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In silico approaches to evaluate the binding affinity of Verbascoside on Sirtuin1 (SIRT1) receptor for the treatment of diabetic wound healing

Chaired by DR. ALFREDO BERZAL-HERRANZ;
Co-Chaired by PROF. DR. MARIA EMÍLIA SOUSA

pharmaceuticals MDPI

Ankit Majie, **Rajdeep Saha, Shlok Kumar, Riya Aryan, Biswatrish Sarkar***

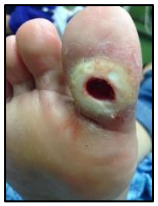
Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Mesra, Ranchi, JH, India 835215

* Corresponding author: biswatrishsarkar@bitmesra.ac.in

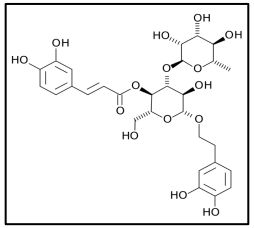
Graphical Abstract

Sirtuin 1 (SIRT1)

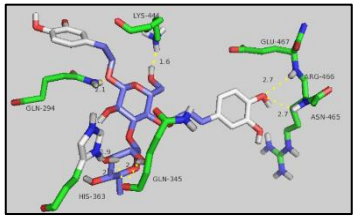
Literature Study → Target Disease → Selection of Target Protein / Selection of Ligand → Molecular Docking → Scoring and Visualization



Diabetic Wound



Verbascoside



Abstract:

The Diabetes Mellitus is one of the leading metabolic disorders which leads to chronic wounds of the lower limbs. Complications like abnormal vasculopathy and functioning of endothelial cells, decreased glucose-6-phosphate dehydrogenase, inadequate remodeling of extracellular matrix, decreased nitric oxide synthase, neuropathy, and secondary infections delay the process of wound healing which finally leads to amputation of the lower extremities. In-vitro and in-vivo studies exploring the role of the SIRT1 receptor in diabetic wounds have shown decreased expression of the receptor along with an increase in the levels of reactive oxygen species (ROS). Treatment with specific SIRT1 agonists in animal models has demonstrated an increase in angiogenesis and a faster rate of wound healing. Verbascoside has a potential role in wound healing by proliferation and keratinocyte migration, synthesis of extracellular matrix, increasing neutrophil and macrophage function, and increasing angiogenesis. Thus, a molecular docking study was conducted to evaluate the interaction between Verbascoside and the SIRT1 receptor (PDB ID: 4ZZJ). The least binding energy was found to be -9.6 kcal/mol which suggested a high binding interaction between the receptor and the ligand. The interacting amino acids include ARG274, GLU467, PRO468, LEU469, PRO470, PHE474, GLU477, ARG649, and VAL657 which is the common binding pocket for polyphenols. However, in-vitro and in-vivo studies are required to further evaluate the activity of Verbascoside in diabetic wound healing.

Keywords: Binding interaction; Chronic wounds; Extracellular matrix; Metabolic disorders; Reactive oxygen species.

Introduction

Diabetic Wound

- Most common complication of Diabetes Mellitus (DM).
- Results from poor glycemic control.
- Can lead to osteomyelitis of foot and amputation of lower limbs [1].

