# Exploring the Therapeutic Potential of Natural Products: A Computational and Pharmacophore-Based Study of Antidiabetic Agents

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**ABSTRACT:**
Natural products have long served as a foundational source for drug discovery, offering unique chemical structures and diverse biological activities that are challenging to replicate synthetically. This study provides a comprehensive exploration of various plant-derived compounds—such as trigonelline, resveratrol, pterostilbene, curcumin, vanillin, and phytochemicals from Triphala—as potential therapeutic agents in addressing metabolic and oncological disorders. Utilizing a computational framework, we performed molecular docking, pharmacophore modelling, and protein–ligand interaction analyses to assess binding affinities and interaction profiles with key anti-diabetic and anti-ulcer targets. Notably, nigelline demonstrated superior binding affinity and stability at the active sites of insulin-stimulating proteins, outperforming standard drugs like buformin. Similarly, S-allyl-L-cysteine-S-oxide mirrored the pharmacophoric features of glibenclamide, validating its potential as a natural insulin secretagogue. Curcumin derivatives and Triphala compounds also exhibited promising inhibitory activities against glucose-regulating enzymes, suggesting their utility in managing postprandial hyperglycemia. Furthermore, gurmarin, a peptide from *Gymnema sylvestre*, showed insulin-mimetic properties through effective binding to the insulin receptor. The findings highlight the untapped potential of natural products as templates for safer, plant-based drug development and underscore the value of integrating bioinformatics and in silico approaches to streamline early-stage drug discovery.

Keywords: Nigelline, S-allyl-L-cysteine-S-oxide, Gurmarin, Trigonelline, Resveratrol, Pterostilbene, Curcumin, Vanillin, Triphala, Docking, AutoDock Vina, Diabetes, Ulcer.

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## 1. Introduction

Drug discovery is a multifaceted, cross-disciplinary process focused on finding new compounds that can meet unmet medical needs, enhance patient outcomes, and revolutionize treatment approaches. The path from identifying a potential drug target to obtaining approval for a commercially viable therapy can take many years—often decades—and requires extensive research, thorough testing, and considerable investment (El-Tanani et al., 2025; Rai et al., 2025).

Natural products have been essential in the field of drug discovery for hundreds of years, forming the basis for numerous life-saving medications. These compounds, sourced from plants, microorganisms, animals, and marine life, possess a wide range of chemical compositions and biological activities that render them important candidates for pharmaceutical innovation. Below is a summary of the significance of natural products in drug discovery (Nasim et al., 2022; Gohtori et al., 2023; Chaachouay & Zidane, 2024).

Natural products are valuable leads for drug discovery since they typically possess unique chemical structures. Many medications used today—including anti-inflammatory, anticancer, and antibacterial agents—were originally derived from natural sources. A significant proportion of existing drugs, including antibiotics, anticancer agents, and anti-inflammatory medications, are derived from nature. Their structural complexity—featuring chiral centers, fused ring systems, and rare functional groups—makes them particularly valuable for interacting with biological targets (Chen et al., 2022; Banday et al., 2024).

Notable natural compounds such as trigonelline, resveratrol, pterostilbene, cinnamon-derived cinnamaldehyde, curcumin, and vanillin have been studied for a wide array of pharmacological properties. These include antioxidant, anti-inflammatory, neuroprotective, and anticancer activities. For instance, trigonelline and curcumin show potential in modulating inflammation and oxidative stress, while pterostilbene and resveratrol are under investigation for their anticancer and cardioprotective effects. Cinnamaldehyde demonstrates promising results in reducing blood glucose levels and inflammatory markers, and vanillin exhibits apoptotic and antioxidant properties that may benefit cancer and inflammatory disease management (Rayan et al., 2017; Peng et al., 2024).

Given the challenges associated with synthetic drug development—such as adverse effects, drug resistance, and prolonged development timelines (often exceeding 15 years)—natural products offer a compelling alternative. Modern drug development strategies increasingly focus on repurposing or optimizing bioactive compounds from natural sources to accelerate therapeutic innovation.

1. Synthetic modifications to enhance therapeutic potential: The development of combinatorial libraries of various plant-derived compounds guided the lead optimization process in drug discovery. These libraries included Nimbolide, Azadiradione, Epoxyazadiradione, cedrelone, and nimbin.

2. Drawing inspiration from the pharmacophore of natural products: As molecular scaffolds and with the aid of bioinformatics tools, a total of 370 molecules were designed. Out of these, 90 were synthesized and tested at a partner facility in the USA, with 22 molecules tested at the NIH (National Institutes of Health). Around 10 of these compounds showed potential as lead candidates. The pure compounds were further evaluated using bioinformatics and in vivo methods to explore and enhance their therapeutic effectiveness

## 2. Materials and Methodology

### 2.1 Ligand Structure Retrieving

The 3D structures of the compounds nigelline, buformin, glibenclamide, S-allyl-L-cysteine-S-oxide, gurmarin, demethoxycurcumin, and bisdemethoxycurcumin were retrieved from the PubChem database in SDF format. Structural optimization and energy minimization were performed using Chem3D software, employing the MMFF94 force field to obtain the most stable conformations suitable for docking studies. This approach follows that of Saleem et al. (2024), who prepared *Nigella sativa* phytocompounds for multi-target analysis in diabetes and obesity. Similarly, natural products such as trigonelline, resveratrol, pterostilbene, curcumin, and vanillin, along with bioactive phytochemicals from Triphala—namely ellagic acid, gallic acid, propyl gallate, β-glucogallin, and mucic acid 1,4-lactone 5-O-gallate—were selected based on their reported antioxidant, antidiabetic, and anti-inflammatory properties. This strategy aligns with the findings of Sharma et al. (2025), who demonstrated the anti-inflammatory docking potential of Triphala phytoconstituents, and Yahara et al. (2022), who performed in silico screening of flavonoids against α-amylase and α-glucosidase. Moreover, the optimization protocol was consistent with that of Rahman et al. (2024), who analyzed the docking potential of *Nigella sativa* essential oil components after structural minimization, and da Silva Lopes et al. (2024), who evaluated curcumin analogs using MMFF94 force fields for aldose reductase inhibition. These studies collectively validate the rationale and robustness of the ligand preparation pipeline adopted in the current work.

### 2.2 Protein Structure Analysis

The 3D structure of the target protein involved in insulin secretion was obtained from the Protein Data Bank (PDB) and preprocessed using PyMOL by removing water molecules and heteroatoms. AutoDock Tools was used to add polar hydrogens and assign Kollman charges, preparing the protein for docking with synthetic drugs and Triphala phytochemicals. A similar protein preparation and docking protocol was employed by Alrouji et al. (2025) in their study on mangiferin–transferrin interactions, as well as by Sharma and Bala (2025) and Rudrapal et al. (2022), who explored the therapeutic potential of Triphala using in silico approaches. These studies reinforce the reliability of the computational workflow adopted here.

### 2.3 Pharmacophore Modeling

Pharmacophore features for glibenclamide, S-allyl-L-cysteine-S-oxide, and selected Triphala phytochemicals were generated to identify key interaction points:

Green: Hydrogen bond acceptors
Magenta: Hydrogen bond donors
Cyan: Hydrophobic regions

These models helped compare the structural and functional interaction patterns between synthetic drugs and bioactive natural compounds, particularly those from Triphala, to assess their potential as insulin secretagogues.

### 2.4 Molecular Docking Protocol

Docking simulations were conducted using AutoDock Vina to evaluate the binding affinities and interaction profiles of the ligands with the protein's active site. Ligands included nigelline, buformin, and amino acid residues such as alanine 333, cysteine 276, and threonine 182. A grid box was generated around the arginine (ARG) residues, believed to be functionally relevant for insulin stimulation. Default docking parameters were retained, and ten conformations per ligand were generated. Compounds derived from Triphala were included in this docking run to assess their comparative efficacy against synthetic controls. This approach follows the docking protocols of Alrouji et al. (2025) and Khan et al. (2024), who used combined spectroscopic and computational methods to explore the binding mechanisms of mangiferin and naringenin with human transferrin. These studies support the relevance of AutoDock-based docking for evaluating ligand–protein interactions in therapeutic research.

### 2.5 Visualization and Interaction Analysis

Post-docking analyses were performed using Discovery Studio Visualizer. Binding poses and molecular interactions—such as hydrogen bonds, hydrophobic contacts, and π–π interactions—were examined in detail. Active site residues, including ALA333, CYS276, and THR283, were highlighted in the docked complexes of glibenclamide, S-allyl-L-cysteine-S-oxide, and Triphala-derived phytochemicals. Special attention was given to hydrogen bonding and π-stacking interactions that may contribute to glucose-lowering potential. Drug Targets: Anti -Ulcer: Potassium-transporting ATPase alpha chain 1. Anti–Diabetic: Protein tyrosine phosphatase 1B, Anti –Diabetic: Alpha-glucosidase Inhibitors (Maltase-Glucoamylase), Anti –Diabetic: Sensitizers (Peroxisome proliferator-activated receptor alpha Anti -Ulcer: Potassium voltage-gated channel subfamily H member 2.

