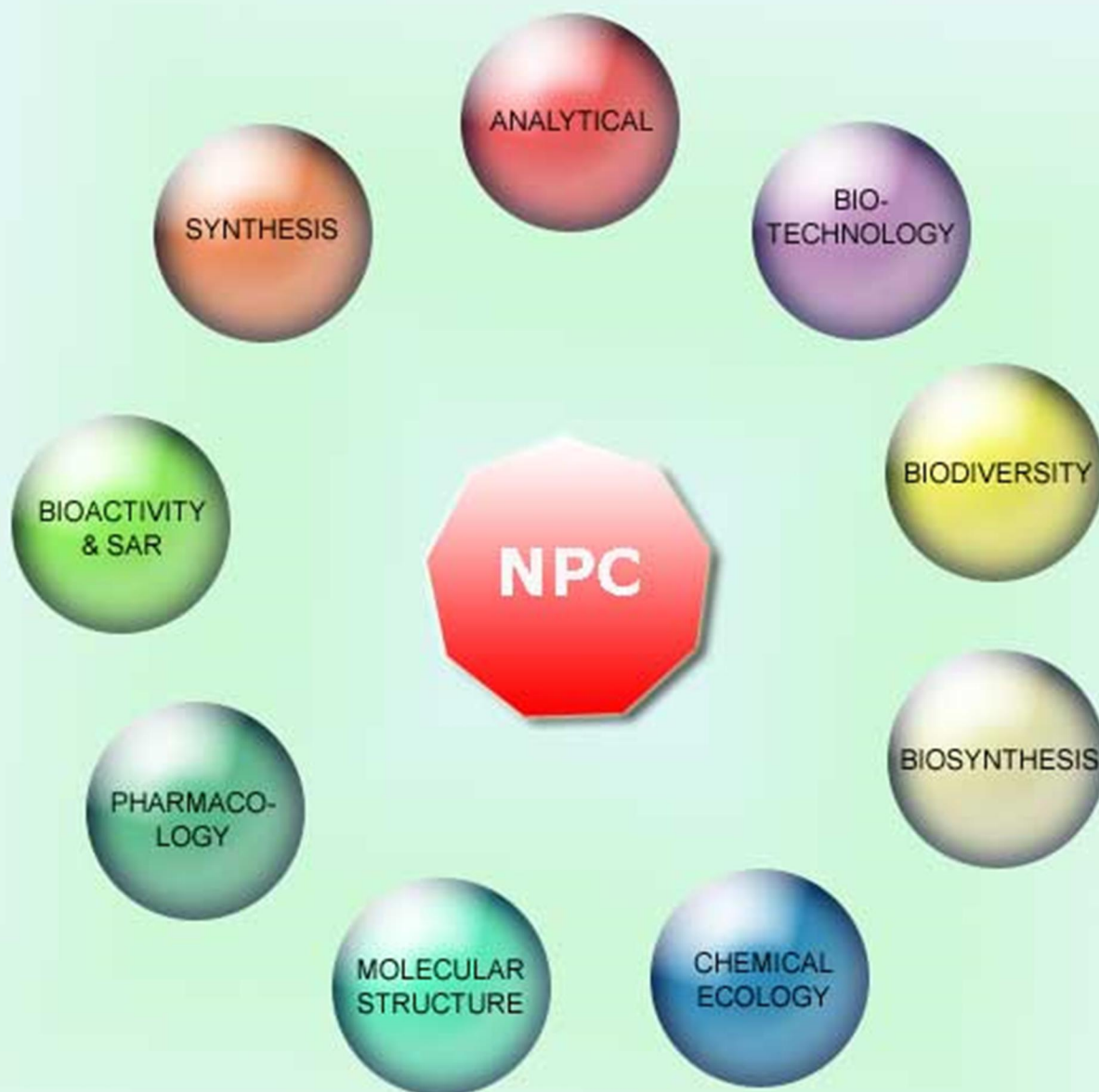


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Changes in the Content of the Glycosides, Aglycons and their Possible Precursors of *Rhodiola rosea* during the Vegetation Period

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Phytochemical participants in the biosynthetic pathway of salidroside and cinnamyl alcohol glycosides were studied from seven *Rhodiola rosea* L. individuals originating from a wild population. Plants were grown in a phytotron and samples were taken at 3 weekly intervals during the vegetation period. Based on HPLC analysis, all the key compounds to which roseroot medicinal property is attributed were detected, with salidroside being the most dominant, followed by its aglycone, tyrosol. The contents of all compounds were 2-3 times more in the rhizomes than in roots. The highest content of salidroside, tyrosol, rosarin, rosavin and cinnamyl alcohol was recorded in rhizomes and at the beginning of shoot elongation. The seven roseroot individuals showed a very high deviation in their chemical content at each sampling time. Our statistical analysis showed that the trend of salidroside accumulation in the rhizome was the most similar in all studied plants. These results have important implications for choosing a reasonable harvest time to obtain the maximum phytochemical content and a better understanding of active compounds formation in *R. rosea* L.

