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Investigating the Therapeutic Promise of *Mimosa pudica* for Diabetes: A Computational Perspective

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Abstract

The rising global incidence of diabetes mellitus underscores the urgent demand for innovative antidiabetic agents. This study investigates the therapeutic potential of *Mimosa pudica* L. (commonly known as the sensitive plant), recognized for its traditional medicinal uses, as a possible antidiabetic agent through an in-silico approach. Utilizing bioinformatics tools and databases, we conducted a comprehensive analysis of the phytochemical constituents of *Mimosa pudica*, concentrating on their molecular interactions and potential inhibitory effects on key diabetes-related enzymes, specifically 11β-Hydroxysteroid Dehydrogenase Type 1 (11β-HSD1), Glutamine-Fructose-6-Phosphate Transaminase (GFAT), SIRT6, and Protein-Tyrosine Phosphatase 1B (PTP1B). Our findings reveal that certain bioactive compounds within *Mimosa pudica* exhibit strong binding affinity to these targets, suggesting potential inhibitory actions. This computational study provides compelling preliminary evidence for the antidiabetic efficacy of *Mimosa pudica*, positioning it as a candidate for further in-vitro and in-vivo investigations. The research highlights the significance of integrating computational methods in exploring plant-based therapeutics, which could revolutionize diabetes management strategies.

Keywords: *Mimosa pudica*, antidiabetic, molecular docking, phytochemical

INTRODUCTION

Blood glucose, or glucose, is a primary energy source for the body. Diabetes is a condition that impairs the body's ability to produce or effectively use insulin, a hormone that regulates blood sugar levels. When insulin function is disrupted, it can lead to elevated blood sugar levels, which can have serious health consequences. These consequences include heart disease, stroke, kidney disease, and nerve damage (Banday et al., 2020).

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels, resulting from defects in insulin secretion, insulin action, or both. According to the World Health Organization (WHO), the global prevalence of diabetes has been rapidly rising, affecting over 463 million people worldwide in 2019, with projections suggesting that this number could exceed 700 million by 2045. The condition poses significant health challenges, including complications such as cardiovascular disease, nephropathy, and neuropathy, leading to substantial economic and healthcare burdens (Zheng et al., 2018).

Medicinal plants are a rich source of natural compounds that have been used for centuries to treat various ailments. However, the identification and characterization of bioactive compounds from medicinal plants is a challenging and time-consuming process that requires extensive experimental validation (Chaachouay & Zidane, 2024). Current pharmacological treatments for diabetes, while effective, often come with side effects and limitations, creating a pressing need for novel therapeutic agents. Traditional medicine has long utilized various plants for managing diabetes, with *Mimosa pudica*, commonly known as the sensitive plant, emerging as a notable contender. This perennial herb, native to tropical and subtropical regions, is characterized by its unique ability to respond to touch by folding its leaves—a phenomenon known as thigmonasty. *Mimosa pudica* is renowned for its diverse medicinal properties, including anti-inflammatory, antioxidant, and antidiabetic effects (Adurosakin et al., 2023). It has a rich history in traditional medicine, where it is employed for a myriad of health conditions, including inflammation, pain, and gastrointestinal disorders. Recent phytochemical studies have identified various bioactive compounds in *Mimosa pudica*, such as flavonoids, alkaloids, and tannins, which contribute to its therapeutic effects. These compounds are believed to exert significant antioxidant activity, helping to mitigate oxidative stress—a key factor in the pathophysiology of diabetes (Rizwan et al., 2022). The growing body of research surrounding *Mimosa pudica* highlights its potential as a natural remedy for diabetes, warranting further investigation into its pharmacological properties.

