In silico elucidation of antidiabetic activity and ADMET evaluation of bitter melon (*Momordica charantia* L.) bioactive compounds targeting peroxisome proliferator activated receptor gamma

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Abstract

Bitter melon (*Momordica charantia*)*, a tropical and subtropical vine, has been extensively studied for its bioactive compounds and their potential therapeutic benefits. The present study evaluate the molecular docking results, drug-like characteristics, and pharmacokinetic properties of cucurbitanes, karounidiols, and momordicin derived from bitter melon. The aim was to assess their potential in treating type 2 diabetes mellitus (T2DM) by comparing them with a well-established drug control and conducting an ADMET assessment. The study employed molecular docking analysis to evaluate the binding affinity and binding site characteristics of the identified compounds with the PPARG protein. Furthermore, a comprehensive ADMET assessment was conducted to evaluate the absorption, distribution, metabolism, excretion, and toxicity profiles of the compounds. The results indicates that all tested compounds exhibit higher affinity and a comparable binding site with the PPARG protein compared to pioglitazone. Moreover, the favorable ADMET profiles and minimal potential for acute toxicity indicate the suitability of these compounds for further therapeutic development. However, further research is required to confirm the degree of agonist properties and validate their therapeutic potential comprehensively.*

Keywords*:* bitter melon, disease, *in silico*, PPARG, T2DM

1. Introduction

A chronic metabolic condition known as diabetes mellitus is defined by increased blood glucose levels characterized on by abnormalities in metabolism caused by deteriorated insulin function (Kotwas *et al*., 2021). It is the primary cause of serious medical problems and one of the leading causes of death worldwide (Ismail *et al*., 2021). The World Health Organization reports that more than 415 million people globally are currently affected by diabetes. The International Diabetes Federation (IDF) estimates that by 2035, the number of people with diabetes worldwide will reach 592 million (Kotwas *et al*., 2021; Ismail *et al*., 2021). Critically, it has become one of the leading causes of death worldwide and is recognized as a significant public health priority (Kotwas *et al*., 2021; Khan *et al*., 2020). Accumulating evidence demonstrated that diabetes patients had higher rates of overweight, dyslipidemia, smoking, poor physical activity, and inflammation (Khan *et al*., 2020; DasNandy *et al*., 2022).

T2DM is characterized by decreased insulin sensitivity due to insulin resistance, impaired insulin production, and pancreatic beta-cell dysfunction, all leading to decreased glucose uptake by the liver, muscle, and adipose tissues (Olokoba *et al*. 2012). The development of T2DM is significantly driven by both genetic and environmental factors, particularly lifestyle (Bellou *et al*., 2018). Individuals with a family history of T2DM are at an especially high risk of developing the condition, showing a strong genetic predisposition. Numerous genes have been closely associated with the onset of T2DM, including TCF7L2, PPARG, FTO, KCNJ11, NOTCH2, WFS1, CDKAL1, IGF2BP2, SLC30A8, JAZF1, and HHEX (Olokoba *et al*., 2012).

This research focused on PPARG, a type II nuclear receptor belonging to the nuclear hormone receptor superfamily. According to Gupta *et al*. (2010), it is mostly expressed in adipose tissue and has essential roles in metabolism, including glucose homeostasis, which is disrupted in cases of T2DM. Also, it has a crucial role in controlling adipogenesis in white adipose tissue, driving fibroblastic progenitors into adipocytes (Frkic *et al*., 2021; Cataldi *et al*., 2021; Gupta *et al*., 2010). Therefore, PPARG was identified as a prominent target for anti-diabetic treatment. On the other hand, PPARG agonists like Pioglitazone and Rosiglitazone are commonly used to manage hyperglycemia in T2DM, alongside sulfonylureas, biguanides, and α-glucosidase inhibitors. However, these drugs can cause side effects such as severe hypoglycemia, weight gain, and low target specificity, reducing their therapeutic efficacy

(Padhi *et al*., 2020). This highlights the need for new drugs with fewer adverse effects and better specificity.

Bitter melon is known for its immune-modulating, antiviral, antibacterial, and anti-cancer properties (Sun *et al*., 2023; Çiçek, 2022; Dandawate *et al*., 2016). Traditionally, it has been used in Turkish and Indian medicine for various ailments, including diabetes, infections, wound healing, digestive issues, and inflammatory conditions (Sur and Ray, 2020; Dandawate *et al*., 2016). Other studies also demonstrated that bitter melon is widely used as a therapeutic remedy for diabetes-related ailments. It shows notable antidiabetic and hypolipidemic effects, suggesting its potential as an adjunct to conventional medical interventions for diabetes management and prevention of associated complications (Kim *et al*., 2020; Joseph and Jini, 2013). Although the role of bitter melon in diabetes management is well-documented, the exact molecular mechanisms by which its key compounds interact with crucial regulatory proteins, such as PPARG, remain unclear. Thus, this study aims to bridge the gap in understanding the anti-diabetic potential of bitter melon bioactive compounds by employing molecular docking and pharmacokinetic analysis to evaluate their role as PPARG agonists. By comparing these compounds with a well-established drug control, this study assessed their binding affinity, pharmacokinetic properties, and drug-like potential. This computational approach provides insights into the mechanism of action, supporting future experimental validation and drug development for diabetes treatment.

2. Methodology

2.1. Ligand Preparation

This study employed three chemicals that were primarily identified in bitter melon: cucurbitanes (CID. 71306377), karounidiols (CID. 159490), and momordicin (CID. 57518366). Pioglitazone (CID. 4829), which acts as a PPARG agonist, was employed as a control. Before docking, the structure of the ligand was obtained from the PubChem database (Kim *et al*., 2025). The ligand's structure is stored in *sdf* format to facilitate its interpretation by the docking software.

2.2. Target Protein Preparation

The PPARG serves as a protein target for bioactive substances and control drugs in this study. The PPARG protein's structure was constructed via SWISS-MODEL webserver (2025) (Waterhouse *et al*., 2024). The protein sequence from PPARG was initially obtained from the UniProt website under the protein ID P37231 prior to conducting docking with the ligands (Coudert *et al*., 2023).

