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REVIEW

Rhodiola rosea L. and Alzheimer's Disease: From Farm to Pharmacy

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***Rhodiola rosea* L. (roseroot) is a common member of the family Crassulaceae, known as one of the most important popular medicinal plants in the northern region of Europe. The roots of *R. rosea* possess a wide range of pharmacological activities such as antioxidant, antiinflammatory, anticancer, cardioprotective, and neuroprotective effects that are because of the presence of different phytochemicals such as phenols and flavonoids. In addition, the presence of salidroside, rosavins, and *p*-tyrosol are responsible for its beneficial effects for the treatment of on depression, fatigue, and cognitive dysfunction. A plethora of studies report that *R. rosea* has potent neuroprotective effects through the suppression of oxidative stress, neuroinflammation, and excitotoxicity in brain tissues and antagonism of oncogenic p21-activated kinase. However, to our knowledge, no review articles have been published addressing the neuroprotective effects of *R. rosea*. Therefore, the present article aims at critically reviewing the available literature on the beneficial effects of *R. rosea* on as a therapeutic strategy for the treatment of Alzheimer's disease and other neurodegenerative diseases where oxidative stress plays a major role in disease development and progression. We also discuss the cultivation, phytochemistry, clinical impacts, and adverse effects of *R. rosea* to provide a broader insight on the therapeutic potential for this plant. Copyright © 2016 John Wiley & Sons, Ltd.**

Keywords: Neurodegeneration; Neuroinflammation; Neurotoxicity; Oxidative stress; *Rhodiola rosea*.

INTRODUCTION

Alzheimer's disease (AD) is one of the most common debilitating age-related neurodegenerative disorders, which causes dementia in the elderly. It is associated with progressive cognitive impairment and dementia, eventually leading to complete incapacity and death (Birks, 2006; Reitz *et al.,* 2011). Ageing represents the main risk factor for developing AD (Lindsay *et al.,* 2002). However, cardiovascular diseases, obesity, diabetes, traumatic brain injury, cigarette smoking, and alcohol abuse are other important risk factors of major concern. AD was first reported in a 51-year-old woman who suffered from progressive dementia, by the German psychiatrist and neuropathologist, Alois Alzheimer, in 1907 (Berchtold and Cotman, 1998). Since then, while extensive progress has been made in AD research, the exact etiology and pathogenesis of the disease remain unclear. Although AD remains untreatable, it has been reported that mental stimulation and exercise training can delay cognitive impairment in patients who suffer from AD.

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Histopathologically, AD is characterized by the presence of extracellular amyloid plaques containing aggregated amyloid beta (Aβ) peptides and intracellular neurofibrillary tangles containing hyperphosphorylated tau protein. A wealth of evidence has shown that marked increases in oxidative stress are present in the AD brain in addition to the well-established pathology. Increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) induces oxidative stress and cell death in neural tissues of the brain. ROS and RNS are well known to induce oxidative damage to biological macromolecules, including proteins and lipids resulting in the cross-linking of cytoskeletal biological macromolecules (Yu, 1994; Stadtman and Berlett, 1997; Toyokuni, 1999; Patel *et al.,* 2000). In addition, accelerated production of ROS and RNS leads to oxidative injuries to RNA and DNA leading to a variety of mutations and cell death. With respect to the high metabolic activity as well as high levels of polyunsaturated fatty acids and low levels of antioxidant enzymes and non-enzymatic antioxidants, the brain is highly susceptible to oxidative stress. Because of regional differences in total brain antioxidant activity, it is likely that selective regional susceptibilities for oxidative stress exist in the brain.

Pathological evidence has shown that oxidative stress plays a crucial role in both the initiation and progression of AD. It has been reported that in AD, cholinergic neurons in the forebrain are highly vulnerable to oxidative

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stress (Yankner, 1996; Gibbs and Aggarwal, 1998). In addition, increased levels of F_2-isoprostanes, a marker for lipid peroxidation in the neuronal tissues, have been reported in multiple regions of the brain and cerebrospinal fluid of patients with AD (Praticò *et al.,* 1998; Montine *et al.,* 2005). Furthermore, in the neural tissues, oxidative stress is associated with increasing in the level of protein carbonyls that can induce DNA damage. The levels of protein carbonyls and 3-nitrotyrosine and markers of oxidative damage to DNA and RNA, such as 8-hydroxydeoxyguanosine, are higher in AD brains compared with age-matched controls (Butterfield and Kanski, 2001). As well, the activities of several endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase have been observed in both the central nervous system and peripheral nervous system tissues of AD patients (Pratico and Sung, 2004). Elevations in oxidative stress markers have also been reported in mild cognitive impairment, an intermediate state between normal ageing and dementia (Ansari and Scheff, 2010). This suggests that oxidative damage in AD may commence prior to the onset of the disease. Therefore, oxidative stress may represent an early alteration during the development of the disease.

