Title	INVESTIGATION OF PHOSPHODIESTERASE 5 INHIBITORS FROM SOME THAI MEDICINAL PLANTS.
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ABSTRACT

In Thailand, many medicinal plants have been used traditionally as sexual performance enhancers. They could be a potential source for phosphodiesterase5 (PDE5) inhibitors which can be used for erectile dysfunction. In the previous study, we found that some of these plants could inhibit mixture PDEs. In this study, we aimed to determine PDE5 inhibitory activity of these Thai medicinal plants. The active plant extracts were further studied and the PDE5 inhibitors were isolated and identified. Moreover, PDE5 inhibitory activity of some natural product analogs was explored.

From 60 plant extracts tested, *Caesalpinia sappan* L., *Kaempferia parviflora* Wall. ex Baker, *Acacia auriculaeformis* A. Cunn., *Senna surattensis* (Burm.f.) Irwin & Barneby, *Curcuma longa* L., *Curcuma zedoaria* (Berg) Roscoe, *Curcuma petiolata* Roxb., *Curcuma* sp. (Nang-Kam) and *Eulophia macrobulbon* (Parish & Rchb. f.) Hook. f. showed the PDE5 inhibitory effect. The chemical constituents isolated from *K. parviflora* were selected and explored on inhibitory activity against PDE5. The results showed that 7-methoxyflavones from this plant could inhibit PDE5 in micromolar range. The most potent inhibitory activity was obtained from 5,7-dimethoxyflavone. It suggested that methoxy group at C-5 position of 7-methoxyflavones was necessary for PDE5 inhibitory effect. Moreover, from bioassay guided fractionation, we could isolate PDE5 inhibitors from *E. macrobulbon*.

Spectroscopic data revealed that these active compounds belonged to phenanthrene groups. The most potent inhibitor was 1-(4′-hydroxybenzyl)-4,8-dimethoxyphenanthrene-2,7-diol which had IC_{50} value of 1.67±0.54 µM. Interestingly, a new 9,10-dihydrophenanthrene compound i.e. 9,10-dihydro-4-(4′-hydroxybenzyl)-2,5-dimethoxyphenanthrene-1,7-diol was found and showed mild activity on PDE5 with IC_{50} value of 62.26±32 µM. As PDE5 was also profound in lungs, the effect of crude ethanolic extract of *E. macrobulbon* on rat pulmonary artery was investigated. Interestingly, the vasorelaxant activity of this plant extract was clearly observed. The further study related to the use of the extract or its constituents on pulmonary hypertension can be worthwhile.

Beside natural substances, the synthesis analogs, dihydroisoquinoline (DHIQ) and tetrahydroisoquinoline (THIQ), were investigated on the mixture PDEs and PDE5 inhibitory activities. Comparing between isoquninoline derivatives, DHIQ structure showed higher inhibition effects on both tests. The reason of these observations might be (1) weaker base of DHIQ which had more electron density around nitrogen atom and (2) more rigid conformation of DHIQ. The substitution on C-1 position of DHIQ was the crucial point for PDEs and PDE5 inhibitory activity.

In conclusion, this study showed the potential of natural products as a source of PDE5 inhibitors. Three groups of compound i.e. flavones, phenanthrenes and DHIQ could be leads for the development of PDE5 inhibitors.