2.3. Molecular Docking and Visualization Process

The current study involved the utilization of PyRx software (v.0.8, 2025) for the purpose of molecular docking (Dallakyan and Olson, 2015). The integration of PyRx software with Open Babel enables the optimization of energy for particular ligands prior to the initiation of the molecular docking procedure (Dallakyan and Olson, 2015). Subsequently, the molecular docking outcomes are visualized utilizing BIOVIA Discovery Studio Visualizer (v.2016, 2025), followed by the evaluation of the chemical interactions and implicated amino acid residues within the protein-ligand complex (Hidayatullah *et al*., 2021).

2.4. Target Protein and ADMET Prediction

The assessment of the chemical structure and chemical characteristics of bioactive compounds was conducted using the SwissADME (2025) (Daina *et al*., 2017). Concurrently, the Swiss Target Prediction website was utilized to forecast target proteins from a particular bioactive compound. To investigate the pharmacokinetic characteristics of bitter melon bioactive compounds, the pkCSM web server (2025) was utilized to assess the absorption, distribution, metabolism, excretion, and toxicity properties (Pires *et al*., 2015).

3. Results and Discussion

Based on predictive analysis, PPARG has an important role in regulating some biological processes and molecular functions related to T2DM, such as cellular response to insulin stimulus or glucose homeostasis, which are highly dysregulated in the cases of T2DM (Figure 1). Furthermore, an assessment was conducted on the protein targets derived from the three bioactive compounds present in bitter melon. It was shown that a significant proportion of cucurbitanes, specifically 33.3%, had a predominant affinity towards the

family A G protein-coupled receptor group. Regarding the karounidiols, it was found that 40% of its value was directed towards the nuclear receptor protein group, while the remaining 20% was directed towards the cytochrome P450 protein group. Approximately 33.3% of studies have indicated that the momordicinin predominantly interacts with the nuclear receptor protein group, whereas approximately 26.7% of studies have focused on the enzyme group (Figure 2).

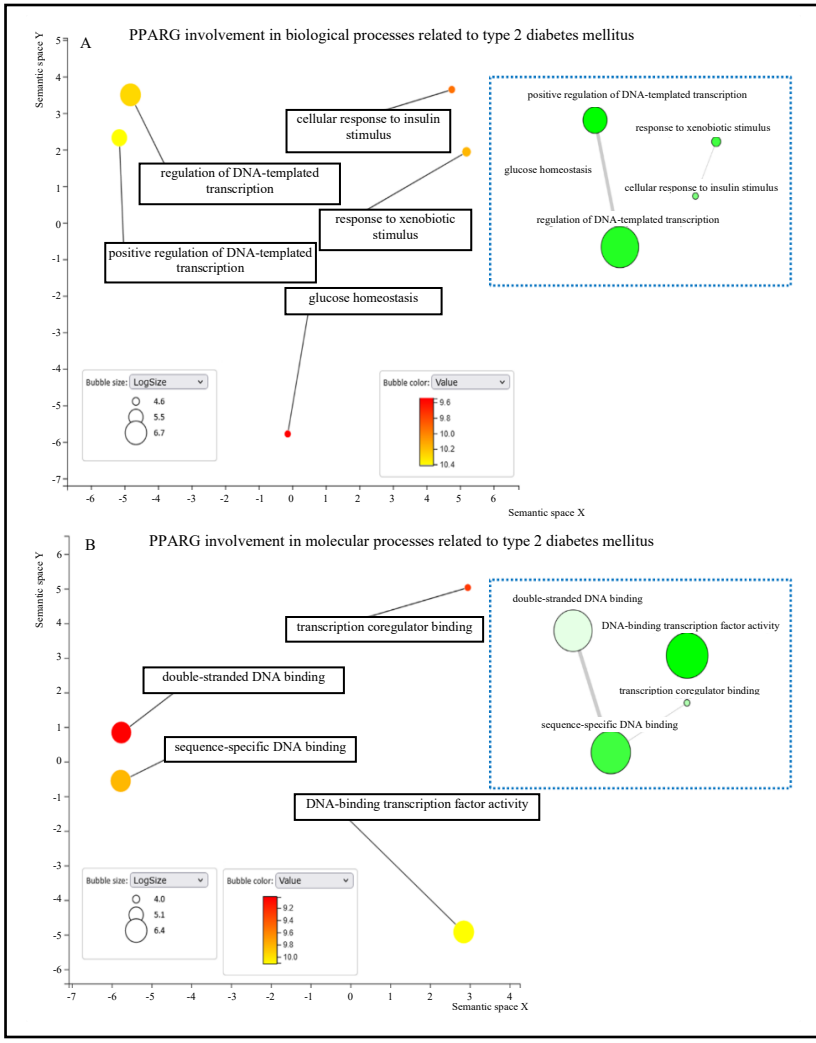

Figure 1. The predicted roles of PPARG in type 2 diabetes mellitus. PPARG involvement in biological processes (A); PPARG involvement in molecular functions related to type 2 diabetes mellitus (B)

