Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 12s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Molecular Docking and Computational Analysis of Chemical Constituents of *Tinospora cordifolia* as Potential DPP-4 Inhibitors for Diabetes Management.

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Cite this paper as: Nidhi Bharadwaj, Alok Bihari Das, Dr Reddy Sunil, Sonia Devi, Perli.Kranti Kumar, Santosh Bhadkariya, Saloni Kakkar, Chethan I A, (2025) Molecular Docking and Computational Analysis of Chemical Constituents of Tinospora cordifolia as Potential DPP-4 Inhibitors for Diabetes Management. *Journal of Neonatal Surgery*, 14 (12s), 955-960.

ABSTRACT

Tinospora cordifolia, a well-known medicinal plant, has been traditionally used for its wide range of therapeutic properties, including antidiabetic effects. In this study, we investigated the potential of five key chemical constituents of Tinospora cordifolia 10-Hydroxycolumbin, 11-Hydroxymustakone, 20-Beta-Hydroxyecdysone, 8-Hydroxytinosporide, and AMRITOSIDE-A as inhibitors of dipeptidyl peptidase-4 (DPP-4), a key enzyme in glucose metabolism. Molecular docking simulations were performed using AutoDock VINA, and the results were analyzed for binding affinity, hydrogen bonding, and hydrophobic interactions. Among the compounds tested, 8-Hydroxytinosporide showed the highest docking score (-9.0 kcal/mol) with extensive interactions, followed by 10-Hydroxycolumbin and 20-Beta-Hydroxyecdysone. The interactions of these compounds with DPP-4 suggest their potential as natural DPP-4 inhibitors. Although Amritoside-A and 11-Hydroxymustakone demonstrated weaker binding affinities, further optimization of these compounds could enhance their activity. This study provides valuable insights into the antidiabetic potential of Tinospora cordifolia and supports its exploration as a source of novel DPP-4 inhibitors for diabetes therapy.

Keywords: *Tinospora cordifolia, DPP-4 inhibitors, Molecular docking, AutoDock VINA, Diabetes, 8 Hydroxytinosporide, 10-Hydroxycolumbin, Computational drug design, Phytochemicals, Natural products..*

1. INTRODUCTION

Tinospora cordifolia, also known as *Guduchi* or *Amrita* in various traditional systems of medicine, is a well-known herbaceous plant used extensively in Ayurvedic medicine for its therapeutic properties.[1] This plant is recognized for its potent pharmacological activities, including immunomodulatory,[2] anti-inflammatory,[3] antioxidant,[4] antidiabetic,[5] and hepatoprotective effects.[6] The active chemical constituents present in *Tinospora cordifolia*, such as alkaloids, glycosides, and terpenoids, contribute significantly to its medicinal benefits.[8] Among its many therapeutic applications, *Tinospora*

cordifolia has gained attention for its potential role in managing diabetes, particularly Type 2 diabetes mellitus (T2DM), which is a growing global health concern.[9]

Type 2 diabetes is characterized by insulin resistance and impaired insulin secretion, leading to hyperglycemia and various complications such as cardiovascular diseases, nephropathy, and neuropathy.[10] One of the key enzymes involved in regulating glucose metabolism is dipeptidyl peptidase-4 (DPP-4), a serine protease that breaks down incretin hormones such as GLP-1 (glucagon-like peptide-1). [11]GLP-1 plays a crucial role in insulin secretion, and its inactivation by DPP-4 contributes to the dysregulation of glucose homeostasis. Inhibiting DPP-4 can prolong the action of GLP-1, improving insulin secretion and lowering blood glucose levels. Consequently, DPP-4 inhibitors have become a prominent class of drugs in the management of T2DM, with several DPP-4 inhibitors like sitagliptin, vildagliptin, and saxagliptin currently available in the market.[12]

Given the therapeutic potential of *Tinospora cordifolia* in treating diabetes, several studies have focused on identifying and characterizing the bioactive compounds present in this plant that could act as natural DPP-4 inhibitors. [13]Previous research has shown that various constituents of *Tinospora cordifolia* possess antidiabetic properties, but their exact mechanisms of action at the molecular level remain largely unexplored. In this study, we aim to conduct a molecular docking study to investigate the binding potential of five key chemical constituents of *Tinospora cordifolia*, namely 10-HYDROXYCOLUMBIN, 11-HYDROXYMUSTAKONE, 20-BETA-HYDROXYECDYSONE, 8-HYDROXYTINOSPORIDE, and AMRITOSIDE-A, with the DPP-4 enzyme. These compounds were selected due to their reported biological activities and their presence in *Tinospora cordifolia*.[14]

