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Editors

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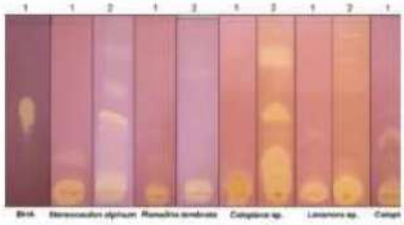
21 articles in this issue

Thin layer chromatography analysis of antioxidant constituents of lichens from Antarctica

Hari Datta Bhattarai, Babita Paudel ... Joung Han Yim

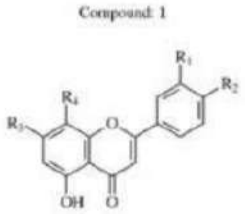
Natural Resource Letter | Published: 17 June 2008 | Article: 481



Preliminary phytochemical investigation of *Lychnis flos-cuculi* herbs

Michał Tomczyk

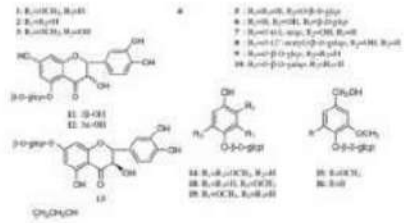
Natural Medicine Note | Published: 17 June 2008 | Article: 473



Chemical constituents of *Hypericum erectum* Thunb.

Erika Matsuoka, Koichi Machida & Masao Kikuchi

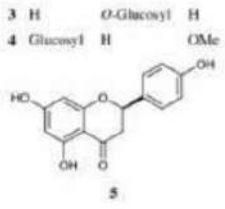
Natural Medicine Note | Published: 17 May 2008 | Article: 467



Free-radical-scavenging principles from *Phlomis caucasica*

Abbas Delazar, Araz Sabzevari ... Satyajit Dey Sarker

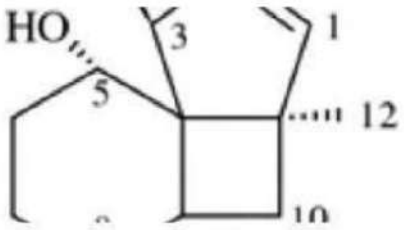
Natural Medicine Note | Published: 17 May 2008 | Article: 464



A new sesquiterpene from *Artemisia vulgaris*

Consolacion Y. Ragasa, Jenny P. de Jesus ... John A. Rideout

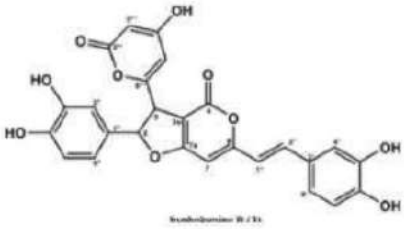
Natural Medicine Note | Published: 26 April 2008 | Article: 461



HPLC profiling of *Phellinus linteus*

Kazuo Kojima, Yukio Ogihara ... Akito Nagatsu

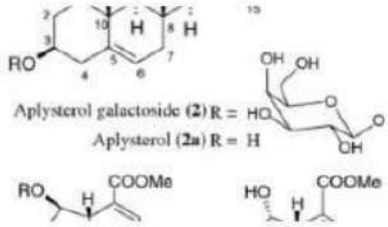
Note | Published: 04 June 2008 | Pages: 441 - 446



Iridoid glucoside and sterol galactoside from *Mussaenda macrophylla*

Biswanath Dinda, Santanu Majumder ... Yoshihiro Harigaya

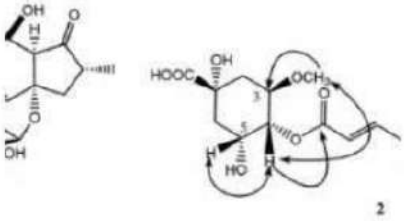
Note | Published: 14 August 2008 | Pages: 447 - 451



Chemical and biologically active constituents of *Pteris multifida*

Liva Harinantenaina, Katsuyoshi Matsunami & Hideaki Otsuka

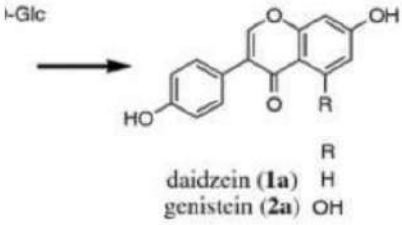
Note | Published: 14 June 2008 | Pages: 452 - 455



