ABC AHP NCNPR
Botanical Adulterants Program
BOTANICAL ADULTERANTS BULLETIN

Adulteration of Rhodiola (*Rhodiola rosea*) Rhizome and Root and Extracts

By Ezra Bejar, PhD,[a] Roy Upton,[b] and John H. Cardellina II,[c] PhD

[a]*American Botanical Council, PO Box 144345, Austin, TX 78714*
[b]*American Herbal Pharmacopoeia, PO Box 66809, Scotts Valley, CA 95067,*
[c]*ReevesGroup, 1137 Treefern Drive, Virginia Beach, VA 23451*
Corresponding author: email

Keywords: *Rhodiola rosea*, rhodiola, rhodiola root, rhodiola root extract, arctic root, arctic rose, golden root, adulterant, adulteration, substitution, *Rhodiola crenulata,* Crassulaceae

Goal: The goal of this bulletin is to provide timely information and/or updates on issues of adulteration, substitution, potential interchangeable use, and mislabeling of *Rhodiola rosea* rhizome/root, in particular with other species from the genus *Rhodiola*, e.g., *R. crenulata*. The bulletin may serve as guidance for quality control personnel, the international herbal products industry, regulators, and extended natural products community in general. It is also intended to summarize the scientific data and analytical methods on the occurrence of species substitution and/or adulteration, the market situation, and economic and safety consequences for the consumer and the industry.

1. General Information

1.1 Common name for *Rhodiola rosea*: Rhodiola[1]

The American Herbal Products Association's second edition of *Herbs of Commerce*[1] also applies the Standard Common Name "rhodiola" to *R. algida* and *R. kirilowii.* (see section 1.10)

Rhodiola rosea
Photo ©2017 Steven Foster

1.2 Other common names:

English: Arctic rose, king's crown, roseroot, Arctic root, rosewort, snowdown rose[1-4]

Chinese: Hong jing tian (红景天)[1,3,5-8]

Danish: Rosenrod

Dutch: Rozewortel

French: Orpin rose, rhodiole, racine arctique, racine d'or

German: Rosenwurz

Italian: Rhodiola, rodiola, radice d'oro, radice ártica

Japanese: Iwa-benkei (イワベンケ)

Mongolian: Yagaan mugez, altan gagnuur[9]

Norwegian: Rosenrot

Russian: *Rodióla rózovaya* (Родиола розовая), *zolotoy koren* (золотой корень – golden root)

Spanish: Raíz dorada Siberiana, raíz del Ártico, rizoma de Rhodiola

Swedish: Rosenrot

1.3 Accepted Latin binomial: *Rhodiola rosea* L.[10]

1.4 Synonyms: *Sedum rhodiola* DC., *Sedum rosea* (L.) Scop., *Sedum roseum* (L.) Scop.[10]

1.5 Common Names for *Rhodiola crenulata*:

English: Bigflower rhodiola root,[11, 12] Rhodiola crenulata[1]

Chinese: Da hua hong jing tian (大花红景天)

1.6 Botanical family: Crassulaceae

1.7 Distribution: *Rhodiola rosea* is native to boreal areas of Eastern Europe, China, and North America; its range extends from China to Russia, US Northern states, northern Canada, and Alaska. In New England it occurs along the Maine Coast and in southern Vermont. Disjunctive populations extend from the southern Appalachians to North Carolina. Taxonomic lumpers include the genus *Rhodiola* in a broader concept of *Sedum,* though most modern floras follow Linnaeus in segregating *Rhodiola* from *Sedum*. It is important to be aware that some references to *Rhodiola rosea* may treat the species as *Sedum rosea* or *Sedum roseum*. In the Arctic, plants typically occur in crevices or among patches of moss and other vegetation, often near shores.[9,10] The highest plant densities are found on grassy or rocky slopes on the weather side of coasts (in the north) or mountains (in the south). Depending on the latitude, the plants grow at altitudes up from 800–3000 m. In China, *Rhodiola rosea* grows in the northern to central provinces of Xinjiang, Gansu, Shanxi, Hebei, and Jilin.

