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# In Silico Analysis of Phytocompounds from Hedychium ellipticum Targeting TXNIP for Antidiabetic Potential

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***Abstract***

***Introduction:*** *Diabetes mellitus is a chronic metabolic disorder with increasing global prevalence, particularly impacting populations in low-income regions. Current antidiabetic therapies, though effective, are often accompanied by adverse effects. There is a growing interest in identifying safer, plant-based alternatives. This study investigates phytochemicals from Hedychium ellipticum, a traditional medicinal plant, for their potential to inhibit Thioredoxin-Interacting Protein (TXNIP), a key protein in diabetes progression.*

***Methods:*** *Bioactive compounds from Hedychium ellipticum were selected through literature surveys and retrieved in 3D structure from PubChem. TXNIP protein structure (PDB ID: 4GEI) was refined for docking using AutoDock tools. Blind molecular docking simulations were performed to assess binding affinities and interaction types. Docked complexes were visualized using BIOVIA Discovery Studio. Root Mean Square Deviation (RMSD) analysis validated complex stability.*

***Results:*** *Nine phytochemicals exhibited binding affinities ranging from −6.4 to −9.6 kcal/mol. Phytol demonstrated the strongest binding (−9.6 kcal/mol), though without hydrogen bonding. Most interactions involved alkyl and Van der Waals forces, suggesting non-covalent modulation of TXNIP activity. RMSD values stabilized around 2.2 Å, confirming simulation stability.*

***Discussion:*** *The docking results highlight the potential of Hedychium ellipticum-derived phytochemicals as TXNIP modulators, particularly phytol, which exhibited the strongest binding affinity. Despite the absence of hydrogen bonds, the predominance of Van der Waals and alkyl interactions suggests effective non-covalent inhibition. The RMSD analysis further supports the conformational stability of ligand-protein complexes. These findings align with existing literature emphasizing the antidiabetic potential of plant-based compounds. However, in vitro and in vivo studies are essential to validate the pharmacological efficacy and safety of these candidates.*

***Conclusion:*** *Phytocompounds from Hedychium ellipticum showed promising interactions with TXNIP, supporting their potential as lead compounds for antidiabetic drug development. Further experimental validation is recommended to confirm these in silico findings and explore their therapeutic relevance.*

***Keywords:*** *Hedychium ellipticum, TXNIP, diabetes mellitus, molecular docking, phytochemicals, AutoDock, in silico analysis.*

## 1. INTRODUCTION

Diabetes mellitus (DM) is a widespread metabolic disorder that affects individuals globally, regardless of socioeconomic status.[1] Type 1 diabetes is typically diagnosed in children, particularly between infancy and 14 years of age, whereas Type 2 diabetes has been more commonly observed in adults, though its incidence is also increasing among younger populations. [2-4] As of 2014, approximately 8.5% of adults aged 18 and above were affected by diabetes. In 2019, the disease directly caused an estimated 1.5 million deaths, nearly half of which occurred in individuals under the age of 70. [5-9] The burden of premature deaths from diabetes was notably higher in low-income countries, with projections suggesting that over 629 million people could be affected by 2049. [10,11]

Despite the availability of various antidiabetic medications, long-term use can lead to undesirable side effects, often due to off-target drug actions. [12,13] For example, some drugs interfere with Angiotensin-Converting Enzyme (ACE), potentially causing angioedema—a serious condition marked by swelling of the throat, tongue, and face, which can lead to breathing difficulties. [14,15] Skin reactions, scarring, and allergic responses—particularly to insulin and its formulation additives such as zinc protamine and meta-cresol—are also reported. [16-19] In certain cases, patients may even fail to respond adequately to otherwise effective medications. Some commonly prescribed antidiabetic treatments and their associated side effects include:

**1. Biguanides**: Often the first-line treatment for Type 2 diabetes, it improves insulin sensitivity and lowers blood glucose levels but may cause lactic acidosis with prolonged use. [20]

