Journal of Applied Pharmaceutical Science Vol. 13(Suppl 1), pp 041-050, September, 2023
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2023.135162
ISSN 2231-3354

Identification of effective natural compounds as HIF-1Alpha mimetics for diabetic wound healing; A systematic *in-silico* study

Esakkimuthukumar Mariappan[1], Akey Krishna Swaroop[1], Preeya Negi[1], Saranya RajanBabu[1], Dhinesh Kumar Murugesan[1], Nadimpalli Prudhvi Varma[2], Jubie Selvaraj[1*]

[1]Department of Pharmaceutical Chemistry, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Ooty, India.
[2]Department of Pharmaceutical Analysis, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Ooty, India.

ARTICLE HISTORY

Received on: 30/04/2023
Accepted on: 25/07/2023
Available Online: 20/09/2023

Key words:
Natural compounds, HIF-1α, diabetic wound, pharmacophore, virtual screening, impaired wound healing.

ABSTRACT

The Von Hippel-Lindau (VHL) E3 ubiquitin ligase is responsible for the degradation of hypoxia-inducible factor 1α (HIF-1α) under hydroxylation. Computer-aided drug design leads to the discovery of HIF-1α mimetics for the stabilization of hydroxylated α subunit of HIF-1α from subsequent proteasomal degradation to improve diabetic wound healing. The protein-protein interaction (PPI) networking confirms the interaction between the VHL—HIF-1α proteins. So, VHL is the potential target to stabilize the HIF-1α. A set of natural compounds as an inhibitor of PPI between VHL—HIF-1α is identified by structure-based virtual screening. The free HIF-1α leads to accelerates wound closure in both normal and diabetic conditions, with a more significant effect being observed in the diabetic condition. The natural products were designed as HIF-1α mimetics through *in-silico* Pharmacophore modeling followed by structure-based virtual screening and molecular simulation. In the pharmacophore modeling, 2 acceptors and 1 donor pharmacophore are generated. In the virtual screening process, generated pharmacophore gives a data set of natural compounds that have the same pharmacophoric feature. Based on the docking and absorption, distribution, metabolism, elimination, toxicity studies, the potential inhibitor (ZINC ID: ZINC15959407, ZINC12884117) of PPI is identified.

INTRODUCTION

Diabetic wound healing remains a real problem. In diabetic patients, wound healing is slow and complicated because it irregulates some pathways that are related to wound healing. Appropriate treatment is crucial because it is one of the most frequent causes of lower-limb amputation and can become life-threatening (Guo and DiPietro, 2018; Li *et al*., 2022). The wound has multiple interconnected compartments, which allow infection to travel from one ulcer to another (Mohammed *et al*., 2022; Qureshi *et al*., 2022). When combined with sensory loss, patients can continue to walk on these infected sores, which helps the infection spread (Akkus and Sert, 2022). Hypoxia-inducible factor-1α (HIF-1α) in the process of maintaining cellular homeostasis, proteins are continuously produced and aimed for destruction. The system composed of ubiquitin and proteasome is the main mechanism for protein degradation (Ming *et al*., 2023; Soares *et al*., 2018). The Cullin-RING ligase family includes the Von Hippel-Lindau protein (VHL), an E3 ubiquitin ligase (Bulatov and Ciulli, 2015). Several human genes' transcription is regulated by the transcription factor HIF-1α, mostly those involved in hypoxia adaptation, which is the primary substrate of VHL (Semenza and Wang, 1992). HIF-1α expression levels are closely controlled when tissue oxygen levels are normal. The HIF-1α oxygen-dependent degradation domain (ODD) contains two unique proline residues that are hydroxylated by prolyl hydroxylase domain (PHD) enzymes at iron- and oxygen-dependent rates. As a result of this modification, VHL specifically recognizes and ubiquitinates HIF-1α, which helps in the ubiquitin-proteasome degradation (Tanimoto *et al*., 2000).

Although the exact mechanism underlying the instability of HIF-1α caused by hyperglycemia is still unknown,

*Corresponding Author
Jubie Selvaraj, Department of Pharmaceutical Chemistry, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Ooty, India.
E-mail: jubie @ jssuni.edu.in

here we have compelling evidence that the protein-protein interaction (PPI) between VHL and HIF-1α can be blocked to address diabetic wound problems effectively (Semenza and Wang, 1992). HIF-1α degradation is reduced in response to hypoxia, but growth factors encourage HIF-1α protein production without regard to hypoxia. As a result, it can prevent HIF-1α degradation caused by the oxygen sensor in normoxic settings and helps with diabetic wound healing (Semenza, 2001).

Numerous disorders, including those with inflammation, anemia, chronic neurodegeneration, ischemia and, more recently, mitochondrial dysfunction, have been linked to the relevance of this HIF-1α (Deng *et al*., 2023). Natural substances that inhibit the pathway of PPI may activate HIF-1α expression and upregulate genes related to hypoxic response, potentially offering the best approach to improve diabetic wound healing. This is because HIF-1α controls numerous pathways that are directly related to diabetic wound healing. In fact, a variety of diseases have shown promise for the use of small-molecule PHD inhibitors (Esfahani *et al*., 2015). Among them, compound FG-4592, which is N- [(4-hydroxy-1-methyl-7-phenoxy-3-isoquinolinyl)carbonyl]- glycine, has advanced to a phase III clinical trial to examine its effectiveness and safety in patients receiving hemodialysis for chronic kidney disease who have anemia (Beck *et al*., 2017). Furthermore, a number of PHD enzymes' non-HIF-1α substrates have been found (Ortmann *et al*., 2014). Because PHD enzymes are localized in cells and tissues and have distinct substrate specificities, a lack of selectivity of the particular compound could result in undesirable side effects (Li *et al*., 2021; Rabinowitz, 2013).

