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In Silico Screening of Chemical Compounds from Green Chiretta (*Andrographis paniculata* (Burm. F.) Nees) as Cyclooxygenase-2 Inhibitors

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ABSTRACT

Andrographis paniculata (Burm. F.) Nees commonly called Green Chiretta has been shown to have numerous pharmacological activities including anti-inflammatory activity. The present study aimed to determine the potential cyclooxygenase-2 inhibitory activity of compounds from Green Chiretta via *in silico* approach. The 3D structure of the enzyme cyclooxygenase-2 was obtained from Protein Data Bank (PDB) with code 1CX2. The 2D structures of forty-four compounds from Green Chiretta were obtained from "Take Out 'Jamu' KnapSack" website. The 2D structures were converted to 3D structures using ACD/ChemSketch programme. Optimization of the ligands was performed using VEGA ZZ programme. The docking of the 44 compounds with the target receptor cyclooxygenase-2 was done using the ArgusLab programme. The docking results were reported in terms of the change in free energy (ΔG). Docking results showed that two chemical compounds; 14-Deoxyandrographolide and Andrographic acid from Green Chiretta have the potential as cyclooxygenase-2 inhibitor, and showed synergistic activity with andrographolide with low free energy change (ΔG) of -12.7837 Kcal/mol and -13.4661 Kcal/mol for 14-Deoxyandrographolide and Andrographic acid, respectively. These results therefore revealed the potential of *Andrographis paniculate* as source of anti-inflammatory drug candidates with selective cyclooxygenase-2 inhibitory activity.

Keywords: *Andrographis paniculata* (Burm. F.) Nees, *In Silico*, Cyclooxygenase-2, Molecular docking.

Introduction

In recent years, researchers have invested billions of dollars in the discovery, design, and development of new drugs.[1] These research efforts involve several stages, including the isolation of compounds from natural sources,[2] structural modification, synthesis of new compounds, bioassay testing, virtual screening, and identifying significant hits.[3] However, despite isolating hundreds of thousands of compounds from natural sources, only a few prove to be truly bioactive.[4] This situation has led to the saying that drug research is like searching for a needle in a haystack.[5] The advancement in computational techniques has significantly aided new drug design, particularly in visualizing molecular characteristics.[6] Molecular modeling, a computational simulation technique based on chemical theory and experimental data, allows scientists to create and analyze molecules and their protein targets.[7] It involves manipulating, calculating, and predicting the chemical, physicochemical, and biochemical properties of these molecules.[8] Molecular modeling has found extensive applications in the pharmaceutical and chemical industries.[9]

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In this context, computers play a crucial role in rationally proposing and evaluating compounds, potentially making the drug discovery process more effective.[10] Computational methods can also help study drug interactions with their targets, including potential toxic properties of the compounds and their metabolites.[11]Additionally, computer-based approaches save resources, time, and effort in the search for new drugs.[12]
One notable Indonesian medicinal plant with pharmacological activity is Green Chiretta (*Andrographis paniculata* (Burm. F.) Nees) locally known as 'Sambiloto'.[13] The plant has been used in Ayurvedic and Chinese medicine for thousands of years to treat malaria, diarrhea, hepatitis, infections, and digestive disorders.[14]
A study demonstrated that ethanol fraction of Green Chiretta, administered at doses of 0.396 mg/100 g body weight, 3.96 mg/100 g body weight, and 39.6 mg/100 g body weight, significantly reduced edema induced by 1% carrageenan. Qualitative chemical analysis revealed that the ethanol fraction contained flavonoid and terpenoid compounds.[15]
Andrographolide, the major diterpene found in this plant, is believed to be responsible for its various biological effects.[16] Recently, standardized dry extracts containing total andrographolide or pure andrographolide have been used for treating viral infections and inflammation.[17] Andrographolide has been reported to exhibit anti-inflammatory activity by inhibiting cyclooxygenase-2 expression in lipopolysaccharide-induced human fibroblast cells.[18]
Data obtained from the "Take Out 'Jamu' KnapSack" website indicate that chemical compounds from Green Chiretta (*Andrographis paniculata* (Burm. F.) Nees) include not only andrographolide (the main diterpene lactone) but also a steroid compound, four phenolic compounds, 16 flavonoids, and 22 andrographolide derivatives.[19] Based on this information, the present study seek to identify chemical compounds from Green Chiretta with potential cyclooxygenase-2 inhibitory activity via *in silico* approach.