**2. Sulfonylureas**: These stimulate the pancreas to release more insulin. However, they can cause hypoglycemia, resulting in dizziness, sweating, and confusion. [21]
**3. Meglitinides**: Similar to sulfonylureas, they prompt insulin release but are rapidly cleared from the body. Side effects include low blood sugar and weight gain. [22]
**4. Thiazolidinediones**: These enhance insulin sensitivity but may cause fluid retention, weight gain, and elevated LDL cholesterol. Serious risks include heart failure, bone fractures, and bladder cancer. [23]
**5. Alpha-glucosidase inhibitors**: Taken with meals, they slow carbohydrate digestion but often lead to gastrointestinal discomfort such as gas, abdominal pain, and diarrhea. [24]
**6. DPP-4 inhibitors**: These enhance insulin production but may cause mild respiratory issues and abdominal pain. [25]
**7. Insulin therapy**: Often used when oral medications are no longer effective. Side effects can include headache, dry mouth, dizziness, rashes, and occasional allergic reactions. [26]

Despite the effectiveness of these treatments, the search for safer, more targeted therapies continues, especially to reduce complications and enhance patient quality of life. [27] Reducing the cost and time associated with new drug development is a major priority in the pharmaceutical industry. [28] One of the most effective ways to achieve this is through the use of Computer-Aided Drug Design (CADD). These computational techniques have revolutionized early-stage drug discovery by allowing researchers to screen thousands of molecules from various chemical databases for properties such as toxicity, stability, and drug-likeness—before entering costly laboratory trials. [29,30]
In the search for novel antidiabetic agents, medicinal plants offer a valuable reservoir of bioactive compounds. One such promising plant is Hedychium ellipticum, a member of the Zingiberaceae family. [31] This genus includes over 80 species found throughout tropical and subtropical Asia, with India—particularly the Western Ghats and Northeastern regions serving as a key center of diversity. Traditionally used in folk medicine, Hedychium ellipticum is known for its rich phytochemical profile, including flavonoids, terpenoids, and phenolic compounds. [32,33] These constituents are recognized for their antioxidant, anti-inflammatory, and potential antidiabetic properties. However, despite its ethnobotanical importance, scientific research on its therapeutic efficacy especially in the context of diabetes is still in its early stages, highlighting the need for further pharmacological and mechanistic studies.

## 2. MATERIAL AND METHODS

### 2.1. Retrieval and preparation of ligands

Different phytochemicals of the plant Hedychium ellipticum were selected from literature survey. Three-dimensional (3D) structures of selected compounds were downloaded from pubchem in SDF format. The ligand molecules were prepared, for docking by open babel in AutoDock. The roots were detected and torsion count was done. The prepared molecules were saved in PDBQT format

### 2.2. Retrieval and preparation of Protein.

Thioredoxin-Interacting Protein (TXNIP) was chosen as the target protein for this study due to its significant role in the progression of diabetes. The three-dimensional structure of its N-terminal domain was obtained in PDB format from the Protein Data Bank using the PDB ID: 4GEI (Figure 1). To prepare the protein for docking studies, unnecessary components such as water molecules, heteroatoms were removed and further processing was done using AutoDock tools, where polar hydrogens were added Kollman charges (−4.666) were assigned. A three-dimensional grid box was defined to blind docking, with dimensions of 126× 126 × 126 Å, ensuring the target region was accurately covered. After all modifications and energy minimization, the final prepared protein structure was saved in PDBQT format, making it ready for molecular docking simulations.

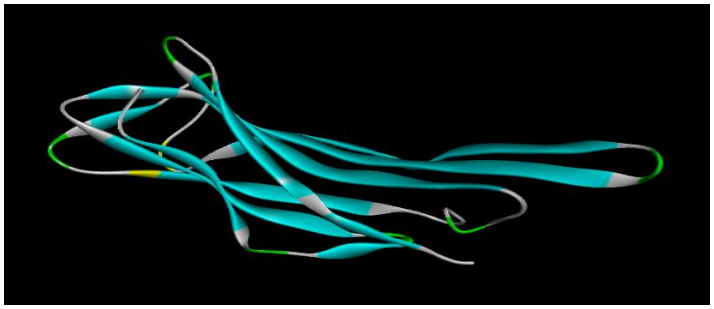

Fig 1:Shows the TXNIP structure

### 2.3. Binding affinity and molecular docking

To assess the binding affinity and interaction potential of certain phytochemicals, molecular docking of the N-terminal domain of TXNIP was performed. The AutoDock program was used to execute blind docking using the target protein and ligand molecules produced PDBQT files. An out.pdbqt file with details on different binding conformations was created from the docking data. Protein–ligand complexes were created using these output files and the protein structure; they were then stored in PDB format for analysis. BIOVIA Discovery Studio (3D) was used to see and study the interactions of the docked complexes. The complexes with the strongest hydrogen bond interactions and the lowest binding energies were selected for more study, suggesting that they might be effective treatment options.

