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RESEARCH ARTICLE

Virtual screening of metabolites from mulberry (*Morus alba* L.) leaves as anti-hyperglycemic agents through molecular docking against multiple targets

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Abstract

Background: Mulberry (*Morus alba* L.) leaves have been widely studied as an anti-hyperglycemic agent. However, the mechanism of action and metabolites responsible for their anti-hyperglycemic activity are not yet known. **Objective:** This research aims to virtually screen active compounds from mulberry leaves using the molecular docking method against multi-targets related to hyperglycemia activity. **Method:** A total of 157 metabolites from mulberry leaves were made into 10 conformers and docked by using PLANTS against 12 different targets. Three best compounds for each target were then filtered, analyzed based on Lipinski's rule of five, and plotted into a BOILED-Egg diagram to analyze their oral bioavailability. **Result:** Sixteen compounds dominated the top ranking of docking scores against 12 different targets. Sanggenol M is one of the most promising compounds that are capable of scoring a high ranker in 7 different targets: α-glucosidase, dipeptidyl peptidase-4, free fatty acid receptors-1, glycogen phosphorylase, glucagon receptor, ATP-sensitive potassium channel, and AMP-activated protein kinase. However, Lipinski's rule of five and BOILED-Egg diagram analysis predicted that Sanggenol M has poor oral bioavailability. **Conclusion:** Sanggenol M has a good potential to be developed into an antihyperglycemic agent and further development needs to be done to increase its oral bioavailability.

Introduction

Over the past years, diabetes has remained a significant health concern in Indonesia. As stated by the International Diabetes Federation (IDF), Indonesia is the fifth highest country globally regarding the estimated number of individuals with undiagnosed diabetes (Novida *et al*., 2023). Research indicates that the incidence of diabetes mellitus rose from 8.5% in 2018 to 11.7% in 2023, as determined by blood sugar assessments (Ministry of Health Republic of Indonesia, 2023). The increasing prevalence of diabetes has sparked a heightened interest in natural treatments, particularly *Morus alba* leaves, which have shown promising antihyperglycemic effects. Morus alba leaves have been studied for their prospective use as antihyperglycemic agents, highlighting their effectiveness in inhibiting enzymes related to carbohydrate digestion, such as α-amylase and α-glucosidase (Han *et al*., 2020; Silva *et al*., 2021).

Studies have revealed that M. *alba* leaves possess flavonoids, alkaloids, and other phytochemicals that demonstrate hypoglycemic effects (Morales Ramos *et al*., 2021; Yang *et al*., 2023). Numerous studies on metabolic profiling have been undertaken to identify the active compounds present in Morus alba leaves. These compounds include cyanidin-3-glucoside, cyanidin-3-rutinoside, quercetin-glucoside, kaempferol-glucoside, and sanggenon. (Aelenei *et al*., 2019; Park *et al*., 2021; Jan *et al*., 2022; Salem *et al*., 2022; Zhou *et al*., 2022).

The numerous outcomes derived from metabolite profiling studies have not been sufficiently complemented with isolation and bioactive testing to confirm which compounds are responsible for the

antihyperglycemic effects of M. *alba* leaves. This problem can be addressed by using a virtual screening approach to discover bioactive compounds that are integral to the antihyperglycemic activity of Morus alba leaves. This can be done by utilising suitable methods, for instance, molecular docking studies by using PLANTS. Thus, research related to virtual screening was performed in order to investigate compounds responsible for the antihyperglycemic activity of Morus alba leaves. PLANTS is used in this study due to its capability to differentiate active and inactive ligands in the virtual screening approach (Korb *et al*., 2006).