Microbial metabolism of soy isoflavones by human intestinal bacterial strains

Ryota Tsuchihashi, Seiichi Sakamoto ... Junei Kinjo

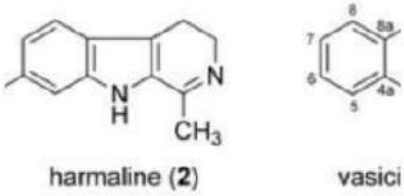
Note | Published: 23 July 2008 | Pages: 456 - 460



Alkaloids from the seeds of *Peganum harmala* showing antiplasmodial and vasorelaxant activities

Adil Astulla, Kazumasa Zaima ... Hiroshi Morita

Natural Medicine Note | Published: 04 June 2008 | Pages: 470 - 472



Glycosidic constituents of the leaves of an Okinawan Leguminosae plant, *Derris trifoliata* Lour.

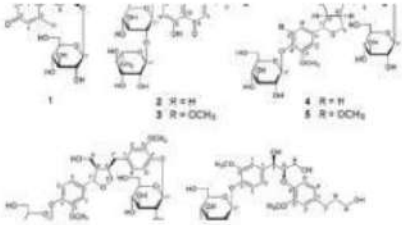
Yoshio Takeda, Kaori Yano ... Mitsunori Aramoto

Natural Medicine Note | Published: 11 June 2008 | Pages: 476 - 478

Glycosides from whole plants of *Glechoma hederacea* L.

Masao Kikuchi, Junichi Goto ... Yasunori Yaoita

Natural Medicine Note | Published: 17 June 2008 | Pages: 479 - 480



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NATURAL MEDICINE NOTE

Alkaloids from the seeds of *Peganum harmala* showing antiplasmodial and vasorelaxant activities

Adil Astulla · Kazumasa Zaima · Yosuke Matsuno · Yusuke Hirasawa · Wiwied Ekasari · Aty Widyawaruyanti · Noor Cholies Zaini · Hiroshi Morita

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Abstract Bioassay-guided purification from the seeds of *Peganum harmala* led to the isolation of harmine (**1**), harmaline (**2**), vasicinone (**3**), and deoxyvasicinone (**4**). Harmine (**1**) and harmaline (**2**) showed a moderate in vitro antiplasmodial activity against *Plasmodium falciparum*. Quinazoline alkaloid, vasicinone (**3**), showed a vasorelaxant activity against phenylephrine-induced contraction of isolated rat aorta.

Keywords *Peganum harmala* · Antiplasmodial activity · Vasorelaxant activity · Harmine · Harmaline · Vasicinone · Deoxyvasicinone

Peganum harmala L. (Zygophyllaceae), the so-called "Harmal" is native in the steppe areas of semiarid and predesert regions, such as Xinjiang in China [1]. It has been used as an entheogen in the Middle East [2]. The seeds contain about 2 to 6% alkaloids, and the active alkaloids of Harmal seeds, harmine and harmaline, have been isolated from the seeds of *P. harmala* [2].

Apart from widespread use of these β-carboline alkaloids, which show monoamine oxidase inhibition [3] and are used as a psychoactive drug to treat Parkinson's disease [4, 5], they have exhibited various bioactivities, such as anti-bacterial activity [6, 7], cytotoxicity against human cancer cell lines [8], antitumoral activity [9, 10], anti-oxidant activity [11], enzyme inhibition [12], immunomodulator properties [13], vasodilator activity on rat aorta [14, 15], and antileishmanial activity toward parasites of *Leishmania infantum* [16, 17].

We recently reported that some alkaloids and peptides showed antiplasmodial activity [18] and vasorelaxant activity on rat aorta [19, 20]. On continuing the search for chemical constituents with antiplasmodial and vasorelaxant activities in medicinal plants, we examined the isolation of alkaloids with antiplasmodial and vasorelaxant activities from the seeds of *P. harmala*.