Molecular docking is a widely used computational method to predict the interaction of small molecules with target proteins.[15] This technique provides valuable insights into the binding affinity, stability, and mechanism of interaction between the ligand (bioactive compound) and the receptor (protein).[16] In this study, we employed AutoDock VINA, a powerful molecular docking tool, to simulate the interactions between the chemical constituents of *Tinospora cordifolia* and the DPP-4 enzyme. The X-ray crystallographic structure of DPP-4 (PDB ID: 4LKO) was used as the receptor, and the binding modes of the ligands were predicted to assess their potential as DPP-4 inhibitors.[17]

The objective of this study is to identify which of the selected compounds from *Tinospora cordifolia* may serve as potential candidates for further experimental validation and development as DPP-4 inhibitors. By using a computational approach, this study offers a systematic and efficient method to explore the antidiabetic potential of *Tinospora cordifolia* and contributes to the ongoing search for natural alternatives to synthetic DPP-4 inhibitors.[18]

Material and Method-

The chemical constituents of *Tinospora cordifolia* selected for this study include:

1. 10-HYDROXYCOLUMBIN
2. 11-HYDROXYMUSTAKONE
3. 20-BETA-HYDROXYECDYSONE
4. 8-HYDROXYTINOSPORIDE
5. AMRITOSIDE-A

These compounds were obtained from previous phytochemical studies of *Tinospora cordifolia*. The chemical structures of these compounds were retrieved from PubChem and ChemSpider databases and were used as input for molecular docking studies.

Preparation of Protein Structure

The X-ray crystallographic structure of the DPP-4 enzyme (PDB ID: 4LKO) was obtained from the Protein Data Bank. The structure was cleaned and prepared using Discovery Studio, which involved the removal of water molecules, heteroatoms, and ligands present in the original structure. The protein was then protonated and optimized for docking studies.

Molecular Docking

Molecular docking simulations were performed using AutoDock VINA to predict the binding affinity of the chemical constituents of *Tinospora cordifolia* to the DPP-4 enzyme. The structures of the selected compounds were prepared using Chem3D and converted to PDBQT format for docking. The grid box was centered on the active site of the DPP-4 enzyme, with dimensions optimized for the docking of each compound. The docking results were analyzed based on binding affinity scores (kcal/mol) and interactions between the ligands and active site residues of the DPP-4 enzyme.

Visualization and Analysis

The results of the docking studies were visualized using Discovery Studio, which allowed the examination of the binding modes of the ligands within the DPP-4 enzyme's active site. The interactions, including hydrogen bonds, hydrophobic interactions, and electrostatic interactions, were analyzed to assess the strength and stability of the ligand-enzyme complex.

2. RESULT AND DISCUSSION-

The molecular docking studies revealed important insights into the binding interactions of the five chemical constituents of *Tinospora cordifolia* with the DPP-4 enzyme. The docking scores and identified key residues involved in hydrogen bonding and hydrophobic interactions are presented in the table below. Each ligand demonstrated varying binding affinities, with the docking scores ranging from -9.0 to -6.5 kcal/mol.(Table-1)

10-HYDROXYCOLUMBIN

The docking score for 10-HYDROXYCOLUMBIN was -7.9 kcal/mol, indicating a strong binding affinity with the DPP-4 enzyme. The ligand formed hydrogen bonds with critical residues, including Arg125, Glu205, Glu206, Tyr547, Tyr662, and Tyr666. Notably, Tyr662 and Tyr666 exhibited pi-pi interactions, enhancing the stability of the complex. Hydrophobic interactions were observed with Val656, Val711, Trp659, and Tyr662, which contribute to the overall binding affinity and structural stability of the ligand-enzyme complex. The strong interaction of 10-HYDROXYCOLUMBIN with both polar and non-polar residues suggests that it could be a promising candidate for further experimental validation as a potential DPP-4 inhibitor.

11-HYDROXYMUSTAKONE

11-HYDROXYMUSTAKONE exhibited a docking score of -6.5 kcal/mol, which is slightly weaker compared to 10-HYDROXYCOLUMBIN but still indicates a reasonable binding potential. Hydrogen bonding was observed with Arg125, Glu205, Tyr662, Asn710, and Ser209. The hydrophobic interactions were limited to pi-pi stacking interactions between Tyr662 and Tyr666. While the binding interactions are not as extensive as those observed with 10-HYDROXYCOLUMBIN, the ligand still demonstrates potential for DPP-4 inhibition, though it may require further optimization for stronger binding.

