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Rhodiola rosea L. as a putative botanical antidepressant

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ABSTRACT

Background: Rhodiola rosea (*R. rosea*) is a botanical adaptogen with putative anti-stress and antidepressant properties. Evidence-based data supporting the effectiveness of *R. rosea* for depression in adults is limited, and therefore a comprehensive review of available animal and human studies suggesting a putative antidepressant action is warranted.
Purpose: A review of the literature was undertaken to ascertain studies of possible antidepressant mechanisms of action and studies of the safety and effectiveness of *R. rosea* extracts in animals and adult humans.
Methods: A search of MEDLINE and the Russian state library database was conducted (up to October 2015) on *R. rosea*.
Results: *Mechanism of action: R. rosea* extracts and its purified constituent, salidroside, has been shown to produce a variety of mediator interactions with several molecular networks of neuroendocrine-immune and neurotransmitter receptor systems likely to be involved in the pathophysiology of depression. A wide variety of preclinical in vivo and *ex vivo* studies with laboratory animals suggests the presence of several biochemical and pharmacological antidepressant-like actions.
Effectiveness: Clinical assessment of *R. rosea* L. rhizome extracts in humans with various depressive syndromes is based upon results from two randomized, double-blind, placebo-controlled trials of 146 subjects with major depressive disorder and seven open-label studies totaling 714 individuals with stress-induced mild depression (diagnosed as asthenic syndrome or psychoneurosis). Overall, results of these studies suggests a possible antidepressant action for *R. rosea* extract in adult humans.
Safety: In contrast to most conventional antidepressants, *R. rosea* extract appears to be well-tolerated in short-term studies with a favorable safety profile.
Conclusions: *R. rosea* demonstrates multi-target effects on various levels of the regulation of cell response to stress, affecting various components of the neuroendocrine, neurotransmitter receptor and molecular networks associated with possible beneficial effects on mood.

1. Introduction

1.1. Use of herbal medicines

Over the last 3 decades, the use of herbal remedies has become widespread. The World Health Organization has estimated that at least 4 billion people, or 80% of the world's population, uses complementary and alternative medicines (CAMs) for some aspect of their health care needs. Between 1990 and 1997, CAM use in the U.S. increased almost 5-fold (Eisenberg et al. 1998), and by 1997 about 33% of Americans used herbal remedies. Over the last decade, many CAM therapies have become mainstream in the US, and it is anticipated that CAM use will continue to increase with growing consumer acceptance. The widespread use of botanical preparations reflects many factors including a rise in the

Abbreviations: 5-HTP, 5-hydroxytryptophan; BDA, Beck Depression Inventory; CAM, complementary and alternative medicines; CGI/C, Clinical Global Impression – Change over time; CGI/S, Clinical Global Impression – Severity; CNS, central nervous system; CRA, corticotropin-releasing hormone; DSM-IV, Diagnostic and Statistical Manual, Fourth Edition; GABA, gamma amino butyric acid; GAD, generalized anxiety disorder; GPCR, G-protein coupled receptor; HPA, hypothalamus – pituitary – adrenals axis; HRSA, Hamilton Anxiety Rating Scale; HRSD, Depression Rating Scale; JNK, stress activated phosphorylated c-Jun N-terminal kinases; MAO-A, monoamine oxidase A; NA, nor-adrenalin; NO, nitric oxide; NPY, neuropeptide Y; PK, protein kinase.

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prevalence of chronic diseases, an increase in public access to healthcare information, a reduction in tolerance of medical paternalism, and an increased sense of consumer entitlement to a higher quality of life. These social factors are complemented by an escalating cost of conventional medication which is often seen as more toxic than CAM therapy (Jonas 1998). Because herbal remedies do not undergo the exhaustive testing and regulatory procedures of the U.S. Food and Drug Administration (FDA) applied to conventional drugs, CAM therapies represent a unique marketing opportunity for new and established drug companies. As a result there is an increasing need for scientific research and reliable information on the use of botanical products (Blumenthal 1998). There is also a need for careful evaluation of selected botanical therapies for specific medical conditions in order to *"separate the pearls from the mud"* (Jonas 1998). However, in the U.S. there is currently no formal mechanism for establishing the safety and efficacy of CAM products by the FDA. This deficiency was noted in a report to the U.S. Congress entitled *The White House Commission on Complementary and Alternative Medicine Policy* (http://www.whccamp.hhs.gov/fr1.html; http://www.whccamp.hhs.gov) which concluded that CAM and conventional drugs should be held to the same rigorous standards of good science. This conclusion was echoed in a *New England Journal of Medicine* editorial which stated that *"there cannot be two kinds of medicine – conventional and alternative. There is only medicine that has been adequately tested and medicine that has not, medicine that works and medicine that may or may not work."* (Angell and Kassirer 1998)

1.2. Epidemiology and treatment of depression

Depression is one of the most common and debilitating psychiatric conditions with a lifetime prevalence rate of about 16.2% (Murray and Lopez 1997). Epidemiological studies have shown an increased frequency of affective illness with increasing age. In particular, older women have been noted to have an increased risk of depression that is almost twice that of men; attributed to perturbations in sex steroids occurring during the peri- and postmenopausal periods (Anthony and Aboraya 1992; Kessler et al. 1993). Although hormonal factors have been hypothesized to underlie gender differences in vulnerability to mood disorders, evidence for this assertion is lacking (Richardson and Robinson 2000). Other, more compelling factors linked with depression appear to be disproportionately represented in women. For example, disparities in ethnic, cultural, economic, psychosocial, environmental and age longevity differences from men may be more likely to place women at a greater risk for developing depression (Belle and Doucet 2003; Hammen 2003).

Depression is also associated with a high risk of suicide and medical co-morbidity, and nearly 70% of patients with depression have incomplete response after 8 weeks of conventional antidepressant therapy and more than 30% fail to respond at all (Rush et al. 2004, 2006). At least 75% of depressed patients who recover during initial antidepressant therapy will have a relapse or recurrence within 2 years, and 33% will have an episode lasting longer than 2 years (Keller 2001). Although antidepressants (like serotonin reuptake inhibitors) are now standard therapy for depression, many individuals go un-diagnosed and untreated for years. Moreover, of those who do receive antidepressant therapy, many receive inadequate therapy (Rush et al. 2004, 2006). However, despite their widespread use, these agents have substantial limitations. For example, there is limited clinical data showing that these agents provide consistent benefit (versus placebo) in patients with more mild forms of depression (Elkin et al. 1995; Fournier et al. 2010). Most randomized clinical trials of antidepressant efficacy routinely exclude patients with mild illness because of the expectation that conventional antidepressants will not provide an advantage versus placebo. Moreover, treatment-emergent adverse events with conventional antidepressants are more likely to occur in less severely ill patients (Mao et al. 2015), and often result in treatment noncompliance and treatment discontinuation (Hollon et al. 2002). In addition, conventional antidepressants may suppress, rather than eliminate, depressive symptoms in many patients (Hollon and Shelton 2001), and there is little evidence to suggest that symptom suppression reduces overall risk of depressive relapse (Frank et al. 1990). Although conventional antidepressants may be slightly more effective than psychotherapy (DeRubeis et al. 2005), these agents are also associated with substantial adverse events such as weight gain, insomnia, drowsiness, hypertension, reduced libido, suicidal ideation, and withdrawal (Amsterdam et al. 1997; Michelson et al. 1999, 2000; Zajecka et al. 1999).

Finally, conventional antidepressant therapy can constitute a financial burden, with the result that many individuals decline therapy and go un-treated. In addition, individuals may decline antidepressant therapy due to insufficient health insurance, cultural or religious beliefs, or personal reasons related to stigma of mental illness. As a result, many individuals will seek CAM remedies for their depressive symptoms. Thus, it is not surprising that depressive symptoms are among the most common reasons for consumers choosing CAM therapy (Barnes et al. 2004). The identification of safe and effective CAM therapies for depression is, therefore, of public health relevance in reducing the illness-related burden of depression (Fang and Schinke 2007; Givens et al. 2007a, 2007b).

