EasyChair Preprint

№ 10159

In-Silico Testing on the Activity of Flavonoids (Tamarixetin) as Natural Compounds in Reducing Blood Sugar Levels

Ulfah Widyastuti Arsal, Andi Ariyandy, Ika Yustisia and Sulfahri

May 15, 2023

In-Silico Testing On The Activity Of Flavonoids (Tamarixetin) As Natural Compounds In Reducing Blood Sugar Levels

A W Ulfah[1)], Ariyandy A[2)], Yustisia I[1),] Sulfahri[3)]

[1)]Biomedical Sciences, Postgraduate School, Hasanuddin University, Makassar, Indonesia
[2)]Department of Physiology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
[3)]Department of Biology, Faculty of Mathematics and Natural Sciences, Hasanuddin University, Makassar, Indonesia

Email: widyastutiulfah@gmail.com

Abstract

Chromolaena Odorata is a plant from the *Asteraceae* family that grows rapidly from tropical origin, this plant is declared to have many chemical compounds that have medical steads. This work aimed at evaluating chemical compounds Tamarixetin dan Kaempferide from *Chromolaena Odorata* for antidiabetic based on reverse docking studies. Structures of chemical constituents of *Chromolaena Odorata* (Tamarixetin) were collected from published literature. The water molecule and ligands were removed by using PyMOL v1.7.4.5 Software (Schrödinger). Molecular docking experiments were performed using the PyRx 0.8 software. Prediction and significant descriptors of Physicochemical Properties, Lipophilicity, Pharmacokinetics, and Druglikeness properties of the compounds were predicted using Swissadme. These findings that *Chromolaena Odorata* has better potential as an antidiabetic based on its binding affinity and intermolecular interactions. The binding affinity of Tamarixetin with Mitogen-activated protein kinase 1 is -7.3, while the binding affinity Mitogen-activated protein kinase 1 with the control compound metformin is -4,6. AMES Test showed that Tamarixetin is not carcinogenic. Druglikeness's prediction showed that Tamarixetin fulfills the rules of Lipinski, Ghose, Veber, Egan, and Muegge with a 0.55 Bioavailability Score.

1. Introduction

Diabetes mellitus is a disease characterized by hyperglycemia that involves various pathogenic processes including the destruction of the pancreatic β-cells with subsequent insulin insufficiency which causes insulin resistance (Howlader et al., 2021). Pancreatic beta cells (β-cells) produce the hormone insulin which enables the absorption of glucose into the cells to offer electricity and is likewise worried in lots of different functions (Tan et al., 2019). In 2014, 422 million people worldwide have been diagnosed with diabetes and contributing to nearly 5 million deaths globally (Jude et al., 2020).

Insulin resistance change glucose homeostasis and the accumulation of fat (Konermann, 2019). High fat has prompt brokenness in lipid digestion, high fat and sugar diet results in free fatty acid accumulation which might trigger the mitogen enacted protein kinase (MAPK) which might prompt insulin signaling pathway damage (Zhuo et al., 2018).

Chromolaena Odorata is a bush that past six decades, the plant has drawn in expanding consideration attributable to its ethnomedicinal use in many non-industrial nations particularly in Africa and Asia (Eze & Jayeoye, 2021). *Chromolaena Odorata* is one of the spices that has a place with Asteraceae, which act as a traditional medicinal plant. A few pieces of this plant are broadly used to treat a wound, consumes, skin contaminations just as to have anticancer, antidiabetic, hostile to hepatotoxic, mitigating, antimicrobial, and cell reinforcement properties (Zahara, 2019).

The leaves of *Chromolaena Odorata* have been accounted for to contain alkaloids, saponins, tannins, flavonols (tamarixetin and kaemferide), flavonones (eupatilin), chalcones, phenolic acids such as ferulic acid and protocatechuic acid. Tamar- ixetin and kaempferide have been known to be a strong enemy of oxidant,anti-provocative and against diabetic specialists (Onkaramurthy et al., 2013).

