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Vasorelaxant Alkaloids from *Spirospermum penduliflorum* (Menispermaceae), a Plant Used to Treat Hypertension in Malagasy Traditional Medicine

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*SPIROSPERMUM PENDULIFLORUM* Thouars (Menispermaceae) is widely used on the eastern coast of Madagascar to treat hypertension. The aim of the present study was to analyse the vasorelaxant properties of different leaf extracts. The activity of the *n*-hexane, dichloromethane and methanol extracts was tested on phenylephrine-contracted aorta. The dichloromethane extract was shown to be the most effective. Further fractionation of this extract led to the isolation of an active fraction relaxing phenylephrine-contracted aorta with an IC50 of 0.18 ± 0.03 µg/mL which was much less effective on KCl induced contractions. Bioassay-guided fractionation of this fraction led to the isolation of two aporphine alkaloids, neolitsine and dicentrine, which at concentrations of 0.1 µM and 1 µM displaced to the right the phenylephrine-concentration-contraction curve. Our results show that *Spirospermum penduliflorum* extracts possess vasorelaxant activity in vitro that could be related to the presence of dicentrine in the extracts having an α1 antagonist activity. This finding is not in accord with the previous studies by Rasoanaivo et al. where no alkaloids were detected in the leaves of *Spirospermum penduliflorum*.

**Keywords:** *Spirospermum penduliflorum*, Menispermaceae, Aporphine alkaloids, Antihypertensive activity.

Madagascar is one of the lands where traditional medicine based on the use of plants has an important place in society. Several plants in the Malagasy flora are alleged to possess therapeutic virtues and are widely used by the local population. Many of these plants are used without pharmacological or phytochemical data or clinical evaluation. Our studies lead us to investigate plants used for the treatment of hypertension. Among these, *Spirospermum penduliflorum* (Menispermaceae) is mentioned to be effective against arterial hypertension. The aim of the present study was to verify the traditional use of the plant and to determine the nature of the bioactive compounds by a bio-guided fractionation approach combining chromatographic methods with vasorelaxant activity tests.

When tested on phenylephrine-contracted aorta (Figure 1), the *n*-hexane, dichloromethane (DCM) and methanol (MeOH) extracts showed significant vasorelaxant activity characterized by log IC50 (µg/mL) values of 1.4 ± 0.02, < -0.5 and 0.29 ± 0.01, respectively (Table 1). Isoprenaline, used as a reference standard, exhibited vasorelaxant activity with an IC50 of 1.7 ± 0.5 µg/mL.

Fractionation of the dichloromethane extract was then undertaken by preparative TLC giving 4 fractions named RR1, RR2, RR3 and RR4. Each fraction was tested at 1 µg/mL for its vasorelaxant activity on rat aorta contracted by phenylephrine (Table 1). RR4 showed the highest vasorelaxant activity, which was further investigated.

![Figure 1: Relaxing effect of different extracts of *Spirospermum penduliflorum* leaves in rat aorta contracted by phenylephrine (1 µM). (n = 6).](image)

**Table 1:** Vasorelaxing activities of the four fractions of the DCM extract on phenylephrine-induced contraction of rat aorta at 1µg/mL.

<table>
<thead>
<tr>
<th>Fractions</th>
<th>RR1</th>
<th>RR2</th>
<th>RR3</th>
<th>RR4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relaxation (%) (n = 4)</td>
<td>12.5 ± 0.09</td>
<td>100 ± 8.50</td>
<td>7.2 ± 0.6</td>
<td>37.5 ± 0.4</td>
</tr>
</tbody>
</table>

The relaxation of phenylephrine-induced contraction by RR1 was tested in rat aorta with (E+) and without endothelium (E-). Figure 2A shows that the activity of RR1 was not significantly different in either the presence or absence of functional endothelium: the log IC50 values (µg/mL) were -0.74 ± 0.03 and -0.61 ± 0.02 in the presence and absence of endothelium, respectively (IC50 values were 0.18 and 0.24 µg/mL, p > 0.05). To determine the potential role of β-adrenergic receptors in the vasorelaxant effect of RR1, aorta rings were pre-incubated with propranolol (1 µM) before the contractile response to phenylephrine.
Figure 2A shows that propranolol did not affect the vasorelaxant activity of RR1. Log IC 50 (µg/mL) of RR1 in the presence of propranolol was -0.54 ± 0.02 (0.29 µg/mL).