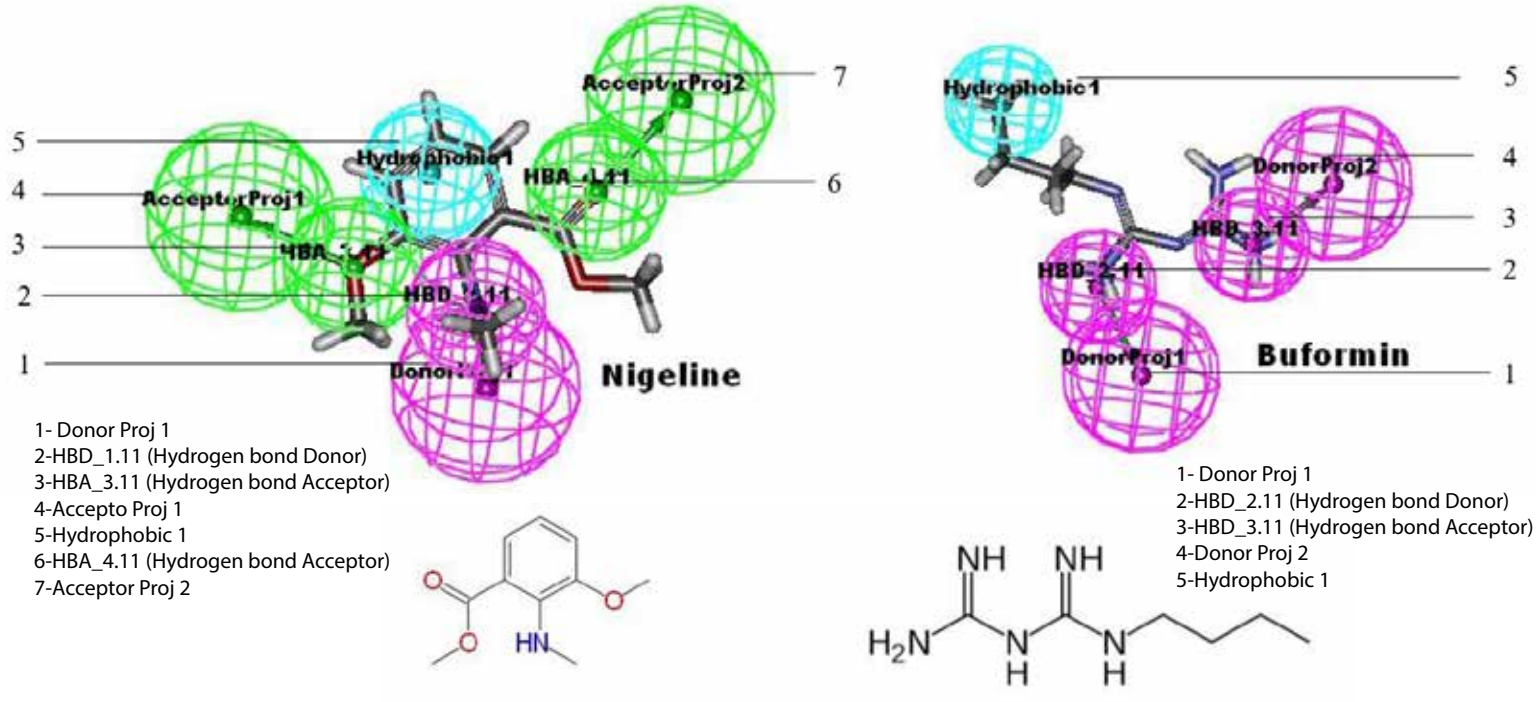
## 3. Results and Discussion: Docking Study of Nigelline

The docking scores derived from AutoDock Vina indicate that nigelline, with a docking score of 32.263, exhibited higher binding affinity compared to buformin, which showed a score of 27.989. Both compounds interacted with the arginine (ARG) 83 residue, while nigelline also formed additional interactions with ARG107, suggesting a stronger and more stable binding conformation.

**Table 1: Docking Scores of Sequence Compounds-Nigelline & Buformin with Protein Targets**

| Compound | Amino Acid Binding | Dock Score Kcal/mol |
|---|---|---|
| Nigelline | Arginine (ARG) 107, 83 | 32.263 |
| Buformin | Arginine (ARG) 83 | 27.989 |

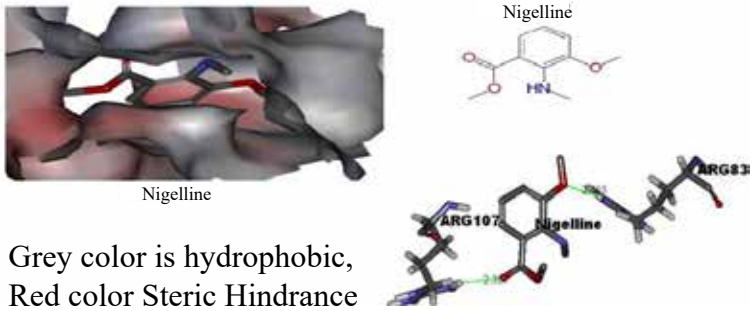
## Pharmacophore comparison




Green: Hydrogen bond acceptor, Magenta: Hydrogen Bond Doner, Cyan: Hydrophobic

**Fig. 1**

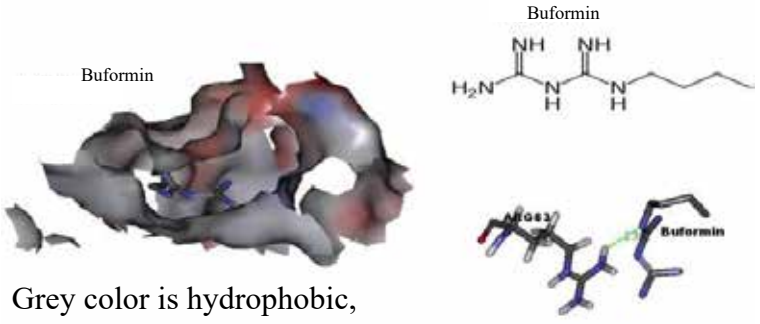
Binding of leads to Active site of protein to increase the more glucose level in tissue




Grey color is hydrophobic, Red color Steric Hindrance

**(A)**

Binding of leads to Active site of protein to increase the more glucose level in tissue




Grey color is hydrophobic, Red color Steric Hindrance

**(B)**

**Fig. 2**

### 4. Intermolecular Interactions of Pharmacophore and Binding Sites

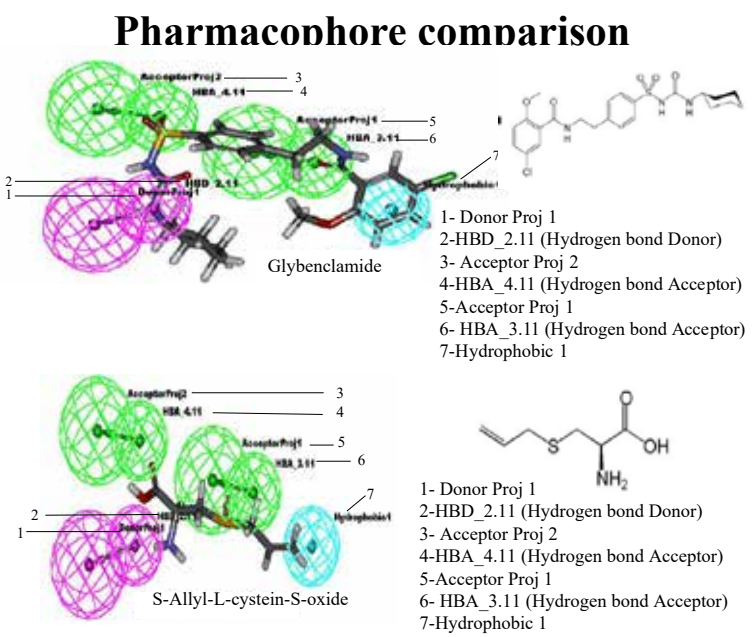
Pharmacophore mapping and molecular docking experiments indicate that nigelline demonstrates significantly stronger binding affinity and interaction stability compared to buformin. Nigelline's ability to form multiple hydrogen bonds and hydrophobic interactions—particularly through simultaneous engagement with key residues ARG83 and ARG107—leads to stronger electrostatic stabilization and overall enhanced binding. These key residues are critical for stabilizing protein–ligand complexes, and the dual interaction observed in the nigelline complex indicates a strong and specific binding mode.

Buformin, in contrast, exhibited fewer binding interactions, engaging mainly with ARG83 and lacking sufficient hydrogen bonding and hydrophobic contacts, which corresponded to its lower docking score. Molecular surface visualization further supports these findings, revealing that nigelline binds more snugly into the hydrophobic binding pocket and effectively overcomes moderate steric hindrance.

The higher docking score and favorable interaction profile of nigelline suggest greater inhibitory potential, making it a strong candidate for therapeutic development in metabolic and gastrointestinal disorders, such as diabetes and ulcers. Its pharmacophoric features—comprising multiple hydrogen bond donors and acceptors, along with

hydrophobic regions—are well aligned with the structural requirements of the target protein's binding site.