Neuroinflammation also appears to play a prominent role in the pathogenesis of AD. Microglial cells, the resident immune cells of the brain, have been shown to be recruited to AD-associated Aβ plaques and in close proximity to neurofibrillary tangles (Rogers *et al.,* 1988; Griffin *et al.,* 1989). Increased levels of several inflammatory molecules have been reported, including complement compounds, cytokines, macrophage colony-stimulating factor, transforming growth factor-α, C-reactive protein, S100β, and arachidonic acid (Hensley, 2010). These inflammatory markers are capable of producing ROS and RNS, which are elevated in the AD brain and amply evidenced. Despite this, the exact role of the primacy and consequences of neuroinflammation as an initiator or accelerator of AD remains unclear. Current research suggests that neuroinflammation represents an early and continuous feature in AD that is amenable to pharmacological exploitation.

Glutamate neurotoxicity has also been thought to play critical roles in the pathophysiology of AD and other neurodegenerative disorders, including hypoxic-ischemic brain injury, epileptic seizures, and Parkinson's disease. L-glutamate (L-glu) is the most abundant excitatory neurotransmitter in the central nervous system (CNS). It plays a crucial role in the neurological processes including cognition, learning, and memory (Collingridge and Lester, 1989). However, hyperactivation of glutaminergic receptors, under pathophysiological conditions, induces neuronal damage and cell death via apoptosis and energy restriction, known as excitotoxicity (Olney *et al*., 1971). Therapeutic strategies that attenuate L-glu-induced excitotoxicity are potential candidates for the treatment of AD.

Dendritic spine defects are a common feature in AD and human developmental mental retardation syndromes (Fiala *et al*., 2002). While it is likely that dendritic spine defects occur secondarily to upstream deficits in mental retardation, the exact significance of dendritic spine defects in AD pathology was strengthened by the recent finding that the genes associated with mental retardation are linked to the X chromosome (Ramakers, 2002). These studies identified a clustering of proteins in the postsynaptic pathways modulating spine actin assembly and disassembly and spine morphogenesis (Kichina *et al*., 2010). Most important are p21-activated kinases (PAKs), which represent a downstream signaling effector of the Rho/Rac family of small GTPases (Kichina *et al*., 2010). PAKs have been shown to be involved in multiple signal transduction pathways in mammalian cells (Maruta, 2014). For instance, PAK1 has been shown to be decreased in the hippocampus from postmortem AD brain, accompanied by relocalization of activated PAKs to the membrano-cytoskeletal fractions (Zhao *et al*., 2006). A recent study showed that a dominant-negative form of PAK1 sensitizes, while the wild-type form ameliorated toxicity induced by cytotoxic Aβ oligomers in cultured primary neurons (Zhao *et al*., 2006). Dominant-negative PAK1 has been shown to antagonize other PAK isoforms, following expression in mouse forebrain-affected synapse morphology and consolidation of long-term memory (Hayashi *et al*., 2004).

In respect to this, much attention has been paid to antioxidants as a therapeutic strategy for the treatment of AD (Choi *et al*., 2012; Feng and Wang, 2012; Galasko *et al*., 2012; Mecocci and Polidori, 2012). Plants and plant products are rich sources of natural polyphenolic antioxidants such as flavonoids, which can scavenge free radicals while demonstrating potent antiinflammatory properties and low adverse effects (Nabavi *et al*., 2012b; Nabavi *et al*., 2013b; Nabavi *et al*., 2014; Nabavi *et al*., 2015c). At present, there are numerous scientific evidences regarding the beneficial effects of natural products in human diseases (Nabavi *et al*., 2012a; Nabavi *et al*., 2013a; Nabavi *et al*., 2015a; Nabavi *et al*., 2015b; Nabavi *et al*., 2015d). *Rhodiola rosea* L. is an important plant species from the genus *Rhodiola*. It is most abundant in Eastern Europe and Asia where it is used as a traditional medicine for a variety of different ailments (Brown *et al*., 2002; Panossian *et al*., 2010). The aim of this paper is to critically review the scientific evidence regarding the beneficial effects of *R. rosea* in AD and lay foundation for its future research.

RHODIOLA ROSEA L.