## 3. RESULT

### 3.1. Binding affinity and interactions in molecular docking

A range of interaction strengths among the chosen phytochemicals was shown by the docked protein–ligand complexes' binding affinities, which varied from -9.6 to -6.4 kcal/mol (Table 1). With the lowest binding energy (−9.6 kcal/mol), the chemical phytol indicated a substantial potential interaction. Nevertheless, in spite of this positive score, the complex showed no hydrogen bonds, suggesting that there were no substantial polar interactions between the protein target and phytol. On the other hand, the majority of the phytochemicals interacted with the TXNIP protein by alkyl or Van der Waals forces. These non-covalent interactions imply that the substances may bind to both the active site and allosteric areas, which might indirectly modulate the protein's activity. This demonstrates the phytochemicals' varied binding patterns and their capacity to alter TXNIP activity via a variety of binding mechanisms.

| Chemical name | Class | RUN | RMSD (kcal/mol) |
|---|---|---|---|
| Eucalyptol | Monoterpene oxide | 30 | -7.08 |
| Sabinene | Monoterpene | 20 | -6.98 |
| β-Caryophyllene | Sesquiterpene | 89 | -8.96 |
| Linalool | Monoterpene alcohol | 13 | -6.68 |
| α-Humulene | Sesquiterpene | 87 | -9.01 |
| Germacrene D | Sesquiterpene | 77 | -8.35 |
| Phytol | Diterpene alcohol | 90 | -9.50 |
| α-Pinene | Monoterpene | 13 | -6.40 |
| Farnesene | Sesquiterpene | 15 | -7.08 |

**1. Eucalyptol**

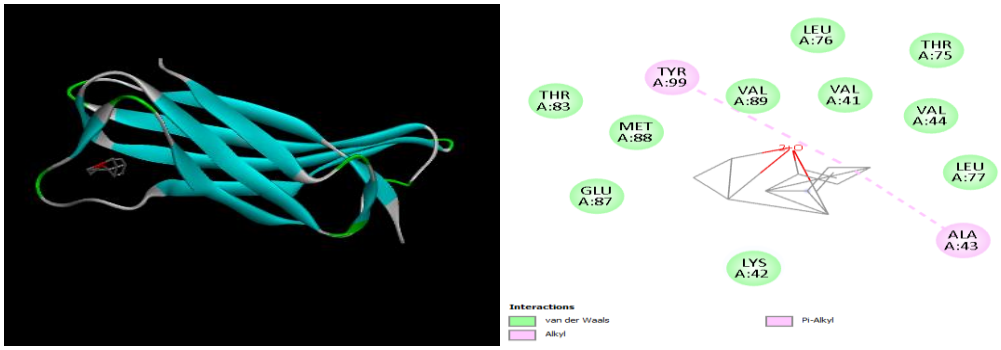


Fig.2 (a) Eucalyptol interaction with TXNIP in blind docking (b) 2D structure of Eucalyptol and surrounding amino acid residues involved in interaction during blind docking

**2. Sabinene**

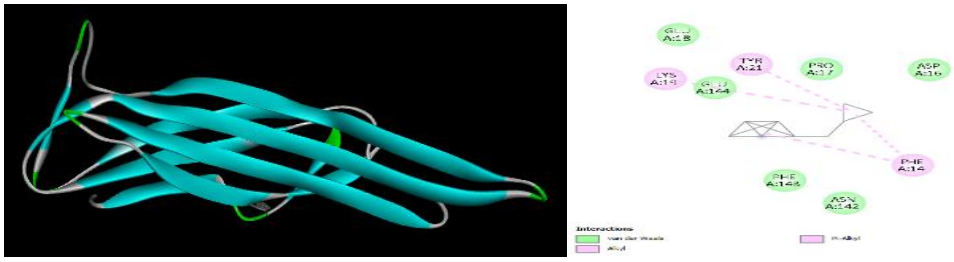

Fig.3 (a) Sabinene interaction with TXNIP in blind docking (b) 2D structure of Sabinene and surrounding amino acid residues involved in interaction during blind docking