20-BETA-HYDROXYECDYSONE

20-BETA-HYDROXYECDYSONE displayed a docking score of -7.6 kcal/mol, which is comparable to 10-HYDROXYCOLUMBIN. The ligand formed hydrogen bonds with several residues, including Arg125, Arg358, Glu205, Glu206, Tyr662, Asn710, Ser209, and Ser630. The interaction with Tyr662 was particularly notable, involving both pi-pi and pi-alkyl interactions, which contribute to the stability of the complex. Hydrophobic interactions were observed with Phe357 and Tyr666, further stabilizing the ligand-enzyme complex. The broad range of interactions, especially with the hydrophobic residues, suggests that 20-BETA-HYDROXYECDYSONE has a high binding affinity and could be a strong candidate for further study as a DPP-4 inhibitor.

8-HYDROXYTINOSPORIDE

8-HYDROXYTINOSPORIDE demonstrated the highest docking score of -9.0 kcal/mol, indicating the strongest binding affinity among the compounds studied. This ligand formed hydrogen bonds with Arg125, Glu205, Tyr662, Asn710, and Ser209. Notably, the hydrophobic interactions with Phe357, Tyr666, and Tyr662 (involving pi-pi stacking) further enhance the ligand's stability within the DPP-4 enzyme active site. The presence of multiple interactions, both hydrophobic and hydrogen bonding, suggests that 8-HYDROXYTINOSPORIDE is highly effective in binding to the DPP-4 enzyme and may be a highly promising lead compound for further experimental studies.

AMRITOSIDE-A

AMRITOSIDE-A exhibited a docking score of -7.2 kcal/mol, which places it between 11-HYDROXYMUSTAKONE and 20-BETA-HYDROXYECDYSONE in terms of binding affinity. The ligand formed a hydrogen bond with Ser87 but did not exhibit any significant hydrophobic interactions. This limited interaction pattern suggests that while AMRITOSIDE-A can bind to the DPP-4 enzyme, its affinity is weaker compared to the other constituents, especially those with extensive hydrophobic interactions. Further modification of AMRITOSIDE-A may be required to enhance its binding affinity and overall potency as a DPP-4 inhibitor.

3. DISCUSSION

The docking results highlight the varying binding affinities and interaction profiles of the chemical constituents of *Tinospora cordifolia*. 8-HYDROXYTINOSPORIDE emerged as the most promising candidate with the strongest docking score and extensive interactions with both polar and non-polar residues, suggesting a high potential for DPP-4 inhibition. 10-HYDROXYCOLUMBIN and 20-BETA-HYDROXYECDYSONE also demonstrated strong binding affinities, with multiple hydrogen bonding and hydrophobic interactions contributing to their stability within the active site of the DPP-4 enzyme.

11-HYDROXYMUSTAKONE, while still showing reasonable binding affinity, had fewer hydrophobic interactions, which

may limit its efficacy as a DPP-4 inhibitor. AMRITOSIDE-A, on the other hand, showed a relatively weaker interaction profile, primarily involving hydrogen bonds with a single residue, indicating the need for further optimization to enhance its binding affinity.

These findings suggest that *Tinospora cordifolia* contains several bioactive compounds with promising potential as DPP-4 inhibitors. Further in vitro and in vivo studies are necessary to validate these computational results and evaluate the pharmacological activities of these compounds. Additionally, structure-activity relationship (SAR) studies could be conducted to optimize these compounds for better potency and selectivity as potential therapeutic agents for diabetes management.

Table-1- Docking Score with Drug Interaction (H-bond and Hydrophobic bond)

