

RHODIOLA ROSEA

Regularly, on the Italian herbalist market, we see an unexpected interest for exotic plants or those from distant countries, which everyone wants and looks for. The mechanism by which this happens is often a consequence of the appearance in the media of some information about new discoveries and new research into exotic plant properties.

While during the past years the *Uncaria tomentosa* has captured the interest of the public and of the operators, the year 2000 has been undoubtedly dominated by *Rhodiola rosea* or *Rhodiola sacra* (Praix ex Hamet).

Unknown until a few months before, it soon became a sort of impossible treasure: everybody talked about it and wanted it, while the commercial importers were worrying about looking for something which they had not even heard about just a few weeks before.

The *Rhodiola rosea* had all the properties to become a myth: it is a small plant, of insignificant appearance, but with a respectful pedigree.

First of all it grows in some of the most inhospitable places on earth, especially in cold temperatures: the remote plateaus of Tibet, the frozen plains of Siberia, the inhospitable mountains of China and the peninsula of

Scandinavia. However, at present some experiments of cultivation of this plant are taking place nearer to us, in the familiar landscape of Austria. Secondly, the *Rhodiola rosea* is a medicinal plant with a rich and fascinating history: the ancient Tibetan monastic orders held it in high consideration since it was useful to keep a sharp and vigilant mind during the long hours of meditation. The Vikings used it to bear the harshness of life, while for the ancient Chinese it was a long life elixir, advisable to old people and to who wanted to strengthen physical and mental energy. The *Rhodiola rosea* was even actively employed by Russian astronauts who were looking for a way to increase their mental and intellectual performances, necessary to carry out the hard tasks involved in space exploration.

Finally, we must consider that we are talking about an adaptogen, a category of natural products to which our markets have always showed a great interest, thanks also to the increased level of stress in modern life. But what do we know today about this plant, unknown to many people? Which assertions, among the many that advertising messages have familiarized us to, are really justified on the base of scientific studies carried out up to now?

BOTANY AND CHEMISTRY

It is a perennial plant, 40 cm high. It has a well developed rhizome and root, and it is this part that is generally employed. The rarity of this plant (in certain regions it is called "golden root") makes its harvest from the wild very difficult and this kind of harvest risks quickly exhausting the available resources. Many countries (China, Poland, Austria) have started specific programs of domestication and cultivation that, at present, are still in experiment. The plant needs 3-4 years to become productive, when the root is picked (the rest of the plant is thrown away), cleaned, dried and extracted. The *Rhodiola rosea* contains several active principles, the most important are (Fan et al., 1999):

- hydroquinones, 4 hydrobenzoic acid, caffeic acid, 4-hydrocinnamic acid, suberic acid, protocatechuic acid, gallic acid, epigallocatechin 3-0 gallate, 2-phenylethyl beta-D-glucopyranoside, 3-0-galloylepigallocatechin-(4beta→8)-epigallocatechin+++3-0-gallate, 2-phenylethyl alpha-L-arabinopyranosyl-(1→6)-beta-D-glucopyranoside, sacranoside A, beta-D-glucopyranosyl 4-hydroxibenzoate, rhodiocyanoside A, rhodiocyanoside, sarmentosine, heterodendria, arbutine and 4-0-(beta-D-glucopyranosyl)-gallic acid (Fan et al. 1999).

Undoubtedly the most important component for pharmacological activity is represented by hydroxide salts to which the extracts in commerce are generally standardized. In particular, these are generally standardized in hydroxide salts at 1%, which are synthesized by a process of glucosylation from

tyrosol (Ming 1988). Following the great exploitation of wild sources in Asia, today in China there are serious worries about the bear ability of such high level of exploitation. Consequently, some methods of cultivation in vitro of different species of *Rhodiola* have been started: it is a very promising field of application, even if it is only in theory, for the present time (Xu et al. 1998). More complex is what we can say about rhosavin: it is one of the salts of hydroxide of *Rhodiola* rosea, to which some American products are standardized (Rhosavin of Pharmanex). In fact, the affirmations by which the real active principle should be the rhosavin and not the hydroxide salt, are not really convincing and are limited to divulgative instead of scientific literature. (Germano and Ramazanov 1999).