Key enzymes involved in glucose metabolism and insulin signaling have become crucial targets in diabetes research. 11β-Hydroxysteroid Dehydrogenase Type 1 (11β-HSD1) is pivotal in the local conversion of cortisone to cortisol, influencing glucose metabolism and insulin sensitivity. Inhibition of 11β-HSD1 has shown potential in improving insulin sensitivity and reducing hyperglycemia, marking it as a promising target for antidiabetic therapies (Kupczyk et al., 2022). Glutamine-Fructose-6-Phosphate Transaminase (GFAT) regulates the hexosamine biosynthetic pathway, which is critical in the development of insulin resistance. Modulating GFAT activity could enhance insulin sensitivity and improve glycemic control (Ruegenberg et al., 2020). SIRT6, a member of the sirtuin family, plays a role in various cellular processes, including glucose homeostasis and inflammation, with activation linked to improved metabolic health (Smirnov et al., 2023). Lastly, Protein-Tyrosine Phosphatase 1B (PTP1B) negatively regulates insulin signaling; its inhibition can enhance insulin sensitivity and lower blood glucose levels, making it another vital target for diabetes intervention (Deshpande et al., 2020). Targeting these enzymes through natural compounds, such as those found in *Mimosa pudica*, could provide a novel strategy for diabetes management.

Recent advancements in computational methods, particularly molecular docking and bioinformatics, offer valuable insights into the interaction between bioactive compounds and their biological targets. Molecular docking is a powerful technique used to predict the preferred orientation of small molecules when bound to a protein, allowing researchers to estimate binding affinities and identify potential inhibitors (Mohanty & Mohanty, 2023). This approach enables the screening of large libraries of compounds, facilitating the discovery of new therapeutic agents by simulating how they interact with specific enzymes involved in disease pathways (Pinzi & Rastelli, 2019). In the context of this study, molecular docking will be employed to analyze the interactions between the phytochemical constituents of *Mimosa pudica* and the key diabetes-related enzymes mentioned earlier. By elucidating these interactions, we aim to provide a scientific basis for the traditional use of *Mimosa pudica* in diabetes management and contribute to the development of effective plant-based therapeutic strategies.

Moreover, the integration of computational techniques with traditional medicinal knowledge presents a unique opportunity to explore the therapeutic potential of lesser-studied plants. This holistic approach not only enhances our understanding of the specific mechanisms through which these plants exert their effects but also paves the way for the identification of novel compounds that could be developed into effective antidiabetic medications. By leveraging the wealth of information available through computational databases, researchers can rapidly assess the bioactivity of various phytochemicals, thus accelerating the drug discovery process.

Furthermore, the emphasis on natural products in drug development aligns with the growing interest in holistic and sustainable healthcare solutions. As consumers increasingly seek alternatives to synthetic pharmaceuticals, plant-based remedies are gaining traction in the healthcare community. The exploration of *Mimosa pudica* and other medicinal plants through computational methods may not only validate their traditional uses but also contribute to a more sustainable approach to diabetes management. This study underscores the significance of integrating computational analyses in the exploration of phytochemicals, potentially paving the way for novel antidiabetic interventions.

METHODOLOGY

Computational drug discovery was employed to identify potential anti-inflammatory and antidiabetic agents from *Mimosa pudica*. Molecular docking, a computational technique used to predict the interaction between molecules, was instrumental in this process. The PyRx software was utilized to conduct molecular docking simulations. Ligands derived from *Mimosa pudica* were docked against target proteins associated with inflammation and diabetes. This approach aimed to identify compounds with high binding affinity and favorable binding poses, suggesting potential therapeutic activity. By employing molecular docking, this research sought to discover novel molecules with improved properties compared to existing anti-inflammatory and antidiabetic agents.

System Setup for Molecular Docking

Computational drug discovery was carried out using PyRx, an open-source virtual screening tool. AutoDock Vina served as the docking engine within PyRx, predicting the binding affinity and mode of small molecules to macromolecules (Trott & Olson, 2010). Discovery Studio was employed for visualization. The simulations were conducted on a Windows 11 Pro system with an 11th Gen Intel Core i9 processor.

