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Monoamine oxidase inhibition by *Rhodiola rosea* L. roots

Daphne van Diermen[a], Andrew Marston[a], Juan Bravo[b], Marianne Reist[b], Pierre-Alain Carrupt[b], Kurt Hostettmann[a,*]

[a] *Laboratory of Pharmacognosy and Phytochemistry, School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Quai Ernest-Ansermet 30, CH-1211 Geneva 4, Switzerland*
[b] *LCT-Pharmacochemistry, School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Quai Ernest-Ansermet 30, CH-1211 Geneva 4, Switzerland*

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ABSTRACT

Aim of the study: Rhodiola rosea L. (Crassulaceae) is traditionally used in Eastern Europe and Asia to stimulate the nervous system, enhance physical and mental performance, treat fatigue, psychological stress and depression. In order to investigate the influence of *Rhodiola rosea* L. roots on mood disorders, three extracts were tested against monoamine oxidases (MAOs A and B) in a microtitre plate bioassay.
Materials and methods: Methanol and water extracts gave the highest inhibitory activity against MAOs. Twelve compounds were then isolated by bioassay-guided fractionation using chromatographic methods. The structures were determined by ^{1}H, ^{13}C NMR and HR-MS.
Results: The methanol and water extracts exhibited respectively inhibitions of 92.5% and 84.3% on MAO A and 81.8% and 88.9% on MAO B, at a concentration of 100 μg/ml. The most active compound (rosiridin) presented an inhibition over 80% on MAO B at a concentration of 10^{-5} M ($pIC_{50} = 5.38 \pm 0.05$).
Conclusions: The present investigation demonstrates that *Rhodiola rosea* L. roots have potent antidepressant activity by inhibiting MAO A and may also find application in the control of senile dementia by their inhibition of MAO B.

1. Introduction

Rhodiola rosea L. (Crassulaceae), the most investigated species of the genus *Rhodiola*, grows at elevated altitudes in the Arctic and in mountainous regions throughout Europe and Asia, where it is also known as "golden root" or "arctic root" (Saratikov and Krasnov, 1987). The perennial plant reaches a height of 30–70 cm and produces yellow flowers; its thick rhizome has a rose-like fragrance when cut. The roots have been used for centuries in the traditional medicine of Asia, Scandinavia and Eastern Europe to stimulate the nervous system, enhance physical and mental performance, improve resistance to high altitude sickness and to treat fatigue, psychological stress and depression (Saratikov and Krasnov, 1987; Wagner et al., 1994; Panossian et al., 1999; Spasov et al., 2000; Panossian, 2003; Shevtsov et al., 2003; Panossian and Wagner, 2005). *Rhodiola rosea* contains flavonoids, monoterpenes, triterpenes, phenolic acids, phenylethanol derivatives (salidroside and tyrosol) and phenylpropanoid glycosides such as rosin, rosavin and rosarin specific to this plant (Ganzera et al., 2001)

Investigation by Russian researchers has revealed that *Rhodiola rosea* root extracts produce favorable changes in a variety of physiological functions, including neurotransmitter levels and central nervous system (CNS) activity (Stancheva and Mosharrof, 1987; Brown et al., 2002). These findings may explain the influence of *Rhodiola rosea* on mental disorders such as depression and senile dementia.

Although many studies have provided evidence that administration of *Rhodiola rosea* extract elicits antidepressant activity (Kurkin et al., 2006; Darbinyan et al., 2007; Perfumi and Mattioli, 2007; Panossian et al., 2008), the mechanism of action of *Rhodiola rosea* in the treatment of nervous system disorders still remains unclear.

