Rhodiola: an ordinary plant or a promising future therapy for pulmonary hypertension? a brief review

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Abstract: Pulmonary hypertension (PH) is a chronic, complex, and progressive disease that eventuates in fatality. Research efforts over the past decades have resulted in therapeutic options that improve quality of life and prolong survival of patients, but they do not offer a cure. We propose a philosophical model that a disturbed balance of yin and yang results in pulmonary vascular remodeling, the hallmark of PH pathology. The model may be useful in exploring the wisdom of traditional Chinese medicine and incorporating it into mainstream PH research. In this context, the medicinal plant *Rhodiola* can be of profound interest owing to its variety of health-friendly attributes. *Rhodiola* has been shown to be beneficial in high-altitude-related symptoms and acute exacerbation of PH; moreover, improvement of PH has been demonstrated experimentally in chronically hypoxic rats. The beneficial effects of *Rhodiola* in PH may be attributable to its potential targeting of the signaling pathways, such as endothelin-1, nitric oxide, vascular endothelial growth factor, angiotensin-converting enzyme, nuclear factor κ-B, tumor necrosis factor α, and interleukin-6. Alterations in these mediators are implicated in PH pathogenesis, the characteristics of which include chronic pulmonary vasoconstriction, vasoproliferation, and vascular inflammation. Salidroside, one of the compounds extracted from *Rhodiola*, has been found to provide therapeutic benefits in experimental PH. As the data are limited and the field is in its infancy, further studies including in-depth analysis of the therapeutic effects on various animal models of PH are desirable. We believe that future PH research should place an adequate and special emphasis on exploring and promoting the potential of traditional Chinese medicine, and to this end, the medicinal plant *Rhodiola* offers a promising field on which to embark.

Keywords: *Rhodiola*, pulmonary hypertension, pulmonary vascular remodeling, Chinese medicine, salidroside.

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INTRODUCTION

Pulmonary hypertension (PH), a complex and heterogeneous group of diseases, represents a severe and life-threatening medical condition that in all of its clinical forms affects around 100 million people across the world.[1,2] Although initial pathological events might differ between various PH groups, the molecular mechanisms, the progression of the disease, and different clinical manifestations are often shared.[3] PH is characterized by a sustained increase of pulmonary artery pressure giving rise to an increased workload to the right ventricle, culminating in right heart failure and an inevitable outcome of death. The intense scientific studies on PH, especially during the past decade, have resulted in considerable in-depth understanding of the pathomechanisms and discoveries of potential therapeutics, such as phosphodiesterase-5 inhibitor, prostacyclin analogues, and endothelin-receptor antagonists.[1,4] Despite the fact that these therapeutic approaches improved the quality of life and prolonged survival of the patients, novel clinical options and strategies to achieve the ultimate goal of PH as a curable disease are still in front of us.[4,5] Recent years have witnessed an emergence of new therapeutic approaches, and others are expected in the years ahead, suggesting that the field of PH research has been receiving considerable focus. Nevertheless, there should be no incertitude that the search for new targets and drugs should adopt a comprehensive approach by keeping the doors to all alternative lines of research open. We underscore the notion that promotion and further exploration of the medical knowledge possessed by Eastern civilization may serve as one of the potential directions to be pursued, and the field of traditional Chinese medicine may offer a reasonable starting point. It is worth noting that the Chinese herb-derived compounds triptolide, a diterpenoid triepoxide from *Tripterygium wilfordii* Hook F., and ruscogenin, a major steroidal sapogenin from *Radix Ophiopogon japonicus*, have shown therapeutic potential in experimental models of PH.[6-8] This encouraging evidence, although emerging gradually and at a slow pace, substantiates the rationale to explore the potential of Chinese medicine to the benefit of PH patients. In our review, we will discuss the current state of knowledge on the medical plant *Rhodiola* and its therapeutic potential in PH. Before embarking on a discussion of *Rhodiola*, we will try to generate a philosophical concept of pulmonary vascular remodeling as a consequence of the disturbed yin and yang balance.