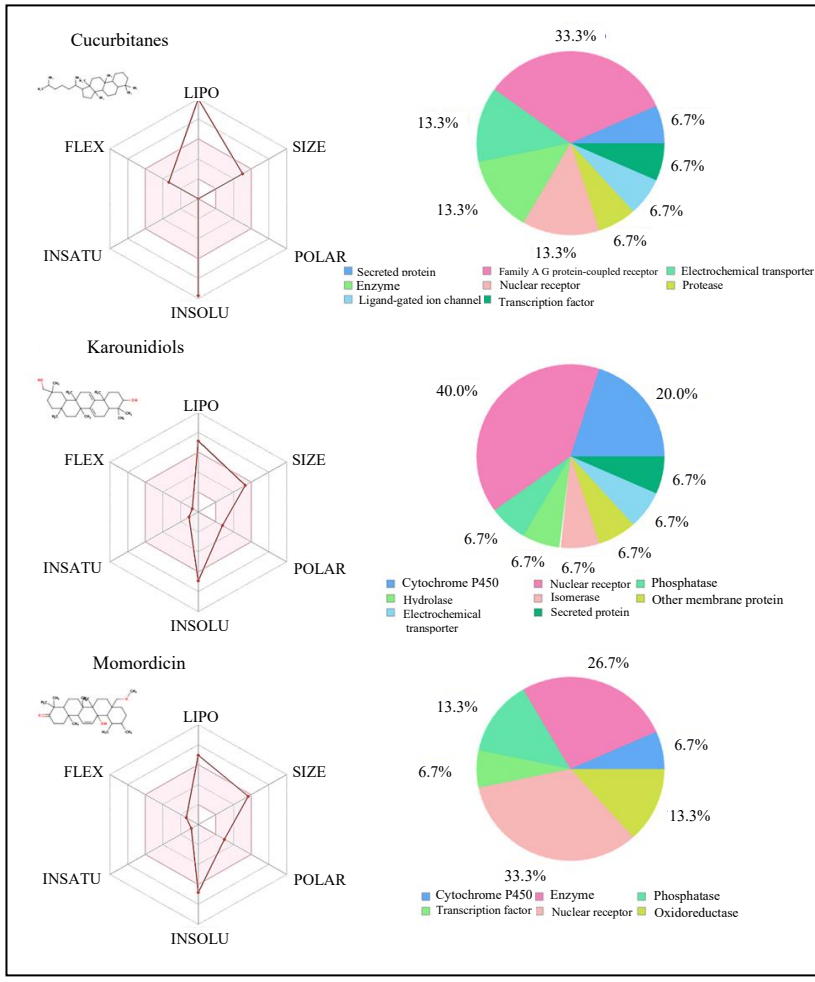

Figure 2. The chemical structure, chemical properties, and predicted target protein of cucurbitanes, karounidiols, and momordicin

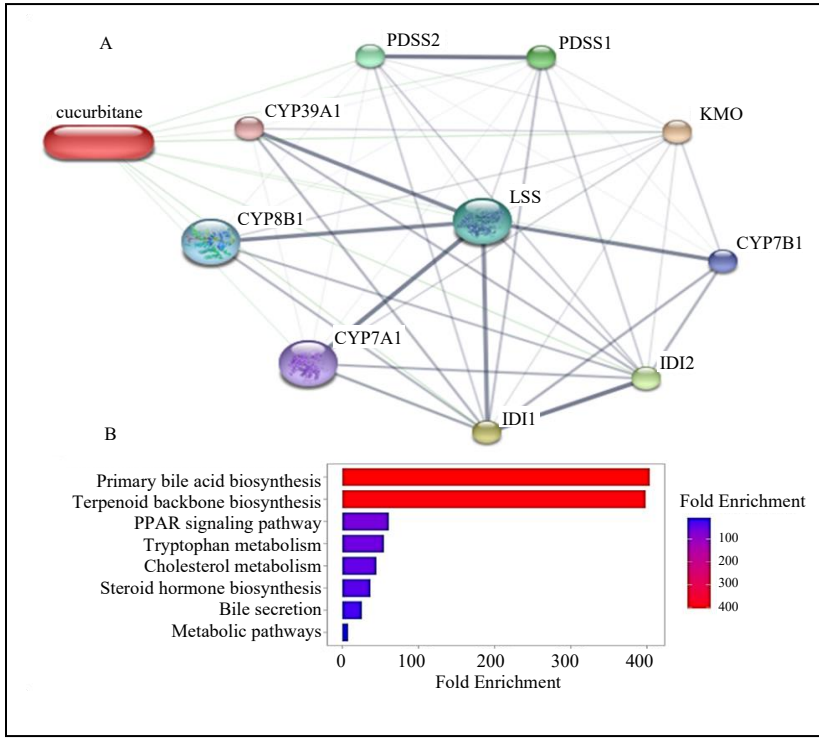

Figure 3. The expanded prediction of cucurbitanes target proteins and its possible target pathways according to KEGG (Kanehisa *et al*., 2017).

To the greater extend, the analysis focuses on specific target protein and its possible target pathways to better understanding on what aspect the bitter melon compounds are involved in. As demonstrated by the findings, cucurbitanes have specific target on some of proteins which related to the T2DM pathways, such as PPAR signaling pathways, cholesterol metabolism pathways, or metabolic pathways (Figure 3). These findings indicate that the bitter melon bioactive compounds might directly target the T2DM pathway via one of the important pathways, PPAR signaling. According to Janani and Ranjitha (2015), upon their contact with particular ligands, nuclear receptors undergo translocation to the nucleus, where they undergo structural modifications and exert regulatory control over gene transcription. Insulin-sensitizing medications known as PPARG-agonists are employed in the management of hyperglycemia accompanied with insulin resistance. Thus far, PPARG agonists, including rosiglitazone and pioglitazone, have garnered significant popularity for their efficacy in managing T2DM. However, the

PPARG-agonists commonly elicit adverse effects such as edema, anemia, liver dysfunction, and heart failure (Hernandez-Quiles *et al*., 2021; Wang *et al*., 2017; Janani and Ranjitha, 2015).

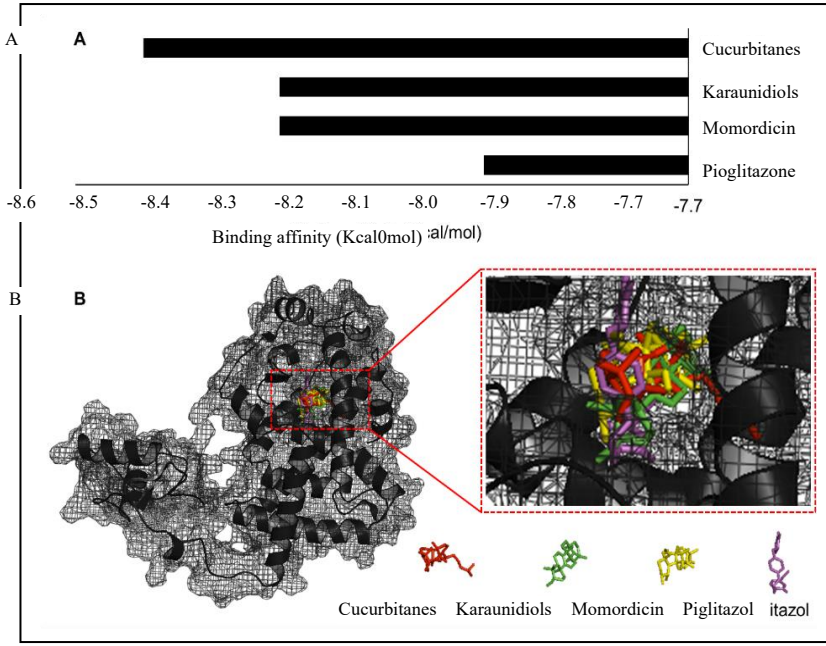

Figure 4. Molecular docking of PPARG protein with bitter melon bioactive compounds and control drug. Binding affinity of ligands against the PPARG protein (A); 3D structure visualization of cucurbitanes, karounidiols, momordicin, and control drug agaisnt the PPARɣ protein (B)

