MOLEKUL
www.jmolekul.com

Articles

https://doi.org/10.20884/1.jm.2020.15.2.579

# Reverse Docking, Molecular Docking, Absorption, Distribution, and Toxicity Prediction of Artemisinin as an Anti-diabetic Candidate

**Ruswanto Ruswanto[1]*, Richa Mardianingrum[2], Siswandono Siswandono[3], Dini Kesuma[4]**

[1]Department of Pharmacy, Sekolah Tinggi Ilmu Kesehatan Bakti Tunas Husada, Tasikmalaya, Indonesia
[2]Department of Pharmacy, University of Perjuangan, Tasikmalaya, Indonesia
[3]Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia
[4]Faculty of Pharmacy, University of Surabaya, Surabaya, Indonesia

*Corresponding author email: ruswanto@stikes-bth.ac.id

**Received** September 18, 2019; **Accepted** June 01, 2020; **Available online** July 27, 2020

**ABSTRACT.** Aldose reductase is an enzyme that catalyzes one of the steps in the sorbitol (polyol) pathway that is responsible for fructose formation from glucose. In diabetes, aldose reductase activity increases as the glucose concentration increases. The purpose of this research was to identify and develop the use of artemisinin as an anti-diabetic candidate through in silico studies, including reverse docking, receptor analysis, molecular docking, drug scan, absorption, and distributions and toxicity prediction of artemisinin. Based on the results, we conclude that artemisinin can be used as an anti-diabetic candidate through inhibition of aldose reductase.

**Keywords:** aldose reductase, artemisinin, molecular docking, reverse docking

## INTRODUCTION

Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin or when the body is unable to use insulin effectively. In 2014, 8.5% of adults aged 18 years and over suffered from diabetes. In 2016, diabetes was the direct cause of around 1.6 million deaths. Diabetes is classified as type 1 diabetes (insulin-dependent) and type 2 diabetes (non-insulin-dependent) (World Health Organization, 2016). Fidarestat is an aldose reductase inhibitor studied in the treatment of diabetes neuropathy (Steuber, Heine, Podjarny, & Klebe, 2008). Aldose reductase is an enzyme that is normally present in many other parts of the body, and it catalyzes one of the steps in the sorbitol(polyol) pathway that is responsible for fructose formation from glucose. Aldose reductase activity increases as the glucose concentration increases in individuals with diabetes in the tissues that are not insulin sensitive (Várkonyi, 2008).

Artemisinin is a sesquiterpene lactone compound that consists of three isoprene units that are bound to cyclic esters. The (+) artemisinin has been used as an antimalarial drug by the Chinese since 168 BC. This compound was first isolated in 1972 from the Qinghao plant (*Artemisia annua* L.) by Chinese chemists, and it has a peroxide bridge that is the main proponent of antimalarial drug activity (Li, 2012). The need for malaria medicine in the world is very high, while the artemisinin produced from the Qinghao plant cannot be sufficient. This situation prompted several researchers to make synthetic antimalarial drugs based on the structure of artemisinin (Aderibigbe, 2017; Muangphrom, Seki, Fukushima, & Muranaka, 2016; Walsh, Coughlan, Heneghan, Gaynor, & Bell, 2017).

Aside from being an antimalarial drug (Das, 2015; Guo, 2016), artemisinin has also been investigated as an antituberculosis (Zheng et al., 2017); anticancer (Li, Li, Wu, Wang, & Yu, 2016; Slezakova, 2017; Wong et al., 2017), and anti-diabetic drug (Helal, Abou-Aouf, Khattab, & Zoair, 2014).

Drug repurposing is a strategy for identifying new uses for approved or investigational drugs that are outside the scope of the original medical indication. Successful drug repositioning occurred in 2015 with the identification and use of aspirin for colorectal cancer, in 2014 with the identification of ketoconazole for Cushing syndrome, and in 2007 with the use of Raloxifene for breast cancer (Pushpakom et al., 2018).

Apart from experimentation, with computational chemical methods, the structure of a new drug compound with new activity can be predicted. One of the computational methods used in the design and development of new drugs is the docking method (Kitchen, Decornez, Furr, & Bajorath, 2004). The molecular docking approach can be used to model interactions between small molecules and proteins at the atomic level, which allows for the characterization of the behavior of small molecules at the target

protein-binding site and explanation of the important biochemical processes (Kharkar, Warrier, & Gaud, 2014). The docking procedure involves two principal steps: prediction of the ligand conformation and the position and orientation on the sites (commonly referred to as poses) and binding affinity assessments. The docking method can be used to study interactions between one drug and one target receptor (docking) as well as to study one drug with many target receptors (reverse docking). Some research has been done either by docking or reverse docking (Liu et al., 2010; Ruswanto et al., 2018).

The purpose of this research was to identify and develop the use of artemisinin as an anti-diabetic candidate through in silico studies, including the identification of receptor targets (reverse docking), receptor analysis, molecular docking, drug scans, absorption and distribution, and toxicity prediction of artemisinin.