The association between the VHL and HIF-1α proteins was validated by PPI networking. The pair of proteins complex is also accessible in the protein data bank (PDB id: 1lm8). Therefore, a promising method to enhance the healing of diabetic wounds is to limit the PPI of VHL and HIF-1α (Esakkimuthukumar *et al*., 2022; Song *et al*., 2023). Protein-protein interfaces may be more effective, according to recent success stories. Small compounds have been found in some investigations to binding to "hotspots" on the contact surfaces involved in PPI with druglike potencies. Surprisingly, compared to the contact atoms of the target protein's natural protein companion, these tiny molecules bind to the target protein's contact surface more firmly and profoundly. Targeting the interfaces between interacting proteins for therapeutic purposes utilizing naturally occurring, "druglike" compounds that are frequently less expensive and easier to obtain has garnered a lot of interest. The theory suggested that natural chemicals could be purposefully created to act as inhibitors of VHL/HIF-1α PPI interaction by HIF-1α mimicking (Jones and Thornton, 1996). Inhibiting PPI improves diabetic wound healing by increasing the HIF-1α level. HIF-1α is directly influencing many pathways that help diabetic wound healing (Fig. 1).

MATERIALS AND METHODS

Software's used

For pharmacophore modeling various VHL inhibitors and HIF1α mimetics were collected through a literature survey. The collected molecules were of diverse chemical structures. Software's like String, PharmaGist, ZINCPharmer, MarvinSketch, PDB, Swiss-Pdb Viewer, PyRx 0.9, Discovery Studio Visualizer, SwissADME, and PreADMET were used for this study to identify the natural compounds that can be used for diabetic wound healing.

PPI networking

PPI s can really be predicted analytically as well; some resources concentrate primarily on this task, employing a range of techniques. The integration of known and expected interactions is also offered by a collection of online services looking for maximum coverage and comprehensiveness. Global functional relationships between proteins are the subject of the STRING database (Search Tool for the Retrieval of Interacting Genes/Proteins) (Szklarczyk *et al*., 2015).

The main point of access is the protein search box on the STRING website's home page. It supports multiple protein queries, can limit searches to particular organisms or clades of organisms, and employs a weighted method to determine identified matches (Szklarczyk *et al*., 2023).

Moving things on to the network view once a protein or group of proteins has been discovered. From there, one can examine the interaction evidence, modify the score cut-offs and network size limitations, and access comprehensive details regarding the interacting proteins. By selecting "advanced" mode (from the menu in the tool panel below the network), users can cluster, rearrange, and test for statistical enrichments in the network. In the most recent version of STRING (11.5), the latter function has been improved: Disease connections and tissue annotations are now included in enrichment detection and may be statistically enriched in a specific network. The partner databases TISSUES and DISEASES, which also share STRING's protein sequence and namespaces, are communicated with STRING in order to provide this functionality. By combining automated text-mining and knowledge imports, these databases assign protein-to-protein interaction as well as proteins to tissues or disease entities (Powell *et al*., 2014).

Pharmacophore modeling

PharmaGist online software was used to simulate the pharmacophores. A pharmacophore is a chemical framework that describes the essential properties that give a molecule its biological activity. They can be used to find novel compounds that meet the pharmacophore requirements and are therefore anticipated to be active. Using the structural details of the active ligands that bind to the target, pharmacophore models can be created. A set of active ligands are used to create novel ligands in the ligand-based pharmacophore modeling approach. The pharmacophores were simulated using the online tool PharmaGist (Pirhadi *et al*., 2020). An outline of the chemical elements that give a molecule its biological activity is known as a pharmacophore. They have the potential to find novel chemicals that meet the requirements of pharmacophores and are, therefore probably active. Using the structural details of the active ligands that bind to the target, pharmacophore models can be created. A set of active ligands is used to create new ligands in the ligand-based pharmacophore modeling approach. In our study, we selected the target molecule as VHL protein

