significant antioxidant activities have been documented for various *Rhodiola* species extracts. In Russian and Chinese folk medicine, the plant is used for stimulating the

nervous system and decreasing mental and physical fatigue. It has been shown in pharmacological investigations that, *R. rosea* possess antioxidant, antiaging, anti-cancer and anti-cardiovascular disease properties. As a dietary supplement, numerous preparations of extracts are used worldwide including teas, homeopathic preparations and tinctures as well as standardized extract. *Rhodiola rosea* has enormous traditional and pharmacological use in supporting mood and cognitive function.

Rhodiola rosea is a versatile, safe and easily accessible plant which offers resistance to the physical, chemical and biological stressors without interacting with other food or drugs. The remarkable therapeutic effects of this plant in prevention and treatment of variety of human diseases, makes this plant very valuable for further investigation in the area of pharmaceutical industries.

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