Dipeptidyl peptidase IV inhibition of phytocompounds from *Artocarpus champeden* (Lour.) Stokes: *In silico* molecular docking study and ADME-Tox prediction approach

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**Abstract**

The present study examines the potential activity prediction based on free binding energy (ΔG) and interaction confirmation of phytocompounds from *Artocarpus champeden* (Lour.) Stokes with macromolecule protein receptor of dipeptidyl peptidase IV (DPP-IV) using *in silico* molecular docking studies and physicochemical and pharmacokinetic properties (ADME-Tox) prediction approaches. The active subsites of the DPP-IV receptor macromolecule protein Protein Data Bank (ID: 1 × 70) were docked using Autodock v4.2.6 (100 docking runs). A grid box of 52 × 28 × 26 Å points spaced by 0.37 Å was centered on the active site of x = 40.926 Å; y = 50.522 Å; z = 35.031 Å. For ADME-Tox prediction, Swiss ADME online-based application programs were used. The results show that 12 pythocompounds from *A. champeden* have the potential as DPP-IV inhibitors based on ΔG value and interaction conformation. There are five pythocompounds with lower ΔG values and inhibition constants than the native ligand and seven pythocompounds with ΔG values and inhibition constants close to the native ligand. The 12 compounds form an interaction conformation at the active subsites of the DPP-IV receptor. At the same time, the results of the ADME-Tox prediction analysis showed that the 12 compounds had different physicochemical and pharmacokinetic properties.

**Key words:** ADME-tox, *Artocarpus champeden* (Lour.) stokes, dipeptidyl peptidase IV, free binding energy, *in silico* molecular docking

**INTRODUCTION**

*Artocarpus champeden* (Lour.) Stokes belongs to the Moraceae family, locally known as “Chempedak,” an annual fruit plant with a tall, strong woody tree. This fruit plant is a native that grows wild in tropical forests, mainly in India,
Vietnam, Myanmar, Thailand, Malaysia, and Indonesia. This plant is widespread in Sumatran, Kalimantan, Sulawesi, Maluku, and West Papua in Indonesia. Traditionally, this plant treats diarrhea, fever, malaria, and diabetes mellitus. However, no scientific evidence has been reported of A. champeden as a potential antidiabetic agent to the best of our knowledge. Therefore, our team is interested in researching the potential of this plant.

Meanwhile, several studies have isolated and identified phytocompounds found in A. champeden. However, data regarding the potential pharmacological activity of phytocompounds from A. champeden is still minimal, mainly as antidiabetic, whereas it has traditionally been used for generations. This series of work fills research gaps by examining the potential activity and interactions of phytocompound from A. champeden using the in silico molecular docking study and ADME-Tox prediction approach.

In silico molecular docking is a modeling method based on computer simulation to search for possible bindings of the test ligand and receptor-interacting under topographical conditions and the match between both molecules with the conformation that has the best interaction. ADME-Tox prediction is performed using an online-based application such as SWISSADME, which aims to study physicochemical and pharmacokinetic properties. Some studies that have been reported successfully related to the use of these application programs include ADMET analysis of three relevant natural components of the medicinal plant, ADMET prediction of mangosteen derivates, and ADME-Tox prediction of phytocompounds from Merremia peltata, and drug-likeness prediction of bioactive compounds from Punica granatum L.

The current study predicts the interaction conformation and the potential activity of phytocompounds from A. champeden with macromolecules protein of dipeptidyl peptidase IV (DPP-IV) as a receptor target, hoping to fill research gaps on an in silico assay scale, thereby accelerating the development of further studies.

MATERIALS AND METHODS

Hardware and software
The analysis of molecular docking was carried out by a computer HP Pavilion, Autodock-v4.2.6, AutodockTools, ChemOffice-Pro-v15.00 PerkinElmer, Phyton Molecular Viewer (PMV-1.5.6), OpenBabel GUI, Accelrys Discovery Studio Visualizer 4.0, Software, and SWISSADME (http://www.swissadme.ch/) online tools program.

In silico molecular docking study
Native ligand and receptor preparation
The protein structure of macromolecule DPP-IV complexes with native ligand sitagliptin Protein Data Bank (PDB ID: 1 × 70, with 2.1Å resolution) was downloaded from the Research Collaboratory for Structural Bioinformatics PDB via the website: https://www.rcsb.org/. Macromolecule DPP-IV receptors and native ligand were separated using PMV-1.5.6. Gasteiger charges were added to each ligand atom. Water molecules were eliminated from each protein receptor and protonated. Then, a native ligand and protein receptor was prepared and converted in the PDBQT format (.pdbqt) using AutodockTools and OpenBabel programs.