Rhodiola rosea L. (roseroot, golden root, or Arctic root) is a genus of herbaceous perennial plants that belongs to the family Crassulaceae (Rohloff, 2002; Ming *et al*., 2005). *Rhodiola* species grow wild in high-altitude areas as well as other cold parts of continental Asia, Europe, and America (Brown *et al*., 2002; De Bock *et al*., 2004). In continental Asia, the genus *Rhodiola* is abundant in the Altai Mountains located between Mongolia and Siberia regions (Furmanowa *et al*., 1995; Galambosi, 2006). In the continental Europe, it is widely distributed in Iceland and the British Isles between Scandinavia and several mountains such as Pyrenees, Alps, Carpathian as well as other mountains in the Balkan area (Brown *et al*., 2002; Wiedenfeld *et al*., 2007; Panossian *et al*., 2010). In addition, some varieties of *Rhodiola* have been found in different high-altitude regions of Alaska, Canada as well as other mountains of the North American continent (Brown *et al*., 2002). It is an herbaceous perennial flowering member of the genus *Rhodiola* that has a wide range of medicinal effects in the traditional

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medicine. It is widely distributed in the Arctic and mountainous area of the Europe and Asia and traditionally used for treatment of human diseases especially mental diseases (Adaptogen, 2001; Brown *et al*., 2002). In addition to *R. rosea*, there are over 200 species from the genus *Rhodiola* (Platikanov and Evstatieva, 2008) of which at least 20 species (such as *Rhodiola alterna* S.H. Fu, *Rhodiola brevipetiolata* (Fröd.) S.H. Fu, *Rhodiola crenulata* (Hook.f. & Thomson) H.Ohba, *Rhodiola kirilowii* (Regel) Maxim., *Rhodiola quadrifida* (Pall.) Fisch. & C.A.Mey, *Rhodiola sachalinensis* Boriss., *and Rhodiola sacra* (*Prain ex Raym.-Hamet*) S.H. Fu) are known to have different medicinal effects in traditional medicine (Adaptogen, 2001; Brown *et al*., 2002; Goldstein *et al*., 2008; Li *et al*., 2009).

RHODIOLA ROSEA L. CULTIVATION

Up till now, cultivation experiments have been performed in Russia, Sweden, Poland, Finland, and Germany (Galambosi, 2006; Platikanov and Evstatieva, 2008; Galambosi *et al*., 2009; Kylin, 2010; Adamczak *et al*., 2014) that show that *R. rosea* can be successfully cultivated in cool and moist climates with precipitation (Galambosi, 2006; Platikanov and Evstatieva, 2008; Galambosi *et al*., 2009; Kylin, 2010; Adamczak *et al*., 2014). However, it does not prefer shaded areas (Kucinskaite *et al*., 2006). It is well grown in deep soil in which it can easily penetrate (Galambosi, 2006). Moreover, *R. rosea* prefers moderately rich and well-drained slightly acidic soils (pH 6–7) (Galambosi, 2006; Platikanov and Evstatieva, 2008). It can also grow in sandy loam soils and even rocks (Alm, 2004; Galambosi, 2006). There are negligible reports regarding the beneficial effects of fertilizers for the cultivation of *Rhodiola* (Galambosi, 2006; Platikanov and Evstatieva, 2008; Galambosi *et al*., 2009; Kylin, 2010; Adamczak *et al*., 2014). However, it has been reported that the root size of *Rhodiola* in weak soils is significantly lower than that occurring in the cultivation that is because of insufficient nutrients required for *Rhodiola* (Galambosi, 2006; Platikanov and Evstatieva, 2008; Galambosi *et al*., 2009; Kylin, 2010; Adamczak *et al*., 2014). It has also been reported that *R. rosea* can be propagated by seedlings, root division as well as seed germination (Furmanowa *et al*., 1995; Galambosi, 2006). The propagation of seedlings is the most effective method for larger scale cultivation of *R. rosea* (Galambosi, 2006; Platikanov and Evstatieva, 2008).

PHYTOCHEMISTRY OF *RHODIOLA ROSEA* L.