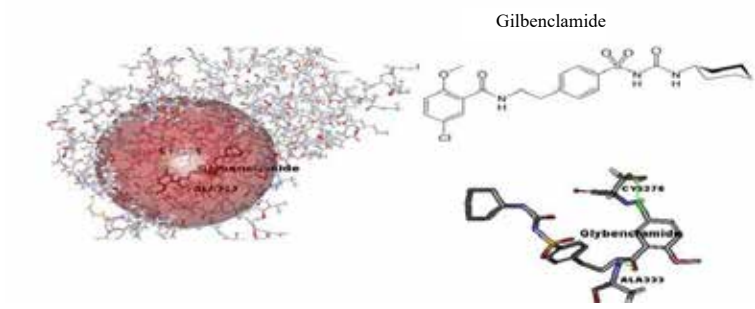
Recent computational studies corroborate nigelline's superior binding affinity and interaction stability when compared to buformin. For instance, Saleem et al. (2024) identified *Nigella sativa* compounds, such as kaempferol, as strong binders to key metabolic proteins, highlighting their antidiabetic potential. Similarly, Dalli et al. (2022) demonstrated that *Nigella sativa* essential oil inhibits α-amylase activity and hemoglobin glycation, further supporting its therapeutic relevance. Collectively, these findings position nigelline as a promising natural lead compound for future drug development.




Green: Hydrogen bond acceptor, Magenta: Hydrogen Bond Doner, Cyan: Hydrophobic

**Fig. 3**

Binding of leads to Active site of protein stimulate the beta cell to secrete insulin




Binding of leads to Active site of protein stimulate the beta cell to secrete insulin

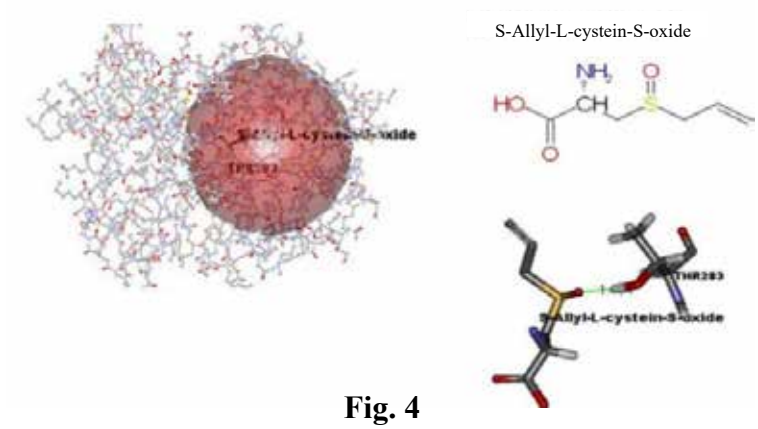



**Fig. 4**

## 5. Docking Study of S-Allyl-L-cysteine-S-oxide

Molecular docking analysis revealed that glibenclamide exhibited a high binding affinity, with a docking score of 75.678, forming interactions with alanine 333 and cysteine 276 at the active site of the protein. For comparison, the natural compound S-allyl-L-cysteine-S-oxide demonstrated a moderate docking score of 45.105, primarily interacting with threonine 283. Although its docking score was lower than that of the synthetic control, S-allyl-L-cysteine-S-oxide formed key interactions that matched the pharmacophoric features of glibenclamide, reinforcing its potential as a natural insulinotropic agent. This is further supported by the findings of Shafiq et al. (2024), who employed integrated computational modeling, MM-GBSA, ADMET, and DFT analyses to evaluate garlic-derived flavonoids alliuocide G and alliuocide A, confirming their multi-target binding efficacy and electronic stability for potential use in metabolic disease treatment.

Pharmacophore models and molecular docking studies revealed promising antidiabetic potential for S-allyl-L-cysteine-S-oxide, a natural compound derived from garlic, in comparison with glibenclamide, a conventional sulfonylurea medication. The pharmacophore models identified key interaction features, including hydrogen bond acceptors, hydrogen bond donors, and hydrophobic centers, represented in green, magenta, and cyan, respectively. Glibenclamide exhibited a well-defined pharmacophoric pattern, comprising two hydrogen bond acceptors, one hydrogen bond donor, and one hydrophobic center.

Notably, S-Allyl-L-cysteine-S-oxide closely replicated this profile, implying structural and functional equivalence. Molecular docking again confirmed this similarity; Glibenclamide bound well at the protein's active site, interacting closely with ALA333 and CYS276, showing strong binding affinity and an optimal orientation favorable for insulin release. Similarly, S-Allyl-L-cysteine-S-oxide formed key interactions, particularly with THR283, exhibiting favorable binding and spatial accommodation despite its simpler structure. These observations imply that S-Allyl-L-cysteine-S-oxide has insulinotropic activity by mimicking Glibenclamide's binding properties. The data support the prediction that naturally occurring compounds with similar

**Table 2: Docking Scores of Sequence Compounds- Glibenclamide & S-Allyl-L-cysteine- S-oxide with Protein Targets**

| Compound | Amino Acid Binding | Dock Score Kcal/mol |
|---|---|---|
| Glibenclamide | Alanine 333, Cystine 276 | 75.678 |
| S-Allyl-L-cysteine-S-oxide | Threonine 182 | 45.105 |

pharmacophoric properties can be effective insulin secretagogues and provide a promising avenue for the development of safer, plant-based antidiabetic drugs. This is supported by recent findings from Zhai et al. (2018) and Torres-Reyes et al. (2024), who demonstrated that S-allyl cysteine sulfoxide (alliin) improved glucose metabolism and insulin sensitivity in diet-induced obese mice, further highlighting its potential as a nutraceutical agent in diabetes management.

## 6. Docking study of Gurmarin

There are few herbal plants whose chemical composition is similar to human insulin, for example, *Momordica charantia* and *Gymnema sylvestre*. These plants contain a protein called Gurmarin, which resembles the insulin peptide.

Pharmacophore comparison between insulin and Gurmarin highlighted structural similarities, and protein–protein docking studies confirmed that Gurmarin binds effectively to the insulin receptor in a manner similar to insulin itself. These results suggest that Gurmarin may act as an insulin mimetic, potentially initiating receptor-mediated glucose uptake. These findings are supported by recent molecular docking studies conducted by Zhai et al. (2018) and El Oirdi (2024), which demonstrated that natural compounds, including Gurmarin, exhibit significant binding affinities to the insulin receptor, suggesting their role in modulating insulin receptor activity. Collectively, these insights underscore the therapeutic potential of plant-derived compounds such as curcuminoids, S-Allyl-L-cysteine-S-oxide, and Gurmarin as safer, natural alternatives or adjuncts in diabetes management.

**Pharmacophore comparison**

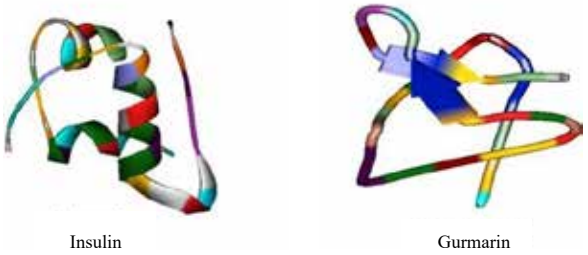



**Fig. 5**

**Protein - protein docking**

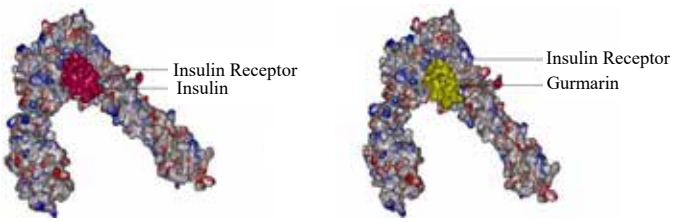


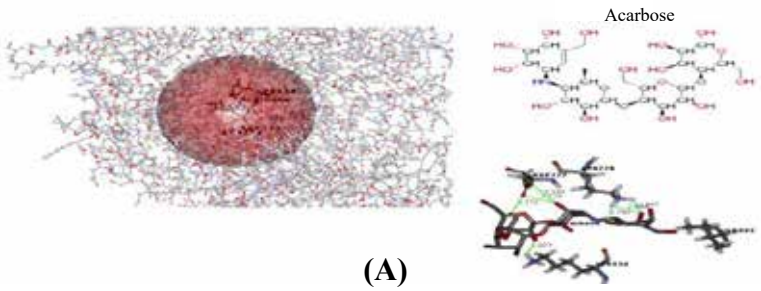

**Fig. 6**

## 7. Docking Study of Curcumin

**Table 3: Docking Scores of Sequence Compounds- Acarbase, Demethoxycurcumin and Bisdemethoxycurcumin with Protein Targets**

