

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

4 Mrs. Mina Shahlari

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6

7 **Abstract**

8 Rhodiola rosea is a remarkable herb that has been a part of traditional medicine systems in
9 order to stimulate the nervous system, to protect the body against oxidative stress, free radical
10 damage, inflammation, and virus infection. Rhodiola rosea is included among a class of plant
11 derivatives called adaptogens, an agent that helps the body adapt to various stressors.
12 Adaptogens have been claimed to treat a wide variety of medical conditions, from fatigue to
13 cancer. The studies on Rhodiola rosea have shown that the plant has anti-stress, anti-anxiety,
14 antifatigue, and anti-depressant properties with no significant side effects. Rhodiola rosea has
15 been considered in drug development because of its pharmacological activities throughout the
16 world, especially in parts of Europe, Asia, and Russia. Rhodiola Rosea has shown more
17 efficiency and safety than pharmaceutical drugs for anxiety and depression, which typically
18 can have side effects, such as digestive upset, mood and sleep disorders.

19

20 **Index terms**— antifatigue, antidepressant, Alzheimer's disease, cancer and memory enhancement.

21 I. Introduction Rhodiola rosea, also known as golden root or Lignum rhodium, is a perennial herbaceous plant
22 in the Crassulaceae family which has been used as a natural medicine from ancient times. This perennial
23 plant reaches a height of 30-70 cm with a thick rhizome and yellow, fragrant flowers. It is a remarkable
24 herb that is valued in traditional medicine in Eastern and Northern Europe, Asia, China, and Russia for its
25 unique pharmacological activity. [1] The plant has been categorized as an "adaptogen" by Russian researchers
26 due to its ability to elevate body resistance to physical, chemical or biological stressors, treat fatigue, promote
27 longevity, and support cognition and mood wellbeing. [2] Rhodiola rosea (SHR-5 extract) has been indicated as an
28 adaptogen in the situation of fatigue, poor mental performance and depression. [3] Rhodiola rosea phytochemical
29 extracts, are the source of important biological activities which is used widely in the treatment of a wide range of
30 diseases like those of the nervous and cardiovascular systems, Alzheimer's and Parkinson's disease, cancer, and
31 inflammatory diseases. [4] The studies of pharmacological activities of R. rosea have revealed its hepato-protective
32 and Monoamine oxidase A (MAO-A) inhibitory effects, in addition to the antiviral and antibacterial activities
33 of this plant. [5] Phenylethanoid (salidroside, ?-tyrosol), phenylpropanoid glycoside (rosarin, rosavin, rosin) and
34 monoterpene (rosiridin) are responsible for the bioactivity of R. rosea. Salidroside, rosarin, rosavin, rosin, and ?-
35 tyrosol are the most critical plant constituents used for therapeutic activities. Salidroside and ?-tyrosol have been
36 found in all Rhodiola species but the other active glycosides: rosavin, rosin, and rosarin have not been detected
37 in other genus of Rhodiola species. The compound rosavins (rosavin, rosin, and rosarin) are the compounds that
38 contain the highest percent of R. rosea, which was not identified in other species. The compound salidroside is
39 the most biologically active compound which shares many of its effects with rosavin. [5,6] The absence of adverse
40 drug interactions and side effects associated with R. rosea in the clinical trials make it possible to be used as
41 a safe medication. Rhodiola rosea also can be applied as an adjuvant to enhance therapeutic effects of other
42 medicines in a number of disorders such as chronic pneumonia, chronic tuberculosis, vascular dystonia, cancer
43 (reduction of metastasis), and in reducing the debilitating effects of radiotherapy and chemotherapy. [3,5]

1 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.

