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Antinociceptive effect and toxicological study of the aqueous inner stem bark extract of *Kokoona zeylanica* on rats

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Kokoona zeylanica Thw. (family :celastraceae;Sinhala: Kokun) is an endemic plant used in traditional medicine of Sri Lanka for headache and snake bites. However, its antinociceptive activity has not been scientifically investigated so far. The aim of this study was to examine the antinociceptive potential, toxicity and phytochemistry of aqueous inner stem bark extract (ISBE) of *K. zeylanica*. Phytochemical screening of the ISBE showed the presence of alkaloids, flavonoids, tannins/polyphenols, steroids, terpenoids and saponins. Antinociceptive activity was investigated using rats in three test models of nociception (tail flick, hot plate and formaline tests). The results showed that the oral administration of ISBE at different dose (750, 1500, 2500 mg kg^{-1}) led to significant ($P < 0.05$) antinociceptive activity (when evaluated in hot plate and formaline tests but not in tail flick test). The 2500 mg kg^{-1} dose had the highest antinociceptive activity compared to the control. The antinociceptive activity of ISBE had a rapid onset (within 1 h) and a fairly long duration of action (up to 5 h) with a peak effect at 1 h. The antinociceptive activity was dose dependent. In formalin test,

the ISBE caused graded inhibition of both phases of formalin-induced pain. The impairment of the early and the late phases indicate that the ISBE is effective against acute nocieceptive pain and continuous inflammatory pain respectively. Also the suppression of both phases indicates that the ISBE has peripherally mediated antinociceptive action as well. Further, the antinociceptive activity was not associated with harmful side-effects or toxicity even following subchronic administration and the extract was not cytotoxic towards brine shrimps lethality assay. Pretreatment with naloxone and atropine failed to block the antinociceptive activity. On the other hand, metochlopramide significantly ($P < 0.05$) curtailed the antinocieceptive action time indicating that the antinociceptive action was mediated centrally at supraspinal level mainly via dopaminergic mechanisms. In addition, it is likely that antioxidant activity (by TBARs assay) and the mild sedative activity (determined by Hole board test) at high dose of the ISBE could have played an auxiliary role in inducing antinociception. Dopaminergic, antioxidant and sedative activities of ISBE could arise from its steroidal, phenolic and flavanoid constituents. It is concluded that ISBE of *K.zeylanica* has marked safe oral antinociceptive action.

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