Preparation of phytocompounds as a test ligand
In this study, the structure of phytocompounds from A. champeden was collected from some literature as shown in Figure 1. Each phytocompounds were prepared as a test ligand using ChemDraw® Pro v15 to build a two-dimension structure of each phytocompounds. Chem three-dimensional (3D)® Pro v15 was converted to a 3D structure, minimized using the MMFF94 force field, and saved to PDB (.pdb).

Analysis of in silico molecular docking
According to its protocols, the analysis of in silico molecular docking of 41 phytocompounds from A. champeden was conducted using Autodock 4.2.6. Using the Lamarckian Genetic Algorithm (LGA) based on the lowest free energy of binding (ΔG), the native ligand was simulated in various conformations for best binding to the protein DPP-IV receptor binding site. The parameters of LGA were: elitism of 1, crossover rate of 0.8, the mutation rate of 0.02, the population size of 150, energy evaluation of 2500,000, and 100 runs. Moreover, the grid box comprised of 52 × 28 × 26Å points spaced by 0.375Å was centered on the active site of x = 40.926Å; y = 50.522Å; z = 35.031Å (XYZ-coordinates) according to a previous study. The grid condition was used for molecular docking analysis of 41 phytocompounds from A. champeden. The results of molecular docking data were visualized using Accelrys Discovery Studio Visualizer-4.0.

Determination of ADME-tox prediction
According to the literature, ADME-Tox prediction of the best docking results was determined using SWISSADME online tools. Briefly, each phytocompounds (PDB format) structure was converted in SMILES format using OpenBabel GUI. SWISSADME online tools program was used to determine ADME-Tox of 12 phytocompounds.

RESULTS

In silico molecular docking study
Validation of molecular docking method
In the present study, the docking results of the native ligand (sitagliptin) demonstrated a root mean square deviation (RMSD) value of 0.55 Å (<2 Å) with a binding free energy (ΔG) value of ~8.59 kcal/mol (inhibition constant
Figure 1: 2D structure of phytocompounds from *Artocarpus champeden*. 2D: Two-dimension

Figure 2 shows that the overlay position between the docking results and the original native ligand does not significantly different positions according to the RMSD of 508.58 nM) and clusters of 82% for 100 times running.
value <2 Å, indicating that the grid size and grid center of the docking process was different valid.

The docking results of 41 phytocompounds from A. champeden in Table 1 show that five compounds had a lower ΔG value and inhibition constant than the native ligand. Seven compounds have ΔG value and inhibition constant close to the native ligand.

**Studies on molecular interaction**

Figure 3 demonstrates visualization of native ligand interaction with active site residue of DPP-IV macromolecule receptors. In Figure 4, it was shown that 12 phytocompounds have conformational interactions with subsites of the DPP-IV receptor.

**ADME-tox prediction**

The ADME-Tox properties prediction of selected 12 phytocompounds from A. champeden according to the molecular docking study is presented in Table 2. The physicochemical properties prediction provides an overview of bioavailability levels of phytocompounds, as shown in Figure 5.

![Figure 2: Visualization of original (yellow) and re-docked (green) native ligand overlay position](image)

![Figure 3: Visualization of (a) two-dimension and (b) three-dimension of molecular interaction between native ligand against macromolecule of DPP-IV receptor (PDB ID: 1X70). PDB: Protein Data Bank, DPP-IV: Dipeptidyl peptidase IV](image)

**DISCUSSION**

The result of re-docking of native ligand indicates the level of validity of grid box and box size used with an RSMD value of 0.55 Å (<2 Å), which refers to the previous study,[17,19] indicating that the grid size and grid center of the docking process was different valid. The docking result demonstrated native ligand and test ligand interaction with the active site of DPP-IV receptor macromolecules.