2 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 ??, 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, ?-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]

3 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 R Ref: [8] 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]

4 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 antitumor 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 1µg/ml and 32µg/ml dose dependently by induction of G1-phase and/or G2phase 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

103 by estrogen. Resistance of estrogen receptor negative (ER-) tumors to anti-hormone therapy is the main concern
104 in breast cancer treatment. Investigations of the effects of salidroside on the breast cancer showed its inhibitory
105 properties on human breast cancer MDA-MB-231 cells. The result indicated that salidroside in concentration
106 between 5 μ m and 80 μ m dose dependently induced cellcycle arrest and apoptosis cell death in ER-negative and
107 ER-positive tumors in human breast cancer. [18] Thyroid cancer is the most frequent endocrine neoplasia and
108 accounts for about 2% of cancer-related deaths. Management options for thyroid cancer include total or near
109 total thyroidectomy, radioiodine therapy and pharmacotherapy. These patients may have neuropsychological
110 concerns such as depressive moods or developed cardiovascular problems such as hypertension, electrocardiogram
111 abnormalities, and diastolic dysfunction. In numerous studies, *R. rosea* has demonstrated CNS stimulating,
112 neuro-, cardioprotective and antidepressant effects. Since most of these symptoms are in fact the clinical aspect
113 of hypothyroidism, *Rhodiola rosea* is recognized to aid in patient preparation during the hormone withdrawal
114 period. Oxidative stress increases when thyroid hormones are missing during hypothyroidism. Studies in rats
115 reveal that supplementation with *R. rosea* extract can protect cells from oxidative injuries in dosedependent
116 manner. This finding has also been replicated in human. *Rhodiola rosea* have potentially additional benefits as
117 an adaptogen that tends to be a regulator, having normalizing effects on the organism. Hypothyroidism can be
118 considered as a stressor and then *R. rosea* as an adaptogen that could help the organism's responding. [19]

119 5 c) Alzheimer's Disease

120 Alzheimer's disease (AD) is a progressive brain disorder characterized by the memory and cognitive impairments.
121 Neuropathologically, AD is defined by the accumulation of amyloid plaques and neurofibrillary tangles in certain
122 region of the brain which are important in memory and can cause the loss of synaptic connection between cells.
123 One of the most important parts of unraveling the AD mystery is discovering what causes the disease. It has
124 been suggested that oxidative stress and dysfunction of neurogenesis play important roles in pathogenesis of AD.
125 [20] Beta-amyloid (A β) peptide, the hallmark of Alzheimer disease induces an oxidative damage to neurons and
126 finally causes neurons death. Reduced levels of anti-oxidative activity have been observed in the specific regions
127 of the central nervous system of AD patients. Now researchers are paying great efforts to find potent natural
128 antioxidant with neuroprotective potentials. Salidroside, an active compound occurring naturally in *Rhodiola*
129 *rosea* L. is protective against (A β)induced oxidative stress by the induction of antioxidant enzymes, thioredoxin
130 (Trx), heme oxygenase-1 (HO-1), and peroxiredoxin-1(Prxl); the down regulation of proapoptotic protein Bax
131 and the up regulation of antiapoptotic Bcl-X1. Pathophysiology of neurodegenerative diseases such as AD has
132 shown that A β is associated with ROS generation which leads to mitochondrial dysfunction, lipid peroxidation
133 and apoptosis. Exposure to ROS also inhibits neurogenesis, which is the onset of cognitive impairments and
134 memory deficits. Salidroside could decrease the intracellular ROS level and restore the abnormal mitochondrial
135 membrane potential (MMP). The neuroprotective effect of Salidroside may offer long-term protection in the
136 pathogenesis of AD. [20,21]