Monoamine oxidases regulate the metabolic degradation of catecholamines and serotonin by oxidative deamination in the central nervous system or peripheral tissues. Monoamine oxidase (MAO) A plays a pivotal role in the degradation of biogenic amines such as epinephrine, norepinephrine, and serotonin (Shih and Thompson, 1999). MAO A inhibitors have proven to be effective in the pharmacological treatment of depression (Priest et al., 1995). MAO B is the main enzyme implicated in the metabolism of dopamine (Novaroli et al., 2005). Several studies have shown that MAO B is implicated in aging-related neurodegenerative diseases such as Parkinson's disease (Castagnoli et al., 2003; Magyar and Szende, 2004) and in the formation of plaque-associated astrocytes present in brains of patients suffering from Alzheimer's disease (Saura et al., 1994).

The present report aims at explaining the influence of *Rhodiola rosea* root extracts on mood disorders by studying its effect on the regulation of neurotransmitters by monoamine oxidase. To this end, three extracts, dichloromethane, methanol and water, were tested

* Corresponding author. Tel.: +41 22 379 34 01; fax: +41 22 379 33 99.
E-mail address: Kurt.Hostettmann@unige.ch (K. Hostettmann).

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against both MAOs A and B in a microtitre plate assay. Since the latter two extracts presented MAO inhibitory activity a bio-guided fractionation of the extracts was undertaken in order to identify the active compounds. Twelve compounds were isolated and identified by means of spectroscopic and chemical methods, including 1D and 2D NMR experiments and HR-MS analysis. The MAO inhibitory activity is reported here, together with the main components of each active extract that account for the demonstrated activity.

2. Material and methods

2.1. General

^{1}H and ^{13}C NMR spectra were recorded in CD_3OD at 500 and 125 MHz, respectively, on a Varian Unity Inova NMR instrument. TMS was used as internal standard. HR-MS spectra were acquired on a Micromass LCT Premier instrument. Thin layer chromatography (TLC) was carried out on silica gel 60 F254 Al sheets (Merck) using $CHCl_3$–MeOH–H_2O (65:35:5) as eluent. Low pressure liquid chromatography (LPLC) was performed on a Lobar RP-18 column (LiChroprep 40–63 μm, 310 mm × 25 mm i.d., Merck). Medium pressure liquid chromatography (MPLC) was carried out on a RP-18 LiChroprep column (40–63 μm; 460 mm × 50 mm i.d., Merck). Centrifugal partition chromatography (CPC) was performed on a CCC-1000 instrument (Pharma-Tech Research Corp., Baltimore, MD, USA). Total volume of the three coils was 320 ml and the rotation speed was 1000 rpm. The CPC solvent was pumped at a flow rate of 3 ml/min by a 600A pump (Waters Assiociates, Inc., Milford, USA). Elution was monitored at 254 nm with a Knauer (Berlin, Germany) UV–vis. detector and a LKB (Bromma, Sweden) model 2210 integrator. HPLC–UV/DAD was carried out on a HP1100 (Agilent) with a Symmetry RP-18 column (5 μm; 150 mm × 3.9 mm i.d., Waters) using a MeOH–H_2O gradient (2:98–100:0) in 30 min. The detection was performed at 210, 254 and 360 nm.

2.2. Plant material

The roots of *Rhodiola rosea* L. (Crassulaceae) as authenticated by Egidio Anchisi (Orsières, VS, Switzerland) were collected in Val d'Aoste, Italy, in November 2005. A voucher specimen (no. 2005006) is deposited in the Laboratory of Pharmacognosy and Phytochemistry, Section of Pharmaceutical Sciences, University of Geneva. The roots were washed, cut, freeze-dried and powdered.

2.3. Monoamine oxidase inhibition assay

Human MAOs A and B Supersomes TM, purchased from BD Gentest (Woburn, MA, USA), are mitochondrial membrane fractions of insect cells containing human recombinant MAOs A and B. MAO inhibition assays were carried out with a fluorescence-based method (end-point reading) adapted from a standard BD Gentest protocol. The substrate used for the assay was kynuramine, which is non-fluorescent until it undergoes oxidative deamination by MAO resulting in the fluorescent metabolite 4-hydroxyquinoline (Novaroli et al., 2005). Product formation was quantified by comparing the fluorescence emission of the samples to that of known amounts of authentic metabolite 4-hydroxyquinoline.