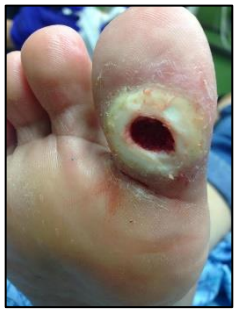


Fig 1. Diabetic foot ulcer

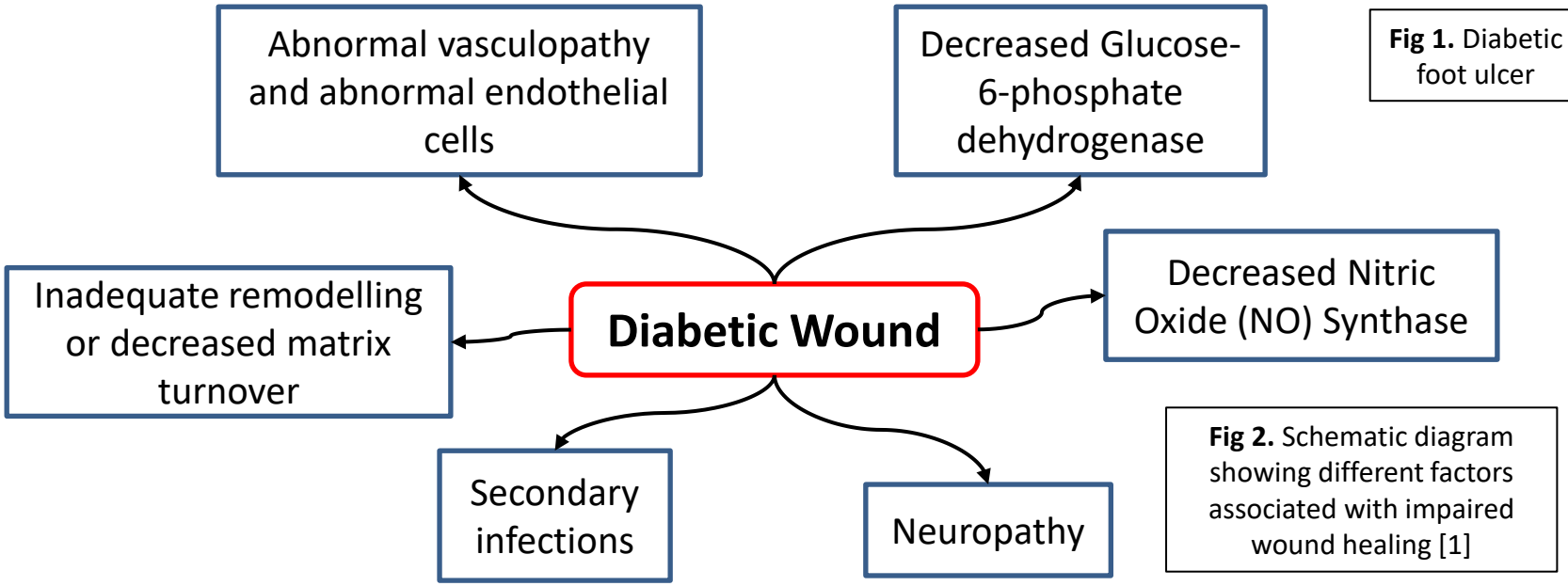


Fig 2. Schematic diagram showing different factors associated with impaired wound healing [1]

Image source: Oliver, T. I. and Mutluoglu, M. (2022) Diabetic Foot Ulcer. StatPearls Publishing. Available at: https://www.ncbi.nlm.nih.gov/books/NBK537328/.

Introduction

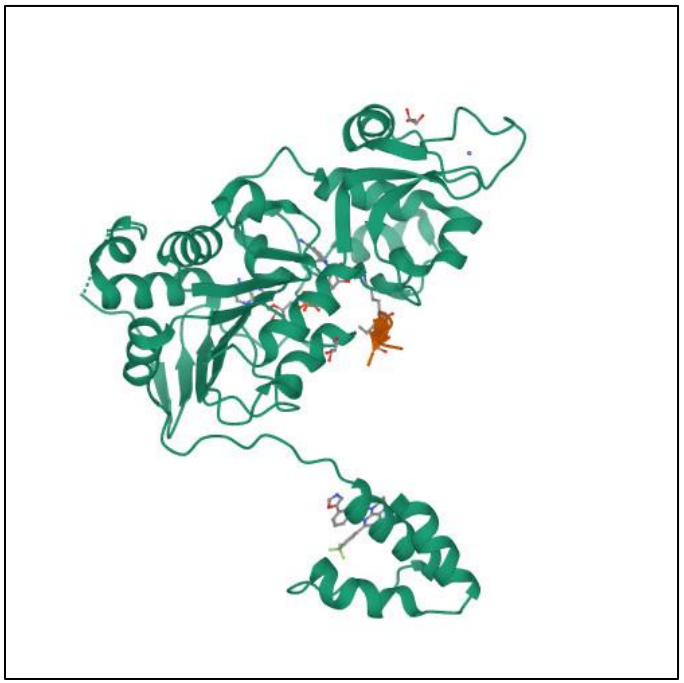


Fig 4. Structure of Sirtuin 1 (SIRT1) (PDB ID: 4ZZJ)

