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POTENTIAL OF SECONDARY METABOLITE OF *Jasminum sambac* AS DIABETES MELLITUS MEDICINE BY MOLECULAR DOCKING METHOD

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Abstract

Diabetes mellitus (DM) is a non-infectious disease with a high prevalence in Indonesia. The study explored the potential of the phytochemical component of *Jasminum sambac* to treat DM. The potential of *Jasminum. sambac* as a candidate for DM therapy was demonstrated through *in silico* analysis using several databases and computer-aided drug discovery tools. The bioactive compounds analyzed were obtained from KnapSACK databases. The screening was done to find compounds by estimating bioavailability prediction on the SwissADME. The SwissTargetPrediction tool connects predictions of target proteins from compounds that pass screening to various probable proteins and utilizes the String-DB to show the network between target proteins and associated diseases. After finding the target protein, continue docking the chemical compound to the target protein using PyRx with AutoDock 4.2.6. The search results for the compounds in *Jasminum sambac* found nine active substances with good bioavailability. The results of the pharmacological network found four proteins associated with *Jasminum sambac*, among others: GCGR, GSK3B, PPARA, and PPARG. In addition, in-depth analysis was done on the molecular interactions that occurred, how these compounds bind the enzymes found in humans, and their potential to be inhibitors of diabetes mellitus. Proteins such as GCGR, GSK3B, PPARA, and PPARG bind to the compounds found in *Jasminum sambac*, such as (-)-alpha-cadinol and linalyl benzoate. Thus, it can be said that Jasminum sambac can have anti-diabetic activity.

Keywords: *Diabetes Melitus; Jasminum sambac; in silico; molecular docking*,

Background

Diabetes mellitus (DM), also known in Indonesia as "kencing manis" is a long-lasting condition that can last a lifetime. An elevated blood sugar or hyperglycemic condition caused by a decrease in insulin in the pancreas is a sign of metabolic disorders that causes diabetes to develop (Lestari, Zulkarnain and Sijid, 2021). Indonesia is the fourth most diabetic country, behind the United States, China, and India. Moreover, the number of people suffering from DM in Indonesia is expected to increase by 2-3 times by 2030 compared to 2000 (Dwi Hardika *et al.*, 2016).
Developing new drugs, therapies, and appropriate lifestyle management strategies is usually the focus of research on diabetes treatment (Harreiter and Roden, 2019). *Jasminum sambac*, better known as the Arabian jasmine, is one of the plants well-known by the Indonesian people (Jamil and Alghifari, 2023). In Indonesia, this plant is used as a mixture in some beverages. However, these flowers have a high aesthetic and aromatic value (Khan *et al.*, 2021). The claim that *J. sambac* has the potential to treat diabetes mellitus has not been supported by scientific research.
This study focuses on how medicinal plants can cure or reduce the effects of diabetes mellitus. The trial uses the in silico method to test a drug candidate protein bound to a compound that will be produced as a drug that directly treats diabetes mellitus (Gaál and Balogh, 2019). *In silico* research is a type of research that uses computer simulation and specific software to predict interactions between drugs and pathogens in the body (Sutan Mulia Ananda and Gemah Nuripah, 2022). Network pharmacology, which combines pharmacologists and databases, gains momentum thanks to system biology, bioinformatics, and high throughput histology. Based on the low efficacy of highly selective single-target drugs, it combines biological networks with polypharmacology (Aihaiti *et al.*, 2021). Molecular docking is in silico-based technique that is popular in drug discovery, allows the identification of new compounds that have therapeutic benefits, projecting ligan-target interactions at the molecular level or describing the relationship between structures and activities (SAR) (Pinzi and Rastelli, 2019). This study aims to discover how developing new drugs, therapies, and appropriate lifestyle management strategies is usually the focus of research on diabetes treatment using *J. sambac.*

Methods

Tools

This study was conducted using several online databases and software. Online database used were KNApSAcK (https://www.knapsackfamily.com/KNApSAcK), Pubchem (https://pubchem.ncbi.nlm.nih.gov/), SwissADME (http://www.swissadme.ch/), SwissTargetPrediction (http://www.swisstargetprediction.ch/), string-DB (https://string-db.org/), Protein Data Bank (https://www.rcsb.org/), and Proteins.Plus (https://proteins.plus/). The software applications used were Avogadro, BIOVIA Discovery Studio Visualizer version 4.5, and PyRx version 0.8.