Keywords: *Rhodiola rosea*, Roseroot, HPLC, Rosin, Rosavin, Rosarin, Tyrosol, Salidroside, Cinnamyl alcohol.

Rhodiola rosea L. (*Crassulaceae*), known as golden root or roseroot, is a herb commonly known as a folk medicine with general immune-stimulant properties that has been used for centuries. Roseroot is a dioecious perennial plant with a rose-like aroma from its thick rhizome, which contains pharmacologically important secondary metabolites. The medicinal properties of *R. rosea* and its secondary metabolites, namely rosine, rosavin, rosarin and salidroside, are extensively investigated in different aspects by many scholars worldwide. The multipurpose medicinal characters of roseroot have been proved by research experiments and human clinical studies which are comprehensively reviewed by Panossian and co-workers [1] and Hung and co-workers [2].

Phytochemical analysis of roseroot underground tissues has confirmed so far the presence of several compound classes such as essential oils, cinnamic alcohol glycosides, flavonoids, organic acids, fats, phenolics, including tannins, and proteins [3-11]. The medicinal properties of roseroot are mostly related to the amphiphilic phenylethanoid tyrosol and its glycoside, salidroside (*p*-hydroxyphenylethyl-*O*- β -D-glucopyranoside), along with cinnamic alcohol glycosides (rosin, rosavin and rosarin), known as phenylpropanoids. Earlier studies considered the effect of plant age [10, 12-14], plant origin [10, 15], harvesting time [14, 16] and cultivation methods [8] on roseroot phytopharmaceuticals. No work has been reported based on sampling (root and rhizome) in a controlled environment. Up to now the dynamics of the accumulation of the glycosides of roseroot have not been fully explored and only a few studies have been published [12, 13, 16-19].

The yearly increase in total phenylethanoid and phenylpropanoid concentrations in *Rhodiola rosea* grown in Poland is reported [12]. The same findings have been reported for salidroside and rosavin [13]. After several years of study, Weglarz *et al.* [10] concluded high intraspecific variability concerning accumulation of these compounds and the variation of active compounds during plant

development was confirmed. Buchwald *et al.* [16] measured the content of the active compounds every two weeks during the vegetation period emphasizing the significant effects of harvesting time on roseroot phytochemicals, but only in the roots.

The aim of this experiment therefore was trying to describe the accumulation pattern of salidroside and cinnamyl alcohol glycosides by increasing the number of studied specimens in a controlled environment at different phenological phases.

The results of HPLC analysis are presented in Tables 1 and 2 from rhizome and root samples, respectively. All compounds of our interest have been detected in the root and rhizome with salidroside being the highest both in the root and rhizome. The content of all compounds was 2-3 times more in the rhizome samples than in those of the roots. Rosarin content was remarkably higher in the rhizome than in the roots, being of the same order of magnitude as that of salidroside.

Table 1: Content of the key compounds in rhizomes of *R. rosea* during the vegetation period (% of dry weight)^a.

Compound	June 7	June 28	July18	August 9	August 30
	Mean \pm SD	Mean \pm SD	Mean \pm SD	Mean \pm SD	Mean \pm SD
Cinnam. alcohol	0.68 \pm 0.11	0.88 \pm 0.31	0.76 \pm 0.11	0.72 \pm 0.19	0.77 \pm 0.10
Rosin	0.15 \pm 0.11	0.06 \pm 0.04	0.10 \pm 0.06	0.08 \pm 0.04	0.07 \pm 0.03
Rosavin	0.10 \pm 0.08	0.27 \pm 0.20	0.15 \pm 0.14	0.07 \pm 0.07	0.06 \pm 0.05
Rosarin	1.27 \pm 1.05	2.64 \pm 1.76	1.52 \pm 1.49	1.00 \pm 1.49	0.82 \pm 0.65
Tyrosol	1.20 \pm 0.75	1.84 \pm 0.89	0.78 \pm 0.26	0.83 \pm 0.63	0.83 \pm 0.44
Salidroside	1.67 \pm 0.74	2.73 \pm 0.94	1.33 \pm 0.91	0.95 \pm 0.90	0.93 \pm 0.63

^a The values are mean \pm SD (*n* = 7).