1.3. Overview of CAM treatment of depression

– Data from a national survey from 1990 to 1997 found that CAM use for depression symptoms rose from 20.2% to 40.9% (Eisenberg 1998), while a subsequent survey of individuals with mental disorders confirmed these findings (Unitzer et al. 2000; Druss and Rosenheck 2000). Kessler et al. (2001a) noted that psychiatric symptoms like depression, anxiety, fatigue, and insomnia are among the most frequent reasons for CAM use. Moreover, many individuals taking conventional antidepressants will augment these with CAM agents or switch to CAM therapy due to antidepressant-induced side effects, inadequate response, cost, or a desire to exert personal control over their treatment (Brown and Gerbarg 2001; Wu et al. 2007; Stratton and McGivern-Snofsky 2008).

In a follow up survey (Tindle et al. 2005), herbal remedy use for depression rose from 12.1% to 18.6%. In a separate survey more than 2000 U.S. adults, 53.6% of respondents endorsing depressive symptoms reported using CAM therapy in the preceding year, with herbal remedies near the top of the list (Kessler et al. 2001b). A recent literature survey of CAM treatment studies of late-life mood and anxiety disorders for the period 1966–2006, identified 885 studies of which only 33 met minimal inclusion criteria of ≥ 30 subjects treated for ≥ 2 weeks. Overall, 67% of the studies were positive, with positive studies generally having a lower Scientific Quality of Investigation score for methodology (versus negative studies) (Meeks et al. 2007).

Although evidence-based data to support the efficacy of many herbal remedies for depression is limited, several recent reviews are of relevance. The most frequently studied remedies were St. John's Wort (*Hypericum perforatum*), s-adenosylmethionine, tryptophan (TRP), 5-hydroxytryptophan (5-HTP), and omega-3 fatty acids. Other CAM remedies with less evidence of antidepressant activity include folic acid, *lavendula augustifolia, ginko biloba*, chamomile, and *crocus sativus*.

1.4. Rhodiola rosea – *an overview*

1.4.1. General

There are several comprehensive monographs describing the cultivation, photochemistry, and pharmacology of *R.rosea* (Saratikov 1973; Kelly 2001; Brown et al. 2002; Saratikov and Krasnov 2004; Panossian and Wikman 2005; Panossian et al. 2010; Cuerrier and Ampong-Nyarko 2014).

Briefly, *R. rosea*, also known as roseroot or golden root, belongs to the family *Crassulaceae* (Panossian et al. 2010). It has a long history as a medicinal plant in Iceland, Norway, Sweden, France, Greece, and Russia. Traditional folk medicine used *R. rosea* to increase endurance and work performance, longevity, tolerance to high altitude sickness, and to treat fatigue, weakness, impotence, and other nervous system disorders. In Siberia, a bouquet of golden root is still given to couples on their wedding to enhance fertility. In Asia, *R. rosea* tea is used to treat and prevent flu-like infection during the winter. Mongolian doctors prescribe it for cancer and tuberculosis. For centuries, the location of golden root and the process of *R. rosea* extraction were guarded secrets. Siberians secretly transported the herb down ancient trails to the Caucasus where it was traded for Georgian wine, garlic, and honey. In 1961, GV Krylov, a Russian botanist and taxonomist, led an expedition to the cedar taiga in the Altai mountains of Siberia where he located and identified golden root as *R. rosea*. These extracts were found to contain compounds, termed 'adaptogens', that protected animals and humans from mental and physical stress, toxins, and infections. The quest for CAMs to enhance physical and mental endurance led to the discovery of phenylpropanoids, which were specific to *R. rosea*. In Sweden, *R. rosea* was classified as an adaptogenic remedy in 1985 (Sandberg and Bohlin 1993). The Swedish Pharmaceutical *Lakemedelsboken* 1997/98 described *R. rosea* as a plant with a 'stimulant' action in the group of registered herbal medicines (Sandberg 1998). In Denmark, *R. rosea* was registered as a medical product in the category of botanical drugs (Sandberg 1998). Botanicals are widely used in Scandinavia to increase mental capacity during stress, as a psychostimulant, and as a general adaptogen (Sandberg 1998). *R. rosea* has also been used to enhance emotional tone and affect.

At least 140 compounds have been identified in *R. rosea* rhizomes extract that may have medicinal properties (Panossian et al. 2010; Saratikov and Krasnov 2004). Among 86 nonpolar monoterpene hydrocarbons, monoterpene and aliphatic alcohols, geraniol (a rose-like odor substance) was the most abundant volatile constituent of *R. rosea* (Rohloff 2002). Its oxygenated glucoside rosiridin (Kurkin and Zapesochnaya 1986) has been shown to be a potent inhibitor of monoamine oxidase A and B in vitro (van Diermen et al. 2009), suggesting a possible mechanism for *R. rosea's* putative antidepressant, anxiolytic and activating properties in animals and humans. In addition, more than 50 polar compounds (including monoterpenes, cyanogenic glycosides, phenylpropanoids, flavonoids, flavolignans and other gallic acid derivatives) may also contribute to its CNS actions (Kurkin, and Zapesochnaya 1986; Saratikov and Krasnov 2004; Panossian et al. 2010).

1.4.2. Effects on CNS

The direct stimulation of noradrenalin, dopamine, serotonin and cholinergic receptors in selected brain regions may produce the complex psychotropic, stimulant, and adaptogen actions of *R. rosea's* (Saratikov et al. 1978; Lazarova et al. 1986; Petkov et al. 1986). For example, small doses of *R. rosea* extract, or of its active constituent rodosin, were found to increase spontaneous bio-electrical activity of the brain possibly via effects on the reticular formation in the brainstem (Saratikov et al. 1965, 1978; Marina 1968; Marina and Alekseeva 1968; Saratikov 1973; Kurkin and Zapesochnaya 1986),while medium doses of *R. rosea* enhanced conditioned avoidance behavior in rats and facilitated learning based upon positive reinforcement (Saratikov et al. 1965, 1973). Furthermore, a single dose of *R. rosea* extract improved learning and retention in rats subjected to the maze negative (punitive) reinforcement test after 24 h and after 10 days post *R. rosea* administration (Lazarova et al. 1986; Petkow et al. 1986). A recent electroencephalographic study of rat frontal cortex, hippocampus, striatum and reticular formation in animals given *R. rosea* showed a frequency pattern comparable to that of methylphenidate and the antidepressant paroxetine within 35 min of administration (Dimpfel 2013).

2. Methods

We used STN-easy service, which is based on all comprehensive databases, including BIOSIS, CAplus, TOXCENTER, EMBASE, NAPRALET, PubMed, etc. https://stneasy.fiz-karlsruhe.de/html/english/login1.html?service=STN

We used also, original publications from Russian State Library in Moscow.

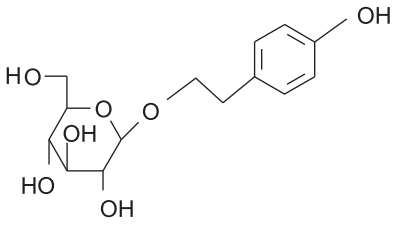
Additionally, we used the library of the Swedish Herbal Institute, which maintains a complete collection of full text Russian articles and their English versions on this topic collected since 1943.

3. *R. rosea* for the treatment of depression

3.1. Evidence based on studies in animals

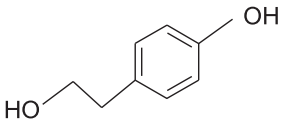
Wikman and Panossian (2002) initially showed that various extracts of *R. rosea* root and rhizome exhibited antidepressant-like activity in mice exposed to the Porsolt behavioral despair forced swimming test. Using this paradigm, *R. rosea* extract activity was comparable with that of imipramine and amitriptyline, and superior to that of *Hipericum perforatum* L extract. Perfumi and Mattioli (2007) demonstrated significant, albeit not dose-dependent, induction of antidepressant-like effects of a single oral dose of *R. rosea* extract 10, 15 mg/kg and 20 mg/kg in mice. Subsequently, Mattioli et al. (2009) found that repeated administration of *R. rosea* extract for 3 weeks reversed stress-induced elevations in sucrose intake, stress related behaviors, weight gain and dysregulated estrous cycles in female rats following 6 weeks of chronic mild stress. These effects were comparable to those of the antidepressant fluoxetine; although neither *R. rosea* nor fluoxetine influence the behavioral and physiological parameters in non-stressed animals (Mattioli et al. 2009).