Rhodiola crenulata (J.D. Hooker & Thomson) H Ohba is native to the high mountains and plateaus close to the Himalayas of China, Bhutan, Nepal, and the Indian province of Sikkim. In China, *R. crenulata* is found in the southwestern provinces of Xizang (Tibet), Qinghai, Sichuan, and Yunnan.[12,13]

1.8 Plant part and form: *Rhodiola rosea* raw material is sold in the United States in bulk, either in the form of dried rhizome, dried rhizome/root, or standardized extracts of dried rhizome or dried rhizome/root. According to the United States Pharmacopeia (USP), the raw plant material consists of the dried roots and rhizomes of *R. rosea* L. containing not less than (NLT) 0.3% of the phenylpropanoid glycosides rosarin, rosavin and rosin (these three compounds are also collectively referred to as 'rosavins') calculated as rosavin, and NLT 0.08% of salidroside, calculated on a dry weight basis.[8] Hydro-alcoholic extracts of *R. rosea* roots and rhizomes should contain NLT 90.0% and not more than (NMT) 110.0% of the labeled amount of the above-mentioned phenylpropanoid glycosides (rosavins), and NLT 90.0% and NMT 110.0% of the labeled amount of salidroside.[7] In Canada, *R. rosea* is sold as the dried root/rhizome, as an extract (standardized to contain 1–6% rosavins, or 0.8–3% salidroside), or as a tincture.[14] *Rhodiola rosea* is sold in the European Union (EU) as dried root/rhizome, an herbal tincture or dry extract, (drug:extract ratio 1.5–5:1, extraction solvent 67–70% ethanol, v/v).[10]

1.9 General use(s): *Rhodiola rosea* has a long history of use as a medicinal plant, appearing in the body of collected knowledge (materia medica) of many European countries[15] and included in several traditional herbal systems in Asia and North America.[5,6,14] Between 1748 and 1961, diverse medicinal applications for *R. rosea* have been reported in the scientific literature of Sweden, Norway, France, Germany, Iceland, and the Soviet Union, principally considered as an adaptogen, or an agent stabilizing physiological processes and promoting homeostasis, with various health-promoting effects.[2,15] In Europe it is considered a traditional herbal medicinal product used for temporary relief of stress symptoms, such as fatigue and sensation of weakness.[5,16] Uses in the EU, Australia, and New Zealand include support of cognitive function, such as mental focus and mental stamina, a source of antioxidants, and a source of immune function-enhancing constituents.[15,16] In North America and Brazil, it is primarily used as an adaptogen, and to improve athletic performance by reducing recovery time after prolonged exercise.[2,14,17-19] In Central Asia, *R. rosea* was used traditionally as a remedy for the prevention and treatment of cold and flu.[2] In Mongolia, *R. rosea* is traditionally used for fever, lung inflammation, and strengthening of the body, as well as a mouthwash for bad breath.[6] Mongolian doctors also prescribe it as a medicine for tuberculosis and cancer.[2]

The genus *Rhodiola* has about 90 species possibly having originated in the mountainous regions of southwest China and the Himalayas. Altogether, over 20 species are used throughout Asia, in some cases interchangeably. Specific uses are given today in traditional Chinese medicine (TCM) to *R. crenulata, R. kirilowii, R. quadrifida, R. sacra,* and *R. yunnanensis*; the last four species have been often used as a substitute and even sold as *R. crenulata* in the Chinese markets.[9] *Rhodiola crenulata* uses include tonification of qi, activation of blood circulation, and unblocking the meridians.[11] Other species also mentioned as being used in TCM include *R. atuntsuensis, R. algida, R. coccinea, R. himalensis,* and *R. subopposita*. In Tibetan medicine, species such as *R. alsia* and *R. chrysanthemifolia* have also been used as a substitute to the more popular *R. crenulata*.[9]

According to Chinese traditional medicine expert Subhuti Dharmananda, PhD of the Institute for Traditional Medicine in Portland, Oregon, the herb entered into some folk applications (local uses, not tied to the theoretical framework of TCM), but it was not an herb commonly recorded in standard Chinese materia medica. *Hong jing tian* is the Chinese denomination given to the root and rhizome of several *Rhodiola* species. It is described as an adaptogenic herb that regulates physiological functions, and is believed to have a central stimulant action. Its general tonic actions are similar to those of ginseng (*Panax ginseng*, Araliaceae) and root and rhizome of *Eleutherococcus senticosus* (Araliaceae). [S. Dharmananda email to Stefan Gafner, May 5, 2017]

1.10 Nomenclature considerations: In the United States, many rhodiola products in the marketplace bear the *R. rosea* binomial in the nutritional/supplement facts panel listing ingredients on the label. Due to this species-specific statement, any mixing, dilution, substitution, or replacement with other *Rhodiola* species will lead to a product's being considered misbranded. Regardless of the law, the interchangeable use of different species within the same genus may create some variations in chemical composition, which could affect quality, safety and efficacy.