Chemical Constituent	Docking Score	H-bond Residue	Hydrophobic Residue
10-HYDROXYCOLUMBIN	-7.9	Arg125, Glu205, Glu206, Tyr547,Tyr 662, Tyr666	Tyr662(Pi-Pi), Tyr666(Pi-Pi-T shape), Val656(alkyl), Val711(Alkyl), Trp659(Pi-alkyl), Tyr662(Pi-alkyl)
11-HYDROXYMUSTAKONE	-6.5	Arg125, Glu205, Tyr662,Asn710, Ser209	Tyr662(Pi-Pi), Tyr666(Pi-Pi-T shape),
20-BETAHYDROXYECDYSONE	-7.6	Arg125, Arg358, Glu205, Glu206, Tyr 662, Asn710, Ser209, Ser630	Phe357(Pi-Pi),Tyr666(Pi-Pi T shape, Pi-alkyl), Arg358(Pi-alkyl)
8-HYDROXYTINOSPORIDE	-9	Arg125, Glu205, Tyr 662, Asn710, Ser209	Phe357(Pi-Pi),Tyr666(Pi-Pi T shape), Tyr 662(Pi-pi stacked)
AMRITOSIDE-A	-7.2	Ser87	No Hydrphobic Interactions

4. CONCLUSION

In this study, we conducted molecular docking simulations to explore the binding affinity of five key chemical constituents of *Tinospora cordifolia* with the DPP-4 enzyme, a crucial target for diabetes treatment. The results showed that 8-HYDROXYTINOSPORIDE exhibited the strongest binding affinity, followed by 10-HYDROXYCOLUMBIN and 20-BETA-HYDROXYECDYSONE. These compounds formed multiple hydrogen bonds and hydrophobic interactions with the enzyme's active site, suggesting their potential as effective DPP-4 inhibitors. AMRITOSIDE-A and 11-HYDROXYMUSTAKONE demonstrated weaker binding, which may limit their effectiveness as DPP-4 inhibitors but still warrants further optimization.

The findings of this study underscore the potential of *Tinospora cordifolia* and its constituents as a source of natural compounds for the development of new antidiabetic agents. The computational approach utilized in this research provides valuable insights into the molecular mechanisms by which these compounds interact with DPP-4, paving the way for future experimental validation.

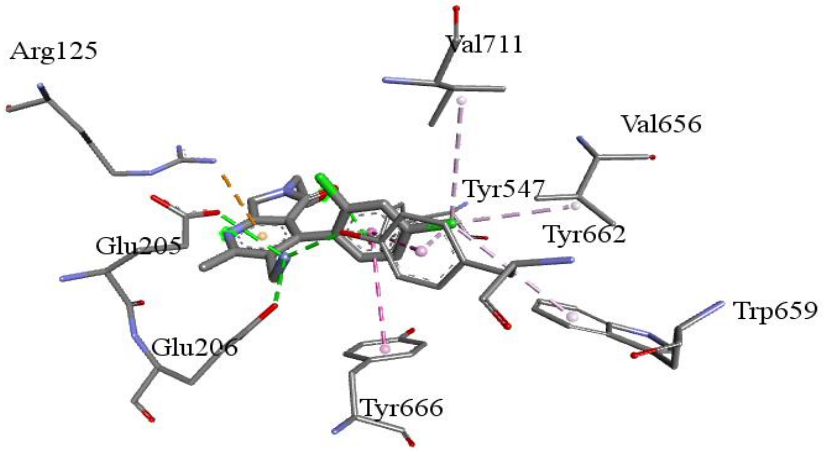

Fig-1 Bond Interactions of Co-crystallize ligand with PDB Id- 4LKO

Future Prospects

The promising docking results of several *Tinospora cordifolia* constituents indicate their potential for further development as DPP-4 inhibitors. However, in vitro and in vivo studies are essential to validate these computational predictions and to assess the pharmacokinetic and pharmacodynamic properties of the compounds. Specifically, the compounds with the highest docking scores such as 8-HYDROXYTINOSPORIDE and 10-HYDROXYCOLUMBIN should be prioritized for laboratory testing to confirm their DPP-4 inhibitory activity and their effect on glucose metabolism.

In addition to experimental validation, future research could focus on optimizing the identified bioactive compounds. Structure-activity relationship (SAR) studies could help refine these molecules to improve their potency, selectivity, and stability as potential therapeutic agents. Furthermore, exploring the synergy between these compounds and existing antidiabetic drugs could lead to combination therapies that enhance treatment efficacy while minimizing side effects.

Another exciting avenue for future work would be the exploration of the molecular dynamics (MD) simulations to better understand the flexibility and conformational changes of the ligand-enzyme complexes over time. This could offer deeper insights into the stability and dynamics of the ligand binding process, further guiding the optimization of these compounds.

Finally, clinical trials will be essential to assess the safety, efficacy, and therapeutic potential of these compounds in humans. If successful, these natural compounds could contribute to the development of novel, safe, and effective treatments for Type 2 diabetes, particularly in light of the growing global incidence of this disease.

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