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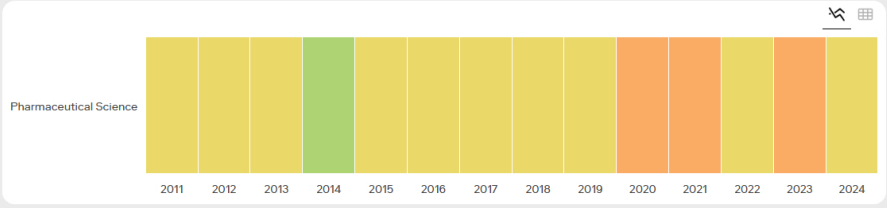

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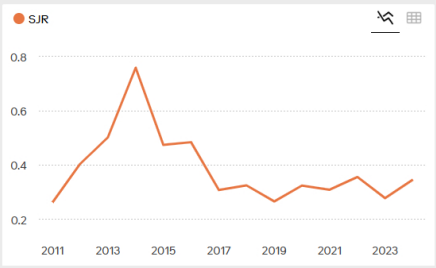

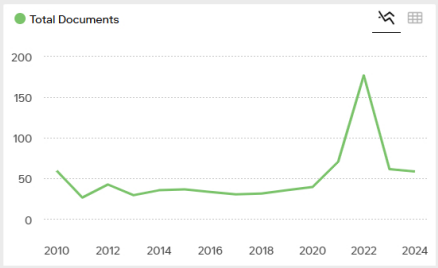

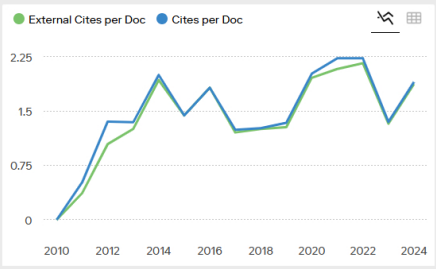

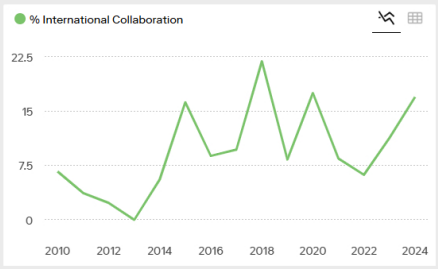

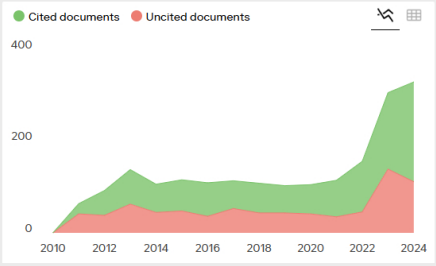

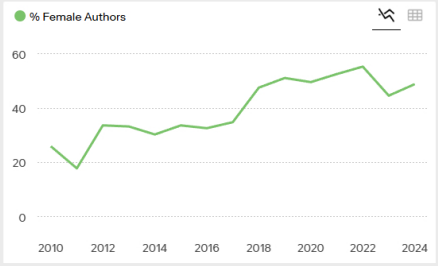

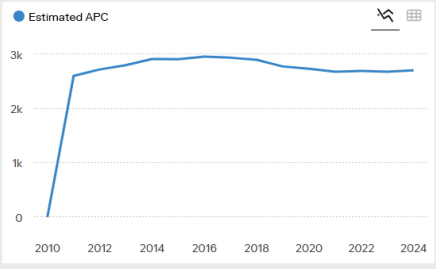

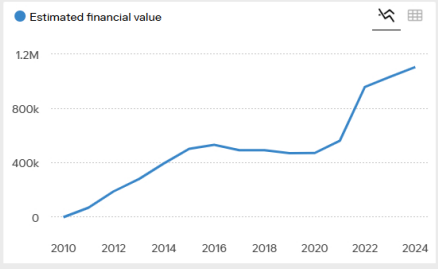

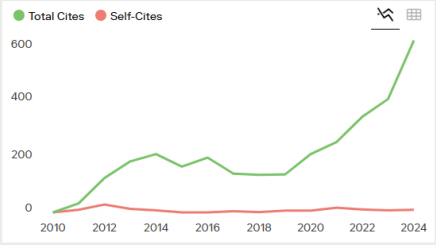

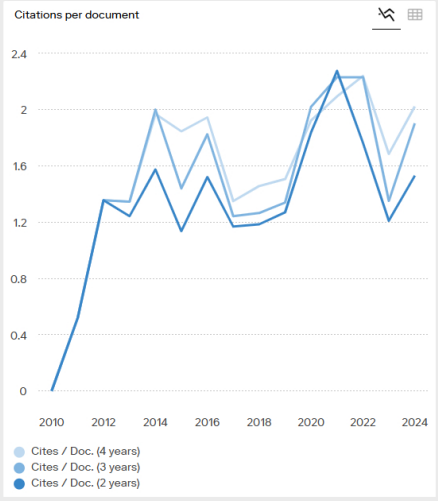

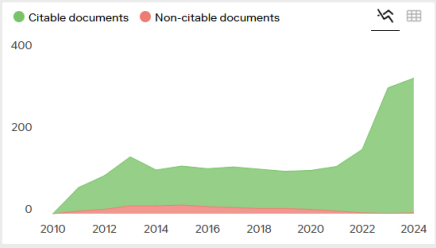

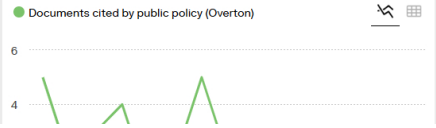

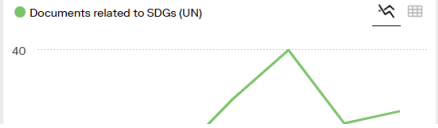

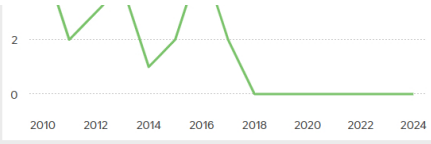

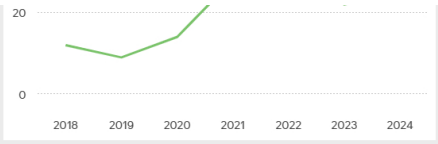

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ORIGINAL ARTICLE

Dipeptidyl peptidase IV inhibition of phytocompounds from *Artocarpus champeden* (Lour.) Stokes