Materials and Methods

Ligands preparation

The 2D model of the ligands (selected compounds from the Green Chiretta plant) were downloaded from the "Take Out 'Jamu' KnapSack" website. Subsequently, the 2D chemical structures of the ligands were converted to 3D structures using the ACD/ChemSketch programme and saved in MDL Molfiles [V2000] (*.mol) format. The 3D chemical compound models are essential for both VEGA ZZ and ArgusLab programmes. The ligands in the 3D format were then optimized using the VEGA ZZ programme. Optimization was necessary to prepare the ligands for docking and ensure that the ligands align with the conditions required by the docking software. During the optimization process, the AutoDock force field and Gasteiger charges were incorporated to improve charge distribution.[20] Finally, minimization optimization was performed to minimize the energy of the interaction, seeking the smallest optimal energy state where the structure is in the most stable conformation for docking.

Protein preparation

The 3D structure of the enzyme cyclooxygenase-2 with PDB code: 1CX2 was downloaded from the Protein Data Bank (PDB).

Molecular docking simulation

Finally, molecular docking simulations were conducted using the ArgusLab programme.[6] ArgusLab is a programme used for molecular docking between chemical compounds (ligands) and proteins (receptors). In the docking process, forty-four (44) chemical compounds from the Green Chiretta plant (*Andrographis paniculata* (Burm. F) Nees) were docked to the SC-558 binding site of cyclooxygenase-2.

Results and Discussion

In silico screening is performed to discover potential inhibitors of proteins or enzymes linked to diseases. The advantage of *in silico* screening lies in its ability to differentiate between active and inactive compounds, thus saving time and other resources. *In silico* screening involves screening a large library of compounds, and the data obtained are sorted based on certain predetermined criteria.[21] Compounds which do not bind to the target receptors are excluded from further experiments. In this study, forty-four (44) compounds from the Green Chiretta plant (*Andrographis paniculata* (Burm. F) Nees) were docked with the enzyme cyclooxygenase-2 (PDB: 1CX2). The choice of chemical compounds from the Green Chiretta plant was based on the fact that certain compounds, particularly andrographolide, have been reported to exhibit anti-inflammatory activity by inhibiting cyclooxygenase-2.[22]

The docking results between the test ligands and cyclooxygenase-2 enzyme are presented in Table 1.Ligands interact with binding sites on the receptor via specific amino acids on receptors. The interaction between ligands and receptors occurs via hydrogen bonding, van der Waals forces, and/or electrostatic interactions.[23] When using ArgusLab, only hydrogen bonds between ligands and receptor amino acids can be determined.[2] The distance between the ligand and receptor amino acids affects the strength of the ligand-receptor binding (affinity).[6] Smaller bond distances indicate greater ligand-receptor affinity.[24] The hydrogen bonding between the ligands and the receptor amino acids is presented in Table 2.

The cyclooxygenase enzyme catalyzes the formation of prostaglandins, which are inflammatory mediators and metabolic products of arachidonic acid. The cyclooxygenase enzyme consists of two isoforms: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is constitutive and maintains normal physiology and homeostasis, while COX-2 is induced in inflamed cells.[25]

In the PDB database, the COX-2 enzyme with the code 1CX2 forms a complex with SC-558 (1-phenylsulfonamide-3-trifluoromethyl-5-parabromophenylpyrazole), which is a selective inhibitor of cyclooxygenase-2. The amino acid residues that constitute the binding site for SC-558 include 516 ALA, **527** ALA, 120 ARG, 513 ARG, 192 GLN, 526 GLY, 90 HIS, 517 ILE, 352 LEU, 359 LEU, 384 LEU, 531 LEU, 522 MET, 381 PHE, 518 PHE, 353 SER, 530 SER, 387 TRP, 348 TYR, 355 TYR, 385 TYR, 116 VAL, 349 VAL, and 523 VAL**.**