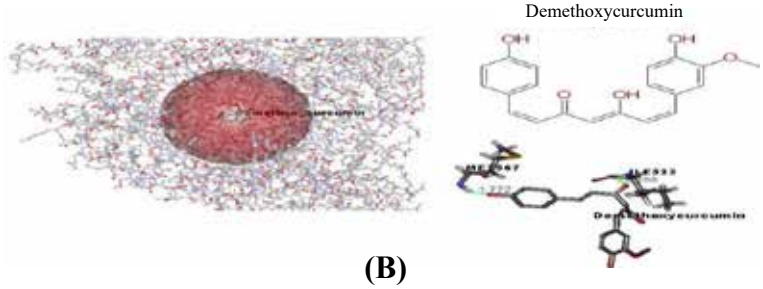
| Compound | Amino Acid Binding | Dock Score Kcal/mol |
|---|---|---|
| Acarbase | Isoleucine 523, lysine 776, Aspartic acid 777, Lysine 534 | 58.425 |
| Demethoxycurcumin | Isoleucine 523, Methionine 567 | 58.213 |
| Bisdemethoxycurcumin | Isoleucine 523 | 54.045 |

Binding of leads to Active site of protein to reduces the glucose level in blood



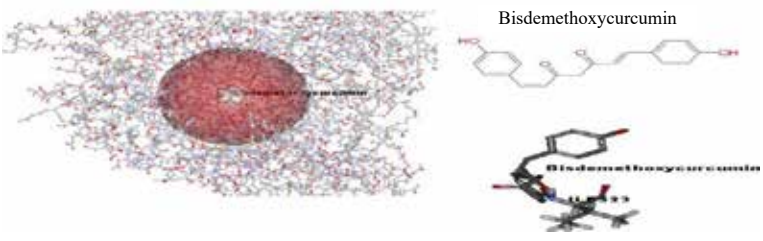

**(A)**

Binding of leads to Active site of protein to reduces the glucose level in blood




**(B)**

Binding of leads to Active site of protein to reduces the glucose level in blood




**(C)**

**Fig. 7**

Acarbose, an α-glucosidase inhibitor, in molecular docking experiments was found to have a good binding affinity, with a docking score of 58.425, interacting with several amino acid residues such as Isoleucine 523, Lysine 776, Aspartic acid 777, and Lysine 534. The two natural compounds Demethoxycurcumin and Bisdemethoxycurcumin also showed similar binding affinities, with docking scores of 58.213 and 54.045, respectively. Demethoxycurcumin evidenced interactions with Isoleucine 523 and Methionine 567, whereas Bisdemethoxycurcumin interacted only with Isoleucine 523. These findings indicate that both curcumin derivatives have the ability to replicate Acarbose's pattern of interaction, presenting promising natural alternatives for postprandial hyperglycemia management.

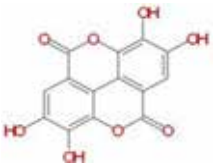
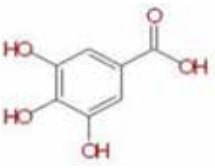
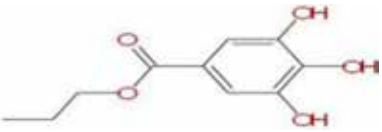
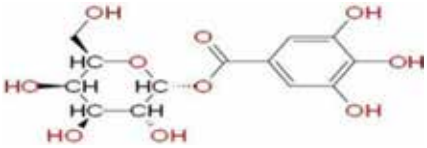
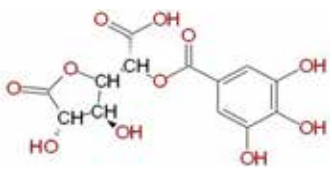
The docking results confirm that all three compounds—Acarbose, Demethoxycurcumin, and Bisdemethoxycurcumin—effectively bind to the active site of the target protein involved in glucose regulation. Acarbose, as expected, exhibited strong and stable interactions with several crucial residues, validating its known role in inhibiting enzymes responsible for carbohydrate digestion.

Demethoxycurcumin demonstrated good binding affinity, forming interactions with key residues such as MET567 and ILE523, suggesting potential efficacy. Bisdemethoxycurcumin also showed favorable binding, particularly with ILE523, indicating its ability to interact within the active site in a manner similar to acarbose.

Overall, these findings suggest that Demethoxycurcumin and Bisdemethoxycurcumin may serve as viable natural alternatives or complementary agents for managing blood glucose levels.

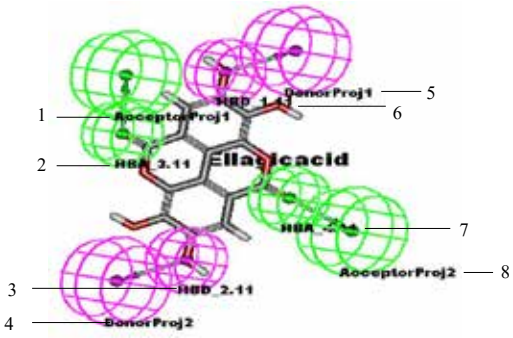
## 8. Docking Study of Triphala

**Table 4: Triphala Bioactive compounds**

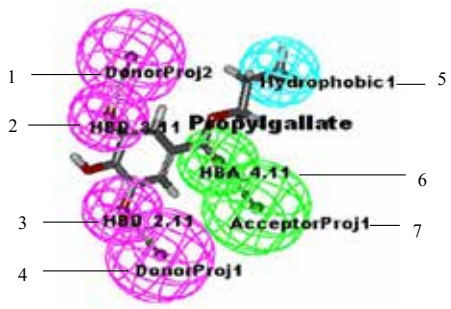
| Name And Structure | No. of Atoms | Molecular Composition | Molecular Formula | Molecular Surface Area |
|---|---|---|---|---|
| **Ellagic Acid**  | 22 | C: 0.556, H: 0.020, O: 0.424 | $C_{14}H_6O_8$ | 249.05 |
| **Gallic Acid**  | 12 | C: 0.494, H: 0.036, O: 0.470 | $C_7H_6O_5$ | 162.18 |
| **Propyl Gallate**  | 15 | C: 0.566, H: 0.057, O: 0.377 | $C_{10}H_{12}O_5$ | 212.67 |
| **Beta -Glucogallin**  | 23 | C: 0.470, H: 0.049, O: 0.482 | $C_{13}H_{16}O_{10}$ | 306.44 |
| **Mucic acid 1,4-lactone 5-o gallate**  | 28 | C: 0.454, H: 0.035, O: 0.511 | $C_{13}H_{12}O_{11}$ | 308.76 |

** The proton number is not included in the number of atoms.*

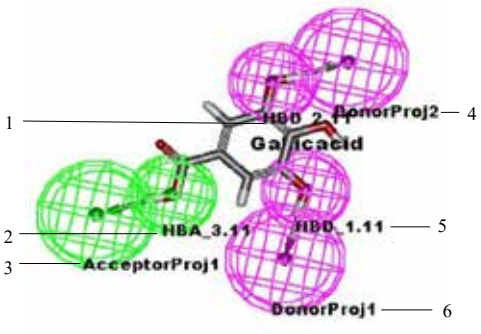
# PHARMACOPHORE FOR NATURAL LEADS PRESENT IN TRIPHALA




1-Acceptor Proj 1
2-HBA_3.11 (Hydrogen bond Acceptor)
3-HBD_2.11 (Hydrogen bond Donor)
4-Donor Proj 2
5-Donor Proj 1
6-HBD_1.11 (Hydrogen bond Donor)
7-HBA_4.11 (Hydrogen bond Acceptor)
8-Acceptor Proj 2




1-Donor Proj 2
2-HBD_3.11 (Hydrogen bond Donor)
3-HBD_2.11 (Hydrogen bond Donor)
4-Donor Proj 1
5-Hydrophobic 1
6-HBA_4.11 (Hydrogen bond Acceptor)
7-Acceptor Proj 1



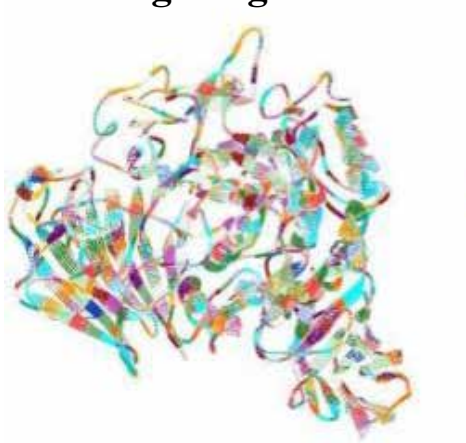

1-HBD_2.11 (Hydrogen bond Donor)
2-HBA_3.11 (Hydrogen bond Acceptor)
3-Acceptor Proj 1
4-Acceptor Proj 2
5-HBD_1.11 (Hydrogen bond Donor)
6-Donor Proj 1