In silico molecular docking study and ADME-Tox prediction approach

Supandi, Supandi; Wulandari, Mesy Savira[1]; Samsul, Erwin[1]; Azminah, Azminah[2]; Purwoko, Reza Yuridian[3]; Herman, Herman[1]; Kuncoro, Hadi[1]; Ibrahim, Arsyik[1]; Silfi Ambarwati, Neneng Siti[4]; Rosmalena, Rosmalena[5]; Azizah, Rizqi Nur[6]; Paramita, Swandari[7]; Ahmad, Islamudin[1].

Author Information

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OPEN

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.

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.[1] 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*.[2345] 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.[6789] ADME-Tox prediction is performed using an online-based application such as SWISSADME, which aims to study physicochemical and pharmacokinetic properties.[1011] 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,[12] ADMET prediction of mangosteen derivates,[13] ADME-Tox prediction of phytocompounds from *Merremia peltata*,[14] and drug-likeness prediction of bioactive compounds from *Punica granatum* L.[15]

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

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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.[7,16]

Preparation of phytocompounds as a test ligand

In this study, the structure of phytocompounds from *A. champeden* was collected from some literature,[2,3,4,5] 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).[8]

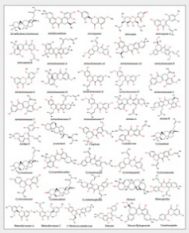

Figure 1: 2D structure of phytocompounds from *Artocarpus champeden*. 2D: Two-dimension

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.[7] 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.[17] 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.[18]

Determination of ADME-tox prediction

According to the literature, ADME-Tox prediction of the best docking results was determined using SWISSADME online tools.[11] 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.[18]

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 of 508.58 nM) and clusters of 82% for 100 times running. [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 value <2 Å, indicating that the grid size and grid center of the docking process was different valid.

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

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.

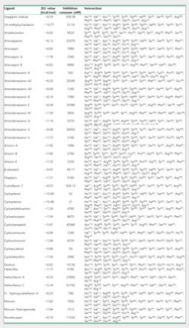

Table 1: Docking results characteristic and ligand-receptor interaction

Studies on molecular interaction

Figure 3 demonstrates visualization of native ligand interaction with active site residue of DPP-IV macromolecule receptors.

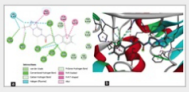

Figure 3: Visualization of (a) two-dimension and (b) three-dimension of molecular interaction between native ligand against macromolecule of DPP-IV receptor (PDB ID: 1X70). PDB: Protein Data Bank, DPP-IV: Dipeptidyl peptidase IV

In Figure 4, it was shown that 12 phytocompounds have conformational interactions with subsites of the DPP-IV receptor.

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

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.

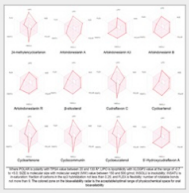

Figure 5: Bioavailability radar representation of the 12 best docking findings of *Artocarpus champeden* phytocompounds

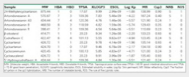

Table 2: ADME-Tox properties prediction of twelve best docking results using SWISSADME online tools software

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 S_1, S_1', S_2', S_2, and S_2 extensive.[20,21,22] The test ligand activity can generally be predicted based on interactions at subsites (S_1, S_2, and S_2 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-VI 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] 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-methylencycloartanon, β-sitosterol, cycloartenol, cycloartenon, and cycloeucalenol have an excellent brain penetration (TPSA <70Å^2), and seven other compounds have good gastrointestinal penetration (with TPSA <140Å^2).[25] XLOGP3 shows the lipophilicity and polarity value prediction of phytocompounds. The higher the value, the lower the polarity.[26,27] ESOL indicates the solubility levels of phytocompounds. The lower the values,[28] the lower solubility.[29] Figure 5 demonstrated that the phytocompounds of artonindonesianin (A3, B, and R), β-sitosterol, cycloartenol, and 5'-hydroxycudraflavon 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.

Financial support and sponsorship

Nil.

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 Exotic Fruits Reference Guide. 20181st Edition London Academic Press:121–7
Cited Here

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
Cited Here | Google Scholar

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

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

ORIGINAL ARTICLE

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

Supandi Supandi, Mesy Savira Wulandari[1], Erwin Samsul[1], Azminah Azminah[2], Reza Yuridian Purwoko[3], Herman Herman[1], Hadi Kuncoro[1], Arsyik Ibrahim[1], Neneng Siti Silfi Ambarwati[4], Rosmalena Rosmalena[5], Rizqi Nur Azizah[6], Swandari Paramita[7], Islamudin Ahmad[1]

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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,