Methods

Material

A total of 157 compounds from recent studies were used as study samples (Aelenei *et al*., 2019; Park *et al*., 2021; Jan *et al*., 2022; Salem *et al*., 2022; Zhou *et al*., 2022). A total of 12 different targets related to hyperglycemic activity were used in this study, including α-glucosidase (PDB ID: 2QMJ) (Sim *et al*., 2008), α-amylase (PDB ID: 4GQR) (Williams *et al*., 2012), dipeptidyl peptidase-4/DPP-4 (PDB ID: 2RGU) (Eckhardt *et al*., 2007), free fatty acid receptors-1/FFAR-1 (PDB ID: 4PHU) (Srivastava *et al*., 2014), peroxisome proliferator-activated receptor-γ/PPARγ (PDB ID: 6TSG) (Gellrich *et al*., 2020), Sodium glucose co-transporter-2/SGLT-2 (PDB ID: 8HDH) (Hiraizumi *et al*., 2024), aldose reductase (PDB ID: 3DN5) (Eisenmann *et al*., 2009), glycogen phosphorylase (PDB ID: 3DDS), fructose-1,6-biphosphatase/FBPase (PDB ID: 6LW2) (Thomson *et al*., 2009), glucagon receptor/GcGr (PDB ID: 7S15) (Griffith *et al*., 2022), ATP-sensitive potassium channel/AsPc (PDB ID: 5YW7) (Wu *et al*., 2018), and AMP-activated protein kinase/AMPK (PDB ID: 7MYJ) (Ovens *et al*., 2022). The software used included Windows 10 Pro and the Linux Ubuntu 22.4 operating system, MarvinView, PyMol, and LIGPLOT. The hardware used in this study is an ASUS ROG laptop with specifications of an Intel (R) Core (TM) i7-6700HQ CPU @ 2.60GHz processor and 8 GB of RAM memory.

Preparation of ligands and target receptors

The ligands were prepared by obtaining their 3D structures from the PubChem database. The ligands were then protonated at pH 7.4 and were subsequently made into 10 different conformations. A total of 12 different targets related to hyperglycemic activity were downloaded from the Protein Data Bank (PDB). The receptors were subjected to preprocessing to eliminate any water molecules and heteroatoms that could potentially hinder the docking process. The binding site was delineated based on established active sites.

Docking protocol

Docking simulations were performed using the PLANTS (Korb *et al*., 2006). The parameters were optimised based on the PLANTS user manual, which includes defining the search space around the specified binding site to a distance of 5 Å from the ligand's coordinates (Korb *et al*., 2006).

Validation of docking results

To ensure the validity of the docking results, a redocking procedure was executed with the native ligand of the target protein. The Root Mean Square Deviation (RMSD) was determined to measure the accuracy of the docking poses. In addition, the docking scores were analysed in comparison to known inhibitors.

Analysis of docking interactions

The analysis of the interactions between the ligands and the target protein was conducted utilising visualisation software, including PyMOL and LIGPLOT. Significant interactions, such as hydrogen bonds and hydrophobic contacts, were characterised to clarify the binding mechanism of the ligands. Additionally, the docking results were examined to determine the most promising candidates for further evaluation.

Analysis of physicochemical properties

The structure of the best three compounds on each target was converted into SMILE and was copied into the SwissADME web tool (http://www.swissadme.ch) to assess their physicochemical properties. The compounds were then analysed based on their placement in the BOILED-Egg (Brain Or IntestinaL EstimateD permeation) diagram (Daina & Zoete, 2016), the Topological Polar Surface Area (TPSA) value, and compliance with Lipinski's rule of five.

Results

Validation of docking results

Validation of target receptor (n=3) yielded an RMSD value of 1.85 ± 0.10, 1.57 ± 0.09, 1.46 ± 0.45, 1.84 ± 0.15, 1.01 ± 0.01, 0.60 ± 0.00, 1.03 ± 0.06, 2.15 ± 0.05, 1.64 ± 0.00, 1.23 ± 0.27, 2.16 ± 0.07, and 1.58 ± 0.11 respectively for α-glucosidase, α-amylase, DPP-4, FFAR-1, PPARγ, SGLT-2, aldose reductase, glycogen phosphorylase, FBPase, GcGr, AsPc, and AMP-activated

protein kinase/AMPK. The majority of targets yield an RMSD value < 2^0A, confirming the reliability of the docking method (Miladiyah *et al*., 2017). However, there are two targets that yielded RMSD values between 2.0-2.2^{0}A. These values are considered to be acceptable according to several studies (Sándor *et al*., 2010; Ramírez & Caballero, 2018).