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### 3. β-Caryophyllene

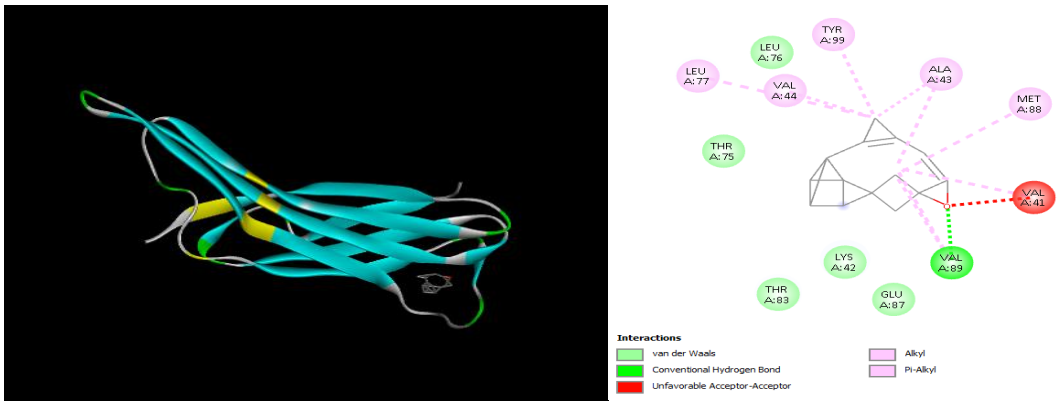


Fig.4 (a) β-Caryophyllene interaction with TXNIP in blind docking (b) 2D structure of β-Caryophyllene and surrounding amino acid residues involved in interaction during blind docking

### 4. Linalool

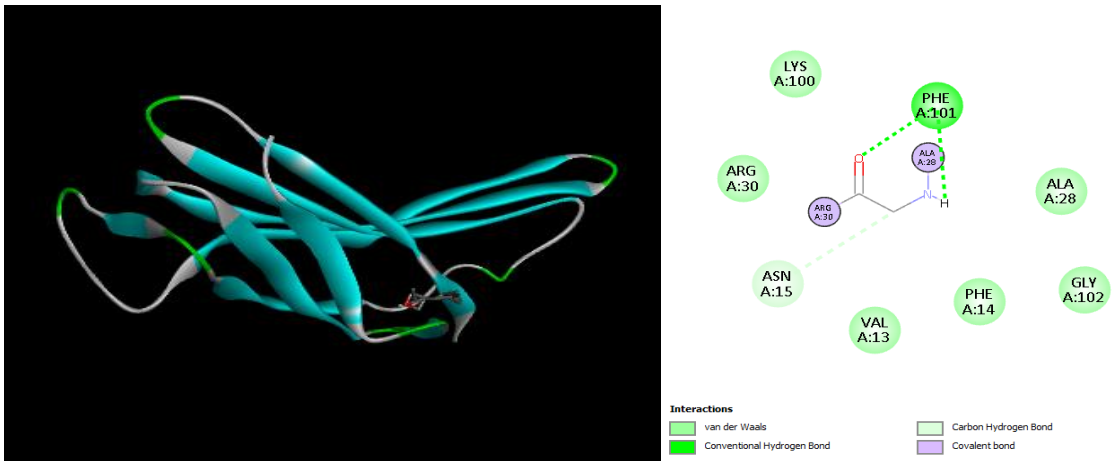


Fig.5 (a) Linalool interaction with TXNIP in blind docking (b) 2D structure of Linalool and surrounding amino acid residues involved in interaction during blind docking