137 6 d) Adaptogenic and antifatigue effects

138 Adaptogens are unique group of herbal ingredients which help strengthen the body's response to stress, enhance
139 its ability to cope with anxiety, and fight fatigue. They have the unique ability to adapt their function according
140 to the body's specific needs and do not disturb bodily functions at normal levels. *Rhodiola rosea* is known as
141 a plant's adaptogens because it possesses anti-fatigue and anti-stress activities that can increase mental and
142 physical working performance against a background of fatigue or stress. [22] The phenylpropanoid glycoside
143 called salidroside, flavonoids, Phenolic, polyphenolic, and flavolignans are thought to be the main components
144 of stress-protective and adaptogens of *Rhodiola rosea*. Other constituents isolated from *R. rosea*, including
145 rhodioniside, rhodioloside A-E, rhodiolin, rosin, rosavin, rosarin, rosiridin, rosiridol, rhodalgin, acetylrhodalgin,
146 and lotaustralin, might also be responsible for *R. rosea*'s stimulant or adaptogenic effects. Such compounds
147 can play an active role in increasing energy, stamina, strength and mental capacity required in fight to fight
148 situation to help the body to adapt and resist physical, chemical, and environmental stresses. [22,23] Clinical
149 efficacy of adaptogens in behavioral and mental disorder has been reviewed. It is now accepted that adaptogens
150 have shown anti-fatigue, anti-depressant, anxiolytic, nootropic, and CNS stimulating effects. Adaptogens do
151 not possess any side effects of conventional drugs such as addiction, tolerance and abuse potentials, or impair
152 mental function, neither do they cause psychotic symptoms with long term use. [24] Neuro-degenerative disorders
153 characterized by the progressive loss of structure or function of neurons in the brain region involved in learning
154 and memory. *Rhodiola rosea* as an adaptogen could induce a positive effect in neuro-degenerative disorders
155 due to their inhibitory effects on the formation of p-SAPK (phosphorylated stress-activated protein kinase).
156 Related data may be considered to add further support to the hypothesis that adaptogens have beneficial effect
157 on mental performance and cognitive function. [22] The key point of action of adaptogens on stress appears to
158 be related to the regulation of homeostasis via hypothalamic-pituitary-adrenal axis and regulation of molecular
159 chaperones, stress-activated c-Jun, N-terminal protein kinase, forkhead box O transcription factor DAF-16,
160 cortisol, nitric oxide (NO) and beta-endorphin. [24] The optimal corticosteroid level is required for efficient
161 cognitive function. Significant changes (up or down) in circulating levels of corticosteroids have been accepted as
162 the reason for cognitive impairment. Regulatory effects of *R. rosea* on the basal level of salivary cortisol results