The potential involvement of voltage-dependent Ca2+ channels (VDCs) in the relaxing activity of RR1 was tested by measuring the effect of RR1 on KCl-induced contraction. When KCl (100 mM) was used to evoke the contraction of the aorta, RR1 produced a concentration-dependent relaxation. However, RR1 was less potent in inhibiting KCl-contraction than phenylephrine-contraction (Figure 2B). The IC 50 value for KCl-contraction was higher than 30 µg/mL (n = 6).

The developed TLC chromatogram of RR1 showed two well separated spots at Rf 0.62 and 0.81, which gave positive reactions with Dragendorff’s reagent. Fractionation by successive open column chromatography, followed by purification on preparative TLC led to the isolation of two active compounds, 1 and 2.

Comparison of our spectroscopic and mass spectrometric data with those in the literature, and with a reference sample, led us to the identification of compound 1 as dicentrine [1,2], and compound 2 as neolitsine [2].

Because of the small amount of neolitsine that could be isolated, the determination of its pharmacological profile was not possible. Dicentrine was tested for its relaxing activity on phenylephrine-induced contraction in endothelium-denuded artery rings. As shown in Figure 3A, preincubation of the aorta with dicentrine shifted the concentration-contraction curve of phenylephrine to the right, in a concentration-dependent manner. The EC 50 value of phenylephrine was significantly increased from 12 nM to 52 nM and 341 nM in the absence and in the presence of 0.1 µM and 1 µM of dicentrine, respectively (logEC 50 values were -7.9 ± 0.02 in control aorta, -7.14 ± 0.05 and -6.47 ± 0.03, in the presence of 0.1 µM and 1 µM dicentrine, respectively, p < 0.05 dicentrine vs control). Dicentrine also relaxed aorta pre-contracted with phenylephrine, with a logIC 50 (M) value of-5.53 ± 0.05 (IC 50 value was 2.95 µM) (Figure 3B).

High blood pressure represents the main cause of death in the world. A recent study in 2009 on the prevalence of hypertension in Antananarivo, Madagascar revealed that 28.0% of the adult population suffer from this disease with a mean age of 49 years. High blood pressure prevalence increased from 19.1% in 2000 to 28.0% in 2009 in Antananarivo [3].

Traditional phytomedical practice is common in Madagascar and Spirospermum penduliflorum is used as a traditional medicine to treat hypertension. We showed here that crude extracts of its leaves exhibited significant concentration-dependent relaxation on rat aorta pre-contracted by phenylephrine, the dichloromethane extract being the most effective (IC 50 < 0.3 µg/mL). We further studied the mechanism of action of the most active fraction (RR1) after a first fractionation of this extract. We found that the vasorelaxant activity was not inhibited by the beta-adrenergic antagonist propranolol indicating that the active compound(s) relaxed rat aorta by a mechanism other than the stimulation of the beta-adrenergic receptor.

When vasoconstriction was evoked by KCl (100 mM), RR1 was markedly less active than on phenylephrine pre-contracted aorta. This reduced relaxant activity of RR1 on KCl-induced contraction indicates that its activity is not related to inhibition of VDCs but to an alpha adrenergic receptor inhibition. Vasorelaxant activity can also be mediated by an effect of endothelium-released nitric oxide (NO). We observed that the activity on RR1 was not affected by removing the endothelium, indicating that endothelial NO does not contribute to the effect of RR1.