Research Methods

The secondary metabolite of *J. sambac* was obtained from KNApSAcK, and PubChem was used to see the compound configuration and SMILES code (Kim, 2021). The SMILES code was added to SwissADME using the Boiled-Egg method to predict bioavailability and SwissTargetPrediction to predict proteins which can interact with secondary metabolite compounds (Lena *et al.*, 2023). Next, the list of emerging proteins inserted into StringDB enriches proteins by looking for predictions of proteins associated with the immune system (Ge *et al.*, 2020).

Result and Discussion

Network Pharmacology Analysis

The secondary metabolite of *J. sambac* was obtained from the KNApSAcK online database. There are 18 compounds obtained **Table** 1. SwissADME made bioavailability predictions using the Boiled-Egg method to identify highly bioavailable compounds **Figure** 1. The physicochemical space that is most likely to absorb the brain is the yellow region, also known as egg yellow, while the white region represents the physical chemical space of the molecules most likely to be absorbed by the intestinal tract (Daina and Zoete, 2016). Nine compounds have good bioavailability **Table 2**.

Table 1. A list secondary metabolite of *J. sambac* obtained from KNApSAcK online database

No.	Name of Compound	Compound Code
1	Betulinic-acid	Molecule 1
2	(Z,Z,Z)-3,6,9-Dodecatrien-1-ol	Molecule 2
3	(Z)-Jasmone	Molecule 3
4	Linalool	Molecule 4
5	E-beta-farnesene	Molecule 5
6	Nerolidol	Molecule 6
7	(+)-8-Hydroxypinoresinol	Molecule 7
8	Oleoside	Molecule 8
9	(-)-alpha-Cadinol	Molecule 9
10	Benzenemethanol	Molecule 10
11	Benzaldehyde	Molecule 11
12	Oleoside 11-methyl ester	Molecule 12
13	Linalyl benzoate	Molecule 13
14	3-Methylcyclopentene	Molecule 14
15	Sambacolignoside	Molecule 15
16	Phenethyl primeveroside	Molecule 16
17	Sambacin	Molecule 17
18	2,2,3,4-Tetramethylpentane	Molecule 18

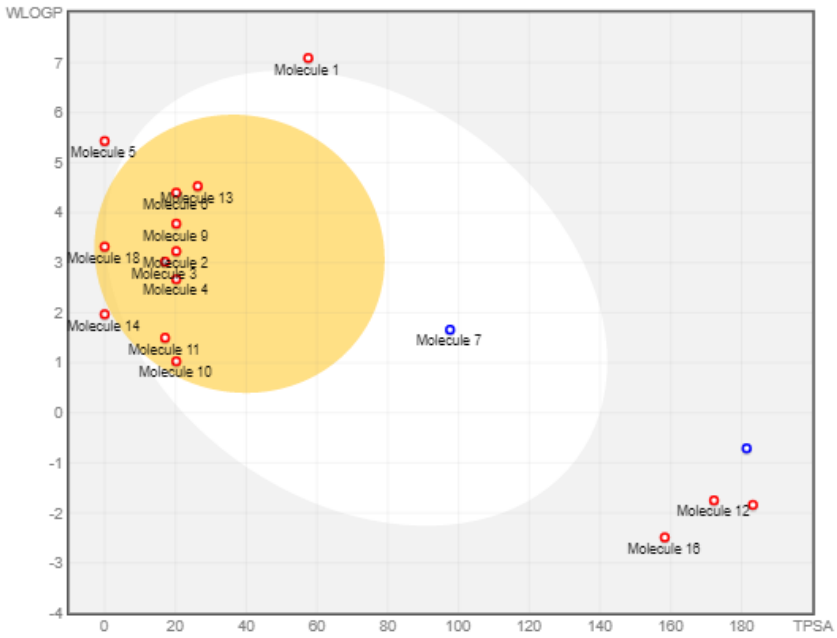

Figure 1. Bioavailability prediction of the secondary metabolite of *J. sambac* using BOILED-Egg

Table 2. List of selected compounds that have high oral bioavailability using the Boiled-Egg method.