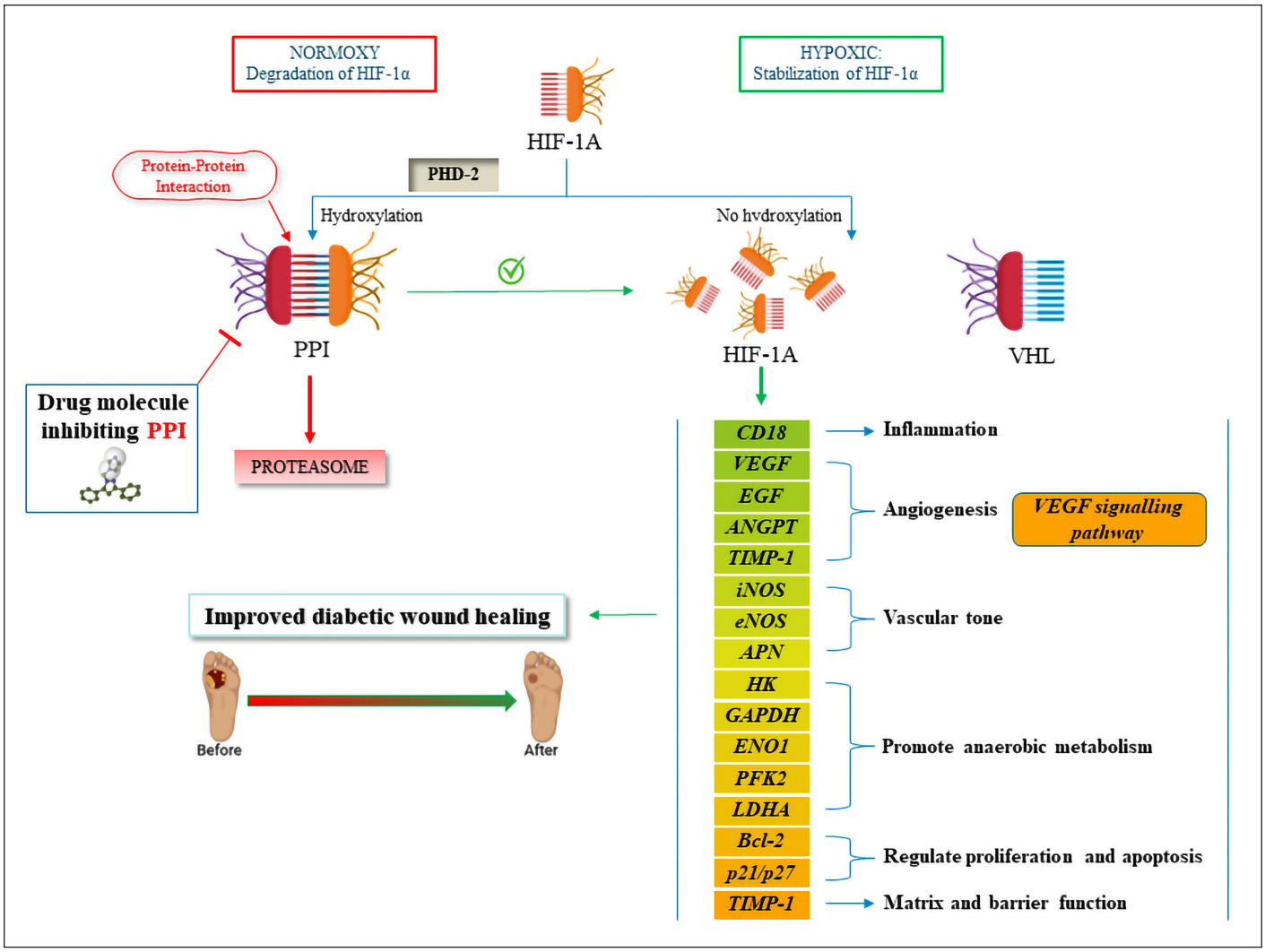


Figure 1. Inhibiting PPI improve diabetic wound healing by increasing the HIF-1α level. HIF-1α is directly influencing many pathways that help for diabetic wound healing.

(PDB ID: 4W9H). Based on the literature survey, we selected 36 molecules as input to generate pharmacophore. The PharmaGist web server automatically generates the pharmacophore model that has the same pharmacophoric features of input molecules (Muhammed and Esin, 2021).

Virtual screening

A virtual screening process was performed in ZINCPharmer that have a library of synchronized molecules. An uploaded set of pharmacophore characteristics is any single-conformer molecular structure file that complies with Open Babel. As pharmacophore query features, all of the molecular features that have been found are active. But because a ligand by itself cannot reveal the specifics of an interaction. So, the pharmacophoric features based on the ligand structures helped to identify compounds with similar pharmacophore using ZINCPharmer. The input pharmacophore has two hydrogen bond acceptors and one hydrogen bond donor. The "hit" compounds included those with all the requisite pharmacophore properties. Natural compounds are chosen from the top hit molecules. The natural molecules passed the initial tests. The chosen compounds go through molecular docking analysis (Quazi *et al*., 2021).

Molecular docking

The most popular methods in structure-based drug design are molecular docking because docking is effective in predicting interactions between the synthesized compound and the target protein's binding site (PDB ID: 4W9H). These interactions make it possible to understand both the fundamental biological functions of the docked complex as well as the behavior of the chemicals (Dallakyan and Olson, 2015). Docking analysis is performed using the PyRx program. Select the downloaded MOL file of the 100 natural compounds identified from the ZINC database library uploaded in PyRx (Swaroop *et al*., 2022). Energy minimization of the input compounds is performed. The VHL protein (PDB ID: 4W9H) is selected as the target protein. Based on the protein's active site, a grid box is created. The PyRx tool will construct nine models of different poses for each ligand and forecast the binding sites inside the box and positions inside the coordinate box, and this

gives the binding energy of each molecule with the selected protein (Meng *et al*., 2011).

Absorption, distribution, metabolism, elimination, toxicity (ADMET) studies

Analyzing a lead compound's ADMET properties is crucial during the drug development process because the majority of compounds are withdrawn during the preclinical stages due to ADMET inadequacies. SwissADME and PreADMET are two computational methods that aid in predicting a compound's druglike qualities. Freely accessible at http://www.swissadme.ch, the SwissADME web application described here is made for easy submission and result analysis, even for individuals who are not familiar with CADD. SwissADME is used to calculate the ADME parameters, physicochemical descriptors, pharmacokinetic traits, druglike nature, and medicinal chemistry friendliness of the indicated compounds (Mekky *et al*., 2022). The toxicity of the designed compounds is identified by PreADMET online bioinformatics tool. The study provides parameters such as 1) toxicity prediction, 2) ADMET prediction, 3) drug-likeness prediction, and 4) molecular descriptor calculation (Viana Nunes *et al*., 2020).

RESULTS

PPI networking

The PPI helps to confirm the interaction between the two proteins. Our target is to inhibit the PPI between VHL—HIF-1α from improving diabetic wound healing. Version 11.5 of the STRING database has 3,281,414 PPIs. The brute force method previously described is used to find STRING Subnetwork biomarkers, which are then analyzed in terms of PPI scores. STRING database has PPI ratings ranging from 0.150 to 0.999. The VHL—HIF-1α proteins have a PPI score of 0.999, shown in Figure 2. That shows the strong interaction between these two proteins, and also, the complex of these two proteins is available (PDB id: 1lm8). Based on the findings, we confirm the interaction between the two proteins.