## EXPERIMENTAL SECTION

### Ligand Preparation

The artemisinin structure is already available in the PubChem database (https://pubchem.ncbi.nlm.nih.gov/compound/68827), and then the artemisinin structure was done protonation and conformational by MarvinSketch (Purnomo, 2013).

### Target Receptor Identification by Inverse Docking

The artemisinin structure that has been made in the preparation process with the file format ".mol2" was uploaded on the website http://lilab-ecust.cn/pharmmapper/index.html. Submit the file, then download the results of the work on *Get Result* by entering the *Job ID* code given after uploading the file (Liu et al., 2010).

### Docking Validation

Docking was executed using Autodock version 4.2 software. The artemisinin structure was docked to obtain the lowest binding energy with the protein target using the Lamarckian genetic algorithm (LGA) AutoDock calculation method on grid box x, y, and z respectively 22, 18, and 22, spacing 0.375 Angstroms and grid box center position 17,789; – 8,179 and 16. Data analysis was performed using the root-mean-square deviation (RMSD). The docking method was said to be proper if the RMSD was less than or equal to 2 Å. If the RMSD was greater than 2 Å, it means that the method could not be trusted (Adelin, 2013).

### Target Receptor Analysis

Target receptor analysis was performed by looking at the aldose reductase (code PDB: 2PDY) profile on the following website: http://www.ebi.ac.uk/pdbsum/. By entering the 2PDY code, the profile data from the target receptor appeared. This analysis was carried out at target receptors that were validated in the docking validation process (De Beer, Berka, Thornton, & Laskowski, 2014).

### Docking and Interaction Visualization

The docking process was done using Autodock version 4.2 software. Then, the test compound was docked at the receptor-binding site following the grid box that was used in the validation. The results obtained from this docking process were in the form of the binding affinity of the compounds or ligands. Furthermore, using LigPlot software, the interaction between the ligand and the active site of the receptor could be seen (Wallace, Laskowski, & Thornton, 1996).

### Lipinski's Rule of Five (Drug Scan)

Drug scan analysis was carried out on artemisinin compounds and if a chemical compound with a certain pharmacological or biological activity has chemical properties and physical properties that would make it a likely orally active drug in humans (Lipinski's rule of five) using MarvinSketch software (Lipinski, Lombardo, Dominy, & Feeney, 1997).

The observation of the drug was performed by observing the rule of good medicine (Lipinski's rule of five) and oral bioavailability of ligand. The parameters for Lipinski's rule of five (RO5) were the following: molecular weight < 500 g/mol, lipophilicity < 5, donor hydrogen bond < 5, acceptor hydrogen bond < 10, and refractory molar among 40 and 130 (Athar, Lone, & Jha, 2017; Choy, 2011).

### The Absorption, Distribution and Toxicity Prediction

The PreADMET program was accessed at http://Preadmet.bmdrc.org/. The structure of each compound was converted to mol files (*.mol2). The program automatically calculated the predicted absorption for Caco-2, human intestinal absorption (HIA), and bound plasma receptors (Rozano, Zawawi, Ahmad, & Jaganath, 2017), while the identification of toxicity parameters was Ames test, carcinogenic in mice, and inhibition on hERG.

## RESULTS AND DISCUSSION

The in-silico study of artemisinin compounds was performed in several stages, including docking, prediction of absorption-distribution, prediction of toxicity, and screening of similar drug compounds (drug scans) to test the use of these compounds as anti-diabetic candidates.

### Ligand Preparation Results

Ligand preparation was carried out before the in-silico test so that the ligand of the artemisinin compound was ready for treatment in the subsequent procedure. The first preparation was done by drawing the structure using MarvinSketch.

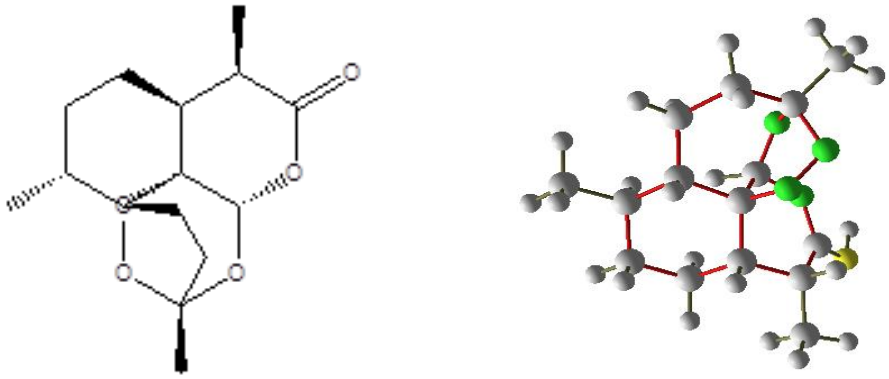
### Target Identification Results

Tuberculosis receptors that could have potential as artemisinin compounds were identified with a web server-based program, PharmMapper (http://lilab-ecust.cn/pharmmapper/), designed to identify potential target receptor candidates for small molecules. Identification was carried out by examination using a pharmacophore mapping

approach that was also used to determine the interaction between pharmacophore compounds with receptors (Wang et al., 2017).