Docking results

The result from the docking study was presented in Table I. The reference ligand present in each crystal structure served as a control for the molecular docking analyses. It was observed that none of the test compounds surpassed the docking values of the control across the four different receptors or enzyme targets: FFAR-1, SGLT-2, Glycogen phosphorylase, and Glucagon receptor. Alternatively, one compound exhibited a higher docking score than the control for FBPase, while three compounds did so for α-glucosidase. There are at least six targets associated with antihyperglycemic activity that demonstrate high docking scores to numerous metabolites derived from M. *alba* leaves. Specifically, α-amylase, DPP-4, PPARγ, aldose reductase, ATP-sensitive potassium channel, and AMPK targets showed robust binding to over 25 active metabolites from M. *alba* leaves, indicating a high antihyperglycemic potential of the leaves. Among 157 metabolites tested, several metabolites exhibited excellent docking scores. Sanggenol M stands out as the most promising compound for delivering antihyperglycemic effects due to its strong binding to multiple targets. Sanggenol M demonstrated superior docking values when compared to various clinically approved medications that served as reference and control ligands in this study. Notably, these include acarbose (targeting α-glucosidase), linagliptin (acting on DPP IV), and glibenclamide (interacting with the ATP-sensitive potassium channel). Other metabolites with promising antihyperglycemic properties are sanggenol P, morusimic acid E, ramumorin B, and delphinidin Malonylglucoside. Collectively, these five compounds are capable of binding effectively to at least three different targets linked to antihyperglycemic activity (see Table I).

Table I: **Result of virtual screening through molecular docking studies against 12 different targets related to antihyperglycemic activity. The best 3 compounds were filtered out of 157 compounds tested. The docking study was performed using 10 conformers of each compound and replicated 3 times.**

Target	Control (Docking score)	#	Best 3 compounds	Docking score	Important amino acid interaction
Alpha-glucosidase (2QMJ)	Acarbose (-112.24 ± 0.57)	3	Sanggenon T	-113.74 ± 0.51	(D327, D203), F450, F575
			Quercetin-O-sucroside	-113.71 ± 1.21	(D327, D443, R526), F450, F575
			Sanggenol M	-113.20 ± 0.70	(Q603, E404, T205), F450
Alpha-Amylase (4GQR)	Myricetin (-81.52 ± 0.11)	87	Ramumorin B	-110.43 ± 0.32	(H229), W59, Y62, E223
			Morusimic acid E	-109.13 ± 2.05	(D197, E223), W59, Y62
			Isosanggenol P	-105.57 ± 0.15	(R195), W59, Y62
dipeptidly peptidase-4 (DPP-4) (2RGU)	Linagliptin (-97.83 ± 1.29)	51	Sanggenol M	-131.25 ± 0.57	(Y547, P550, H740), Y547, Y662, Y631
			Ramumorin B	-121.31 ± 0.49	(Y662, H740), Y662, Y547, W629, Y631
			Delphinidin malonylglucoside	-120.51 ± 1.78	(Q206, N710), Y662, Y547, W629, Y631
free fatty acid receptors 1 (FFAR1) (4PHU)	Fasiglifam (-122.41 ± 0.99)	0	Sanggenol M	-120.49 ± 0.08	(A146, D152), W174, F142, F87
			Rosmarinic acid	-116.96 ± 0.20	(R258), F142, F87
			Mulberroside E	-114.56 ± 1.72	(Y240, Q172), F142, F87
peroxisome proliferator activated receptor-γ (PPARγ) (6TSG)	Tetrac (-83.33 ± 0.03)	78	Delphinidin malonylglucoside	-115.14 ± 0.14	(Y327, H323), F363, F287, Y327
			1,3-dicaffeoylquinic acid	-114.04 ± 0.06	(G284), F282, Y327
			Sanggenol P	-113.55 ± 0.45	Y327, Y363
sodium glucose co-transporter-2 (SGLT2) (8HDH)	Canaglifozin (-138.59 ± 0.01)	0	1,3-dicaffeoylquinic acid	-123.23 ± 0.09	(Q457, T87, H80), F98
			Sanggenol P	-121.00 ± 0.18	(K154), F98, Y526, Y290
			Dehydroanggenol P	-120.73 ± 0.07	(W291), Y290
aldose reductase (3DN5)	IDD 594 (-94.57 ± 0.01)	54	Isosanggenol G	-131.30 ± 0.02	(L300, S159), Y209, Y48, F122, F115
			Dihydrokuwanon S	-130.25 ± 0.12	(S159), Y209, Y48, F122, F115
			Dehydroanggenol P	-126.45 ± 0.06	Y209, Y48, F122, F115
	Anthranilimide	0	Morusimic acid E	-113.84 ± 0.50	(R193), Y83, Y157, F311