Pharmacophore modeling

Pharmacophore modeling is a computer-assisted approach to discovering novel ligands based on biological structures. Molecular similarity assessments of compounds with known and unknown moieties are compared using ligand-based screening approaches, regardless of methodology. A virtual screening technique was developed based on structural similarities between known and putative active ligands. Molecules having comparable structural properties are thought to perform similarly. As a result, some approaches search huge databases for structurally related compounds using a known active ligand as a query. (Mol2—Mol2 format) SylbylMol2 format Up to 35 molecules can now be stored in a single Mol2 file or multiple Mol2 files compacted into a single zip file given as input Supplementary Table 1. The primary output page is shown in Supplementary Figure S1. There are numerous tables on this page. The input molecules are listed in the upper table, their number of atoms, and their assigned physicochemical properties. Based on the number of aligned molecules, a score is generated. The pharmacophore with the highest number of aligned molecules and with the highest score is selected. A link to a web page that displays the molecules in a Jmol applet may be found at the top of the table. The Jmol file is the generated pharmacophore. Physical and chemical properties, as well as the separation between any two values, are determined using the PyMOL software. Two acceptor areas and one donor region make up the pharmacophore that we were able to collect (Fig. 3). Hydrogen bond acceptors and donors, acidic and basic groups, aliphatic and aromatic hydrophobic moieties are the most

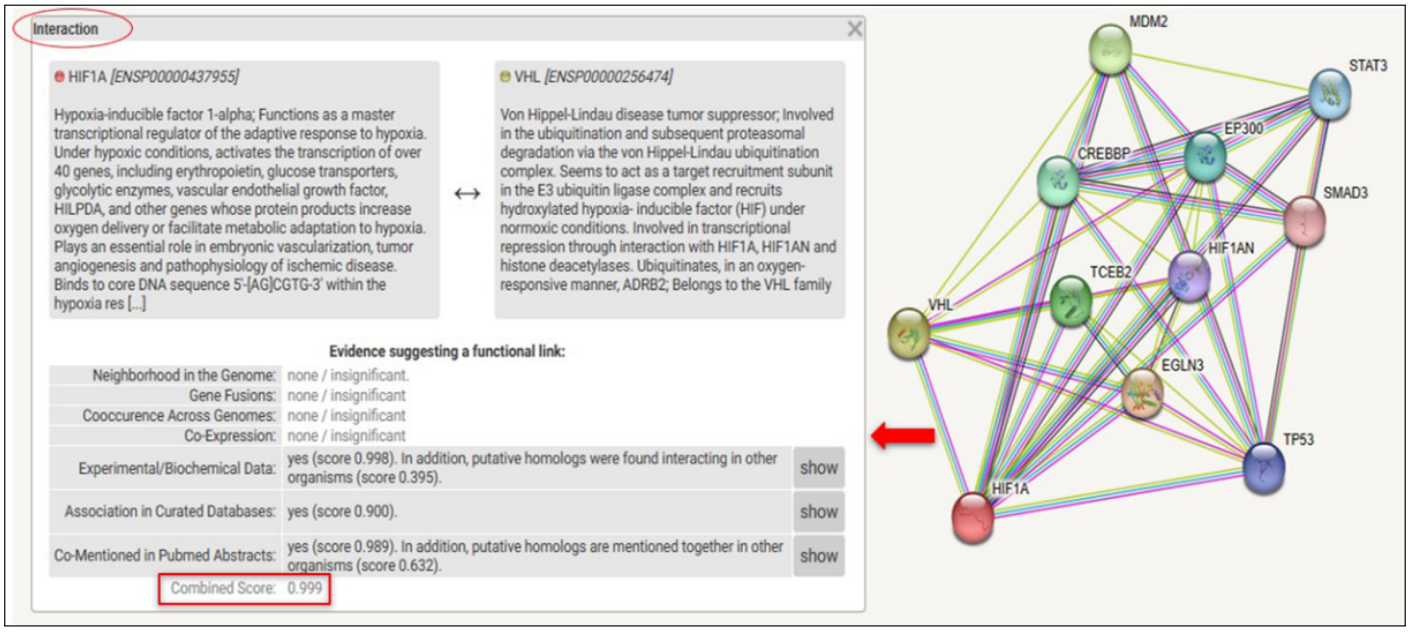


Figure 2. PPI of VHL—HIF-1α and STRING score for the PPI.

Table 1. Selected ZINC natural products from ZINCPharmer.

ZINC15671848	ZINC28768623	ZINC72326279	ZINC04556861	ZINC04252729
ZINC33882759	ZINC68606228	ZINC19371180	ZINC20113052	ZINC08635778
ZINC14687899	ZINC20411260	ZINC64220199	ZINC35425218	ZINC04478699
ZINC08295947	ZINC04228241	ZINC05377736	ZINC20757821	ZINC04124398
ZINC12883664	ZINC08791878	ZINC20762718	ZINC49543335	ZINC30903975
ZINC35426341	ZINC13125491	ZINC08254146	ZINC05178949	ZINC04531089
ZINC20463915	ZINC12483187	ZINC02556572	ZINC15708452	ZINC15958031
ZINC79192882	ZINC14812957	ZINC05932590	ZINC04084683	ZINC00525811
ZINC00039361	ZINC20465683	ZINC62001361	ZINC08791933	ZINC04236496
ZINC03812865	ZINC04556941	ZINC08765120	ZINC20464078	ZINC22922187
ZINC32123983	ZINC03841274	ZINC13690996	ZINC02140959	ZINC04098646
ZINC12529886	ZINC019371180	ZINC15672046	ZINC00517799	ZINC02140959
ZINC04217381	ZINC09033636	ZINC20466834	ZINC15959407	ZINC25073484
ZINC08585032	ZINC08299784	ZINC20113485	ZINC12483481	ZINC13508258
ZINC12484016	ZINC13540404	ZINC00895179	ZINC12884117	ZINC15674498
ZINC04260283	ZINC34857851	ZINC03869911	ZINC20757510	ZINC34857851
ZINC03872191	ZINC16026543	ZINC00113378	ZINC68606000	ZINC28768623
ZINC12892556	ZINC04258961	ZINC00912163	ZINC15672046	ZINC12529888
ZINC15708054	ZINC08765143	ZINC00156683	ZINC03021496	ZINC05220422
ZINC16975391	ZINC32124335	ZINC05397553	ZINC20756821	ZINC20610967

widely employed properties for defining pharmacophore. A hydrogen bond donor is that part of hydrogen bond which is generally a more electronegative atom and donates the hydrogen. While hydrogen bond acceptor generally contains a lone pair of an electron that participates in the hydrogen bonding.