The DPP-IV receptor has some active site areas at subsites area of amino acid residues known as S₁, S₁', S₂, S₂', and S₂ ext.[20-22] The test ligand activity can generally be predicted based on interactions at subsites (S₁, S₂, and S₂ ext.) of the DPP-IV receptor.[21,22]

In this study, it was found that five phytocompounds had lower ΔG values than the native ligand, including 24-methylencycloartanon, cycloartenon, cycloartenol, β-sitosterol, and cycloeucalenol, and seven phytocompounds that had an ΔG value close to the native ligand include cudraflavon C, artoindonesianin A, 5'-hydroxycudraflavon A, artoindonesianin B, artoindonesianin R, artoindonesianin A3, and cyclocommunin. In addition, the 12 phytocompounds showed conformational interactions that were specific to the active subsite of the DPP-IV receptor. Each amino acid residue of the active subsites of the DPP-IV receptor can form seven different interaction conformations with the test ligand.[23]

The ADME-Tox properties play a crucial role in the drug industry. They are generally used in drug development, mainly using the computer-aided drug design approach to reduce unwanted effects. 24-Methylencycloartanon has an MW value that is in the unacceptable range, while the others are in the acceptable range. Artoindonesianin A, artoindonesianin A3, artoindonesianin B, artoindonesianin R, cudraflavon C, cyclocommunin, and 5'-hydroxycudraflavon A obey the Lipinski rule, except six other compounds (RO5 value >0).[24]
### Table 1: Docking results characteristic and ligand-receptor interaction