In this study, the prepared compound was uploaded to the PharmMapper webserver to analyze potential receptor targets. Several target receptor candidates with the potential to fit the fit score and z'-score parameters were obtained. The identification results for the top 10 receptor targets are given in **Table 1**. From the results, it can be seen tuhat the top 10 receptor codes are selected receptors. The highest fit score was found for the receptor with the code 2PDY, which had a z'-score of 2.22103 and a fit score of 3.699. The more positive of the z'-score value, it means more significant the target receptor is towards the test compound, while the more negative the z'-score value, it means the target receptor maybe not enough significant (Wang et al., 2016).

The pharmacophore features of artemisinin can be seen in **Table 2** and **Figure 2**, the four identified aldose reductase receptors have the same number of hydrophobic molecules, which causes the formation of hydrophobic bonds between molecules. This hydrophobic bond forms between the non-polar region of the drug molecules and the non-polar region of the biological receptor, whereas hydrogen and hydrophobic bonds affect the conformational stability that occurs between artemisinin compounds and receptor targets.



(**a**) (**b**)

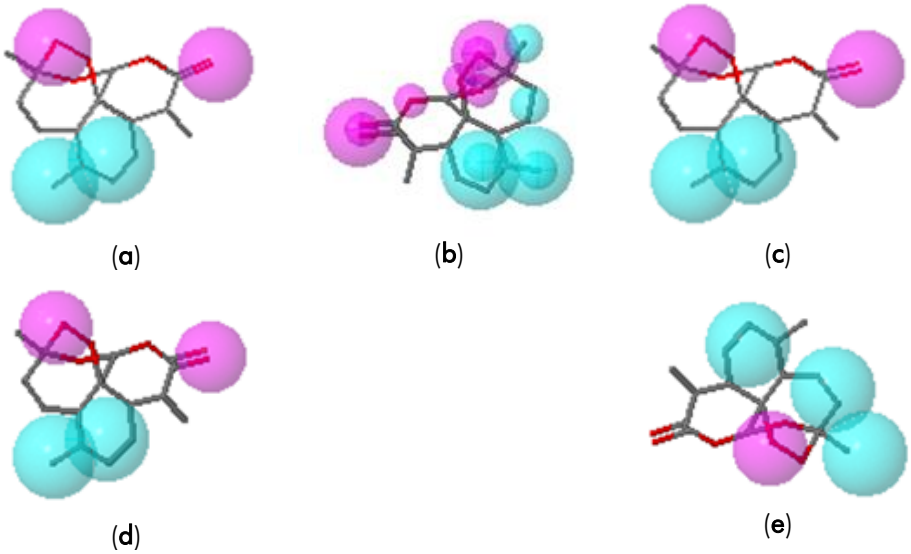
**Figure 1.** Artemisinin structure. (**a**) 2D structure and (**b**) 3D structure that was optimized with ChemOffice 2004 software.

**Table 1.** PharmMapper Results of artemisinin compounds.

| Rank | PDB ID. | Target Name | Number of Features | Fit Score | Normalized Fit Score | Z'score |
|---|---|---|---|---|---|---|
| 1 | 2PDY | Aldose reductase | 4 | 3.699 | 0.9248 | 2.22103 |
| 2 | 1PWM | Aldose reductase | 4 | 3.657 | 0.9142 | 2.06726 |
| 3 | 2PDW | Aldose reductase | 4 | 3.645 | 0.9114 | 1.97695 |
| 4 | 2PD9 | Aldose reductase | 4 | 3.596 | 0.8989 | 1.76382 |
| 5 | 2PEO | 3-phosphoinositide-dependent protein kinase 1 | 4 | 3.498 | 0.8744 | 1.22248 |
| 6 | 1LNM | Bilin-binding protein | 4 | 3.496 | 0.8739 | 0.59119 |
| 7 | 1RCJ | Beta-lactamase SHV-1 | 4 | 3.491 | 0.8728 | 0.42665 |
| 8 | 2NW4 | Androgen receptor | 4 | 3.368 | 0.8421 | 0.79402 |
| 9 | 1T87 | Camphor 5-monooxygenase | 4 | 3.244 | 0.8110 | -0.1831 |
| 10 | 3D9Z | Carbonic anhydrase 2 | 4 | 3.219 | 0.8046 | 0.10992 |