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Vietnam, Myanmar, Thailand, Malaysia, and Indonesia.[1] 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*.[2-5] 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.[6-9] ADME-Tox prediction is performed using an online-based application such as SWISSADME, which aims to study physicochemical and pharmacokinetic properties.[10,11] 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,[12] ADMET prediction of mangosteen derivates,[13] ADME-Tox prediction of phytocompounds from *Merremia peltata*,[14] and drug-likeness prediction of bioactive compounds from *Punica granatum* L.[15]

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.[7,16]

Preparation of phytocompounds as a test ligand

In this study, the structure of phytocompounds from *A. champeden* was collected from some literature,[2-5] 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).[8]

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.[7] 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.[17] 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.[18]

Determination of ADME-tox prediction

According to the literature, ADME-Tox prediction of the best docking results was determined using SWISSADME online tools.[11] 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.[18]

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

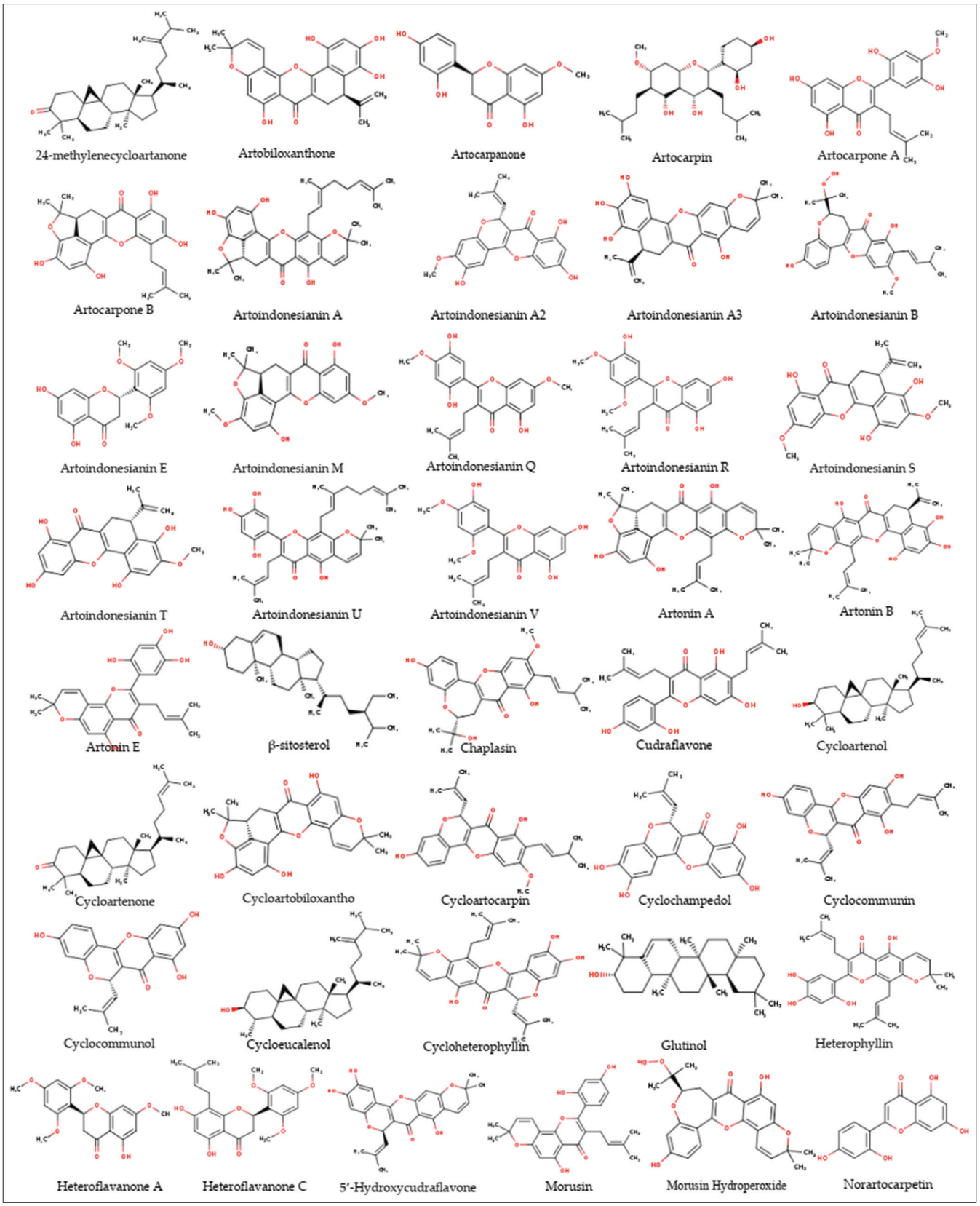

Figure 1: 2D structure of phytocompounds from *Artocarpus champeden.* 2D: Two-dimension

of 508.58 nM) and clusters of 82% for 100 times running. 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

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.

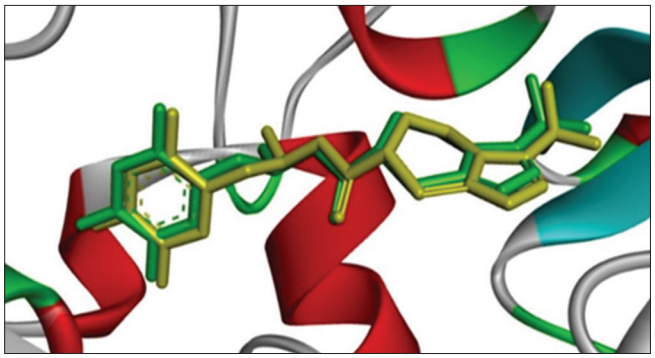

Figure 2: Visualization of original (yellow) and re-docked (green) native ligand overlay position