Prediction of Bioavailibility	Compound Code
High Bioavailability	Molecule 2, Molecule 3, Molecule 4, Molecule 6, Molecule 9, Molecule 10, Molecule 11, Molecule 13, Molecule 18
Low Bioavailability	Molecule 1, Molecule 5, Molecule 7, Molecule 8, Molecule 12, Molecule 14, Molecule 15, Molecule 16, Molecule 17

Of the nine secondary metabolite compounds that pass Boiled-Egg, further analysis using SwissTargetPrediction was used to predict the interaction of the compound with the protein targeted in the research (Daina, Michielin and Zoete, 2019). There are 226 proteins that are predicted to have interaction with compounds. All known and predicted inter-protein relationships, including physical and functional interactions, are included in the String-DB database (Szklarczyk *et al.*, 2021). From network pharmacology analysis, it found four proteins that are closely related to diabetes mellitus, such as PPARG, PPARA, GCGR, and GSK3B.

PPARA is a protein that has the ability to control the expression of insulin response proteins in liver cells that can control hyperglycaemia through regulation of 110 lipid metabolism (Azeem and Hakeem, 2023). GCGR is the G-protein-paired receptor (GPCR) most commonly found in island cells and liver cells. After glucagon binds to GCGR specifically, glucagons promote the breakdown of glycogen in the liver and increase blood glucose levels, which can stimulate the release of insulin so that it plays an important role in glucose metabolism and the formation of diabetes (Jia *et al.*, 2022). GSK3B is an important glycogen synthesis enzyme involved in blood glucose regulation, insulin deficiency, and IR. In addition, GSK3B acts as a substrate of a negatively regulated insulin signal pathway, which, if genetically reduced, will enhance the homeostasis of insulin-resistant glycose (Liu *et al.*, 2020). Of the four proteins taken by one of the

proteins, PPARG, no research has confirmed the association of the protein as an antidiabetic. These four are proteins that will be subsequently validated by the molecular docking method.

Table 3. The list code of proteins resulting from the secondary metabolite of *J. sambac* using SwissTargetPrediction

Proteins Code
ABHD6, ABL1, ACE, ACHE, ACP1, ADA, ADH1A, ADH1B, ADH1C, ADRA1A, ADRA2A, ADRA2B, ADRA2C, AKR1B10, AKR1C3, ALDH2, ALDH3A1, ALOX5, AR, ATP12A, AVPR1A, BACE1, BCHE, BRS3, C5AR1, CA1, CA12, CA2, CA3, CA4, CA9, CACNA1B, CASR, CCNB3, CDK1, CCNB1, CCNB2, CCR1, CCR5, CCR8, CD38, CD81, CDC25A, CDC25B, CDK1, CES2, CHEK1, CHRM1, CHRM2, CHRM3, CHRM4, CHRM5, CNR1, CNR2, CSF1R, CTSB, CTSH, CTSK, CTSL, CXCL8, CYP11B1, CYP11B2, CYP17A1, CYP19A1, CYP2C19, CYP2C9, CYP3A4, CYP51A1, DAO, DNMT3A, DRD2, DRD3, DRD4, EDNRA, EGFR, EIF2AK1, ELANE, EPHX1, EPHX2, ERN1, ESR1, ESR2, F2R, FABP3, FABP4, FABP5, FDFT1, FFAR1, FNTA, FNTB, G6PD, GABBR2, GABBR1, GABRA2, GABRB2, GABRG2, GCGR, GCK, GLI1, GLI2, GPBAR1, GPR88, GRM2, GRM5, GSK3B, GSR, HDAC1, HDAC6, HMGCR, HMOX1, HPGDS, HRH3, HRH4, HSD11B1, HSD11B2, HSD17B2, HSD17B3, HTR1A, HTR2A, HTR7, ICMT, IL6ST, IMPDH2, JAK1, JAK2, JAK3, KCNA3, KCNA5, KCNH2, KCNN4, KDR, KIT, LRRK2, LYPLA1, LYPLA2, MAOA, MAOB, MAPK14, MAPK8, MDM2, METAP1, MGLL, MPO, MTNR1A, MTNR1B, NPC1L1, NPY2R, NPY5R, NQO1, NR1H2, NR1H3, NR1I3, NR3C1, NR3C2, OPRD1, OPRK1, OPRL1, OPRM1, OXTR, P2RX7, PABPC1, PARP1, PDE10A, PDE2A, PDE4D, PDE7A, PER2, PGGT1B, PGGT1B, FNTA, PGR, PIN1, PLA2G1B, PLA2G2A, POLB, PPARA, PPARD, PPARG, PRCP, PREP, PRKCA, PRKCB, PRKCD, PRKCE, PRKCG, PRKCH, PRKCQ, PSEN2, PSENEN, NCSTN, APH1A, PSEN1, APH1B, PTAFR, PTGS1, PTGS2, PTPN1, PTPN11, PTPN2, PTPN6, PTPRF, PYGL, RAPGEF4, RASGRP1, RGS4, RORA, RORC, SCN5A, SCN9A, SERPINA6, SHBG, SIGMAR1, SIRT2, SLC10A2, SLC5A7, SLC6A2, SLC6A3, SLC6A4, SLC6A9, SOAT1, SQLE, SRD5A1, SRD5A2, SREBF2, TBXA2R, TBXAS1, TERT, TGFBR1, THRB, TRPA1, TRPM8, TRPV1, TRPV3, TSPO, TTL, TYK2, TYMS, UGT2B7