The first edition of *Herbs of Commerce* (1992),[20] formerly the basis for standard nomenclature for herbal dietary supplements in the United States and the official document for commercial nomenclature cited in the Code of Federal Regulations (CFR), does not include any *Rhodiola* species. The second edition of *Herbs of Commerce* (2000)[1] includes *R. algida, R. kirilowii,* and *R. rosea* under the standardized common name "rhodiola" — which means these species should be labeled as "rhodiola" — or with the correct scientific name. The roots and rhizomes of these species are also assigned the Chinese pinyin name *hong jing tian. Rhodiola crenulata* is listed separately with the standardized common name of "*Rhodiola crenulata"* and the Chinese pinyin name *da hua hong jing tian*. However, the CFR codification was not updated to include this second edition of *Herbs of Commerce*. In the *Pharmacopoeia of the Peoples' Republic of China* (2010 Edition - Part I), the officially accepted species is *Rhodiola crenulata* and the medicinally used part is the dried root and rhizome. However, the Chinese pharmacopoeia lists *hong jing tian* rather than *da hua hong jing tian* as the common name of *R. crenulata*.

2. Market

2.1 Importance in the trade and market dynamics: The use of *R. rosea* as an ingredient in dietary supplements is quite extensive. According to the market research company SPINS, sales of *R. rosea* in the natural channel in the United States have been stable for four consecutive years from 2013–2016 (Table 1). *Rhodiola rosea* ranked #35 in 2013, and #36 in 2016, with sales in the range of US $2.2–2.5 million in the years 2013–2016. However, in the Mainstream Multi-outlet channel, *R. rosea* ranked #11 in 2013 with $17.7 million in sales, sliding to #28 in 2016 with $10.1 million in sales. The decrease in the Mainstream Multi-outlet channel is thought to be multifactorial.[21]

As noted above, the sales data for 2013–2016 (Table 1) indicate a gradual decrease in sales of *R. rosea*-based products in the United States. Retail pricing for the rhizome

Table 1. Rhodiola Dietary Supplement Sales in the US from 2013–2016

Channel	2013		2014		2015		2016	
	Rank	Sales [US$]	Rank	Sales [US$]	Rank	Sales [US$]	Rank	Sales [US$]
Natural[a]	35	2,214,255	32	2,561,873	35	2,461,235	36	2,588,730
Mainstream Multi-Outlet[b]	11	17,716,775	17	14,188,978	27	10,624,592	28	10,080,448

[a] According to SPINS (SPINS does not track sales from Whole Foods Market.)

[b] According to SPINS/IRI (The Mainstream Multi-Outlet channel was formerly known as the Food, Drug, and Mass Market channel [FDM], exclusive of possible sales at Walmart, a major retailer in the US and beyond.) Sources: Smith T, et al.[22]; T. Smith (American Botanical Council) e-mail to S. Gafner, September 2, 2015 and September 3, 2015. K. Kawa (SPINS) e-mail to S. Gafner, July 11, 2016.

is in the range of US $30–100/kg dried rhizome, according to an informal Internet search conducted in September 2016. However, standardized *R. rosea* extract (3% rosavins/1% salidroside) is sold by suppliers to dietary supplement manufacturers in a price ranging from 80–110 €/kg in the EU and US $70–100/kg, depending on the extract quality. (A. Bily [Naturex] oral communication to E. Bejar, Oct. 5, 2016)

2.2 Supply sources: The largest natural resources for *R. rosea* are in Russia. The major part of the growing range cannot be exploited due to difficulties in access or sparse populations. Most *R. rosea* raw material is collected in China by wildcrafters, whose subsistence depends on selling their fresh produce at regional collection sites. Most of the root plant material is gathered in the summertime from a minimum of four-year-old plants by digging under the plant, removing most of the rhizome/root and (hopefully) leaving a part of the rhizome/root for the plant to regenerate over the next years. *Rhodiola crenulata* is often collected for the Chinese market in some regions in China and Mongolia where both species may share ecological niches. Wildcrafters should be able to distinguish *R. rosea* from *R. crenulata* easily during the collection season, since *R. rosea* has yellow flowers with yellow to reddish buds, while *R. crenulata* flowers are purple.[7]

The Xinjiang region is one of the most prolific producers of *R. rosea* with 4–5 collection sites selling about 500 tons of dry rhizomes annually. The dried roots/rhizomes are cleaned, dried, and sold to one of several East China extract manufacturers; most such extracts are sold abroad. Other regions of China, Mongolia, Kazakhstan, Russia, and North America have a more limited supply of *R. rosea*, and their contribution to the US market is small, except for a few select products. Most Mongolian and Kazakhstani *R. rosea* end up in the Russian market at a higher price. (A. Bily and C. Pierron [Naturex] oral communication to E. Bejar, September 29, 2016).

Projects for cultivation of *R. rosea* exist in Denmark, Germany, Canada, Alaska, Bulgaria, Switzerland, and Norway. Production in the latter two countries is small and limited to supply local and regional markets.