Virtual screening

The created pharmacophore from ZINCPharmer, illustrated in Figure 4, was used for the virtual screening. ZINCPharmer is a web-based virtual screening tool for compounds that are readily available for purchase. We sent the molecules to a server for storage. We hope that a sizable community of medicinal chemists and structural biologists will use this tool to build virtual screening libraries. To narrow down the database chemicals based on pharmacophoric characteristics, the ZINCPharmer application offers a number of filters such as max hit per conformer-1, Max hits per molecule-2, Max total hits-100, Max RMSD 2 Å, Molecular weight 0–500 Da, Rotatable bonds 0–8. For our research, we chose the natural product database. ZINCPharmer generated 2,437 natural molecules. Based on the molecular weight (≤500 Da), number of rotatable bonds (≤8), and RMSD values (<2 Å), 100 hits were selected from the natural product database, and the ZINC IDs of top 100 hits are shown in Table 1.

Molecular docking

The docking study used 100 natural compounds optioned from Pharmacophore modeling and virtual screening for the purpose of diabetic wound healing. The top hits and the co-crystals are subjected to docking by using PyRx 9.0.

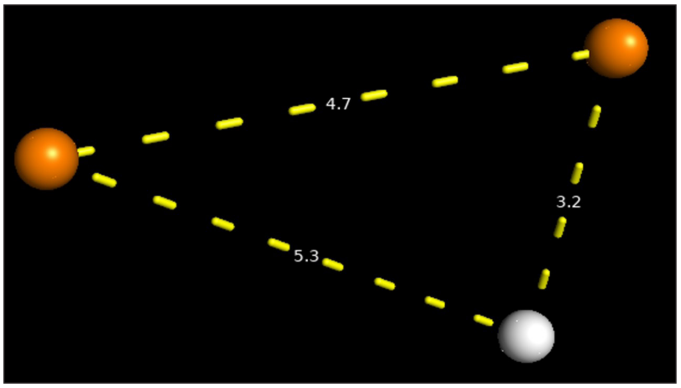


Figure 3. Generated pharmacophore by PyMOL visualizer.

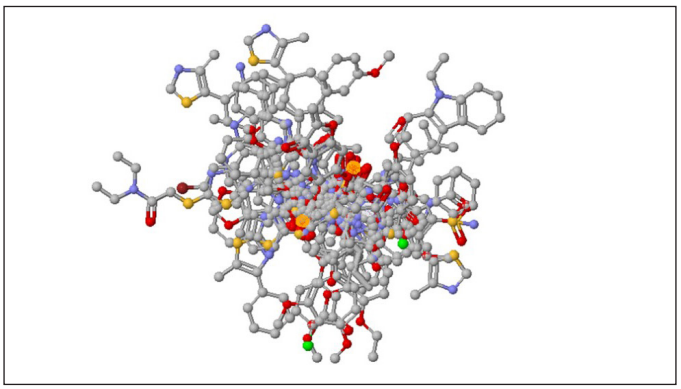


Figure 4. Generated Pharmacophore in ZINCPharmer.

The VHL (PDB id: 4W9H) protein is used as a macromolecule for docking. The binding energy of the co-crystal is −8.6, and in the 100 hit molecules, 15 molecules have shown better binding energy compared with the co-crystal Table 2. Those 22 molecules have better interaction with the target protein compared with co-crystal. So, these molecules are selected for further studies. 2D interactions of top hits are shown in Table 3.

ADMET studies

In the present study, we used the SwissADME online software tool, which is available free for users to evaluate the ADME properties of 14 natural compounds which have top, binding energy in docking. The phytoconstituents of the molecules were analyzed for ADME properties and depicted in respected Supplementary Table 2. The PreADMET server was used to anticipate features that are pertinent to pharmacology. PreADMET, a group of 14 organic chemicals, is intended to act primarily on the processes of diabetic wound healing. Administration of these natural compounds does not cause any hazardous effects, and all toxic parameters are within the acceptable range Supplementary Table 3.

DISCUSSION

HIF-1α controls angiogenesis, epithelialization, granulation tissue growth, and tissue repair. HIF-1α levels fall when diabetic wounds heal, even when the environment is normoxic. Management of hypoxia-induced reactions is crucial for diabetic wound healing. In hypoxia, hyperglycaemia impacts HIF-1α stability via a VHL-dependent mechanism. HIF-1α is hydroxylated on prolyl residues within its ODD domain, and this process is called proline hydroxylation. After proline hydroxylation, a complex between VHL and HIF-1α develops in addition to the standard oxygen-dependent binding of VHL to HIF-1α. ODD of HIF-1α and

Table 2. Docking result between ligand with the receptor (4W9H).

S. no.	ZINC ID	Binding affinity (kcal/mol)
1	ZINC15959407	−9.7
2	ZINC12884117	−9.4
3	ZINC12529886	−9.3
4	ZINC05932590	−9.3
5	ZINC20113052	−9.1
6	ZINC20757510	−9
7	ZINC05397553	−8.9
8	ZINC15672046	−8.8
9	ZINC30903975	−8.8
10	ZINC08765120	−8.8
11	ZINC20610967	−8.8
12	ZINC12892556	−8.7
13	ZINC49543335	−8.7
14	ZINC13690996	−8.6
15	ZINC14687899	−8.6
16	Co-crystal	−8.5