Antidepressant like activity of *R. rosea* extract ($ED_{50} = 7.0$ mg/kg), or *R. rosea* extract combined with piperine and various purified constituents (e.g., rhodioloside, rosavin, rosin, rosarin, tyrosol, cinnamic alcohol, cinnamaldehyde and cinnamic acid) was compared with – imipramine and *Hypericum perforatum* extract in rats exposed to the Porsolt behavioral despair test (Panossian et al., 2008a, 2008b; Kurkin et al. 2006). At 20 mg/kg, *R. rosea* extract exhibited a greater antidepressant-like effect than either imipramine 30 mg/kg or *H. perforatum* 20 mg/kg. Rhodioloside (salidroside), and tyrosol (Fig. 1) were the active constituents of the *R. rosea* extract; whereas rosavin, rosarin, rosin, cinnamic alcohol, cinnamaldehyde, cinnamic acid were inactive. A fixed combination of rhodioloside, rosavin, rosarin and rosin was more active than any of the individual components alone, suggesting a synergistic activity (Panossian et al., 2008b). Although rosiridine has been found to be an active inhibitor of MAO-A enzyme in a MAO-A bioassay of mitochondrial membrane fractions of insect cells containing human recombinant MAO-A and MAO-B (van Diermen et al. 2009), its concentration is so minute in *R. rosea* extract to preclude MAO inhibition as the cause of antidepressant-like activity (van Diermen et al. 2009).



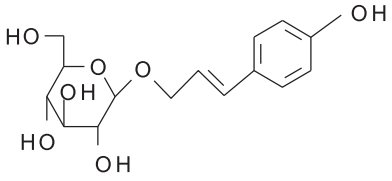
Salidroside

Chemical name: 2-(4-Hydroxyphenyl) ethyl-β-D-glucopyranoside
Synonym: Rhodioloside



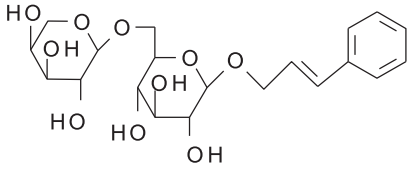
Tyrosol

Chemical name: 4-(2-Hydroxyethyl)phenol
Synonyms: p-Hydroxyphenethyl alcohol
2-(4-Hydroxyphenyl)ethanol
4-Hydroxyphenylethanol



Triandrin

Chemical name: (2R,3S,4S,5R,6R)-2-(hydroxymethyl)-6-[Є-3-(4 hydroxyphenyl) prop-2-enoxy]oxane-3,4,5-triol



Rosavin

Chemical name: 3-[6-O-(α-Labinopyranosyl)-β-D-glucopyranosyl]-oxy-1-phenylpropene
Synonym: Cinnamyl-O-[α-L-arabinopyranosyl- (1->6)- β-D-glucopyranoside]

Fig. 1. Chemical structures and names of active compounds Rhodiola rosea.

Antidepressant-like effects of salidroside were also found in the olfactory bulbectomized rat model of depression. Chronic treatment for 2 weeks with salidroside significantly reduced TNF-α and IL-1β levels and increased glucocorticoid receptor and brain-derived neurotrophic factor (BDNF) expression in the hippocampus, as well as reducing the production of hypothalamic corticotropin-releasing hormone (CRH) and serum corticosterone (Yang et al. 2014).

R. rosea extract 1500 mg/kg also appeared to enhance serotonin levels and promote proliferation and differentiation of neural stem cells in the hippocampus of the stress-induced rat model of depression – a process thought to play a possible role in repairing injured hippocampal neurons (Qin et al. 2008; Chen et al. 2009). These findings are supported by other studies in rats (e.g., Mannucci et al. 2012). Similarly, oral administration of *R. rosea* extract 0.1 mL produced a significant increase in rat brainstem concentrations of noradrenalin, dopamine and serotonin (versus that of control rats). In addition, the concentrations of noradrenalin and dopamine decreased, and the concentration of serotonin increased, in the cerebral cortex (versus control rats). In contrast, while hypothalamic concentrations of noradrenalin and dopamine increased 3-fold, serotonin significantly decreased compared to control rats (Stancheva and Mosharrof 1987). *R. rosea* extract also enhanced the effects of neurotransmitters in the brain via increasing the permeability of the blood brain barrier to precursors of dopamine and serotonin (Stancheva and Mosharrof 1987).

Panossian et al. (2007) examined mediators of stress response (i.e., protein kinase (PK), phosphorylated kinase (JNK), nitric oxide (NO), cortisol, testosterone, prostaglandin E_2, leukotrene, and thromboxane) before and after 7 days of rhodioloside (salidroside), extracts of *E. senticosus, S. chinensis, R. rosea, Bryonia alba, P. ginseng*, or placebo in laboratory rabbits exposed to 2 h of immobilization stress. JNK, NO, and cortisol increased by 200–300% (versus baseline) in the placebo group; while, NO and cortisol concentrations were unchanged. Rhodioloside and extracts of *S. chinensis* and *R. rosea* produced the greatest inhibition of stress-induced JNK (Panossian et al. 2007).

3.2. Active principles and possible mechanisms of action in depression

While most conventional antidepressant drugs for depression modulate brain monoamine and indolamine activity (Nutt 2008) recent data suggest that the antidepressant effect of *R. rosea* may be associated with key mediators of stress response, regulation of homeostasis of HPA axis activity (Fig. 2), modulation of G-protein coupled receptor (GPCR) signaling pathways (Fig. 3) and other molecular networks involved in depression (Panossian et al. 2012, 2013, 2014) (Tables 1–4). Mechanisms of action of *R. rosea* extract (and its active constituents) were studied in experiments on isolated cells (Panossian et al. 2012, 2013, 2014; Wiegant et al. 2008; Boon-Niermeijer et al. 2000; Schriner et al. 2009), nematodes (Wiegant et al. 2009), laboratory animals (Panossian et al. 2007, 2008a, 2008b; Panossian and Wagner 2005; Prodius et al. 1997) and humans (Olsson et al. 2009).

Another putative antidepressant mechanism of *R. rosea* extract may be its effect on neuropeptide-Y (NPY) mediated upregulation of heat shock protein Hsp-70 which, in turn, down-regulates stress-induced JNK protein (suppressing glucocorticoid receptors and increasing cortisol) (Panossian et al. 2007) (Fig. 2). NPY is thought to play a role in the pathophysiology of depression (Heilig et al. 1988). Several studies have suggested that NPY may produce antidepressant-like activity in the rat forced swimming test (Redrobe et al. 2002; Stogner and Holmes 2000). Human studies have also suggested that NPY may play a "buffering" role in adaptation to stress (Morales-Medina et al. 2010; Morgan et al. 2001; Morgan et al. 2000). Pre-clinical and clinical evidence also suggests a mood and cognitive enhancing action for NPY (Fletcher et al. 2010; Morgan et al. 2000). For example, NPY has been shown