2.3 Raw material forms: Dried rhizome/root is sold in whole or powdered form, or after extraction with alcohol-water mixtures and subsequent spray-drying. The extract may contain suitable added substances as carriers. Various lots of extracts are often mixed to meet standardization requirements of the USP monographs.[7,8]

Because wildcrafters collect exclusively the rhizome (with root material), and leave parts of the root behind with the aerial parts of the plant to regenerate, it is rare to find adulteration of *R. rosea* rhizome with aboveground plant parts. However, suppliers from China sell *R. rosea* aerial plant (herb), flowers, and stems according to their certificates of analysis. The sale of *R. rosea* herb and flower extracts, correctly labeled as such, is not within the scope of this bulletin.

3. Substitution

3.1 Known substitutes and adulterants: The main concern regarding the authenticity and quality of *R. rosea* is the admixture of, or substitution with, rhizome/root material from other *Rhodiola* species. Over 90 *Rhodiola* species have been documented in the world and in China 73 different *Rhodiola* species have been reported, mainly in the northwest and southwest regions, such as Tibet and the Sichuan province.[19] Many *Rhodiola* species have similar pinyin names (*hong jing tian*)[23] and are used interchangeably in China and other parts of Asia, including *R. crenulata R. heterodonta*, *R. kirilowii*, *R. quadrifida*, and *R. semenovii*.[1,15,19] However, *R. crenulata* is the only species formally accepted in the PPRC.[11] Because of the number of imports from Asia, mainly from China, to the United States and to the European herbal supplement industry, *R. rosea* raw materials are often mixed or interchanged with other Asian species, including *R. crenulata,* but also other *Rhodiola* species.[19,23] Adulteration with materials other than those from the *Rhodiola* genus, e.g., with 5-hydroxytryptophan, has been described by Booker et al.,[19] but seems to be infrequent.

Herbal medicine experts have expressed contrasting views about the interchangeable use of *R. rosea* and other *Rhodiola* species in standard-setting documents and reference textbooks. The European Medicines Agency's community herbal monograph specifies the use of *R. rosea* for rhodiola-containing products that are marketed as an herbal drug for temporary relief of symptoms of stress.[4,5] Similarly, the highly regarded German textbook *Wichtl – Teedrogen und Phytopharmaka*[24] indicates that rhizomes from other *Rhodiola* species may appear as adulterants of *R. rosea*. However, the USP *Herbal Medicines Compendium* lists *R. crenulata, R. kirilowii, R. sacra, R. sachalinensis*, and *R. yunnanensis,* as confounding materials for *R. rosea* rhizome.[8] This is a more accurate way to characterize the substitution or admixing of related species within a genus. In the United States, by regulatory definition, replacement by, or admixing with a species that is listed under the same common name in the American Herbal Products Association's *Herbs of Commerce*, 1st edition,[20] is considered substitution, unless the product label notes a particular species in the "active ingredients" section. Hence, products labeled to contain "rhodiola", but not specifying a particular species of *Rhodiola*, may be derived from a number of *Rhodiola* species (see section 1.1).

3.2 Sources of information supporting substitution of rhodiola and frequency of occurrence: With the use of a rapid resolution liquid chromatography (RRLC, a variation of high-performance liquid chromatography [HPLC]) method, Ma et al. found that approximately one-third of the commercial rhodiola rhizome powder extract samples they tested did not show a consistent RRLC profile and lacked the characteristic peaks of rosarin, rosavin, and rosin present in authentic *R. rosea* rhizome.[25] However, absence of rosavins may not always be indicative of adulteration. If not handled properly, rosavins may be subject to enzymatic degradation and thus not be present in a finished product

(Y-C Ma email to Stefan Gafner, May 26, 2017).

Booker et al. analyzed 39 raw materials of products from different vendors in the United Kingdom (UK) labeled as *R. rosea*. Most products were sold without any registration (i.e., generally unlicensed food supplements available on the Internet or from retail outlets), although the researchers included two Traditional Herbal Medicine products registered under the traditional herbal medicine products directive (THMPD).[19] Registration of a product under the THMPD requires the submission of appropriate data supporting the safety of the product (qualitative and quantitative composition, manufacturing process and controls, potential risks to the environment, therapeutic benefits and dosage, contraindications and known adverse reactions, pharmacovigilance data, and packaging information), but does not include the need for preclinical or clinical data. Products were compared to *R. rosea* crude drug reference material and two bulk powders. The samples were analyzed by ^{1}H-NMR (nuclear magnetic resonance) spectroscopy and high-performance thin-layer chromatography (HPTLC). Results from ^{1}H-NMR were evaluated statistically using principal component analysis (PCA). *Rhodiola rosea* products registered under the THMPD were confirmed to contain authentic *R. rosea*, but seven (about 25%) unregistered food supplements labeled as *R. rosea* products were determined to be substituted with various other *Rhodiola* species, and in one instance adulterated with synthetic 5-hydroxytryptophan (5-HTP). The PCA model used to analyze ^{1}H NMR spectroscopy data appeared to discriminate poorly between dietary supplement products containing *R. rosea* extracts and those extracts containing *R. crenulata* or other *Rhodiola* species when using the entire NMR spectrum, likely due to the presence of excipients. Restricting the ^{1}H NMR spectrum to the aromatic region allowed the distinction among *R. rosea* and various other *Rhodiol*a species. The HPTLC method detected both admixed/substituted and adulterated samples effectively.[19]