### 5. α-Humulene

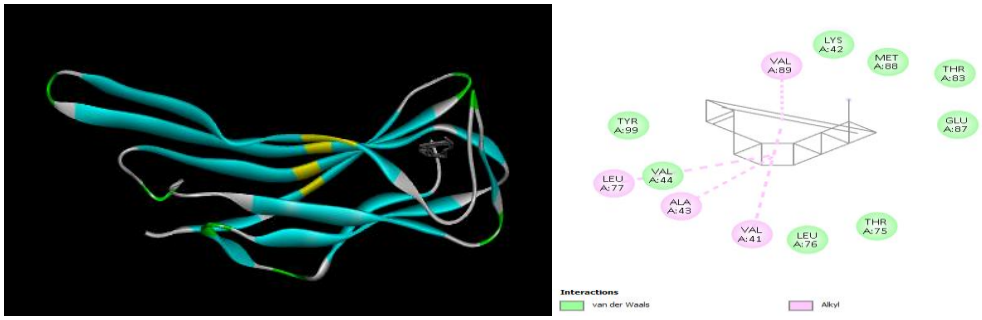


Fig.6 (a) α-Humulene interaction with TXNIP in blind docking (b) 2D structure of α-Humulene and surrounding amino acid residues involved in interaction during blind docking

### 6. Germacrene D

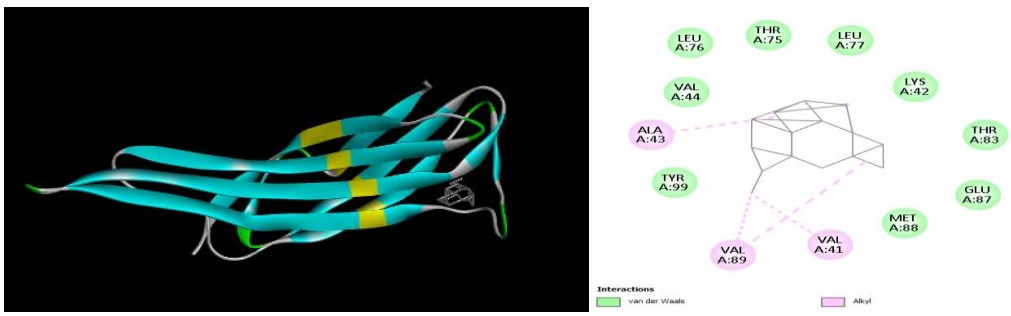


Fig.7 (a) Germacrene D interaction with TXNIP in blind docking (b) 2D structure of Germacrene D and surrounding amino acid residues involved in interaction during blind docking

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**7. Phytol**

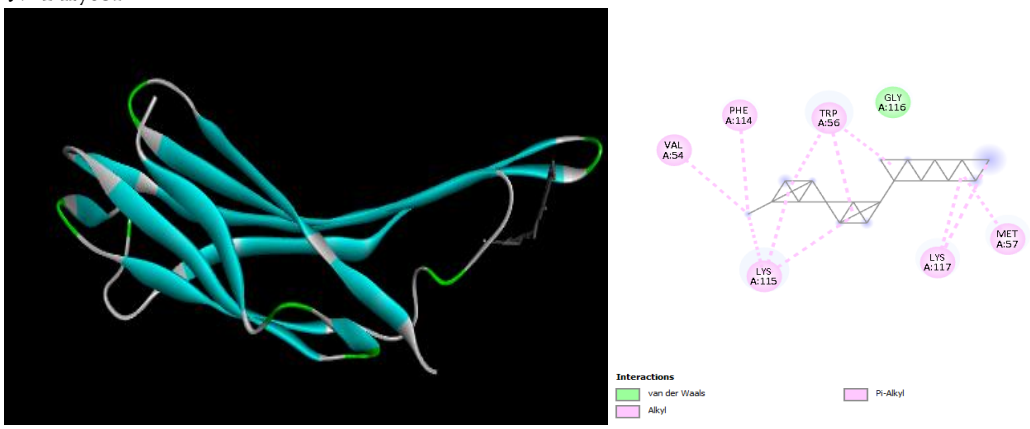


Fig.8 (a) Phytol interaction with TXNIP in blind docking (b) 2D structure of Phytol and surrounding amino acid residues involved in interaction during blind docking