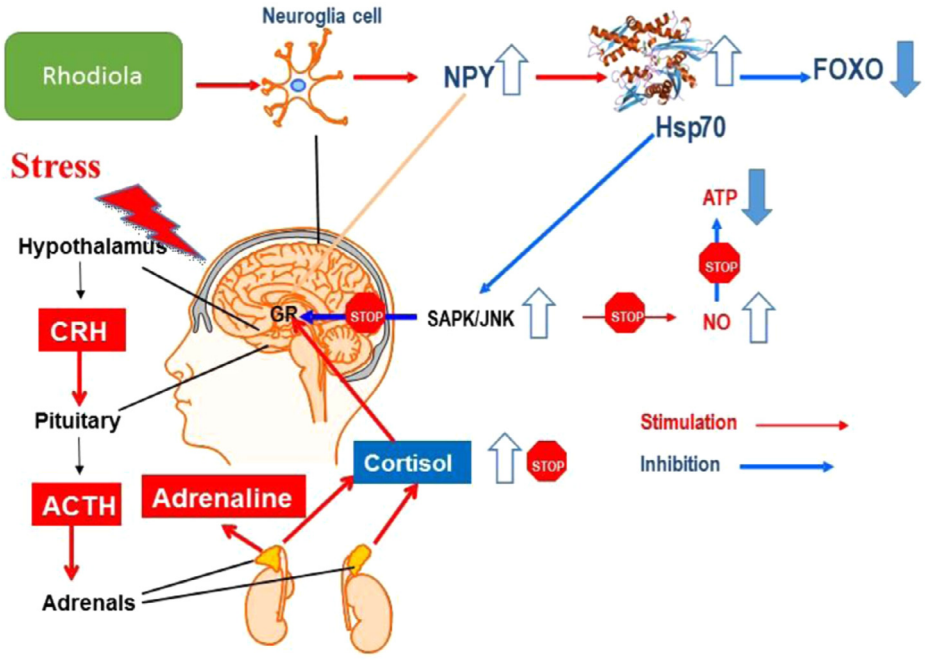


Fig. 2. Hypothetical mechanism of action of Rhodiola and salidroside on stress system in depression. Stress induced release of CRH from hypothalamus followed by release of ACTH from pituitary simulates release of adrenal hormones and NPY in order to cope the stress. Feedback regulation of overreaction is initiated by cortisol release from adrenal cortex followed by binding to glucocorticoids receptors (CR in brain. This signal stops the further release of brain hormones and stress induced increase of cortisol is decreasing to normal level in blood circulation system. Whilst short and mild stress (eustress) is essential to life, severe stress can cause disease depression, which is associated with generation of active oxygen containing molecules, including nitric oxide, which is known to inhibit ATP formation. Stress induced signaling proteins JNK were found to inhibit GR (Wang et al., 2005), consequently this feedback normalization is blocked and cortisol content in blood of depressive patients is permanently high. That is associated with impaired memory, ability to concentrate, fatigue and other symptoms. Rhodiola and salidroside suppresses elevated JNK and cortisol in stress. Rhodiola and salidroside stimulate formation of Hsp70, which are known to inhibit JNK. Consequently, nitric oxide does not increase anymore and ATP generation is not suppressed; (adapted from reference Panossian, 2013).

Table 1
Target molecules affected by *R.rosea* and salidroside.

Target molecule	Test article	Cell type/animal	Concentration/Dose	Effect	Reference
BNDF	Salidroside	Hippocampus, rats and mice	20 and 40 mg/kg 12 and 24 mg/kg	Increase	Yang et al. (2014) Zhu et al. (2015)
CREB	Salidroside	Neural stem cells; respiratory epithelial cells	5 μM	?	Jin et al. (2016)
		HBE16 cells	50 and 100 μM	Activity decrease	Li et al. (2013)
CREB tCREB/MITF/tyrosinase pathway	*R. rosea* hydrolisate	Mouse melanoma cells (B16F0)		Inhibits	Chiang et al. (2014)
TrkB	Salidroside	Hippocampus, rats and mice	12 and 24 mg/kg	Increase	Zhu et al. (2015)
Glucocorticoid receptor	Salidroside	Hippocampus, rats;	20 and 40 mg/kg	Increase	Yang et al. (2014)
Corticotropin-releasing hormone (CRH)	Salidrosid	Hippocampus, rats;	20 and 40 mg/kg	Decrease	Yang et al. (2014)
Serotonin receptor 1A	*R. rosea* extract	Brain, rat	5,10,20, 40 mg/kg	Increase	Mannucci et al. (2012)
Serotonin	*R. rosea* extract	Hippocampus, rat	1.5, 3.0, 6.0 g/kg	Increase	Qin et al. (2008) Chen et al. (2009)
		Brain, rat	5,10,20, 40 mg/kg	Increase	Mannucci et al. (2012)
	Salidroside	Prefrontal cortex, mice	12 and 24 mg/kg	Decrease	Zhu et al. (2015)
Noradrenaline	Salidroside	Prefrontal cortex, mice	12 and 24 mg/kg	Decrease	Zhu et al. (2015)
MAO-A	*R. rosea* extracts, Rosiridin	Insect mitochondrial MOA containing fraction	10(−5) M	Inhibits	Van Dearman et al. (2009)
p-JNK	*R. rosea* Salidroside	Blood serum, rabbits	1.0 mg/kg, 0.5 mg/kg	Decrease	Panossian et al. (2007)
NO	*R. rosea* Salidroside	Blood serum, rabbits	1.0 mg/kg, 0.5 mg/kg	Decrease	Panossian et al. (2007)
Cortisol	*R.rosea*	Human saliva, Blood serum, rabbits	576 mg daily	Decrease	Olsson et al. (2009)
	R. rosea Salidroside		1.0 mg/kg, 0.5 mg/kg		Panossian et al. (2007)
NPY	Salidroside	Human neuroglia cell line T98G	1–10 μM	Increase	Panossian et al. (2012)
HSF1	Salidroside	Human neuroglia cell line T98G	1–10 μM	Increase	Panossian et al. (2012)
Hsp70	Salidroside	Human neuroglia cell line T98G	1–10 μM	Increase	Panossian et al. (2012)