Bioguided fractionation of the RR1 fraction led to the isolation of two aporphine alkaloids identified as dicentrine and neolitsine. Indeed, the Menispermaceae family is known to be a rich source of aporphine alkaloids [4-6]. Previous studies of the root bark of Spirospermum penduliflorum have shown the presence of the bisbenzylisoquinoline alkaloids limacine and palmitine, and aporphine alkaloids [7,8]. The authors mentioned that they did not detect alkaloids in the leaves. That was not corroborated by our study. It is well known that production of secondary metabolites such as alkaloids is influenced by numerous factors such as the age of the plant or the leaves, and the nutrients present in the soil [9]. The influence of factors on alkaloid production could be the cause of this discordance, probably linked to the sensitivity of the detection method used.
In agreement with the interaction of the R1 fraction with the adrenergic pathway, dicentrine induced a concentration-dependent parallel shift of the phenylephrine concentration-contraction curve, suggesting that it could act as an antagonist of the α1-adrenoceptor. This result is in accordance with those reported in the literature. Indeed, a previous study on dicentrine isolated from Linderia megaphylla showed that it is an α1-adrenoceptor competitive antagonist [10]. Other studies on dicentrine corroborated this allegation [11,12]. Literature data also report that neolitnine is a potent vasorelaxing agent on precontracted rat aorta preparations [13]. The presence of dicentrine and neolitnine may support the use of the plant as an antihypertensive, but standardisation is necessary as it seems that the alkaloid concentration may be highly variable; such a quality control method has recently been described [14]. However, the total safety of the use of the plant is uncertain because dicentrine and neolitnine were shown to be cytotoxic [15-17], and so further toxicological studies are needed.

Experimental

Plant material: Fresh leaves of Spirospermum penduliflorum were collected from the east coast of Madagascar. Botanical identification was made by the botanist Benja Rakotonirina. A voucher specimen was deposited at the herbarium of IMRA (n° AML13).

Chemical compounds: The following reagents were purchased from Sigma (St Louis, MO): isoprenaline, acetylcholine, D-glucose, phenylephrine, propranolol, prazosin, dimethylsulfoxide and N-nitro-L-arginine. Dicentrine was isolated from Sequoia Research Products (Pangbourne, UK). Methanol, ethylacetate, and dichloromethane were purchased from Scharlab (Barcelona, Spain). All the salts (KCl, NaCl, NaHCO3, MgCl2 and CaCl2) were purchased from Prolabo (VWR international, Haasrode, Belgium).

Extraction: The plant material used was in the form of finely ground, dried leaves. Extraction was performed by successive maceration of the plant material (750 g) in increasing polarity solvents, namely n-hexane, dichloromethane, and methanol (2.5 L of each). The extracts were filtered and dried under reduced pressure.

Rat aorta: Wistar rats of either sex weighing between 200 to 300 g were used in the study. Animals were sacrificed, the thoracic aorta isolated and cut into rings of 2 mm in length. The rings were mounted under a tension of 2 g in organ baths containing Krebs solution (NaCl 122 mM, KCl 5.9 mM, NaHCO3 15 mM, MgCl2 1.25 mM, CaCl2 1.25 mM, and glucose 11 mM). When required, the endothelium was removed from the rat aorta rings by gently rubbing the luminal surface with a cotton rod before mounting the aorta ring in the organ bath. The bath solution was maintained at 37°C and gassed with 95% O2 and 5% CO2. Aorta were equilibrated in the medium for 2 h and the bath solution was changed every 30 min. After 1 h of equilibration, the tension was adjusted to 2 g. Contractures and relaxations were recorded with an UgoBasile 7003 isometric force transducer. All experiments were performed in accordance with international guidelines and the local ethics committee.

Pharmacological experiments

Relaxing activity on the contraction induced by phenylephrine: The relaxing activity was tested on phenylephrine pre-contracted aorta either in the absence or presence of endothelium. In both cases, after the equilibration, phenylephrine (1 µM) was added to the organ bath (20 mL) to induce contraction. At the steady-state contraction, acetylcholine (1 µM) was injected into the bath solution to relax the aorta in order to verify the presence of endothelium and its integrity. After 60 min of recuperation time, the artery rings were stimulated with phenylephrine (1 µM) and cumulative concentrations of the extracts (from 0.3 to 50 µg/mL), from a stock solution in DMSO/H2O (10:90, v/v) were added into the organ bath (20 mL) at the steady-state of contraction to evaluate the vasorelaxant activity. When required, aorta rings were incubated in the presence of propranolol (1 µM) for 30 min before inducing the contraction with phenylephrine.

