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# 11

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## *Impact of Rhodiola rosea on Skin*

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Mahtab Jafari

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### ***Rhodiola rosea***

*Rhodiola rosea* (*R. rosea*) belongs to the plant family of *Crassulaceae* and grows primarily in high altitudes in the mountainous arctic areas of Tibet, Russia, China, and India. In addition to *R. rosea*, 200 other species of *Rhodiola* have been identified, and 20 of them are currently used in traditional medical systems to combat a number of physical and mental disorders such as depression, anxiety, and fatigue.<sup>1</sup> In 1775, *R. rosea* was listed in the first Swedish pharmacopeia with all its medicinal properties<sup>2</sup> and it has been the most studied *Rhodiola* species in Russia, China, Scandinavia,<sup>3</sup> and more recently in the United States. In 1948, two Russian scientists evaluated the chemical composition and biological activities of a number of herbs, including *R. rosea*. They discovered that some herbs protected against a variety of biological, environmental, and psychological stressors. Based on their work, the term “adaptogen” was coined and *R. rosea* was considered a potent adaptogenic herb.<sup>4</sup>

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### **Phytochemistry of *R. rosea***

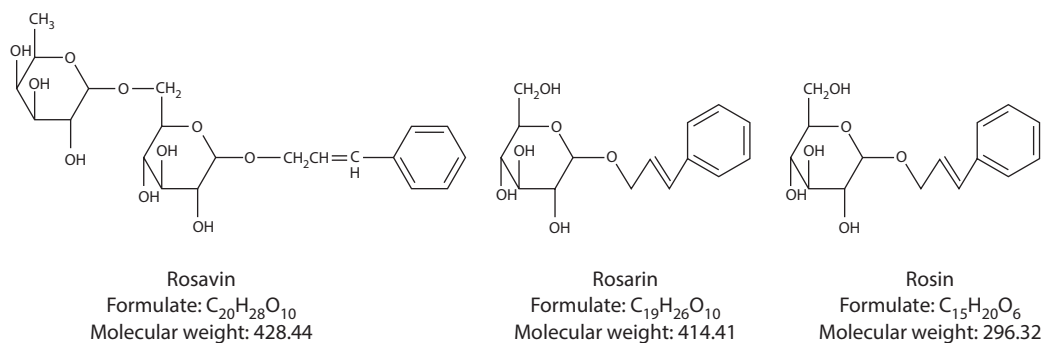
Phytochemical evaluation of *R. rosea* root reveals the presence of as many as 140 compounds.<sup>5</sup> Many of these compounds are also found in other *R. rosea* species, but the presence of three phenylpropanoids (rosavin, rosin, and rosarin) is unique to *R. rosea*<sup>6</sup> (Figure 11.1). *Rhodiola rosea* extracts that have been used in animal and clinical studies are usually standardized to a minimum of 3% phenylpropanoids (rosavin, rosin, and rosarin) and 1% of the phenyl ethanol derivatives (salidroside and tyrosol).<sup>7</sup>

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### **Health Benefits of *R. rosea***

An impressive but still limited body of literature supports the health benefits of *R. rosea* without any reported serious adverse effects. As early as the 1940s, Russian government scientists observed that the plant boosted the body’s response to stress. They also observed that unlike amphetamines and stimulant substances, *R. rosea* was not addictive and it did not result in a “crash” or a rebound period of profound fatigue.<sup>8</sup> In recently published studies, *R. rosea* resulted in significant improvement in stress induced physical and mental fatigue in medical students under examination, night duty physicians, and military cadets.<sup>9,10</sup> Based on observational and prospective clinical studies, the plant appears promising in improving mental and physical performance in stressful conditions. Because of these published studies, *R. rosea* has become a popular dietary supplement. Today, many people consume *R. rosea* in an attempt to improve physical and mental performances. Early Soviet studies on *R. rosea* are summarized in the National Pharmacopeia of the USSR in a chapter titled “*R. rosea* Rhizome and Roots.”<sup>11</sup>

Mechanistically, the plant is purported to work centrally and peripherally on monoamine and opioid synthesis, transport, and receptor activity.<sup>12,13</sup> In doses ranging from 150 mg to 300 mg, *R. rosea* has been found to stimulate the release of dopamine (DA), and serotonin (5-HT).<sup>1</sup> Over seven decades of research, *R. rosea* has passed extensive toxicological studies and is considered a safe plant for human use.<sup>14</sup>



**FIGURE 11.1** Chemical structures of rosavin, rosin, and rosarin.

In spite of a number of reported clinical benefits with *R. rosea* as an anti-oxidative, anti-cancer, anti-viral, anti-stress, anti-anxiety, and anti-depressive agent, many of these studies lack solid research methodologies and reproducibility.