THE YIN AND YANG CONCEPT AND PH

The general philosophy of traditional Chinese medicine can be seen through the prism of the concept of the yin and the yang.[9] The harmonic equilibrium between the yin and the yang, as two opposite forces, maintains a living system in a healthy state.[9] The disease appears when the balance between these two forces is disturbed, and the general aim of the medicine would be to return to the lost equilibrium.[9] The concept of the yin and the yang seems applicable to PH. The PH pathogenesis, which is characterized by sustained pulmonary vasoconstriction and vascular remodeling, is crucially linked to inappropriate regulation/functions of several molecular players. The sustained vasoconstriction occurs as a result of an imbalance between pulmonary vasodilators and vasoconstrictors.[1,10] Moreover, the theory of imbalance between two kinds of forces holds true for pulmonary vascular remodeling, the pathological hallmark of PH.[1] Pulmonary vascular remodeling is characterized by histomorphological changes involving all structural layers of the pulmonary arteries and is manifested as neomuscularization of nonmuscularized vessels and complex vascular features such as neointima formation and plexiform lesions.[10-12] The homeostatic imbalance of proliferation, survival, and apoptosis of vascular cells has been implicated in the process of pulmonary vascular remodeling, and the altered vascular cell phenotype, in turn, is attributable to a disturbed balance among several molecular mediators (e.g., transforming growth factor-β, cytokines and chemokines, different growth factors, bone morphogenetic protein, matrix metalloproteinases, and Notch 3).[1,13-15] When the literature is put together, the model of the yin and the yang seems able to explain the gist of molecular pathogenesis. Therefore, we would like to create a philosophical concept of pulmonary vascular remodeling as a sequel of disturbed balance of the yin and the yang, in order to connect the Chinese wisdom with the conventional

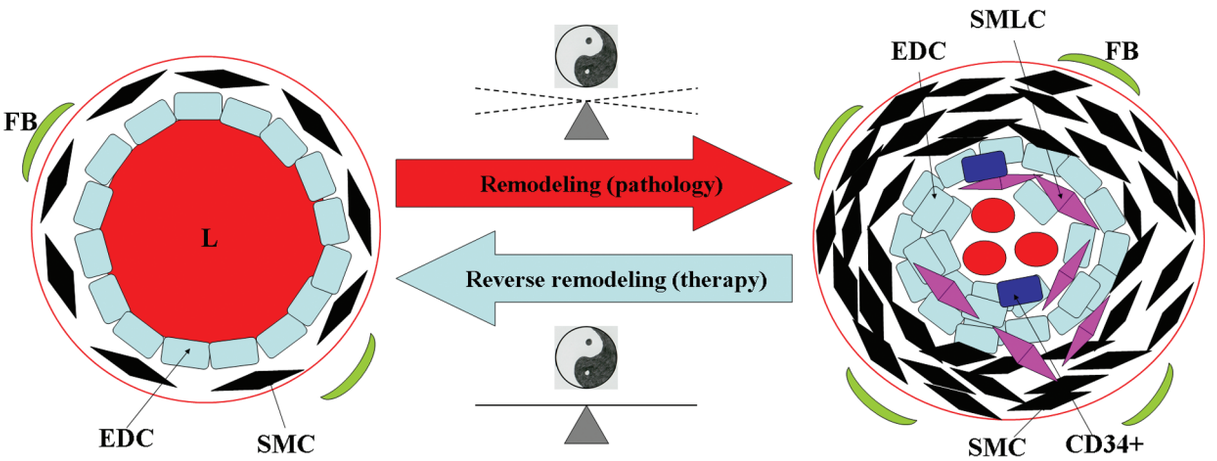

Figure 1. Yin and yang concept and pulmonary vascular remodeling. An imbalance between the yin and the yang will lead to the remodeling process, a hallmark of pulmonary hypertension pathology, and a subsequent shift from a healthy vessel (*left*) to a diseased vessel (*right*). The aim of the medicine is to restore the lost harmony between the yin and the yang and to reverse remodeling, with a consequent return to a healthystate. FB, fibroblast; SMC, smooth muscle cell; EDC, endothelial cell; L, lumen of pulmonary artery; CD34+, CD34+ precursor cell; SMLC, smooth muscle-like cell;[47] ☯, yin-yang symbol.