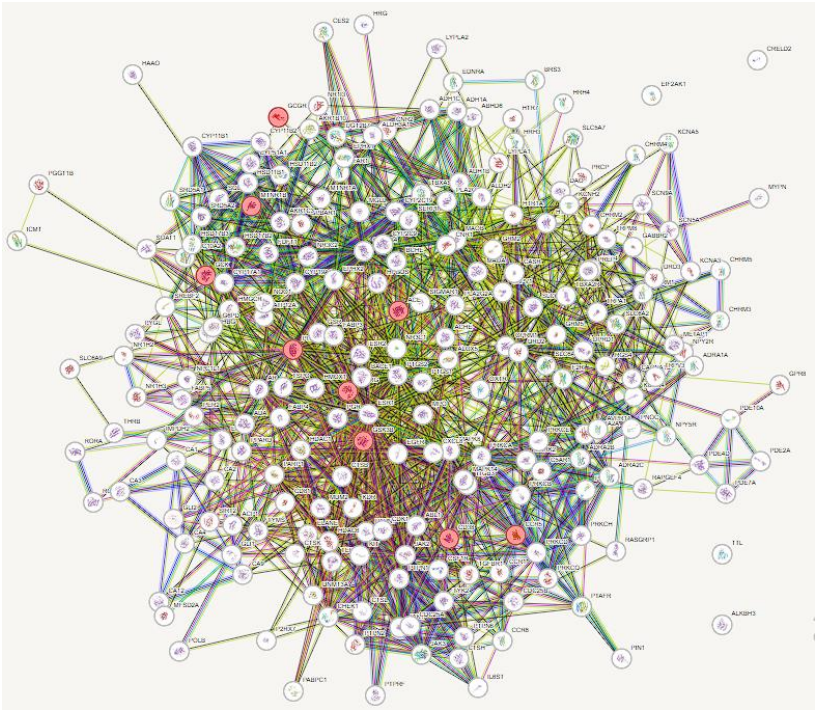

Figure 2. Network pharmacology prediction results using StringDB. The red color indicates a protein associated with diabetes mellitus.