The study analyzed the interaction of SC-558, a selective cyclooxygenase-2 inhibitor, with the cyclooxygenase-2 active site. Compared to andrographolide, SC-558 is smaller in size and exhibits a specific interaction within the binding pocket by forming a hydrogen bond with Arginine 513. If other compounds form a similar interaction by hydrogen bonding with Arginine 513 (located lower in the binding pocket), they may also have the potential to be selective cyclooxygenase-2 inhibitors. The docking results were expressed in terms of free energy change (ΔG). ΔG, which represents the Gibbs free energy (in Kcal/mol), indicates the stability of ligand-receptor interactions at the receptor binding site. The ΔG value is related to the ligand's affinity for the protein, where the lowest energy corresponds to the most stable and optimal conformation for drug design. Among the 44 chemical compounds from the Green Chiretta plant (*Andrographis paniculata* (Burm. F) Nees) that have been docked, 33 compounds exhibited inhibitory activity against cyclooxygenase-2. The compounds with free energy change (ΔG) values ranging from -5 Kcal/mol to -8 Kcal/mol include; 5-Hydroxy-7,8-dimethoxyflavone 5-glucoside (-5.30086 Kcal/mol), Wogonin 5-glucoside (-6.76125 Kcal/mol), 5,7,2',3'-Tetramethoxyflavanone (-7.42476 Kcal/mol), 3-*O*-Caffeoylquinic acid (-8.26211 Kcal/mol), 5-Hydroxy-7,2',6'-trimethoxyflavone (-8.48988 Kcal/mol), 5-Hydroxy-3,7,8,2'-tetramethoxyflavone (-8.5251 Kcal/mol), 14-Deoxy-17-hydroxyandrographolide (-8.9228 Kcal/mol), Paniculide B (-8.93127 Kcal/mol).

The compounds with free energy change (ΔG) values ranging from -9 Kcal/mol to -12 Kcal/mol, include; Paniculide C (-9.00354 Kcal/mol), Ferulic acid (-9.02602 Kcal/mol), Caffeic acid (-9.19314 Kcal/mol), Apigenin 7,4'-dimethyl ether (-9.37429 Kcal/mol), 12R,13R-Hydroxyandrographolide (-9.71033 Kcal/mol), Dihydroskullcap flavone I (-9.84311 Kcal/mol), 7S-Hydroxy-14-deoxyandrographolide (-9.88904 Kcal/mol), 5-Hydroxy-7,8-dimethoxyflavanone (-9.98736 Kcal/mol), 12S-Hydroxyandrographolide (-10.073 Kcal/mol), 7-*O*-Methylwogonin (-10.3516 Kcal/mol), Neoandrographolide (-10.4905 Kcal/mol), Isoandrographolide (-10.7042 Kcal/mol), Paniculide A (-10.8031 Kcal/mol), 14-Deoxy-11-oxoandrographolide (-10.8275 Kcal/mol), 7R-Hydroxy-14-deoxyandrographolide (-10.9307 Kcal/mol), 14-Deoxy-11,14-didehydroandrographolide (-10.9378 Kcal/mol), Andrograpanin (-10.9618 Kcal/mol), Cinnamic acid (-11.0665 Kcal/mol), Andropanolide (-11.1708 Kcal/mol), 14-Acetylandrographolide (-11.3242 Kcal/mol), 5,4'-Dihidroxy-7,8,2',3'-tetramethoxyflavone (-11.5625 Kcal/mol), 12S,13S-Hydroxyandrographolide (-11.7843 Kcal/mol), Andrographolide (-12.0902 Kcal/mol), 14-Deoxyandrographolide (-12.7837 Kcal/mol)

Only one compound (Andrographic acid) had free energy change (ΔG) greater than -13 Kcal/mol, with ΔG of 13.4661 Kcal/mol.

From the docking results obtained, two chemical compounds exhibited synergistic inhibitory activity with andrographolide (-12.0902 Kcal/mol) and had lower free energy change **(ΔG)** values. these compounds were 14-Deoxyandrographolide with a ΔG of -12.7837 Kcal/mol, and Andrographic acid with a ΔG of -13.4661 Kcal/mol. Both compounds (14-Deoxyandrographolide and Andrographic acid) belong to the terpenoid group, specifically diterpenoids, similar to andrographolide, which is a major component in the Green Chiretta plant (*Andrographis paniculata* (Burm. F.) Nees). In general, the direct interaction between a macromolecular protein (receptor) and a ligand is crucial for the formation of ligand-receptor complexes.