Rhodiola rosea has a rich variety of phytochemical content including cinnamoyl glycosides (phenylethanoids), flavonoids, phenylpropanoids, essential oil (monoterpenes), phenolic acids, cyanogenic glucosides as well as polysaccharides and oligomeric proanthocyanidins (Zhou *et al*., 2014) (Fig. 1). Flavonoids appear to be the main constituents in *R. rosea* as mainly, i.e. herbacetin, gossypetin, and kaempferol derivatives. Early studies originating from the 1980s indicated that the plant contains a number of flavonoids such as tricin (4′,5,7-trihydroxy-3′,5′-dimethoxyflavone) and its 7- and 5-O glucosides, herbacetin (3,4′,5,7,8-pentahydroxyflavone), and its derivatives; rhodionin (herbacetin 7-O-α-rhamnopyranoside), rhodiosin (herbacetin 7-O-3″-O-β-D-glucopyranosyl-α-L-rhamnopyranoside), rhodiolin (a flavonolignan), rhodionidin (herbacetin-7-*O*-α-L-rhamnopyranose-8-*O*-β-D-glucopyranoside), rhodiolgin (gossypetin-7-*O*-α-L-rhamnopyranoside), rhodiolgidin (go ssypetin-7-*O*-α-L-rhamnopyranose-8-*O*-β-D-glucopyranoside), rhodalin (herbacetin-8-*O*-β-D-xylopyranoside), rho dalidin (herbacetin-8-O-β-D-xylopyranose-3-*O*-β-D-gluco pyranoside), the flavonoid glycosides; gossypetin-7-O-L-rhamnopyranoside and rhodioflavonoside, rhodioflavo noside, kaempferol-3-O-β-d-glucopyranosyl-7-O-α-l-rhamn-opyranoside, kaempferol 3-O-β-d-glucopyrano side-(2→1)-β-d-xylopyranoside 3, and herbacetin-8-O-

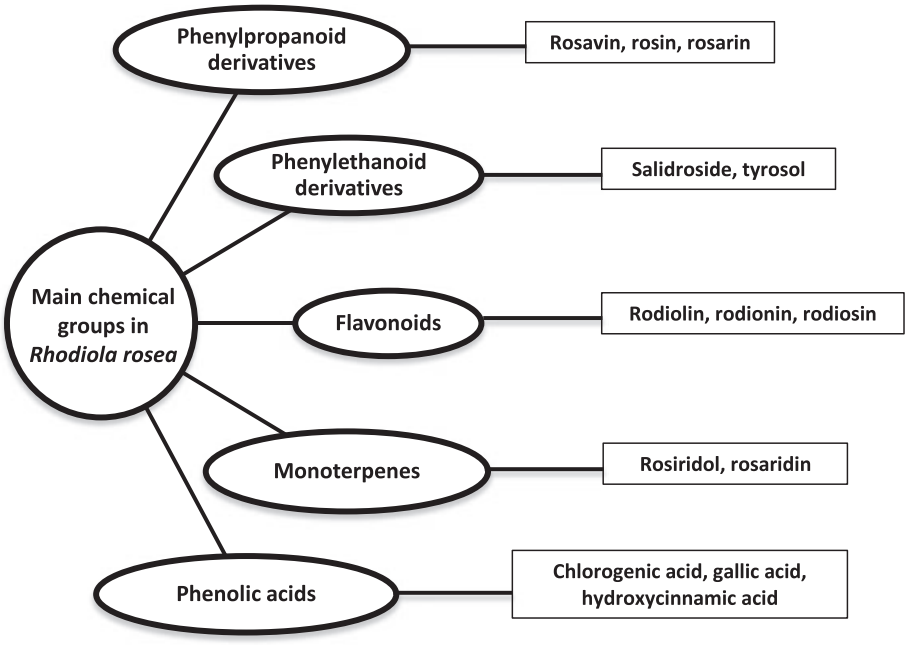


Figure 1. Main chemical classes present in *Rhodiola rosea* L.

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β-d-glucopyranoside. In addition, Tolonen and Uusitalo (Tolonen and Uusitalo, 2004) detected several flavonoid derivatives in the flowers of *R. rosea* identified as rhodiolgidin, rhodiolgin, rhodionin as well as some unidentified flavonol-glucoside mixtures using a fast and simple LC-MS method. Isolation of the common flavonoid derivatives apigenin, luteolin, kaempferol, quercetin, cosmosiin, astragalin, linocinamarin, rutin, and nicotiflorin was reported by Jeong *et al.* (Jeong *et al.*, 2009) as well as kaempferol-7-O-alpha-L-rhamnopyranoside, herbacetin-7-O-alpha-L-rhamnopyr-anoside, herbace-tin-7-0-(3″-O-beta-D-glucopyran-oside)-alpha-L-rhamnopyranoside, and 5,7,3′, 5′-tetrahydroxy-flavanone.