Target	Control (Docking score)	#	Best 3 compounds	Docking score	Important amino acid interaction
glycogen phosphorylase (GP) (3DDS)	(114.18 ± 0.22)		Sanggenol M	-113.76 ± 0.03	(R193), Y83, Y157
			Guangsangon C	-111.46 ± 0.18	(G28, Q32), F16
fructose-1,6-bisphosphatase (FBPase) (6LW2)	N-arylsulfonyl-4-arylamino-indole-2-carboxamide (-111.26 ± 0.21)	1	Morusimic acid E	-114.39 ± 2.41	(K112, T27, Q20), Y113, F16
			Delphinidin malonylglucoside	-107.89 ± 1.32	(Q20, G21), F16
			Rosmarinic acid	-107.34 ± 0.56	(M18), V17
glucagon receptor (GCGr) - GLP 1 (7S15)	Danuglipron -141.96 ± 0.52	0	Hydroxyisokuwanon G	-131.09 ± 0.48	(R380, K197), W33, F230, F381, F385
			Sanggenol M	-128.72 ± 0.14	(R380, K197, L217), W33, F381
			Sanggenol P	-124.57 ± 1.34	(K202, L217, Q221), W33, F381
ATP-sensitive potassium channel (5YW7)	Glibenclamide (-100.69 ± 1.50)	33	Sanggenol M	-124.69 ± 0.56	(Y377, S1238), F433, F591
			Sanggenon T	-119.45 ± 0.02	(Y377, R1246), F433, F591
			Hydroxyisokuwanon G	-114.21 ± 0.67	(R1246), Y377, F433
AMP-activated protein kinase (AMPK)	ZQV (-90.89 ± 0.03)	29	Sanggenol M	-103.36 ± 0.39	(N48), K31, K29
			Mulberroside E	-100.45 ± 0.30	(N48, D88), K29, F27, F90
			Ramumorin B	-98.75 ± 0.81	(N48), F27, V24

*Amino acid residue (under bracket) indicating hydrogen bonds, no bracket indicating hydrophobic interaction
Number of compound(s) with docking score higher than control

Analysis of docking interactions

The analysis of the interaction between Sanggenol M and various targets reveals that Sanggenol M interacts with multiple amino acid residues. For example, as illustrated in Table I and Figure 1, Sanggenol M engages in hydrogen bonding with R380, K197, and L217, alongside hydrophobic interactions with W33 and F381. Analysis through 3D visualisation with PyMOL (see Figure 1b) reveals that sanggenol M has a similar binding pose compared to danuglipron, which serves as the reference ligand in the glucagon receptor (7S15). Both Sanggenol M and Danuglipron are capable of interacting with amino acid residues W-33 and R380, which are considered to be important amino acid residues in ligand-protein interactions, as shown by the crystal structure (Griffith *et al*., 2022).