Role of Sirtuin 1 (SIRT1) in diabetic wound [2]

Blood Glucose Homeostasis

Attenuation of p53 acetylation

↓

IGFBP3/IGF-1/Akt pathway activation

Anti-inflammatory activity

- Suppression of pro-inflammatory factors
- TNF-α inhibition
- Deacetylation of NF-κB subunit (RelA/p65)

Remodeling of Collagen

Suppression of MMP-9 expression

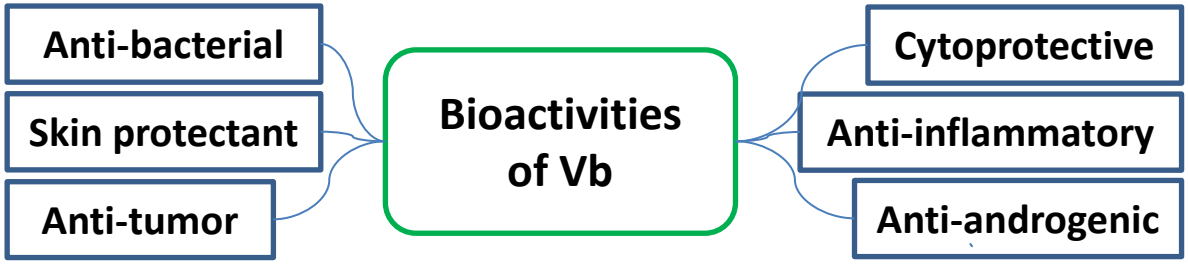
↓

Prevention of collagen degradation

Image source: Dai, H., Case, A.W., Riera, T.V., Considine, T., Lee, J.E., Hamuro, Y., Zhao, H., Jiang, Y., Sweitzer, S.M., Pietrak, B. and Schwartz, B., 2015. Crystallographic structure of a small molecule SIRT1 activator-enzyme complex. Nature communications, 6(1), pp.1-10.

Introduction

Verbascoside (Vb) is a water-soluble Phenylethanoid glycoside (PhGs). [3]



Potential role in wound healing [3]

- ↑ proliferation and keratinocyte migration
- ↑ synthesis of ECM
- ↑ proliferation and fibroblast migration
- ↑ neutrophil function
- ↑ macrophage function
- ↑ angiogenesis
- ↑ function and endothelial cell migration

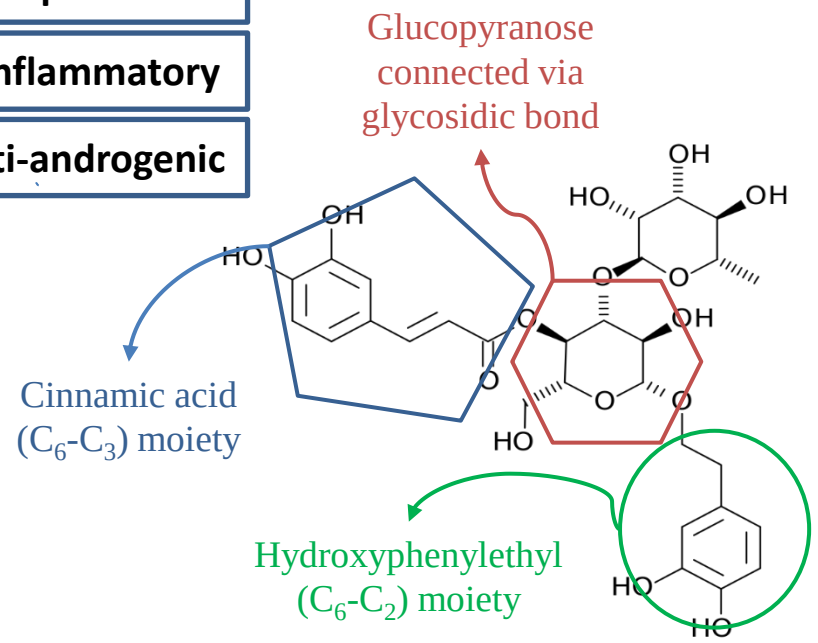


Fig 3. 2-(3,4-Dihydroxyphenyl)ethyl α-L-rhamnopyranosyl-(1→4)-{5-O-[(2E)-3-(3,4-dihydroxymethyl)prop-2-enoyl]-β-D-glucopyranoside}