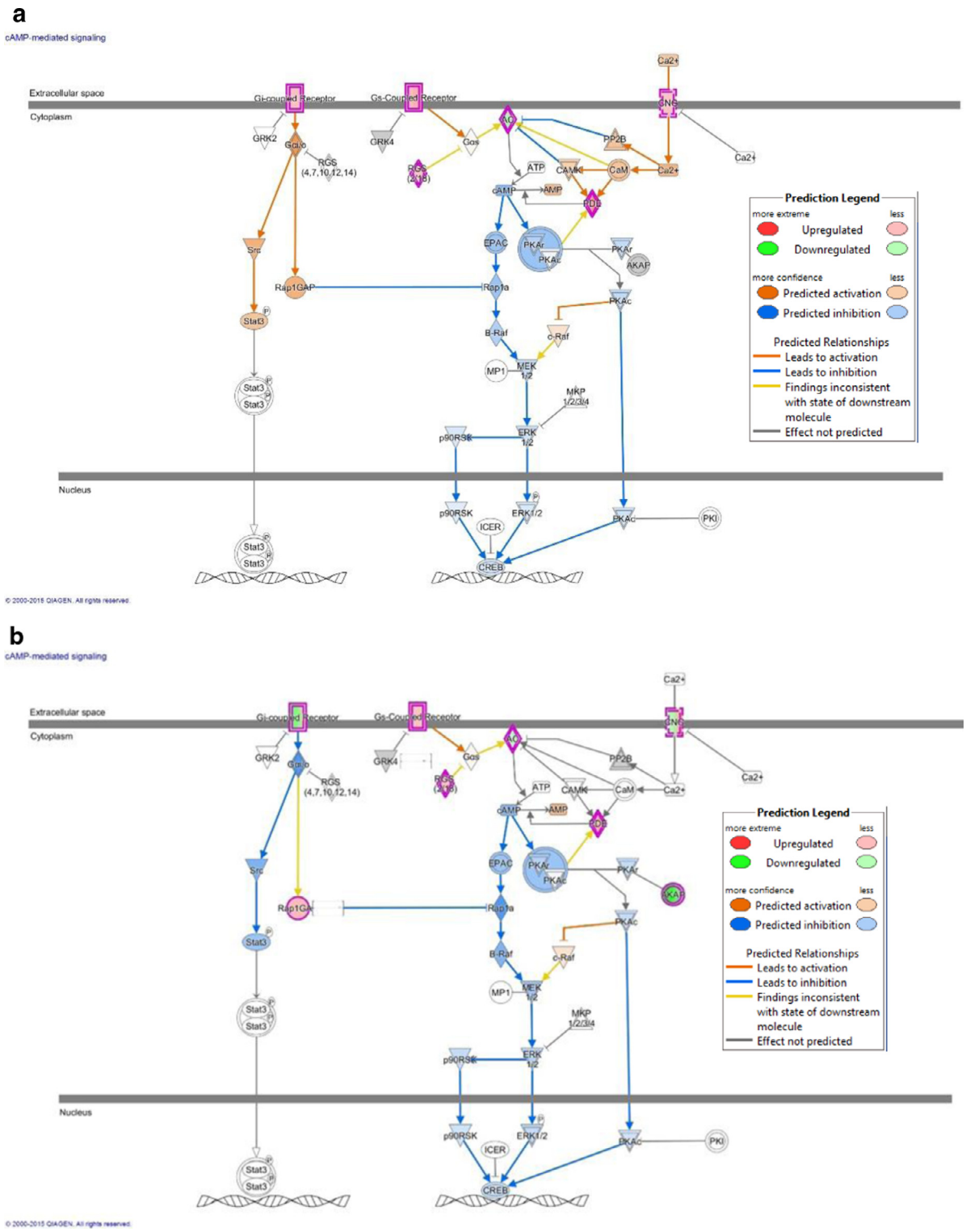


Fig. 3. Hypothetic molecular mechanisms by which Rhodiola (a) and salidroside (b) regulates GTP-binding protein coupled receptors (GPCR) and cAMP-mediated mediated pathways. They downregulate expression of adenylate cyclase (AC) which activates generation of cAMP from ATP and upregulate expression of phosphodiesterases (PDE) which activates degradation of cAMP. Predicted downstream effect of Rhodiola and salidroside is an inhibition of protein kinase A (PKAc) and MEK mediated pathways followed by inhibition of cAMP response element-binding protein (CREB), a transcription factor, which is involved in both the mechanism of action of antidepressants as well as the disease itself (Carlezon et al. 2005; Blendy, 2006). CREB is known to initiate the transcription of brain-derived neurotrophic factor (BNDF). Several evidences indicate that chronic stress induced downregulation of hippocampal BDNF expression is the key component of depression (Vásquez et al. 2014; Mlyniec et al. 2014). Salidroside was found to increase expression of BNDF in hippocampus of rats (Yang et al. 2014; Zhu et al. 2015), Table 1. There are similarities and differences in the effects of salidroside and Rhodiola SHR-5 total extract. Both Rhodiola extract and salidroside upregulates the G_s subunit of the receptor, and presumably inhibits cAMP/PKA/ERK signaling pathways. However, it seems that Rhodiola inhibits this pathway via an alternative link by upregulation of the membrane receptor – CNC, which is involved in activation of Ca2/CaM/PDA. One more is related to the effect on The G_s alpha subunit (or Gs protein) activates the cAMP-mediated pathway by activating adenylate cyclase. G_i alpha subunit of GPCR: Rhodiola upregulates, while salidroside – downregulates the gene, which encodes expression of this protein. Consequently, effect of Rhodiola leads to activation the transcription factor Stat3 signaling pathway, while salidroside – to the inhibition Stat3, which is known to control IL6-dependent regulation of serotonin transporter (CERT) function and depression-like behavior (Kong et al. 2015). Regulated genes are shown in purple colored frames; up-regulated genes are represented in rose, down regulated in green color; predicted inhibition/downregulation – in blue color, predicted activation/upregulation – in yellow-brownish color.

Table 2
Effect of Rhodiola on genes involved in mood and depressive disorders.

Disease or Function Annotation	*p*-Value	Molecules	# Molecules
Mood disorders	3.73E – 04	*ADRA2B, ALOX12, AQP4,CA9,CACNB2,CCKBR,CHRNA1,CHRNB4,CHRNG,DDC,ESR1,GRIA3,GRIK2,GRIN1,KCNK2,MTNR 1A,MYOM1,NCAM1,NDUFS7,PDE11A,SCN11A,SCN2B*	22
Depressive disorder	7.90E – 04	*ADRA2B, AQP4,CACNB2,CCKBR,CHRNA1,CHRNB4,CHRNG, ESR1,GRIA3,GRIN1,KCNK2,MYOM1,NCAM1,PDE11A*	14

Table 3
Effect of Rhodiola on genes involved in depression[§].

Symbol	Entrez Gene Name and summary – target protein; http://www.ncbi.nlm.nih.gov/gene/	Fold change	Depression-related Biological Process and Role in Cell	Related disease
ADRA2B	**Adrenoceptor alpha 2B** Alpha-2-adrenergic receptors are members of the G protein-coupled receptor superfamily. These receptors are critical for regulating the neurotransmitter release from sympathetic nerves and adrenergic neurons in the central nervous system.	2.928	Activation of MAPK cascade; activation of protein kinase B activity; adrenergic receptor signaling pathway; cell-cell signaling; GPCR-signaling pathway; negative regulation of epinephrine and norepinephrine secretion; positive regulation of neuron differentiation; signal transduction	Attention deficit hyperactivity disorder, hypertension, cardiovascular disorder, multiple sclerosis, heart disease, post-traumatic stress disorder, stroke, major depression, bipolar disorder, Parkinson's disease, attention deficit disorder, psychomotor agitation, insomnia, mood disorder, anxiety disorder, social anxiety disorder, Alzheimer's disease, panic disorder, depressive disorder, psychosis
AQP4	**Aquaporin 4** This gene encodes a member of the aquaporin family of intrinsic membrane proteins that function as water-selective channels in the plasma membranes of many cells. The encoded protein is the predominant aquaporin found in the brain.	3.01	Nervous system development; protein homooligomerization; renal water absorption; response to glucocorticoid stimulus; response to radiation; sensory perception of sound; transmembrane transport; regulation of dopamine and L-glutamic acid	Major depression, Huntington's disease, Parkinson's disease
CACNB2	**Calcium channel, voltage-dependent, beta 2 subunit** This gene encodes a subunit of a voltage-dependent calcium channel protein that is a member of the voltage-gated calcium channel superfamily.	−3.387	Axon guidance; calcium ion import; calcium ion transport; neuromuscular junction development; synaptic transmission; visual perception	Hypertension, hypercholesterolemia, hyperlipidemia, mania, depressive disorder, migraines, short-QT syndrome 4, Brugada syndrome, bipolar disorder, Alzheimer's disease
CCKBR	**Cholecystokinin B receptor** This gene encodes a G-protein coupled receptor for gastrin and cholecystokinin (CCK), regulatory peptides of the brain and gastrointestinal tract.	−2.621	Behavioral defense response; feeding behavior; phospholipase C-activating G-protein coupled receptor signaling pathway; GABAergic; positive regulation of synaptic transmission, glutamatergic; sensory perception; signal transduction; regulation of alpha catenin	Withdrawal syndrome, hypergastrinemia, Huntington's disease, major depression, hyperphagia
CHRNA1	**Cholinergic receptor, nicotinic, alpha 1 (muscle)** The muscle acetylcholine receptor consists of five subunits of four different types: two alpha subunits and one beta, gamma, and delta subunit. This gene encodes an alpha subunit that participates in acetylcholine binding/channel gating.	−2.77	Ion transmembrane transport; musculoskeletal movement; neuromuscular synaptic transmission; neuron homeostasis; signal transduction; synaptic transmission	Depressive disorder, seizures, psychomotor agitation, schizophrenia, stroke, coronary disease, etc.
CHRNB4	**Cholinergic receptor, nicotinic, beta 4 (neuronal)**	5.464	Behavioral response to nicotine; ion transport; locomotor behavior; regulation of membrane potential; regulation of neurotransmitter secretion; smooth muscle contraction; synaptic transmission; synaptic transmission	Seizures, psychomotor agitation, schizophrenia, schizoaffective disorder, depressive disorder
CHRNG	**Cholinergic receptor, nicotinic, gamma (muscle)** The mammalian acetylcholine receptor is a transmembrane glycoprotein with several subunits. This gene encodes the gamma subunit, which participates in neuromuscular organogenesis and ligand binding.	−5.028	Acetylcholine-activated cation-selective channel activity; acetylcholine receptor activity; cation transport; ion transmembrane transport; muscle contraction; regulation of membrane potential; signal transduction; synaptic transmission	Psychomotor agitation, schizophrenia, depressive disorder, Escobar syndrome, lethal multiple pterygium syndrome
ESR1	**Estrogen receptor 1** This gene encodes an estrogen receptor, which is a ligand-activated transcription factor composed of several domains that are important for hormone binding, DNA binding, and transcription activation. The protein localizes to the nucleus, and estrogen and its receptors are essential for sexual development and reproductive function, as well as the development of other tissues, such as bone. Estrogen receptors are also involved in pathological processes including breast cancer, endometrial cancer, and osteoporosis.	−7.516	Cellular response to estradiol stimulus; elevation of cytosolic calcium ion concentration; gene expression; intracellular steroid hormone receptor signaling pathway; male gonad development; negative regulation of the I-kappaB kinase/NF-kappaB cascade; phospholipase C-activating G-protein coupled receptor signaling pathway; positive regulation of the nitric oxide biosynthetic process; signal transduction; transcription	Breast cancer, weight gain, atherosclerosis, obesity, depressive disorder, Alzheimer's disease, etc.