In the rhizome samples, an intense increase in content was detected from the first sampling time to the 2nd in the case of salidroside, tyrosol, rosavin and rosarin, whilst the cinnamyl alcohol content was more or less stable. The studied compounds in the root samples were also quite stable during the vegetation period. Significant differences were hard to detect, because of the big variation of the

Table 2: Content of the key compounds in roots of *R. rosea* during the vegetation period (% of dry weight)^a

Compound	June 7	June 28	July 18	August 9	August 30
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Cinnam. alcohol	0.30 ± 0.06	0.29 ± 0.09	0.16 ± 0.04	0.23 ± 0.11	0.22 ± 0.10
Rosin	0.08 ± 0.05	0.05 ± 0.05	0.05 ± 0.03	0.03 ± 0.02	0.04 ± 0.01
Rosavin	0.03 ± 0.03	0.01 ± 0.02	0.01 ± 0.01	0.02 ± 0.02	0.02 ± 0.01
Rosarin	0.28 ± 0.10	0.20 ± 0.11	0.13 ± 0.03	0.16 ± 0.09	0.15 ± 0.08
Tyrosol	0.70 ± 0.47	0.72 ± 0.62	0.30 ± 0.18	0.37 ± 0.24	0.37 ± 0.18
Salidroside	0.94 ± 0.64	0.88 ± 0.78	0.54 ± 0.23	0.73 ± 0.25	0.73 ± 0.32

a) The values are mean ± SD (*n* = 7)

metabolites. In the root samples, significant differences could be seen only in the case of rosarin (data not shown).

In the rhizome samples significant differences could be seen in the case of rosarin, salidroside and tyrosol (data not shown). It is also interesting that a trace of all compounds were detected by HPLC in the leaves (data not shown) indicating that the formation of these compounds can possibly take place in the aerial parts of the plant or they are somehow transported up to the leaves.

The remarkable chemical variation among different populations of roseroot plants has already been reported [15, 20], and also the significant intrapopulation variation is not new, as it was measured for salidroside and cinnamyl alcohol content [10]. Based on our HPLC analysis, no clear trends could be observed among the individuals at each sampling interval.

The seven roseroot individuals showed a very high deviation in their chemical content at each sampling time.

Salidroside content varied between 0.11 and 2.37 % in the roots and between 0.25-3.78% in rhizomes, while the tyrosol content varied from 0.14-1.64 % in roots and from 0.21-3.32 % in rhizomes of the 7 specimens during the sampling time. The same high fluctuation was also observed in regard to cinnamyl alcohol and its glycosides: cinnamic alcohol varied from 0.08-0.42% (root) and from 0.51-1.47% (rhizome); rosin from 0.0002-0.18% (root) and 0.015-0.31%

(rhizome); rosavin from 0.004-0.066% (root) and 0.005-0.7% (rhizome); rosarin from 0.03-0.44% (root) and 0.24-5.38% (rhizome). These high variations indicate that the harvesting time should be carefully chosen to obtain the plant materials which contain the minimum required content of roseroot pharmaceutical compounds (0.8-1% of salidroside and 3% of total rosavins according to the Russian Pharmacopoeia [21]).

To achieve a better understanding of the metabolites formation pattern, we also examined the direction of the changes of the content of each compound. The tyrosol content, along with salidroside, in rhizomes of our samples showed a sudden increase from the first to the 2nd sampling time, followed by a sudden decrease in the 3rd, and a gradual decrease to the 4th and the 5th sampling times.

In the roots of our samples a different accumulation (opposite) pattern was observed in which there was a mild decrease from the first to the 2nd and 3rd, and a mild increase from the 3rd to the 4th and 5th stages, which is very similar to a pattern reported by Bozhilova [18]. Not surprisingly, the tyrosol and its aglycon (salidroside) content were always in correlation during the vegetation period. Rosarin and rosavin content in the rhizome also increased from the first to the 2nd and gradually decreased till the end of the sampling period, but no such pattern was observed in regard to cinnamyl alcohol and rosin, neither in roots nor in the rhizomes.

The changes in the rosin content were very versatile in the rhizome and no common trends could be detected, while in the roots the only regularity was that the content slightly decreased during the vegetation time. The content of cinnamyl alcohol in the roots decreased from the 1st to 3rd and slightly increased from the 3rd to the 5th stage, which again was not similar to its pattern in the rhizome. In the rhizomes though, most of the compounds had their maximum in the second sampling time, which was the beginning of shoot elongation and rapid mass production (in contrast with Platikanov and Evstatieva [14]) and their minimum content at the fructification stage.