Relaxing activity on KCl induced contractions: After 2 h equilibration with Krebs solution, the medium was removed and replaced with depolarizing solution containing: NaCl 27 mM, KCl 100 mM, NaHCO3 15 mM, MgCl2 1.25 mM, CaCl2 1.25 mM, and glucose 11 mM to induce contraction. After contraction had reached a maximum, the organ was rinsed 3 times with normal Krebs solution. After 30 min equilibration, the medium was replaced by depolarizing Krebs solution. Cumulative concentrations of the extracts (from 0.03 to 10 µg/mL) from a stock solution in DMSO/H2O (10:90, v/v) were added to the organ bath (20 mL) at the steady state of contraction.

Phenylephrine concentration-response curves: Concentration-response curves of phenylephrine (from 10-7 M to 3x10-5 M) were realized in endothelium-denuded aorta rings either without or in the presence of different concentrations of dicentrine (0.1 µM and 1 µM from stock solution in DMSO/H2O (10:90, v/v)). Contraction was expressed as percent of the maximum response obtained in the absence of inhibitor in the same artery ring. The concentration-effect curves were built and the concentrations of phenylephrine producing 50% of the maximum aorta contraction (EC50) were calculated and compared.

Chromatographic methods: TLC was realized on silica gel 60F254 plates (Merck) using n-hexane/ethyl acetate/ethanol/NH4OH (6/2.5/0.01) as mobile phase. The separated components were visualized under visible and ultraviolet light (254 and 365 nm) or using Dragentorff’s spray reagent. Fractionation was made by successive open CC using either silica gel 60 (0.063 – 0.200 mm, Merck Darmstadt, Germany) as stationary phase or Sephadex Gel LH-20 (Pharmacia Biotech Healthcare, Diegem, Belgium) using as eluant a mixture of dichlomethane-methanol (1:1, v/v). Final purification was achieved by preparative TLC on Silica Gel 60 GF254 plates (Merck Darmstadt, Germany). The mobile phase was a mixture of ethyl acetate/methanol (9:1).

Identification method: Identification of the isolated compounds was performed with a LCQ Advantage Thermo Finnigan (Waltham, MA, USA) mass spectrometer piloted by X-Calibur software. Mass spectra were determined using an APCI source in positive mode, a vaporizer temperature of 455°C, a sheath gas flow rate of 45 (a.u.) and a capillary voltage of 2V. 13C and 2H NMR spectra were recorded on a Bruker Avance DRX-400 spectrometer in CDCl3, CD3OD or DMSO at 400 MHz (1H) and 100 MHz (13C), at 30°C. A combination of COSY, HMQC, HMBC and ROESY experiments were used when necessary for the assignment of 1H and 13C chemical shifts.

Statistical analysis: The relaxant effect of the tested products was expressed as percent of the steady-state contraction induced by the agonist or the KCl-depolarizing solution. The log values of EC50, which is defined as the concentration producing 50% of the maximum response, or of IC50 (concentration inhibiting the contraction by 50%) were determined from the non-linear combination of COSY, HMQC, HMBC and ROESY experiments.
regression of the experimental data (Prism, GraphPad) and used for the statistical analysis. Each test was repeated in 3 inter-day experiments. The results are presented as the mean ± S.E.M. of n observations. Values were analyzed using Student’s t-test and were considered to be significantly different when p< 0.05.

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References


Eight New Alkyne and Alkene Derivatives from Four Saussurea Species Collected in China
Yoshinori Saito, Yoko Iwamoto, Yasuko Okamoto, Takayuki Kawahara, Xun Gong, Chiaki Kuroda and Motoo Tori

The Apoptotic Activity of one VLC Fraction of the Sponge Petrosia tuberosa on Human Cervical Cells and the Subsequent Isolation of a Bioactive Polyacetylene
Avin Ramanjooloo, Girish Beedessee, Deepak Arya, Rob WM. van Soest, Thierry Cresteil and Daniel E.P. Marie

Chemical Characterization, Mineral Content and Radical Scavenging Activity of Sideritis scardica and S. raeseri from R. Macedonia and R. Albania
Marija Karapandzova, Bujar Qazimi, Gjoshe Stefkov, Katerina Bačeva, Trajče Stafilov, Tatjana Kadičkova Panovska and Svetlana Kulevanova