(*continued on next page*)

Table 3 (*continued*)

Symbol	Entrez Gene Name and summary – target protein; http://www.ncbi.nlm.nih.gov/gene/	Fold change	Depression-related Biological Process and Role in Cell	Related disease
GRIA3	**Glutamate receptor, ionotropic, AMPA 3** Glutamate receptors are the predominant excitatory neurotransmitter receptors in the mammalian brain and are activated during various normal neurophysiologic processes. These receptors are heteromeric protein complexes composed of multiple subunits that are arranged to form ligand-gated ion channels.	3.031	Glutamate receptor signaling pathway; ion transmembrane transport; ion transport; regulation of receptor recycling; synaptic transmission; long-term potentiation, long-term depression, plasticity, excitatory postsynaptic potential, depolarization, depotentiation, depression,	Tremor, X-linked mental retardation, major depression, Alzheimer's disease, bipolar disorder
GRIN1	**Glutamate receptor, ionotropic, N-methyl-D-aspartate 1** The protein encoded by this gene is a critical subunit of the N-methyl-D-aspartate receptors. These members of the glutamate receptor channel superfamily are heteromeric protein complexes with multiple subunits arranged to form a ligand-gated ion channel. These subunits are critical for the plasticity of synapses, which is believed to support memory and learning.	3.864	Apoptosis, plasticity, synaptic transmission, long-term potentiation, cell death, transmembrane potential, excitotoxicity, cytotoxicity, communication, homeostasis	Schizophrenia, Alzheimer's disease, Parkinson's disease, bipolar disorder, major depression, obsessive-compulsive disorder, multiple sclerosis, frontal lobe dementia, Lewy body disease, bipolar depression, binge eating disorder, opioid dependence, morbid obesity, autosomal dominant mental retardation type 8, attention deficit hyperactivity disorder, drug abuse, Down's syndrome, ataxia, frontotemporal dementia, anxiety disorder, autism, open-angle glaucoma, cognition disorder, postoperative pain, delirium, Huntington's disease, depressive disorder, dementia, breast cancer, partial seizure, tuberculosis, urinary tract infection, Lennox-Gastaut syndrome, epileptic seizure, hypophagia, starvation, neurodegeneration, bipolar I disorder
KCNK2	**Potassium channel, subfamily K, member 2** This gene encodes one of the members of the two-pore-domain background potassium channel protein family. This type of potassium channel is formed by two homodimers that create a channel that releases potassium from the cell to control the resting membrane potential.	3.411	G-protein coupled receptor signaling pathway; ion transport; potassium ion transmembrane transport; potassium ion transport; regulation of ion transmembrane transport; stabilization of membrane potential; synaptic transmission	Seizures, major depression, prostatic carcinoma, Huntington's disease
MYOM1	**Myomesin 1**	2.732	Muscle contraction	Major depression
NCAM1	**Neural cell adhesion molecule 1** This gene encodes a cell adhesion protein that is involved in cell-to-cell interactions and cell-matrix interactions during development and differentiation. The encoded protein is involved in the development of the nervous system and cells involved in the expansion of T cells and dendritic cells, which are critical for immune surveillance.	2.657	Aging; axon guidance; cell surface receptor signaling pathway; learning or memory; multicellular organismal response to stress; negative regulation of cell death; neuron development; neuron projection development; organ regeneration; peripheral nervous system axon regeneration; positive regulation of calcium-mediated signaling; regulation of the sensory perception of pain; thalamus development	Major depression, bipolar disorder
PDE11A	**3′,5′-cyclic-nucleotide phosphodiesterase (PDE)** The 3′,5′-cyclic nucleotides cAMP and cGMP are the second messengers among numerous signal transduction pathways. The 3′,5′-cyclic nucleotide phosphodiesterases (PDEs) catalyze the hydrolysis of cAMP and cGMP to form the corresponding 5′-monophosphates and provide a mechanism for down-regulating cAMP and cGMP signaling. This gene encodes a member of the PDE protein superfamily.	5.776	cAMP catabolic process; cGMP catabolic process; metabolic process; signal transduction	Physical disability, cardiovascular disorder, diabetes mellitus, major depression

§ Adapted from reference Panossian et al., 2014.

to mediate monoamine and serotonin receptors involved in stress induced depression (Crespi 2011; Quarta et al. 2011; Luo et al. 2008; Hökfelt et al. 1999), and, higher levels of NPY have been observed in soldiers who present with low psychological distress or who belong to the elite Special Forces branch (Morgan et al. 2001). In contrast, reduced levels of NPY have been observed in some individuals with major depression and in brain tissue of suicide victims (Morales-Medina et al. 2010). *R. rosea* and salidroside appear to stimulate expression and release of NPY in neuroglial cells (Panossian et al. 2012). If depression is associated with reduced levels of NPY expression, this finding may suggest a possible mechanism for *R. rosea's* putative antidepressant activity.

Other possible mediators of an antidepressant activity for *R. rosea* are Hsp70 and JNK (Fig. 2), which are known to interact with GRs (Grad and Picard 2007) that may be involved in the pathogenesis of depression (Barden 2004; Budziszewska 2002; Chrousos and Kino 2009; Juruena et al. 2013). In this regard, *R. rosea* extract regulates more than 50 genes involved in regulation of behavior, mood and depressive disorders (Panossian et al. 2013, 2014) (Tables 1–4). For example, among deregulated genes are

Table 4
Top three physiological system functions affected by Rhodiola, salidroside, triandrin, and tyrosol in T98G cells.

Rhodiola extract			Salidroside			Tyrosol			Triandrin		
	p-Value	# Genes		*p*-Value	# Genes		*p*-Value	# Genes		*p*-Value	# Genes
Behavior	7.69E–07–1.02E–02	50	**Behavior**	2.14E–06–1.83E–02 40	40	Hair and skin development and function	1.29E–02–3.73E-02	6	Tissue development	2.53E–03–3.74E–02	14
Nervous system function	3.60E – 06–1.00E – 02	65	Nervous system function	6.77E – 05–1.91E – 02 60	60	Hematological system function	1.29E – 02–3.73E – 02	10	Cardiovascular system function	6.86E – 03–3.74E – 02	4
Humoral Immune Response	2.39E – 05–6.52E – 03	28	Cardiovascular system function	1.13E – 04–1.91E – 02 24	24	Hematopoiesis	1.29E – 02–3.73E – 02	4	Organismal development	6.86E – 03–3.74E – 02	8

genes encoding G-Protein Coupled Receptors (GPCR), which are localized on the cell membranes and play an important role in transmitting signals from many hormones, neurotransmitters, and other signaling molecules inside the cell. Thus, salidroside down-regulates the *HTR1A* gene encoding serotonine G-protein coupled receptors, which is known to activate an intracellular second messenger cascade resulting in excitatory or inhibitory neurotransmission. Activation of serotonin receptors modulate the release of many neuro- transmitters including glutamate, GABA, DA, NA, and acetylcholine, as well as many hormones including oxytocin, prolactin, vasopressin, cortisol, corticotropin, substance P, and others. These observations suggest that the effects of *R. rosea* and salidroside on expression of genes involved in regulation of functions of CNS can be associated with beneficial effects of *Rhodiola* in depression (Panossian et al. 2014).

3.3. *Human studies suggestive of* R. rosea *antidepressant-like activity*

3.3.1. *Early* R. rosea *studies of neurasthenic disorders*

Many early *R. rosea* studies were performed in the former Soviet Union and were poorly designed and conducted (Table 5). Standardized psychological measures were rarely used, and many did not use randomization or blinding techniques. Moreover, Soviet diagnostic nosology was much different from those used in most other countries (Rezvyy et al. 2005; Keith and Regier 1989; Miller 1985). For example, the Soviet diagnosis of asthenia included a heterogeneous group of subjects with a variety of psychological and physical symptoms, making study results difficult to interpret. Key symptomatic characteristics of the Soviet asthenic syndrome were generalized weakness, reduced work capacity, concentration and memory problems, irritability, headaches, insomnia, and anorexia. The symptoms tended to occur after intensive work requiring mental exertion.

