Acute pain relief effect of essential oil from the leaves of *Zanthoxylum piperitum* (L.) DC. (Rutaceae) through glutamatergic pathway.

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Glutamate is one of the major excitatory neurotransmitters involved in the activation of nociceptive fibres. The consequence of its action affects central and peripheral activities. The essential oil from *Zanthoxylum piperitum*(ZP) exhibits a significant effect in the first phase of the formalin test, which involves neurogenic pain. Previous reports suggested that glutamate neurotransmission also plays an important role as a pain modulator during this first phase. Therefore, the aims of this study were to evaluate the potential of ZP essential oil (ZPEO) in reducing the acute pain caused by glutamate and to verify whether this effect is central or peripheral. Fresh leaves (150 g) of ZP were collected in Dublin on May 2015 and their essential oil was obtained via hydro-distillation in a Clevenger-type apparatus for 2 h. The oil was then analyzed by gas chromatography and its components were identified by comparison of both mass spectra and linear retention indices with spectral library and literature. ZPEO was given (p.o.) to Swiss Webster mice (25-30 g) at doses of 10, 30 or 100 µl kg^{-1} and these mice were investigated using the glutamate and hot plate test. The glutamate nociception is mediated by *N*-methyl-D-aspartate (NMDA), non-NMDA receptors, and by the release of nitric oxide. This test involved intra-plantar injections of glutamate (20 µmol) into the mouse hind paw and counting the amount of time it spent licking this paw. The hot plate test (HP) mainly involves the central anti-nociception, measured through behavioural components (such as jumping, withdrawing or licking the hind paw) on a heated plate at a constant temperature (55 °C). Measurements were taken at 30 min intervals after treatment (30, 60, 90, 120, 150 and 180 min). In the glutamate test, the 100 µl and 30 µl doses of ZPEO presented significant inhibition showing licking time reduction rates of 58 % and 22 %, respectively, when compared to the vehicle group (cooking soybean oil). No significant effect was observed for 10 µl kg^{-1}. The hot plate test showed no activity for the 3 tested doses. Chemical analysis of ZPEO confirmed the presence of 29 compounds. The major components of ZPEO are beta-phellandrene (29.4 %), (*E,E*)-farnesyl acetate (14.5 %), beta-citronellol (10.3 %), alpha-pinene (9.7 %) and beta-citronellal (6.8 %). From this investigation, ZPEO was only able to inhibit glutamate-induced licking at higher doses and the fact that none of these doses were able to increase the pain threshold on the hot plate suggests that ZPEO components affects the peripheral pain pathway.

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