### ***Rhodiola rosea* as an Anti-Aging Botanical Extract**

According to a number of reports, alcoholic and aqueous extracts of *Rhodiola* species have significant free radical scavenging activities. These activities are often attributed to the existence of a variety of antioxidant compounds such as p-tyrosol, organic acids (gallic acid, caffeic acid, and chlorogenic acid), and flavonoids (catechins and pro-anthocyanidins) in *Rhodiola* species.<sup>15,16</sup> In a study that examined the active oxygen scavenging activity of traditional nourishing tonic herbal medicines, it was reported that 19 isolated compounds in a *Rhodiola* species, *R. sacra*, had scavenging activities against superoxide anion and hydroxyl radicals.<sup>17</sup> In another study, *R. rosea* lowered mitochondrial superoxide levels and afforded elevated protection against the superoxide generator paraquat in fruit flies.<sup>18</sup> The anti-aging and lifespan extension properties of *R. rosea* appears to be conserved in model species such as yeasts, worms, and flies.<sup>18–21</sup> These observations suggest that *R. rosea* may be a viable treatment to slow aging and abrogate age-related diseases in a range of species, potentially including humans.

### **The Impact of *R. rosea* on Cultured Skin Cells**

The skin is continuously subjected to environmental oxidative stresses such as UVA/UVB, abrasive liquids, radiation, and air pollution, among others.<sup>22</sup> This creates an abundance of free radicals, which damage DNA and other macromolecules, disrupt the normal cell cycle, and can lead to chronic skin diseases such as psoriasis and skin cancer.<sup>23</sup> Preventive measures such as sunscreen and protective clothing are readily available, yet skin cancer is still the most common cancer in the United States (Centers for Disease Control [CDC]). While studies of *R. rosea* for skin application are limited, the extract appears as a potential antioxidant, which may prove useful in restoring normative cellular function to skin cells.

Keratinocytes comprise most of the epidermis—the outermost layer of the skin—and contain an anti-oxidant system for protection. This inherent shielding capacity includes the enzymes catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx), which protect and regulate glutathione (GSH) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH). When exposed to oxidative compounds *in vitro*, human keratinocytes that were pre-incubated with *R. rosea* extract exhibited higher SOD and CAT activity, but after cells were stressed, only GSH was protected, not GAPDH.<sup>24</sup> The efficacy of *R. rosea* varies with the type of oxidative insult, preserving cell membrane integrity for 24 hours in some cases.<sup>24</sup> Keratinocytes undergoing radiation or extreme temperatures as a method of creating oxidative damage had increased cell viability when pre-incubated with *R. rosea*<sup>25</sup> or salidroside.<sup>26</sup> Use of *R. rosea* after UV exposure also appeared to mediate the inflammatory and immune response,

normalizing multiple neuropeptides and cytokines that responded in a dose-dependent manner.<sup>27</sup> The skin is also comprised of adipocytes and nerve cells, both of which exhibited elevated oxygen respiration when *R. rosea* was used.<sup>25</sup> This observed metabolic increase suggests improved health and capability of nerve cells to signal, as well as the breakdown of triglycerides to glycerol.<sup>25</sup>

The mechanism of action of *R. rosea* when it comes to antioxidant activity and cell survival is not yet established. The protective effects of *R. rosea* are not only limited to skin cells. In a recent study, it was reported that *R. rosea* protected two other cell lines *in vitro* as well. Surprisingly, in this study, the upregulation of major antioxidant defenses (SOD, CAT, GPx) was not reported as the main cause.<sup>28</sup>

*Rhodiola rosea* has also been tested as an immunomodulator compound to ameliorate sensitive skin.<sup>27</sup> Keratinocytes that were exposed to ultraviolet radiation were incubated with various doses of *R. rosea*/L-carnosine-associated compound (RCAC) for 48 hours. A dose-dependent return of the pro-inflammatory and immunosuppressive cytokines, interleukin 1 alpha, interleukin-10, and tumor necrosis factor alpha to baseline levels was observed. *Rhodiola rosea*/L-carnosine-associated compound (RCAC) also resulted in the reduction of neurotransmitters involved in inflammatory response, calcitonin-related peptide (CGRP), substance P and also an increase in POMC (an antagonist to proinflammatory cytokines). These observations were also validated in a randomized placebo controlled clinical study by the same authors in the same publication using an RCAC serum. The RCAC serum group reported increased skin comfort and a reduced dryness sensation. These observations suggest that RCAC may be beneficial in the treatment of sensitive skin disorders.<sup>27</sup>