The active compounds derived from bitter melon, including cucurbitanes, karounidiols, and momordicinin, were subjected to molecular docking analysis. A comparison was made between the protein-ligand interaction and pioglitazone as control drug (Ipsen *et al*., 2020; Alam *et al*., 2019). The molecular docking analysis revealed that the three active compounds from bitter melon exhibited higher potential binding affinity values and demonstrated better interaction with the target protein compared to the control drug (Figure 4A). Notably, the visualization results also indicate that those compounds have identical binding site location with the control drug (Figure 4B). This suggests that those compounds might possess the ability to activate PPARG, thereby in turn eliciting an anti-diabetic reaction.

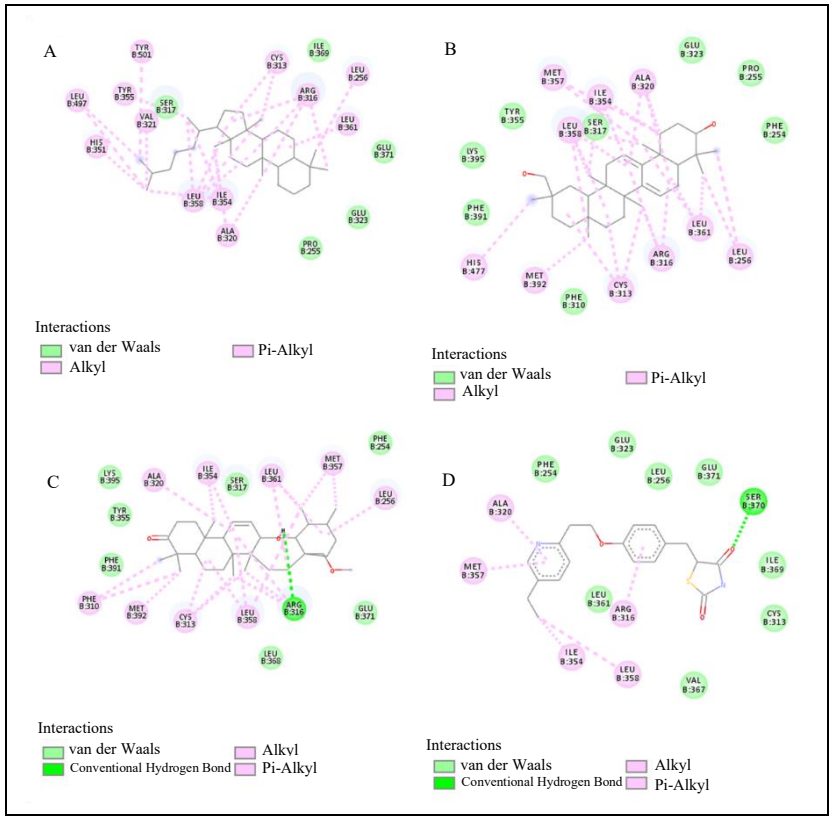

Figure 5. The 2D structure and interaction visualization of cucurbitanes (A), karounidiols (B), momordicin (C) and Pioglitazone (D) against the PPARG protein

A study has shown that cucurbitane from the *Momordica charantia* fruit enhance insulin sensitivity and glucose homeostasis in streptozotocin-induced diabetic mice, highlighting its potential for the prevention and management of diabetes (Han *et al*., 2018). Additionally, research has summarized the potency of *Momordica charantia* compounds, including karounidiols, in regulating glucose absorption in the gut and stimulating its uptake into muscles, thereby contributing to improved glucose homeostasis (Tripathy *et al*., 2018). In the same way, momordicinin has demonstrated anti-diabetic potential by inhibiting α-amylase activity, suggesting its role in diabetes management (Kulkarni *et al*., 2021).