163 in an improvement in cognitive function. [3] Rhodiola rosea combines well with other adaptogens and tonics in
164 appropriate dosages. The herbal drug ADAPT-232 is based on the synergistic effect of the three most efficient
165 adaptogen plants, Rhodiola rosea, Schisandra Chinensis and Eleutherococcus senticosus in a fix combination.
166 Administration of single and repeated doses of ADAPT-232 has been shown to increase physical energy as well as
167 mental performance and cognitive function. [25] ADAPT-232 significantly increases secretion and release of stress
168 hormones, neuropeptide Y (NPY) and Heat Shock Protein 72 (Hsp 72) which increase tolerance and adaptation
169 to stress. These pathways contribute to the anti fatigue effect of ADPAT, increase the attention and improve
170 the cognitive function . [24] Furthermore, a number of studies have investigated the effects of ADAP-232 on
171 pneumonia patients. Clearly, adjuvant therapy on pneumonia patients with ADAPT-232 has a positive effect
172 on the recovery of the patients, by decreasing the duration of the acute phase of the illness, increasing mental
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174 performance of the patients during the rehabilitation period and by improving their quality of life. [25] e)
175 Anti-depressant and general anxiety Depression is a severe despondency and sadness accompanied by a feeling of
176 desperation and inadequacy. The mechanism of depression is complex. The therapeutic effects of anti-depressants
177 such as Tricyclic antidepressants (TCAs), Monoamine oxidase inhibitors (MAOLs) and Selective serotonin
178 reuptake inhibitors (SSRIs) come with a number of side effects like psychomotor impairment and dependence
179 liability. [26] The use of Alternative Medicine especially natural products for the treatment of mental disorders
180 have been increased in the U.S and worldwide. The most common reason for people to use complementary
181 therapies is that they want to avoid the common side-effects of prescription antidepressant drugs. A few natural
182 psychotropics have been more extensively examined in well-designed, placebo-controlled, double-blind studies.
183 Rhodiola rosea is one of these second-tier natural products for mood disorders. [27] The standardized extract SHR-
184 5 (3%rosavin and 0.8% salidroside) from R. rosea have a significant antidepressant activity in mild to moderate
185 depression. The symptoms evaluated were emotional instability, decreased motivation, cognitive complains and
186 susceptibility to stress. [28] Significant improvement in the overall symptom of depression and mood deficiencies
187 was observed in a 6-week monitoring study in Sweden, which R. rosea was given daily with a dosage of two
188 tablets a day, each containing 170mg of the extract. [28] The role of serotonin, a monoamine neurotransmitter,
189 is usually known and associated with depression, however, serotonin also has some cognitive functions, including
190 the enhancement of memory and learning. Regulation of serotonin at synapses is a major mechanism of action
191 possibly contributing to pharmacological antidepressants. Central and peripheral serotonin levels decreases in
192 patients with depression. Monoamine oxidase type A has an important role in degradation of biogenic amines such
193 as epinephrine, norepinephrine, and serotonin. Monoamine oxidase inhibitors (MAOIs) prevent the breakdown of
194 monoamine neurotransmitters including serotonin and therefore increases the concentrations of neurotransmitter
195 in the brain. MAOIs therapy with synthetics drugs are known to interact negatively with other medications
196 and even with food. MAOIs can cause death if they are taken in overdose extent. There is evidence that R.
197 rosea acts as monoamine oxidase inhibitors and influences the level and activity of biogenic monoamines such
198 as serotonin, norepinephrine, and dopamine in the nerve terminal. Rhodiola rosea inhibits the activity of the
199 enzymes responsible for monoamine degradation (monoamine oxidase and catechol-0 methyl transferase). [4,3]
200 General anxiety disorder (GAD) is a common disorder that involves chronic worrying, nervousness and tension.
201 There are different types of medication for GAD, including antidepressants, Benzodiazepines, and serotonin
202 reuptake inhibitors. Patients who do respond to conventional treatment often experience adverse side effects that
203 may interfere with their consistency. Rhodiola rosea is safe and tolerable alternative medicine. Administration
204 of R. rosea in dosages of 2-3 capsules each containing 100-170 milligrams daily approximates to the perfect dose
205 to gain beneficial effects. [29]

206 7 f) Anti-inflammatory and neuroprotective effect

207 In general, inflammation is a localized reaction of the body tissues to infections, irritation, injuries, or disorders
208 of the immune system which produce redness, warmth, swelling, and pain. As we age, the level of inflammatory
209 immune cytokines increases and we get vulnerable to a number of inflammation-linked diseases, such as cancer,
210 arthritis, muscle weakness, fatigue, sleep disorder, Alzheimer's and Parkinson's disease. An enormous amount of
211 research has demonstrated the link between chronic low-level brain inflammation and elevated brain glutamate
212 levels, which are a neurotransmitter normally involved in learning and memory. In some cases, glutamate can be
213 an excitotoxin that is involved in nerve-cell death in various neurodegenerative disorders including Alzheimer's
214 and Lou Gehrig's disease. Glutamate not only influence amyloid ? production (the cause of Alzheimer's disease),
215 but also amyloid ? can change the levels of glutamate in the brain which increase the vulnerability of cortical
216 neurons to glutamate cytotoxicity. It has been shown in several studies that R. rosea could improve inflammation
217 and neurotoxicity in cortical neuronal cells. Rhodiola rosea modulates the neuronal over action and endogenous
218 anti-inflammatory. [29-30] Microglia, a type of glial cell, acts as the first and main form of active immune defense in
219 the central nervous system (CNS), and thus plays a key role in the inflammatory reaction. Inflammatory process,
220 in the central nervous system leads to neuronal cell death, and inflammatory response is mediated by the activated
221 microglia, which remove the damaged cell by phagocytosis. The chronic activation of microglia may in turn cause
222 neuronal damage through the secretion of cytotoxic molecules such as proinflammatory cytokines (interleukin-
223 1 β (IL-1), IL-6 and TNF- α), proteases, and reactive oxygen species (ROS), and nitric oxide (NO). Therefore,
224 suppression of microglia-mediated inflammation can appear to be the most promising option in neurodegenerative