The types of interactions within drug-receptor complexes are similar to those between other organic molecules, including covalent bonds, ionic interactions (electrostatic), dipole-dipole and ion-dipole interactions, hydrogen bonds, hydrophobic interactions, and Van der Waals interactions. Spontaneous bond formation between atoms occurs with a decrease in free energy **(**ΔG**)** (negative sign).

Table 1: The docking results between compounds from Green Chiretta (*Andrographis paniculata* (Burm. F) Nees) and cyclooxygenase-2

No.	Compound Name	Free Energy Change (ΔG) (Kcal/mol)	Note
1.	Caffeic acid	-9.19314	(+)
2.	Apigenin 7,4'-dimethyl ether	-9.37429	(+)
3.	3-*O*-Caffeoylquinic acid	-8.26211	(+)
4.	Ferulic acid	-9.02602	(+)
5.	(-)-beta-Sitosterol	0	(-)
6.	7-*O*-Methylwogonin	-10.3516	(+)
7.	5,4'-Dihidroxy-7,8,2',3'-tetramethoxyflavone	-11.5625	(+)
8.	Wogonin 5-glucoside	-6.76125	(+)
9.	5-Hydroxy-7,8-dimethoxyflavone 5-glucoside	-5.30086	(+)
10.	5-Hydroxy-7,8,2'-trimethoxyflavone 5-glucoside	0	(-)
11.	5,2',3'-Trihydroxy-7,8-dimethoxyflavone 3'-glucoside	0	(-)
12.	5-Hydroxy-7,8,2',3' tetramethoxyflavone 5-glucoside	0	(-)
13.	5,4'-Dihidroxy-7,8,2',3'-tetramethoxy flavone 5-glucoside	0	(-)
14.	5-Hydroxy-3,7,8,2'-tetramethoxyflavone	-8.5251	(+)
15.	5-Hydroxy-7,8 dimethoxyflavanone	-9.98736	(+)
16.	Andrographidin A	0	(-)
17.	Paniculide A	-10.8031	(+)
18.	Paniculide B	-8.93127	(+)
19.	Paniculide C	-9.00354	(+)
20.	5-Hydroxy-7,2',6'-trimethoxyflavone	-8.48988	(+)
21.	Skullcapflavone 1,2'-*O*-beta-D-glucopyranoside	0	(-)
22.	Dihydroskullcap flavone I	-9.84311	(+)
23.	14-Deoxyandrographolide	-12.7837	(+)
24.	Ninandrographolide	0	(-)
25.	14-Deoxy-11,14-didehydroandrographolide	-10.9378	(+)
26.	14-Deoxy-11-oxoandrographolide	-10.8275	(+)
27.	Andrograpanin	-10.9618	(+)
28.	Neoandrographolide	-10.4905	(+)
29.	Andrographolide	-12.0902	(+)
30.	Andrographic acid	-13.4661	(+)
31.	Cinnamic acid	-11.0665	(+)
32.	14-Acetyl-3,19-isopropylideneandrographolide	0	(-)
33.	14-Acetylandrographolide	-11.3242	(+)
34.	5,7,2',3'-Tetramethoxyflavanone	-7.42476	(+)
35.	12R,13R-Hydroxyandrographolide	-9.71033	(+)
36.	12S,13S-Hydroxyandrographolide	-11.7843	(+)
37.	7R-Hydroxy-14-deoxyandrographolide	-10.9307	(+)
38.	7S-Hydroxy-14-deoxyandrographolide	-9.88904	(+)
39.	12S-Hydroxyandrographolide	-10.073	(+)
40.	14-Deoxy-17-hydroxyandrographolide	-8.9228	(+)
41.	3-*O*-beta-D-Glucopyranosylandrographolide	0	(-)
42.	Andrographiside	0	(-)
43.	Andropanolide	-11.1708	(+)
44.	Isoandrographolide	-10.7042	(+)