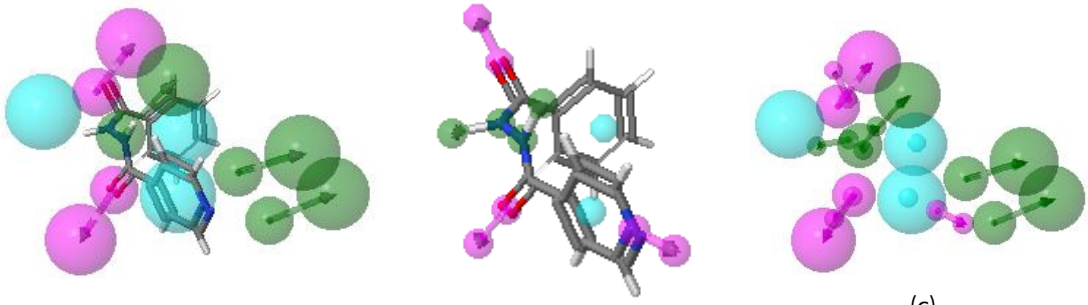
**Table 2.** Pharmacophore features of artemisinin in the top five receptors.

| No. | Target receptor | Number of pharmacophore features | | | | | |
|---|---|---|---|---|---|---|---|
| | | Hydrophobic | Positive | Negative | Donor | Acceptor | Aromatic |
| 1 | Aldose reductase | 2 | 0 | 0 | 0 | 2 | 0 |
| 2 | Aldose reductase | 2 | 0 | 0 | 0 | 2 | 0 |
| 3 | Aldose reductase | 2 | 0 | 0 | 0 | 2 | 0 |
| 4 | Aldose reductase | 2 | 0 | 0 | 0 | 2 | 0 |
| 5 | 3-phosphoinositide-Dependent receptor kinase 1 | 3 | 0 | 0 | 0 | 1 | 0 |



(a) (b) (c) (d) (e)

**Figure 2.** Pharmacophore model features of artemisinin with receptor targets. (**a**) Aldose reductase-2PDY, (**b**) aldose reductase-1PWN, (**c**) aldose reductase-2PDW, (**d**) aldose reductase-2PD9, and (**e**) 3-phosphoinositide-dependent receptor kinase 2-PE0.



(a) (b) (c)

**Figure 3.** The pharmacophore models of artemisinin in aldose reductase: (a) molecule and pharmacophore, (b) models of the molecule and molecular features, and (c) pharmacophore model and molecular features. The following colors correspond to features of the pharmacophore: hydrophobic, cyan; positive (cations), blue; negative (anions), red; hydrogen bond donor, green; and hydrogen bond acceptor, magenta

## Docking Validation

This step involved re-docking of fidarestat from the crystal structure (2PDY) to the active site using the same procedure as the docking procedure used in this study, which was performed by Autodock. Afterward, the comparison between the fidarestat obtained from the redocking and the fidarestat on the PDB file resulted in RMSD. As we know, fidarestat is a drug used for the treatment of neuropathic diabetes through the aldose reductase mechanism (Steuber et al., 2008). An RMSD value of 0.48 Å was obtained and the overlaid structures can be seen in **Figure 4**.

The RMSD was 0.48 Å, indicating that the conformation of the re-docking results was similar to the results of the x-ray crystallography. This RMSD also proves that the docking method was valid for docking of the test compound.

## Target Receptor Analysis

The best receptor target (2PDY) of artemisinin that has been identified from PharmMapper was analyzed using the PDBSum server (http://www.ebi.ac.uk/thornton-srv/databases/cgi-bin/pdbsum/GetPage.pl?pdbcode=index.html).

The analyzed receptor target was the best-sequenced target, aldose reductase (2PDY), analyzed by the Ramachandran Plot parameter to determine the quality of the receptor structure being modeled. The plot that describes the amino acid residues in the receptor structure is called a Ramachandran Plot. Each receptor amino acid has one angle phi (ϕ) and psi (ψ) so that each amino acid residue can be described as a plot/coordinate. The quality of the receptor structure can be assessed based on a plot of non-glycine residues located in the disallowed region. A receptor has poor (very unstable) structural quality if the non-glycine residues in the disallowed region number more than 15%. In addition, receptor analysis is also seen from the active site of the target receptor, which is an area where the substrate molecules bind and undergo reaction chemistry. The active site consists of residues

that form a temporary bond with the substrate (binding site) and residues that catalyze a reaction with the substrate (Jorgensen, 1991).

Based on the Ramachandran plot analysis, the aldose reductase receptor (2PDY) shows the number of good amino acids, which is larger than or alike to 91.7% in the greatest favored region so it can be assumed that the structure of receptor has excellent property (Lakshmi et al., 2014). A clearer result can be viewed in **Figure 5**.

Another way to observe the constancy of the receptor structure is to look at the plot of non-glycine residues that are located in disallowed regions. The protein structure is good if the number of residues in disallowed regions is less than 0.8% (Halkides, 2013; Lakshmi et al., 2014).

