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Antinociception effect of *Piper betle* extracts in rats

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The aim of this study was to investigate the antinociceptive activity of *P.betle* L. (Family: Piperaceae, S. *Bulath*) hot water extract HWE) and cold ethanolic extract (CEE) using three models namely hot plate, tail flick and formalin test. In addition, the mode of antinociceptive activity also was determined.

Different doses of HWE / CEE s (125, 200, 300 & 500 mg/kg) and distilled water (DW) were orally administrated to separate groups of healthy adult male rats (n = 9 /group). To another group of rats (n= 6) pethidine (25 mg/kg) was subcutaneously injected as the positive drug. The hot plate and tail flick latencies were determined before the treatment (pre- treatment) and hourly up to 5 hours after the treatment (post treatment). Formalin test was done to both extracts of *P. betle* that posses significant antinociceptive activity in hot plate or tail flick tests.

Results showed that a marked antinociceptive effect was evident when assessed by the hot plate test (200/300 mg/kg and 125/500 mg/kg doses of CEE: up to 5 h and 2 h respectively ; 200 and 300 mg/kg doses of HWE : up to 5 h and 3 h respectively) and the formalin test but not in the tail flick test. To evaluate a mechanism for antinociceptive activity of *P. betle*, CEE was used since the activity was higher in CEE. None of the parameters in the "Rat hole – board test" was altered and failed to inhibit heat induced haemolysis of rat erythrocytes in vitro. The antinociception action of CEE was not blocked by metoclopramide, a dopamine receptor antagonist. However, subcutaneous administration of naloxone significantly impaired the reaction time induced by CEE in the hot plate test.

The results indicated that *P. betle* is effective against acute phasic pain and the effect is mediated centrally at the supraspinal level. Antinociceptive activity of the CEE was not mediated via sedation and the antinociception is unlikely to be due to membrane stabilizing effect. The mechanism of action of the antinociception may be through the opioid receptors as the effect of *P. betle* was blocked by nalaxone. Therefore, it can be concluded that both HWE and CEE of Sri Lankan grown *Piper betle* leaves have antinociceptive activity in rats and isolation of active compounds in *P. betle* extracts is likely to yield agents with potential for antinociceptive drug development.

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