Phenylpropanoids and cinnamyl alcohol glycosides (or phenyl ethanoids) constitute a large quantity in *R. rosea*. Thesalidroside (rhodioloside) [β-D-glucopyranoside of β-(p-hydroxyphenyl)ethanol] (Fig. 2) is the first cinnamyl glycoside reportedly isolated from this species in 1967 (Troshchenko and Kutikova, 1967). Kurkin *et al.* (Kurkin *et al.*, 1991) successfully isolated 11 phenylpropanoid and cinnamyl glycosidic compounds from the callus culture of the plant, some of which were identified as *p*-coumaric acid 4′-glucoside and 1-glucoside, caffeic acid 3′-glucoside, triandrin, lariciresinol 4-glucoside, vimalin, rosarin, and rosin (Fig. 2). Later, cinnamyl-(6′-O-β-xylopyranosyl)-O-β-glucopyranoside and 4-methoxy-cinnamyl-(6′-O-α-arabino pyranosyl-O-β-glucopyranoside were obtained from *R. rosea* as new phenylpropanoid derivatives, in addition to picein and benzyl-O-beta-glucopyranoside (Tolonen *et al.*, 2003). Rosarin, rosin, and rosavin were also quantified in the roots of the plant using high-performance thin layer chromatography and reverse-phase HPLC methods (Fig. 2). Among these derivatives, salidroside needs a special mention as it possesses many potent biological activities. Although its presence was earlier reported from a number of plant genera such as *Salix* species, *Rhododendron ponticum*, *Comus* sp., *Forsythia* sp., *Strychnos nux-vomica*, *Rehmannia glutinosa*, *Linaria japonica*, *Penstemon acuminatus*, etc., it is most common in *Rhodiola* species and occasionally serves as a chemotaxonomic marker. Salidroside is the main substance in *R. rosea*, which is responsible for many pharmacological activities reported by the plant as well as the reference compound in quality assessment of preparations containing roseroot extracts. *R. rosea* roots also yielded rhodiolosides A–E, identified as five new monoterpene glycosides. Their corresponding chemical structures were elucidated as (2E,6E,4R)-4,8-dihydroxy-3,7-dimethyl-2,6-octadienyl β-D-gluco pyranoside (rhodioloside A), (2E,4R)-4-hydroxy-3,7-dimethyl-2,6-octadienyl α-D-glucopyranosyl(1→6)-β-D-glucopyranoside (rhodioloside B), (2E,4R)-4-hydroxy-3,7-dimethyl-2,6-octadienyl β-D-glucopyranosyl (1→3)-b-D-glucopyranoside (rhodioloside C), (2E,4R)-4,7-dihydroxy-3,7-dimethyl-2-octenyl β-D-glucopyranoside (rhodioloside D), and (2E)-7-hydroxy-3,7-dimethyl-2-octenyl α-L-arabinopyranosyl(1→6)-β-D-glucopyranoside (rhodioloside E) (Ma *et al.*, 2006).

Moreover, a few studies have shown that the plant contains essential oils. For instance, the sample of *R. rosea* was found to contain myrtenol (36.9%), *trans*-pinocarveol (16.1%), geraniol (12.7%), and dihydrocumin alcohol (12.1%) as the major components. In another study, the essential oils obtained from three samples of *R. rosea* from Bulgaria, China, and India were analyzed, and geraniol was determined as the chief compound in Bulgarian and Chinese samples, whereas phenylethyl alcohol was the major oil in the Indian sample. Other chemicals found in *R. rosea* were reported as lotaustralin (a cyanogenic glucoside) (Fig. 2), β-sitosterol, and oligomeric proanthocyanidins composed of (−)-epigallocatechin and its 3-O-gallate esters, polysaccharides, and lignins. Rosiridol, the oxygenated derivative of geraniol, was identified as the aglycon of rosiridin, suggested to be an important bioactive compound for *R. rosea* (Fig. 2) (Van Diermen *et al.*, 2009).

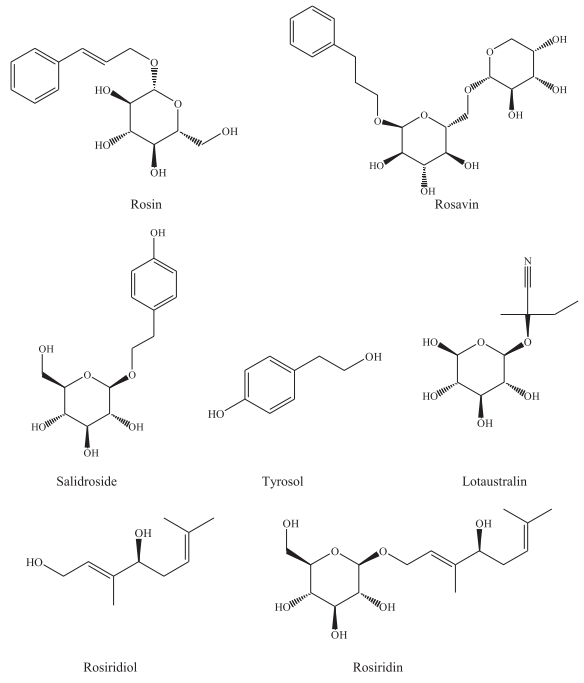


Figure 2. Main compounds found in *Rhodiola rosea* L.