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 S_1, S_1', S_2', S_2, and S_2 extensive.[20-22] The test ligand activity can generally be predicted based on interactions at subsites (S_1, S_2, and S_2 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 cyclocommunim. In addition, the 12 phytocompounds showed conformational interactions that were specific to the active subsite of the DPP-VI 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]

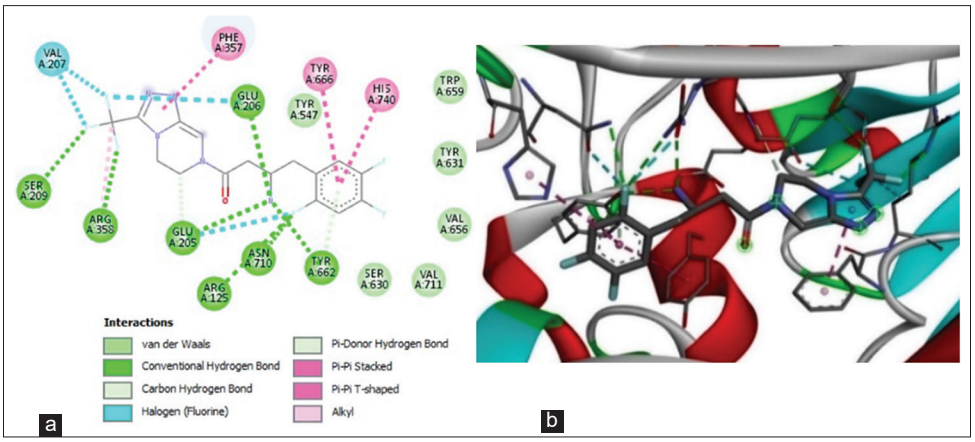

Figure 3: Visualization of (a) two-dimension and (b) three-dimension of molecular interaction between native ligand against macromolecule of DPP-IV receptor (PDB ID: 1X70). PDB: Protein Data Bank, DPP-IV: Dipeptidyl peptidase IV