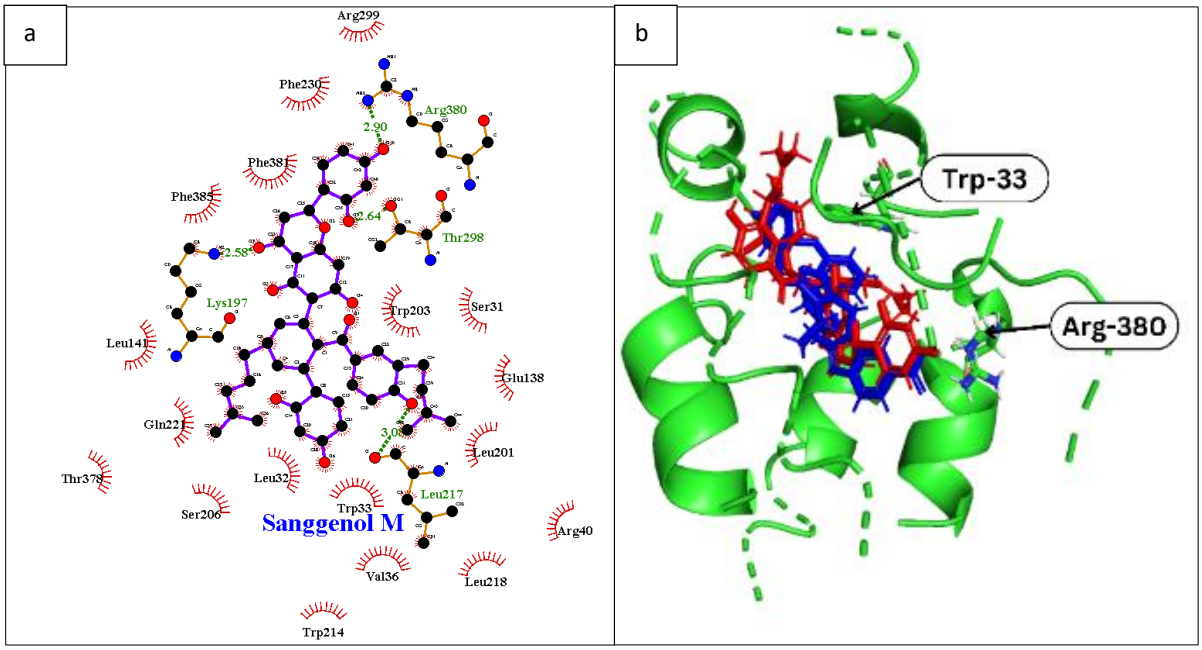

Figure 1: Visualisation of interaction between Sanggenol M and Glucagon Receptor (PDB ID:7S15). Visualisation was performed using LIGPLOT (a) and Pymol (b). Sanggenol M is depicted as the red stick and the reference ligand (Danuglipron) is depicted as the blue stick

Analysis of physicochemical properties

Based on the compliance of Lipinski's rule of five, only six compounds from the highest docking scores complied with the rule: Sanggenon T, Ramumorin B, Rosmarinic acid, Mulberroside E, Dihydrokuwanon S, and Guangsangon C. High-rank compounds such as Sanggenol M, Morusimic acid E, Sanggenol P, and Delphinidin malonylglucoside each violate at least one of Lipinski's rules of five. Notably, only Ramumorin B exhibits a high docking value on three different targets while also adhering to Lipinski's rule of five.

Alternatively, out of 16 metabolites, only molecules 13 (Isosanggenol G) and 14 (Dihydrokuwanone S) are found to be orally bioavailable according to the Boiled EGG diagram (see Figure 2). The red colouration of Dihydrokuwanone S indicates its inability to interact with the P-glycoprotein substrate in the brain, which contributes to a prolonged action duration for this particular compound. In contrast, metabolites with high docking values, including Sanggenol M (Molecule 3), Morusimic acid E (Molecule 4), Sanggenol P (Molecule 11), and Delphinidin malonylglucoside (Molecule 7), do not appear in the white area of the Boiled EGG plot, reflecting their poor oral bioavailability.