| Ligand                        | ΔG value (kcal/mol) | Inhibition constant (nM) | Interaction                                                                 |
|-------------------------------|---------------------|---------------------------|-----------------------------------------------------------------------------|
| Sitagliptin (native)          | −6.13               | 508.58                    | His740, Val711, Asn710, Tyr666, Tyr667, Ser630, Tyr547, Arg358, Phe357, Ser209, Phe208, Val207, Gly206, Glu205, Arg125 |
| 24-methylocyloartenon         | −10.77              | 12.16                     | His740, Val711, Asn710, Arg609, Tyr666, Tyr662, Trp659, Val656, Tyr631, Ser630, Tyr547, Arg358, Phe357, Ser209, Phe208, Val207, Gly206, Glu205, Arg125 |
| Artobiloxanthon               | −6.92               | 8520                      | Tyr630, Tyr666, Tyr662, Ser552, Pro550, Gly549, Tyr547, Arg358, Phe357, Ser209, Phe208, Val207, Gly206, Glu205, Arg125 |
| Artocarpanon                 | −6.13               | 32070                     | His740, Val711, Asn710, Arg609, Tyr666, Tyr662, Val666, Tyr631, Ser630, Tyr547, Phe357, Ser209, Val207, Gly206, Glu205, Arg125 |
| Artocarpin                   | −6.95               | 7990                      | His546, Val711, Asn710, Arg609, Tyr666, Tyr662, Val666, Tyr631, Ser630, Tyr547, Phe357, Ser209, Val207, Gly206, Glu205, Arg125 |
| Artocarpin A                | −7.76               | 2040                      | His740, Val711, Asn710, Arg609, Tyr666, Tyr662, Tyr631, Ser630, Ser552, Pro550, Gly549, Tyr547, Phe357, Ser209, Gly206, Glu205, Arg125 |
| Artocarpin B                | −6.82               | 9990                      | Asn110, Arg609, Tyr666, Tyr662, Arg358, Phe357, Ser209, Val207, Gly206, Glu205, Arg125 |
| Artoindonesianin A           | −8.50               | 592                       | Asn110, Arg609, Tyr666, Tyr662, Tyr631, Ser630, Tyr547, Phe357, Glu206, Arg125 |
| Artoindonesianin A2          | −6.20               | 28340                     | Arg609, Tyr666, Asp635, Tyr662, Ser630, Tyr547, Phe357, Ser209, Val207, Gly206, Glu205, His126, Arg125 |
| Artoindonesianin A3          | −8.06               | 1240                      | His740, Val711, Arg609, Tyr666, Tyr662, Trp659, Val656, Tyr631, Ser630, Tyr547, Arg358, Phe357, Ser209, Val207, Gly206, Glu205, Arg125 |
| Artoindonesianin B           | −8.14               | 1080                      | His740, Val711, Arg609, Tyr666, Tyr662, Val656, Tyr631, Ser630, Tyr547, Arg358, Phe357, Ser209, Phe208, Val207, Gly206, Glu205, Arg125 |
| Artoindonesianin E           | −6.26               | 25580                     | Arg609, Tyr666, Tyr662, Ser552, Pro550, Gly549, Tyr547, Arg358, Phe357, Ser209, Val207, Gly205, Glu205, Arg125 |
| Artoindonesianin M           | −7.39               | 3850                      | Arg609, Tyr666, Tyr662, Ser630, Tyr547, Arg358, Phe357, Ser209, Phe208, Val207, Gly205, Glu205, Arg125 |
| Artoindonesianin Q           | −7.19               | 5370                      | His740, Val711, Arg609, Tyr666, Asp635, Tyr662, Trp659, Val656, Tyr631, Ser630, Tyr547, Arg358, Phe357, Ser209, Val207, Gly206, Glu205, His126, Arg125 |
| Artoindonesianin R           | −8.10               | 1160                      | His740, Val711, Asn710, Arg609, Tyr666, Tyr662, Tyr631, Ser630, Ser552, Pro550, Gly549, Tyr547, Phe357, Ser209, Val207, Gly206, Glu205, His126, Arg125 |
| Artoindonesianin S           | −6.60               | 14410                     | His740, Arg609, Tyr666, Tyr662, Trp659, Val656, Tyr631, Ser630, Tyr547, Phe357, Ser209, Val207, Gly206, Glu205, His126, Arg125 |
| Artoindonesianin T           | −6.22               | 27750                     | His740, Arg609, Tyr666, Tyr662, Trp659, Tyr631, Ser630, Tyr547, Ser209, Val207, Gly206, Glu205, His126, Arg125 |
| Artoindonesianin U           | −6.08               | 34950                     | His740, Val711, Asn710, Arg609, Tyr666, Tyr662, Tyr631, Ser630, Ser552, Pro550, Gly549, Tyr547, Phe357, Ser209, Val207, Gly206, Glu205, Arg125 |
| Artoindonesianin V           | −7.73               | 2140                      | His740, Val711, Asn710, Arg609, Tyr666, Tyr662, Tyr631, Ser630, Ser552, Pro550, Gly549, Tyr547, Phe357, Ser209, Val207, Gly206, Glu205, Arg125 |
| Artonin A                    | −7.95               | 1490                      | His740, Val711, Asn710, Arg609, Tyr666, Tyr662, Tyr631, Ser630, Tyr547, Arg358, Phe357, Ser209, Val207, Gly206, Glu205, Arg125 |
| Artonin B                    | −7.60               | 2700                      | Tyr666, Tyr667, Tyr631, Tyr635, Ser552, Cys651, Pro550, Gly549, Tyr547, Arg358, Phe357, Ser209, Val207, Gly206, Glu205, Arg125 |
| Artonin E                    | −7.70               | 2250                      | His740, Asn710, Arg609, Tyr666, Tyr662, Ser630, Pro550, Gly549, Tyr547, Arg358, Phe357, Ser209, Phe208, Val207, Gly206, Glu205, Arg125 |
| β-sitosterol                  | −9.97               | 49.17                     | His740, Val711, Asn710, Arg609, Tyr666, Tyr662, Trp659, Val656, Tyr631, Ser630, Tyr547, Arg358, Phe357, Ser209, Phe208, Val207, Gly206, Glu205, Arg125 |
| Chaplalin                    | −7.21               | 5160                      | His740, Val711, Arg609, Tyr666, Tyr662, Trp659, Val656, Tyr631, Ser630, Tyr547, Arg358, Phe357, Ser209, Val207, Gly206, Glu205, Arg125 |
| Cudraflavon C                | −8.53               | 558.13                    | Val711, Arg609, Tyr666, Tyr662, Trp659, Val656, Tyr631, Ser630, Tyr547, Arg358, Phe357, Ser209, Val207, Gly206, Glu205, Arg125 |
| Cycloartenol                | −10.06              | 42                        | His740, Val711, Asn710, Arg609, Tyr666, Tyr662, Val656, Tyr631, Ser630, Tyr547, Arg358, Phe357, Ser209, Val207, Gly206, Glu205, Arg125 |
| Cycloartenon                | −10.48              | 21                        | His740, Val711, Asn710, Arg609, Tyr666, Tyr662, Trp659, Val656, Tyr631, Ser630, Tyr547, Arg358, Phe357, Ser209, Val207, Gly206, Glu205, Arg125 |
Table 1: Contd...