225 disease therapy. Since overproduction of NO plays an important role in neuroinflammatory disease, the effect
226 of the *R. rosea* on nitric oxide production was investigated in lipopolysaccharide (LPS)-induced microglia cells.
227 *Rhodiola rosea* has shown to strongly inhibit NO production and the expression of Inducible nitric oxide synthase
228 (iNOS), the key enzyme for NO in LPS-stimulated microglia cells. [30] g) Antiviral activity

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230 The influenza is an acute infectious disease caused by an RNA virus of the family orthomyxovirus. Influenza virus
231 infects the epithelial cells of respiratory tract that causes acute pulmonary diseases. Influenza outbreak usually
232 occurs in winter, killing numerous people in pandemic years. The epidemic outbreaks of influenza are associated
233 with influenza virus type A and B. Type C virus is associated with minor symptoms. Two neuraminidase
234 inhibitors have been approved by FDA (zanamivir and oseltamivir) to treat influenza virus infection. Both of
235 these inhibitors are active against influenza virus A and B, however, they have several toxic effects in the digestive
236 and autonomic nervous system. The flavonols Kaempferol, Herbacetin, Rhodiolinin, Rhodionon and Rhodiosin
237 were isolated from *Rhodiola rosea*. The compounds showed neuraminidase inhibitory and anti-influenza virus
238 activities. The in vitro anti-influenza virus activities of flavonoids were evaluated using two influenza viral strains,
239 H1N1 and H9N2, testing their ability to reduce virus-induced cytopathic effect (CPE) in MDCK, Madin-Darby
240 Canine Kidney Cells (virus tissue culture). Anti-influenza activity depends on the position and the number
241 of hydroxyl groups on the flavonoids backbone. Kaempferol showed the highest activity against two influenza
242 viruses, H1N1 and H9N2 with the half maximal effective concentration (EC₅₀) values of 30.2 and 18.5 μM. [31]
243 Coxsackievirus B3 (CVB3) is important human pathogen that belongs to picornavirus family. CVB3 is the most
244 common cause of viral myocarditis, a serious disease that can further lead to dilated cardiomyopathy and cardiac
245 failure and also often induce pancreatitis and aseptic meningitis. Although a few vaccines have been reported
246 to be effective in a murine CVB3-induced myocarditis model, there are no effective therapeutic agents against
247 CVB3 for the clinic up to now. Slidroside (p-hydroxyphenethyl-β-D-glucoside) which is extracted from *R. rosea*
248 demonstrated antiviral activity while not affecting the normal physiological function of the host cells. Salidroside
249 exhibited obvious antiviral activity in vitro and protected myocardial cells against CVB3 infection. The antiviral
250 activities of salidroside against CVB3 may be related to modulating serum superoxide dismutase (SOD), serum
251 nitric oxide (NO), serum catalase (CAT), and serum Malondialdehyde (MDA) activities to protect heart muscle
252 against the harmful effect of free radicals. Also salidroside has the ability to increase the hemoglobin capacity to
253 carry oxygen, which provides protection for the myocardial cells from hypoxemia. Since salidroside also has shown
254 antiviral activities against CVB3 in vitro, the findings have significant implications for a potential therapeutic
255 agent for treatment of viral myocarditis and influenza virus infections which is worthy of further future researches.
256 [32] h) Antidiabetic