The dried seeds of *P. harmala* (500 g) were extracted with MeOH, and the extract was partitioned between EtOAc and 3% tartaric acid. Water-soluble fractions, which were adjusted at pH 10 with saturated Na_2CO_3, were extracted with $CHCl_3$. $CHCl_3$-soluble materials were subjected to a silica gel column (NH_3-saturated $CHCl_3$/EtOAc/MeOH, 20:1:1) followed by a preparative silica gel TLC (NH_3-saturated $CHCl_3$/MeOH, 9:1) to give harmine (**1**, 0.05%) [11], harmaline (**2**, 0.03%) [11], vasicinone (**3**, 0.002%) [21, 22], and deoxyvasicinone (**4**, 0.004%) [6, 7] (Fig. 1).

Although vasorelaxant effects of harmine (**1**) and harmaline (**2**) have already been evaluated [14, 15], there is no report on the of quinazoline alkaloids, vasicinone (**3**) and deoxyvasicinone (**4**). After achieving a maximal response to thoracic aortic rings with endothelium by phenylephrine (PE, 3×10^{-7} M), vasicinone (**3**) showed vasorelaxant action at 3×10^{-5} M (Fig. 2), whereas deoxyvasicinone (**4**) did not. The vasorelaxant activity of vasicinone (**3**) was observed in a concentration-dependent manner. Treatment with N^G-monomethyl-L-arginine (L-NMMA, 10^{-4} M), an inhibitor of nitric oxide (NO) synthase, inhibited vasicinone-induced vasorelaxation. The vasodilator effect of **3**

A. Astulla · K. Zaima · Y. Matsuno · Y. Hirasawa · H. Morita (✉)
Faculty of Pharmaceutical Sciences, Hoshi University, Shinagawa, Tokyo 142-8501, Japan
e-mail: moritah@hoshi.ac.jp

W. Ekasari · A. Widyawaruyanti · N. C. Zaini
Faculty of Pharmacy, Airlangga University, Jalan Dharmawangsa Dalam, Surabaya 60286, Indonesia

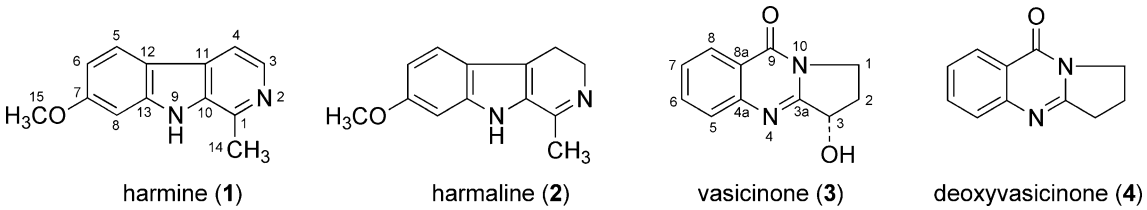

Fig. 1 Structures of harmine (**1**), harmaline (**2**), vasicinone (**3**), and deoxyvasicinone (**4**)

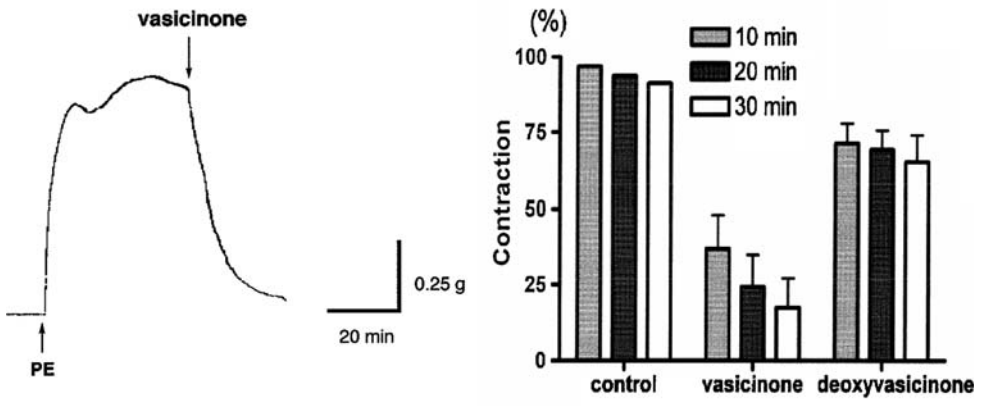

Fig. 2 Typical recording of vasicinone (**3**, 3×10^{-5} M) and the relaxation responses of **3** and deoxyvasicinone (**4**, 3×10^{-5} M) on aortic rings precontracted with 3×10^{-7} M phenylephrine (PE)

may be mediated through the increased release of NO from endothelial cells.