RHODIOLA ROSEA L. IN TRADITIONAL MEDICINE

Rhodiola rosea has been used in traditional medicine from ancient times till current times for the treatment of diarrhea, hysteria, hernias, headaches as well as cognitive dysfunctions. Additionally, it has been widely used as an astringent in traditional herbal medicine. It has also been reported that *Rhodiola* infusion possesses a beneficial effects on mouth pain and kidney stones, swellings, back pain, as well as mood disorders (Panossian *et al.*, 2010; ; Cropley *et al.*, 2015). In addition to these beneficial effects, it has been reported that *Rhodiola* infusion has significant effects on hair growth (Panossian *et al.*, 2010; Zhu *et al.*, 2014). In traditional medicine, its roots are also used for mitigation of different skin diseases (Mamedov *et al.*, 2005). According to Grasnytjar, dried roots of *Rhodiola* have beneficial effects on freckles, scurvy, as well as physical and mental weakness. It has also been reported that *Rhodiola* has a stimulant effect as well as vasoconstrictive and hemostatic activity on hemorrhoids (Sandberg and Bohlin, 1993; Linné, 2005). It has also been reported that *R. rosea* can be used for the treatment of different mental diseases such as schizophrenia. *R. rosea* is currently

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known as an adaptogen for treatment of fatigue and weakness in the traditional herbal medicine (Panossian, 2003; Ishaque *et al*., 2012).

CLINICAL IMPACT OF *RHODIOLA ROSEA* L.

A search in http://clinicaltrial.gov/ with keywords '*Rhodiola rosea*', 'Roseroot' and 'Golden root' (6 October 2014) demonstrated that there are only three clinical trials on the beneficial effects of *R. rosea*. The first clinical trial is aimed at evaluating the beneficial role of *R. rosea* in comparison with placebo on shift work nurses. The second clinical trial evaluates the antidepressant effect of *R. rosea* in comparison with the antidepressant, sertraline, in patients who suffered from major depressive disorder. The last clinical trial examines the beneficial effects of *R. rosea* in comparison with ginseng and placebo in patients who suffered from mild depression. Details of clinical trials on *R. rosea* are presented in Table 1.

TOXICITY OF *RHODIOLA ROSEA* L.

At present, scientific reports regarding the adverse effects of *R. rosea* are negligible (Adaptogen, 2001; Ming *et al*., 2005). However, it has been reported that the median lethal dose (LD_{50}) for *R. rosea* extract is 3360 mg/kg body weight in rat (Khanum *et al*., 2005). Therefore, it can be concluded that equivalent dosage in a 70-kg man is about 235.2 g, which represents a very high amount of extract. The safety of daily consumption of *R. rosea* in humans (at doses 200 to 600 mg per day) remains negligible (Udintsev and Schakhov, 1991). It has also been reported that the consumption of *R. rosea* may be associated with hyperactivity, jittery, and/or agitation (Uyeturk *et al*., 2013). Consumption of *R. rosea* in the first weeks can interfere with sleep and/or induce extra-vivid dreams in consumers (Hartwich, 2010). Additionally, *R. rosea* should not be consumed in patients who suffer from bipolar disorder, because of its potent antidepressant activity that can trigger a manic episode (Gerbarg *et al*., 2014).

NEUROPROTECTIVE EFFECTS OF *RHODIOLA ROSEA* L.

Oxidative stress

Rhodiola rosea is composed of large tuberous roots composed of several active compounds including phenolics, flavonoids, and phenylpropanoids (Devasagayam *et al*., 2004). The oligomeric proanthocyanidin (OPCRR), a kind of phenolics, have demonstrated potent antioxidant activity (Hernández-Santana *et al*., 2014). One study evaluated the effects of OPCRR on the antioxidant enzymes activity and lipid peroxide content *in vivo*. In particular, three biochemical biomarkers were evaluated, including SOD, glutathione peroxidase (GSH-Px), and malondialdehyde (MDA) in serum, heart, liver, and brain tissues in mice. The data showed that OPCRR significantly increased SOD and GSH-Px activities, while reducing the MDA content in mice (Zhou *et al*., 2014). The data suggests indicated that OPCRR is a potent natural antioxidant because of its considerable antioxidant activities both *in vitro* and *in vivo*.