Table 1: Docking results characteristic and ligand-receptor interaction

Ligand	ΔG value (kcal/mol)	Inhibition constant (nM)	Interaction
Sitagliptin (native)	−8.59	508.58	His^{740}; Val^{711}; Asn^{710}; Tyr^{666}; Tyr^{662}; Trp^{659}; Val^{656}; Tyr^{631}; Ser^{630}; Tyr^{547}; Arg^{358}; Phe^{357}; Ser^{209}; Phe^{208}; Val^{207}; Glu^{206}; Glu^{205}; Arg^{125}
24-methylcycloartanon	−10.77	12.16	His^{740}; Val^{711}; Asn^{710}; Arg^{669}; Tyr^{666}; Tyr^{662}; Trp^{659}; Val^{656}; Tyr^{631}; Ser^{630}; Tyr^{547}; Arg^{358}; Phe^{357}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; Arg^{125}
Artobiloxanton	−6.92	8520	Tyr^{670}; Tyr^{666}; Tyr^{662}; Tyr^{630}; Ser^{552}; Pro^{550}; Gly^{549}; Tyr^{547}; Arg^{358}; Phe^{357}; Ser^{209}; Phe^{208}; Val^{207}; Glu^{206}; Glu^{205}
Artocarpanon	−6.13	32070	His^{740}; Val^{711}; Asn^{710}; Arg^{669}; Tyr^{666}; Tyr^{662}; Val^{656}; Tyr^{631}; Ser^{630}; Tyr^{547}; Phe^{357}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; His^{126}; Arg^{125}
Artocarpin	−6.95	7990	His^{740}; Val^{711}; Asn^{710}; Arg^{669}; Tyr^{666}; Tyr^{662}; Val^{656}; Tyr^{631}; Ser^{630}; Tyr^{547}; Phe^{357}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; His^{126}; Arg^{125}
Artocarpon A	−7.76	2040	His^{740}; Val^{711}; Asn^{710}; Arg^{669}; Tyr^{666}; Tyr^{662}; Tyr^{631}; Ser^{630}; Ser^{552}; Pro^{550}; Gly^{549}; Tyr^{547}; Phe^{357}; Ser^{209}; Glu^{206}; Glu^{205}; Arg^{125}
Artocarpon B	−6.82	9990	Asn^{710}; Arg^{669}; Tyr^{666}; Tyr^{662}; Tyr^{547}; Arg^{358}; Phe^{357}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; Arg^{125}
Artoindonesianin A	−8.50	592	Asn^{710}; Arg^{669}; Tyr^{666}; Tyr^{662}; Tyr^{631}; Ser^{630}; Tyr^{585}; Ser^{552}; Cys^{551}; Pro^{550}; Gly^{549}; Tyr^{547}; Arg^{358}; Phe^{357}; Arg^{356}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; Arg^{125}
Artoindonesianin A2	−6.20	28340	Arg^{669}; Tyr^{666}; Asp^{663}; Tyr^{662}; Tyr^{631}; Ser^{630}; Tyr^{547}; Phe^{357}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; His^{126}; Arg^{125}
Artoindonesianin A3	−8.06	1240	His^{740}; Val^{711}; Arg^{669}; Tyr^{666}; Tyr^{662}; Trp^{659}; Val^{656}; Tyr^{631}; Ser^{630}; Tyr^{547}; Arg^{358}; Phe^{357}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; Arg^{125}
Artoindonesianin B	−8.14	1080	His^{740}; Val^{711}; Arg^{669}; Tyr^{666}; Tyr^{662}; Val^{656}; Tyr^{631}; Ser^{630}; Tyr^{547}; Arg^{358}; Phe^{357}; Ser^{209}; Phe^{208}; Val^{207}; Glu^{206}; Glu^{205}; Arg^{125}
Artoindonesianin E	−6.26	25580	Arg^{669}; Tyr^{666}; Tyr^{662}; Ser^{552}; Pro^{550}; Gly^{549}; Tyr^{547}; Arg^{358}; Phe^{357}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}
Artoindonesianin M	−7.39	3850	Arg^{669}; Tyr^{666}; Tyr^{662}; Ser^{630}; Tyr^{547}; Arg^{358}; Phe^{357}; Ser^{209}; Phe^{208}; Val^{207}; Glu^{206}; Glu^{205}; Arg^{125}
Artoindonesianin Q	−7.19	5370	His^{740}; Val^{711}; Arg^{669}; Tyr^{666}; Asp^{663}; Tyr^{662}; Trp^{659}; Val^{656}; Tyr^{631}; Ser^{630}; Tyr^{547}; Arg^{358}; Phe^{357}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; His^{126}; Arg^{125}
Artoindonesianin R	−8.10	1160	His^{740}; Val^{711}; Asn^{710}; Arg^{669}; Tyr^{666}; Tyr^{662}; Tyr^{631}; Ser^{630}; Ser^{552}; Pro^{550}; Gly^{549}; Tyr^{547}; Phe^{357}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; His^{126}; Arg^{125}
Artoindonesianin S	−6.60	14410	His^{740}; Arg^{669}; Tyr^{666}; Tyr^{662}; Trp^{659}; Val^{656}; Tyr^{631}; Ser^{630}; Tyr^{547}; Phe^{357}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; His^{126}; Arg^{125}
Artoindonesianin T	−6.22	27750	His^{740}; Arg^{669}; Tyr^{666}; Tyr^{662}; Trp^{659}; Tyr^{631}; Ser^{630}; Tyr^{547}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; His^{126}; Arg^{125}
Artoindonesianin U	−6.08	34950	His^{741}; Val^{711}; Asn^{710}; Arg^{669}; Tyr^{666}; Tyr^{662}; Tyr^{631}; Ser^{630}; Ser^{552}; Pro^{550}; Gly^{549}; Tyr^{547}; Phe^{357}; Ser^{209}; Glu^{206}; Glu^{205}; Arg^{125}
Artoindonesianin V	−7.73	2140	His^{741}; Val^{711}; Asn^{710}; Arg^{669}; Tyr^{666}; Tyr^{662}; Tyr^{631}; Ser^{630}; Ser^{552}; Pro^{550}; Gly^{549}; Tyr^{547}; Phe^{357}; Ser^{209}; Glu^{206}; Glu^{205}; Arg^{125}
Artonin A	−7.95	1490	His^{740}; Val^{711}; Asn^{710}; Arg^{669}; Tyr^{666}; Tyr^{662}; Tyr^{631}; Ser^{630}; Tyr^{547}; Arg^{358}; Phe^{357}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; Arg^{125}
Artonin B	−7.60	2700	Tyr^{666}; Tyr^{662}; Tyr^{631}; Tyr^{585}; Ser^{552}; Cys^{551}; Pro^{550}; Gly^{549}; Tyr^{547}; Arg^{358}; Phe^{357}; Arg^{356}; Ser^{209}; Glu^{206}; Glu^{205}; Arg^{125}
Artonin E	−7.70	2250	His^{740}; Asn^{710}; Arg^{669}; Tyr^{666}; Tyr^{662}; Ser^{630}; Pro^{550}; Gly^{549}; Tyr^{547}; Arg^{358}; Phe^{357}; Ser^{209}; Phe^{208}; Val^{207}; Glu^{206}; Glu^{205}; Arg^{125}
β-sitosterol	−9.97	49.17	His^{740}; Val^{711}; Asn^{710}; Arg^{669}; Tyr^{666}; Tyr^{662}; Trp^{659}; Val^{656}; Tyr^{631}; Ser^{630}; Tyr^{547}; Arg^{358}; Phe^{357}; Ser^{209}; Phe^{208}; Val^{207}; Glu^{206}; Glu^{205}; Arg^{125}
Chaplasin	−7.21	5160	His^{740}; Val^{711}; Arg^{669}; Tyr^{666}; Tyr^{662}; Trp^{659}; Val^{656}; Tyr^{631}; Ser^{630}; Tyr^{547}; Arg^{358}; Phe^{357}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; Arg^{125}
Cudraflavon C	−8.53	558.13	Val^{711}; Arg^{669}; Tyr^{666}; Tyr^{662}; Trp^{659}; Val^{656}; Tyr^{631}; Ser^{630}; Tyr^{585}; Tyr^{547}; Arg^{358}; Phe^{357}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; Arg^{125}
Cycloartenol	−10.06	42	His^{740}; Val^{711}; Asn^{710}; Arg^{669}; Tyr^{666}; Tyr^{662}; Val^{656}; Tyr^{631}; Ser^{630}; Tyr^{547}; Arg^{358}; Phe^{357}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; Arg^{125}
Cycloartenon	−10.48	21	His^{740}; Val^{711}; Asn^{710}; Arg^{669}; Tyr^{666}; Tyr^{662}; Trp^{659}; Val^{656}; Tyr^{631}; Ser^{630}; Tyr^{547}; Arg^{358}; Phe^{357}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; Arg^{125}

Contd..

Table 1: Contd...