Reactions were performed in black, flat bottom polystyrene 96-well microtitre plates with enhanced assay surface (Fluoro-Nunc/LumiNunc, MaxiSorpTM Surface, NUNCtM, Roskild, Denmark) using a final volume of 200 μl. The wells containing 140 μl of potassium phosphate buffer (0.1 M, pH 7.4, made isotonic with KCl), 8 μl of an aqueous stock solution of kynuramine (0.75 M to get a final concentration corresponding to its km value), and 2 μl of the sample solution (final concentration of 1%, v/v), were preincubated at pH 7.4, 37 °C for 10 min. As positive control, 2 μl of pure DMSO were used in place of the inhibitor solution. Diluted MAO (50 μl) was then delivered to obtain a final protein concentration of 0.015 mg/ml in the assay mixture. Incubation was carried out at 37 °C and the reaction was stopped after 20 min by addition of 75 μl of NaOH (2N). Fluorescence emission at 400 nm was measured with a 96-well microplate fluorescent reader (FLx 800, Bio-Tek Instruments, Inc., Winooski, VT, USA). Inhibition measure of the extracts and fractions were done in duplicate since only an approximate measure of the inhibition was necessary for the bio-guided fractionation.

Extracts and fractions were tested at a final concentration of 100 μg/ml while the purified compounds were at 10^{-5} M, in DMSO. Data analysis was performed with Prism 4.0 (GraphPad Software, Inc., CA, USA). The degree of inhibition IC_{50} was assessed by a sigmoidal dose–response curve. The standard deviation was calculated for the sigmoidal regression.

Table 1
MAO A and B inhibitory activities of *Rhodiola rosea* L. root extracts (at 100 μg/ml) and the bio-guided isolated compounds (at 10^{-5} M).

Sample	Inhibition (%)[b]	
	MAO A	MAO B
DCM extract	50.5 ± 0.1	66.9 ± 0.3
MeOH extract	92.5 ± 0.1	81.8 ± 0.3
Water extract	84.3 ± 0.8	88.9 ± 0.3
Fraction G-2	96.8 ± 0.2	81.4 ± 0.6
Fraction G-8	21.6 ± 0.2	88.5 ± 0.4
Salidroside (**1**)	–	35.8 ± 2.5
EGCG dimer (**2**)	43.1 ± 0.4	37.7 ± 0.5
Rhodioloside B and C mixture (**3**, **4**)	–	61.9 ± 3.0
Rosarin (**5**)	–	–
Cinnamyl alcohol (**6**)	27.7 ± 0.6	43.2 ± 1.5
Rhodiocyanoside A (**7**)	–	27.7 ± 4.8
Triandrin (**8**)	–	40.8 ± 3.5
Rosavin (**9**)	–	–
Tyrosol (**10**)	–	26.3 ± 0.7
Rosin (**11**)	–	–
Rosiridin (**12**)	16.2 ± 2.3	83.8 ± 1.1
L-Deprenyl[a]	36.0 ± 1.0	99.5 ± 0.2
Clorgyline[a]	100.0 ± 0.2	80.2 ± 0.9

[a] Reference compound.
[b] Inhibition lower than 15% was considered as inactive.

2.4. Extraction and isolation

Dried and powdered roots of *Rhodiola rosea* (1 kg) extracted sequentially with CH_2Cl_2 (3 × 24 h) and MeOH (3 × 24 h) at room temperature yielded, after removing the solvent under vacuum, 27 g of crude DCM extract (2.7%, w/w) and 160 g of MeOH crude extract (16%, w/w). A crude water extract (1.5 g, 30%, w/w) was obtained by extraction of 5 g of roots at room temperature during 24 h.