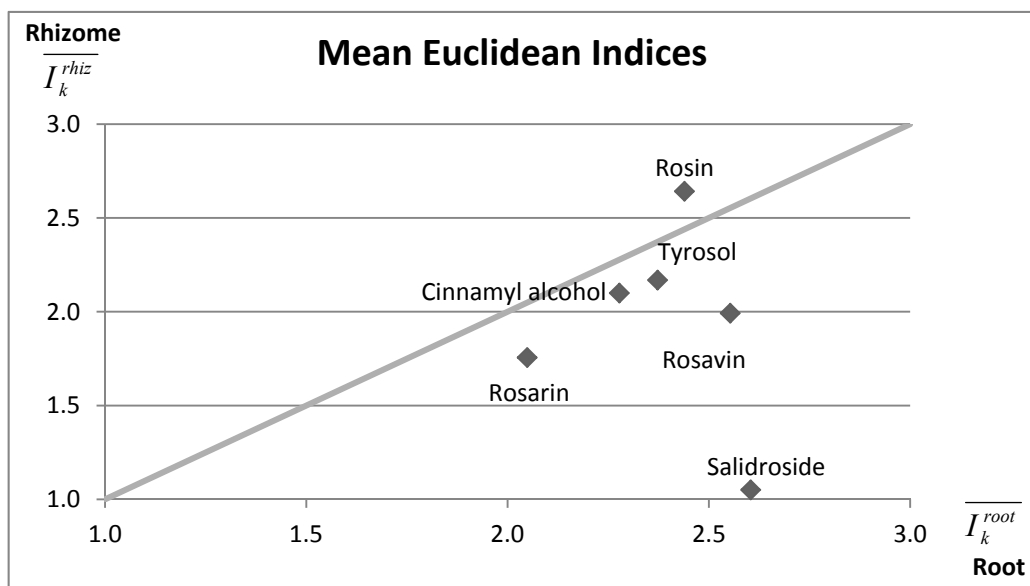


Figure 1: Pairs of dissimilarity indices of studied compounds. $P_k = \left(\overline{I_k^{root}}; \overline{I_k^{rhizome}} \right)$ (*k* = rosin, rosavin, rosarin, cinnamic alcohol, salidroside and tyrosol). The indices are calculated using the distances between the characteristic codes of the accumulation processes introduced in section *Statistical analysis*. The closer a point is to the origin, the more similar characters of accumulation patterns are detectable among the plants. The points under the diagonal line represent compounds the accumulation processes of which are more similar in the rhizome while if a point is above the diagonal line, the similarity is more expressed in the root.

The similarity of the plants with regard to the accumulation of a given compounds was examined with the method described in the "Experimental". Repeated measures using an ANOVA method resulted in only slightly significant differences between the contents measured at five points of time merely in the cases of rosin (F root (2.6; 15.8) = 5.02, F rhizome (1.8; 10.9) = 7.07) and salidroside in rhizome (F rhizome (2.2; 12.9) = 26.4), so we focused not on the nominal values of the contents, but the characteristics of the accumulation, i.e. whether the glycosides had increased, decreased or been invariant from time to time.

Figure 1 shows that the trend of salidroside accumulation in the rhizome is very similar in all studied plants. All studied plants had the same character curve for this compound as the similarity index is very close to its origin at the Y axis. The Figure also shows that the similarity is higher in the rhizome than in the root as the index points are under the diagonal line. Generally we can also say that the accumulation pattern of all compounds (except rosin) was slightly more similar in the rhizome than in the roots.

Despite the quantitative phytochemical variation in roseroot at different vegetation sites and from plants of different ages under different cultivation techniques which has already been reported [10, 12-17], our results showed that even individuals from the same origin in the same growing environment and same soil condition are still behaving very differently in the case of metabolites production.

These results have important implications for choosing a reasonable harvest time to obtain the maximum phytochemical content and a better understanding of active compounds formation in root and rhizome of *R. rosea* during the vegetation period.

Experimental

Plant material: Rhizome cuttings of equal size were collected from 7 individual *Rhodiola rosea* specimens in a natural population on the Hochkar, Göstling Alps; Austria (47°48'N, 14°56'E) right after snow melting (07.06.2013). The cuttings were planted in 1:1:1 mixture of perlite, black peat and lime soil in 2 L containers.

The plants were transferred to a plant growth chamber (Weiss Technik SGC-120.UK) where the temperature and relative humidity were kept at 17/12°C and 60/80% day/night, respectively and with 14 h of daylength. Light was provided by fluorescent light tubes (12×36W Philips 840 TL-D 1G; 4000K) with a light intensity of 10 Klux at the level of the plants. Root and rhizome samples were taken every 3 weeks until the end of August individually from each plant.