Malaria caused by parasites of the genus *Plasmodium* is one of the leading infectious diseases in many tropical and some temperate regions. The emergence of widespread chloroquine-resistant and multiple-drug-resistant strains of malaria parasites leads to the need for the development of new therapeutic agents against malaria [23, 24]. Since harmine (**1**) and harmaline (**2**) have already been reported to have an inhibitory activity against some parasites [16, 17], the inhibitory effect on the *Plasmodium* parasite was evaluated. Harmine (**1**) and harmaline (**2**) showed a moderate in vitro antiplasmodial activity against *Plasmodium falciparum* (IC_{50} **1** 8.0 μg/ml; **2** 25.1 μg/ml) [25, 26], whereas vasicinone (**3**) and deoxyvasicinone (**4**) did not show an effect (>10 μg/ml).

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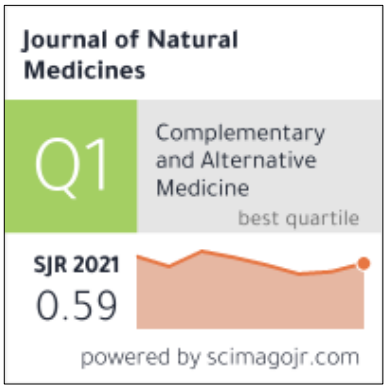

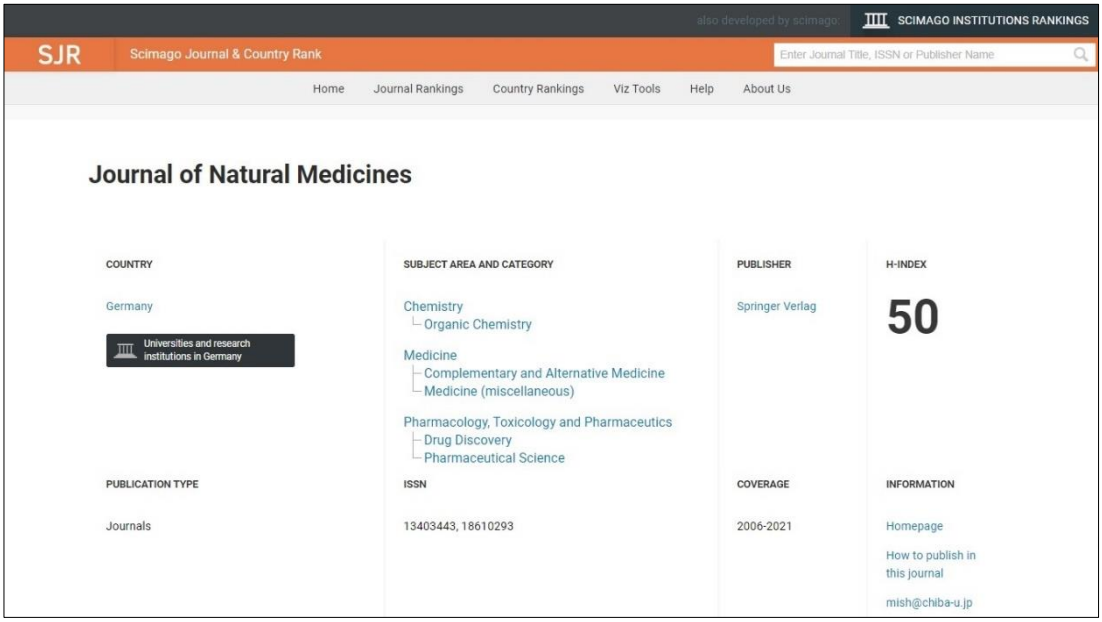

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