**Fig. 8**

## Drug Targets



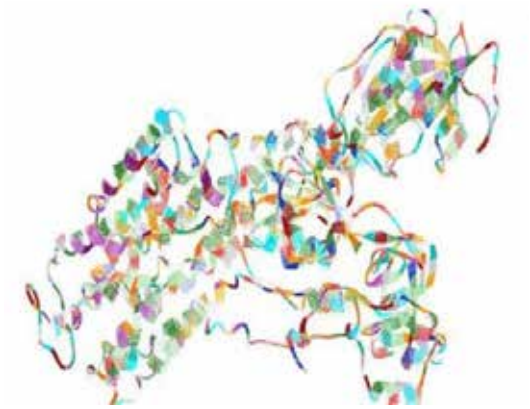
**(A) Anti –Diabetic : Protein tyrosine phosphatase 1B**



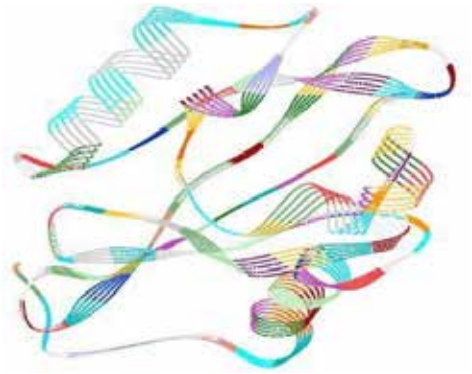
**(B) Anti –Diabetic : Alpha-glucosidase Inhibitors (Maltase-Glucoamylase)**



**(C ) Anti –Diabetic :Sensitizers (Peroxisomeproliferator-activated receptor alpha**



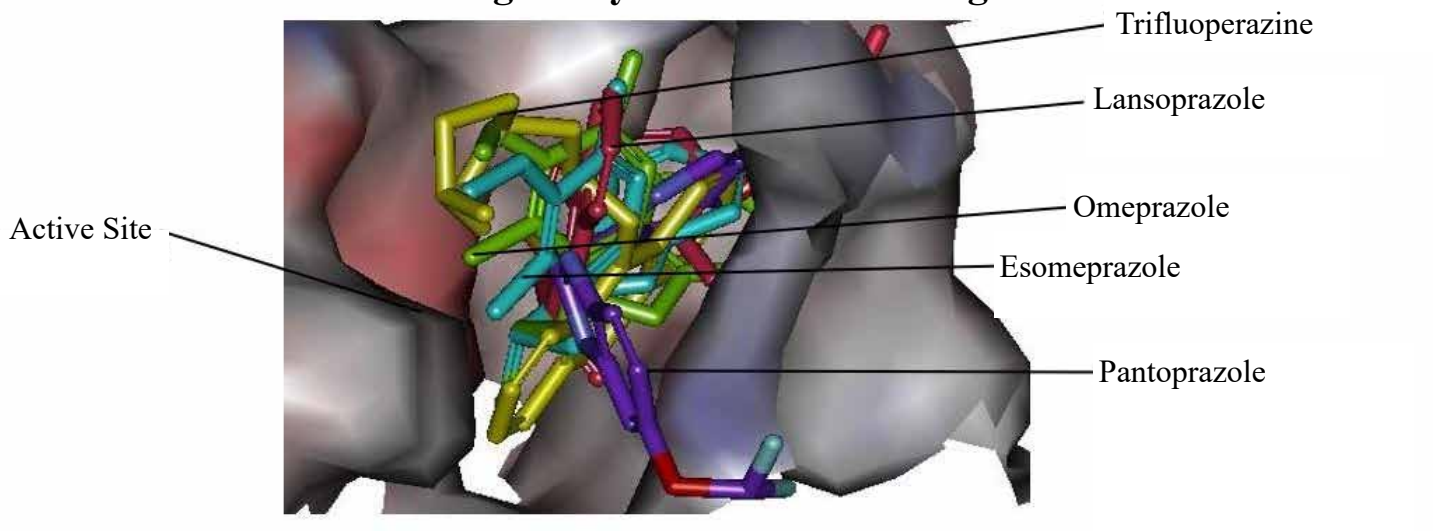
**(D) Anti -Ulcer :Potassium-transporting ATPase alpha chain 1**



**(E) Anti -Ulcer :Potassium voltage-gated channel subfamily H member 2**

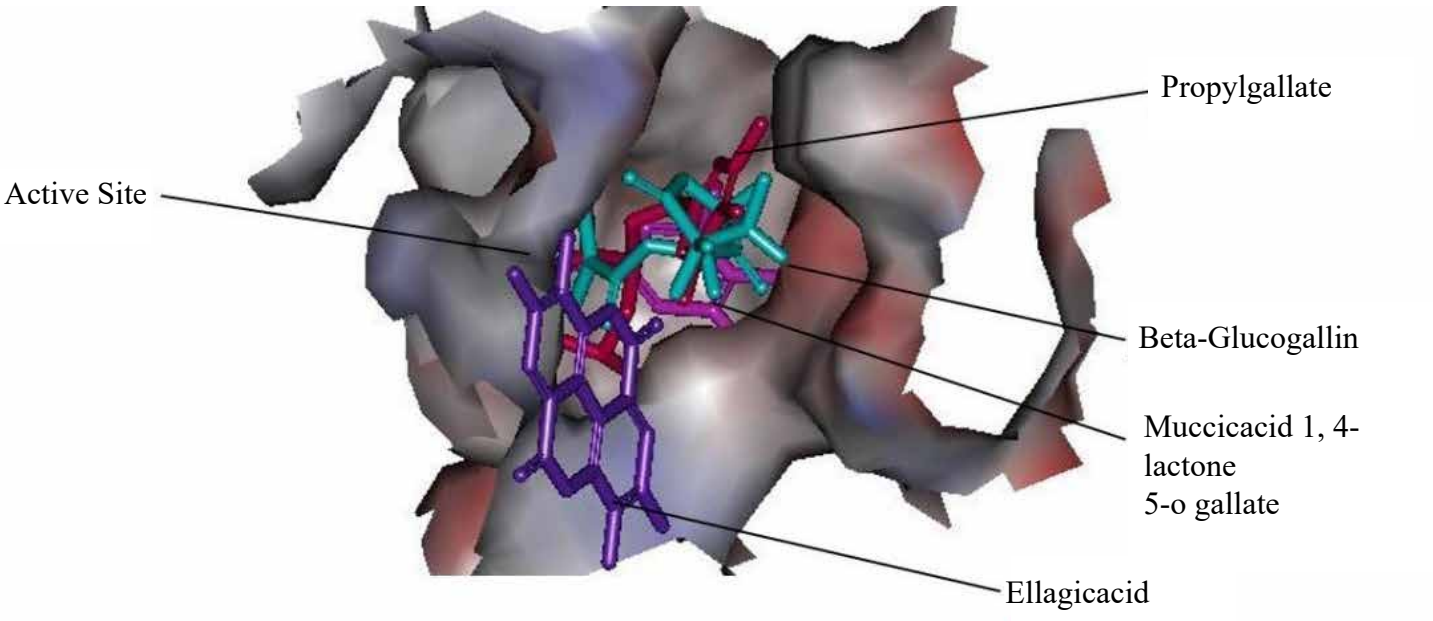
**Fig. 9**

## Docking Analysis: Anti-Ulcer Targets




Drugs binding to the active site of Potassium transporting ATPase alpha chain 1

**Fig. 10**




Triphala chemical constituents binding to the active site of
Potassium-transporting ATPase alpha chain 1

More H+ Inside the cell

Less H+ Inside the cell

**Fig. 11**

**Table 5: Drugs vs dock score**

| Drugs | Dock score | Natural compound | Dock score Kcal/mol |
|---|---|---|---|
| Lansoprazole | 64.508 | Mucic acid 1, 4lactone 5-o gallate | 53.565 |
| Trifluoperazine | 63.972 | Beta-Glucogallin | 48.639 |
| Pantoprazole | 58.787 | Ellagic acid | 35.259 |
| Esomeprazole | 58.148 | Propyl gallate | 34.491 |
| Omeprazole | 56.566 | Gallic acid | 0 |

