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

by Wiwied Ekasari

Submission date: 01-Nov-2021 11:29AM (UTC+0800)
Submission ID: 1689571219
File name: C-09 - J Nat Med_naskah.pdf (70.76K)
Word count: 1594
Character count: 8583

J Nat Med (2008) 62:470–472
DOI 10.1007/s11418-008-0259-7

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

Received: 22 February 2008 / Accepted: 28 April 2008 / Published online: 4 June 2008

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

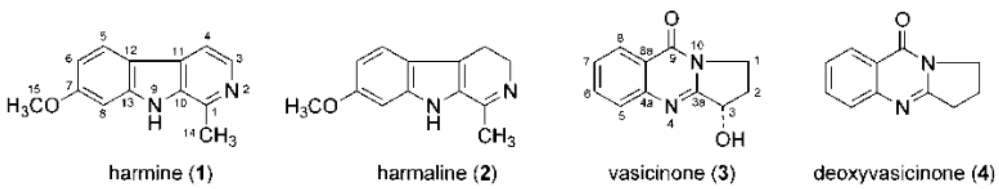

Fig. 1 Structures of harmine (**1**), harmaline (**2**), vasicinone (**3**), and deoxyvasicinone (**4**)

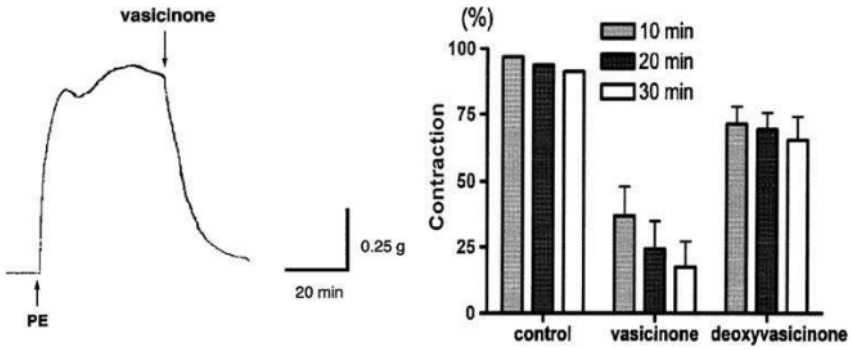

Fig. 2 Typical recording of vasicinone (**3**, 3×10^{-5} M) and the relaxation responses of **3** and deoxyvasicinone (**4**, 3×10^{-5} M) on aortic rings precontracted with 3×10^{-7} M phenylephrine (PE)

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).

Acknowledgments This work was supported by a grant-in-aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, and a grant by the Open Research Center Project. We also acknowledge the financial support provided by the Faculty of Pharmacy, Arlangga University, Indonesia.

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