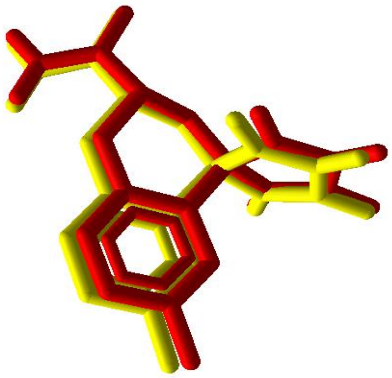
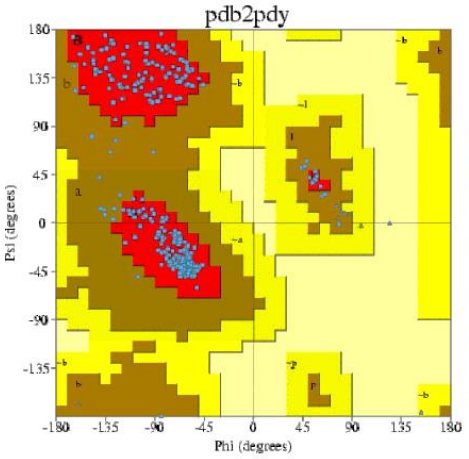


**Figure 4.** The overlaid image of the crystal structure of fidarestat (yellow) and the re-docking results (red)




| | | No. of residues | %-tage |
|---|---|---|---|
| Most favoured regions | [A,B,L] | 254 | 91.7% |
| Additional allowed regions | [a,b,l,p] | 23 | 8.3% |
| Generously allowed regions | [~a,~b,~l,~p] | 0 | 0.0% |
| Disallowed regions | [XX] | 0 | 0.0% |
| Non-glycine and non-proline residues | | 277 | 100.0% |
| End-residues (excl. Gly and Pro) | | 2 | |
| Glycine residues | | 16 | |
| Proline residues | | 20 | |
| Total number of residues | | 315 | |

**Figure 5.** Ramachandran plot statistics.

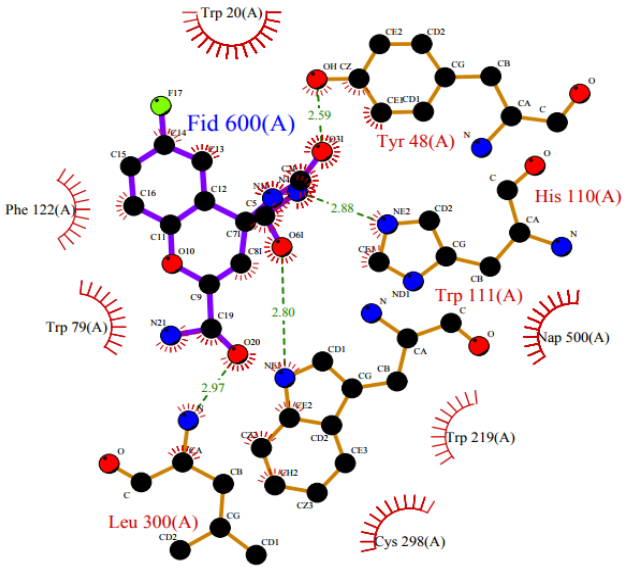



**Figure 6.** The Interaction of fidarestat with aldose reductase (2PDY code by PDBsum analysis).

**Table 3.** The free energy binding (ΔG) and constant of inhibition (Ki)

| Compounds | ΔG (kcal/mol) | Ki |
|---|---|---|
| Artemisinin | –8.75 | 383.73 nM |
| Fidarestat | –7.23 | 5.04 $\mu$M |

Based on the Ramachandran plot observations (**Figure 5**), the receptor structure (2PDY) has a good property, this can be noticed from the residual plot found in the disallowed regions [X, X] is a smaller amount than 0.8%, which is 0.0%.

On the active site of the aldose reductase (2PDY) target receptor with fidarestat, five hydrogen bonds with Tyr 48 amino acid residues, 2 on His 110, Trp 111 and Leu 300 and five hydrophobic interactions with Trp 20, Phe 122, Trp 79, Cys 298, and Trp 219. (**Figure 6**).

## Docking Results

Docking was carried out using Autodock version 4.2 software. The artemisinin compounds were docked to realize the smallest binding energy using the LGA AutoDock calculation method, tGA, and SA Monte Carlo on grid box x, y, and z respectively 22, 18, and 22, spacing 0.375 Angstroms and grid box center position 17.789; –8.179 and 16.9. From the re-docking results, the RMSD value is 0.48 Å and is illustrated by the overlay structure between the natural ligands and re-docking results, as shown in **Figure 4**.

During the docking procedure, the water at the receptors is eliminated first because if the clusters of compounds and receptors are surrounded by water molecules, the surrounding water molecules will combine. This phenomenon results in an escalation in entropy and a decrease in free energy, which stabilizes the drug-receptor complex. Through this procedure, hydrogen is also combined, which is important for the interaction between the compound and the receptor. The docking results of artemisinin against aldose reductase (2PDY) were related with fidarestat, which are compounds that have been found to work on aldose reductase receptors.