Neuroinflammation

The activation of microglia is a major feature in the pathogenesis of AD (McGeer and McGeer, 1999). Several studies have demonstrated that activated microglia can produce significant quantities of inflammatory mediators capable of releasing large amounts of ROS, nitric oxide (NO), and proinflammatory cytokines such as TNF-α, interleukin-1β (IL-1β), and interleukin-6 (IL-6), culminating in neuronal cell death (Gonzalez-Scarano and Baltuch, 1999). Therefore, drugs with antiinflammatory properties represent a promising therapeutic strategy for the treatment of AD. NO is the main mediator of neuroinflammation. Lee *et al.* (2013) investigated the neuroprotective effect of *R. rosea* constituents on the NO production after the activation of murine microglial BV2 cells by lipopolysaccharides. The study showed that the *R. rosea* constituents, rosarin, and salidroside suppressed the generation of NO in activated microglia in a dose-dependent manner. The expression of inducible nitric oxide synthase (iNOS) was heavily increased by LPS leading to increased production of TNF-α. The study also showed that rosarian and salidroside can inhibit LPS-induced iNOS expression and decreased the production of TNF-α, IL-1β, and IL-6 that are induced by LPS in BV2 microglia cells in a

Table 1. Details of our search in http://clinicaltrial.gov/ with keywords '*Rhodiola rosea*', 'Roseroot' and 'Golden root'

NCT number	Study start	Study type	Condition	Title
NCT01278992	January 2011	Interventional	Fatigue	*Rhodiola rosea* for Mental and Physical Fatigue
NCT01098318	June 2010	Interventional	Depression	*Rhodiola rosea* Therapy of Major Depressive Disorder
NCT01006460	November 2009	Interventional	Depression, stress	A Study With Arctic Root Compared With the Extract When Combined With Schizandra and Russian Root (Adapt 232), Standardized Ginseng Extract and Placebo Regarding Impact on the Level of Energy, Ability to Work Under Stress, Quality of Life and Wellbeing, in Middleaged Women Who Are Still Employed

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dose-dependent manner (Lee *et al.,* 2013). TNF-α, which potentiates damage to neuronal cell, is a costimulator that is thought to be mediated in the regulation of iNOS gene, via the mitogen-activated protein kinase (MAPK) and NF-κB signaling pathway (Gautron *et al.*, 2002). The study further showed that oral administration of *R. rosea* extract significantly decreased iNOS and proinflammatory cytokine expression in the kidney and prefrontal cortex of the brain (Lee *et al.*, 2013). This suggests that *R. rosea* constituents can cross the blood–brain barrier and enter the brain to suppress inflammation in the CNS.

Excitotoxicity

R. rosea constituents have been shown to suppress L-Glu-induced excitotoxicity *in vitro* in primary cortical neurons *in vitro*. More specifically, rosin and salidroside prevented neuronal toxicity following 18-h exposure with L-glu at pathophysiological concentrations as evidenced by the lactate dehydrogenase assay (Lee *et al.*, 2013).

Effect on oncogenic kinase PAK1

Salidroside, one of the major ingredients in *R. rosea*, has been shown to activate 5′ AMP-activated protein kinase (AMPK) (Li *et al.*, 2008). Similarly, *R. rosea* extract (10–25 μg/ml) has been shown to promote life span in *Caenorhabditis elegans* by activating FOXO. This longevity transcription factor can activate the heat shock protein, HSP16. As AMPK is necessary for activation of FOXO, the life extension properties of *R. rosea* extract are most likely attributed to salidroside (Wiegant *et al.*, 2009). Moreover, salidroside has also been shown to attenuate tumor-induced angiogenesis, which is dependent on both PAK1 and AMPK. It is well established that activation AMPK alone cannot ameliorate angiogenesis (Skopińska-Rózewska *et al.*, 2008). Taken together, these studies suggest that salidroside can exert neuroprotection by inhibiting PAK1 and activating AMPK.