MeOH extract (5 g) was fractionated by CPC with $CHCl_3$:MeOH:*n*-BuOH:H_2O (7:6:3:4) as solvent system. The lower phase was first used as mobile phase, giving 14 fractions (G-1–14). Seven further fractions (G-15–21) were subsequently obtained by elution in the reversed-phase mode (upper phase as mobile phase). Fractions were pooled together according their similarity on thin-layer chromatography. This separation led to the isolation of 130 mg of salidroside (fraction G-10, **1**) and 600 mg of epigallocatechin gallate dimer (fraction G-15, **2**).

Fraction G-2 was separated by LPLC with a MeOH–H_2O step gradient yielding 10.0 mg of a mixture of rhodioloside B and C (**3**, **4**), 1.4 mg of rosarin (**5**), 5 mg of salidroside (**1**), 0.7 mg of cinnamyl alcohol (**6**).

Fraction G-8 was chromatographed by LPLC with a MeOH–H_2O step gradient to afford 400 fractions. Fractions were pooled

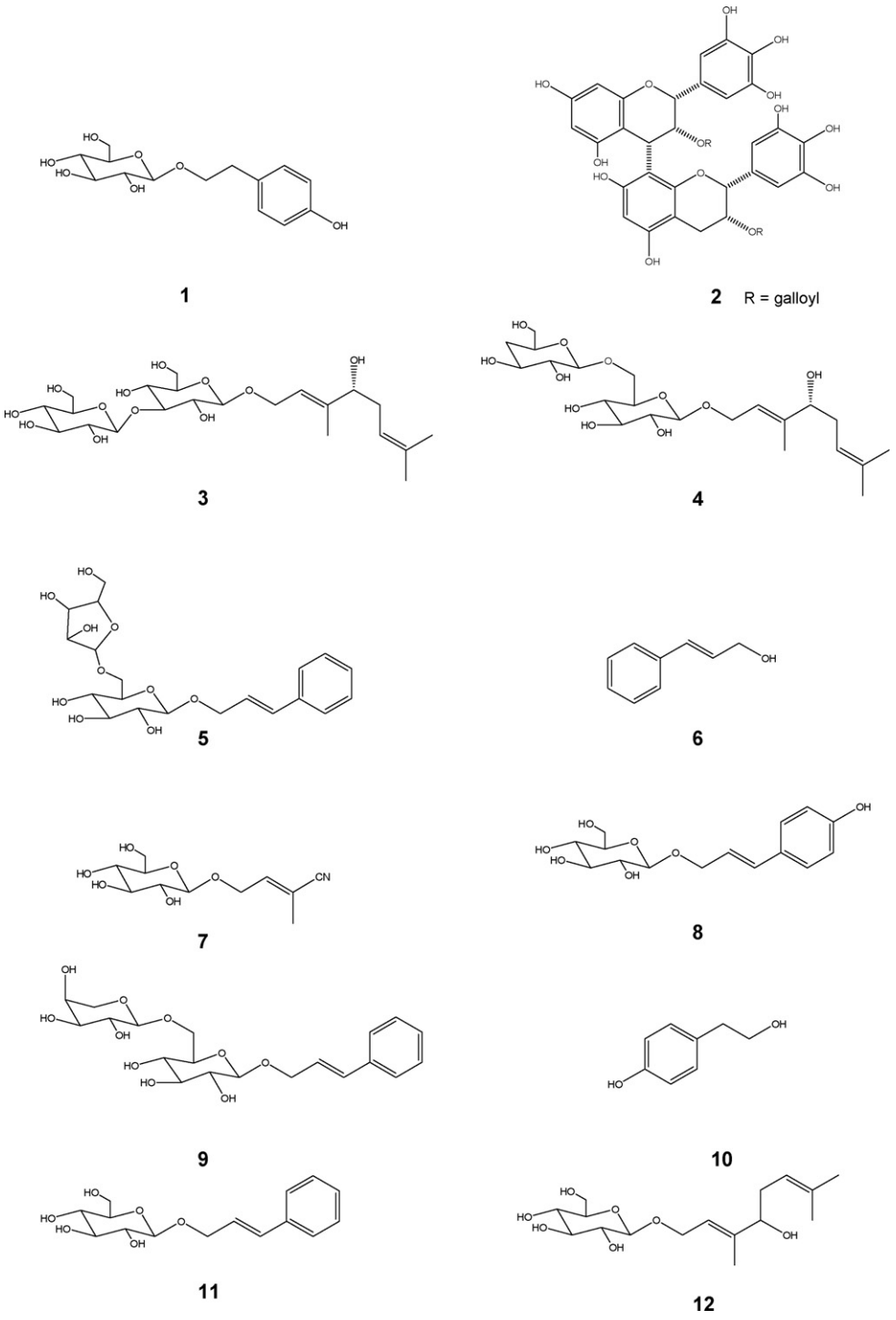

Fig. 1. Structures of the compounds isolated from the methanol and water extracts of the roots of *Rhodiola rosea* L.

according to the HPLC/UV trace at 366 nm yielding 25 mg of rhodiocyanoside A (**7**), 20 mg of salidroside (**1**), 3 mg of triandrin (**8**) and 6 mg of rosavin (**9**).

Tannins in the water extract were removed on a polyamide cartridge by solid phase extraction. The purified extract (350 mg) was separated by MPLC with MeOH–H_2O step gradient (10:90–70:30 in 5% steps) to afford four fractions. This purification led to the isolation of 3.0 mg of tyrosol (fraction 1, **10**), 2 mg of rosin (fraction 2, **11**), 2 mg of rosarin (fraction 3, **5**) and 20 mg of fraction 4. Separation of fraction 4 by CPC with $CHCl_3$:MeOH:isopropanol:H_2O (5:6:1:4; lower phase as mobile phase) yielded 3 mg of rosavin (**9**) and 8 mg of rosiridin (**12**).