The impact of *Rhodiola* species and their putative active compounds has also been tested on skin pigmentation disorders with non-conclusive results.<sup>29</sup> Tyrosinase is considered a major enzyme in skin pigmentation disorders in the elderly. In a recent study, using guinea pig skin, salidroside, a major putative active compound in *R. rosea*, was tested as an inhibitor of melanogenesis and tyrosinase activity of skin cells. UV radiation was used to induce and upregulate tyrosinase activity and melanosomes, two factors that contribute to the formation of irregular pigmentation in skin tissue. Topical application of salidroside did appear effective in melanin synthesis inhibition compared to the control group, with similar efficacy to other melanin suppressing compounds such as arbutin and peonol. This study suggests testing topical salidroside in pigmentation disorders and for skin lightening after prolonged UV exposure, but further clinical studies must be completed to validate these results.<sup>29</sup> In another study, the inhibitory effects of a number of *Rhodiola* species and their putative active compounds were tested on tyrosinase activation. The oligomeric proanthocyanidins (OPCs) commonly found in *Rhodiola* species resulted in anti-tyrosinase activity but salidroside did not show any inhibitory effects on tyrosinase activity.<sup>30</sup> Since these studies had conflicting results, the impact of *R. rosea* on skin pigmentation disorders needs to be evaluated in future clinical studies.

Although there are only a few published studies on the protective effects of *R. rosea* on skin, this botanical extract appears to be promising as a protective skin therapy. Future clinical studies are needed to validate and confirm the findings of the *in vitro* studies.

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## ***Rhodiola rosea* and Potential Skin Applications**

*Rhodiola rosea* creams and lotions are available from a variety of manufacturers, many of which advertise their products as wrinkle reducing skin care products. While these claims may be based on small human clinical trials, *R. rosea* is among many ingredients used in these skin products and the observed benefits cannot be solely attributed to *R. rosea*.

Skin-related research that does isolate *R. rosea* directly relating to topical use is limited to few *in vivo* animal and human studies concerning ectopic tumors, wound healing, and skin sensitivity.

Cutaneous angiogenesis from grafted syngeneic tumors on Balb/c mice was significantly reduced by oral administration of *R. rosea* extract. This followed a dose response curve (50–400 µg), with higher concentrations yielding greater inhibition of blood vessel differentiation.<sup>31</sup> Similar results were obtained in a parallel study utilizing human kidney cancer tissue grafts instead of the syngeneic tumors.<sup>31</sup> The mechanism in which *R. rosea* inhibits angiogenesis is unclear, but there appears to be a definitive correlation between ingesting *R. rosea* and controlling malignant cutaneous angiogenesis.

Accelerated wound healing was reported in a pilot study utilizing another species of *Rhodiola*, *R. imbricata*.<sup>32</sup> Rats were subjected to dermal wounds and were treated with topical *R. imbricata* extract or a providone-iodine ointment as a control. The treatment group wound sites contracted faster, and contained elevated levels of DNA and collagen precursors.<sup>32</sup> A higher level of this ubiquitous structural protein is critical to dermal repair as well as restoration of skin elasticity. Since *R. imbricata* upregulated multiple cytokines and overall cell immunity,<sup>33</sup> it was purported that *R. imbricata* had immunomodulation properties, which expedited wound healing.

*R. rosea* was also utilized along with the lactic acid stinging test in which volunteers reported increased skin comfort and reduced dryness sensation after application of *R. rosea*/L-carnosine-associated compound (RCAC) for 28 days, when compared to a placebo group.<sup>27</sup> A smaller but significant subgroup of the test also measured for water loss from the skin, which was decreased after 28 and 56 days.

Cosmetic manufacturers have reported positive impacts of topical *R. rosea*, but since their products are composed of a number of active ingredients, the benefits cannot be attributed to *R. rosea* only.

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## Conclusion

A limited yet promising body of literature suggests that *R. rosea* may be used to prevent and manage skin aging, malignant cutaneous angiogenesis, wound healing, and skin sensitivity. Since the majority of the benefits are observed in *in vitro* and animal studies, controlled clinical studies are needed to validate the use of *R. rosea* in topical products to protect human skin.

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