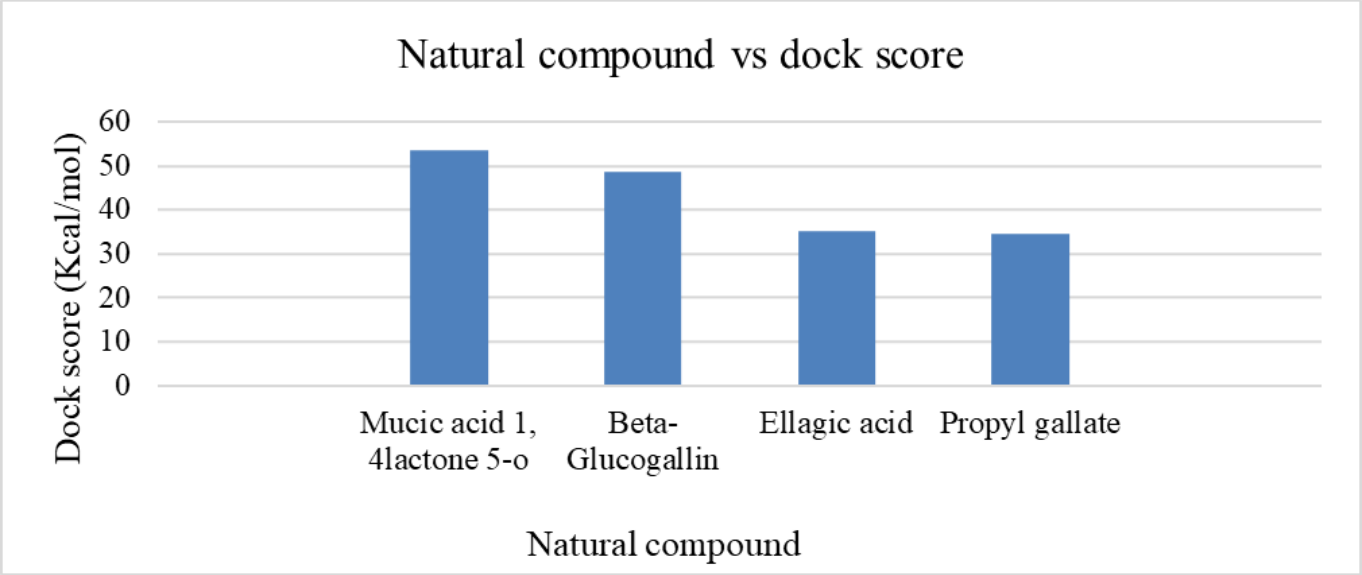



**Fig. 12**

Triphala is a traditional herbal formulation widely used in Ayurvedic medicine, renowned for its diverse therapeutic properties. It is composed of three medicinal fruits: Amalaki (Emblica officinalis), Bibhitaki (Terminalia bellirica), and Haritaki (Terminalia chebula)—each contributing unique health benefits.

Triphala is valued for its antioxidant, anti-inflammatory, and detoxifying effects. It is commonly used to support digestive health, enhance immunity, and promote overall well-being. Its rich phytochemical profile—including tannins, flavonoids, and phenolic compounds—underpins its broad spectrum of medicinal applications, making it a cornerstone of herbal medicine in India and beyond.

The accompanying table provides a summary of the molecular properties of Triphala constituents, including their atomic composition, molecular formula, and surface area. These structural features are critical in understanding their potential biological activity.

Figure 12 presents the comparative docking scores (in kcal/mol) of four natural compounds—Mucic acid 1,4-lactone 5-O-gallate, Beta-Glucogallin, Ellagic acid, and Propylgallate—against the Potassium-transporting ATPase alpha chain 1. The results reveal differential binding affinities among the compounds.

Among the natural compounds tested, Mucic acid 1,4-lactone 5-O-gallate exhibited the most favorable docking score, indicating strong potential interaction with the target protein. Beta-Glucogallin followed closely, while Ellagic acid and Propylgallate displayed comparatively lower binding affinities. Structural features such as lactone and gallate moieties appear to enhance binding affinity at the ATPase target site, highlighting the importance of molecular architecture in natural product-based drug discovery. These findings align with the structure-based pharmacological

Receptor 2: Potassium voltage-gated channel subfamily H member 2

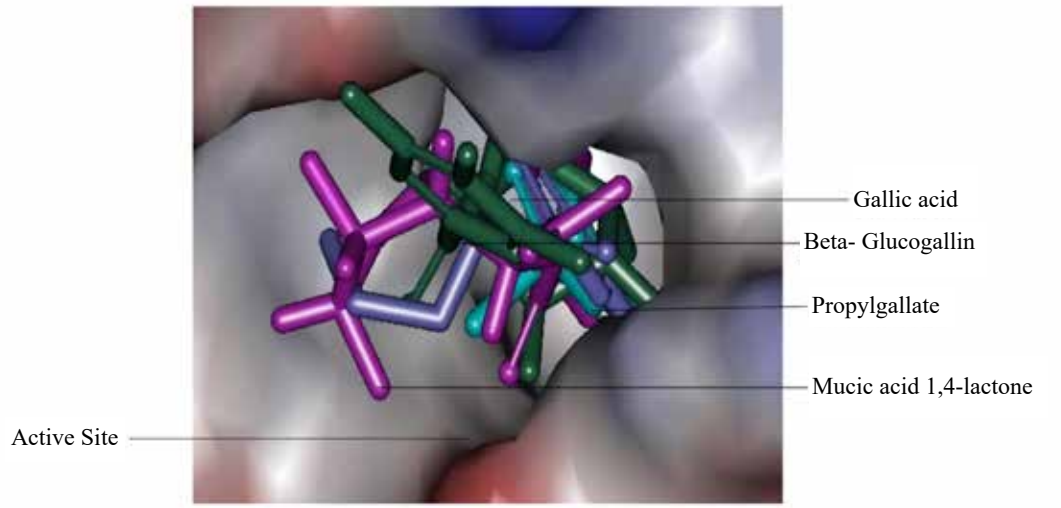
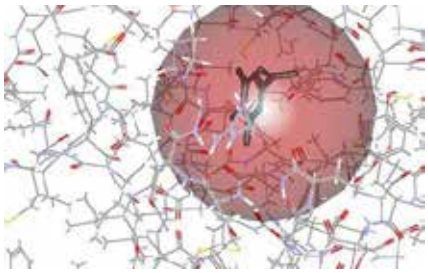
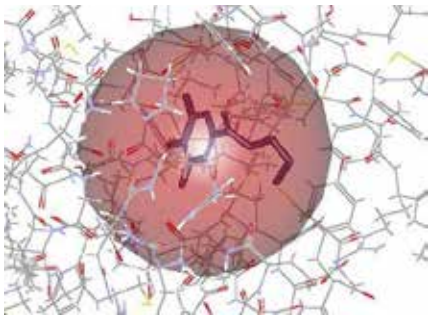



**Fig. 13**

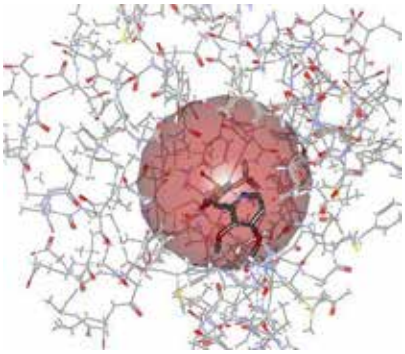
Triphala chemical constituents binding to the active site of Potassium voltage-gated channel subfamily H member 2



(A) Binding of Gallic acid to Potassium voltage-gated channel subfamily H member 2



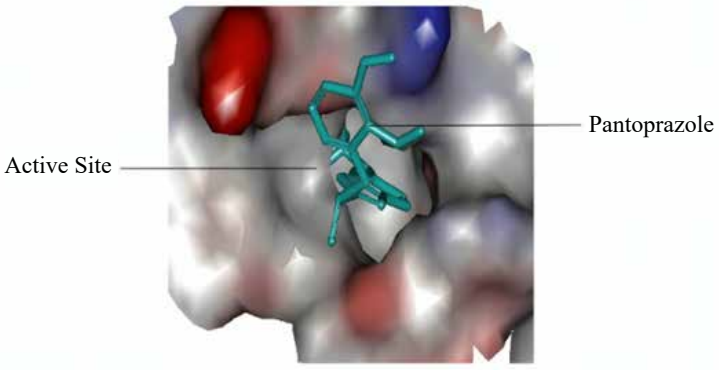
(B) Binding of Propylgallate to Potassium voltage-gated channel subfamily H member 2



(C )Binding of Pantoprazoleto Potassium voltage-gated channel subfamily H member 2

**Fig. 14**

## ANTI-ULCER




Drugs binding to the active site of Potassium voltage gated channel subfamily H member 2

**Fig. 15**

**Table 6: Docking of Drugs vs natural compounds**

| Drugs | Dock score | Natural compound | Dock score Kcal/mol |
|---|---|---|---|
| Lansoprazole | 0 | Propyl gallate | 32.384 |
| Trifluoperazine | 0 | Gallic acid | 22.314 |
| Pantoprazole | 2.337 | Mucic acid 1, 4lactone 5-o gallate | 15.357 |
| Esomeprazole | 0 | Beta-Glucogallin | 11.814 |
| Omeprazole | 0 | Ellagic acid | 0 |

insights reported by Zhen et al. (2025) and the work of Donadio et al. (2021), who demonstrated how specific flavonoid structures interact with microbial proteins to exert antibacterial effects.

Molecular docking analysis was conducted to evaluate the binding affinities of five standard drugs and five natural compounds toward a potassium channel-related protein target. The results, summarized in Table 6, indicate significant variation in binding potential among the tested molecules.

Among the standard drugs, Pantoprazole exhibited a moderate docking score of 2.337, suggesting a weak interaction with the target site. In contrast, Lansoprazole, Trifluoperazine, Esomeprazole, and Omeprazole all displayed docking scores of zero, indicating either the inability to form stable binding conformations or a complete lack of interaction under the docking conditions employed. These outcomes may stem from structural incompatibility with the binding pocket of the Potassium voltage-gated channel subfamily H member 2 or from limitations in conformational flexibility.