research and development strategies in the Western world (Fig. 1). An imbalance between the yin and the yang (representing several known and yet-to-be identified molecules/mediators) will lead to a remodeling process and subsequent shift from a "healthy vessel" state to a "diseased vessel" state. A successful therapeutic strategy should therefore aim to restore the lost harmony between these two forces, thereby reversing the structural alteration of pulmonary vasculature to a normal physiological state (Fig. 1). Although one should be cautions to avoid oversimplification, we believe that our proposed model may be useful in exploring the wisdom of traditional Chinese medicine and incorporating it into the mainstream of modern medical science. Traditional Chinese medicine may complement contemporary knowledge and efforts and may offer alternative strategies for unmet medical needs. As already mentioned, we will discuss *Rhodiola*, a medical plant, and its potential therapeutic efficacy for PH.

RHODIOLA SPP.: SIMPLE OR "MAGIC" MEDICAL PLANTS?

A genus of *Rhodiola* covers different species that exist in the mountain regions of China and Siberia (Altai) and Arctic geographic locations in Siberia, Europe, and North America.[9,16,17] The plant species of this genus, particularly *Rhodiola rosea*, have been used for thousands of years in China as part of traditional Chinese medicine for different therapeutic purposes.[9] Interestingly, the plant has also been known to European scholars, prevalently during the eighteenth century.[17] The famous naturalist, a father of the binomial nomenclature, Carl Linnaeus, in his work *Materia Medica* (1749), suggested the use of the *Rhodiola* root for the treatment of different medical conditions.[17] The medicinal values of *Rhodiola* are attributable not only to its beneficial effects, including central nervous system stimulation, antidepression, headache mitigation, cardio- and hepatoprotection, but also to its activities as antioxidant, antifatigue, anticancer, adaptogen, and life span–augmenting agents.[16-18] The whole list of health-friendly attributes of *Rhodiola* is suggestive of "magic" medicine. At the same time, however, several logical questions arise as to what makes this plant therapeutically beneficial for various diseases and conditions. The answer is not yet fully understood, and it requires profound studies in the future. It is noteworthy that several pharmacologically active compounds from the plant extract, such as salidroside/rhodioloside, p-tyrosol, rhodiolin, rosavin, rosarin, rosiridin, rosin, herbacetin glycosides, kaempferol, etc., have been identified.[16,17,19] The list of compounds may be expected to expand, requiring more and more studies that will contribute to unwrapping the secret of the "magic." In the following section we will dis-

cuss *Rhodiola* vis-à-vis potential therapeutic application in PH.

RHODIOLA IN PH: ILLUSIONARY OR PROMISING?

Most of the knowledge and traditional wisdom on medical values of *Rhodiola* are available in the Chinese literature, and very little can be found in modern medical science. This fact inhibits the visibility of the work in the scientific community worldwide and limits the true assessment of *Rhodiola* as a potential therapeutic strategy, particularly for PH. Nevertheless, the available data will be discussed in the context of the known molecular mechanisms of PH so as to evaluate whether the future of *Rhodiola* as a treatment approach for PH is illusionary or promising. Evidently, PH pathogenesis, which is characterized by vasoconstriction and vasoproliferation accompanied by vascular inflammation, is attributable to a disturbed balance of several molecular mediators, such as vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), basic fibroblast growth factor (bFGF), angiotensin-converting enzyme (ACE) and angiotensin II (Ang II), tumor necrosis factor α (TNFα), interleukin-6 (IL-6), nuclear factor κ-B (NF-κB), nitric oxide (NO), and endothelin-1 (ET-1).[1,20-24] It is important to point out that many other pathological culprits play a role in the pathology of PH, in addition to these mentioned here; however, we would like to highlight only those that available literature used in our review suggests as potential targets for *Rhodiola* (Fig. 2).

