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Diabetic wound healing of aloe vera major phytoconstituents through TGF-β1 suppression *via in-silico* docking, molecular dynamic simulation and pharmacokinetic studies

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ABSTRACT

To restore the integrity of the skin and subcutaneous tissue, the wound healing process involves a complex series of well-orchestrated biochemical and cellular events. Due to the existence of various active components, accessibility and few side effects, some plant extracts and their phytoconstituents are recognised as viable options for wound healing agents. To find possible inhibitors of diabetic wound healing, four main constituents of aloe vera were identified from the literature. TGF-β1 and the compounds were studied using molecular docking to see how they interacted with the active site of target protein (PDB ID: 6B8Y). The pharmacokinetics investigation of the aloe emodin with the highest dock score complied with all the Lipinski's rule of five and pharmacokinetics criteria. Conformational change in the docked complex of Aloe emodin was investigated with the Amber simulation software, *via* a molecular dynamic (MD) simulation. The MD simulations of aloe emodin bound to TGF-β1 showed the significant structural rotations and twists occurring from 0 to 200 ns. The estimate of the aloe emodin-TGF-β1 complex's binding free energy has also been done using MM-PBSA/GBSA techniques. Additionally, aloe emodin has a wide range of enzymatic activities since their probability active (Pa) values is >0.700. 'Aloe emodin', an active extract of aloe vera, has been identified as the key chemical in the current investigation that can inhibit diabetic wound healing. Both *in-vitro* and *in-vivo* experiments will be used in a wet lab to confirm the current computational findings.

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Introduction

Hyperglycemia is a chronic endocrine system disorder known as diabetes mellitus (DM). It is typified by persistent hyperglycaemia over an extended period, which finally results in organ failure. Most people on the planet now live with diabetes, which has turned into a global public health emergency. By 2045, type-2 diabetes is predicted to affect 783 million people worldwide, up from 537 million in 2021 (Khalid et al., 2022). Type-2 diabetes is already recognised as a fast-expanding public health pandemic that affects over 300 million people globally (Maheri et al., 2022). DM often causes a delay in wound healing and angiopathy appears to play a substantial role. Diabetic foot ulcers affect 15–25% of persons with type 2 diabetes. Diabetic ulcers can cause several cases of destruction of the integumentary system, including the dermis and epidermis, as well as subcutaneous tissue. Of those afflicted, 14–24% requires amputation. Lower-extremity amputation due to diabetic foot ulcers is a high-risk treatment with a 5-year death rate of 50–59%, which is greater than many malignancies (Beheshtizadeh et al., 2023). All the elements of this phase appear to be dysregulated in diabetes, delaying wound healing. Keratinocytes, fibroblasts and smooth muscle cells express fewer tissue factors in diabetic wounds, which has a detrimental effect on the development of the first haemostatic plug (Bao et al., 2009). In addition, it has been noted that hyperglycaemia and hyperlipidaemia affect cytokine release, chemotaxis, adhesion and phagocytic activity (Peppa et al., 2009). Research on the acceleration and enhancement of diabetic ulcer healing is prioritised because of the severe consequences that follow diabetic ulcers.

Following any type of injury, the skin's anatomic integrity is restored by the intricate yet well-organized biological process of wound healing. Numerous intracellular and extracellular activities that are primarily controlled by a class of enzymes interact throughout the healing process (Satish & Kathju, 2010; Khalid et al., 2022). Fibrin clot production occurs once blood arteries are damaged and skin tissue is injured (Peppa et al., 2009). This clot supplies the substrate

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