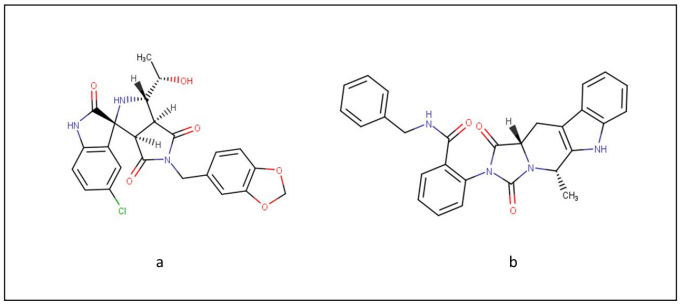


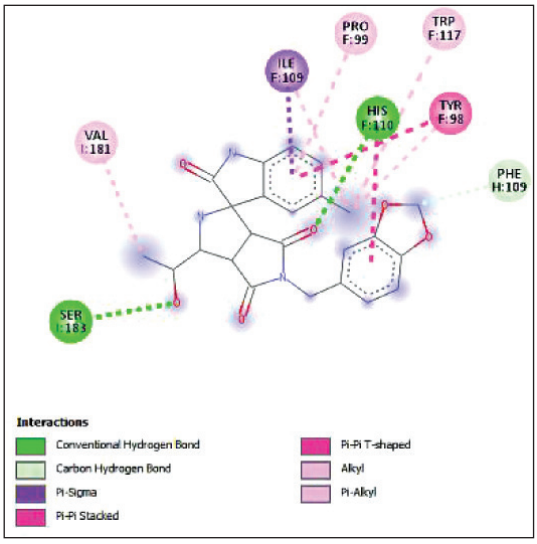
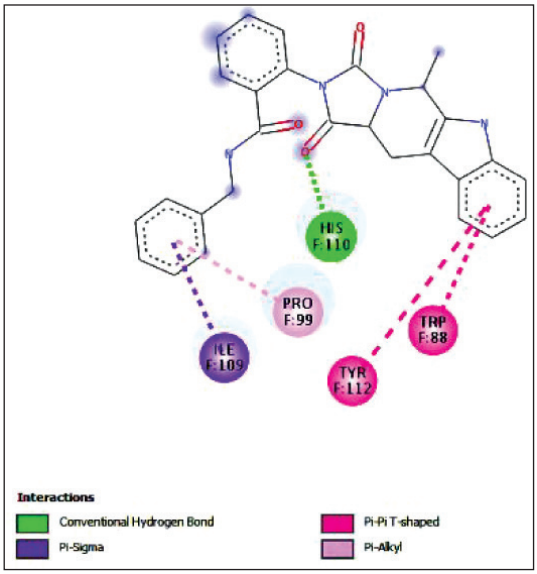
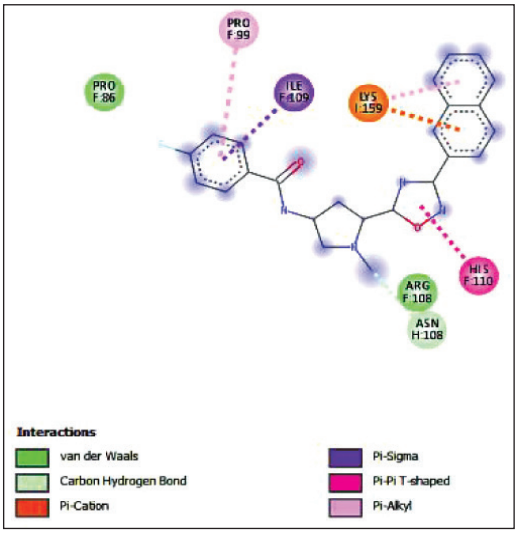
Figure 5. Generated Pharmacophore in ZINCPharmer.

VHL complex takes place through the proteasome degradation pathway. We are introducing a natural substance that interacts with VHL protein to inhibit this Proteasomal degradation of VHL: HIF-1α. So, the HIF-1α level will be stabilized. The current study focuses on natural substances because there is a pressing need to advance research in this area in order to identify therapies and cures for diabetic wound healing. Several *in-silico* techniques are used to create the HIF-1A mimics. STRING program validates the interaction between HIF-1A:VHL proteins. Through a review of the literature, 35 molecules of HIF-1A mimetics, and VHL inhibitors have been obtained (15, 28–34). Using these compounds, the PharmaGist program creates a pharmacophore model with the particular pharmacophoric features of two hydrogen bond acceptors and one hydrogen bond donor that will function as HIF-1A mimics. Virtual screening is carried out using ZINCPharmer based on the chosen pharmacophore. We found 100 natural compounds through a virtual screening approach that will bind to the catalytic packet of the VHL protein and block the PPI of the HIF-1A:VHL protein. A docking research study is carried out for the co-crystal [(2S,4R)-1-[(2S)-2-acetamido-3,3-dimethylbutanoyl]-4-hydroxy-N-[[4-(4-methyl-1,3-thiazol-5-yl)phenyl] and the selected 100 natural molecules against the VHL protein (4W9H). In comparison to the co-crystal, those 15 molecules had a greater binding affinity. SwissADME and PreADMET are used to calculate the ADMET properties of those 15 compounds. We identified two natural compounds (Fig. 5) that may act as potential drugs to treat diabetic wounds based on the complete *in-silico* analysis. By applying molecular modelling tools, HIF-1α mimics are created as natural products as a solution to improving diabetic wound healing.