Extraction and HPLC analysis: Samples (~5 g) for HPLC analysis were dried at 50°C overnight. Plant tissues (0.5 g) were ground and 70% methanolic extraction was performed using an ultrasonic bath for 1 h, followed by centrifugation and filtration.

Chromatographic analysis was performed using a Waters 1525 binary pump, a 717 autosampler with 2998 PDA detector on a reversed phase Thermo Hypersil ODS 250×4.6 5 μm column at 40°C with a neutral mobile phase (purified water and acetonitrile) using a gradient system at a flow rate of 1.0 mL/min and UV detection at 205, 222, 254 and 275 nm simultaneously. Peaks were identified by comparison of retention time and spectral data with adequate parameters of standards. The *Rhodiola rosea* Standards Kit (Chroma Dex) included rosin, rosavins, rosin, salidroside and tyrosol, while tyrosine and cinnamyl alcohol were purchased from Sigma. Quantification was performed based on the peak area. The

content of the determined compounds was calculated as mg 100 g⁻¹ dry matter.

Statistical analysis: The variation was very high among the 7 plants, so the regular repeated measures of the ANOVA method was insufficient to detect significant differences because of the high standard deviation values. Therefore, we focused not on the nominal values of the contents but the characters of the accumulation, i.e. whether any of the compounds had increased, decreased or were invariant from time to time.

Definition and comparison of the values of dissimilarity index of the accumulation process of compounds: In order to learn the similarity and express the dissimilarity of the character of the compound accumulation process in time, we introduced a ten-dimensional *characteristic code of accumulation process* for each of the 6 compounds in root and rhizome of all the 7 plants. That is to say that we calculated 6*2*7 ten dimensional codes $C_k^l(i) = (c_k^l(i)_{t_2}, c_k^l(i)_{t_3}, \dots, c_k^l(i)_{t_s}, \dots, c_k^l(i)_{t_5})$, $k =$ rosin, rosavin, rosin, cinnamyl alcohol, salidroside and tyrosol, $l =$ rhizome or root and $i = 1, 2, \dots, 7$ for the plants. The way of calculation was as follows:

- dimension t_s was for the change from sampling time t to s ; ($t = 1, 2, \dots, 4$; $s = 2, 3, \dots, 5$);
- The value of a code is equal to +1 or -1 if the compound content is increasing/decreasing and the rate of increase/decrease is above the 10% of the mean of the glycoside content measured in 5 sampling stages, respectively. The value of a code is equal to 0 if the change of glycoside content is below the 10% of the mean (Figure 1).

The *characteristic code of accumulation process*

$C_k^l(i)$ is suitable to describe the process for a fixed type of compounds, plant and place of accumulation; moreover, we can compare the plants, the compounds and the rhizome-root pairs according to their dissimilarity expressed by the distance of the characteristic codes.

Therefore, we calculated the Euclidean distances of all pairs of curves as dimensionless quantities:

$$D_k^l(j, i) = D_k^l(i, j) = \sqrt{\sum_{t=1}^4 \sum_{s=2}^5 (c_k^l(i)_{t_s} - c_k^l(j)_{t_s})^2}$$

($k =$ Rosin, rosavin, rosin, cinnamyl alcohol, salidroside and tyrosol, $l =$ rhizome or root, $i, j = 1, 2, \dots, 7$) and took the sum of *dissimilarity measures* $D_k^l(j, i)$ for all the individuals $i = 1, 2, \dots, 7$:

$$I_k^l(i) = \sum_{j \neq i} D_k^l(i, j).$$

$I_k^l(i)$ is called *dissimilarity index of plant i , calculated for compound k* . Let us denote by \bar{I}_k^l the mean of values $I_k^l(i)$ taken over all plants and call it *mean dissimilarity index of compound k* :

$$\bar{I}_k^l = \frac{1}{7} \sum_{i=1}^7 I_k^l(i).$$

If we represent 6 points $P_k = \left(\bar{I}_k^{\text{root}}, \bar{I}_k^{\text{rhizome}} \right)$ for $k =$ rosin, rosavin, rosin, cinnamyl alcohol, salidroside and tyrosol, we can state that the closer a point is to the origin, it represents the more similar set of curves (Figure 1). Moreover, if a point is under the identity line, the curves for rhizome are more similar, while if it is above the identity line, the similarity is more expressed in root.

For the data analysis and representation, MS Excel 2013 was used.

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