The anti-asthenic action of R. rosea in healthy individuals was initially reported by Krasik et al. (1970a, 1970b), and appeared to be confirmed in 128 individuals age 17–55 years old with pronounced fatigue (Krasik et al. 1970a, 1970b). Several early open-label studies of asthenic syndrome also suggested that *R. rosea* extract may also be effective in reducing associated depression-like symptoms. For example, Mikhailova (1983) reported that 58 patients with exogenous organic asthenia, characterized by general weakness and fatigue, diurnal worsening of fatigue in the morning, and hypersomnia during the day (i.e., symptoms suggestive of DSM-IV bipolar type II depression) were reduced during *R. rosea* extract administered for 1–4 months. Only one patient reported an adverse event (i.e., sleep disorder). However, this was an open-label, uncontrolled study.

The effect of *R. rosea* extract on various types of Soviet era neuroses was initially reported in an open-label study of 20 healthy subjects and 45 patients with symptoms of insomnia, irritability and somatic complaints (Saratikov et al. 1965). *R. rosea* extract had beneficial effects in 16 of 20 patients after three days of single dose administration with improvement of stereotypical answers and resignation reaction, improved memory as well as active and passive attention, and other symptoms of depression. After 10 days of repeated *R. rosea* administration, motor and cognitive symptoms improved with an increase in conditional motor reflex values and an improvement in the interaction of motor and cognitive systems in all 45 patients. There was also an improvement in appetite, irritability and anxiety levels.

In other psychiatric disorders, *R. rosea* was observed to confer a synergistic effect when used in combination with psychotropic drugs (Sudakov et al. 1986). The authors hypothesized that the positive effects of *R. rosea* resulted from a stimulant action and reduction in side effects produced by the psychotropic drugs. Moreover, the addition of *R. rosea* to the nootropic drug therapy

Table 5
Summary of clinical studies of various Rhodiola preparations in depression[§].

Pathophysiological condition	Reference	Study design	Duration of the treatment, weeks	Number of patients	Jadad score (max 5)[a]	Quality level of evidence[b]
Depression	Darbinyan et al. (2007)	R,PC,DB	6	91	5	1b
	Mao et al. (2014, 2015)	R,PC,DB	12	57	5	1b
	Brichenko et al. (1986)	OL, C	?	78/56**	0	IIa
Asthenic – depressive syndrome (stress– induced mild depression)	Krasik et al., (1970a,b)	OL, UC	2–3	128*	0	–
	Krasik et al., (1970a,b)	OL, UC	2–3	135/27*	0	–
	Mikhailova, (1983)	OL	8	58	0	–
	Mesheryakova et al. (1975)	OL	?	25	0	–
Neurosis*** (stress– induced depression)	Saratikov et al. (1965)	OL	1.5	65*	0	–
	Kaliko and Tarasova (1966)	PC, SB	?	70/80*	1	IIb
Anxiety	Bystritsky et al. (2008)	OL	10	10	0	III

• *Grade A. Evidence levels quality Ia, Ib* - Requires at least one randomized controlled trial as part of the body of literature of overall good consistency addressing the specific recommendation;
• *Grade B. Evidence levels IIa, IIb, III* - Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation;
• *Grade C. Evidence level IV* - Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities but indicates absence of directly applicable studies of good quality.
§ adapted from reference Panossian and Wikman (2010).
R – Randomized, PC – placebo– controlled; DB – double– blind; SB – single blind, CO – crossover, UC – uncontrolled, C- controlled, OL – open label trial;
* mixed patients population, sick/healthy subjects.
** adjuvant therapy with antidepressants, control group – tricyclic antidepressants.
*** Neurotic, stress-related and somatoform disorders (F40–F48)
[a] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17: 1-12.
[b] According to WHO, FDA and EMEA: Ia - meta-analyses of randomized and controlled studies; Ib – evidence from at least one randomized study with control; IIa – evidence from at least one well-performed study with control group; IIb – evidence from at least one well-performed quasi-experimental study; III – evidence from well-performed non-experimental descriptive studies as well as comparative studies, correlation studies and case-studies; and IV – evidence from expert committee reports or appraisals and/or clinical experiences by prominent authorities.
Grade of recommendation based on the European Medicines Agency Assessment Scale [European Medicines Agency. Committee on Medicinal Products EMEA/HMPC/104613/2005. Available at http://www.emea.europa.eu/pdfs/human/hmpc/10461305en.pdf (Accessed 01/03/2009)]:

seemed to lend an additive benefit to the nootropic treatment in patients with amnestic and cognitive disorders (Sudakov et al. 1986); although this benefit was less pronounced in patients with agitated dementia (Sudakov et al. 1986).

Similarly, Brichenko et al. (1986) reported that patients in depressive states of varying aetiology spent less time in hospital, experienced increase in activities, interest, and physical productivity, and a reduction in side effects of their antidepressant when *R. rosea* was added to their antidepressant treatment regimen. Although the mechanism of side effect reduction during tricyclic antidepressant therapy is unknown, *R. rosea* also appears to have a similar beneficial effect on side effects of neuroleptic medication in patients with schizophrenia (Krasik et al. 1970a, 1970b) – suggesting an anti-dopaminergic action.

On the strength of these, and other clinical reports, the Pharmacological Committee of the Ministry of Health of the Soviet Union recommended the medicinal use of *R. rosea* extract for patients with asthenia syndrome, various neuroses, vascular dystonia, hypotension, and asthenic schizophrenia (Mashkovskij 1977; Rhizome and roots of Rhodiola rosea, 1990; Extractum Rhodiolae fluidum 1996). *R. rosea* extract was also recommended for (i) its stimulant properties for healthy individuals with fatigue, post-viral asthenia, reduced libido, impotence, and to counteract side effects of various anticholinergic psychotropic drugs.

3.3.2. *More recent* R. rosea *studies*

In the more modern diagnostic era, one open-label study by Bystritsky et al. (2008) examined *R. rosea* (Rhodax®) 340 mg daily for 10 weeks in 10 subjects with DSM-IV generalized anxiety disorder (GAD), Table 5. In this open-label, proof-of-concept study, a significant reduction in mean Hamilton Anxiety Rating Scale (HRSA) (Hamilton 1959) scores was observed at endpoint ($p = 0.01$), and this finding also appeared to be associated with a similar reduction in Hamilton Depression Rating Scale (HRSD) (Hamilton 1960) scores at endpoint ($p = 0.001$).

Darbinyan et al. (2007) conducted a randomized, double-blind, placebo-controlled trial of *R.* rosea (SHR-5) extract (Swedish Herbal Institute, Vallberga, Halland, Sweden) in 89 subjects with mild to moderate DSM-IV major depressive disorder, aged 18–70 years old. Subjects received either *R. rosea* extract 340 mg daily ($n = 31$), *R. rosea* extract 680 mg daily ($n = 29$), or placebo ($n = 29$) for 6 weeks. At study endpoint, the mean HRSD score significantly declined for both doses of *R. rosea* ($p < 0.0001$, respectively). No significant reduction in HRSD score was observed during placebo ($p = 0.2206$). Endpoint analysis found lower mean HRSD scores for both *R. rosea* treatment conditions versus placebo ($p < 0.001$, respectively) (Panossian and Wikman 2014). Although this was a randomized, double-blind controlled study, the outcome magnitude of the difference in HSRD scores among the three treatment conditions have been questioned – as a true drug-placebo difference for each *R. rosea* dosing group of this magnitude is unlikely in an under-powered pilot trial of this design.

More recently, Mao et al. (2014, 2015) performed a randomized double-blind, 12-week, proof-of-concept trial of *R. rosea* versus sertraline (a conventional antidepressant) versus placebo. The study sought to obtain preliminary safety and efficacy data on the relative antidepressant action of *R. rosea* extract versus sertraline in outpatients with mild to moderate major depressive disorder (Mao et al. 2014, 2015). Subjects were at least 18 years old and had a DSM-IV Axis I diagnosis of major depressive disorder ascertained using the *Structured Clinical Interview for DSM-IV* interview format (First et al. 2001). Subjects had a minimum baseline total HRSD score 10 and a baseline Clinical Global Impression Severity (CGI/S) (Guy 1976) score of 3 ('mild') or 4 ('moderate'). Exclusion criteria were a primary DSM-IV Axis I diagnosis other than depression, use of a conventional or alternative psychotropic

agent, actively suicidal, uncontrolled medical condition pregnant or nursing, or receiving medication known to produce mood changes.