From the results of docking in **Table 3**, it can be seen that the artemisinin has a lower free energy binding (ΔG) than a comparative compound (Fidarestat). Therefore, the artemisinin can be expected to have better activity than fidarestat as an anti-diabetic candidate, which acts on the aldose reductase receptor. If the free energy binding was lower, it means the drug-receptor interaction was better and more stable. In adding to the free energy binding value, in **Table 3** the value of the constant of inhibition (Ki) can also be seen. The enzyme inhibition constant (Ki), also known as the inhibitor dissociation constant, is an equilibrium constant of a reversible inhibitor for complexion with its target enzyme. Unless otherwise specified, all inhibitors described hereafter are reversible inhibitors. $K_i$ is associated with thermodynamic parameters in $\Delta G = RT \ln(K_i)$, where $\Delta G$, $R$, and $T$ are the absolute binding free energy, the gas constant, and the absolute temperature, respectively (Darras et al., 2017). From the reaction equilibrium among the receptor and the compound, the lesser the Ki value the more the reaction equilibrium leans to favor the formation of receptor–compound complexes. The Ki of artemisinin was lesser than fidarestat, so it can be predicted that the artemisinin has inhibition on the aldose reductase receptor better than fidarestat.

Besides, from the docking results, visualization of the 2D interactions between artemisinin and fidarestat compounds with aldose reductase receptors can be seen, as shown below.

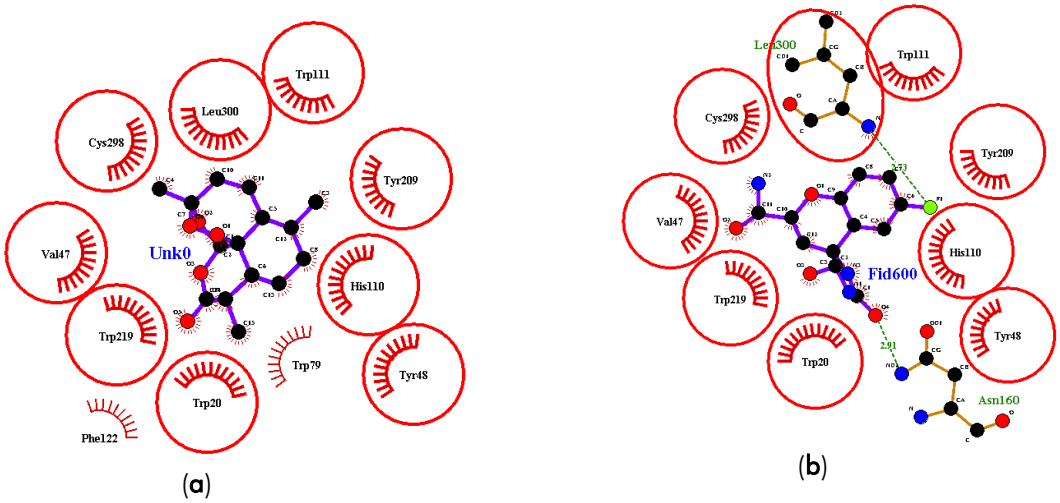



**Figure 7.** The visualization of the 2D interaction between artemisinin (**a**) and fidarestat (**b**) with aldose reductase receptors by the docking method.

From **Figure 7**, it can be seen that the interactions between artemisinin compounds and aldose reductase are only hydrophobic interactions, namely with Cys 298, Leu 300, Trp 111, Tyr 209, His 110, Tyr 48, Trp 79, Trp 20, Phe 122, Trp 219, and Val 47 (11 interactions). The interaction between fidarestat and aldose reductase involves two interactions of hydrogen with Leu 300 (2.73Å) and Asn 160 (2.91 Å) and eight hydrophobic interactions with Cys 298, Val 47 Trp 219 Trp 20, Trp 111, Tyr 209, His 110, and Tyr 48.

### Drug Scan Results

From the results through the webserver at http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp# anchortag, the artemisinin fulfilled the Lipinski's RO5, which has a log P < 5, a molecular weight of < 500 g/mol, hydrogen bond acceptor <10, hydrogen bond donor < 5, and refractory molar between 40 and 130 (Lipinski et al., 1997). The weight of molecular is correlated to the distribution of the drug. If the molecular weight is small, it will have a small molecular size. Therefore, it will make it easier for the drug to breach the biological membrane. The drug scan of results can be seen in **Table 4**.

The partition coefficient (log P) is related to lipophilicity, which is the chemical dissolving capacity in fat, oil, and non-polar solvents. The drug must be lipophilicity enough to breach the lipid bilayer, but it should not be too lipophilicity, affecting the drug to not breach back out of the membrane, which will source the drug to be toxic because it keeps on elongated in the body.

The number of donors and acceptors of hydrogen bonds is related to the biological activity of a drug, which can affect the chemical-physical properties such as boiling point, melting point, solubility in water, capability in forming chelate, and acidity, whereas Refractory molar is correlated to the polarisation total of the drug, which is very reliant on the index of refractive, pressure and temperature. This polarisation is related to the shape of molecular and relative mass, which is usually the greater number of electrons, the easier it is to experience polarisation.