Phytochemical and Micromorphological Traits of Geranium dalmaticum and G. macrorrhizum (Geraniaceae)
Dario Kremer, Dubravka VITALI Ćepo, Valerija Đurđić, Ivna Dragojević Müller, Ivan Kosalec, Nada Bezić and Edith Stabentheiner

GC-MS Fingerprints and Other Physico-chemical Characteristics of Rare Unifloral Prunus cerasus L. Honey
Piotr Marek Kusi, Igor Jerković, Carlo Ignazio Giovanni Tuberoso, Zvonimir Marijanović and Mladenka Šarolić

Volatile Fraction Composition and Total Phenolic and Flavonoid Contents of Elionurus hensii—Antioxidant Activities of Essential Oils and Solvent Extracts
Yin Yang, Marie-Cécile De Cian, Samuel Nsikabaka, Pierre Tomi, Thomas Silou, Jean Costa and Julien Paolini

Leaf Essential Oils of Six Vietnamese Species of Fissistigma (Annonaceae)
Martina Höferl, Do Ngoc Dai, Tran Dinh Thang, Leopold Jirovetz and Erich Schmidt

Studies on the Antimicrobial and Antioxidant Activity and Chemical Composition of the Essential Oils of Kitai belia vitifolia
Pavle Mašković, Marija Radojković, Mihailo Ristić and Slavica Solajtić

Angiotensin Converting Enzyme Inhibition Activity of Fennel and Coriander Oils from India
Sushil Kumar Chaudhary, Niladri Maity, Neelesh Kumar Nema, Santanu Bhadra, Bishnu Pada Saha and Pulok Kumar Mukherjee

Effect of Coriander Oil (Coriandrum sativum) on Planktonic and Biofilm Cells of Acinetobacter baumannii
Andrea F. Duarte, Susana Ferreira, Rosário Oliveira and Fernanda C. Domingues

Essential Oil from Caesalpinia peltophoroides Flowers – Chemical Composition and in vitro Cytotoxic Evaluation
Bianca A. de Carvalho, Olivia S. Domingos, Murilo Massoni, Marcelo H. dos Santos, Marisa Ionta, João Henrique G. Lago, Carlos R. Figueiredo, Alisson L. Matsuo and Marisi G. Soares

Antimicrobial, Antioxidant, and Cytotoxic Activities of the Essential Oil of Tarchonanthus camphoratus
Nasser A. Awadh Ali, Mohamed A. Al-Fatimi, Rebecca A. Crouch, Annika Denkert, William N. Setzer and Ludger Wessjohann
Natural Product Communications
2013
Volume 8, Number 5
Contents

Gerald Blunden Award (2012)  Page
Cytotoxic Agents of the Crinane Series of Amaryllidaceae Alkaloids
Jerald J. Nair, Jaume Bastida, Francesc Viladomat and Johannes van Staden 553

Original Paper

Chemosystematics of the Thai Liverwort Cheilolejeunea (Marchantiophyta, Lejeuneaceae)
Phiangphak Sukkharak and Yoshinori Asakawa 565

Cytotoxic Properties of Marrubium globosum ssp. libanoticum and its Bioactive Components
Mariangela Marrelli, Filomena Conforti, Daniela Rigano, Carmen Formisano, Maurizio Bruno, Felice Senatore and Francesco Menichini 567

Cytotoxic Scalarane Sesterterpenoids from a Marine Sponge Hippospongia sp.
Yuh-Ming Fuh, Mei-Chin Lu, Chia-Hung Lee and Jui-Hsin Su 571

Ursane-Type Saponins from Zygophyllum cornutum
Soumyen Bancharif-Betina, Tomofumi Miyamoto, Chiaki Tanaka, Zahia Kabouche, Anne-Claire Mitaine-Offert and Marie-Alethe Lacaille-Dubois 573

Vasorelaxant Alkaloids from Spirospermum penduliflorum (Menispermaceae), a Plant Used to Treat Hypertension in Malagasy Traditional Medicine
Guy E. Raelelson, Manny H. Rafamantananana, René Razafindrazaka, Adolphe Randriantsoa, Suzanne Urverg-Ratsimamanga, Nicole Morel and Joëlle Quetin-Leclercq 575