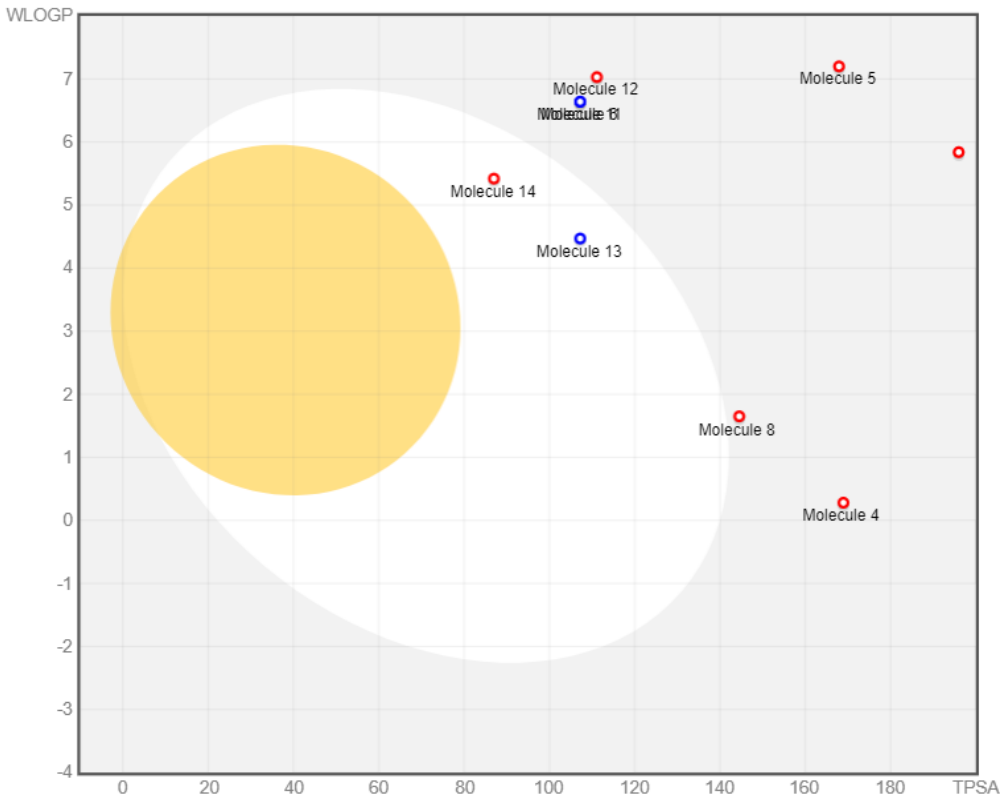

Figure 2: BoiLeD-EGG diagram of 16 high-ranker compounds from Morus alba leaves. Compounds in the white egg region have good oral absorption, whereas compounds in the egg yolk have good CNS penetration.

Discussion

Sanggenol M demonstrated the most potential to be developed as an antihyperglycemic agent in this study. To date, there is insufficient evidence concerning the in vitro and in vivo activities of Sanggenol M as an antihyperglycemic agent. However, other types of Sanggenol have been reported to play a critical role in increasing insulin sensitivity and reducing insulin resistance (Ko *et al*., 2021; Ren *et al*., 2022). Additionally, the similarity in the interaction patterns with the target between Sanggenol M compared to the reference ligand within the crystal structure of the target and the high docking score of this compound suggests that it may actually possess significant potential to be developed as an antihyperglycemic agent.

Sangenol M, despite its high in silico potential, suffers from inadequate oral bioavailability. This is due to

Sanggenol M containing multiple polar hydroxyl groups, which contribute to its high total polar surface area, resulting in increased solubility in polar solvents and lowering its absorption. To enhance the bioavailability of Sangenol M, further research is necessary, including approaches such as structural simplification and the alteration of polar groups. Additionally, innovations in pharmaceutical technology, such as nanoparticle-based drug delivery systems, could be explored to enhance the oral bioavailability of Sangenol M.

Conclusion

Virtual screening protocol confirmed that Sanggenol M has good potential to be developed into an anti-hyperglycemic agent, as shown by its robust docking score against seven different targets. However, Sanggenol M is predicted to have poor oral bioavailability based on Lipinski's rule of five and the Boiled egg plot analysis. Further development is necessary to increase its oral bioavailability.

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References

Aelenei, P., Luca, S. V., Horhogea, C. E., Rimbu, C. M., Dimitriu, G., Macovei, I., Silion, M., Aprotosoaie, A. C., & Miron, A. (2019). *Morus alba* leaf extract: Metabolite profiling and interactions with antibiotics against *Staphylococcus* spp. including MRSA. *Phytochemistry Letters*, **31**(April), 217–224. https://doi.org/10.1016/j.phytol.2019.04.006

Daina, A., & Zoete, V. (2016). A BOILED-Egg to predict gastrointestinal absorption and brain penetration of small molecules. *ChemMedChem*, **11**(11), 1117–1121. https://doi.org/10.1002/cmdc.201600182

Eckhardt, M., Langkopf, E., Mark, M., Tadayyon, M., Thomas, L., Nar, H., Pfrengle, W., Guth, B., Lotz, R., Sieger, P., Fuchs, H., & Himmelsbach, F. (2007). 8-(3-(R)-aminopiperidin-1-yl)-7-but-2-ynyl-3-methyl-1-(4-methyl-quinazolin- 2-ylmethyl)-3,7-dihydropurine-2,6-dione (BI 1356), a highly potent, selective, long-acting, and orally bioavailable DPP-4 inhibitor for the treatment of type 2 diabetes. *Journal of Medicinal Chemistry*, **50**(26), 6450–6453. https://doi.org/10.1021/jm701280z

Eisenmann, M., Steuber, H., Zentgraf, M., Altenkämper, M., Ortmann, R., Perruchon, J., Klebe, G., & Schlitzer, M. (2009). Structure-based optimization of aldose reductase inhibitors originating from virtual screening. *ChemMedChem*, **4**(5), 809–819. https://doi.org/10.1002/cmdc.200800410

Gellrich, L., Heitel, P., Heering, J., …. & Merk, D. (2020). L-Thyroxin and the nonclassical thyroid hormone TETRAC are potent activators of PPARÎ. *Journal of Medicinal Chemistry*, **63**(13), 6727–6740. https://doi.org/10.1021/acs.jmedchem.9b02150