Preparation of Ligands and Macromolecules

Three-dimensional structures of ligands from *Mimosa pudica* were retrieved from the PubChem database in SDF format. These ligands were converted to PDB format using OpenBabel. Receptors associated with antidiabetic mechanisms were selected from the Protein Data Bank. These included: 11β-HSD1 (PDB Code: 1XU7), GFAT (PDB Code: 2ZJ3), SIRT6 (PDB Code: 3K35), and PTP1B (PDB Code: 4Y14). These receptors were chosen based on their known roles in diabetes-related pathways.

Binding Energy Calculation

Molecular docking simulations were performed using PyRx. Docking parameters such as grid box size, exhaustiveness, and the number of poses were adjusted. The binding affinity and binding pose of each ligand with the receptor were evaluated. The following docking parameters were used: Exhaustiveness = 8, Num_modes = 9, Energy_range = 3. Binding affinity is a measure of ligand-receptor interaction strength. Lower binding affinity indicates higher binding stability.

Interaction Visualization

The interactions between the bioactive compounds from *Mimosa pudica* and the target macromolecules associated with diabetes were visualized using Discovery Studio Visualizer. This software allows for detailed analysis of binding poses, which refer to the orientation and conformation of a ligand when it binds to a receptor. Understanding the binding pose is crucial, as it can significantly influence the binding affinity and overall interactions between the ligand and the receptor.

Data Analysis

For data analysis, the binding affinities of the ligands derived from *Mimosa pudica* that were docked to the diabetes-related macromolecules were extracted from PyRx and converted into CSV format. The results were then analyzed to identify the compounds with the highest binding affinity scores, providing insight into their potential as effective therapeutic agents.

RESULTS AND DISCUSSION

Molecular docking is a computational technique employed to model interactions between molecules at the molecular level. The results are expressed as binding affinity or binding energy (in kcal/mol), with more negative values indicating stronger interactions. In the current study, all 40 ligands derived from *Mimosa pudica* were successfully docked to four receptors/macromolecules known for their antidiabetic properties.

Table 1. Result of Computational Binding Affinity

Ligands	Receptors				Grand Total
	1XU7	2ZJ3	3K35	4Y14	
Crocin	-9.42	-8.27	-8.98	-8.18	-8.71
Betulinic_Acid	-9.93	-8.43	-8.77	-7.09	-8.58
Stigmasterol	-10.69	-7.29	-9.36	-6.89	-8.56
Ergosteryl_acetate	-9.90	-7.81	-9.38	-6.90	-8.50
Rutin	-9.57	-7.88	-8.26	-7.81	-8.38
Apigetrin	-8.50	-8.47	-8.93	-7.28	-8.29
Cassiaoccidentalin_B	-9.11	-7.82	-8.46	-7.64	-8.26
Beta-Sitosterol	-9.54	-7.19	-9.21	-6.43	-8.09
Isoorientin	-9.03	-8.06	-8.19	-7.01	-8.07
Myricetin	-9.01	-7.42	-8.62	-6.76	-7.95
Luteolin	-9.26	-7.04	-8.41	-7.00	-7.93
Orientin	-7.88	-7.43	-8.74	-7.54	-7.90
Apigenin	-8.67	-7.16	-8.43	-6.92	-7.79