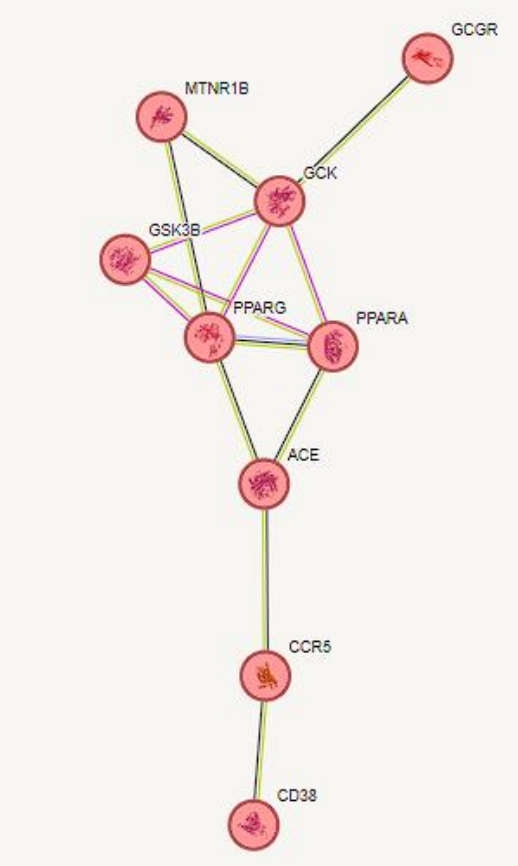

Figure 3. Proteins associated with diabetes mellitus with more specific relationship pathways

The PPARG gene encodes the PPAR-gamma protein, a transcription factor that controls genes required for lipid and glucose homeostasis. PPAR-gamma activation in adipocytes supports the correct and balanced secretion of adipocytokines such as adiponectin and leptin, which aid in mediating insulin action in peripheral tissues and maintaining insulin sensitivity (Jang *et al.*, 2023). While, in PPARA or PPAR-alpha, The creation of PPAR-alpha agonists has attracted a lot of attention, partly because of its possible benefits for maintaining lipid homeostasis. Triglyceride and VLDL levels decrease as a result of lipoprotein remodeling, which is facilitated by lipoprotein lipase activation (Nicholls and Uno, 2012). The human glucagon receptor (GCGR) is a seven transmembrane-spanning class B G protein-coupled receptor (GPCR) that plays an important role in glucose homeostasis and type 2 diabetes pathogenesis (Gao *et al.*, 2023). The human glucagon receptor (GCGR) is a seven transmembrane-spanning class B G protein-coupled receptor (GPCR) that plays an important role in glucose homeostasis and type 2 diabetes pathogenesis (Gao *et al.*, 2023). GSK-3 beta regulates glycogen metabolism by controlling glycogen synthesis, and it modulates mitochondrial permeability and cytochrome C release to regulate apoptosis. GSK-3beta also activates the transcription factor NF-B and is involved in a variety of biological processes such as embryonic development, cell differentiation, and insulin response (Lin *et al.*, 2020).

Molecular Docking Analysis

The molecular docking method is widely used in modern drug design by studying the conformation of ligands adopted in macromolecular target binding sites. This molecule docking technique also counts the free energy that binds ligands-receptors by looking at essential phenomena in the

process of intermolecular identification (Hui *et al.*, 2022). This method also calculates the free energy that binds the ligands-receptors by examining the critical phenomena involved in intermolecular identification (Mun *et al.*, 2022).

The four proteins that resulted from network pharmacology analysis: PPRA (PDB ID = 3KDT), PPARG (PDB ID = 8HUP), GCGR (PDB ID = 5XEZ), and GSK3B (PDB ID = 5F94), will be docked with nine compounds that pass Boiled-Egg. Based on the data obtained (Table 4), it is seen that the four ligands that have a role as comparators have a binding energy of -8.53 kcal/mol with PPARA, -7.49 kcal/mol with PPARG, 7 kcal/mol with GCGR, and -5.92 kcal per mol with GSK3B. The two compounds, Molecule 9 and Molecule 13 have lower energy binding and pKi compared to ligand from protein PPARG and GSK3B. The interaction between the compound and the target protein will be stronger when both are at the lowest energy conditions. Thus, the lower the energy of binding between the compound and the target protein, the stronger the interaction. The predictive value of the inhibition constant (pKi), in addition to the magnitude of the binding energy, also affects the strength of the interaction; the smaller the pKi value, the stronger the interactions (Muchlisin *et al.*, 2022).