Griffith, D. A., Edmonds, D. J., Fortin, J. P., … & Tess, D. A. (2022). A small-molecule oral agonist of the human glucagon-like peptide-1 receptor. *Journal of Medicinal Chemistry*, **65**(12), 8208–8226. https://doi.org/10.1021/acs.jmedchem.1c01856

Han, X., Song, C., Feng, X., Wang, Y., Meng, T., Li, S., Bai, Y., Du, B., & Sun, Q. (2020). Isolation and hypoglycemic effects of water extracts from mulberry leaves in Northeast China. *Food and Function*, **11**(4), 3112–3125. https://doi.org/10.1039/d0fo00012d

Hiraizumi, M., Akashi, T., Murasaki, K., Kishida, H., Kumanomidou, T., Torimoto, N., Nureki, O., & Miyaguchi, I. (2024). Transport and inhibition mechanism of the human SGLT2–MAP17 glucose transporter. *Nature Structural and Molecular Biology*, **31**(1), 159–169. https://doi.org/10.1038/s41594-023-01134-0

Jan, B., Zahiruddin, S., Basist, P., Irfan, M., Abass, S., & Ahamad, S. (2022). Metabolomic profiling and identification of antioxidant and antidiabetic compounds from leaves of different varieties of *Morus alba* Linn grown in Kashmir. *ACS Omega*, **7**(28), 24317–24328. https://doi.org/10.1021/acsomega.2c01623

Ministry of Health Republic of Indonesia. (2023). *Indonesian Health Survey (SKI) in numbers*. https://repository.badankebijakan.kemkes.go.id/id/eprint/5539vv

Ko, W., Liu, Z., Kim, K., Dong, L., Lee, H., Kim, N. Y., Lee, D., & Woo, E. (2021). Kuwanon t and sanggenon a isolated from *Morus alba* exert anti-inflammatory effects by regulating nf-κb and ho-1/nrf2 signaling pathways in bv2 and raw264.7 cells. *Molecules*, **26**(24), 7642. https://doi.org/10.3390/molecules26247642vv

Korb, O., Stützle, T., & Exner, T. E. (2006). PLANTS: Application of ant colony optimization to structure-based drug design. *Lecture Notes in Computer Science (Including Subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*, **4150**, 247–258. https://doi.org/10.1007/11839088_22

Miladiyah, I., Jumina, J., Haryana, S. M., & Mustofa, M. (2017). In silico molecular docking of xanthone derivatives as cyclooxygenase-2 inhibitor agents. *International Journal of Pharmacy and Pharmaceutical Sciences*, **9**(3), 98. https://doi.org/10.22159/ijpps.2017v9i3.15382

Morales Ramos, J. G., Esteves Pairazamán, A. T., Mocarro Willis, M. E. S., Collantes Santisteban, S., & Caldas Herrera, E. (2021). Medicinal properties of *Morus alba* for the control

of type 2 diabetes mellitus: A systematic review. *F1000Research*, **10**, 1022. https://doi.org/10.12688/f1000research.55573.1

Novida, H., Soelistyo, S. A., Cahyani, C., Siagian, N., Hadi, U., & Pranoto, A. (2023). Factors associated with disease severity of COVID-19 in patients with type 2 diabetes mellitus. *Biomedical Reports*, **18**(1), 8. https://doi.org/10.3892/br.2022.1590

Ovens, A. J., Gee, Y. S., Ling, N. X. Y., … & Langendorf, C. G. (2022). Structure-function analysis of the AMPK activator SC4 and identification of a potent pan AMPK activator. *Biochemical Journal*, **479**(11), 1181–1204. https://doi.org/10.1042/BCJ20220067vv

Park, C. H., Park, Y. E., Yeo, H. J., Yoon, J. S., Park, S-Y., Kim, J. K., & Park, S. U. (2021). Comparative analysis of secondary metabolites and metabolic profiling between diploid and tetraploid *Morus alba* L. *Journal of Agricultural and Food Chemistry*, **69**(4), 1300–1307. https://doi.org/10.1021/acs.jafc.0c06863

Ramírez, D., & Caballero, J. (2018). Is it reliable to take the molecular docking top scoring position as the best solution without considering available structural data? *Molecules*, **23**(5), 1038. https://doi.org/10.3390/molecules23051038