Hyperoside	-7.99	-7.81	-8.27	-7.06	-7.78
Isoquercetin	-8.48	-7.60	-8.10	-6.86	-7.76
Vitexin	-7.86	-7.42	-8.58	-6.83	-7.67
Naringenin	-8.51	-7.09	-8.32	-6.76	-7.67
Isovitexin	-7.88	-7.90	-7.80	-7.03	-7.65
6-Hydroxyflavone	-8.27	-6.98	-8.20	-7.10	-7.64
Cianidanol	-8.47	-7.03	-8.40	-6.63	-7.63
Quercitrin	-7.98	-7.34	-8.08	-6.83	-7.56
Avicularin	-7.90	-7.34	-7.99	-6.92	-7.54
Quercetin	-8.73	-7.00	-7.54	-6.84	-7.53
Chlorogenic_Acid	-8.53	-7.38	-7.74	-6.18	-7.46
Flavone	-8.08	-6.61	-8.08	-6.49	-7.31
Curcumin	-8.60	-6.37	-7.78	-5.64	-7.10
Crocetin	-7.79	-6.82	-6.93	-5.97	-6.88
4-Methylcyclopentadecanone	-7.86	-6.04	-7.11	-5.80	-6.70
Gentamicin_A	-7.14	-6.47	-6.57	-6.10	-6.57
Caffeic_Acid	-6.59	-5.96	-6.76	-5.79	-6.27
Ferulic_acid	-6.39	-5.70	-6.59	-5.66	-6.08
Gallic_Acid	-6.16	-6.21	-6.32	-5.62	-6.08
p-Coumaric	-6.06	-5.34	-6.40	-6.24	-6.01
Protocatechuic_acid	-6.04	-5.86	-6.07	-5.74	-5.93
Cinnamic_Acid	-5.88	-5.06	-5.99	-5.54	-5.62
4-Hydroxybenzoic_acid	-5.63	-5.28	-5.79	-5.52	-5.56
Jasmonic_acid	-6.16	-5.42	-5.52	-5.07	-5.54
Mimosine	-5.86	-5.83	-5.17	-4.81	-5.42
D-Mannosamine	-5.54	-5.94	-5.18	-4.89	-5.39
Indole	-5.59	-4.68	-5.23	-4.87	-5.09
Grand Total	**-7.91**	**-6.84**	**-7.61**	**-6.46**	**-7.21**