Several analyses of crude samples of *R. crenulata* rhizome confirmed that the rhizome does not contain rosavin, but does contain salidroside and other *p*-tyrosol derivatives, a class of compounds also found in *R. rosea*.[15,26] Salidroside is associated with increase of exercise tolerance.[27] Another *Rhodiola* species, *R sachalinensis*, was found to contain both rosavin and salidroside, but at lower concentrations than *R. rosea*;[23,29] contrarily, a TLC analysis by Kurkin et al.[28] did not find any rosavins in *R. sachalinensis*.[2] Booker et al. verified the identity of 45 commercial samples (labeled to contain *R. rosea* [N = 11], *R. crenulata* [N = 7], *R. sachalinensis* [N = 4], *R. quadrifida* [N = 3] or *Rhodiola* spp. [N = 20]), collected from retailers, local markets, and the Internet in China and the UK, by HPTLC and ^{1}H NMR with subsequent statistical analysis. An analysis of the 11 samples labeled to contain *R. rosea* indicated that eight (72.7%) contained other *Rhodiola* species, with four samples containing *R. crenulata* and one *R. serrata*.[23,29] Three of the seven purported *R. crenulata* samples were also composed of the incorrect species, containing either *R. serrata* (N = 2) or an unknown material (N = 1).

An unpublished investigation from 2008 by researchers of the University of Ottawa and the Montreal Botanical Garden of the quality of 20 commercial products sold as tablets, capsules, or liquid extracts on the North American market found salidroside (14.4-45.7 mg/g of product) and rosavins (6.1-68.5 mg/g of product) to be present in every sample. The data, obtained using HPLC-UV, suggest that these products contained authentic *R. rosea* rhizome and root (A. Cuerrier [Montreal Botanical Garden] email to S. Gafner, November 8, 2016).

3.3 Accidental vs intentional substitution: Both intentional and accidental *Rhodiola* substitution seems to occur during collection based on anecdotal (A. Bily and C.Pierron [Naturex], oral communication to E. Bejar, September 29, 2016) and scientific evidence.[23,29,30] This has been confirmed in a systematic field collection study, which identified several factors contributing to a substitution of *Rhodiola* species: (1) the lack of genuine raw material, (2) confusion over the (vernacular) Chinese pinyin name of the plant when sourcing from China, and, (3) deliberate substitution during the (collection and) manufacturing of a dietary supplement.[23] In the Altai region, an area in southern Siberia in Russia, there are 24 different species of the genus *Rhodiola* that could be misclassified as *R. rosea* by collectors.[15]

Resource depletion and habitat destruction have led to the disappearance of *Rhodiola* species in many locations, as most raw materials are wildcrafted and the plant needs several years to regenerate. In some geographical areas, the two most frequently used species, *R. crenulata* and *R. rosea*, are becoming vulnerable or at-risk (one source uses the terms "threatened" and "critically endangered" when referring to specific areas),[31] making them more expensive to obtain.[23,30,31]

Lack of proper collection procedures and the possible interchangeability of *Rhodiola* species may also contribute to *R. rosea* and/or *R. crenulata* being frequently substituted by or accidentally substituted with other *Rhodiola* species. The fact that most *Rhodiola* species (in particular, *R. rosea and R. crenulata*) are morphologically distinct suggests that the lack of raw material definitions and collection guidelines leads collectors to pick or substitute with whatever *Rhodiola* is locally available. After removal of the aboveground parts, the similarity in the root/rhizome morphology makes it practically impossible to distinguish one species macroscopically from the other and separate them before processing, although they can be distinguished chemically.

Different *Rhodiola* species, including *R. rosea* and *R. crenulata*, can be found on the Chinese market. Often, these are neither sold separately nor well-identified; therefore, there is a high potential of substitution and admixing among these species. While *R. crenulata* root/rhizome is preferred over *R. rosea* in TCM, this species is sometimes substituted with *R. rosea, R. serrata*, or other *Rhodiola* species.[23,30]

The prevalence of *R. crenulata* on the Chinese market is most likely due to its greater abundance; it is not considered to be a substitute or an adulterant for *R. rosea*. Over-

all, the Chinese market is driven by Chinese names, not Latin names, and the Chinese name *hong jing tian* as an umbrella term generally refers to multiple species of *Rhodiola*, of which *R. crenulata* is the most abundant in trade. In China, it is rare for vendors to differentiate the various species, and most vendors have little knowledge about rhodiola because it has a short history of use in TCM and trade. They sell it because it is popular as a general health food item but most vendors know little about it beyond its province of origin, which does not always correlate to the species or morphological form.