Structures of purified compounds were elucidated by direct comparisons of their spectral data (^{1}H NMR, ^{13}C NMR and HR-MS) with those found in literature (LaLonde et al., 1976; Zapesochnaya and Kurkin, 1982; Yoshikawa et al., 1995; Fan et al., 2001; Tolonen et al., 2003; Lin and Chen, 2004; Kishida and Akita, 2005; Ma et al., 2006; Yousef et al., 2006; Takaya et al., 2007; Wiedenfeld et al., 2007).

3. Results and discussion

Dichloromethane, methanol and water extracts of *Rhodiola rosea* L. were tested against two enzymes: MAOs A and B, which are

targets in the search for new neuroprotective agents. Prominent inhibitory activity against both MAOs was found in the methanol and water extracts (Table 1). When the concentration of the extracts was 100 μg/ml, the activities relative to the positive controls (L-deprenyl and clorgyline) were for MAO A: 92.5% and 84.3% and for MAO B: 81.8% and 88.9%, respectively.

Bio-guided fractionation of both extracts was undertaken in order to identify the active compounds.

First fractionation of the MeOH extract by CPC yielded eleven fractions with two active fractions and one active pure compound (epigallocatechin gallate (EGCG) dimer, **2**). The active fractions showed an inhibitory activity of over 80% against MAOs A and/or B at a concentration of 100 μg/ml. The major metabolites of the active fractions were isolated by various preparative chromatography methods. Six compounds were purified and identified as salidroside (**1**), cinnamyl alcohol (**6**), rosarin (**5**), rhodiocyanoside A (**7**), triandrin (**8**) and rosavin (**9**). A mixture of rhodioloside B and C (**3**, **4**) isomers was also obtained. Bio-guided fractionation of the water extract by different chromatographic methods afforded five compounds including three phenylpropanoid glycosides: rosin (**11**), rosarin (**5**) and rosavin (**9**), the phenylethanol derivative tyrosol (**10**) and the monoterpene glycoside rosiridin (**12**).