Note: (-): Not active as a cyclooxygenase-2 inhibitor, (+): Active as a cyclooxygenase-2 inhibitor

In this study, docking was performed using the ArgusLab programme, revealing only hydrogen bonds between the ligand and receptor amino acids. 14-Deoxyandrographolide with a ΔG of -12.7837 Kcal/mol did not form hydrogen bond with receptor amino acids (Figure 1a). The ΔG value obtained for 14-Deoxyandrographolide likely results from other interactions between the ligand and receptor. On the other hand, Andrographic acid with a ΔG of -13.4661 Kcal/mol showed specific interactions at the SC-558 binding site, forming hydrogen bond with Arginine 513 (Figure 1b). Based on previous research, compounds that can form hydrogen bonds with Arginine 513 (located lower in the binding pocket) have the potential to be selective cyclooxygenase-2 inhibitors.

Table 2: Hydrogen bonding between ligands from Green Chiretta (*Andrographis paniculata* (Burm. F) Nees) and receptor amino acid

Compound Name	**Number of Hydrogen Bonds**	**Bond Distance (Å)**	**Amino Acid Binding**	**Test Compound Number**	**Amino Acid Number**
Caffeic acid	2	2.394941	385 TYR	36303 O	5734 O
		2.813749	530 SER	36303 O	8060 O
Apigenin 7,4'-dimethyl ether	0	-	-	-	-
3-*O*-Caffeoylquinic acid	3	2.467043	385 TYR	36304 O	5734 O
		2.900803	530 SER	36304 O	8060 O
		2.901094	530 SER	36305 O	8060 O
Ferulic acid	1	2.999107	120 ARG	36296 O	1404 N
(-)-beta-Sitosterol	0	-	-	-	-
7-*O*-Methylwogonin	1	2.795750	355 TYR	36302 O	5210 O
5,4'-Dihidroxy-7,8,2',3'-tetramethoxyflavone	0	-	-	-	-
Wogonin 5-glucoside	1	2.999746	90 HIS	36302 O	864 N
5-Hydroxy-7,8-dimethoxyflavone 5-glucoside	0	-	-	-	-
5-Hydroxy-7,8,2'-trimethoxyflavone 5-glucoside	0	-	-	-	-
5,2',3'-Trihydroxy-7,8-dimethoxyflavone 3'-glucoside	0	-	-	-	-
5-Hydroxy-7,8,2',3' tetramethoxyflavone 5-glucoside	0	-	-	-	-
5,4'-Dihidroxy-7,8,2',3'-tetramethoxy flavone 5-glucoside	0	-	-	-	-
5-Hydroxy-3,7,8,2'-tetramethoxyflavone	0	-	-	-	-
5-Hydroxy-7,8 dimethoxyflavanone	1	2,961674	355 TYR	36302 O	5210 O
Andrographidin A	0	-	-	-	-
Paniculide A	0	-	-	-	-
Paniculide B	2	2.949601	523 VAL	36310 O	7954 N
		2.999978	527 ALA	36301 O	8011 N
Paniculide C	1	2.775938	527 ALA	36303 O	8011 N
5-Hydroxy-7,2',6'-trimethoxyflavone	0	-	-	-	-
Skullcapflavone 1,2'-*O*-beta-D-glucopyranoside	0	-	-	-	-
Dihydroskullcap flavone I	0	-	-	-	-
14-Deoxyandrographolide	0	-	-	-	-
Ninandrographolide	0	-	-	-	-
14-Deoxy-11,14-didehydroandrographolide	0	-	-	-	-
14-Deoxy-11-oxoandrographolide	2	2.848241	385 TYR	36313 O	5734 O
		2.989803	527 ALA	36317 O	8011 N
Andrograpanin	0	-	-	-	-
Neoandrographolide	0	-	-	-	-
Andrographolide	1	2.995034	90 HIS	36310 O	864 N
Andrographic acid	1	2.775532	513 ARG	36313 O	7811 N
Cinnamic acid	0	-	-	-	-
14-Acetyl-3,19-isopropylideneandrographolide	0	-	-	-	-
14-Acetylandrographolide	3	2.998209	120 ARG	36317 O	1404 N
		2.379602	120 ARG	36320 O	1404 N
		2.423805	355 TYR	36320 O	5210 O
5,7,2',3'-Tetramethoxyflavanone	0	-	-	-	-
12R,13R-Hydroxyandrographolide	2	2.731900	120 ARG	36301 O	1404 N
		2.899768	355 TYR	36301 O	5210 O
12S,13S-Hydroxyandrographolide	2	2.790132	517 ILE	36295 O	7862 N
		2.999354	518 PHE	36295 O	7881 N
7R-Hydroxy-14-deoxyandrographolide	1	2.109872	387 TRP	36294 O	5770 N
7S-Hydroxy-14-deoxyandrographolide	1	2.999611	513 ARG	36317 O	7811 N
12S-Hydroxyandrographolide	0	-	-	-	-
14-Deoxy-17-hydroxyandrographolide	2	2.723647	517 ILE	36294 O	7862 N
		2.999796	518 PHE	36294 O	7881 N
3-*O*-beta-D-Glucopyranosylandrographolide	0	-	-	-	-
Andrographiside	0	-	-	-	-
Andropanolide	2	2.994385	517 ILE	36312 O	7862 N
		2.978797	518 PHE	36312 O	7881 N
Isoandrographolide	2	2.772824	530 SER	36300 O	8060 O
		2.999919	120 ARG	36315 O	1404 N