PHARMACOLOGICAL DATA

The extracts of *Rhodiola* rosea have been studied in the past in different experiments and have proved a wide range of pharmacological actions. Currently the literature on the subject is wider than here mentioned: many studies are in Russian and in Chinese, published in dubious scientific tomes. (Germano and Ramazanov 1999). Therefore we will refer exclusively to science journals normally reviewed by Index Medicus and to data banks, so as to limit our attention to data of verified quality. The extracts of *Rhodiola* rosea and compounds such as rhodiocyanosides A and B, rhodiocyanoside D and sacranoside A and B have demonstrated an anti-allergic activity in vitro (inhibition of the release of histamine from peritoneum exudate

cells sensitized with anti-DPN IgE) (Yoshikawa et al. 1996, Yoshikawa et al. 1997). In a recent experiment in vitro the aqueous and methyl alcoholic extract of *Rhodiola* rosea showed an excellent antioxidant activity against the anionic radical superoxide and 8 among its active compounds (hydroquinone, caffeic acid, protocatechuic acid, gallic acid, (-)-epigallocatechin 3-O-gallate, 3-gallo epigallocatechin-(4β-8)-epigallocatechin 3-O-gallate, heterodendrine and gallic acid 4-O-β-D-glucopyranoside) were able to show an antioxidant activity against the medium and high intensity superoxide radical while the 4-hydrobenzoic acid and the 3,4-hydrocynnamic acid inhibited the hydroxide radical (Ohsugi et al. 1999).

In 1991 a study on laboratory animals gave evidence of an ability to inhibit the Pliss lymphosarcoma (Udintsev and Sakhov 1991a) while, again in 1991 another study on animals demonstrated an ability to inhibit the emotoxicity from cyclophosphamide and a development of the antiproliferative activity of this substance (Udintsev and Shankov 1991b). An interesting Korean screening on anti-HIV activity of 93 medicinal plants should also be mentioned. The methyl alcoholic extract of *Rhodiola* rosea has demonstrated the most important inhibitory activity on the HIV-1 protease with a 70.4% inhibition at 100 mg/mL concentration (Sun Min et al. 1999). Finally an original Dutch and Swedish study has demonstrated how *Rhodiola* rosea, like *Eleutherococcus senticosus*, has a protective action against dead embryo cells of *Lymnaea stagnalis* submitted to 3

stress stimulus: shock from heat (43° C for 4 min.), oxidative stress (600 mM of superoxide radical for 2 hours) and stress from heavy metals (150 mM of copper for 1 hour or 20 mM of cadmium for 1 hour) (Boon-Niermeijer et al. 2000).

Even more interesting is the data on the immunostimulating and anti-aging activity, which can be considered the principal indications for *Rhodiola* rosea extract. Studies in vitro realized with the clearance test of carbon by macrophages have revealed an immunostimulating activity comparable to that of the Panax ginseng roots for an extract obtained from *Rhodiola* rosea roots, while those obtained from the rhizome were without activity.

Tests on mice revealed a reduction of the locomotion activity of 38% (relaxation index?) and an increase in muscular strength of 80-128% after they had taken the extracts of *Rhodiola* rosea, regardless of which part of the plant was used. (Furmanowa et al. 1999).

Not considering this data, which is of little value, we must mention what can be considered perhaps the most important discovery of the pharmacological activity of *Rhodiola* rosea extracts. As a matter of fact, the aqueous extracts of *Rhodiola* rosea roots are able to exert a strong inhibitory activity, in vitro, toward polyendopeptidase (Fan et al. 1999, Tezuka et al. 1999). This is an extremely important enzyme in cerebrum that can influence the metabolism of many peptides containing proline, such as vasopressin, substance P, and the hormone that releases tirotropin (TRH). It has been demonstrated that, on labo-

ratory animals, this enzyme is able to transfer many proteins to Amyloid Beta-peptide, one of the complete components of the senile plaques and the cerebrovascular amyloid typical of Alzheimer disease, Down's syndrome and in the process of cerebrum aging (Fukunari et al. 1994). This opens interesting prospects on the use of *Rhodiola* rosea in preventing the cerebral aging process in physiological conditions as well as pathological conditions.