Ren, X., Sun, Y., Guo, Q., Liu, H., Jiang, H., He, X., Li, X., Shi, X., Xiu, Z., & Dong, Y. (2022). Ameliorating effect of the total flavonoids of *Morus nigra* L. on prediabetic mice based on regulation of inflammation and insulin sensitization. *Journal of Agricultural and Food Chemistry*, **70**(39), 12484–12501. https://doi.org/10.1021/acs.jafc.2c04970

Salem, M. A., Salama, M. M., Ezzat, S. M., & Hashem, Y. A. (2022). Comparative metabolite profiling of four polyphenol rich Morus leaves extracts in relation to their antibiofilm activity against *Enterococcus faecalis*. *Scientific Reports*, **12**(1), 20168. https://doi.org/10.1038/s41598-022-24382-4

Sándor, M., Kiss, R., & Keseru, G. M. (2010). Virtual fragment docking by glide: A validation study on 190 protein-fragment complexes. *Journal of Chemical Information and Modeling*, **50**(6), 1165–1172. https://doi.org/10.1021/ci1000407

Silva, D. H. A. da, Barbosa, H. de M., Beltrão, R. L. de A., Silva, C. de F. O., Moura, C. A., Castro, R. N., … Lira, E. C. (2021). Hexane fraction from Brazilian *Morus nigra* leaves improved oral carbohydrate tolerance and inhibits α-amylase and α-glucosidase activities in diabetic mice. *Natural Product Research*, **35**(22), 4785–4788. https://doi.org/10.1080/14786419.2020.1723087

Sim, L., Quezada-Calvillo, R., Sterchi, E. E., Nichols, B. L., & Rose, D. R. (2008). Human intestinal maltase-glucoamylase: Crystal structure of the N-terminal catalytic subunit and basis of inhibition and substrate specificity. *Journal of Molecular Biology*, **375**(3), 782–792. https://doi.org/10.1016/j.jmb.2007.10.069

Srivastava, A., Yano, J., Hirozane, Y., Kefala, G., Gruswitz, F., Snell, G., Lane, W., Ivetac, A., Aertgeerts, K., Nguyen, J., Jennings, A., & Okada, K. (2014). High-resolution structure of the human GPR40 receptor bound to allosteric agonist TAK-875. *Nature*, **513**(7516), 124–127. https://doi.org/10.1038/nature13494

Thomson, S. A., Banker, P., Bickett, D. M., Boucheron, J. A., Carter, H. L., Clancy, D. C., Cooper, J. P., Dickerson, S. H., Garrido, D. M., Nolte, R. T., Peat, A. J., Sheckler, L. R., Sparks, S. M., Tavares, F. X., Wang, L., Wang, T. Y., & Weiel, J. E. (2009). Anthranilimide based glycogen phosphorylase inhibitors for the treatment of type 2 diabetes. Part 3: X-ray crystallographic characterization, core and urea optimization and in vivo efficacy. *Bioorganic and Medicinal Chemistry Letters*, **19**(4), 1177–1182. https://doi.org/10.1016/j.bmcl.2008.12.085v

Williams, L. K., Li, C., Withers, S. G., & Brayer, G. D. (2012). Order and disorder: Differential structural impacts of myricetin and ethyl caffeate on human amylase, an antidiabetic target. *Journal of Medicinal Chemistry*, **55**(22), 10177–10186. https://doi.org/10.1021/jm301273u

Wu, J. X., Ding, D., Wang, M., Kang, Y., Zeng, X., & Chen, L. (2018). Ligand binding and conformational changes of SUR1 subunit in pancreatic ATP-sensitive potassium channels. *Protein and Cell*, **9**(6), 553–567. https://doi.org/10.1007/s13238-018-0530-y

Yang, L., Zhao, J., Fan, S., Liao, J., Chen, Y., & Wang, Y. (2023). Effect of frost on the different metabolites of two mulberry (*Morus nigra* L. and *Morus alba* L.) leaves. *Molecules*, **28**(12), 4718. https://doi.org/10.3390/molecules28124718

Zhou, Q. Y. J., Liao, X., Kuang, H. M., Li, J. Y., & Zhang, S. H. (2022). LC-MS metabolite profiling and the hypoglycemic activity of *Morus alba* L. extracts. *Molecules*, **27**(17), 5360. https://doi.org/10.3390/molecules27175360v