The identities of the isolated compounds were established by HR-MS and comparison of their ^{1}H and ^{13}C NMR spectra with those reported in the literature. Their structures are shown in Fig. 1.

All the metabolites isolated from the active fractions were tested against MAOs A and B (Table 1).

Rosiridin (**12**) and the mixture of rhodioloside B and C isomers (**3**, **4**) exhibited the highest inhibitory activity (over 60% at concentration of 10^{-5} M) against MAO B.

The pIC_{50} ($-\log IC_{50}$) value of rosiridin for MAO B inhibition is estimated to 5.38 ± 0.05. The pIC_{50} value for the positive controls was 7.23 ± 0.04 for MAO B inhibition (L-deprenyl). The pIC_{50} values of rhodioloside B and C were not measured as these compounds were obtained as a mixture.

As the MAO B inhibitory activity of EGCG has already been described by Mazzio et al. (1998), its pIC_{50} for MAO B inhibition was measured although it only presented a moderate inhibition percentage. EGCG dimer gave a pIC_{50} of 4.82 ± 0.04. In the sigmoidal dose–response curve of EGCG dimer for MAO B inhibition, the Hill coefficient in the concentration–response equation is greater than unity. The Hill coefficient is related to the stoichiometry of inhibitor–enzyme interactions. It also represents the steepness of the concentration–response relationship (Robert, 2005). A high Hill coefficient can be diagnostic of non-ideal behavior. Notably, compounds that cause an abrupt inhibition above a critical concentration, hence producing concentration–response relationships with the Hill coefficient much greater than unity, usually reflect a nonspecific mechanism of inhibition. This can result for compounds that act as general protein denaturants. Such compounds do not effect inhibition by a specific interaction with a defined binding pocket on the enzyme molecule and are therefore generally not tractable as drug leads. High Hill coefficients can also result from very tight binding of inhibitors to enzyme targets and from irreversible inhibition of enzymes. Thus, the inhibition activity of EGCG dimer against MAOs A and B is rather attributed to its denaturant effect on proteins than to a specific mechanism of inhibition. Since the activity is not specific and thus not of great interest, the stereochemistry of the EGCG dimer has not been clarified.

The MeOH and water extracts gave over 80% inhibition of MAOs A and B at a concentration of 100 μg/ml. The inhibitory activity of the water extract may be explained by the presence of rosiridin, which gave an inhibition of 83.8% against MAO B at 10^{-5} M (pIC_{50} 5.38 ± 0.05). After fractionation of the methanol extract, three fractions showed elevated inhibitory activity. The activity of these three fractions may be explained by the additive effect of different compounds or possibly by synergism, the most active compounds being rosiridin (**12**), rhodioloside B and C isomers (**3**, **4**), cinnamyl alcohol (**6**), triandrin (**8**) and EGCG dimer (**2**). The activity may also be reinforced by the presence of known flavonoids such as quercetrin which have already been described as moderate MAO inhibitors (Lee et al., 2001; Petsalo et al., 2006).

The phenylpropanoid glycosides rosin (**11**), rosarin (**5**), and rosavin (**9**) have been described in the literature as the molecules responsible for the antidepressant activity (Zapesochnaya et al., 1995; Kurkin et al., 2006). Furthermore, Russian researchers have chosen rosavin as a marker compound. However, in this study, these phenylpropanoid glycosides presented no MAO inhibitory activity in the *in vitro* test.

This is the first report providing direct evidence that the roots of *Rhodiola rosea* have an influence on the levels of serotonin and norepinephrine in the nerve terminals by inhibiting MAOs A and B.

In conclusion, the present investigation demonstrates that extracts of *Rhodiola rosea* L. roots have potent anti-depressant activity by inhibiting MAO A. At the same time, these extracts can influence the progress of problems associated with Parkinsonism or Alzheimer's disease by inhibiting MAO B. These findings reinforce the claims made in ethnomedicine that *Rhodiola rosea* L. can be used as a remedy for depression and other nervous system disorders.

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