**Table 4.** Drug scan test results.

| Parameters | Result |
|---|---|
| Molecular weight | 282 g/mol |
| Lipophilicity (Log P) | 2.394 |
| Hydrogen bond donor | 0 |
| Hydrogen bond acceptor | 5 |
| Refractory molar | 68.047 |

From the scan of drug results presented in **Table 4**, it is recognized that artemisinin has fulfilled the requirements of Lipinski's rules, so it can be expected that artemisinin has good permeability and is easily absorbed.

### Absorption, Distribution and Toxicity Prediction Results

Based on the prediction results of PreADMET, it was known that artemisinin compounds have permeability in the medium category, which was seen from the Caco2 cell parameter value of 25.2822 nm/sec which is in the range of 4–70 nm/sec. This Caco2 cell parameter also describes the active and passive diffusion transport of a drug molecule. Then, from the parameters of HIA, the synthesized compounds fall into the good category (range of 70–100%), with a value of 93.5899%, so that it could be predicted that the compound can reach the target site optimally. The HIA parameter was used to predict the percentage of absorption of a drug in the human intestine, whereas, from the parameters of protein plasma binding (PPB), artemisinin compounds have chemical strongly bonds with plasma receptors, with a %PPB of 93.805%, where the category of %PPB is chemicals strongly bound (if %PPB> 90%) and chemicals weakly bound (if %PPB<90%). The %PPB value indicated the part of the drug that was bound to the plasma receptor that cannot diffuse across the cell membrane so that it could not interact with the target site.

In the further test, the toxicity prediction through http://Preadmet.bmdrc.org/ by the Ames test, the artemisinin was predicted to be mutagenic and carcinogenic in both mice showed negative/non-carcinogenic. Besides, it could be seen from the inhibition on hERG that it could be explained that the artemisinin has a low risk. Therefore, it could be concluded that artemisinin could be safely used as medicines (Schmitz, 2008).

## CONCLUSION

From the reverse docking and molecular docking study, it can be concluded that artemisinin could be used as an anti-diabetic candidate through the aldose reductase mechanism. Also, drug scans, receptor analysis, adsorption, distribution, and toxicity prediction studies were performed. In the future, stability interactions between artemisinin and aldose reduction inhibitors can be further studied through molecular dynamics.

## ACKNOWLEDGEMENTS

The author would like to thank Bakti Tunas Husada STIKes for the facilities and funding for this study.

## REFERENCES

Adelin, T., Frengki, & Dwinna, A. (2013). Penambatan Molekuler Kurkumin dan Analognya Pada Enzim Siklooksigenase-2, *Jurnal Medika Veterinaria*, 7(1), 0853–1943.

Aderibigbe, B. (2017). Design of drug delivery systems containing artemisinin and its derivatives, *Molecules*, 22(2), 323.

Athar, M., Lone, M. Y., & Jha, P. C. (2017). First protein drug target's appraisal of lead-likeness descriptors to unfold the intervening chemical

space, *Journal of Molecular Graphics and Modelling*, *72*, 272–282.

Choy, Bin, Y., & Prausnitz, M. R. (2011). The rule of five for non-oral routes of drug delivery: ophthalmic, inhalation and transdermal, *Pharmaceutical Research*, *28*(5), 943–948.

Darras, F. H. & Pang, Y. P. (2017). On the use of the experimentally determined enzyme inhibition constant as a measure of absolute binding affinity, *Biochemical and Biophysical Research Communications*, *489*(4), 451–454.

Das, A. (2015). Anticancer effect of antimalarial artemisinin compounds, *Annals of Medical and Health Sciences Research*, *5*(2), 93.

De Beer, T. A. P., Berka, K., Thornton, J. M., & Laskowski, R. A. (2014). PDBsum additions, *Nucleic Acids Research*, *42*(D1), 292–296.

Guo, Z. (2016). Artemisinin anti-malarial drugs in China, *Acta Pharmaceutica Sinica B*, *6*(2), 115–124.

Halkides, C. J. (2013). Using molecular models to show steric clash in peptides: an illustration of two disallowed regions in the Ramachandran diagram, *Journal of Chemical Education*, *90*(6), 760–762.

Helal, E. G. E., Abou-Aouf, N., Khattab, A. M., & Zoair, M. A. (2014). Anti-diabetic effect of artemisia annua (Kaysom) in alloxan-induced diabetic rats, *The Egyptian Journal of Hospital Medicine*, *57*,422–430.

Jorgensen, W.L. (1991). Rusting of the lock and key model for protein-ligand binding". *Science*, *254*(5034), 954–5.

Kitchen, D.B., Decornez, H., Furr, J.R., & Bajorath, J. (2004). Docking and scoring in virtual screening for drug discovery: methods and applications. *Nature Reviews. Drug Discovery*, *3*(11), 935–49.

Kharkar, P. S., Warrier, S., & Gaud, R. S. (2014). Reverse docking: a powerful tool for drug repositioning and drug rescue, *Future Medicinal Chemistry*, *6*(3), 333–342.