| Ligand               | ΔG value (kcal/mol) | Inhibition constant (nM) | Interaction                          |
|----------------------|---------------------|--------------------------|--------------------------------------|
| Cycloartobiloxanton  | −7.26               | 4780                     | Val[11]; Asn[10]; Tyr[670]; Arg[699]; Tyr[666]; Tyr[662]; Tyr[651]; Ser[630]; Phe[587]; Arg[388]; Phe[577]; Ser[509]; Val[507]; Glu[506]; Arg[125] |
| Cycloartocarpin      | −7.04               | 6870                     | His[740]; Val[711]; Tyr[666]; Tyr[662]; Trp[599]; Val[566]; Tyr[531]; Ser[630]; Phe[547]; Arg[358]; Phe[354]; Ser[209]; Val[207]; Glu[206]; Arg[125]  |
| Cyclochampedol       | −5.97               | 42060                    | Asn[110]; Arg[669]; Tyr[666]; Tyr[662]; Ser[630]; Phe[357]; Arg[209]; Val[207]; Glu[206]; His[126]; Arg[125] |
| Cyclocoumarin        | −8.06               | 1240                     | Val[711]; Tyr[666]; Tyr[662]; Trp[599]; Val[566]; Tyr[531]; Phe[357]; Val[207]; Glu[206]; Arg[125] |
| Cyclocoumarinol      | −7.06               | 6720                     | His[740]; Val[711]; Tyr[666]; Tyr[662]; Ser[630]; Ser[552]; Pro[506]; Gly[547]; Tyr[547]; Phe[538]; Phe[537]; Ser[209]; Glu[206]; Arg[125] |
| Cycloeculanol        | −9.96               | 50                       | His[740]; Val[711]; Tyr[666]; Tyr[662]; Val[566]; Tyr[531]; Ser[630]; Phe[547]; Arg[358]; Phe[354]; Ser[209]; Val[207]; Glu[206]; Glu[205]; Arg[125] |
| Cyclohexofillin      | −7.54               | 2990                     | Asn[110]; Tyr[666]; Tyr[662]; Tyr[581]; Phe[567]; Phe[547]; Arg[358]; Arg[355]; Ser[209]; Phe[208]; Glu[206]; Glu[125]; Arg[125] |
| Glutinol             | −6.62               | 14130                    | His[740]; Tyr[666]; Tyr[662]; Ser[569]; Ser[209]; Glu[206]; His[126]; Arg[125]  |
| Heterofillin         | −7.15               | 5760                     | Asn[110]; Arg[669]; Tyr[666]; Tyr[662]; Ser[552]; Pro[506]; Gly[547]; Tyr[547]; Arg[358]; Phe[357]; Ser[209]; Val[207]; Glu[206]; Glu[205]; Arg[125] |
| Heteroflavon A       | −6.33               | 22800                    | Arg[669]; Tyr[666]; Ser[547]; Arg[358]; Phe[357]; Ser[209]; Val[207]; Glu[206]; Glu[205]; His[126]; Arg[125] |
| Heteroflavon C       | −5.74               | 61750                    | Arg[669]; Tyr[666]; Ser[547]; Arg[358]; Phe[357]; Ser[209]; Val[207]; Glu[206]; Glu[205]; His[126]; Arg[125] |
| 5'-Hydroxycudraflavon A | −8.33              | 788                      | His[740]; Val[711]; Arg[669]; Tyr[666]; Tyr[662]; Trp[599]; Val[566]; Tyr[531]; Ser[630]; Arg[358]; Phe[547]; Ser[209]; Val[207]; Glu[206]; Glu[205]; Arg[125] |
| Morusin              | −7.82               | 1850                     | His[740]; Val[711]; Tyr[666]; Tyr[662]; Trp[599]; Val[566]; Tyr[531]; Ser[630]; Phe[547]; Ser[126]; Arg[125]  |
| Morusin Hydroperoxide | −7.94              | 1510                     | His[740]; Val[711]; Arg[669]; Tyr[666]; Tyr[662]; Trp[599]; Val[566]; Tyr[531]; Ser[630]; Phe[547]; Ser[126]; Arg[125]  |
| Norartocarpin        | −6.74               | 11550                    | His[740]; Val[711]; Arg[669]; Tyr[666]; Tyr[662]; Tyr[531]; Ser[630]; Gly[547]; Tyr[547]; Arg[358]; Phe[357]; Ser[209]; Glu[206]; Glu[205]; Arg[125] |

All phytocompounds showed the H-bond (acceptor and donor) and skin permeant value in the acceptable range. Based on the topological polar surface area (TPSA) value, which reveals that 24-methylcycloartanoxan, β-sitosterol, cycloartenol, cycloarten, and cycloeculanol have an excellent brain penetration (TPSA <70Å²), and seven other compounds have good gastrointestinal penetration (with TPSA <140Å²). XLOGP3 shows the lipophilicity and polarity value prediction of phytocompounds. The higher the value, the lower the polarity. ESOL indicates the solubility levels of phytocompounds. The lower the values, the lower the solubility. Figure 5 demonstrated that...
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Figure 4: Interaction visualization of twelve best docking results of phytocompounds from Artocarpus champeden against macromolecule of DPP-IV receptor. DPP-IV: Dipeptidyl peptidase IV
the phytocompounds of artonindonesianin (A3, B, and R), β-sitosterol, cycloartenol, and 5′-hydroxycuraflavon A were the acceptable/optimal range of ADME-Tox/physicochemical space for oral bioavailability.