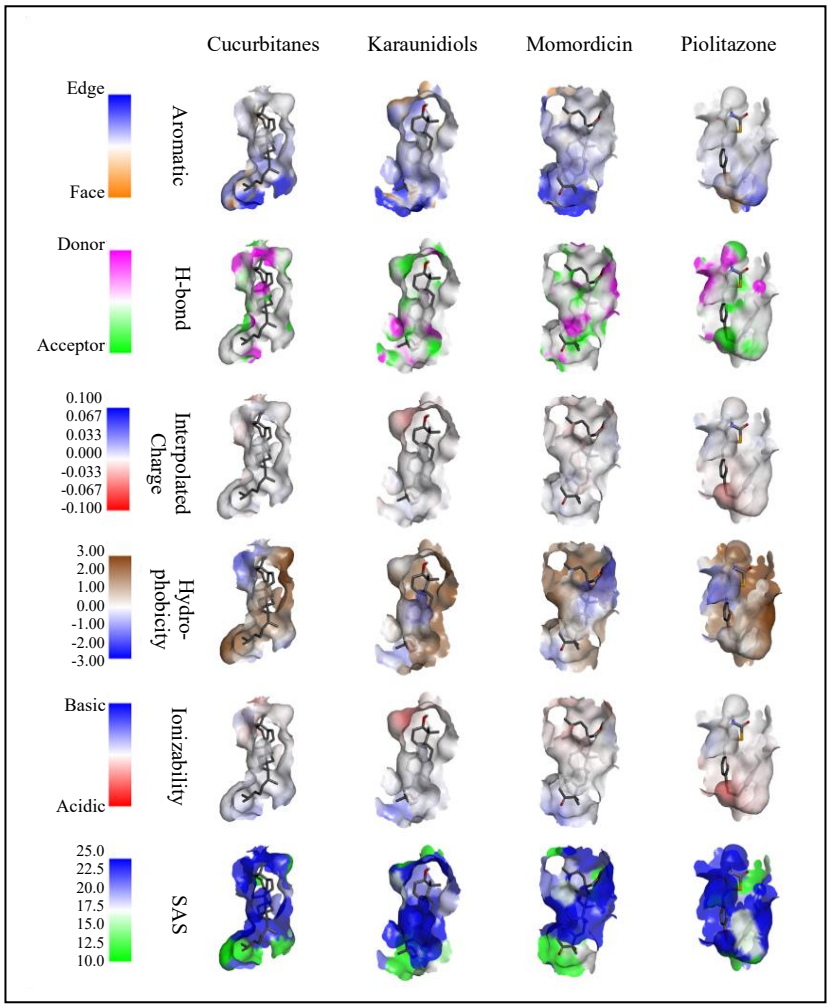

Figure 6. The physicochemical properties of cucurbitanes, karounidiols, momordicin, and Pioglitazone against the PPARG protein including aromatic, H-bonds, interpolated charge, hydrophobicity, ionizability, and solvent accessibility surface (SAS) properties.

The binding affinity refers to the degree of reversible contact between two or more molecules (Kastritis and Bonvin, 2012). In this context, it is seen that all the ligands exhibit negative free energy, suggesting the potential for spontaneous binding in the absence of external energy. Stronger binding between ligands and the receptor protein is indicated by higher negative values of binding affinity. The primary determinant in enhancing the binding

affinity between ligands and receptors is the presence of robust hydrogen bonding (Terefe and Ghosh, 2022; Uzzaman and Mahmud, 2020). Conversely, the phenomenon of interaction among two to three ligands at a shared receptor binding site is typically characterized by a competitive ligand binding model which is mean two ligands possess the ability to effectively bind to the identical receptor site (Salahudeen and Nishtala, 2017).

Table 1. The absorption, distribution, metabolism, excretion, and toxicity properties of cucurbitanes, karounidiols, and momordicin

Property	Model Name	Predicted Value			Unit
		Cucurbitane	Karounidiol	Momordicin	
Absorption	Water solubility	-5.668	-6.186	-6.374	log mol/L
	Caco2 permeability	1.258	1.176	1.159	log Papp in 10^{-6} cm/s
	Intestinal absorption	96.297	93.526	94.964	% Absorbed
Distribution	VDss (human)	-0.164	0.293	0.213	log L/kg
	BBB permeability	0.975	-0.002	-0.142	log BB
	CNS permeability	-0.785	-2.495	-2.605	log PS
Metabolism	CYP2D6 substrate	No	No	No	Yes/No
	CYP3A4 substrate	Yes	Yes	Yes	Yes/No
	CYP2D6 inhibitor	No	No	No	Yes/No
	CYP3A4 inhibitor	No	No	No	Yes/No
Excretion	Total Clearance	0.320	0.054	0.184	log mL/min/kg
	Renal OCT2 substrate	No	No	No	Yes/No

Furthermore, the protein-ligand complex was visualized through molecular docking, yielding a two-dimensional structure that illustrates the nature of the interaction between the protein and the bioactive compounds. In addition, findings were yielded in the form of amino acid residues that engaged in interactions with the ligands (Figure 5). The identification of these specific amino acid residues plays a crucial role in determining the character of chemical interactions between the ligand and the protein. Additionally, the existence of these amino acid residues also influences the specific chemical interactions that take place inside the protein-ligand complex. The

visualization results were then confirmed with a one-to-one comparison between the potent compounds and the drug control, suggesting that they occupied the same binding cavity. Those providing us an insight that these compounds could have a comparable effect on the PPARG activity and its cascade compared to the well-known drug control. The fact that all of them are thought to have agonist effect, instead of antagonist, also supported by their binding site residues, which do not intertwine with the active binding site of the DNA-binding domain (Kroker and Bruning, 2015). This specific binding site has also been reported to interact with other PPARG-agonists belonging to the thiazolidinediones family, including rosiglitazone (Nolte *et al*., 1998).

Structurally, PPARG consists of an activation domain, a DNA-binding domain, a hinge region, and a ligand-dependent ligand-binding domain. The later, located in the C-terminal region of the protein, play a critical role in protein activation as nuclear receptors, which change the protein conformation into an activated state, particularly in the activation domain, which is vital to coactivator recruitment (Gampe *et al*., 2000; Tontonoz and Spiegelman, 2008). However, the key interaction that could drive this kind of conformational change lies in the TZD's head group, which is a thiazolidinedione ring, with certain residues in the LBD. Other dynamic or structural studies are needed to confirm if this effect also happens with different functional groups (Thangavel *et al*., 2017).

The visualization results of docking provided various indicators of the physical and chemical properties of protein-ligand complexes. These indicators encompass aromatic content, hydrogen bonding, interpolated charge, hydrophobicity, ionizability, and structure-activity relationship (Figure 6). The findings indicate that a comparable trend is observed in the bioactive compounds derived from bitter melon compared to the drug control. Based on all parameters employed in this study, this finding suggests that the three chemicals derived from bitter melon exhibit similar physical and chemical characteristics in comparison to the drug control.

Regarding biological systems, the wide range of functionalization of amino acid residues plays a pivotal role in how protein structures react to their environment, particularly in terms of ligand interactions. These interactions are achieved through precise control of side chain positioning and the extended backbone structure (Yan *et al*., 2020). To a greater extent, hydrogen bond plays an important role in drug discovery and development, as it has a

significant impact on chemical and biological processes. Hydrogen bonding occurs when small molecules engage with other molecules, proteins, or membranes. Hydrogen bonding influences important drug-like features such as target affinity and oral availability (Ghiandoni and Caldeweyher, 2023). Furthermore, non-covalent interactions, including van der Waals interactions, are responsible for DNA and protein activity, pharmacological action mechanisms, and liquid and solid water characteristics. Nonetheless, non-covalent interactions are crucial in establishing polymorphism, compressibility, and solubility (Tantardini *et al*., 2020).