Bai et al.[25] systematically investigated the effects of the *Rhodiola* herb on development of pulmonary vascular remodeling and VEGF expression in a rat model of high-altitude-induced PH. The authors demonstrated that an increase in mean pulmonary arterial pressure (mPAP) and right ventricular hypertrophy (RVH) in a high-altitude environment was significantly reduced in rats treated with *Rhodiola*.[25] Furthermore, they analyzed the pulmonary vascular remodeling by electron microscopy and found a noticeable attenuation of remodeling in rats treated with *Rhodiola*, in comparison with a placebo group.[25] Additionally, the authors showed that an increase of VEGF expression as a result of high altitude was lower after the application of the plant extract.[25] Finally, Bai et al.[25] concluded that the *Rhodiola* herb has a potential to attenuate high-altitude-induced PH and vascular remodeling and that VEGF inhibition

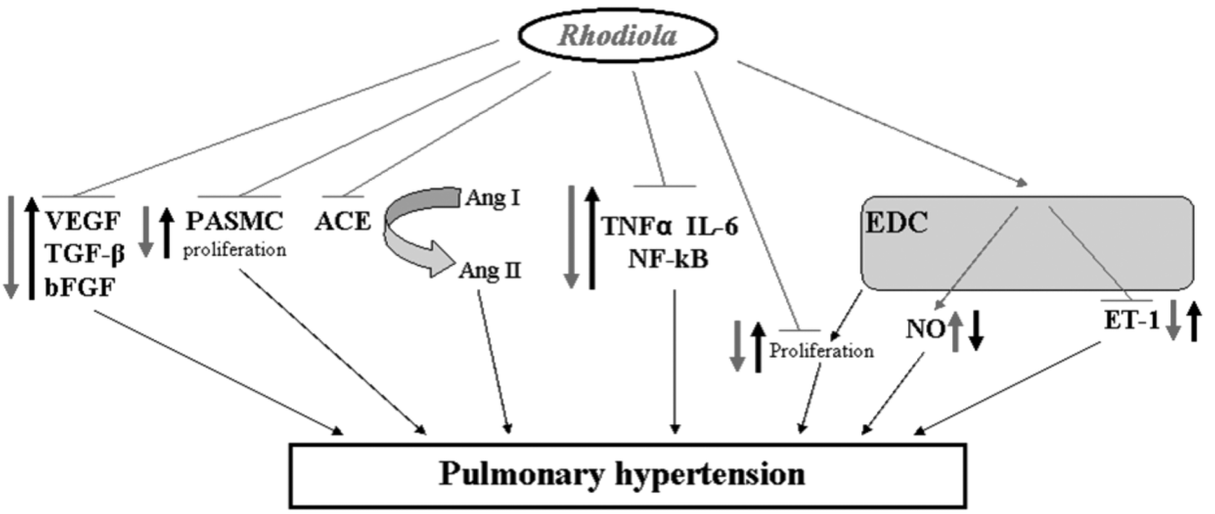

Figure 2. Potential and hypothetical therapeutic targets for *Rhodiola* in pathology of pulmonary hypertension. Some of the signaling pathways/cellular processes identified to be involved in the pathogenesis of pulmonary hypertension are schematically presented. The hypothetical therapeutic application of *Rhodiola* is also shown. Thick black arrows represent the changes that might lead to development of pulmonary hypertension (arrows directed upward denote upregulation; those directed downward indicate downregulation). The thick red arrows indicate the potential effect of *Rhodiola*, with the same interpretation of upward- and downward-oriented arrows. VEGF, vascular endothelial growth factor; ACE, angiotensin-converting enzyme; Ang, angiotensin; TNFα, tumor necrosis factor α; IL, interleukin; NF-κB, nuclear factor κ-B; TGF-β, transforming growth factor β; bFGF, basic fibroblast growth factor; EDC, endothelial cell; PASMC, pulmonary artery smooth muscle cell; NO, nitric oxide; ET, endothelin. A color version of this figure is available online.