As certain *Rhodiola* species, e.g., *R. rosea* and *R. crenulata*, are becoming scarce in the field, other *Rhodiola* species such as *R. fastigiata, R. quadrifida, R. sacra,* and *R. serrata* appear to be replacing them in the market.[32] For example, in a recent analysis of raw material samples purchased from drug stores and hospitals in China, only 40% of the samples labeled to contain *R. crenulata* were conclusively identified as such, while 40% were replaced with *R. serrata*, and the remaining samples with other *Rhodiola* species.[32]

As demand for the rhizome of *R. rosea* and *R. crenulata* increases, so does the cost, creating a greater risk that species substitution will occur.

Although substitution of *R. rosea* products with *R. crenulata* is considered the main problem with respect to authenticity of *R. rosea*,[19,29] field work data suggest that other species are being implicated. A particular case is *R. sachalinensis,* a species that has a similar composition to *R. rosea*, containing rosavins (the marker compounds used to identify *R. rosea*), as well as salidroside, and is considered by some botanists to be the same species as *R. rosea*.[23,32,33] To complicate matters, different populations of *R. sachalinensis* may display differences in their high-performance liquid chromatography-ultraviolet detection (HPLC-UV) fingerprints, making accurate species identification based on chemical analysis difficult.[32] However, substitution with *R. sachalinensis* may become less of a concern, since its growing range has decreased significantly and it is now considered to be critically endangered in China.[9] Conversely, as the various species of *Rhodiola* are used interchangeably within traditional systems, differentiation may be necessary only when claiming to sell a specific species.

3.4 Possible safety issues: According to an assessment report by the European Medicines Agency and a more recent safety review, ingestion of *R. rosea* is considered safe.[4,34] Although no assessments of *R. crenulata* or other *Rhodiola* species that might be used as substitutes have been published, there are no apparent health concerns when *R. rosea* is substituted with other materials from the same genus. There is a report about herb-drug interactions based on the fact that *Rhodiola* species rhizomes contain various amounts of salidroside. Salidroside has been found to significantly inhibit CYP3A4, which is an important drug-metabolizing enzyme. Although the potential for this interaction is based mostly on *in vitro* data, one clinical case report suggests this could be of clinical relevance leading to amplification of the effects of drugs with CYP3A4 mediated metabolism.[34]

3.5 Analytical methods to detect substitution: Roots and rhizomes of *R. rosea* can be distinguished from roots/rhizomes of *R. crenulata* and other *Rhodiola* species by trained experts using botanical, TLC, HPLC, NMR, and genetic methods. The color of the flower allows distinguishing *R. rosea* from *R. crenulata* and other purple-flowering species botanically.[8,9,12,35] Dried rhizomes of various *Rhodiola* species, however, cannot be differentiated macroscopically from one another, but can be distinguished by chemical comparisons to authentic reference materials.

One of the approaches to distinguish *R. rosea* rhizome from other *Rhodiola* species is the presence/absence of rosavins by TLC. The first TLC method to detect rosavins was reported by Kurkin et al.[28] Several other methods have been developed since then, including an HPTLC method with very clear criteria to distinguish *R. rosea* from other *Rhodiola* species.[23,36,37]

Kurkin et al. noted that salidroside was common in the genus *Rhodiola*, but among 11 *Rhodiola* species that were tested, only *R. rosea* contained the rosavins, allowing one to use the presence or absence of these compounds to possibly differentiate among species.[28] The lack of rosavins in *R. sachalinensis* was later refuted by other researchers.[23,29] Various HPLC methods have been reported in the literature to distinguish *R. rosea* chemically from other species.[38-40] The use of rosarin, rosavin, and rosin as marker compounds is critical to ensure identity of *R. rosea* products. Identification of *R. rosea* products containing other *Rhodiola* species may require not only identification of the presence of the rosavins, but also quantification of the amount of each and their ratios. Other methods have been suggested, including NMR-based metabolomics,[23,41] and HPTLC. The suite of methods appears to be helpful in detecting irregularities in commercial *R. rosea* products.

A DNA barcoding approach to identify *Rhodiola* species, based on 189 accessions representing 48 of the 55 species of *Rhodiola* described in the *Flora of China*,[7] has been reported.[42] The results suggested that the internal transcribed spacer (ITS) genomic region was best suited for use as a single-locus barcode, resolving 66% of the *Rhodiola* species. Combining five loci (*rbcL*, *matK*, *trnH-psbA*, *trnLF,* and ITS) increased the resolution to 81% of the species. However, the DNA method may not be considered adequate when used alone in quality control procedures, since close to 20% of species cannot be distinguished, and also due the inability to discern the plant part. Various DNA-based approaches have also shown little success in species identification of highly processed botanical ingredients, e.g., extracts.