Identically appearing capsules containing either pharmaceutical grade *R. rosea* (SHR-5) powdered extract 340 mg (standardized to a content of rosavin 3·07% / rhodioloside 1·95%) (Swedish Herbal Institute, Vallberga, Halland, Sweden), sertraline 50 mg HCl (North Star Pharmaceuticals, Memphis, TN), or placebo (i.e., lactose monohydrate NF) (Spectrum® Quality Products, New Brunswick, NJ) were dispensed. All SHR-5 product was administered under IND #105,063 issued by the U.S. Food and Drug Administration.

The primary outcome was the change in 17-item HRSD score, with change in CGI/C (Guy 1976), and Beck Depression Inventory (BDI) scores (Beck et al. 1961) as secondary outcomes. A standardized treatment emergent adverse event profile was also obtained (National Institute of Mental Health 1985).

Study drug was initiated at one capsule daily for the first 2 weeks. Subjects with ≤ 50% reduction in HRSD score (versus baseline) had the dose increased to 2 capsules daily during weeks 3 and 4 of therapy. This procedure was continued every 2 weeks for subjects with ≤ 50% reduction in HRSD score (versus baseline) up to a maximum dose of 4 capsules daily by study weeks 6 through 12 of therapy. Subjects unable to tolerate study drug had their dosage reduced to a minimum of 1 capsule daily. Outcome measurements were obtained at baseline and after 2, 4, 6, 8 and 12 weeks of treatment. The study was powered to detect relatively large differences between treatment conditions and to identify trends in the data that might inform future study design.

There was no statistically significant difference in change over time for HRSD scores among treatment groups ($p = 0.79$), and the decline in HRSD scores by week 12 was slightly greater for sertraline (–8.2, 95% confidence interval [CI], –12.7 to –3.6) versus *R. rosea* (–5.1, 95% CI: –8.8 to –1.3) and placebo (–4.6, 95% CI: –8. to –0.6). There was also no statistically significant difference in change over time in BDI or CGI/C scores among treatment conditions ($p = 0{\cdot}28$ and $p = 0{\cdot}17$, respectively). However, there were clinically meaningful odds ratios (95% CI) of global improvement by week 12 (versus placebo) of 1.39 (0.38–5.04) and 1.90 (0.44–8.20) for *R. rosea* and sertraline, respectively; indicating that subjects on *R. rosea* had 1.4 times the odds of improvement, and subjects on sertraline had 1.9 times the odds of improvement, by week 12 of treatment versus placebo.

In contrast, more subjects reported study-related adverse events using sertraline (63.2%) versus *R. rosea* (30.0%) or placebo (16.7%) ($p = 0.012$). Two subjects prematurely discontinued sertraline treatment; while no subject prematurely discontinued *R. rosea* or placebo.

3.4. Possible benefits and limitations

The development of a safe and effective alternative botanical pharmacotherapy for depression would be of public health interest for individuals unable, or unwilling, to use conventional antidepressant therapy. Perhaps the greatest limitation to understanding the potential antidepressant benefit of *R. rosea* is the relative lack of any supporting data from older clinical trials conducted in the former Soviet Union. In this regard, virtually all of the older *R. rosea* studies were uncontrolled, not adequately powered, randomized, unblended, included subjects with more than a single psychiatric or psychological diagnosis, used un-validated diagnoses, employed arbitrary *R. rosea* therapy doses for undefined durations, used no conventional antidepressant or stimulant comparator, and provided no longitudinal objective symptom ratings over time. None of the studies utilized an active or inert placebo, and few used pharmaceutical grade botanical product. Moreover, none of the earlier *R. rosea* studies included subjects diagnosed with syndromes easily recognized by Western diagnostic nosologies, and none used longitudinal statistical procedures to examine results.

In contrast, the small body of randomized, double-blind, placebo-controlled studies with standardized, pharmaceutical-grade *R. rosea* extract may be thought to represent the first generation of controlled efficacy and tolerability trials for depression. Despite the limitations of these preliminary *R. rosea* trials, the overall findings suggest that *R. rosea* may produce modest antidepressant effects in subjects with mild to moderate depression, and may be almost as effective as conventional antidepressants albeit with superior tolerability.

Nevertheless, we would note that these modern studies, despite their well-designed and well-controlled aspects, had substantial limitations. For example, the Darbinyan et al. (2007) study reported significant reductions in mean HRSD endpoint scores for *R. rosea* extract 340 mg daily ($n = 31$) and *R. rosea* extract 680 mg daily ($n = 29$) ($p < 0.0001$, respectively), while there was no significant reduction in HRSD endpoint score for placebo ($n = 29$) ($p = 0.2206$). These results, however, are inconsistent with other modern 3-arm randomized controlled antidepressant trials; given the fact that the Darbinyan et al. (2007) study was insufficiently powered to show a significant drug-placebo difference. In contrast, the Mao et al. (2015) study was deliberately not powered to identify statistically significant differences between *R. rosea* and sertraline or placebo efficacy. Nevertheless, while this study identified a somewhat greater (albeit nonsignificant) antidepressant effect for sertraline versus *R. rosea, R. rosea* was substantially better tolerated than sertraline.

Despite these shortcomings, these studies suggest that *R. rosea* may represent a potential alternative treatment for individuals who are intolerant to conventional antidepressants or seek to avoid them. Moreover, it appears that *R. rosea* may exert its antidepressant effects via a broad spectrum of putative mechanisms which make it an attractive treatment from both a heuristic and mechanistic view point. Although the preliminary trials of *R. rosea* suggest an advantageous safety and tolerability profile compared to conventional antidepressant drugs, we would also acknowledge several disadvantages to *R. rosea*. For example, botanical extracts, while highly purified and standardized to active constituents, are still highly complex mixtures of many compounds which may have variable positive and negative effects depending on factors that have crucial impact on reproducibility of pharmacological activity (e.g., growing conditions, regional terroir, genus differences). These production disadvantages set botanical medications against conventional antidepressant drugs which, while less well tolerated, have the advantage of being a single, synthetic, reproducible, compound that always remains identical from batch to batch during production. Moreover, a particular standardized, botanical extract may have a different pharmacokinetic and pharmacodynamic dose-effect compared to a similar botanical extract with a different pharmaceutical standardization. For example, the maximal active antidepressant dose of SHR-5 brand of *R. rosea* extract might be inactive for a different extract of *R. rosea* – although both products were extracted from *Rhodiola* roots that have chemical compositions not identical to one another.

Finally, we acknowledge the difficulties in producing even the purest botanical medicinal products, and further acknowledge that providing reproducible effectiveness over time may be a serious challenge and a limitation of botanical medications in general. However, despite these limitations, the development of botanical remedies for depression and other mental disorders is clearly of interest and may represent a promising potential for future safe, effective, and affordable remedies with superior tolerability and a minimum of adverse events.

4. Conclusion

The considerable advances of quantitative functional genomics now provides more molecularly targeted candidates of disease. Despite these advantages, we are still at the stage of polypharmacy of targeted drugs. While some multi-target drugs offer modest efficacy advantages over single target drugs (and multi-target botanical agents), this is usually offset by unacceptable side effects. As a result, some scientists are turning toward a multi-layered network model of disease, particularly for neuropsychiatric diseases. This has prompted some mainstream drug makers to develop drug candidates with large therapeutic indices plus simultaneous effects on multiple genomic pathways. Paradoxically, such a search prompts a return to pharmocognosy, whereby botanicals, like *R. rosea*, will be nature's answer to simultaneously impacting multiple functional networks.

The work described herein is a beginning, and the path ahead is daunting, given that each plant has multiple genotypes. At least now there is growing recognition that botanical preparations must be standardized and tested without bias according to regulatory standards. If these efforts can attract funding, and are accomplished with scientific integrity, especially for those botanicals with long-standing claims of broadest-based efficacy in multiple diseases, then botanical medicines may lead the way back to a new understanding of acute and chronic disease.

Conflict of interest

Dr. Amsterdam is not a member of any industry-sponsored advisory board or speaker's bureau, and have no financial interest in any pharmaceutical, nutraceutical or medical device company.

Dr. Panossian is not a member of any industry-sponsored advisory board or speaker's bureau. He is an employee of Swedish Herbal Institute, but is not a shareholder in the company.

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