Antinociceptive and antineuropathic effects of Trifolium resupinatum L. on formalin-induced nociception and cervical spinal cord hemi-contusion: Underlying Mechanisms

ABSTRACT

Ethnopharmacological relevance Trifolium resupinatum L. (Fabaceae), known as Persian clover, ethnomedicinally used in Persian folk medicine to treat peritoneal inflammation, rheumatism, and back pain. Aim of the study to investigate the antineuropathic and antinociceptive activities of Trifolium resupinatum leaves essential oil (TREO) in male Wistar rats, as well as to explore the potential mechanisms of action. Materials and methods the antinociceptive activity of TREO and its main constituents, quercetin (Qc) was assessed using the formalin-induced paw licking test. Moreover, the potential mechanisms of antinociception were evaluated through various competitive and non-competitive antagonisms. Additionally, the antineuropathic potential was investigated using the cervical spinal cord hemi-contusion (CCS) model, and the role of phosphorylated Stat-3 was analyzed using Western blotting. Results TREO exerted significant antinociceptive activity ($P < 0.01$) in both phases of the formalin-induced test; however, its effects were more pronounced in the second phase. Modulators of the NO-cGMP-K+ channel pathway significantly reversed the antinociceptive activity of TREO ($P < 0.05$). Additionally, antagonists of TRPV1 and TRPV2, as well as CB1 and GABAA receptors, significantly reversed the antinociceptive effects of TREO ($P < 0.05$). In another study, both TREO and Qc significantly attenuated hyperalgesia and mechanical allodynia ($P < 0.01$) when evaluated using the CCS-induced nociception model. Notably, TREO also reduced the expression levels of interleukin-1 beta, interleukin-2, and tumor necrosis factor alpha in CCS-induced rats ($P < 0.05$). Conclusion TREO and Qc exhibit both antinociceptive and anti-neuropathic activities. The antinociceptive effects are partially mediated through the NO-cGMP-K+ channel pathways, along with the activation of TRPV, GABA, and cannabinoid receptors. Furthermore, the anti-neuropathic activity of TREO may be partially regulated through the inhibition of cytokines.