**8. α-Pinene**

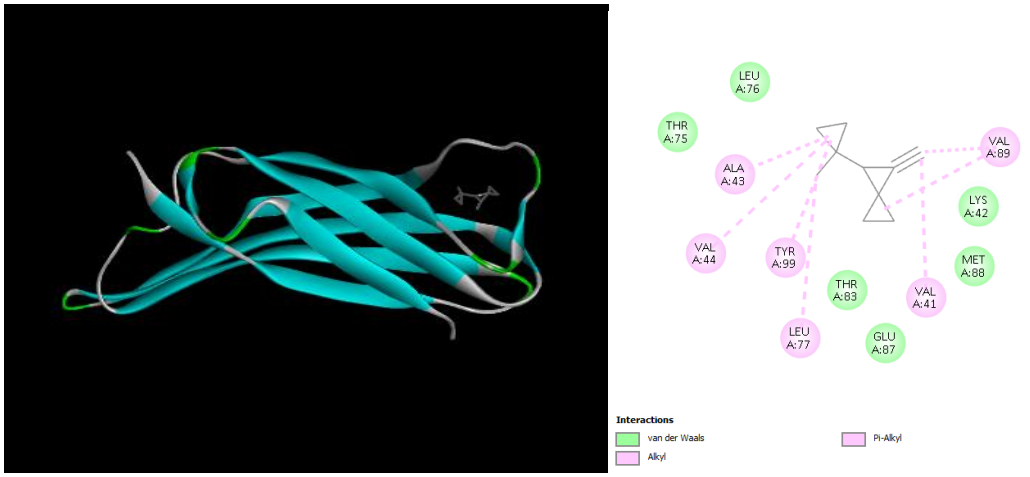


Fig.9 (a) α-Pinene interaction with TXNIP in blind docking (b) 2D structure of α-Pinene and surrounding amino acid residues involved in interaction during blind docking

**9. Farnesene**

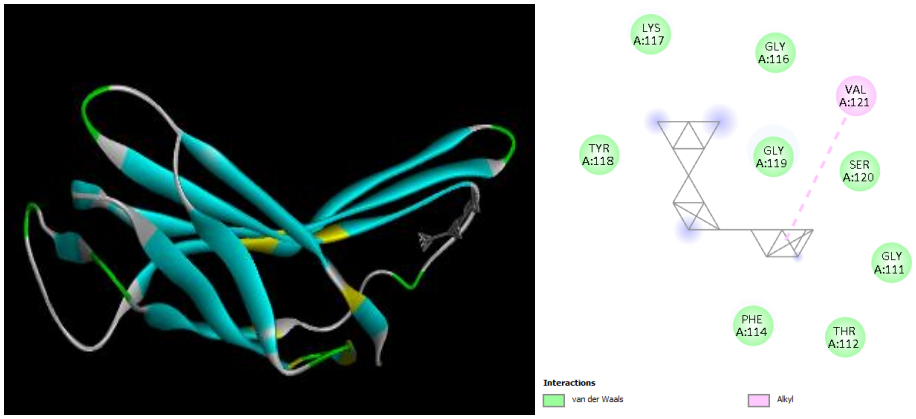


Fig.10 (a) Farnesene interaction with TXNIP in blind docking (b) 2D structure of Farnesene and surrounding amino acid residues involved in interaction during blind docking

### 3.2. Root Mean Square Deviation

The stability of the simulation process was assessed by analyzing the RMSD of the protein's backbone atoms. The RMSD plot demonstrated a gradual increase from an initial value of approximately 1.0 Å, eventually stabilizing and fluctuating around 2.2 Å, indicating that the protein-ligand complex maintained a relatively stable conformation throughout the simulation.

### 3.3. Docking

After examining the molecular interaction findings generated from docking studies involving various natural compounds, we observed that phytochemicals exhibit interactions with TXNIP protein targets.

Parameters such as final intermolecular energy, inhibition constants, and the formation of hydrogen bonds between the ligands and receptor molecules serve as key indicators for evaluating molecular docking outcomes (Ferreira et al., 2015).

During blind docking, the selected phytochemicals were found to form alkyl bonds and Vanderwal bonds with different amino acids residues. Based on blind docking data, these compounds consistently showed alkyl bonds and Vanderwal interactions with different amino acids. The computed binding energies and corresponding inhibition constants of the phytochemicals were found to vary from–6.40 kcal/mol to 9.10 for blind docking (Fig. 2a & 10a), and 2D amino acids interaction (Fig. 2b & 10b).