Interestingly, several natural compounds demonstrated comparatively higher docking scores, suggesting stronger binding affinities. Propylgallate showed the highest docking score (32.384), followed by Gallic acid (22.314) and Mucic acid 1,4-lactone 5-O-gallate (15.357). These results suggest that the polyphenolic structures of these compounds may facilitate stronger hydrogen bonding and hydrophobic interactions within the active site of the target protein. Beta-Glucogallin and Ellagic acid showed lower binding scores (11.814 and 0, respectively), though still notable when compared to most of the standard drugs tested.

The relatively low or zero docking scores observed for several clinically used drugs may be attributed to the specificity of the target protein selected in this experiment. For example, Lansoprazole, which showed no docking activity against the Potassium voltage-gated channel in this

Common feature Pharmacophore comparison of Triphala with Anti –Ulcer Drug

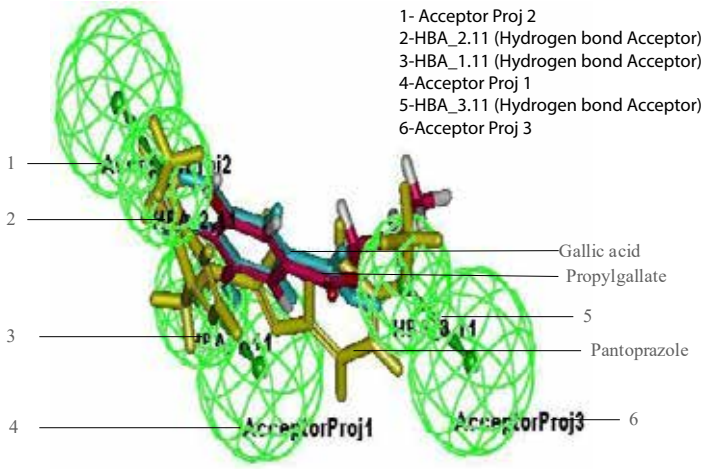



**Fig. 16**

dataset, was previously reported to exhibit a much higher docking score (64.508) when docked against the Potassium-transporting ATPase alpha chain 1, indicating a strong protein target-dependency in docking outcomes.

These findings underscore the potential of selected natural compounds, particularly Propylgallate, as promising candidates for further investigation due to their strong predicted binding interactions. Furthermore, the results emphasize the importance of selecting an appropriate protein target for molecular docking, as binding affinities are highly context-specific, depending on both ligand conformation and active site compatibility. Similar observations were reported by Wu et al. (2024), who noted that the molecular docking of natural peptides requires precise alignment of structural features with active site architecture to yield reliable binding predictions, reinforcing the critical role of structural compatibility in in silico drug discovery.

Molecular docking analysis was performed to evaluate the binding affinities of five selected drugs and five natural compounds against two target proteins: Potassium

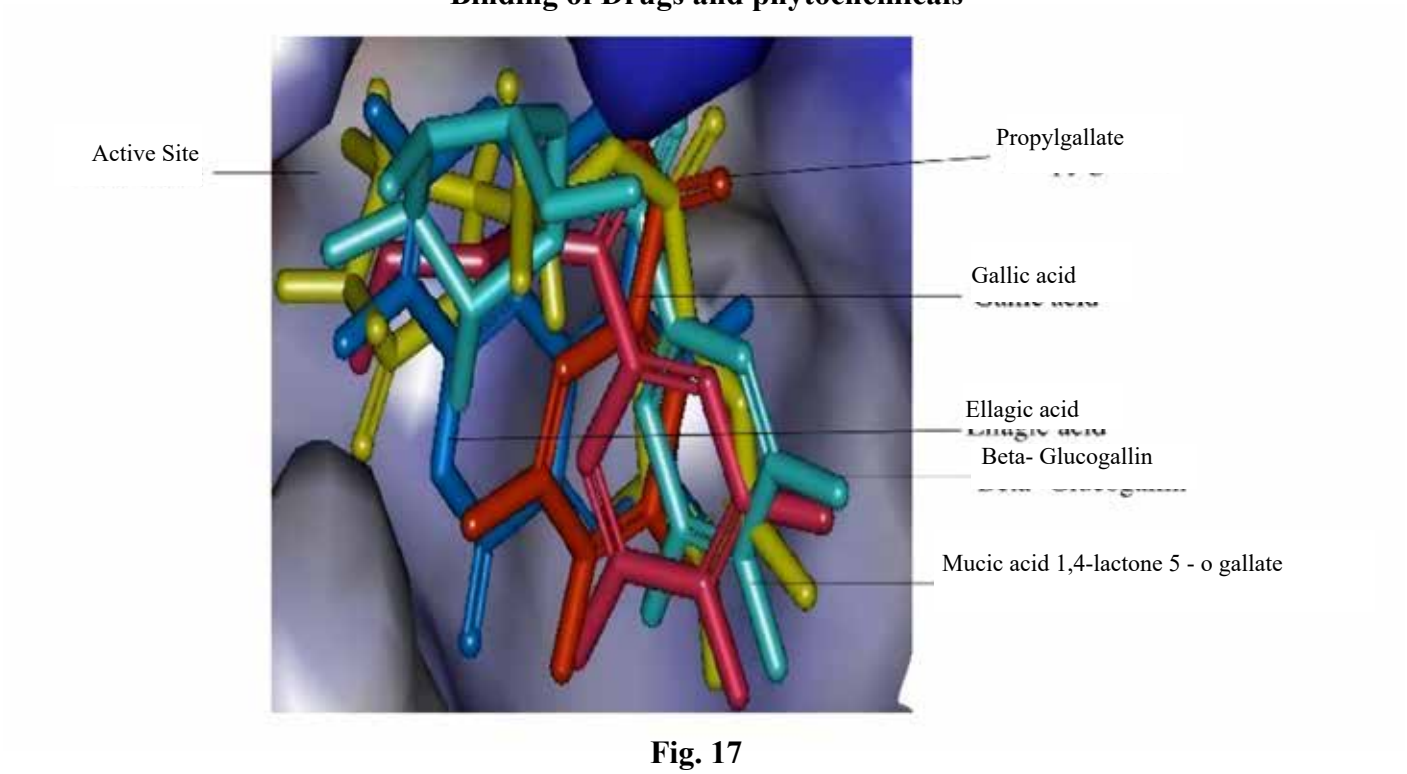



**Fig. 17**

voltage-gated channel subfamily H member 2 and Potassium-transporting ATPase alpha chain 1.

Against Potassium voltage-gated channel subfamily H member 2, Pantoprazole exhibited a moderate docking score of 2.337 kcal/mol, indicating a modest interaction. Among the natural compounds tested, Propylgallate demonstrated the highest binding affinity, with a docking score of 32.384 kcal/mol, suggesting a significantly stronger interaction with the target site compared to the standard drug.

These findings support the potential of selected natural compounds—particularly Propylgallate—as candidates for further investigation due to their strong predicted binding interactions. Moreover, the results underscore the importance of selecting appropriate protein targets for molecular docking, as binding affinities are highly dependent on both ligand conformation and active site compatibility. This observation aligns with the computational study by Hasan et al. (2024), which demonstrated that structural optimization and electronic feature refinement of Omeprazole derivatives significantly enhanced their interaction with Potassium-transporting ATPase, reinforcing the importance of target-specific docking in the rational design of inhibitors.

## 9. Docking Analysis: Anti-Diabetic Targets

For the anti-diabetic target Protein Tyrosine Phosphatase 1B (PTP1B), Rimonabant exhibited the highest docking score (69.887 kcal/mol) among the standard drugs. Among the natural compounds, Mucic acid 1,4-lactone 5-O-gallate

Common feature Pharmacophore comparison of Triphala with Anti –Diabetic Drug

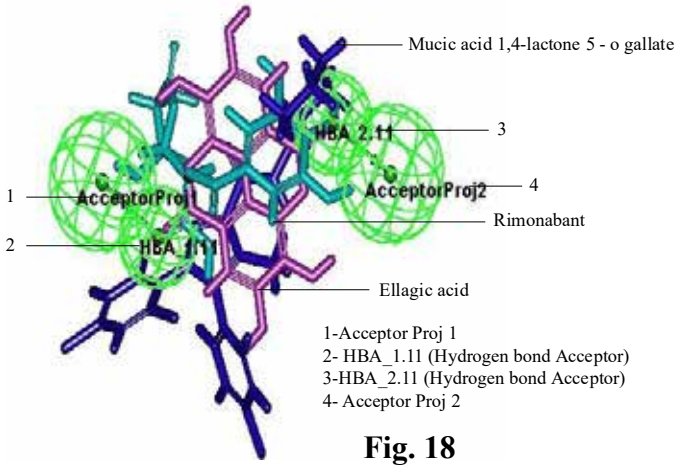
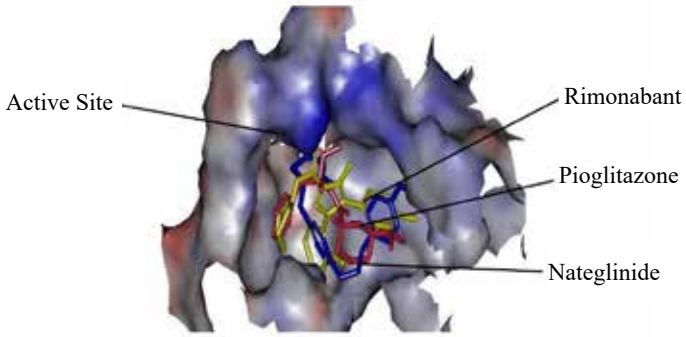