Materials and Method

1. Target protein acquisition

The three-dimensional structure of SIRT1 (PDB ID: 4ZZJ) was downloaded from Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) in PDB format [4].

2. Ligand acquisition

The three-dimensional chemical structure of Verbascoside molecule was downloaded from PubChem database in MOL SDF format [5].

3. Preparation of target protein

The protein was prepared using AutoDock by the following procedure,

- All the water molecules were deleted.
- Polar hydrogens were added.
- Kollman Charges' were assigned.
- The protein was saved in PDBQT format.

Materials and Method

4. Selection of active binding site

The active binding site was selected by analyzing the polyphenol binding site through PyMOL software [6].

5. Evaluation of binding affinity and binding interactions

- Computational ligand-protein docking interaction was used to analyze the interaction between Verbascoside (ligand) and SIRT1 (protein/target).
- Grid point was assigned on the selected active binding site of the protein.
- Molecular docking based on scoring functions was carried out using AutoDock Vina.
- Binding energy of the ligand-protein interactions was evaluated.
- The binding pocket was visualized and interacting amino acids were evaluated based on the polar contacts using the PyMOL software.
- The different poses of the ligand in the binding pocket of the protein were analyzed.

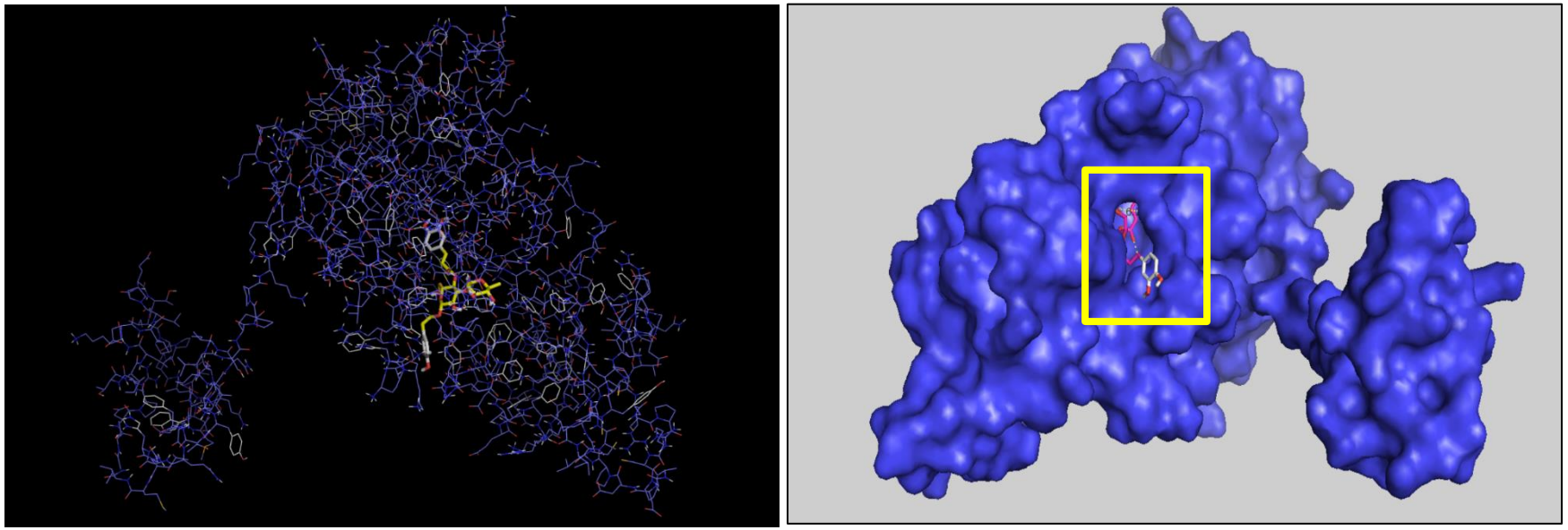
Result and Discussion

Table 1. The binding Energies obtained after molecular docking analysis of Verbascoside (Vb) as ligand and Sirtuin 1 (SIRT1) as protein. The ligand-protein interaction complex are ranked in increasing order of the binding energies.

Docking Poses	Complex	Binding Energy (kcal/mol)	RMSD L.B.	RMSD U.B.
1	Vb_SIRT1	-9.6	0.000	0.000
2	Vb_SIRT1	-9.5	3.555	5.176
3	Vb_SIRT1	-9.5	1.480	2.235

Abbreviations - Vb: Verbascoside; SIRT1: Sirtuin 1; RMSD: Root Mean Square Deviation; L.B.: Lower Bound; U.B.: Upper Bound.

Result and Discussion



(a) (b)

Fig 5. The ligand binding pocket for Verbascoside in SIRT1 protein as visualized through PyMOL software. (a) SIRT1 is represented as lines and Verbascoside as sticks; (b) SIRT1 is represented in the form of surface diagram and Verbascoside as sticks.

Result and Discussion

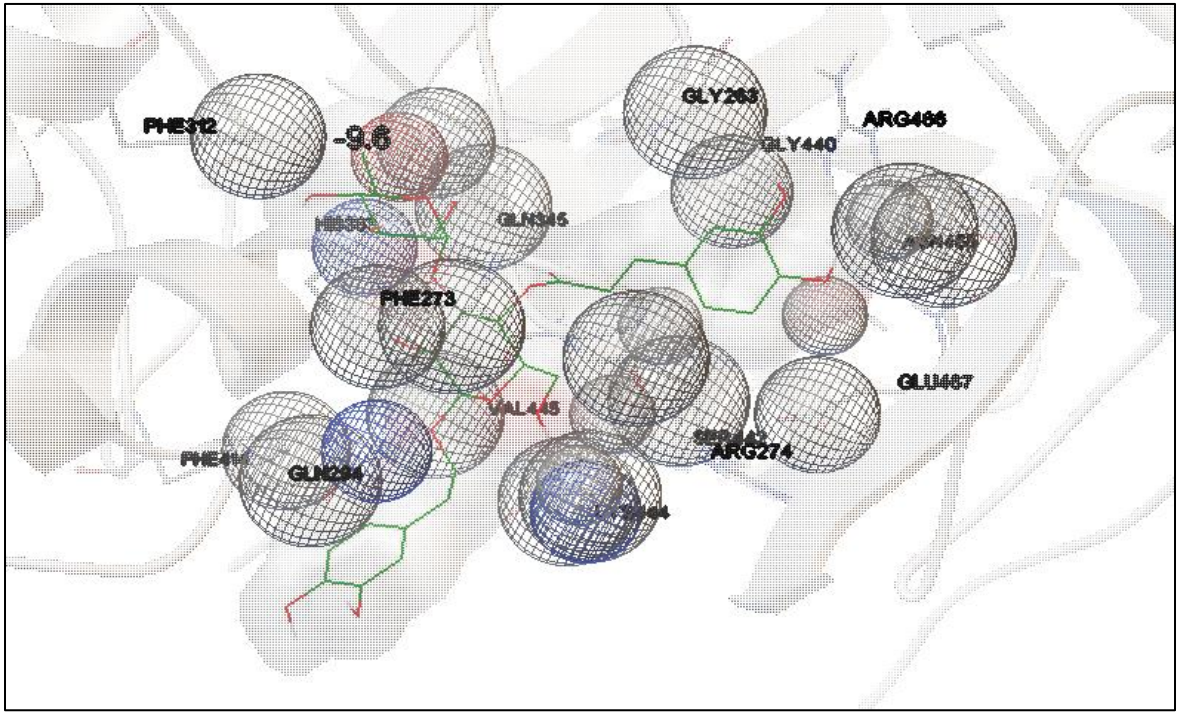


Fig 6. The interacting amino acids of the binding site (represented as hollow spheres) with the Verbascoside molecule. The above figure represents docking pose 1 of the ligand with binding energy of -9.6 kcal/mol. The above visualization have been made through AutoDock software.