Table 4. Results of docking compounds in Jasminum sambac plants with PPARG proteins, PPARA GCGR, and GSK3B

Compound Code	PPARG		PPARA		GCGR		GSK3B	
	Binding affinity kcal/mol	pKi	Binding affinity kcal/mol	pKi	Binding affinity kcal/mol	pKi	Binding affinity kcal/mol	pKi
Molecule 2	-5,91	46,86 µM	-4,63	404,7 µM	-4,43	8,87 µM	-3,91	1,35 mM
Molecule 3	-5,59	75,45 µM	-5,35	119,86 µM	-4,59	429,63 µM	-4,59	427,29 µM
Molecule 4	-5,37	86,09 µM	-5,11	178,43 µM	-3,82	1,6 mM	-4,32	677,99 µM
Molecule 6	-7,4	3,75 µM	-5,4	109,9 µM	-4,22	809,54 µM	-4,67	377,9 µM
Molecule 9	-7,78	1,97 µM	-6,5	17,17 µM	-6,89	17,17 µM	-6,33	22,93 µM
Molecule 10	-4,63	404,37 µM	-4,12	960,93 µM	-4,39	608,11 µM	-4,33	675,39 µM
Molecule 11	-4,42	575,36 µM	-4,28	724,69 µM	-4,77	318,97 µM	-3,95	1,27 mM
Molecule 13	-7,98	1,41 µM	-6,48	17,85 µM	-6,79	10,57 µM	-6.00	40 µM
Molecule 18	-4,77	318,7 µM	-4,24	775,19 µM	-4,68	372.00 µM	-3,57	2,4 mM
Ligand	-7,49	3,26 µM	-8,53	560,06 nM	+2.00e+007	-	-5,92	45,65 µM

The interaction can be seen from the binding and amino acid residues **Table 5**. It is possible to see from the comparative ligands and nine compounds found in *J. sambac* that there is one ligan that does not have amino acids residue in the protein GCGR, so the ligands can not be compared with another compound. If we look at the PPARG protein, there is one compound (molecule 10) that has the same hydrogen bond and hydrophobic interaction residue (Arg288) as the ligand. Molecule 2 and Molecule 13 have two similar hydrophobic interactions with ligand (Phe 264 and His266), and so are molecule 10 but with different residues (Phe266 and Arg 288). In the GSK3B protein, Molecule 3, Molecule 4, Molecule 6, and Molecule 9 also have similar hydrophobic interaction residue with comparator ligands (Leu130). However, PPRA and GCGR proteins do not have similar hydrogen bond and hydrophobic interaction between secondary metabolite compounds and ligands.

Table 5. Interaction of hydrogen binding and hydrophobic interaction of amino acid residues between secondary metabolite of *J. sambac* with 4 proteins (GCGR, GSK3B, PPARA, PPARG)

Compound Code	PPARG		PPARA		GCGR		GSK3B	
	Hydrogen Bonds	Hydrophobic Interactions	Hydrogen Bonds	Hydrophobic Interactions	Hydrogen Bonds	Hydrophobic Interactions	Hydrogen Bonds	Hydrophobic Interactions
Molecule 2	Lys265, Ser342	His266, Phe264	Phe273	Phe273	Lys349	Arg346	Glu97	Leu130, Met101
Molecule 3	Ser342	-	-	-	Lys349	Arg346	Leu130	Leu130
Molecule 4	Lys265, Ser342	Phe264	Phe351	Phe351, Ile272	Lys349, Thr353	-	Leu130	Leu130
Molecule 6	Lys265, Ser342	Gly284, His266, Ile281, Phe264	Phe273	Ile272, Phe273, Phe351	Thr353	Leu399, Lys349, Ser350	Glu97	Leu130, Val70
Molecule 9	-	-	Phe273	Ile272, Phe273, Val444	-	-	Leu130	Leu130, Phe67
Molecule 10	Arg288, Glu291	Arg288, Phe264, Phe287	Phe351	Ile272, Leu347, Phe272, Phe351	Arg346, Asn404, Lys405	Arg346	Glu137	Asp190, Leu189, Lys197
Molecule 11	His266	Ile281	-	-	Arg346, Lys405	-	Leu130, Phe67	Phe67, Val70, Val87
Molecule 13	Lys265, Ser342	His266, Phe264	-	-	Arg346, Lys405	Arg346, Asn404, Leu347, Lys349, Ser350	-	-
Molecule 18	-	-	Arg288, Phe264	Arg288, Gly284, His266, Ile281, Ile341, Phe264	-	-	-	-
Ligand	Arg288, Phe264	Arg288, Gly284, His266, Ile281, Ile341, Phe264	Thr279	Ile339	-	-	Arg111	Leu130

To determine a specific mechanism of action, an interaction between ligands and proteins is required. The analysis results suggest that the (-)-alpha-cadinol and linalyl benzoate indicate that these secondary metabolite compounds can be potential as antidiabetics activity.