In addition, a thorough examination and assessment of the pharmacokinetics of the potential compounds discovered in bitter melon, including several variables such as absorption, distribution, metabolism, excretion, and toxicity, is commonly referred to as ADMET (Table 1). A viable drug candidate should have positive ADMET properties at therapeutic levels while having sufficient activity against the selected biological pathway or protein. The passage of an oral drug across the intestinal epithelial barrier, which controls the rate and extent of human absorption and ultimately impacts its bioavailability, presents a significant challenge. Therefore, Caco-2 and intestinal absorption were employed to evaluate absorption characteristics. Approximately 90% of oxidative metabolic processes are mediated by CYP enzymes, specifically isoforms 1A2, 2C9, 2C19, 2D6, and 3A4. OCT2 initially secretes many cationic drugs, and inhibitors of this enzyme may alter the accumulation of drugs in the kidney, potentially leading to nephrotoxicity. Finally, hepatotoxicity evaluation was one of the key endpoints addressed in the toxicity assessment (Flores-Holguín *et al*., 2021; Guan *et al*., 2018).

The SwissADME analysis reveals that the compounds this study propose have attractive drug-like characteristics. They all have a high intestinal absorption rate, indicating that they could be used orally. In terms of distribution, cucurbitane is projected to easily diffuse to the blood-brain barrier, whereas the others diffuse with reduced permeability, as evidenced by the logBB and logPS values (Carpenter *et al*., 2014; Tuz-Zohura *et al*., 2023). Notably, all had low VDss values, suggesting a minimal potential to cause renal failure and dehydration (Tuz-Zohura *et al*., 2023). Additionally, these compounds are predicted to have comparable cytochrome P450 metabolism patterns. All of them are projected to be metabolized by CYP3A4 and generally act as non-inhibitors of P450, indicating that they will not interfere with the biotransformation of the molecule metabolized by the cytochrome (Srivastava *et al*., 2022). The excretion characteristics, which indicate hepatic consent and

renal clearance, revealed that curcubatine has the highest excretion properties, while the others remained favorable. The toxicity analysis reveals that every compound has an LD50 value greater than 2 mol/kg, indicating a decreased acute toxicity potential (Tuz-Zohura *et al*., 2023). However, karunidol is thought to be the sole compound that impairs liver function. This should be considered as additional study is undertaken to confirm these predictions.

4. Conclusion and Recommendation

Cucurbitanes, karounidiols, and momordicin have shown promising molecular docking results, drug-like qualities, and advantageous pharmacokinetic features. Compared to a pharmacological control, these compounds' potential as T2DM treatment candidates is supported by their better affinity and similar binding site interactions with the PPARG protein. These results highlight the therapeutic value of chemicals derived from bitter melon in regulating PPARG activity, which may aid in generating new antidiabetic medications. Although these findings are promising, it is essential to recognize a few caveats. The study mainly uses *in silico* approaches, which, while predictive, need to be validated by *in vitro* and *in vivo* tests to verify the drugs' safety and biological activity. More research is needed to understand their dynamic behavior and structural changes upon interaction with the PPARG protein to strengthen the evidence for their therapeutic potential. Furthermore, even with the encouraging ADMET evaluation showing good absorption, metabolism, distribution, and excretion characteristics, the possible toxicity of these substances, especially their impact on liver function, remains a serious concern. To validate their safety for therapeutic usage, extensive toxicological investigations are necessary, including targeted studies on the hepatotoxicity profile of karounidiol. To get these molecules closer to clinical development, it will be essential to address these constraints through thorough experimental validation.

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6. References

Alam, F., Islam, M.A., Mohamed, M., Ahmad, I., Kamal, M.A., Donnelly, R., Idris, I., & Gan, S.H. (2019). Efficacy and safety of pioglitazone monotherapy in type 2 diabetes mellitus: A systematic review and meta-analysis of randomised controlled trials. Scientific Reports, 9(1), 5389. https://doi.org/10.1038/s41598-019-41854-2

Bellou, V., Belbasis, L., Tzoulaki, I., & Evangelou, E. (2018). Risk factors for type 2 diabetes mellitus: An exposure-wide umbrella review of meta-analyses. PLoS One, 13(3), e0194127. https://doi.org/10.1371/journal.pone.0194127

Carpenter, T.S., Kirshner, D.A., Lau, E.Y., Wong, S.E., Nilmeier, J.P., & Lightstone, F.C. (2014). A method to predict blood-brain barrier permeability of drug-like compounds using molecular dynamics simulations. Biophysical Journal, 107(3), 630–641. https://doi.org/10.1016/j.bpj.2014.06.024

Cataldi, S., Costa, V., Ciccodicola, A., & Aprile, M. (2021). PPARγ and diabetes: Beyond the genome and towards personalized medicine. Current Diabetes Reports, 21(6), 18. https://doi.org/10.1007/s11892-021-01385-5

Çiçek, S.S. (2022). *Momordica charantia* L.—Diabetes-related bioactivities, quality control, and safety considerations. Frontiers in Pharmacology, 13, 904643. https://doi.org/10.3389/fphar.2022.904643

Coudert, E., Gehant, S., de Castro, E., Pozzato, M., Baratin, D., Neto, T., Sigrist, C.J. A., Redaschi, N., Bridge, A., & UniProt Consortium. (2023). Annotation of biologically relevant ligands in UniProtKB using ChEBI. Bioinformatics, 39(1), btac793. https://doi.org/10.1093/bioinformatics/btac793

Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific Reports, 7, 42717. https://doi.org/10.1038/srep42717

Dallakyan, S., & Olson, A.J. (2015). Small-molecule library screening by docking with PyRx. Methods in Molecular Biology, 1263, 243–250. https://doi.org/10.1007/978-1-4939-2269-7_19

Dandawate, P.R., Subramaniam, D., Padhye, S.B., & Anant, S. (2016). Bitter melon: A panacea for inflammation and cancer. Chinese Journal of Natural Medicines, 14(2), 81–100. https://doi.org/10.1016/s1875-5364(16)60002-x

DasNandy, A., Patil, V.S., Hegde, H.V., Harish, D.R., & Roy, S. (2022). Elucidating type 2 diabetes mellitus risk factor by promoting lipid metabolism with gymnemagenin: An *in vitro* and *in silico* approach. Frontiers in Pharmacology, 13, 1074342. https://doi.org/10.3389/fphar.2022.1074342