257 The anti-diabetic effects of dietary administration of *Rhodiola*-water extract on streptozotocin (STZ)-induce
258 diabetes rat model were investigated. STZ is a toxin with the ability to damage pancreatic beta cells, resulting
259 in hypoinsulinemia and hyperglycemia. The study used STZ mice as a model because it is considered an
260 appropriate model to assess mechanisms of diabetes and evaluate potential therapies. Three days administration
261 of *Rhodiola*-water extract in STZ-diabetic rats resulted in an increase of glucose transporter subtype 4 (GLUT
262 4) in skeletal muscle and a reduction of phosphoenolpyruvate carboxykinase in liver. It has been reported that
263 *Rhodiola*-water extract have a long-term blood glucose level control effect and improves hyperglycemia by an
264 increase of beta-endorphin secretion from adrenal gland to activate opioid μ-receptors to achieve the higher of
265 GLUT 4 gene expression in STZ rats model. [33] Evidence in both experimental and clinical studies shows
266 that increased oxidative stress is the common pathogenic factor causing diabetic mellitus and its complication.
267 Diabetes is a chronic metabolic disorder characterized by hyperglycemia and the inability of tissues to utilize
268 glucose. Hyperglycemia and fluctuation in blood glucose generate oxidative stress through overproduction of
269 reactive oxygen species. Dietary *R. rosea* supplementation results in a significant reduction on blood glucose and
270 lipid peroxide, increased levels of glutathione, glutathione peroxide, catalase, and superoxide dismutase (SOD)
271 in the liver. *Rhodiola rosea* extracts may be effective for correcting hyperglycemia and preventing diabetic
272 complications. [34] Managing diabetes without any side effect is still a challenge. Therefore, it is worth more
273 investigation in the antidiabetic activity of natural products such as *R. rosea* on humans in the future.

274 9 i) Lifespan increasing effects

275 Recent studies on *Drosophila melanogaster* and *Caenorhabditis elegans* have shown that bioactive components of
276 *R. rosea*, particularly salidroside and/or rosavins, may have an effect on lifespan and improve health spans. The
277 plant adaptogens can induce their effects by different routes. Adaptogens can extend the lifespan by increasing an
278 organism's resistance against the damaging effects of different stress conditions. The plants adaptogens such as *R.*
279 *rosea* interfere with the localization of DAF-16, a forkhead/winged-helix transcription factor. The *Caenorhabditis*
280 *elegans* DAF-16 transcription factor is Volume XV Issue III Version I critical for diverse biological processes
281 specifically longevity and stress resistance. *Rhodiola rosea* induce translocation of the DNF-16 transcription
282 factor from the cytoplasm into the nucleus. DAF-16 in the nucleus reprograms the transcriptional activities
283 favoring the transcription of a large number of genes involved in stress resistance and longevity. [35] Moreover
284 dietary conditions are another hypothesis for anti aging effect of *Rhodiola rosea*. The effect of *R. rosea* supplement