Conclusion

The results of the research showed that two secondary metabolite compounds ((-)-alpha-cadinol and linalyl benzoate) in the plant of *Jasminum sambac* can be potential as antidiabetics activity when it have intercatin with GSK3B and PPARG.

References

Aihaiti, Y. *et al.* (2021) 'Therapeutic Effects of Naringin in Rheumatoid Arthritis: Network Pharmacology and Experimental Validation', *Frontiers in Pharmacology*, 12, p. 672054.

Available at: https://doi.org/10.3389/FPHAR.2021.672054/FULL.

Azeem, U. and Hakeem, K.R. (2023) 'Therapeutic mushrooms for diabetes mellitus: Current evidences and future scope', *Therapeutic Mushrooms for Diabetes Mellitus: Current Evidences and Future Scope*, pp. 1–289. Available at: https://doi.org/10.1201/9781003332046.

Daina, A., Michielin, O. and Zoete, V. (2019) 'SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules', *Nucleic Acids Research*, 47(W1), p. W357. Available at: https://doi.org/10.1093/NAR/GKZ382.

Daina, A. and Zoete, V. (2016) 'A BOILED-Egg To Predict Gastrointestinal Absorption and Brain Penetration of Small Molecules', pp. 1117–1121. Available at: https://doi.org/10.1002/cmdc.201600182.

Dwi Hardika, B. *et al.* (2016) 'Faktor-faktor yang berhubungan dengan kejadian Diabetes Melitus tipe II', *majority*, 16(2). Available at: https://juke.kedokteran.unila.ac.id/index.php/majority/article/view/1073 (Accessed: 30 October 2023).

Gaál, Z. and Balogh, I. (2019) 'Monogenic Forms of Diabetes Mellitus', *Experientia supplementum (2012)*, 111, pp. 385–416. Available at: https://doi.org/10.1007/978-3-030-25905-1_18.

Gao, J. *et al.* (2023) 'High glucose-induced glucagon resistance and membrane distribution of GCGR revealed by super-resolution imaging', *iScience*, 26(2). Available at: https://doi.org/10.1016/J.ISCI.2023.105967.

Ge, S.X. *et al.* (2020) 'ShinyGO: a graphical gene-set enrichment tool for animals and plants', *Bioinformatics (Oxford, England)*, 36(8), pp. 2628–2629. Available at: https://doi.org/10.1093/BIOINFORMATICS/BTZ931.

Harreiter, J. and Roden, M. (2019) '[Diabetes mellitus-Definition, classification, diagnosis, screening and prevention (Update 2019)]', *Wiener klinische Wochenschrift*, 131(Suppl 1), pp. 6–15. Available at: https://doi.org/10.1007/S00508-019-1450-4.

Hui, L.Y. *et al.* (2022) 'Multi-Targeted Molecular Docking and Drug-Likeness Evaluation of some Nitrogen Heterocyclic Compounds Targeting Proteins Involved in the Development of COVID-19', *Medicinal Chemistry*, 19(3), pp. 297–309. Available at: https://doi.org/10.2174/1573406418666220616110351.

Jamil, A.S. and Alghifari, M.R. (2023) 'Insight into Jasminum sambac Molecular Docking Interaction with GCK related to Diabetes Mellitus', *Indonesian Journal of Computational Biology (IJCB)*, 2(1), p. 40. Available at: https://doi.org/10.24198/ijcb.v2i1.45616.

Jang, E.J. *et al.* (2023) 'Correlation between PPARG Pro12Ala Polymorphism and Therapeutic Responses to Thiazolidinediones in Patients with Type 2 Diabetes: A Meta-Analysis', *Pharmaceutics*, 15(6). Available at: https://doi.org/10.3390/PHARMACEUTICS15061778/S1.

