Bee Venom Accelerates Wound Healing in Diabetic Mice by Suppressing Activating Transcription Factor-3 (ATF-3) and Inducible Nitric Oxide Synthase (iNOS)-Mediated Oxidative Stress and Recruiting Bone Marrow-Derived Endothelial Progenitor Cells.

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Abstract:

Multiple mechanisms contribute to impaired diabetic wound healing including impaired neovascularization and deficient endothelial progenitor cell (EPC) recruitment. Bee venom (BV) has been used as an anti-inflammatory agent for the treatment of several diseases. Nevertheless, the effect of BV on the healing of diabetic wounds has not been studied. Therefore, in this study, we investigated the impact of BV on diabetic wound closure in a type I diabetic mouse model. Three experimental groups were used: group 1, non-diabetic control mice; group 2, diabetic mice; and group 3, diabetic mice treated with BV. We found that the diabetic mice exhibited delayed wound closure characterized by a significant decrease in collagen production and prolonged elevation of inflammatory cytokines levels in wounded tissue compared to control non-diabetic mice. Additionally, wounded tissue in diabetic mice revealed aberrantly up-regulated expression of ATF-3 and iNOS followed by a marked elevation in free radical levels. Impaired diabetic wound healing was also characterized by a significant elevation in caspase-3, -8 and -9 activity and a marked reduction in the expression of TGF-β and VEGF, which led to decreased neovascularization and angiogenesis of the injured tissue by impairing EPC mobilization. Interestingly, BV treatment significantly enhanced wound closure in diabetic mice by increasing collagen production and restoring the levels of inflammatory cytokines, free radical, TGF-β and VEGF. Most importantly, BV-treated diabetic mice exhibited mobilized long-lived EPCs by inhibiting caspase activity in the wounded tissue. Our findings reveal the molecular mechanisms underlying improved diabetic wound healing and closure following BV treatment.

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