11 L) EFFECT ON PARKINSON'S DISEASE

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

297 10 j) Cardioprotective effects

298 Hyperhomocysteinemia (high homocysteine level in the blood) is a major risk factor of cardiovascular disease.
299 An abnormal accumulation of homocysteine, an amino acid that is produced by human body due to consuming
300 meat, is related to various cardiovascular diseases such as coronary heart disease, stroke and peripheral vascular
301 disease (fatty deposits in peripheral arteries). Homocysteine exert its adverse effect on endothelial function by
302 increasing superoxide production and decreasing the activity of nitric oxide synthase. Homocysteine could be
303 a starting point for the development of atherosclerosis by disturbing vascular permeability, damaging the inner
304 lining of the arteries and promoting blood clots. Slidroside extracted from *Rhodiola* protect rats aortas against
305 homocysteineinduce impairment of endothelium by inhibiting NOX2dependent ROS overproduction. These
306 results suggest that salidroside significantly inhibit ROS overproduction associated with vascular dysfunction, a
307 common pathological process in hypertension and diabetes. [11] k) Effect on Binge eating and Anorexia Binge
308 eating (BE) and Anorexia Nervosa are official eating disorders. Binge eating appears to be characterized by
309 extreme overeating without subsequent purging episodes, usually secretive, and filled with shame. [37] Topiramate
310 or sibutramine are medications that have been suggested to reduce BE. However, their uses are associated with
311 a variety of adverse side effects which causes serious problems, such as cardiovascular disorder and stroke. As
312 a result they have been withdrawn from the market in many European countries. Since stress is a key factor
313 in BE, a reduction of stress response might show an effective mechanism for the treatment of BE. Therefore,
314 due to its anti-stress properties, the effect of Slidroside, an active principle of the dry extract of *R. rosea*, was
315 evaluated for treatment of BE. Studies have shown that Salidroside abolishes BE by suppressing the activation
316 of hypothalamic-pituitary-adrenal (HPA) axis, leading to a reduction of serum corticosterone flowing chronic
317 treatment. [1] Furthermore, new ev iden ce s h ows t h at *R. rosea* may cancel out the anorexia (out of control
318 dieting), another troubling manifestation of stress.

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

327 11 l) Effect on Parkinson's Disease

328 Parkinson's disease (PD) is a chronic and progressive disorder of the nervous system that affects movements
329 of the body and the symptoms continue and worsen over the time. Parkinson's primarily affects neurons in
330 the area of the brain called substantia nigra. Cells within the substantia produce and release dopamine, a
331 neurotransmitter that controls the movement and balance. In patients suffering from Parkinson's, the amount of
332 dopamine produced in the brain decreases. The shaking or tremor may begin to interfere with the daily activities
333 of the PD patients. As these symptoms become more pronounced, patients may have difficulty walking, talking
334 or performing other simple tasks. Although there is no cure, there are treatment options such as medication and
335 surgery to control the symptoms. [39] The new plant preparation Phytomix- Animal experiments demonstrated
336 that PM-40 had a low toxicity. The neuroprotective plant adaptogen can be used in complex therapy for the
337 Parkinson's disease for improving its efficacy. Oral administration of 10% solution of Phytomix-40 to mice
338 with MPTP-induced Parkinson's syndrome reduces the severity of rigidity and increase motor activity. The
339 preparation normalized immunobiological parameters in PD patients and relieved the clinical symptom of the
340 disease. The mechanism of action of PM-40 contributes to the recovery of the dopamine synthesis by healing
341 of damaged neurons. PM-40 can be used with the combination of other standard antiparkinsonian drugs in
342 order to improve their clinical effects and minimize side effects of Parkinson's medication. [39] m) Overview of
343 toxicological and safety data Through the doses administered in clinical trials, there is no report of serious side
344 effects that could be attributed to the extract of *Rhodiola rosea*. The normal usage of *R. rosea* is safe, however,

345 it is important to consider that *R. rosea*, a strong adaptogenic and tonic herb, might have an addictive effect
346 with other substances exhibiting stimulant properties (such as caffeine). [40] Continuous daily use of *R. rosea* for
347 days and months is followed by an interval with no supplementation (three weeks "on" and one week "off"). This
348 clinical recommendation helps avoid possible side effects at higher dosages such as insomnia, irritability, dizziness,
349 dry mouth, and allergy (unspecified). [29] The most commonly used standardized extract has a minimum of 3%
350 rosavin and 1% salidroside. The typical daily dose for chronic administration extracts range from 100-170 mg per
351 day when standardized for 2.6% rosavin. Evidence on the safety and appropriateness of *R. rosea* supplementation
352 during pregnancy and lactation has not been established. [14] IV.