## CONCLUSION

This study sheds light on the antidiabetic potential of phytochemicals from Hedychium ellipticum through targeted molecular interactions with Thioredoxin-Interacting Protein (TXNIP), a key player in oxidative stress and glucose metabolism dysregulation. Using a robust in silico approach, the selected compounds were screened for their binding affinity and interaction profiles, highlighting phytol, α-humulene, and β-caryophyllene as promising candidates. These molecules demonstrated strong binding energies, particularly phytol with a notable −9.6 kcal/mol, suggesting their potential to modulate TXNIP function.

The docking simulations revealed predominantly non-covalent interactions, including Van der Waals and alkyl bonding, which indicate a likelihood of allosteric modulation without disrupting the core protein structure. RMSD analysis further confirmed the conformational stability of the protein-ligand complexes, supporting the reliability of the docking outcomes.

A key strength of this research lies in its novel focus on TXNIP as a molecular target, which remains relatively untapped in current antidiabetic drug discovery efforts. Additionally, Hedychium ellipticum, though rich in traditional therapeutic use, has rarely been studied in the context of diabetes at the molecular level. By integrating traditional botanical knowledge with modern computational methods, this study offers a fresh perspective on natural product-based drug design.

Overall, the findings present a compelling case for advancing these phytochemicals into experimental validation and preclinical testing. This integrative approach not only enhances our understanding of TXNIP modulation but also opens new doors for developing safer and more effective antidiabetic therapies.

**Funding**

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**Conflict of Interest**

The authors have no conflict of interest

**List of abbreviation**

DM Diabetes Mellitus
TXNIP Thioredoxin-Interacting Protein
CADD Computer-Aided Drug Design
3DThree-Dimensional
PDBProtein Data Bank
PDBQT Protein Data Bank, Partial Charge (Q), Torsion (T)
RMSD Root Mean Square Deviation

**REFERENCE**

1. Forouhi NG, Koulman A, Sharp SJ, et al. Differences in the prospective association between individual plasma phospholipid saturated fatty acids and incident type 2 diabetes: the EPIC-InterAct case-cohort study. Lancet Diabetes Endocrinol. 2014;2(10):810–8.
2. Sahoo K, Sahoo B, Choudhury A, Sofi N, Kumar R, Bhadoria A. Childhood obesity: causes and consequences. J Family Med Prim Care. 2015;4(2):187.
3. English E, Lenters-Westra E. HbA1c method performance: the great success story of global standardization. Crit Rev Clin Lab Sci. 2018;55(6):408–19.
4. Burrack AL, Martinov T, Fife BT. T cell-mediated beta cell destruction: autoimmunity and alloimmunity in the context of type 1 diabetes. Front Endocrinol. 2017;8:343.
5. Montane J, Cadavez L, Cadavez-Trigo L, Novials A. Stress and the inflammatory process: a major cause of pancreatic cell death in type 2 diabetes. Diabetes Metab Syndr Obes. 2014;7:25–34.
6. Poitout V, Robertson RP. Minireview: secondary β-cell failure in type 2 diabetes—a convergence of glucotoxicity and lipotoxicity. Endocrinology. 2002;143:339–42.