Ligand	ΔG value (kcal/mol)	Inhibition constant (nM)	Interaction
Cycloartobiloxanton	−7.26	4780	Val^{711}; Asn^{710}; Tyr^{670}; Arg^{669}; Tyr^{666}; Tyr^{662}; Tyr^{631}; Ser^{630}; Tyr^{547}; Arg^{358}; Phe^{357}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; Arg^{125}
Cycloartocarpin	−7.04	6870	His^{740}; Val^{711}; Tyr^{666}; Tyr^{662}; Trp^{659}; Val^{656}; Tyr^{631}; Ser^{630}; Tyr^{547}; Arg^{358}; Phe^{357}; Ser^{209}; Phe^{208}; Val^{207}; Glu^{206}; Glu^{205}; Arg^{125}
Cyclochampedol	−5.97	42060	Asn^{710}; Arg^{669}; Tyr^{666}; Tyr^{662}; Ser^{630}; Tyr^{547}; Arg^{358}; Phe^{357}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; His^{126}; Arg^{125}
Cyclocommunin	−8.06	1240	Val^{711}; Tyr^{666}; Tyr^{662}; Trp^{659}; Val^{656}; Tyr^{631}; Phe^{357}; Val^{207}; Glu^{206}; Glu^{205}; His^{126}; Arg^{125}
Cyclocommunol	−7.06	6720	His^{740}; Val^{711}; Asn^{710}; Tyr^{666}; Tyr^{662}; Tyr^{631}; Ser^{630}; Ser^{552}; Pro^{550}; Gly^{549}; Tyr^{547}; Phe^{357}; Ser^{209}; Glu^{206}; Glu^{205}; Arg^{125}
Cycloeucalenol	−9.96	50	His^{740}; Val^{711}; Asn^{710}; Arg^{669}; Tyr^{666}; Tyr^{662}; Val^{656}; Tyr^{631}; Ser^{630}; Tyr^{547}; Arg^{358}; Phe^{357}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; Arg^{125}
Cycloheterofilin	−7.54	2990	Asn^{710}; Tyr^{666}; Tyr^{662}; Tyr^{585}; Cys^{551}; Pro^{550}; Gly^{549}; Tyr^{547}; Arg^{358}; Phe^{357}; Arg^{356}; Ser^{209}; Phe^{208}; Glu^{206}; Glu^{205}; Arg^{125}
Glutinol	−6.62	14130	Asn^{710}; Tyr^{666}; Tyr^{662}; Tyr^{631}; Ser^{630}; Tyr^{547}; Phe^{357}; Ser^{209}; Glu^{205}; His^{126}; Arg^{125}
Heterofilin	−7.15	5760	Asn^{710}; Arg^{669}; Tyr^{666}; Tyr^{662}; Tyr^{585}; Ser^{552}; Pro^{550}; Gly^{549}; 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^{630}; Tyr^{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^{630}; Tyr^{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^{659}; Val^{656}; Tyr^{631}; Ser^{630}; Arg^{358}; Phe^{357}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; Arg^{125}
Morusin	−7.82	1850	His^{740}; Val^{711}; Tyr^{670}; Arg^{669}; Tyr^{666}; Tyr^{662}; Trp^{659}; Tyr^{631}; Ser^{630}; Tyr^{547}; Phe^{357}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; Arg^{125}
Morusin Hydroperoxide	−7.94	1510	His^{740}; Val^{711}; Arg^{669}; Tyr^{666}; Tyr^{662}; Trp^{659}; Val^{656}; Tyr^{631}; Ser^{630}; Tyr^{547}; Phe^{357}; Ser^{209}; Val^{207}; Glu^{206}; Glu^{205}; His^{126}; Arg^{125}
Norartocarpin	−6.74	11550	His^{740}; Val^{711}; Asn^{710}; Arg^{669}; Tyr^{666}; Tyr^{662}; Tyr^{631}; Ser^{630}; Gly^{549}; Tyr^{547}; Phe^{357}; Ser^{209}; Glu^{206}; Glu^{205}; Arg^{125}

Table 2: ADME-Tox properties prediction of twelve best docking results using SWISSADME online tools software

Sample	MW	HBA	HBD	TPSA	XLOGP3	ESOL	Log Kp	MR	Csp3	NRB	RO5
24-Methylencycloartanon	875.44	1	0	17.07	9.99	2.99e-09	−1.88	138.99	0.90	5	1
Artoindonesianin A	570.67	7	3	109.36	7.83	5.46e-09	−4.22	167.24	0.40	5	1
Artoindonesianin A3	434.44	7	4	120.36	4.76	1.46e-06	−5.57	121.90	0.24	1	0
Artoindonesianin B	468.50	8	3	118.59	4.82	1.59e-06	−5.74	129.43	0.35	8	0
Artoindonesianin R	398.41	7	3	109.36	4.54	5.64e-06	−5.51	110.69	0.23	5	0
β-sitosterol	414.71	1	1	20.23	9.34	1.26e-08	−2.20	133.23	0.93	6	1
Cudraflavon C	422.47	6	4	101.13	5.55	9.82e-07	−4.94	123.45	0.24	5	0
Cycloartenol	426.72	1	1	20.23	9.78	4.14e-09	−1.96	135.14	0.93	4	1
Cycloartenon	424.70	1	0	17.07	9.46	6.78e-09	−2.17	134.18	0.90	4	1
Cyclocommunin	420.45	6	3	100.13	5.85	4.83e-07	−4.71	121.00	0.24	3	0
Cycloeucalenol	426.72	1	1	20.23	9.91	3.99e-09	−1.87	135.40	0.93	5	1
5′-Hydroxycudraflavon A	434.44	7	3	109.36	4.84	1.30e-06	−5.51	121.40	0.24	1	0

MW: Molecular weight, HBA: Acceptable H-bonds, HBD: Donatable H-bonds, TPSA: Topological polar surface area (TPSA<140 $Å^2$ good intestinal absorptions and TPSA <70 $Å^2$ good brain penetration), XLOGP3: Lipophilicity descriptor, ESOL: Estimated solubility in water, Log Kp: Skin permeant, MR: Molar refractivity, Csp3: The fraction of carbon in the sp3 hybridization, NRB: The number of rotatable bonds, RO5: The rule of five Lipinski rules