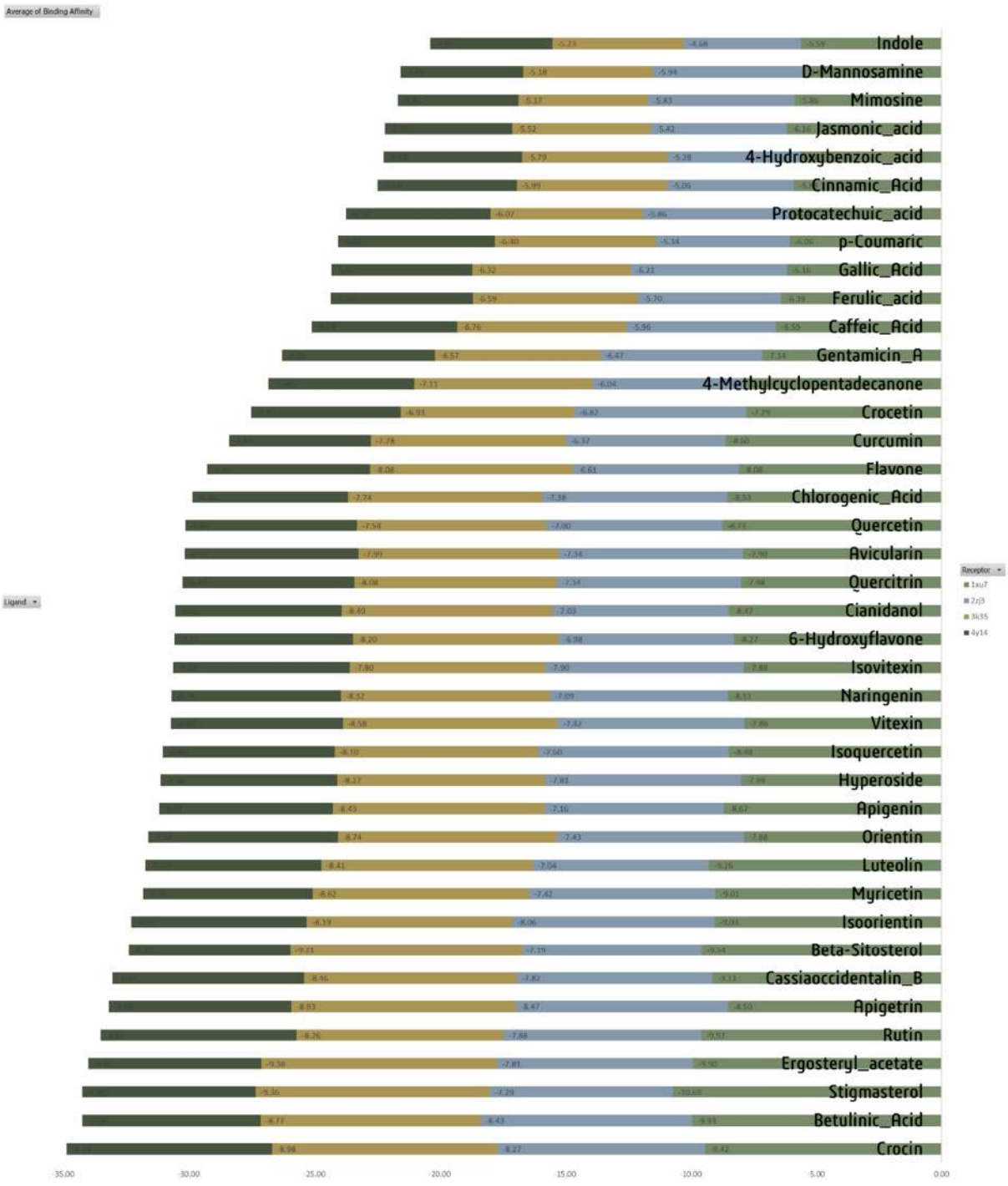

Figure 1. Comparison Chart of Computational Binding Affinity

Figure 2. Binding affinity of *Mimosa pudica* constituents to 11β-hydroxysteroid dehydrogenase (11β-HSD1) receptor (best 10 ligands)

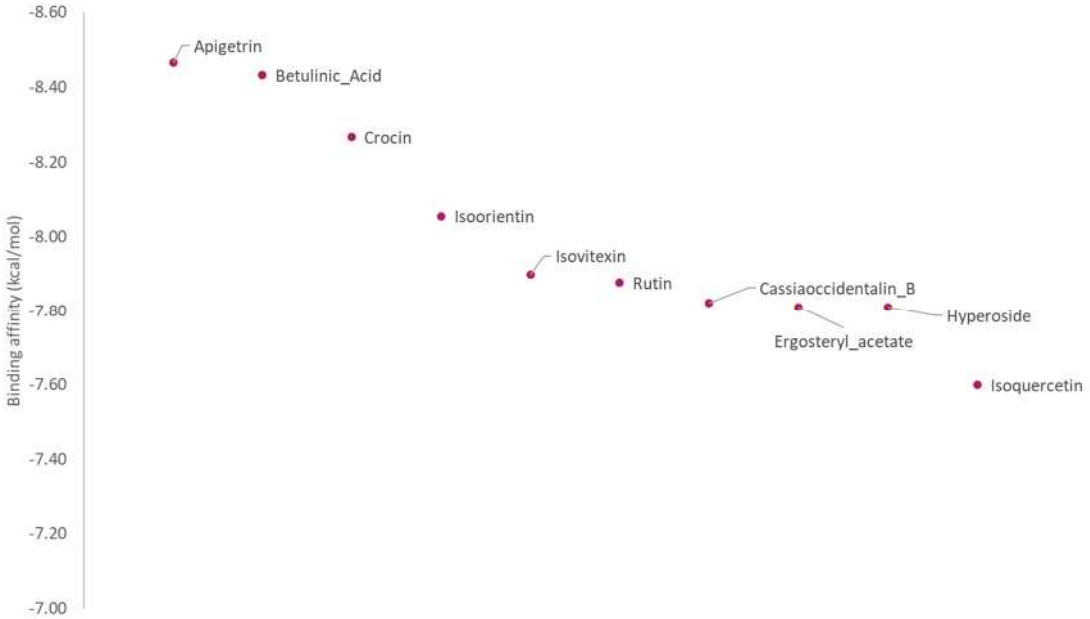

Figure 3. Binding affinity of *Mimosa pudica* constituents to Glutamine-fructose-6-phosphate amidotransferase (GFAT or GFPT) receptor (best 10 ligands)