**Fig. 18**

**Anti-diabetic**




Drugs -binding to the active site of PTP1B

**Fig. 19**

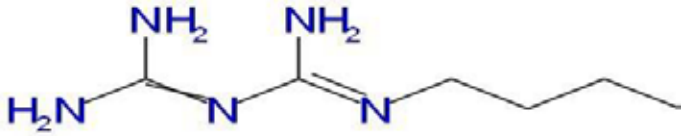
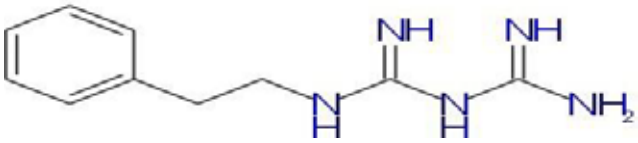
## Table 7: Anti-Diabetic Receptor: Protein tyrosine phosphatase 1B

| Drugs | Dock score | Natural compound | Dock score Kcal/mol |
|---|---|---|---|
| Sibutramine | 0 | Mucic acid 1, 4lactone 5-o gallate | 50.939 |
| Rimonabant | 69.887 | Beta-Glucogallin | 44.493 |
| Metformin | 0 | Ellagic acid | 5.843 |
| Nateglinide | 45.399 | Propyl gallate | 37.232 |
| Pioglitazone | 65.604 | Gallic acid | 24.151 |

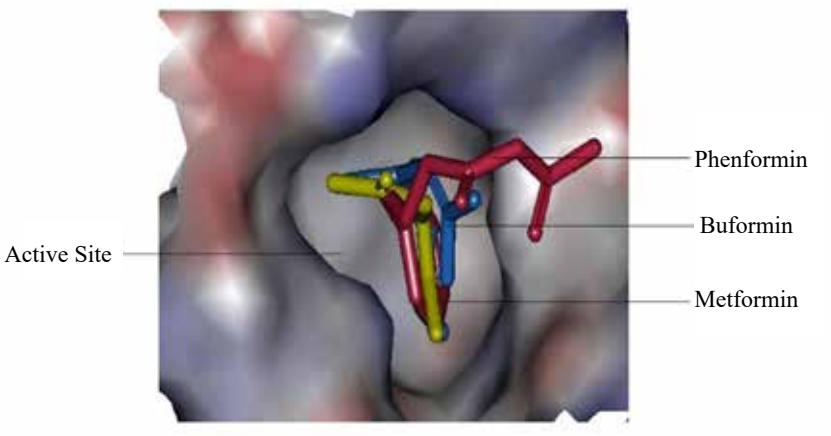
Among the five natural compounds tested, Mucic acid 1,4-lactone 5-O-gallate exhibited the highest docking score, outperforming Gallic acid in binding affinity.

**Anti- Diabetic sensitizers:**

### Table 8: Anti-Diabetic Sensitizers

| Anti-Diabetic Sensitizers | |
|---|---|
| Metformin |  |
| Buformin |  |
| Phenformin |  |

## Sensitizers: Anti-Diabetic



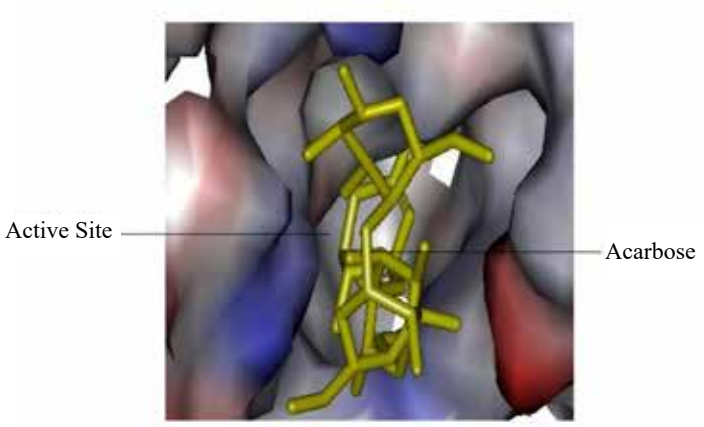

Drugs -binding to the active site of Peroxisome proliferator-activated receptor alpha

**Fig. 20**

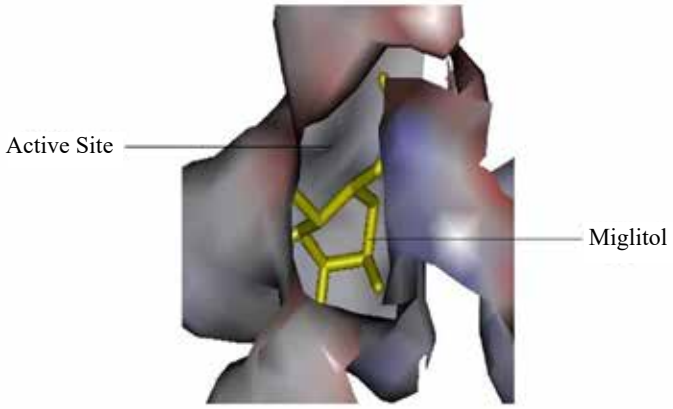
**Table 9: Receptor: Peroxisome proliferator-activated receptor alpha**

| Drugs | Dock score | Natural compound | Dock score Kcal/mol |
|---|---|---|---|
| Metformin | 22.219 | Mucic acid 1, 4lactone 5-o gallate | 0 |
| | | Beta-Glucogallin | 0 |
| Buformin | 31.304 | Ellagic acid | 0 |
| Phenformin | 41.792 | Propyl gallate | 0 |
| | | Gallic acid | 0 |

**Alpha-Glucosidase inhibitors: Anti-diabetic**




Drugs -binding to the active site of Maltase-Glucoamylase




Drugs -binding to the active site of Maltase-Glucoamylase

**Anti-Diabetic = Alpha-glucosidase Inhibitors**

Receptor: Maltase-Glucoamylase

**Fig. 21**

**Table 10. Docking scores of Standard drugs and Natural compounds**

| Drugs | Dock score | Natural compound | Dock score Kcal/mol |
|---|---|---|---|
| Acarbose | 57.52 | Mucic acid 1, 4lactone 5-o gallate | 0 |
| | | Beta-Glucogallin | 0 |
| | | Ellagic acid | 0 |
| Miglitol | 40.342 | Propyl gallate | 0 |
| | | Gallic acid | 0 |

Acarbose shows the highest dock score against Maltase-Glucoamylase

demonstrated the strongest interaction, with a docking score of 50.939 kcal/mol, indicating promising inhibitory potential against PTP1B.

PPAR-α (Sensitizer): Phenformin exhibited the highest binding affinity, with a docking score of 41.792 kcal/mol. None of the Triphala constituents showed effective binding in this docking analysis. Maltase-Glucoamylase (α-glucosidase inhibitor): Acarbose demonstrated strong binding affinity, with a docking score of 57.520 kcal/mol. However, none of the tested natural compounds exhibited significant activity against this target.

**10. Pharmacophore Comparison**

Common structural features such as hydroxyl groups and aromatic rings found in natural products align with key pharmacophores of anti-diabetic and anti-ulcer drugs, as reported by Yuvan et al. (2024). Triphala constituents such as Mucic acid 1,4-lactone 5-O-gallate and Beta-glucogallin mimic structural motifs present in approved drugs, supporting their potential as lead compounds in drug discovery.

Recent studies by Mahapatra et al. (2022) and Hmidene et al. (2022) have demonstrated that natural compounds like flavonoids possess crucial structural features—particularly hydroxyl groups and aromatic rings—that contribute significantly to their antidiabetic activity. These functional groups enhance molecular interactions with enzymes such as α-glucosidase and α-amylase, effectively mimicking the pharmacophores of conventional drugs and supporting their therapeutic potential, as shown by Di Stefano et al. (2018).

Natural compounds from Triphala showed promising docking interactions with key drug targets, particularly for anti-ulcer activity and Protein Tyrosine Phosphatase 1B (PTP1B)-related anti-diabetic effects (Wang et al., 2018). Although limited α-glucosidase inhibition was observed, alternative mechanisms—such as insulin mimicry and insulin sensitization (as demonstrated with *Nigella sativa*, *Allium sativum*, and *Momordica charantia*)—offer additional therapeutic pathways.

**11. Scope and Application**

Interestingly, two natural products—Turmeric (*Curcuma longa*) and *Terminalia chebula* (also known as Inknut)—are traditionally used for dyeing fabrics. This study highlights the opportunity to explore herbal textiles, using these plant extracts for transdermal delivery of bioactive compounds. Such an approach could be especially valuable in wound healing applications, combining fabric technology with phytochemical-based therapy.

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