



RESEARCH PAPER

# IDENTIFICATION OF NEW CHEMICAL ENTITIES AS VHL INHIBITORS FOR DIABETIC WOUND HEALING

Esakkimuthukumar Mariappan, Gokula Krishnan Thiruselvan, Sam Harrison Sam Jenkinson, Saravana Kumar Chellaperumal Appavoo, Suranther Krishnamoorthi, Akey Krishna Swaroop and Jubie Selvaraj\*

*Department of Pharmaceutical Chemistry, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Ooty-643001, Tamil Nadu, India*

\*E-mail: jubie@jssuni.edu.in

Tel.: +91 9894618588.

Received: Dec 08, 2023 / Revised: Aug 28, 2024 / Accepted: Aug 28, 2024

**Diabetes is a kind of endocrine disease that impacts around 6% of the world's population. Globally, 68% of amputations were performed in persons with diabetes. Hypoxia-inducible factor 1-alpha (HIF-1 $\alpha$ ) is a crucial regulator of wound healing in diabetic patients, which includes epithelialization, angiogenesis, granulation, tissue development, and wound contraction. Even though diabetic wounds are hypoxic, HIF-1 $\alpha$  levels are decreased during diabetic conditions. Diabetic wound healing necessitates the modulation of hypoxia-induced responses by VHL–HIF-1 $\alpha$  protein-protein inhibition (PPI). Our proposed hypothesis is to increase HIF-1 $\alpha$  levels by inhibiting VHL and HIF-1 $\alpha$  interactions by small bioactive molecules, accelerating diabetic wound healing. Three features (Two hydrogen bond acceptors and One hydrogen bond donor) pharmacophore model was generated from the existing VHL inhibitors. Virtual screening was done based on the generated pharmacophore, and a library of 700 compounds was selected using ZINCPharmer. Based on the docking analysis the Top 15 HITs were selected & after performing ADMET studies, the Top 2 HITs (ZINC04214700 and ZINC12529886) were identified as potential VHL inhibitors. From this finding, we demonstrated that inhibiting the VHL and HIF-1 $\alpha$  connection is a promising strategy for treating diabetic wounds.**

**Key words:** Diabetic wound, HIF-1 $\alpha$ , VHL, PPI, Pharmacophore, Virtual screening, Docking, ADMET.

## INTRODUCTION

Diabetes is a most common, serious and chronic illness resultant from the error of insulin secretions or action. The possible way of the treatment includes gene therapy, use of biguanides, GLP-1 receptor agonists, PPAR $\gamma$  agonists, including naturally occurring phenolic compounds. This metabolic disease is a significant risk factor for the development of chronic wounds, including foot ulcers, which can lead to severe complications such as amputation, decreased quality of life, and increased

healthcare costs. According to the World Health Organization (WHO), an estimated 422 million people worldwide had diabetes in 2014, and this number is projected to increase to 642 million by 2040 and up to 25% of individuals with diabetes will develop a foot ulcer in their lifetime [1-8]. HIF-1 $\alpha$  is crucial for enhancing the right inflammatory and angiogenic responses in normal cutaneous wounds. HIF-1 $\alpha$  also plays a crucial role in controlling inflammatory reactions, one of the most common causes of