

## *Rhodiola rosea*: From the Adaptogenic Role to the Anti-Adipogenic Effect?

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### Editorial

Many natural phytonutrients have beneficial effects on health [1,2]. In addition, several botanicals have received positive attention, based on their relative safety and the accumulation of evidence of their antiadipogenic and metabolic effects in animals and humans [3]. Natural products can decrease of lipid absorption, energy intake, lipogenesis, pre-adipocyte differentiation and proliferation or increase of energy expenditure, and lipolysis [4]. These properties exist in specific flavonoids [5], chlorogenic acid from green coffee bean [6], and carnosic acid in rosemary [7]. Extracts from *Rhodiola rosea* (RR) root is poorly characterized for its properties on adipocytes and only recently it has been proposed for a the adjuvant treatment of obesity against obesity [8].

RR is a popular plant in traditional medical systems in the Nordic countries, Eastern Europe and Asia. It belongs to the family of Crassulaceae with a notoriety for stimulating physical endurance, attention span, memory, and work productivity [9-11]. The genus *Rhodiola* contains more than 100 different species, and at least 20 of these are used in traditional Asian medicine [12,13]. However, the most of all animal and human studies has been conducted on RR, so whether other species confer the same health benefits is unknown [14,15].

Researches on the RR root phytochemistry has revealed the presence of six distinct groups of chemical compounds: phenylpropanoids (rosavin, rosin, rosarin), phenylethanol derivatives (salidroside, tyrosol); flavonoids (rodiolin, rodionin, rodiosin, acetylrodalgin, triclin), monoterpenes (rosiridol, rosaridin), triterpenes (daucosterol, beta-sitosterol) and phenolic acids (chlorogenic and hydroxycinnamic, gallic acids) [9,16].

According to the Soviet Pharmacopeia [17,18], the extracts of RR - primarily in the form of water/alcohol tinctures or dried root extract - are standardized for both rosavins and salidroside. RR extracts used in most human clinical studies were standardized to minimum 3% rosavins and 0.8-1% salidroside, because the naturally occurring ratio of these compounds in RR root is approximately 3:1 [14].

The main effects of genus *Rhodiola* described are adaptogenic that means 'natural herbal products which are non-toxic in normal doses, produce a non-specific response, and have a normalizing physiologic influence' and stress protective [19,20]. Moreover, *Rhodiola* has been described as antioxidant [21-23], anti-tumour [24,25], antidepressive [26,27], neuroprotective [28,29], cardioprotective [30,31] hepatoprotective [32, 33], and immunostimulating [34-36]. Recently, many other benefits from the use of RR has been found including its ability to regulate blood sugar levels for diabetics and to activate the lipolytic processes [37], mobilizing lipids from adipose tissue to the natural fat burning system of body for weight reduction [8]. In combination with *Citrus aurantium*, RR has been found to decrease

visceral fat weight by 30% of rats fed with high fat diet, having a direct effect on sympathetic tone and on hypothalamic norepinephrine secretion [8]. Although detailed molecular mechanism of the lipid lowering and anti-inflammation effects of salidroside are to be identified, in vivo studies on high fat diet-fed LDLr<sup>-/-</sup> mice demonstrated that this RR compound reduced serum lipid levels and decreased atherosclerotic plaques formation [38].

To date only one paper reported the effect of salidroside on the differentiation of 3T3-L1 adipocytes, the mouse embryonic fibroblast cell line used in biological research on adipose tissue [39]. In this cell line, salidroside promoted 3H-glucose uptaking, significantly suppressed the differentiation down-regulating the expression of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) and CCAAT-enhancer-binding proteins alpha (C/EBP $\alpha$ ) mRNA [39]. Unfortunately this paper is in Chinese so no more specific data can be obtained.

An anti-adipogenic effect of *R crenulata* extract and tyrosol have been found, through a mechanism that involves antioxidant enzyme responses and pentose phosphate pathway. The inhibitory effects on adipogenesis were mediated through regulation of proline-mediated energy metabolism and antioxidant enzymes response via the pentose phosphate pathway [37]. *R crenulata* extract and tyrosol, inhibited adipogenesis and reduced reactive oxygen species (ROS) levels in a dose-dependent manner through an increase of superoxide dismutase activity. Therefore, phenolics can modulate cellular redox environment, that is relevant in obesity-linked metabolic disorders.

In the past, clinical trials performed in Russian Federation provided interesting evidences that the oral administration of 200 mg RR extract with rosavin activates hormone sensitive lipase and mobilizes fatty acids from adipose tissue in healthy volunteers and obese patients [40,41]. Moreover, it has been demonstrated that rosiridin interfered with the degradation of the norepinephrine, that regulates the activity of the hormone-sensitive lipase (HSL) in breaking down fat stored in adipose tissue, by inhibiting the action of monoamine oxidases (MAOs) [42].

Interestingly, RR extracts and in particular salidroside, have been proven to have therapeutic properties in bingeing-related eating disorders in rat model [43]. Since binge eating was evoked by combining stress and repeated episodes of food restriction, the effects of salidroside on this experimental model could be considered an indirect approach to treat the energy intake.

RR is known to induce PPAR $\delta$  expression in cardiomyocytes [31]. PPAR $\delta$  is a homologue of PPAR $\gamma$ , and it plays a role in many tissues such as brain, skin, muscles and adipocytes [44]. PPAR $\beta/\delta$  prevents triglyceride accumulation and increases lipid catabolism in adipocytes [45]. In addition, it increases thermogenesis by up-regulates the expression of HSL and uncoupling protein 1 (UCP1) [45,46]. If RR

upregulated PPAR $\beta/\delta$  in adipocytes as in cardiomyocytes, this could lead to a reduction in lipogenesis and to an increase of lipolysis.

Although to date there are no evidences that indicate an alteration of lipid metabolism as result of *Rhodiola* extracts intake, the effects of *Rhodiola crenulata* root was investigated on metabolic abnormalities in Zucker diabetic fatty (ZDF) rats. The treatment for 4 weeks with *Rhodiola crenulata* root containing salidroside, p-tyrosol, trans-caffeic acid and kenposideA, improved glucose and lipid metabolism disorders in ZDF rats [47].

In evaluating the present knowledge, this interesting adaptogenic plant could be useful to reduce or prevent adipogenesis and to support weight loss. However scientific researches in vitro at cellular and molecular levels are necessary to explain and confirm the benefits of RR on lipid metabolism and adipogenesis. The full specter of pharmacologically active amounts of rosavin, rosin, and rosarin, not only salidroside and p-tyrosol, should be determined to obtain reliable results.

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