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Plant-derived Ajugarin-I alleviates painful neuropathy in STZ-induced diabetic rats via activation of Nrf2 signaling and inhibition of TRPV1/TRPM8 nociceptors

***Aim*:** The aims of the current study were twofold: 1) Evaluate the therapeutic efficacy of Ajugarin-I, a plant-derived diterpene, on neuropathic pain in type 1 diabetes, and 2) elucidate the underlying protective mechanisms of Ajugarin-I, with a particular focus on its effects on oxidative stress and transient receptor potential (TRP) nociceptors, namely TRP melastatin 8 (TRPM8) and TRP vanilloid 1(TRPV1).
***Methods*:** Streptozotocin (STZ)-induced type 1 diabetic rats were treated with either 1 or 5 mg/kg Ajugarin-I, 14 days after STZ injection, for a total treatment duration of 28 days. Pain behavior testing was performed weekly and at study termination. Biochemical analyses were also done at terminal endpoint and included histopathology as well as oxidative stress and inflammatory cytokine measurements.
***Results*:** STZ-induced diabetic rats were hyperglycemic and displayed decreased pancreatic β cell count and atrophy with vacuolization. These changes were accompanied with neuropathic pain symptoms, including thermal hyperalgesia and mechanical allodynia and nerve degeneration. Treatment with Ajugarin-I reduced hyperglycemia, pancreatic damage, pain hypersensitivity, and nerve loss. Mechanistically, Ajugarin-I was found to offset glucose-mediated oxidative stress in the spinal cord and sciatic nerve by upregulating nuclear factor-erythroid factor 2-related factor 2 (Nrf2), the redox sensitive transcription factor as well as the antioxidants catalase and heme oxygenase. It also suppressed pro-inflammatory cytokine production, including TNF-α and IL-1β. Additionally, diabetes-induced TRPV1 and TRPM8 expression levels were normalized by Ajugarin-I treatment.
***Conclusions*:** Overall, this work indicates that Ajugarin-I treatment alleviates painful neuropathy in STZ-induced diabetic rats by activating the antioxidant response and suppressing the inflammatory response as well as TRPV1/TRPM8 nociceptors.

Comments. Painful neuropathy is a disabling complication of type 1 diabetes, associated with a significant burden on both the affected patients and society. However, treatment options remain limited, and a better understanding of pain pathogenesis is needed to develop mechanism-based therapies. Animal models have been pivotal for elucidating disease pathogenesis because they provide experimental strategies and enable testing of novel therapeutic agents, which are otherwise not feasible in human studies. In the current study, Khan et al. characterized the effects of the plant-derived Ajugarin-I on painful diabetic neuropathy using the STZ-induced type 1 diabetic rat, a robust disease model. They found that Ajugarin-I relieved glucose-induced pain behaviors, by activating Nrf2-dependent antioxidant response, reducing pro-inflammatory cytokines, and inhibiting TRPV1/TRPM8 nociceptors. This study supports the existing literature that re-establishing immune and oxidative homeostasis may protect peripheral nerves against hyperglycemia-induced injury. Additionally, it suggests that reducing TRPV1/TRPM8 nociceptors expression may restore thermal and mechanical sensitivity. Lastly, it points towards a favourable pharmacological profile of Ajugarin-I as a therapeutic candidate in the treatment of painful neuropathy.

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Reference. **Reference**. Khan A, Wang F, Shal B, Khan AU, Zahra SS, Haq IU, Khan S, Rengasamy KR. Anti-neuropathic pain activity of Ajugarin-I via activation of Nrf2 signaling and inhibition of TRPV1/TRPM8 nociceptors in STZ-induced diabetic neuropathy. Pharmacol Res. 2022 Sep;183:106392. doi: 10.1016/j.phrs.2022.106392. Epub 2022 Aug 5. PMID: 35940396.
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