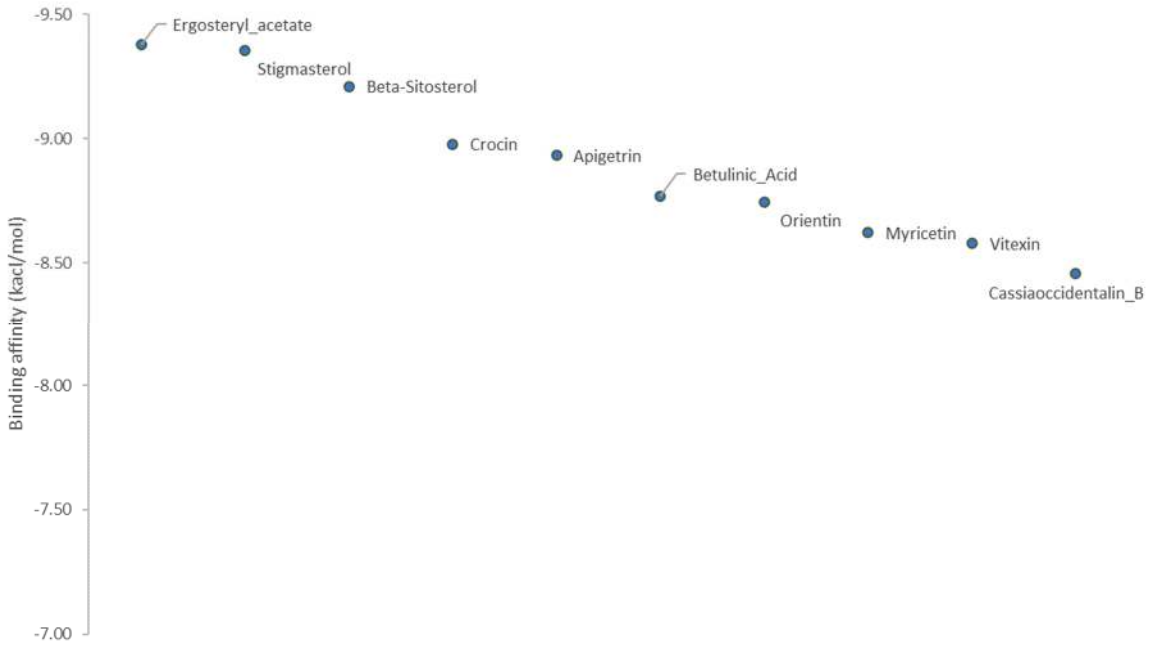

Figure 4. Binding affinity of *Mimosa pudica* constituents to Sirtuin-6 or Mono-ADP ribosyltransferase-sirtuin-6 (SIRT6) receptor (best 10 ligands)