PPARα Signaling is Activated by Cocoa in Mouse Liver
Marco Fidaleo and Claudia Sartori 579

Chemical Analysis of Flowers of Bombax ceiba from Nepal
Khem Raj Joshi, Hari Prasad Devkota and Shoji Yahara 583

Chemical Investigation of Caragana arborescens Shoots
Daniil N. Olennikov, Larisa M. Tankhaeva and Vyacheslav V. Partilkhaev 585

A New Metabolite from the Endophytic Fungus Penicillium citrinum
Xinlan Li, Liang Zhang, Yanyan Liu, Zhiyong Guo, Zhanhguang Deng, Jianfeng Chen, XuanTu and Kun Zou 587

Antioxidant Activity of the Isolavonoids from the Roots of Maackia amurensis
Nadezda I. Kulesh, Sergey A. Fedoreyev, Marina V. Veselova, Natalia P. Mischenko, Vladimir A. Denisenko, Pavel S. Dmitrenok, Yakov F. Zverev and Svetlana V. Zamyatina 589

The Effect of Pyridinecarbothioamides on Isoflavonoid Production in Genista tinctoria Cultures in Vitro
Lenka Tůmová, Věra Klimešová and Anna Vildová 593

A New Homoisoflavanone from the Rhizomes of Polygonatum cyrtonema
Li-She Gan, Jin-Jie Chen, Man-Fei Shi, and Chang-Xin Zhou 597

Two 2-Phenylbenzofuran Derivatives from Morus atropurpurea
Wen-Jing Wang, Dong-Ling Wu, Shen-Tai Liao, Chun-Lin Fan, Guo-Qiang Li, Xian-Tao Zhang, Ying Wang, Xiao-Qi Zhang and Wen-Cai Ye 599

10'-Deoxy-10'-α-hydroxyasclochlorin, a New Cell Migration Inhibitor and Other Metabolites from Acremonium sp., a Fungal Endophyte in Ephedra trifurca
W. M. Anoja P. Wanigesekara, E. M. Kithsiri Wijeratne, A. Elizabeth Arnold and A. A. Leslie Gunatilaka 601

Polyphenols in the Aqueous Extracts of Garden Thyme (Thymus vulgaris) Chemotypes Cultivated in Hungary
Blanka Szilvássy, Gábor Rak, Szilvia Sárosi, Ildikó Novák, Zsuzsanna Plehár and László Abrankó 605

Resveratrol Production from Hairy Root Cultures of Scutellaria baicalensis
Sang-Won Lee, Young Seon Kim, Md. Romij Uddin, Do Yeon Kwon, Yeon Bok Kim, Mi Young Lee, Sun-Ju Kim and Sang Un Park 609

Anti-periodontal Pathogen and Anti-inflammatory Activities of Oxyresveratrol
Waranyoo Phoolcharoen, Sirerat Sootampon, Boonchoo Sritularak, Kittisak Likhiwitayawud, Jintakorn Kuvatanasuchati and Prasit Pavasant 613

The Triple Botanical Origin of Russian Propolis from the Perm Region, Its Phenolic Content and Antimicrobial Activity
Milena Popova, Boryana Trusheva, Rail Khismatullin, Natalia Gavrilova, Galina Legotkina, Jaroslav Lyapunov and Vassya Bankova 617

Comparing Different Solvent Extracts of Rhus semialata var. roxburghiana Stem against Ferrous Ion-Induced Lipid Peroxidation in Mice Liver Mitochondria
Pei-Chin Lin, Wei-Fung Bi, Che-Hsuan Lin, Fei-Peng Lee and Ling-Ling Yang 621

Antioxidant Activity of Solid Preparation of Xingnaojing in SHRSP
Yang Liu, Naomi Yasui, Aya Kishimoto, Jian-ning Sun and Katsumi Ikeda 627

Antioxidant and Anti-tyrosinase Activity of Cissus quadrangularis Extract
Ikuko Suzuki, Hiroki Goto, Nami Higashisaki, Shinichiro Hattori, Kanjana Rotjanapan, Wilairat Leeanansaksiri and Seiji Okada 629

Continued inside backcover