**CONCLUSION**

Analysis of *in silico* molecular docking and ADME-Tox prediction were performed to study the potential pharmacological activity of phytocompounds from *A. champeden* as DPP-IV inhibitors. Our findings show that almost all phytocompounds have potential interaction with the receptor at the active subsites. Nevertheless, 12 phytocompounds have the most similar interaction with the DPP-IV receptor and have different physicochemical properties for bioavailability and pharmacokinetics prediction.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. de Almeida Lopes MM, de Souza KO, de Oliveira Silva E. Cempedak - *Artocarpus champeden*, in de Brito E, Rodrigues S, and de Oliveira Silva E. 1st Edition. Exotic Fruits Reference Guide. London: Academic Press: 2018; 121-7.
2. Achmad SA, Hakim EH, Juliawaty LD, Makmur L, Suyatno S. A new prenylated flavone from *Artocarpus champeden*. J Nat Prod 1996;59:878-9.
3. Hakim EH, Juliawaty LD, Syah YM, Achmad SA. Molecular diversity of *Artocarpus champeden* (Moraceae): A species endemic to Indonesia. Mol Divers 2005;9:149-58.
4. Syah YM, Juliawaty LD, Achmad SA, Hakim EH, Ghisalberti EL. Cytotoxic prenylated flavones from *Artocarpus champeden*. J Nat Med 2006;60:308-12.
5. Widyawaruyanti A, Subehan S, Kalauni SK, Awale S, Nindatu M, Zaini NC, et al. New prenylated flavones from *Artocarpus champeden*, and their antimalarial activity *in vitro*. J Nat Med 2007;61:410-3.
6. Arciniega M, Lange OF. Improvement of virtual screening results by docking data feature analysis. J Chem Inf Model 2014;54:1401-11.
7. Morris GM, Ruth H, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, et al. Software news and updates AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. J Comput Chem 2009;30:2785-91.
8. Wang L, Wu Y, Deng Y, Kim B, Pierce L, Krilov G, et al. Accurate and
reliable prediction of relative ligand binding potency in prospective
drug discovery by way of a modern free-energy calculation
protocol and force field. J Am Chem Soc 2015;137:2695-703.
9. Belew RK, Forli S, Goodsell DS, O’Donnell TJ, Olson AJ.
Fragment-based analysis of ligand dockings improves classification
of actives. J Chem Inf Model 2016;56:1597-607.
10. Daina A, Michielin O, Zoete V. SwissADME: A free web tool
to evaluate pharmacokinetics, drug-likeness and medicinal chemistry
friendliness of small molecules. Sci Rep 2017;7:4271.
11. Pires DE, Blundell TL, Ascher DB. pkCSM: Predicting
small-molecule pharmacokinetic and toxicity properties using
graph-based signatures. J Med Chem 2015;58:4066-72.
12. Verma D, Mitra D, Paul M, Chaudhary P, Kamboj A, Thatoi H, et al.
Potential inhibitors of SARS-CoV-2 (COVID-19) proteases PLpro and
Mpro/3CLpro: Molecular docking and simulation studies of
diverse medicinal plant natural components. Curr Res
Pharmacol Drug Discov 2021;2:100038.
13. Prasetyanti IK, Sukardiman S, Suharjono S. ADMET prediction
and in silico analysis of mangostin derivatives and sinensetin
on maltase-glucoamylase target for searching anti-diabetes drug
candidates. Pharmacog J 2021;13:883-889.
14. Abdurrahman S, Ruslin R, Hasanah AN, Mustarichie R. Molecular
docking studies and ADME-Tox prediction of phytocompounds
from Merremia peltata as a potential anti-alopecia treatment. J Adv
Pharm Technol Res 2021;12:132-9.
15. Arunkumar J, Rajarajan S. Study on antiviral activities,
drug-likeness and molecular docking of bioactive compounds of
Punica granatum L. to Herpes simplex virus-2 (HSV-2). Microb
Pathog 2018;118:301-9.