Note: ALA = Alanine, ARG = Arginine, HIS = Histidine, ILE = Isoleucine, PHE = Phenylalanine, SER = Serine, TRP = Tryptophan, TYR = Tyrosine, VAL = Valine.

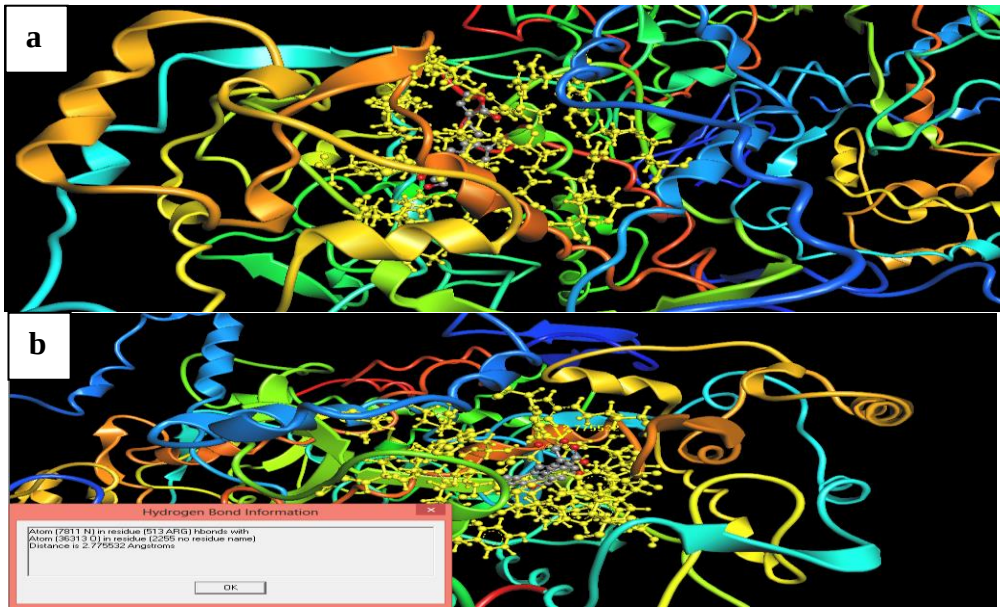

Figure 1: 3D cartoon model of 14-Deoxyandrographolide **(a)** and Andrographic acid **(b)** with SC-558 binding site on cyclooxygenase-2

Conclusion

The findings from this study have shown that two compounds; 14-deoxyandrographolide and andrographic acid from Green Chiretta plant (*Andrographis paniculata* (Burm. F.) Nees) have potential as cyclooxygenase-2 inhibitors. The two compounds showed synergistic activity with andrographolide, exhibiting lower free energy change (ΔG). These compounds are therefore potential anti-inflammatory drug candidates with selective cyclooxygenase-2 inhibitory activity.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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