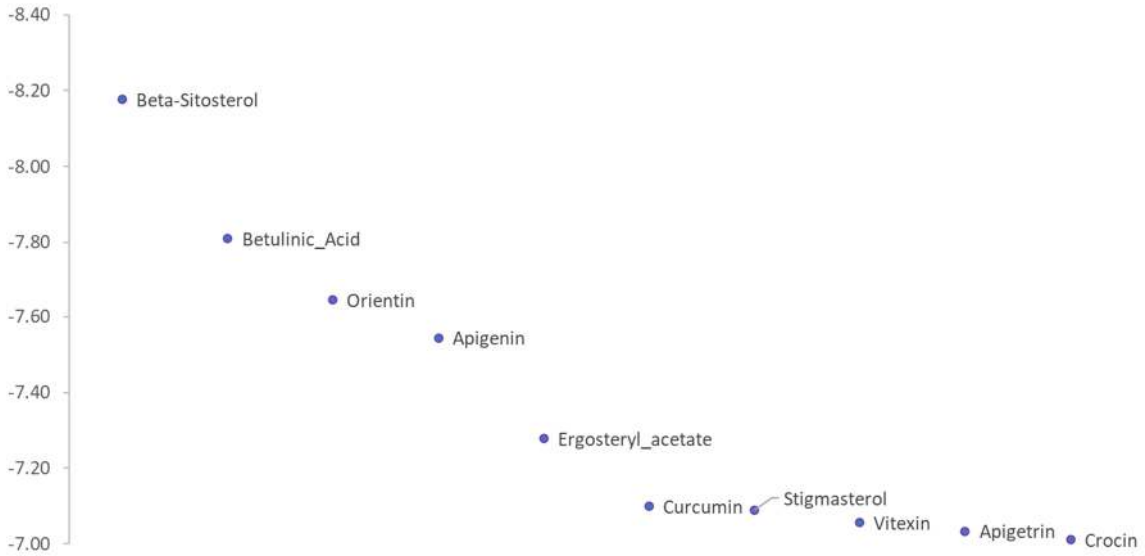

Figure 5. Binding affinity of *Mimosa pudica* constituents of Protein-tyrosine phosphatase 1B (PTP1B) receptor (best 10 ligands)

11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) is an enzyme that catalyzes the conversion of inactive cortisone to active cortisol. Elevated activity of 11β-HSD1 has been linked to the development of type II diabetes and obesity, as excessive cortisol can disrupt glucose metabolism and promote insulin resistance (Kupczyk et al., 2022). Glutamine fructose-6-phosphate amidotransferase (GFAT) plays a crucial role in the hexosamine biosynthetic pathway, which is responsible for producing UDP-N-acetylglucosamine (UDP-GlcNAc), a

critical substrate for protein glycosylation. Alterations in GFAT activity have been associated with insulin resistance and the pathogenesis of diabetes (Oliveira et al., 2021). Protein tyrosine phosphatase 1B (PTP1B) negatively regulates insulin signaling by dephosphorylating tyrosine residues on insulin receptor substrates. Inhibiting PTP1B has been shown to enhance insulin sensitivity and improve glycemic control, making it a promising target for diabetes treatment (Li et al., 2021). Extensive studies on the crystal structure of PTP1B have facilitated the development of potential antidiabetic drugs targeting this enzyme. Insights from these structural analyses are essential for understanding the molecular mechanisms of diabetes and may inform the design of specific inhibitors for therapeutic applications.

The docking was performed successfully, and binding affinity values were obtained. The lower the energy (more electronegative), the stronger the binding to the receptor. Constituents in *Mimosa pudica* showed a good value of binding affinity to four enzymes which have an important role in glucose metabolism, in this study they worked as receptors. Best three ligands having lowest binding affinity in average or highest score are crocin (-8.71 kcal/mol), betulinic acid (-8.58 kcal/mol), and stigmasterol (-8.56 kcal/mol).

The four receptors used give different responses to 4 ligands used as *Mimosa pudica* constituents, with order from best to smallest receptor, consecutively are 11β-Hydroxysteroid dehydrogenase, Sirtuin-6 or Mono-ADP ribosyltransferase-sirtuin-6, Glutamine-fructose-6-phosphate amidotransferase, and the last one is Protein-tyrosine phosphatase 1B.

Conclusion

The in-silico study method is a computational approach to search for new compounds that have medicinal properties from various resources, especially from plants. This research is a contribution to this search method, by exploring the potential of *Mimosa pudica* plants constituents in the treatment of diabetes mellitus, or playing an important role in glucose metabolism.

Although *Mimosa pudica* is not showing an incredibly high score, it has a good binding affinity value, considering its medicinal benefits in modern healthcare approaches focused on diabetes management. In-vitro and in-vivo research need to be done for better results in finding new drugs.

Acknowledgement

None.

Conflict of Interest

The authors confirm that this article content has no conflicts of interest (none to declare).