Flores-Holguín, N., Frau, J., & Glossman-Mitnik, D. (2021). In silico pharmacokinetics, ADMET study and conceptual DFT analysis of two plant cyclopeptides isolated from Rosaceae as a computational peptidology approach. Frontiers in Chemistry, 9, 708364. https://doi.org/10.3389/fchem.2021.708364

Frkic, R.L., Richter, K., & Bruning, J.B. (2021). The therapeutic potential of inhibiting PPARγ phosphorylation to treat type 2 diabetes. Journal of Biological Chemistry, 297(3), 101030. https://doi.org/10.1016/j.jbc.2021.101030

Gampe, R.T. Jr., Montana, V.G., Lambert, M.H., Wisely, G.B., Milburn, M.V., & Xu, H.E. (2000). Structural basis for autorepression of retinoid X receptor by tetramer formation and the AF-2 helix. Genes & Development, 14(17), 2229–2241. https://doi.org/10.1101/gad.802300

Ghiandoni, G.M., & Caldeweyher, E. (2023). Fast calculation of hydrogen-bond strengths and free energy of hydration of small molecules. Scientific Reports, 13(1), 4143. https://doi.org/10.1038/s41598-023-30089-x

Guan, L., Yang, H., Cai, Y., Sun, L., Di, P., Li, W., Liu, G., & Tang, Y. (2018). ADMET-score – a comprehensive scoring function for evaluation of chemical drug-likeness. MedChemComm, 10(1), 148–157. https://doi.org/10.1039/c8md00472b

Gupta, D., Kono, T., & Evans-Molina, C. (2010). The role of peroxisome proliferator-activated receptor γ in pancreatic β cell function and survival: Therapeutic implications for the treatment of type 2 diabetes mellitus. Diabetes, Obesity and Metabolism, 12(12), 1036–1047. https://doi.org/10.1111/j.1463-1326.2010.01299.x

Hidayatullah, A., Putra, W.E., Sustiprijatno, S., Permatasari, G.W., Salma, W.O., Widiastuti, D., Susanto, H., Muchtaromah, B., … & Arizona, A.S. (2021). *In silico* targeting DENV2's prefusion envelope protein by several natural products' bioactive compounds. Chiang Mai University Journal of Natural Sciences, 20(3), 1–20. https://doi.org/10.12982/CMUJNS.2021.059

Han, J.H., Tuan, N.Q., Park, M.H., Quan, K.T., Oh, J., Heo, K.S., Na, M., & Myung, C.S. (2018). Cucurbitane triterpenoids from the fruits of *Momordica charantia* improve insulin sensitivity and glucose homeostasis in streptozotocin-induced diabetic mice. Molecular Nutrition & Food Research, 62(7), e1700769. https://doi.org/10.1002/mnfr.201700769

Hernandez-Quiles, M., Broekema, M.F., & Kalkhoven, E. (2021). PPARγ in metabolism, immunity, and cancer: Unified and diverse mechanisms of action. Frontiers in Endocrinology (Lausanne), 12, 624112. https://doi.org/10.3389/fendo.2021.624112

Ipsen, E.Ø., Madsen, K.S., Chi, Y., Pedersen-Bjergaard, U., Richter, B., Metzendorf, M.I., & Hemmingsen, B. (2020). Pioglitazone for prevention or delay of type 2 diabetes mellitus and its associated complications in people at risk for the development of type 2 diabetes mellitus. Cochrane Database of Systematic Reviews, 11(11), CD013516. https://doi.org/10.1002/14651858.cd013516.pub2

Ismail, L., Materwala, H., & Al Kaabi, J. (2021). Association of risk factors with type 2 diabetes: A systematic review. Computational and Structural Biotechnology Journal, 19, 1759–1785. https://doi.org/10.1016/j.csbj.2021.03.003

Janani, C., & Ranjitha Kumari, B.D. (2015). PPAR gamma gene—a review. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 9(1), 46–50. https://doi.org/10.1016/j.dsx.2014.09.015

Joseph, B., & Jini, D. (2013). Antidiabetic effects of *Momordica charantia* (bitter melon) and its medicinal potency. Asian Pacific Journal of Tropical Disease, 3(2), 93–102. https://doi.org/10.1016/S2222-1808(13)60052-3

Kanehisa, M., Furumichi, M., Tanabe, M., Sato, Y., & Morishima, K. (2017). KEGG: New perspectives on genomes, pathways, diseases and drugs. Nucleic Acids Research, 45(D1), D353–D361. https://doi.org/10.1093/nar/gkw1092

Kastritis, P.L., & Bonvin, A.M. (2012). On the binding affinity of macromolecular interactions: Daring to ask why proteins interact. Journal of the Royal Society Interface, 10(79), 20120835. https://doi.org/10.1098/rsif.2012.0835

Khan, M.A.B., Hashim, M.J., King, J.K., Govender, R.D., Mustafa, H., & Al Kaabi, J. (2020). Epidemiology of type 2 diabetes – global burden of disease and forecasted trends. Journal of Epidemiology and Global Health, 10(1), 107–111. https://doi.org/10.2991/jegh.k.191028.001

Kim, S., Chen, J., Cheng, T., Gindulyte, A., He, J., He, S., Li, Q., Shoemaker, B.A., … & Bolton, E.E. (2025). PubChem 2025 update. Nucleic Acids Research, 53(D1), D1516–D1525. https://doi.org/10.1093/nar/gkae1059

Kim, S.K., Jung, J., Jung, J.H., Yoon, N., Kang, S.S., Roh, G.S., & Hahm, J.R. (2020). Hypoglycemic efficacy and safety of *Momordica charantia* (bitter melon) in patients with type 2 diabetes mellitus. Complementary Therapies in Medicine, 52, 102524. https://doi.org/10.1016/j.ctim.2020.102524

Kotwas, A., Karakiewicz, B., Zabielska, P., Wieder-Huszla, S., & Jurczak, A. (2021). Epidemiological factors for type 2 diabetes mellitus: Evidence from the Global Burden of Disease. Archives of Public Health, 79(1), 110. https://doi.org/10.1186/s13690-021-00632-1