Lakshmi, B., Sinduja, C., Archunan, G., & Srinivasan, N. (2014). Ramachandran analysis of conserved glycyl residues in homologous proteins of known structure, *Protein Science*, *23*(6), 843–850.

Li, Z., Li, Q., Wu, J., Wang, M., & Yu, J. (2016). Artemisinin and its derivatives as a repurposing anticancer agent: what else do we need to do? *Molecules (Basel, Switzerland)*, *21*(10), 1–14.

Li, Y. (2012). Qinghaosu (artemisinin): chemistry and pharmacology, *Acta Pharmacologica Sinica*, *33*(9), 1141–1146.

Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (1997). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development setting, *Advanced Drug Delivery Review*, *23*, 3–26.

Liu, X., Ouyang, S., Yu, B., Liu, Y., Huang, K., Gong, J., & Jiang, H. (2010). PharmMapper server: a web server for potential drug target identification using pharmacophore mapping approach, *Nucleic Acids Research*, *38*, 5–7.

Muangphrom, P., Seki, H., Fukushima, E. O., & Muranaka, T. (2016). Artemisinin-based antimalarial research: application of biotechnology to the production of artemisinin, its mode of action, and the mechanism of resistance of Plasmodium parasites, *Journal of Natural Medicines*, 70(3), 318–334.

Purnomo, H. (2013). *Kimia Komputasi*: *Molekular Docking Plants* [*Protein-Ligan-Ant-System*]. Yogyakarta*: Pustaka Pelajar*.

Pushpakom, S., Iorio, F., Eyers, P. A., Escott, K. J., Hopper, S., Wells, A., & Pirmohamed, M. (2018). Drug repurposing: progress, challenges, and recommendations, *Nature Reviews Drug Discovery*, *18*(1), 41–58.

Rozano, L., Zawawi, M. R. A., Ahmad, M. A., & Jaganath, I. B. (2017). Computational Analysis of *Gynura bicolor* Bioactive Compounds as Dipeptidyl Peptidase-IV Inhibitor. *Advances in bioinformatics*, *2017*, 5124165.

Ruswanto, R., Mardianingrum, R., Lestari, T., Nofianti, T., Tuslinah, L., & Nurmalik, D. (2018). In silico study of the active compounds in bitter melon (Momordica charantia L) as antidiabetic medication, *Pharmaciana*, *8*(2), 194.

Schmitz, G., Hans Lepper, & Michael Heidrich. (2008). Farmakologi dan Toksikologi, Ed.3, Jakarta: *EGC*.

Slezakova, S., & Ruda-Kucerova, J. (2017). Anticancer activity of artemisinin and its derivatives, *Anticancer Research*, *37*(11), 5995–6003.

Steuber, H., Heine, A., Podjarny, A., & Klebe, G. (2008). Merging the binding sites of aldose and aldehyde reductase for detection of inhibitor selectivity-determining features, *Journal of Molecular Biology*, *379*, 991–1016.

Várkonyi, T., & Kempler, P. (2008). Diabetic neuropathy: new strategies for treatment, *Diabetes, Obesity & Metabolism*, *10*(2), 99–108.

Wallace, A.C., Laskowski, R.A., & Thornton, J.M. (1996). LIGPLOT: a program to generate schematic diagrams of protein-ligand interactions. *Protein Engineering*, **8**, 127-134.

Walsh, J. J., Coughlan, D., Heneghan, N., Gaynor, C., & Bell, A. (2007). A novel artemisinin-quinine hybrid with potent antimalarial activity, *Bioorganic and Medicinal Chemistry Letters*, *17*(13), 3599–3602.

Wang, X., Shen, Y., Wang, S., Li, S., Zhang, W., Liu, X., Lai, L., Pei, J., & Li, H. (2017). PharmMapper 2017 update: a web server for potential drug

target identification with a comprehensive target pharmacophore database, *Nucleic Acids Research*, *45*, W356–W360.

Wang, X., Pan, C., Gong, J., Liu, X., & Li, H. (2016). Enhancing the enrichment of pharmacophore-based target prediction for the polypharmacological profiles of drugs, *Journal of Chemical Information and Modeling*, *56*, 1175–1183.

Wong, Y. K., Xu, C., Kalesh, K. A., He, Y., Lin, Q., Wong, W. S. F., & Wang, J. (2017). Artemisinin as an anticancer drug: recent advances in target profiling and mechanisms of action, *Medicinal Research Reviews*, *37*(6), 1492–1517.

World Health Organization. (2016). *Global report on diabetes*. WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland.

Zheng, H., Colvin, C. J., Johnson, B. K., Kirchhoff, P. D., Wilson, M., Jorgensen-Muga, K., & Abramovitch, R. B. (2017). Inhibitors of mycobacterium tuberculosis DosRST signaling and persistence, *Nature Chemical Biology*, *13*(2), 218–225.