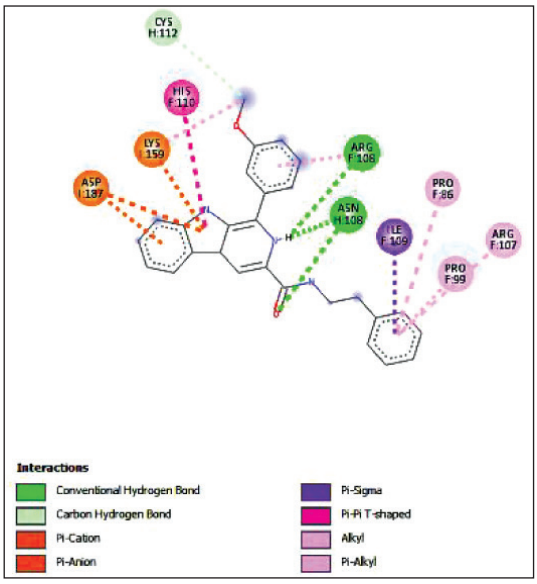
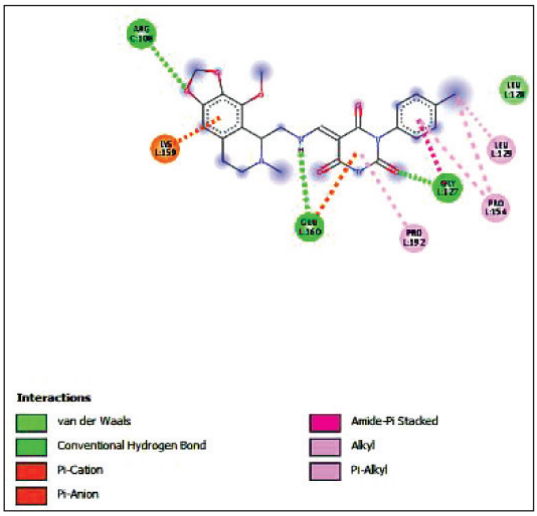
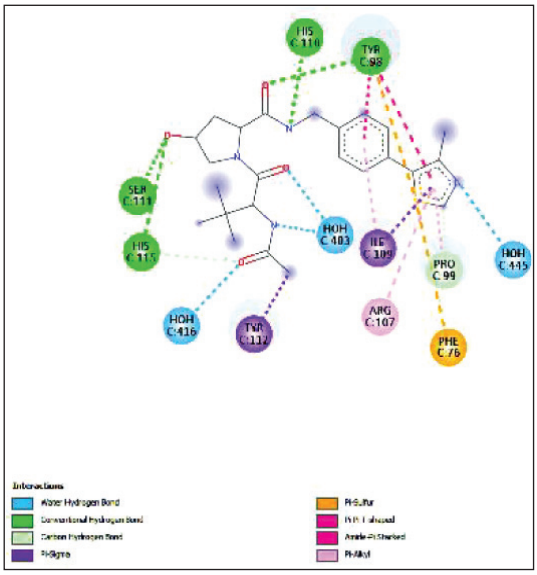
CONCLUSION

This research can help to find better natural product candidates for the treatment of diabetic wound healing. But in diabetic patients, wound healing is impaired because of high blood sugar levels. Increasing the HIF-1α levels could be the best way to design a new diabetic wound-healing drug. The compounds present currently in clinical trials have shown some adverse effects during studies. So, a pair of natural compounds is identified to overcome the problem by using systematic *in-silico* studies. Based on the preliminary study of pharmacophore modeling, we generated a pharmacophore model that consists of two hydrogen bond acceptors and

Table 3. 2D interaction of top five natural compounds and co-crystal.

ZINC id	Binding affinity (kcal/mol)	2D interactions
ZINC15959407	−9.7	
ZINC12884117	−9.4	
ZINC12529886	−9.3	

Continued

ZINC id	Binding affinity (kcal/mol)	2D interactions
ZINC05932590	−9.3	
ZINC20113052	−9.1	
Co-crystal	−8.5	

one hydrogen bond donor. Using generated pharmacophore in virtual screening, we got natural compounds that were the same as the generated pharmacophore from the natural product database. So, the natural products selected as HIF-1α mimetics. The selected natural products binding affinity towards the VHL Protein (4W9H) was analyzed by docking studies, and ADMET studies of the top 14 compounds based on the docking results were also performed. Two effective HIF-1α mimetic were screened from all-natural compounds available by using computer-aided drug design to improve diabetic wound healing.

ACKNOWLEDGMENTS

The authors are thankful to the JSS College of Pharmacy, Ooty, for providing the necessary facilities for research.

FINANCIAL SUPPORT

There is no funding to report.

CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

PUBLISHER'S NOTE

This journal remains neutral with regard to jurisdictional claims in published institutional affiliation.

REFERENCES

Akkus G, Sert M. Diabetic foot ulcers: a devastating complication of diabetes mellitus continues non-stop in spite of new medical treatment modalities. World J Diabetes, 2022; 13(12):1106–21.

Beck J, Henschel C, Chou J, Lin A, Del Balzo U. Evaluation of the carcinogenic potential of roxadustat (FG-4592), a small molecule inhibitor of hypoxia-inducible factor prolyl hydroxylase in CD-1 mice and Sprague Dawley rats. Int J Toxicol, 2017; 36(6):427–39.

Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. Methods Mol Biol, 2015; 1263:243–50.

Deng L, He S, Guo N, Tian W, Zhang W, Luo L. Molecular mechanisms of ferroptosis and relevance to inflammation. Inflamm Res, 2023; 72(2):281–99.

Esfahani M, Karimi F, Afshar S, Niknazar S, Sohrabi S, Najafi R. Prolyl hydroxylase inhibitors act as agents to enhance the efficiency of cell therapy. Expert Opin Biol Ther, 2015; 15(12):1739–55.

Esakkimuthukumar M, Swaroop AK, Patnaik SK, Kumar R R, T K P, Naik MR, S J. A novel family of small molecule HIF-1 alpha stabilizers for the treatment of diabetic wounds; an integrated *in silico*, *in vitro*, and *in vivo* strategy. RSC Adv, 2022; 12(48):31293–302.

Guo S, Dipietro LA. Factors affecting wound healing. J Dent Res, 2010; 89(3):219–9.

Li W, Jiang L, Wu S, Yang S, Ren L, Cheng B , Xia J. A Shape-programmable hierarchical fibrous membrane composite system to promote wound healing in diabetic patients. Small, 2022; 18(11):e2107544.

Li G, Ko CN, Li D, Yang C, Wang W, Yang GJ, Di Primo C, Wong VKW, Xiang Y, Lin L, Ma DL, Leung CH. A small molecule HIF-1α stabilizer that accelerates diabetic wound healing. Nat Commun, 2021; 12(1):3363.

Jones S, Thornton JM. Principles of protein-protein interactions. Proc Natl Acad Sci, 1996; 93(1):13–20.

Mohammed HA, Qureshi KA, Ali HM, Al-Omar MS, Khan O, Mohammed SAA. Bio-evaluation of the wound healing activity of *Artemisia judaica* L. as part of the plant's use in traditional medicine; phytochemical, antioxidant, anti-inflammatory, and antibiofilm properties of the plant's essential oils. Antioxidants (Basel), 2022; 11(2):332.