Kroker, A.J., & Bruning, J.B. (2015). Review of the structural and dynamic mechanisms of PPARγ partial agonism. PPAR Research, 2015, 816856. https://doi.org/10.1155/2015/816856

Kulkarni, P., Lohidasan, S., & Mahadik, K. (2021). Isolation, characterisation and investigation of *in vitro* antidiabetic and antioxidant activity of phytoconstituents from fruit of *Momordica charantia* Linn. Natural Product Research, 35(6), 1035–1037. https://doi.org/10.1080/14786419.2019.1613400

Nolte, R.T., Wisely, G.B., Westin, S., Cobb, J.E., Lambert, M.H., Kurokawa, R., Rosenfeld, M.G., Willson, T.M., Glass, C.K., & Milburn, M.V. (1998). Ligand binding and co-activator assembly of the peroxisome proliferator-activated receptor-gamma. Nature, 395(6698), 137–143. https://doi.org/10.1038/25931

Olokoba, A.B., Obateru, O.A., & Olokoba, L.B. (2012). Type 2 diabetes mellitus: A review of current trends. Oman Medical Journal, 27(4), 269–273. https://doi.org/10.5001/omj.2012.68

Padhi, S., Nayak, A.K., & Behera, A. (2020). Type II diabetes mellitus: A review on recent drug based therapeutics. Biomedicine & Pharmacotherapy, 131, 110708. https://doi.org/10.1016/j.biopha.2020.110708

Pires, D.E., Blundell, T.L., & Ascher, D.B. (2015). pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. Journal of Medicinal Chemistry, 58(9), 4066–4072. https://doi.org/10.1021/acs.jmedchem.5b00104

Salahudeen, M.S., & Nishtala, P.S. (2017). An overview of pharmacodynamic modelling, ligand-binding approach and its application in clinical practice. Saudi Pharmaceutical Journal, 25(2), 165–175. https://doi.org/10.1016/j.jsps.2016.07.002

Srivastava, V., Yadav, A., & Sarkar, P. (2022). Molecular docking and ADMET study of bioactive compounds of *Glycyrrhiza glabra* against main protease of SARS-CoV2. Materials Today: Proceedings, 49(8), 2999–3007. https://doi.org/10.1016/j.matpr.2020.10.055

Sun, K., Ding, M., Fu, C., Li, P., Li, T., Fang, L., Xu, J., & Zhao, Y. (2023). Effects of dietary wild bitter melon (*Momordica charantia* var. abbreviate Ser.) extract on glucose and lipid metabolism in HFD/STZ-induced type 2 diabetic rats. Journal of Ethnopharmacology, 306, 116154. https://doi.org/10.1016/j.jep.2023.116154

Sur, S., & Ray, R.B. (2020). Bitter melon (*Momordica charantia*), a nutraceutical approach for cancer prevention and therapy. Cancers (Basel), 12(8), 2064. https://doi.org/10.3390/cancers12082064

Tantardini, C., Michalchuk, A.A.L., Samtsevich, A., Rota, C., & Kvashnin, A.G. (2020). The volumetric source function: Looking inside van der Waals interactions. Scientific Reports, 10(1), 7816. https://doi.org/10.1038/s41598-020-64261-4

Terefe, E.M., & Ghosh, A. (2022). Molecular docking, validation, dynamics simulations, and pharmacokinetic prediction of phytochemicals isolated from *Croton dichogamus* against the HIV-1 reverse transcriptase. Bioinformatics and Biology Insights, 16, 11779322221125605. https://doi.org/10.1177/11779322221125605

Thangavel, N., Al Bratty, M., Akhtar Javed, S., Ahsan, W., & Alhazmi, H.A. (2017). Targeting peroxisome proliferator-activated receptors using thiazolidinediones: Strategy for design of novel antidiabetic drugs. International Journal of Medicinal Chemistry, 2017, 1069718. https://doi.org/10.1155/2017/1069718

Tontonoz, P., & Spiegelman, B.M. (2008). Fat and beyond: The diverse biology of PPARgamma. Annual Review of Biochemistry, 77, 289–312. https://doi.org/10.1146/annurev.biochem.77.061307.091829

Tripathy, B., Sahoo, N., & Sahoo, S.K. (2021). Trends in diabetes care with special emphasis to medicinal plants: Advancement and treatment. Biocatalysis and Agricultural Biotechnology, 33, 102014. https://doi.org/10.1016/j.bcab.2021.102014

Tuz-Zohura, F., Shawon, A.R.M., Hasan, M.M., Aeyas, A., Chowdhury, F.I., & Khandaker, M.U. (2023). *In-silico* approach to designing effective antiviral drugs against SARS-CoV-2 and SARS-CoV-1 from reported phytochemicals: A quality improvement study. Annals of Medicine and Surgery (London), 85(7), 3446–3460. https://doi.org/10.1097/ms9.0000000000000839

Uzzaman, M., & Mahmud, T. (2020). Structural modification of aspirin to design a new potential cyclooxygenase (COX-2) inhibitors. *In Silico* Pharmacology, 8(1), 1. https://doi.org/10.1007/s40203-020-0053-0

Wang, Q., Imam, M.U., Yida, Z., & Wang, F. (2017). Peroxisome proliferator-activated receptor gamma (PPARγ) as a target for concurrent management of diabetes and obesity-related cancer. Current Pharmaceutical Design, 23(25), 3677–3688. https://doi.org/10.2174/1381612823666170704125104

Waterhouse, A.M., Studer, G., Robin, X., Bienert, S., Tauriello, G., & Schwede, T. (2024). The structure assessment web server: for proteins, complexes and more. Nucleic Acids Research, 52(W1), W318–W323. https://doi.org/10.1093/nar/gkae270

Yan, Y., Carrington, E. J., Pétuya, R., Whitehead, G.F.S., Verma, A., Hylton, R.K., Tang, C.C., Berry, N.G., … & Rosseinsky, M.J. (2020). Amino acid residues determine the response of flexible metal-organic frameworks to guests. Journal of the American Chemical Society, 142(35), 14903–14913. https://doi.org/10.1021/jacs.0c03853