2. Materials and Method

2.1 Ligands Preparation

Structures of the chemical compound *Chromolaena Odorata* (Tamarixetin) were collected from published literature. Chemical 3D structure and SMILES of ligand (α-caesalpin) taken from PubChem compound database (https://pubchem.ncbi.nlm.nih.gov/) with number ID: CID 73823459 and Canonical Smile: COC1=C(C=C(C=C1)C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O)O. The two-dimensional (2D) and the three-dimensional (3D) chemical structures of the ligands were sketched using Avogadro and Discovery Studio and were saved in PDB format.

2.2 Target Selection

The protein potential objective possibility for docking was arranged utilizing 3 databanks, i.e: Pharmmapper (http://lilab.ecust.edu.cn), SuperPred (http://prediction.charite.de), and Swiss Target Forecast (www.swisstargetprediction.ch) and approve utilizing Uniport (https://www.uniprot.org). The protein that was gathered and approved with PDB (Protein Data Bank https:///www.rcsb.org/pdb) than proteins were arranged utilizing clean protein to eliminate the water particles from the design. The water molecule and ligands were taken out by utilizing PyMOL v1.7.4.5 Software (Schrödinger). In this review, the objective protein utilized was Mitogen-activated protein kinase with the 4ZZN code of PDB, because Mitogen-activated protein kinase is a compound as a protein that prompts insulin signaling pathway damage.

2.3 Molecular Docking

Molecular docking tests were performed utilizing the PyRx 0.8 programming. The converse docking process was done utilizing the Vina Wizard includes coordinated into PyRx 0.8 programming which response to the regular compound tamarixetin, the objective protein Mitogen-enacted protein kinase, and the control compound (metformin). Activator mixtures will be a positive control in the docking system.

2.4 Visualization of Molecule and Small Molecule Interaction

The interactions between ligands (tamarixetin) target protein (Mitogen-activated protein kinase), and known inhibitors of target protein (metformin) were visualized and analyzed using PyMol v1.7.4.5 Software (Schrödinger)

2.5 Compound's Properties and ADMET Predictions

Swissadme (http://www.swissadme.ch) and admetSAR (lmmd.ecust.edu.cn:8000) are used to predict the prediction and significant descriptors of Physicochemical Properties, Lipophilicity, Pharmacokinetics, and Druglikeness properties of the compounds.

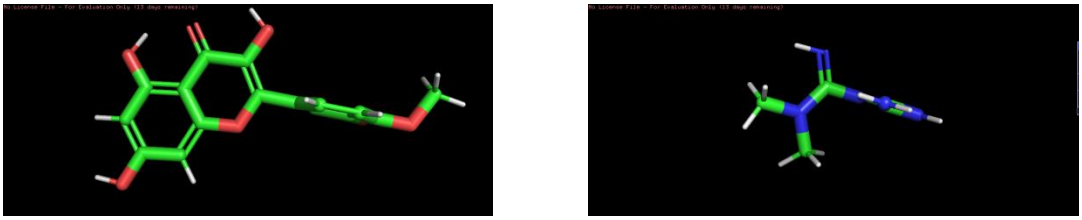
3. Result and Discussion

The leaves of *Chromolaena Odorata* have been reported to contain alkaloids, saponins, tannins, flavonols (tamarixetin and kaemferide), flavonones (eupatilin), chalcones, phenolic acids. Flavonoid (tamarixetin) is reported as the major chemical compound (Onkaramurthy et al., 2013).

Tamarixetin compounds are known to interact with protein Mitogen-activated protein kinase Based on Swiss target prediction. Mitogen-Activated Protein Kinases are evolutionary conserved serine-threonine protein kinases that are activated in response to extracellular stress stimuli (Sidarala & Kowluru, 2016). Mitogen-Activated Protein Kinases drive insulin resistances eventually displaying cell dysfunction, resulting in an inability to control glycemia, and type 2 diabetes (Roth Flach et al., 2016).