353 12 Conclusions

354 *Rhodiola rosea*, which is also known as the golden root, is one of the most studied *Rhodiola* species. As an
355 adaptogen, many health benefits are related to *Rhodiola* drug extracts due to their balancing and regulatory
356 effects. Significant antioxidant activities have been documented for various *Rhodiola* species extracts. In Russian
357 and Chinese folk medicine, the plant is used for stimulating the nervous system and decreasing mental and physical
358 fatigue. It has been shown in pharmacological investigations that, *R. rosea* possess antioxidant, antiaging, anti-
359 cancer and anti-cardiovascular disease properties. As a dietary supplement, numerous preparations of extracts are
360 used worldwide including teas, homeopathic preparations and tinctures as well as standardized extract. *Rhodiola*
361 *rosea* has enormous traditional and pharmacological use in supporting mood and cognitive function.

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

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Figure 1:

367 1

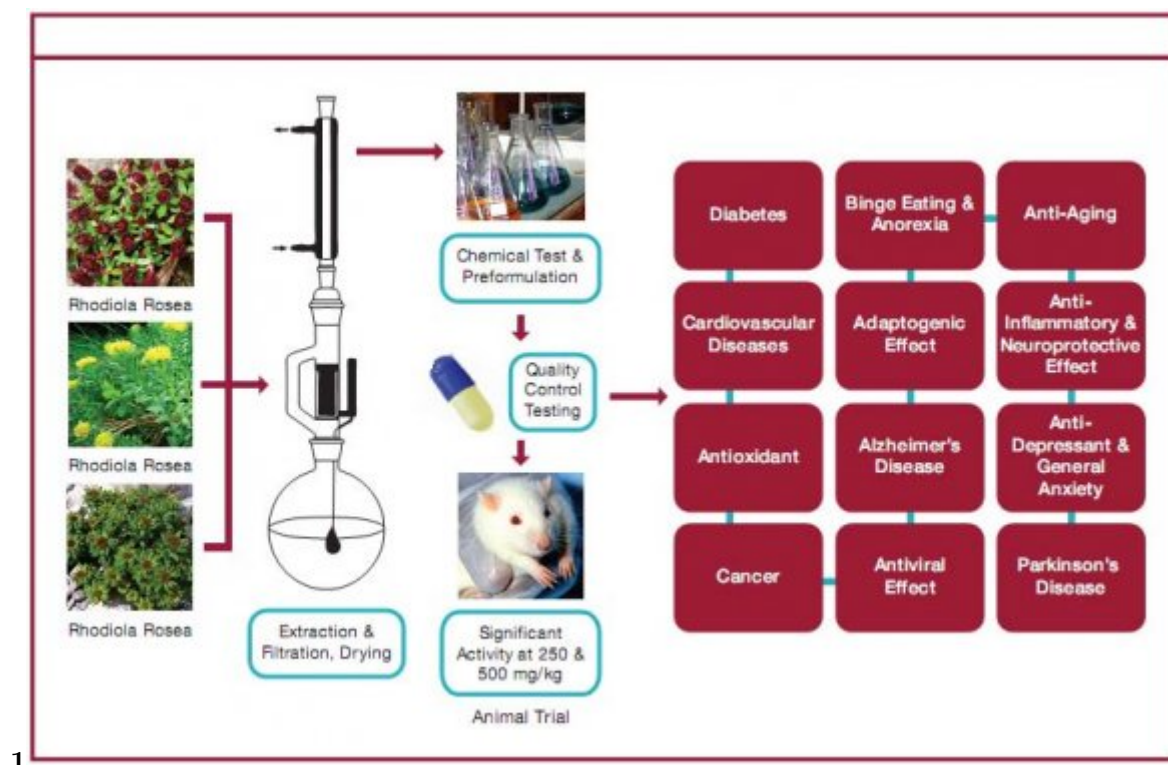


Figure 2: Figure 1

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
<i>Trans</i> -pinocarveol	16.1
Myrtenol	36.9
Geraniol	12.7
Myrtanol	1.0
Perilla alcohol	1.7
Dihydrocumin alcohol	2.1
Cumin alcohol	12.1

Figure 3:

Figure 4:

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