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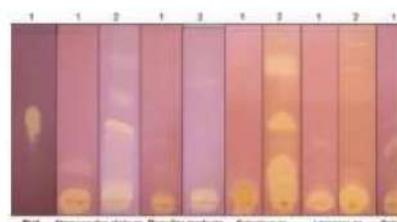
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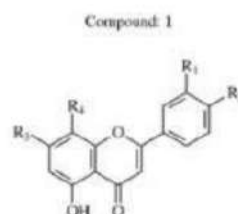
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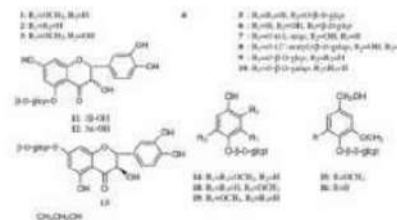
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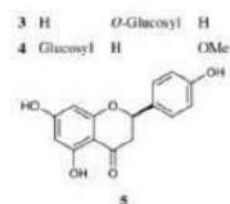
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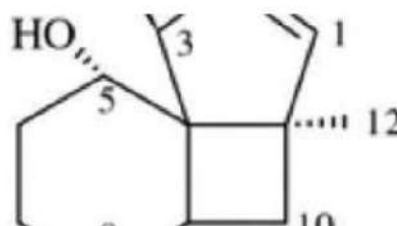
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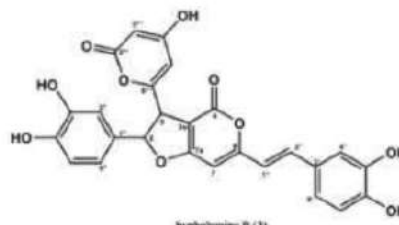
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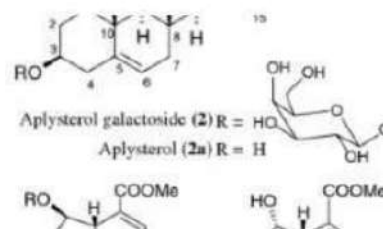
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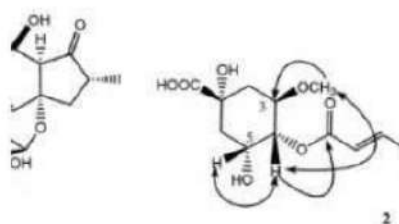
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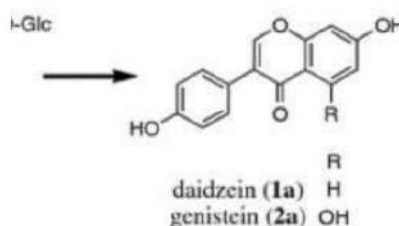
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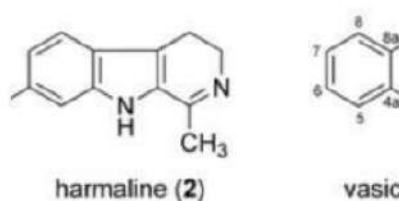
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## Glycosidic constituents of the leaves of an Okinawan Leguminosae plant, *Derris trifoliata* Lour.

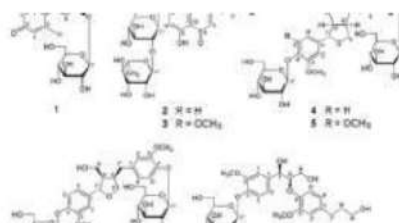
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## Alkaloids from the seeds of *Peganum harmala* showing antiplasmodial and vasorelaxant activities

Adil Astulla · Kazumasa Zaima · Yosuke Matsuno ·  
Yusuke Hirasawa · Wiwied Ekasari · Aty Widawaruyanti ·  
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 pre-desert 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  $\beta$ -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].

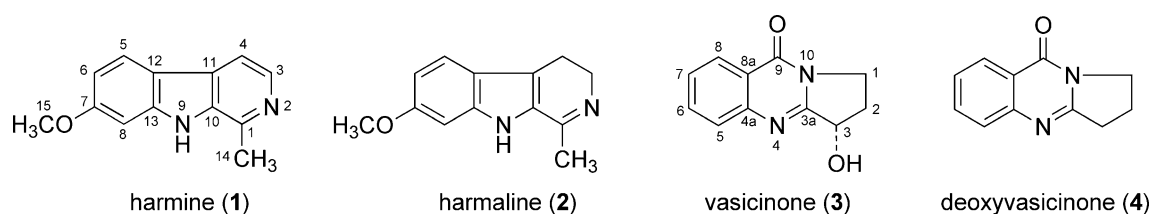
We recently reported that some alkaloids and peptides showed antiplasmodial activity [18] and vasorelaxant activity on rat aorta [19, 20]. On continuing the search for chemical constituents with antiplasmodial and vasorelaxant activities in medicinal plants, we examined the isolation of alkaloids with 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  $\text{Na}_2\text{CO}_3$ , were extracted with  $\text{CHCl}_3$ .  $\text{CHCl}_3$ -soluble materials were subjected to a silica gel column ( $\text{NH}_3$ -saturated  $\text{CHCl}_3/\text{EtOAc}/\text{MeOH}$ , 20:1:1) followed by a preparative silica gel TLC ( $\text{NH}_3$ -saturated  $\text{CHCl}_3/\text{MeOH}$ , 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).

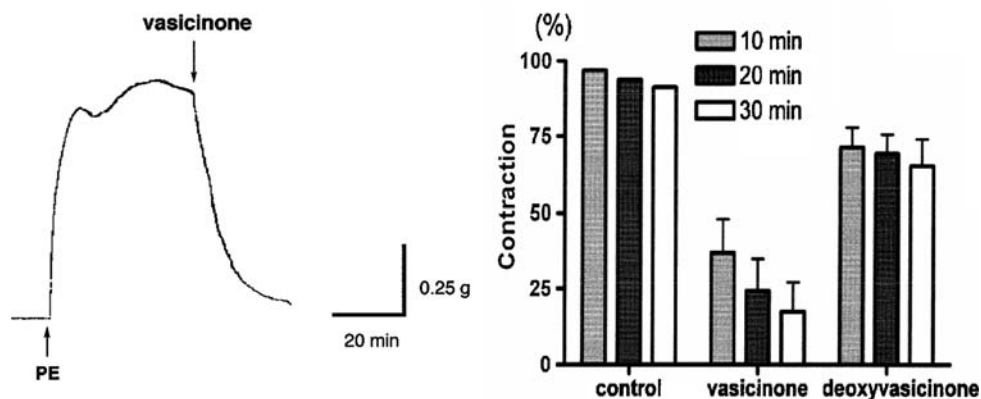
Although vasorelaxant effects of harmine (**1**) and harmaline (**2**) have already been evaluated [14, 15], there is no report on the of quinazoline alkaloids, vasicinone (**3**) and deoxyvasicinone (**4**). After achieving a maximal response to thoracic aortic rings with endothelium by phenylephrine (PE,  $3 \times 10^{-7}$  M), vasicinone (**3**) showed vasorelaxant action at  $3 \times 10^{-5}$  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**

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



**Fig. 2** Typical recording of vasicinone (3,  $3 \times 10^{-5}$  M) and the relaxation responses of 3 and deoxyvasicinone (4,  $3 \times 10^{-5}$  M) on aortic rings precontracted with  $3 \times 10^{-7}$  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<sub>50</sub> 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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