Structure of herbal compound, control compound, and target proteins, visualized in 3D using pyMol (figure 1). It can be known through reverse docking technology The potential of tamarixetin has anti-diabetic potential. The interaction of tamarixetin with Mitogen-Activated Protein Kinases compared with metformin as a control compound. According to the reverse docking result, combining The binding affinity of Mitogen-Activated Protein Kinases protein to Tamarixetin is lower than that of Mitogen-Activated Protein Kinases protein to metformin.

The number of binding affinities indicates the potential of the compound or ligand to interact With its protein (protein target). If the ligand has a lower binding affinity, the inheritance will be stronger Protein targets (Baker et al., 2007). Therefore, lower binding affinity results in lower energy requirements for the ligand Interact with protein targets. Mitogen-Activated Protein Kinases protein plays a role in the regulation of the insulin resistances with natural compounds from *Chromolaena Odorata* Plants that have been visualized in 3D in the PyMol software. Tamarixetin and The Mitogen-Activated Protein Kinases protein is -7.3, and the binding affinity of Mitogen-Activated Protein Kinases to the control compound Metformin is -4.6. Based on this result, comparing tamarixetin and metformin on the enhancement Mitogen-Activated Protein Kinases showed tamarixetin can improve insulin resistance.



a) b)

Figure 1. (a) Chemical 3D Structure of tamarixetin and **(b)** metformin were showed by *software* PyMol

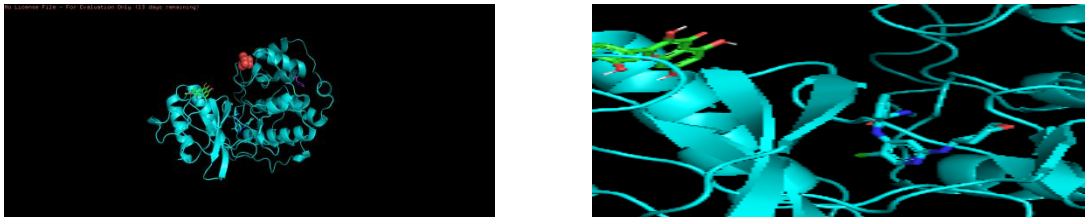


Figure 2. Binding Site of Tamarixetin (green), metformin (blue) with Mitogen-Activated Protein Kinases (blue)

Table 1. The result of *Reverse Docking* Mitogen-Activated Protein Kinases protein with ligand and control activator

Origin of compound	Ligand	Binding Affinity (kkal/mol)
Chromolaena Odorata	Tamarixetin	**-7.3**
Kontrol	Metformin	**-4.6**

Most drugs are aimed at treating some chronic illnesses. Therefore, the drug concentration must be consistent (Doogue & Polasek, 2013). Side effects of tamarixetin compounds on the body were observed by ADMET Evaluated and predicted related to cell permeability, metabolic processes, and bioavailability. The results revealed by the results of this study (AMES test) indicate that tamarixetin is not a potential carcinogen. This compound should not be extracted because it is potentially toxic. The ligand enters the cell membrane and If you meet Lipinski's rule, it will be absorbed by your body. Search results show that tamarixetin meets the rules Rating of Lipinski, Ghose, Veber, Egan, Muegge with a bioavailability score of 0.55. While metformin didn't pass the rule of Muegge.

4. Conclusion

This study proved that due to its binding affinity with -7.3. has potential as an anti-diabetic drug and intermolecular interactions. *Chromolaena Odorata* contains tamarixetin, a potential anti-diabetic drug according to Lipinski, Ghose, Veber, Egan dan Muegge Regel and 0.55 Bioavailability Score.