4. Conclusions

Substitution or mixing of *R. rosea* root/rhizome raw material and extracts with other species, especially *R. crenulata*, remains an issue of regulatory concern for manu-

facturers and marketers of products labeled as *R. rosea*. Substitution of *R. rosea* with other *Rhodiola species* can be detected botanically and through chemical analysis (e.g., HPTLC, HPLC and NMR). The increasing scarcity of wildcrafted *R. rosea* and *R. crenulata*, as well as reliance on complex supply chains involving many stakeholders (especially many collectors in diverse regions, particularly in China), is increasing the likelihood for substitution and admixing with other *Rhodiola* species, particularly *R. fastigiata, R. quadrifida, R. sacra*, and *R. serrata*.

References

1. McGuffin M, Kartesz JT, Leung AY, Tucker AO. *Herbs of Commerce.* 2nd ed. Silver Spring, MD: American Herbal Products Association; 2000.
2. Brown R, Gerbarg P, Ramazanov Z. *Rhodiola rosea* - a phytomedicinal overview. *HerbalGram.* 2002;56:40-52.
3. Moran RV. Rhodiola rosea. *Flora of North America.* Vol 8. New York, NY and Oxford, United Kingdom: Flora of North America North of Mexico. 20+ vols.; 1993-2017:167.
4. Assessment report on *Rhodiola rosea* L., rhizoma et radix London, United Kingdom: European Medicines Agency Committee on Herbal Medicinal Products (HMPC); 2011:1-32.
5. Community herbal monograph on *Rhodiola rosea* L., rhizoma et radix. London, United Kingdom: European Medicines Agency Committee on Herbal Medicinal Products (HMPC); 2012:1-5.
6. *Rhodiola quadrifida* Fisch & Mey and *Rhodiola rosea* L. *Medicinal Plants in Mongolia*. Geneva, Switzerland: World Health Organization (WHO); 2013:163-172.
7. Powdered *Rhodiola rosea* extract. *USP 40 - NF 35*. Rockville, MD: United States Pharmacopeial Convention; 2017:6809-6810.
8. *Rhodiola rosea*. *USP 40 - NF 35*. Rockville, MD: United States Pharmacopeial Convention; 2017:6805-6807.
9. Cuerrier A, Tendland Y, Rapinski M. Ethnobotany and conservation of *Rhodiola* species. In: Cuerrier A, Ampong-Nyarko K, eds. *Rhodiola rosea*. Boca Raton, FL: CRC Press; 2014.
10. *Rhodiola rosea*. Germplasm Resources Information Network [Internet]. United States Department of Agriculture, Agricultural Research Service; 1998. https://npgsweb.ars-grin.gov/gringlobal/taxonomydetail.aspx?31156. Accessed May 24, 2017.
11. *Rhodiola crenulata*. *Pharmacopoeia of the Peoples Republic of China.* Vol 1. Beijing, China: China Medical Science; 2010:376-377.
12. *Rhodiola*. In: Wu Y-Z, Raven PH, eds. *Flora of China.* Vol 8. Beijing, China and St. Louis, MO: Missouri Botanical Garden Press; 2001:251-268.
13. Bohm BA. *The Geography of Phytochemical Races.* Dordrecht, Netherlands: Springer Netherlands; 2009.
14. Rhodiola - *Rhodiola rosea*. Ottawa, ON, Canada: Natural Health Products Directorate, Health Canada; 2013.
15. Panossian A, Wikman G, Sarris J. Rosenroot (*Rhodiola rosea*): traditional use, chemical composition, pharmacology and clinical efficacy. *Phytomedicine.* 2010;17(7):481-493.
16. Hartwich M. The importance of immunological studies on *Rhodiola rosea* in the new effective and safe herbal drug discovery. *Centr Eur J Immunol.* 2011;35(4).
17. Rhodiola rosea. Therapeutic Research Faculty; 2007.
18. Anonymous. *Rhodiola rosea*. Monograph. *Altern Med Rev.* 2002;7(5):421-423.
19. Booker A, Jalil B, Frommenwiler D, et al. The authenticity and quality of *Rhodiola rosea* products. *Phytomedicine.* 2016;23(7):754-762.
20. Moley T, Foster S, Awang D, Hu SY, Kartesz JT, Tucker AO. *Herbs of Commerce.* 1st ed. Austin, TX: American Herbal Products Association; 1992.
21. Smith T, Kawa K, Eckl V, Johnson J. Sales of herbal dietary supplement sales in US increased 7.5% in 2015. *HerbalGram.* 2016;111:67-73.