References

Adurosakin, O. E., Iweala, E. J., Otike, J. O., Dike, E. D., Uche, M. E., Owanta, J. I., Ugbogu, O. C., Chinedu, S. N., & Ugbogu, E. A. (2023). Ethnomedicinal uses, phytochemistry, pharmacological activities and toxicological effects of *Mimosa pudica*- A review. *Pharmacological Research - Modern Chinese Medicine*, *7*, 100241. https://doi.org/10.1016/j.prmcm.2023.100241

Banday, M. Z., Sameer, A. S., & Nissar, S. (2020). Pathophysiology of diabetes: An overview. *Avicenna Journal of Medicine*, *10*(4), 174–188. https://doi.org/10.4103/ajm.ajm_53_20

Chaachouay, N., & Zidane, L. (2024). Plant-Derived Natural Products: A Source for Drug Discovery and Development. *Drugs and Drug Candidates*, *3*(1), 184–207. https://doi.org/10.3390/ddc3010011

Deshpande, T. A., Isshak, M., & Priefer, R. (2020). PTP1B Inhibitors as Potential Target for Type II Diabetes. *Agricultural Research & Technology: Open Access Journal*, *14*(1), 1–13. https://doi.org/10.19080/CRDOJ.2020.14.555876

Kupczyk, D., Bilski, R., Kozakiewicz, M., Studzińska, R., Kędziora-Kornatowska, K., Kosmalski, T., Pedrycz-Wieczorska, A., & Głowacka, M. (2022). 11β-HSD as a New Target in Pharmacotherapy of Metabolic Diseases. *International Journal of Molecular Sciences*, *23*(16), 8984. https://doi.org/10.3390/ijms23168984

Li, D., Zhang, S., Yang, C., Li, Q., Wang, S., Xu, X., Hao, J., & Li, C. (2021). A Novel PTP1B Inhibitor-Phosphate of Polymannuronic Acid Ameliorates Insulin Resistance by Regulating IRS-1/Akt Signaling. *International Journal of Molecular Sciences*, *22*(23), 12693. https://doi.org/10.3390/ijms222312693

Mohanty, M., & Mohanty, P. S. (2023). Molecular docking in organic, inorganic, and hybrid systems: A tutorial review. *Monatshefte Für Chemie - Chemical Monthly*, *154*(7), 683–707. https://doi.org/10.1007/s00706-023-03076-1

Oliveira, I. A., Allonso, D., Fernandes, T. V. A., Lucena, D. M. S., Ventura, G. T., Dias, W. B., Mohana-Borges, R. S., Pascutti, P. G., & Todeschini, A. R. (2021). Enzymatic and structural properties of human glutamine:fructose-6-phosphate amidotransferase 2 (hGFAT2). *The Journal of Biological Chemistry*, *296*. https://doi.org/10.1074/jbc.RA120.015189

Pinzi, L., & Rastelli, G. (2019). Molecular Docking: Shifting Paradigms in Drug Discovery. *International Journal of Molecular Sciences*, *20*(18), 4331. https://doi.org/10.3390/ijms20184331

Rizwan, K., Majeed, I., Bilal, M., Rasheed, T., Shakeel, A., & Iqbal, S. (2022). Phytochemistry and Diverse Pharmacology of Genus Mimosa: A Review. *Biomolecules*, *12*(1), 83. https://doi.org/10.3390/biom12010083

Ruegenberg, S., Horn, M., Pichlo, C., Allmeroth, K., Baumann, U., & Denzel, M. S. (2020). Loss of GFAT-1 feedback regulation activates the hexosamine pathway that modulates protein homeostasis. *Nature Communications*, *11*(1), 687. https://doi.org/10.1038/s41467-020-14524-5

Smirnov, D., Eremenko, E., Stein, D., Kaluski, S., Jasinska, W., Cosentino, C., Martinez-Pastor, B., Brotman, Y., Mostoslavsky, R., Khrameeva, E., & Toiber, D. (2023). SIRT6 is a key regulator of mitochondrial function in the brain. *Cell Death & Disease*, *14*(1), 1–12. https://doi.org/10.1038/s41419-022-05542-w

Trott, O., & Olson, A. J. (2010). AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of Computational Chemistry*, *31*(2), 455–461. https://doi.org/10.1002/jcc.21334

Zheng, Y., Ley, S. H., & Hu, F. B. (2018). Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nature Reviews. Endocrinology*, *14*(2), 88–98. https://doi.org/10.1038/nrendo.2017.151