Ming H, Li B, Jiang J, Qin S, Nice EC, He W, Lang T, Huang C. Protein degradation: expanding the toolbox to restrain cancer drug resistance. J Hematol Oncol, 2023; 16(1):6.

Bulatov E, Ciulli A. Targeting Cullin–RING E3 ubiquitin ligases for drug discovery: structure, assembly and small-molecule modulation. Biochem, 2015; 467(3):365–86.

Muhammed MT, Esin AY. Pharmacophore modeling in drug discovery: methodology and current status. J Turk Chem Soc A Chem, 2021; 8(3):749–62.

Meng XY, Zhang HX, Mezei M, Cui M. Molecular docking: a powerful approach for structure-based drug discovery. Curr Comput Aided Drug Des, 2011; 7(2):146–57.

Mekky AE, Sanad SM, Abdelfattah AM. Tandem synthesis, antibacterial evaluation and SwissADME prediction study of new bis (1, 3, 4-oxadiazoles) linked to arene units. Mendeleev Commun. 2022; 32(5):612–4.

Ortmann B, Druker J, Rocha S. Cell cycle progression in response to oxygen levels. Cell Mol Life Sci, 2014; 71(18):3569–82.

Rabinowitz MH. Inhibition of hypoxia-inducible factor prolyl hydroxylase domain oxygen sensors: tricking the body into mounting orchestrated survival and repair responses. J Med Chem, 2013; 56(23):9369–402.

Soares P, Gadd MS, Frost J, Galdeano C, Ellis L, Epemolu O, Rocha S, Read KD, Ciulli A. Group-based optimization of potent and cell-active inhibitors of the von hippel-lindau (VHL) E3 ubiquitin ligase: structure-activity relationships leading to the chemical probe (2S,4R)-1-((S)-2-(1-Cyanocyclopropanecarboxamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (VH298). J Med Chem, 2018; 61(2):599–618.

Semenza GL, Wang GL. A nuclear factor induced by hypoxia via de novo protein synthesis binds to the human erythropoietin gene enhancer at a site required for transcriptional activation. Mol Cell Biol, 1992; 12(12):5447.

Semenza GL. HIF-1 and mechanisms of hypoxia sensing. Curr Opin Cell Biol, 2001; 13(2):167–71.

Song C, Jiang Y, Cai W, Cheng K, Chen R, Qiu J, Hao Q, Liu Z. 2023. Epimedium/Icariin promotes angiogenesis through HIF-1 signaling pathway. Research Square [Online]. Available via https://www.researchsquare.com/article/rs-2765468/v1 (Accessed 10 May 2023).

Swaroop AK, Esakkimuthukumar M, Patnaik SK, Vasanth P, Jeyaprakash MR, Jawahar N, Jubie S. Dual modulation of IL-6 pathway by flavonoid metal complex as immune boosters for SARS-CoV-2 therapy. ECS Transactions, 2022; 107(1):9771.

Szklarczyk D, Franceschini A, Wyder S, Forslund K, Heller D, Huerta-Cepas J, Simonovic M, Roth A, Santos A, Tsafou KP, Kuhn M. STRING v10: protein–protein interaction networks, integrated over the tree of life. Nucleic acids Res, 2015; 43(D1):D447–52.

Szklarczyk D, Kirsch R, Koutrouli M, Nastou K, Mehryary F, Hachilif R, Gable AL, Fang T, Doncheva NT, Pyysalo S, Bork P, Jensen LJ, von Mering C. The STRING database in 2023: protein-protein association networks and functional enrichment analyses for any sequenced genome of interest. Nucleic Acids Res, 2023; 51(D1):D638–46.

Powell S, Forslund K, Szklarczyk D, Trachana K, Roth A, Huerta-Cepas J, Gabaldón T, Rattei T, Creevey C, Kuhn M, Jensen LJ, von Mering C, Bork P. eggNOG v4.0: nested orthology inference across 3686 organisms. Nucleic Acids Res, 2014; 42(Database issue):D231–9.

Pirhadi S, Damghani T, Avestan MS, Sharifi S. Dual potent c-Met and ALK inhibitors: from common feature pharmacophore modeling to structure based virtual screening. J Recept Signal Transduct Res, 2020; 40(4):357–64.

Qureshi KA, Mohammed SAA, Khan O, Ali HM, El-Readi MZ, Mohammed HA. Cinnamaldehyde-based self-nanoemulsion (CA-SNEDDS) accelerates wound healing and exerts antimicrobial, antioxidant, and anti-inflammatory effects in rats' skin burn model. Molecules, 2022; 27(16):5225.

Tanimoto K, Makino Y, Pereira T, Poellinger L. Mechanism of regulation of the hypoxia-inducible factor-1α by the von Hippel-Lindau tumor suppressor protein. EMBO J, 2000; 19(16):4298–309.

Quazi S, Malik J, Suman KS, Capuzzo AM, Haider Z. Discovery of potential drug-like compounds against Viral protein (VP40) of Marburg Virus using pharmacophoric based virtual screening from ZINC database. BioRxiv, 2021; 2021–05

Viana Nunes AM, das Chagas Pereira de Andrade F, Filgueiras LA, de Carvalho Maia OA, Cunha RLOR, Rodezno SVA, Maia Filho ALM, de Amorim Carvalho FA, Braz DC, Mendes AN. preADMET analysis and clinical aspects of dogs treated with the Organotellurium compound RF07: a possible control for canine visceral leishmaniasis? Environ Toxicol Pharmacol, 2020; 80:103470.

How to cite this article:
Mariappan E, Swaroop AK, Negi P, RajanBabu S, Murugesan DK, Varma NP, Selvaraj J. Identification of effective natural compounds as HIF-1Alpha mimetics for diabetic wound healing; A systematic *in-silico* study. J Appl Pharm Sci, 2023; 13(Suppl 1):041–050.

Supplementary Material

Supplementary data can be downloaded from the link: [https://japsonline.com/admin/php/uploadss/3986_pdf.pdf]