CLINICAL STUDIES

There are three clinical studies on *Rhodiola* rosea extracts. A study on the people of a Tibetan village and their adaptation passing from an altitude of 2500 mt. to an altitude of 4475 mt. after they had taken *Rhodiola* kirilowii. The lack of control, the absence of characterization of the product employed and the lack of specification of the criteria of inclusion make the study of little value

Medical Academy; the students were divided in two groups, one was given a placebo, the other the test substance.

The people were submitted to 4 tests: one on the psychomotor functions, one on the mental work ability (correction test), one on fatigue autoevaluation (questionnaire) and one on the general health condition (scale at 5 points). Substantially, the results of this study revealed a result for the subjects who had taken the *Rhodiola* rosea extract similar to that of the group that had taken a placebo. The researchers identified the main reason for this negative result in the low dose used (Spasov et al. 2000).

The second clinical study was carried out on 56 young Armenian doctors (aged 24-35 years) submitted to night shift duty. The subjects were divided in 2 groups and were submitted to a sequence of 5 tests, according to this scheme:

The tests used had the purpose of

The *Rhodiola* rosea extract was given at a daily dose of 170 mg, corresponding to 4.5 mg of salidroside a day. The results of the test implied a more important intellectual efficiency in the second part of the tests of about 20% of the treated group, compared to the control. The result was not reproduced in the 4th part of the test. At discretion of the doctors, the nights during the fourth part of the test resulted definitely more stressful and with heavier loads of work. The authors concluded that the study showed an effectiveness in the use of *Rhodiola* rosea extract to counter fatigue and moderate levels of stress (Darbinyan et al. 2000).

CONCLUSIONS

At present the *Rhodiola* rosea extract, standardized at 1% in salidroside and generally employed at a dose of 150 mg three times a day (for a total of 4.5 mg of salidroside a day) represents a useful support to deal with

		Test phase		
	I	II	III	IV
Group A	Before taking RRE	After 2 weeks treatment with RRE	After 2 weeks wash-out	After 2 weeks of treatment with placebo
Group B	Before taking placebo	After 2 weeks treatment with placebo	After 2 weeks wash-out	After 2 weeks of treatment with RRE

RRE: *Rhodiola* rosea extract.

(Zhang et al. 1989). Two other randomized double-blind, placebo-controlled clinical studies have been carried out on the anti-aging property of the plant.

In the first study they used an extract of the root of *Rhodiola* rosea standardized in salidroside, at a dose of 50 mg twice a day and it was carried out on 40 Indian students, during the first year examination period at Volgograd

evaluating the intellectual fatigue:

Test 1: speed in determining the association word-meaning;

Test 2: speed in pronouncing a 6 letters word backwards;

Test 3: speed in counting from 99 to 0 backwards;

Test 4: number of 10 remembered words, previously showed to the subject;

Test 5: speed in reorganizing size measures in decreasing order.

moderate stress level and mental fatigue.

The emphasis of *Rhodiola* rosea extract, thanks also to its anti-aging properties at cerebral level, which is perhaps the most important discovery on this minor medicinal plant, remains the improvement of the attention, concentration and intellectual performances. A field of application that makes it an adptogen

particular and more specific for the cerebrum, different from plants like *Panax ginseng* and *Eleutherococcus senticosus*, in a market area which is extremely promising: just consider the success obtained abroad with plants like "Maytenus Laevis Reiss", even if the clinical evidence is definitely more significant in this case.

Finally we must remember that all the available clinical studies talk about a maximum dose of 4.5 mg of salidroside a day (that equals 450 mg a day at 1% or 150 mg a day at 3% of *Rhodiola rosea* extract).

As usual a fractionated dose (150 mg three times a day at 1% or 50 mg three times a day at 3%) offers a more complete covering during the day. Not having been yet documented clinically, the use of a larger dose exposes the patient, according to the current data, to potential risks of overdose or toxicity.

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