22. Smith T, Kawa K, Eckl V. Herbal supplement sales in US increase 7.7% in 2016. *HerbalGram.* 2017;115:56-65.
23. Booker A, Zhai L, Gkouva C, Li S, Heinrich M. From traditional resource to global commodities: a comparison of *Rhodiola* species using NMR spectroscopy-metabolomics and HPTLC. *Front Pharmacol.* 2016;7:254.
24. Lichius JJ, Loew D. Rhodiola rhizoma et radix. In: Blaschek W, ed. *Wichtl - Teedrogen und Phytopharmaka*. 6th ed. Stuttgart, Germany: Wissenschaftliche Verlagsgesellschaft mbH; 2016:554-555.
25. Ma Y-C, Wang X-Q, Hou F, et al. Rapid resolution liquid chromatography (RRLC) analysis for quality control of *Rhodiola rosea* roots and commercial standardized products. *Nat Prod Commun.* 2011;6(5):645-650.
26. Ma C-Y, Tang J, Wang H-x, Gu X-h, Tao G-J. Simultaneous determination of six active compounds in *Rhodiola* L. by RP-LC. *Chromatographia.* 2008;67(5):383-388.
27. Xu J, Li Y. Effects of salidroside on exhaustive exercise-induced oxidative stress in rats *Mol Med Rep*.6(5):1195-1198.
28. Kurkin VA, Zapesochnaya GG, Shchavlinskii AN, Nukhimovskii EL, Vandyshev VV. Method of analysis of identity and quality of *Rhodiola rosea* rhizome. *Khim Farm Zh.* 1985;19(3):185-190.
29. Booker AJ, Zhai L, Heinrich M. A metabolomic and phytochemical based study of *Rhodiola* species sourced from Asia and Europe. *Planta Med.* 2015;81(16):SL3A_03.
30. Xin T, Li X, Yao H, et al. Survey of commercial *Rhodiola* products revealed species diversity and potential safety issues. *Sci Rep.* 2015;5:8337.
31. Allen D, Bilz M, Leaman DJ, Miller RM, Timoshyna A, Window J. *European Red List of Medicinal Plants.* Luxembourg, Luxemburg: Publications Office of the European Union; 2014.
32. Zhao W, Shi X, Li J, Guo W, Liu C, Chen X. Genetic, epigenetic, and HPLC fingerprint differentiation between natural and ex situ populations of *Rhodiola sachalinensis* from Changbai Mountain, China. *PLoS One.* 2014;9(11):e112869.
33. The Plant List. Version 1.1 http://www.theplantlist.org. Accessed May 19, 2017.
34. Semple H, Bugiak B. Toxicology and safety of *Rhodiola rosea*. In: Cuerrier A, Ampong-Nyarko K, eds. *Rhodiola rosea*. Boca Raton, FL: CRC Press; 2014.
35. Compositional guideline: *Rhodiola rosea* dried root (powdered) extract. In: Aging DoHa, ed. Symonston, ACT, Australia: Therapeutic Goods Administration; 2012:1-3.
36. Rumalla C, Avula B, Ali Z, et al. Quantitative HPTLC analysis of phenylpropanoids in *Rhodiola* species. *J Plan Chromatogr – Modern TLC.* 2011;24(2):116-120.
37. *Rhodiola rosea* root (*Rhodiola rosea*). HPTLC Association. http://www.hptlc-association.org. Accessed May 24, 2017.
38. Ganzera M, Yayla Y, Khan IA. Analysis of the marker compounds of *Rhodiola rosea* L. (golden root) by reversed phase high performance liquid chromatography. *Chem Pharm Bull* 2001;49(4):465-467.

39. Wang Q, Ruan X, Jin Z-h, Yan Q-c, Tu S-j. Identification of *Rhodiola* species by using RP-HPLC. *J Zhejiang Univ Sci B.* 2005;6(6):477-482.
40. Avula B, Wang Y-H, Ali Z, et al. RP-HPLC determination of phenylalkanoids and monoterpenoids in *Rhodiola rosea* and identification by LC-ESI-TOF. *Biomed Chromatogr* 2009;23(8):865-872.
41. Ndjoko Ioset K, Nyberg NT, Van Diermen D, et al. Metabolic profiling of *Rhodiola rosea* rhizomes by (1)H NMR spectroscopy. *Phytochem Anal.* 2011;22(2):158-165.
42. Zhang JQ, Meng SY, Wen J, Rao GY. DNA barcoding of *Rhodiola* (Crassulaceae): a case study on a group of recently diversified medicinal plants from the Qinghai-Tibetan Plateau. *PLoS One.* 2015;10(3):e0119921.

REVISION SUMMARY

Version # , Author,	Date Revised	Section Revised	List of Changes
Version 1, E. Bejar, R. Upton, J.H. Cardellina II	n/a	n/a	none