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-methylencycloartanon, β-sitosterol, cycloartenol, cycloartenon, and cycloeucalenol have an excellent brain penetration (TPSA <70$Å^2$), and seven other compounds have good gastrointestinal penetration (with TPSA <140$Å^2$).[25] XLOGP3 shows the lipophilicity and polarity value prediction of phytocompounds. The higher the value, the lower the polarity.[26,27] ESOL indicates the solubility levels of phytocompounds. The lower the values,[28] the lower solubility.[29] Figure 5 demonstrated that

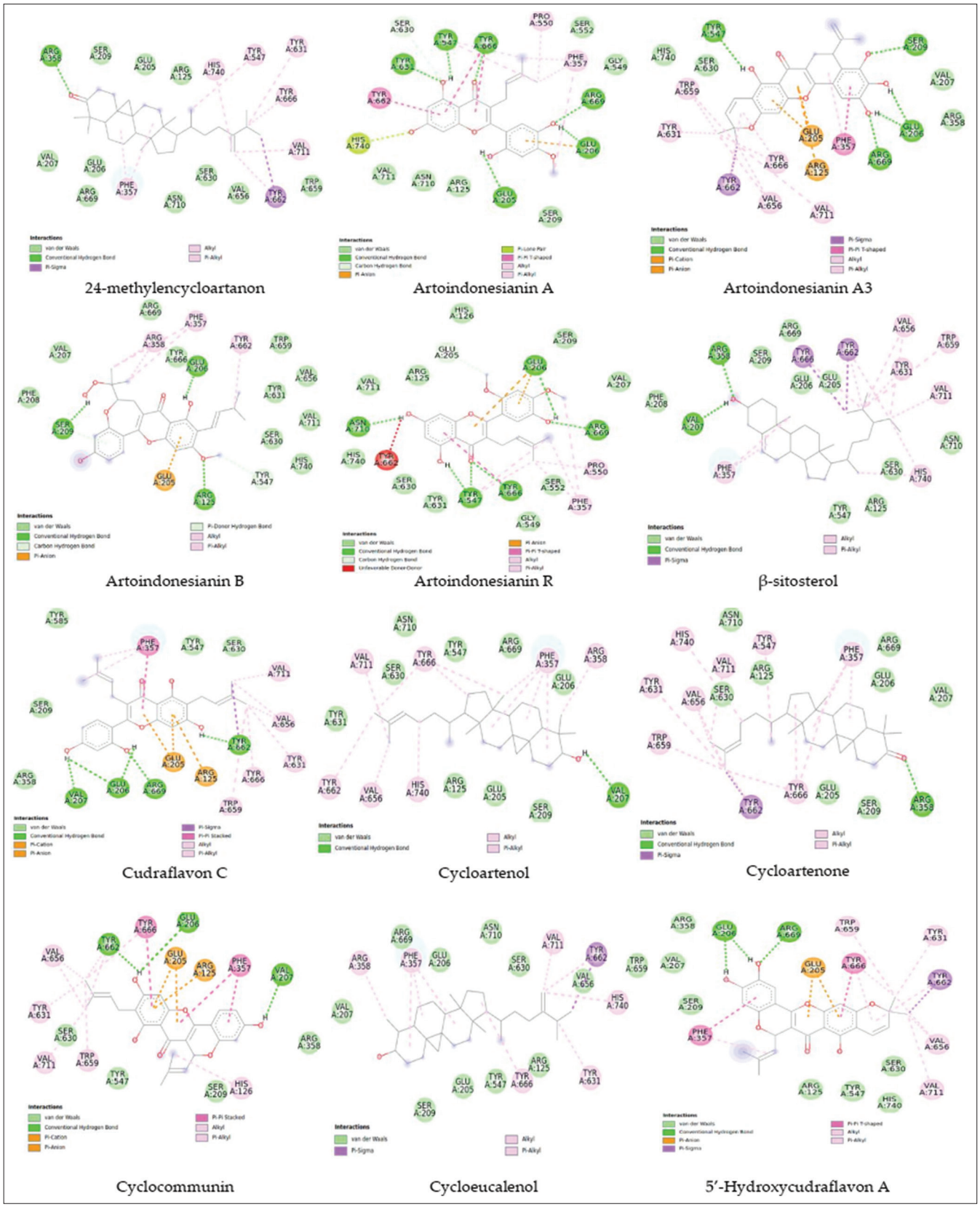

Figure 4: Interaction visualization of twelve best docking results of phytocompounds from *Artocarpus champeden* against macromolecule of DPP-IV receptor. DPP-IV: Dipeptidyl peptidase IV