7. Shalev A, Pise-Masison CA, Radonovich M, et al. Oligonucleotide microarray analysis of intact human pancreatic islets: identification of glucose-responsive genes and a highly regulated TGFβ signaling pathway. Endocrinology. 2002;143(9):3695–8.
8. Minn AH, Hafele C, Shalev A. Thioredoxin-interacting protein is stimulated by glucose through a carbohydrate response element and induces β-cell apoptosis. Endocrinology. 2005;146(5):2397–405.
9. Chen J, Young ME, Chatham JC, Crossman DK, Dell'Italia LJ, Shalev A. TXNIP regulates myocardial fatty acid oxidation via miR-33a signaling. Am J Physiol Heart Circ Physiol. 2016;311(1):H64–75.
10. Shalev A. Minireview: thioredoxin-interacting protein: regulation and function in the pancreatic β-cell. Mol Endocrinol. 2014;28(8):1211–20.
11. Shaked M, Ketzinel-Gilad M, Ariav Y, et al. Insulin counteracts glucotoxic effects by suppressing thioredoxin-interacting protein production in INS-1E beta cells and in Psammomys obesus pancreatic islets. Diabetologia. 2009;52(4):636–44.
12. Chutkow WA, Patwari P, Yoshioka J, Lee RT. Thioredoxin-interacting protein (Txnip) is a critical regulator of hepatic glucose production. J Biol Chem. 2008;283(4):2397–406.
13. Shi Y, Ren Y, Zhao L, et al. Knockdown of thioredoxin-interacting protein attenuates high glucose-induced apoptosis and activation of ASK1 in mouse mesangial cells. FEBS Lett. 2011;585(12):1789–95.
14. El-Azab MF, Baldowski BRB, Mysona BA, et al. Deletion of thioredoxin-interacting protein preserves retinal neuronal function by preventing inflammation and vascular injury. Br J Pharmacol. 2014;171(5):1299–313.
15. Wellen L, Shalev A. Diabetes pathogenic mechanisms and potential new therapies based upon a novel target called TXNIP. Curr Opin Endocrinol Diabetes Obes. 2018;25(2):75–80.
16. Wu MA, Perego F, Zanichelli A, Cicardi M. Angioedema phenotypes: disease expression and classification. Clin Rev Allergy Immunol. 2016;51(2):162–9.
17. Scott SI, Andersen MF, Aagaard L, Buchwald CV, Rasmussen ER. Dipeptidyl peptidase-4 inhibitor induced angioedema—an overlooked adverse drug reaction? Curr Diabetes Rev. 2018;14(4):327–33.
18. Jedlowski PM, Te CH, Segal RJ, Fazel MT. Cutaneous adverse effects of diabetes mellitus medications and medical devices: a review. Am J Clin Dermatol. 2019;20(1):97–114.
19. Ross P, Gray A, Milburn J, et al. Insulin pump-associated adverse events are common, but not associated with glycemic control, socio-economic status, or pump/infusion set type. Acta Diabetol. 2016;53(6):991–8.
20. Jacquier J, Chik CL, Senior PA. A practical, clinical approach to the assessment and management of suspected insulin allergy. Diabet Med. 2013;30(8):977–85.
21. Rosengren A, Jing X, Eliasson L, Renström E. Why treatment fails in type 2 diabetes. PLoS Med. 2008;5(10):e215.
22. Kim D, Baraniuk J. Delayed-type hypersensitivity reaction to the meta-cresol component of insulin. Ann Allergy Asthma Immunol. 2007;99(2):194–5.
23. Gin H, Aubertin J. Generalized allergy due to zinc and protamine in insulin preparation treated with insulin pump. Diabetes Care. 1987;10(6):789–90.
24. Abubakar B, Giaze RT, Haliru A. Clinical investigation of treatment failure in type 2 diabetic patients treated with metformin and glibenclamide at a hospital in northwestern Nigeria. Trop J Pharm Res. 2014;13(9):1521–5.
25. Srivastava AK. The role of fungus in bioactive compound production and nanotechnology. In: Role of Plant Growth Promoting Microorganisms in Sustainable Agriculture and Nanotechnology. 2019.
26. Dufossé L, Fouillaud M, Caro Y. Fungi and fungal metabolites for the improvement of human and animal nutrition and health. J Fungi. 2021;7(4):274.
27. Drews J. Drug discovery today—and tomorrow. Drug Discov Today. 2000;5(1):2–4.
28. Song CM, Lim SJ, Tong JC. Recent advances in computer-aided drug design. Brief Bioinform. 2009;10:579–91.
29. Lavecchia A, Giovanni C. Virtual screening strategies in drug discovery: a critical review. Curr Med Chem. 2013;20(23):2839–60.
30. Lavecchia A, Cerchia C. In silico methods to address polypharmacology: current status, applications and future perspectives. Drug Discov Today. 2016;21(2):288–98.
31. Cheng T, Li Q, Zhou Z, Wang Y, Bryant SH. Structure-based virtual screening for drug discovery: a problem-centric review. AAPS J. 2012;14(1):133–41.
32. Bibi S, Sakata K. Current status of computer-aided drug design for type 2 diabetes. Curr Comput Aided Drug Des. 2016;12:167–77.
33. Saleem S, Bibi S, Yousafi Q, Hassan T, Khan MS, Hasan MM, et al. Identification of effective and nonpromiscuous antidiabetic drug molecules from Penicillium species. Evid Based Complement Alternat Med. 2022;2022:7040547. doi:10.1155/2022/7040547. PMID: 35722152; PMCID: PMC9200499.