Result and Discussion

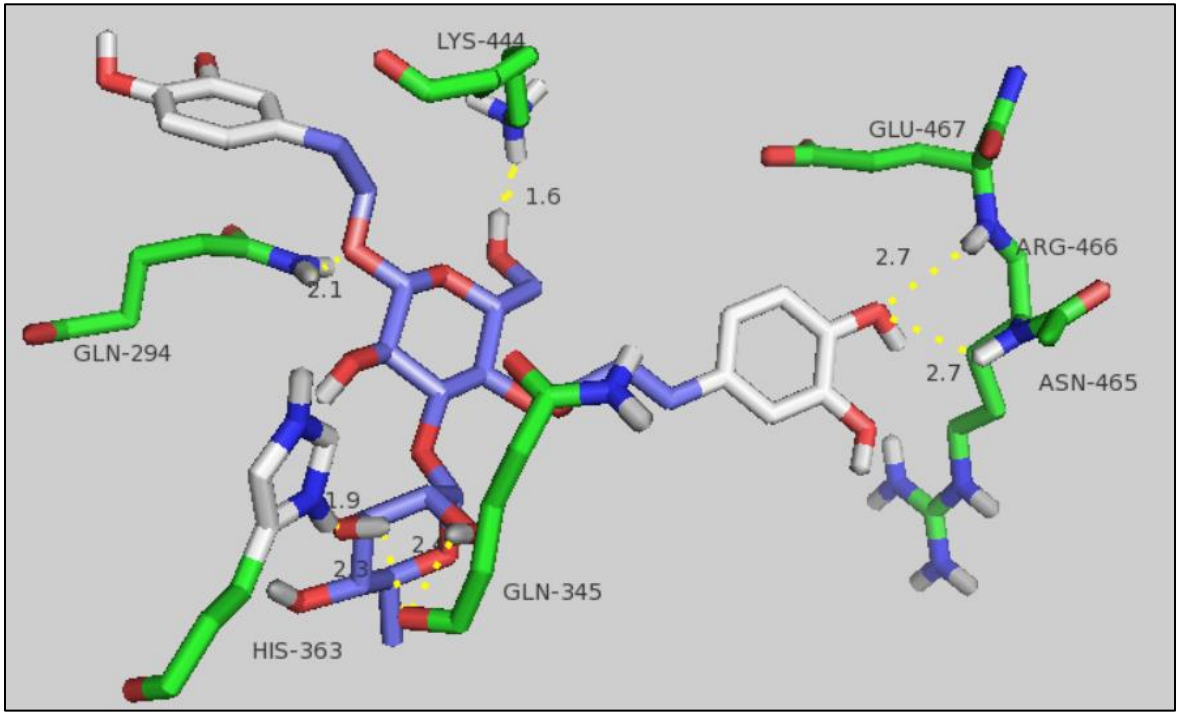


Fig 7. The polar interactions between Verbascoside and the amino acids of the binding site with binding energy of -9.6 kcal/mol as visualized through PyMOL software. The interacting amino acids include LYS-444, GLN-294, HIS-363, GLN-345, GLU-467, ARG-466, and ASN-465. The ligand shows close interaction (1.6-2.9 Å) with the protein.

Conclusion

- Molecular docking studies of Verbascoside (Vb) with SIRT1 shows good binding interaction between the protein and the ligand.
- The diabetic wound healing activity of Vb have not been explored till date.
- However, phenylethanoid glycosides like Vb are large molecules which show less permeation topically.
- So, incorporation of such molecules as nano-formulations can help in effective drug delivery.
- Extensive in-vitro and in-vivo studies are required to confirm this in-silico study.

References

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Acknowledgements