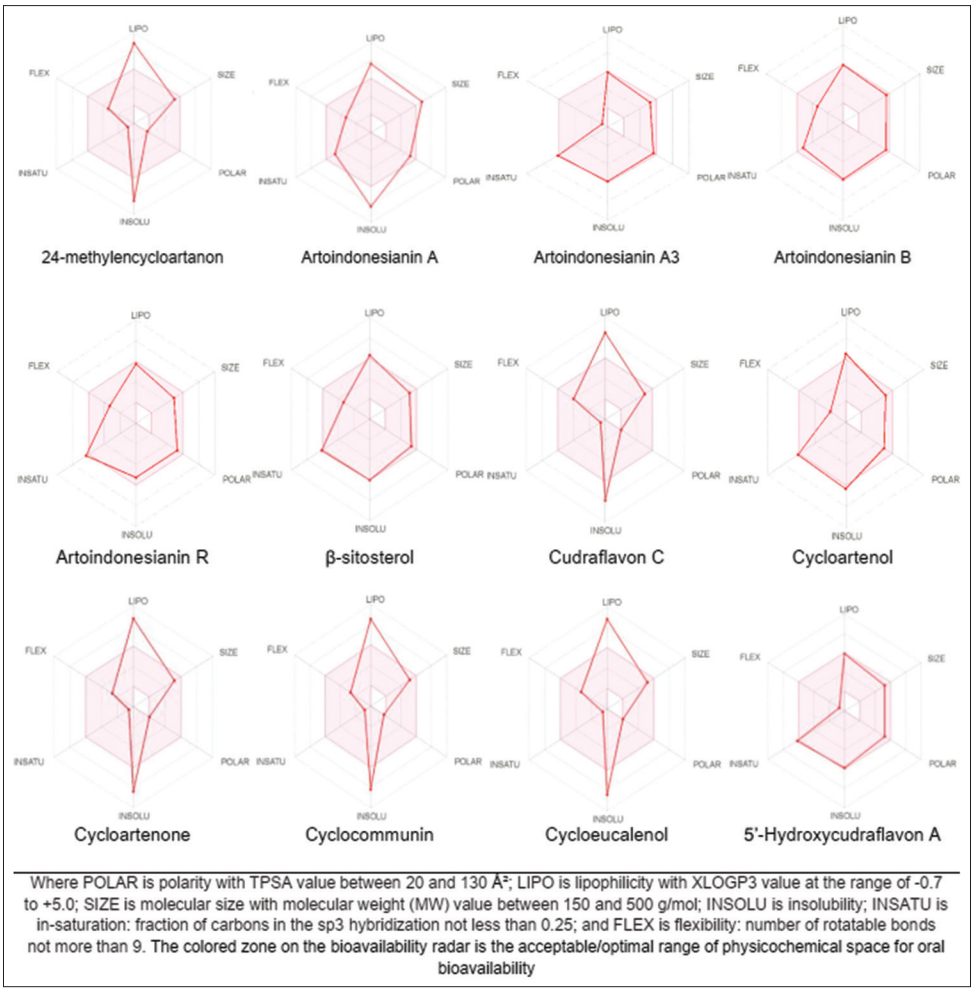

Figure 5: Bioavailability radar representation of the 12 best docking findings of *Artocarpus champeden* phytocompounds

the phytocompounds of artonindonesianin (A3, B, and R), β-sitosterol, cycloartenol, and 5′-hydroxycudraflavon 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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Nil.

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;7:42717.
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 three pertinent 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. Pharmacogn 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.
16. O'Boyle NM, Banck M, James CA, Morley C, Vandermeersch T, Hutchison GR. Open Babel: An open chemical toolbox. J Cheminform 2011;3:33.
17. Ahmad I, Arifianti AE, Sakti AS, Saputri FC, Mun'im A. Simultaneous natural deep eutectic solvent-based ultrasonic-assisted extraction of bioactive compounds of cinnamon bark and sappan wood as a dipeptidyl peptidase IV inhibitor. Molecules 2020;25:E3832.
18. Mahayasih PG, Harizal H, Herman H, Ahmad I. *In silico* identification of natural products from *Centella asiatica* as severe acute respiratory syndrome coronavirus-2 main protease inhibitor. J Adv Pharm Technol Res 2021;12:261-6.
19. Kim BR, Kim HY, Choi I, Kim JB, Jin CH, Han AR. DPP-IV inhibitory potentials of flavonol glycosides isolated from the seeds of *Lens culinaris*: *In vitro* and molecular docking analyses. Molecules 2018;23:E1998.
20. Arulmozhiraja S, Matsuo N, Ishitsubo E, Okazaki S, Shimano H, Tokiwa H. Comparative binding analysis of dipeptidyl peptidase IV (DPP-4) with antidiabetic drugs – An Ab initio fragment molecular orbital study. PLoS One 2016;11:e0166275.
21. Luo F, Fu Y, Ma L, Dai H, Wang H, Chen H, *et al.* Exploration of dipeptidyl peptidase-IV (DPP-IV) inhibitory peptides from silkworm pupae (*Bombyx mori*) proteins based on *in silico* and *in vitro* assessments. J Agric Food Chem 2022;70:3862-71.
22. Zhang X, Wang R, Cheng C, Zhang Y, Ma Y, Lu W. Identification of two novel dipeptidyl peptidase-IV inhibitory peptides from sheep whey protein and inhibition mechanism revealed by molecular docking. Food Biosci 2022;48:101733.
23. Radifar M, Yuniarti N, Istyastono EP. PyPLIF: Python-based protein-ligand interaction fingerprinting. Bioinformation 2013;9:325-8.
24. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev 2001;46:3-26.
25. Daina A, Zoete V. A BOILED-egg to predict gastrointestinal absorption and brain penetration of small molecules. ChemMedChem 2016;11:1117-21.
26. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular properties that influence the oral bioavailability of drug candidates. J Med Chem 2002;45:2615-23.
27. Ghaemi Z, Alberga D, Carloni P, Laio A, Lattanzi G. Permeability coefficients of lipophilic compounds estimated by computer simulations. J Chem Theory Comput 2016;12:4093-9.
28. Daina A, Michielin O, Zoete V. iLOGP: A simple, robust, and efficient description of n-octanol/water partition coefficient for drug design using the GB/SA approach. J Chem Inf Model 2014;54:3284-301.
29. Arnott JA, Planey SL. The influence of lipophilicity in drug discovery and design. Expert Opin Drug Discov 2012;7:863-75.