might represent one of the mechanisms. Corroborating the findings, Shen et al.[26] showed that *Rhodiola* inhibited the aortic remodeling due to atherosclerosis formation in rabbits, and the effect was associated with the decreased expression of VEGF in atherosclerotic plaque (Fig. 2). *Rhodiola* has also been able to inhibit the TGF-β expression and attenuate high-altitude-induced PH in rats.[27]

Huang et al.[16,28] investigated the effects of salidroside, one of the extracts from *Rhodiola*, on chronic-hypoxia-induced PH in rats. The authors showed that increase in mPAP, RVH, and pulmonary vascular remodeling in chronically hypoxic rats was significantly attenuated by salidroside treatment, suggesting the promising therapeutic potency of this extract for PH.[28] Notably, this extract could inhibit the proliferation of rabbit pulmonary artery smooth muscle cells under hypoxia,[29] suggesting that the reduction of pulmonary vascular remodeling might be due to potential antiproliferative properties of salidroside. Moreover, salidroside might also possess anti-inflammatory properties, as observed by Guan et al.[30] in their study on lipopolysaccharide (LPS)-induced lung injury in mice. They demonstrated that pretreatment with salidroside in LPS-induced acute lung injury (ALI) in mice resulted in reduction of inflammatory cells (such as neutrophils and macrophages) in the bronchoalveolar lavage fluid. Additionally, salidroside successfully inhibited the production of some inflammatory cytokines, such as TNFα and IL-6, and suppressed NF-kB DNA-binding activation,[30] strongly implying the potential use of this compound to interfere with augmented inflammation (Fig. 2). In line with this finding, Zhang et al.[31] suggested the protective effects of *Rhodiola* for patients with ALI/acute respiratory distress syndrome. Furthermore, *Rhodiola* root anti-inflammatory features have been demonstrated in different inflammatory conditions, such as carrageenan-induced paw edema, formaldehyde-induced arthritis, and nystatin-induced paw edema in a rat model.[32] As inflammation is believed to play an important role in PH pathogenesis,[33,34] *Rhodiola* extracts may exert beneficial effects on PH by interfering with the inflammatory process.

In addition to the inflammatory process, oxidative stress has been identified as an important pathological feature in PH patients, and there is corroborating evidence from experimental studies that implicate oxidative stress in PH pathogenesis.[35,36] As mentioned above, herbacetin glycosides and kaempferol are among the compounds isolated from *Rhodiola* that possess antioxidant and anti-inflammatory properties.[19] Moreover, *Rhodiola* extract contains other antioxidant compounds such as p-tyrosol, organic acids (gallic and caffeic acids), and flavonoids (catechins and proanthocyanidins).[16,37,38] Indeed, there is experimental evidence that treatment of spontaneously hypertensive rats (SHR) with *Rhodiola* increased the superoxide dismutase activity.[39] Clearly, the anti-inflammatory and antioxidant attributes of *Rhodiola* can be expected to yield therapeutic benefits in PH.[16,18,19,35-38]