Jia, Y. *et al.* (2022) 'Role of Glucagon and Its Receptor in the Pathogenesis of Diabetes', *Frontiers in Endocrinology*, 13. Available at: https://doi.org/10.3389/FENDO.2022.928016.

Khan, I.A. *et al.* (2021) 'Jasminum sambac: A Potential Candidate for Drug Development to Cure Cardiovascular Ailments', *Molecules (Basel, Switzerland)*, 26(18). Available at: https://doi.org/10.3390/MOLECULES26185664.

Kim, S. (2021) 'Exploring Chemical Information in PubChem.', *Current protocols*, 1(8), p. e217. Available at: https://doi.org/10.1002/cpz1.217.

Lena, N. *et al.* (2023) 'Analisis Jejaring Farmakologi Tanaman Jati Belanda (Guazuma ulmifolia Lamk.) Sebagai Imunomodulator', *Journal of Islamic Pharmacy*, 8(1), pp. 1–6. Available at: https://doi.org/10.18860/jip.v8i1.20782.

Lestari, Zulkarnain and Sijid, S.A. (2021) 'Diabetes Melitus: Review Etiologi, Patofisiologi, Gejala, Penyebab, Cara Pemeriksaan, Cara Pengobatan dan Cara Pencegahan', *UIN Alauddin Makassar*, (November), pp. 237–241. Available at: http://journal.uin-alauddin.ac.id/index.php/psb.

Lin, J. *et al.* (2020) 'GSK-3β in DNA repair, apoptosis, and resistance of chemotherapy, radiotherapy of cancer', *Biochimica et biophysica acta. Molecular cell research*, 1867(5). Available at: https://doi.org/10.1016/J.BBAMCR.2020.118659.

Liu, Y. *et al.* (2020) 'LC-Q-TOF-MS Characterization of Polyphenols from White Bayberry Fruit and Its Antidiabetic Effect in KK-AyMice', *ACS Omega*, 5(28), pp. 17839–17849. Available at: https://doi.org/10.1021/ACSOMEGA.0C02759/SUPPL_FILE/AO0C02759_SI_001.PDF.

Muchlisin, M.A. *et al.* (2022) 'Prediksi Bioavaibilitas dan Interaksi Senyawa Metabolit Sekunder Buah Plum (Prunus domestica) Terhadap HMG-CoA Reduktase Secara in silico', *Journal of Pharmacopolium*, 5(1), pp. 1–8. Available at: https://doi.org/10.36465/jop.v5i1.875.

Mun, C.S. *et al.* (2022) 'Multi-targeted molecular docking, pharmacokinetics, and drug-likeness evaluation of coumarin based compounds targeting proteins involved in development of COVID-19', *Saudi journal of biological sciences*, 29(12). Available at: https://doi.org/10.1016/J.SJBS.2022.103458.

Nicholls, S.J. and Uno, K. (2012) 'Peroxisome proliferator-activated receptor (PPAR α/γ) agonists as a potential target to reduce cardiovascular risk in diabetes', *Diabetes and Vascular Disease Research*, 9(2), pp. 89–94. Available at: https://doi.org/10.1177/1479164112441477.

Pinzi, L. and Rastelli, G. (2019) 'Molecular Docking: Shifting Paradigms in Drug Discovery', *International journal of molecular sciences*, 20(18). Available at: https://doi.org/10.3390/IJMS20184331.

Sutan Mulia Ananda and Gemah Nuripah (2022) 'Uji Aktivitas Senyawa Aktif Daun Sirsak sebagai Kandidat Antidepresan dengan Pendekatan In silico', *Jurnal Riset Kedokteran*, pp. 135–172. Available at: https://doi.org/10.29313/jrk.vi.1552.

Szklarczyk, D. *et al.* (2021) 'The STRING database in 2021: Customizable protein-protein networks, and functional characterization of user-uploaded gene/measurement sets', *Nucleic Acids Research*, 49(D1), pp. D605–D612. Available at: https://doi.org/10.1093/nar/gkaa1074.