References

Baker, J. R., Woolfson, D. N., Muskett, F. W., Stoneman, R. G., Urbaniak, M. D., & Caddick, S. (2007). Protein-small molecule interactions in neocarzinostatin, the prototypical enediyne chromoprotein antibiotic. *ChemBioChem*, *8*(7), 704–717. https://doi.org/10.1002/cbic.200600534

Doogue, M. P., & Polasek, T. M. (2013). The ABCD of clinical pharmacokinetics. *Therapeutic Advances in Drug Safety*, *4*(1), 5–7. https://doi.org/10.1177/2042098612469335

Eze, F. N., & Jayeoye, T. J. (2021). *Chromolaena Odorata* (Siam weed): A natural reservoir of bioactive compounds with potent anti-fibrillogenic, antioxidative, and cytocompatible properties. *Biomedicine and Pharmacotherapy*, *141*(March), 111811. https://doi.org/10.1016/j.biopha.2021.111811

Howlader, M., Sultana, M. I., Akter, F., & Hossain, M. M. (2021). Adiponectin gene polymorphisms associated with diabetes mellitus: A descriptive review. *Heliyon*, *7*(8), e07851. https://doi.org/10.1016/j.heliyon.2021.e07851

Jude, E. B., O'Leary, C., Myland, M., Nixon, M., Gooch, N., Shaunik, A., & Lew, E. (2020). Evaluating glycaemic control in patients poorly controlled on oral antidiabetic drugs in real-world setting: Results from assessing the Appropriate Timing of Type 2 diAbetes INtensification (ATTAIN). *Endocrinology, Diabetes & Metabolism*, *3*(1), 1–10. https://doi.org/10.1002/edm2.94

Konermann, S. (2019). 乳鼠心肌提取 HHS Public Access. *Physiology & Behavior*, *173(3)*(1), 665–676. https://doi.org/10.1016/j.tem.2017.10.007.Mitogen-Activated

Onkaramurthy, M., Veerapur, V. P., Thippeswamy, B. S., Madhusudana Reddy, T. N., Rayappa, H., & Badami, S. (2013). Anti-diabetic and anti-cataract effects of *Chromolaena Odorata* Linn.; In streptozotocin-induced diabetic rats. *Journal of Ethnopharmacology*, *145*(1), 363–372. https://doi.org/10.1016/j.jep.2012.11.023

Roth Flach, R. J., Danai, L. V., DiStefano, M. T., Kelly, M., Menendez, L. G., Jurczyk, A., Sharma, R. B., Jung, D. Y., Kim, J. H., Kim, J. K., Bortell, R., Alonso, L. C., & Czech, M. P. (2016). Protein kinase Mitogen-activated Protein Kinase Kinase Kinase Kinase 4 (MAP4K4) promotes obesity-induced hyperinsulinemia. *Journal of Biological Chemistry*, *291*(31), 16221–16230. https://doi.org/10.1074/jbc.M116.718932

Sidarala, V., & Kowluru, A. (2016). The Regulatory Roles of Mitogen-Activated Protein Kinase (MAPK) Pathways in Health and Diabetes: Lessons Learned from the Pancreatic β-Cell. *Recent Patents on Endocrine, Metabolic & Immune Drug Discovery*, *10*(2), 76–84. https://doi.org/10.2174/1872214810666161020154905

Tan, S. Y., Mei Wong, J. L., Sim, Y. J., Wong, S. S., Mohamed Elhassan, S. A., Tan, S. H., Ling Lim, G. P., Rong Tay, N. W., Annan, N. C., Bhattamisra, S. K., & Candasamy, M. (2019). Type 1 and 2 diabetes mellitus: A review on current treatment approach and gene therapy as potential intervention. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews*, *13*(1), 364–372. https://doi.org/10.1016/j.dsx.2018.10.008

Zahara, M. (2019). Description of *Chromolaena Odorata* L. R.M King and H. Robinson as medicinal plant: A Review. *IOP Conference Series: Materials Science and Engineering*, *506*(1), 1–7. https://doi.org/10.1088/1757-899X/506/1/012022

Zhuo, J., Zeng, Q., Cai, D., Zeng, X., Chen, Y., Gan, H., Huang, X., Yao, N., Huang, D., & Zhang, C. (2018). Evaluation of type 2 diabetic mellitus animal models via interactions between insulin and mitogen-activated protein kinase signaling pathways induced by a high fat and sugar diet and streptozotocin. *Molecular Medicine Reports*, *17*(4), 5132–5142. https://doi.org/10.3892/mmr.2018.8504