Sui et al.[40] noted that *Rhodiola* inhibited the growth of human endothelial cell line EVC-304. The findings therefore suggest that *Rhodiola* may exhibit an antiproliferative effect on vascular cells, in addition to the aforementioned promising anti-inflammatory activities. Moreover, *Rhodiola* extracts exerted ACE inhibitory activities,[41] and it would be logical to conclude that ACE inhibition will subsequently reduce the production of potent vasoconstrictor Ang II, suggesting the possible vasodilatory effects of the plant. Indeed, the ACE inhibition has been shown to exert beneficial effects by modulating Ang II signaling through the type I receptor in experimental PH.[21] The ACE inhibition resulted in attenuation of pulmonary vascular remodeling as shown by Jeffery and Wanstall;[42] however, the authors observed significant influence on systemic circulation. Additionally, Wang et al.[39] have recently studied the effects of different doses of *Rhodiola* on SHR and reported that the therapeutic benefits may be associated with its NO-releasing and antioxidant activities. Moreover, there is lack of data on the effects of *Rhodiola* on ACE2, the recently discovered homologue of ACE that has a beneficial role in the cardiopulmonary system.[43] Therefore, future studies should meticulously evaluate any effects of *Rhodiola* on systemic circulation, especially focusing on its long-term use. Additionally, the beneficial effects of *Rhodiola* as reported in various disease conditions should be carefully considered and evaluated.

Finally, we would like briefly to discuss 3 clinical studies performed in China on *Rhodiola*.[44-46] Shi

et al.[45] investigated the effects of Chinese herbal preparations, among them a *Rhodiola rosea* capsule, on de-adaptation to high altitude and found the noticeable reduction of high-altitude-related symptoms, such as fatigue, chest tightness, palpitations, vertigo, drowsiness, lack of attention, and memory loss. Yang et al.[46] found that combination treatment with oxygen and *Rhodiola* in patients with chronic cor pulmonale at high-altitude areas effectively inhibited the serum bFGF levels, which was accompanied by markedly decreased mPAP values. Feng et al.[44] studied the effects of *Rhodiola* on pulmonary arterial pressure in patients with chronic cor pulmonale during acute exacerbation in a high-altitude environment and possible mechanisms. The authors successfully demonstrated the significant improvement of hemodynamic and right ventricle hypertrophic parameters in the patients using *Rhodiola*, compared to the patients treated only with a routine approach.[44] Finally, they suggested that these beneficial improvements might be explained mechanistically due to increased release of NO and reduction of ET-1 released from endothelial cells,[44] implying *Rhodiola* as a hypothetical NO stimulator and ET-1 inhibitor. It is worth noting that the NO-releasing effects of the *Rhodiola* genus have been corroborated by subsequent study on SHR.[39] These findings are of high interest and worth future systematic research.

CONCLUSION AND FUTURE PERSPECTIVES

We believe that future PH research should place an adequate and special emphasis on exploring and promoting the potential of traditional Chinese medicine, and to this end, the medicinal plant *Rhodiola* may provide a promising field on which to embark. *Rhodiola* possesses a variety of health-friendly attributes in addition to its beneficial effects on high-altitude-related symptoms and acute exacerbation of PH. On an experimental level, improvement of PH has been demonstrated in chronically hypoxic rats receiving *Rhodiola*. The beneficial effects may be attributable to its potential targeting of the signaling pathways, such as ET-1, NO, VEGF, ACE and Ang II, NF-κB, TNFα, and IL-6. Alterations in these mediators are believed to contribute to the PH pathogenesis. Moreover, salidroside that is derived from *Rhodiola* has been shown to provide therapeutic benefits in experimental PH. Although the previous studies are related to high-altitude/chronic-hypoxia-induced PH, *Rhodiola* may have potential benefits for other PH forms regardless of initiating stimuli or insults. Nevertheless, the field is obviously in its infancy, as also evident from the limited amount of relevant literature. It is therefore highly desirable that more studies in vitro as well as in vivo on various animal models of PH should be performed in order to understand the pharmacodynamics and pharmacokinetics of *Rhodiola* and its derivatives. The data will be valuable to envisage potential clinical studies. *Rhodiola* may be expected to offer a novel alternative therapeutic strategy for chronic illness such as PH, and, importantly, the therapy will be associated with benefits such as a low risk of side effects, wide availability, and lower cost.

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