Other effects against neurodegeneration

In AD brain, a strong correlation association between neurotoxicity and MAPK activation, has been reported in dystrophic neurons and astroglial cells (Webster *et al.*, 2006). MAPK cascades, which are involved in the apoptotic signal transduction, are induced by neurotoxicity. It is thought that activation of JNK and p38 MAPK is closely associated with cytotoxic insult, whereas the activation of extracellular signal-regulated kinase (ERK) is associated with cell proliferation and acts as an anti-apoptotic signal (Junttila *et al.*, 2008). One study showed that the *R. rosea* constituents, rosarin, and salidroside can inhibit L-glu-induced JNK and p38 MAPK but not ERK phosphorylation (Lee *et al.*, 2013).

CONCLUSION AND RECOMMENDATIONS

In this paper, we critically reviewed the available literatures regarding the neuroprotective effects of the medicinal plant *R. rosea* L., against oxidative stress, neuroinflammation, PAK1, and AD. Taken together, current research using *R. rosea* has been shown to possess both preventive and/or protective effects in AD

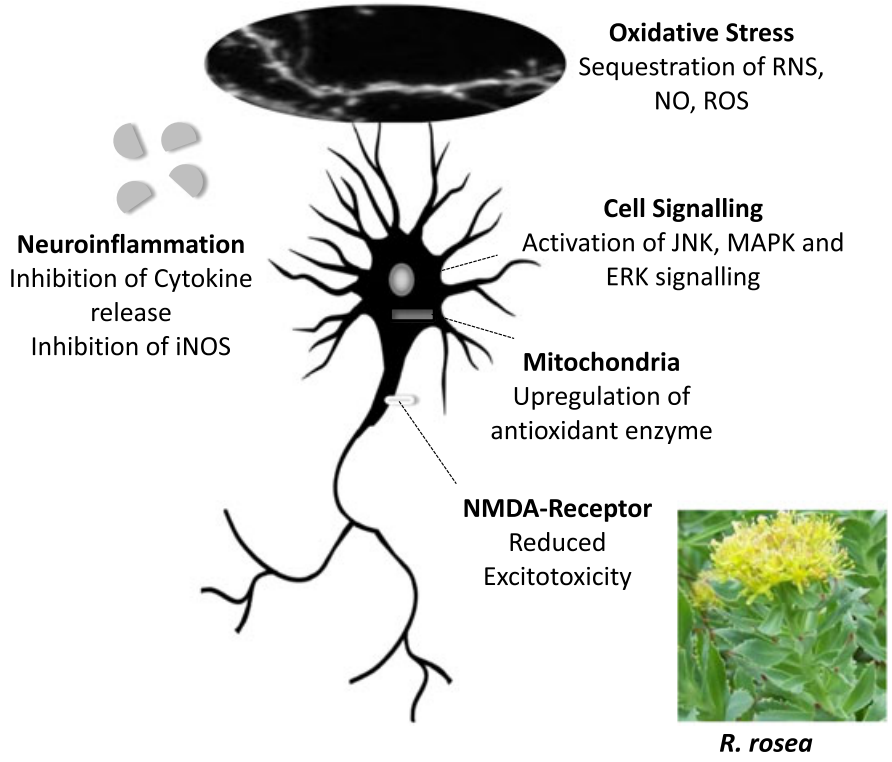


Figure 3. Schematic representation of the neuroprotective effects of *Rhodiola rosea* L. Current research using *R. rosea* has been shown to possess both preventive and/or protective effects in AD through the suppression of oxidative and nitrosative stress, reduction of excitotoxicity, altered intracellular signaling, antiinflammatory effects, and upregulation of endogenous antioxidant enzymes in neuronal tissue.

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through the suppression of oxidative and nitrosative stress in neuronal tissues (Fig. 3). In addition, we showed that *R. rosea* is a non-toxic medicinal plant even at high doses with limited interaction with other drugs. Henceforth, *R. rosea* can be suggested as a potential candidate for future clinical trials aimed at examining the beneficial role of *R. rosea* in AD patients. *R. rosea* can easily be cultivated in some European countries and propagates by seedling propagation. However, there are few clinical trials on the beneficial role of *R. rosea* in humans, and therefore, it can be difficult to make a clear decision about its most effective clinical doses. Respect to negligible adverse effects of *R. rosea*, it can be recommended that future studies should aim to (1) ascertain the best method for large-scale cultivation of *R. rosea*, (2) elucidate the exact molecular mechanisms of neuroprotective effects of *R. rosea*, (3) identify the neuroprotective constituents of *R. rosea* using new phytochemical analysis techniques, (4) ascertain the most effective clinical doses of *R. rosea*, and (5) examine the neuroprotective activities of *R. rosea* through clinical studies.

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None.

Conflict of Interest

The authors disclose no conflict of interest.

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