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Research Article

Molecular Docking and ADME Studies of *Centella Asiatica* as Anti Hyperuricemia

Ahmad Shobrun Jamil*, Prayogi Galie Saputro

ABSTRACT

Centella asiatica is a traditional natural medicine used in a number of Southeast Asian nations. (also known as Centella asiatica L., Urb., or Gotu Kola). The aim of this study is to determine the antihyperuricemia properties of *Centella asiatica* extract and the possibility that they will interact with the XDH enzyme. The XDH enzyme is one of three enzymes that can influence the onset of hyperuricemia with the other two are SLC22A12 and ABCG2. In this research, we employ a computational method in collaboration with a number of applications and databases. ADME analysis was carried on for some *Centella asiatica* constituents to determine their similarities to the drug and bioavailability components. The analysis continued on with molecular docking between the chemical compounds and several enzymes related to hyperuricemia. According to the findings, *Centella asiatica* contains active constituents that can be used as an alternative therapy for hyperuricemia.

Key words: *Centella asiatica*, Hyperuricemia, Molecular docking.

Ahmad Shobrun Jamil*, Prayogi Galie Saputro

Department of Pharmacy, Faculty of Health Science, University of Muhammadiyah Malang Jl. Bendungan Sutami No.188, Sumbersari, Kecamatan Lowokwaru, Kota Malang, Jawa Timur 65145, INDONESIA.

Correspondence

Ahmad Shobrun Jamil

Department of Pharmacy, Faculty of Health Science, University of Muhammadiyah Malang Jl. Bendungan Sutami No.188, Sumbersari, Kecamatan Lowokwaru, Kota Malang, Jawa Timur 65145, INDONESIA.

E-mail: shobrun@umm.ac.id

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INTRODUCTION

Gout is characterized as an arthritic disease brought on by the long-term deposition of monosodium urate (MSU) crystals in and/or around joints. MSU deposits were discovered in a significant number of asymptomatic hyperuricemic patients in several recent ultrasonography studies. Therefore, a gout disease with asymptomatic MSU deposits can be identified. Such asymptomatic deposits appear to precede flares, which appear to be caused by the mobilization of prepared crystals. If not the only risk factor for gout, hyperuricemia appears to be the most significant. Recent research confirms that hyperuricemia is an independent risk factor for renal and cardiovascular disorders. The threshold at which uricemia becomes pathological is contested. This lack of agreement makes it impossible to compare studies using various criteria and hinders both doctors' and patients' comprehension of gout. Given that the risk of developing gout begins at 6,8 mg/dl, we suggest using this threshold as the cutoff point for hyperuricemia. This description matches the minimal uricemia goal of urate-lowering medications exactly (ULDs).[1]

According to RISKESDAS 2018 statistics, the prevalence of joint illness, also known as pain from elevated urate or acute and chronic hyperuricemia, was 7.30% in Indonesia in 2018. When looking at age characteristics, the highest prevalence was seen in people under the age of 75 (18.95%). Additionally, there were more female patients (8.46%) than male patients (6.13%).[2,3]

As indicated by nutrition and lifestyle, there is a striking rise in the prevalence of gout (gout), which is strongly connected with economic development. Gout or arthritis (gout) is a condition brought on by uric acid crystals or deposits in tissues, particularly in joints. Gout is intimately associated with purine metabolism problems, which cause a rise in uric acid levels in the blood (hyperuricemia).

On the basis of the aforementioned information, it is required to do additional research to identify effective treatment medicines with low side effects capable of resolving existing problems, particularly hyperuricemia.[2]

Centella asiatica is a standard traditional therapeutic in India and other regions for various conditions. The aerial parts and roots are utilized medicinally, and their chemical contents have extensive therapeutic applications in antibacterial, anti-inflammatory, anticancer, neuroprotective, antioxidant, and wound-healing actions. Many of its uses have been scientifically confirmed, as they have bioactive constituents. In this article, we assess the pharmacological significance of *C. asiatica* through a rigorous analysis of the relevant literature. More research is required to find additional bioactive chemicals and their precise mechanisms of action.[3]

The following substances are found in *C. asiatica*. They can be applied as anti-hyperuricemia medication to treat increased uric acid levels: centellin, madecassic acid, madasiatic acid, isothankunic acid, pomolic acid, 2alpha-hydroxyursolic acid, quercetin, and kaempferol. To understand more about the *Centella asiatica's* potential as a therapy for hyperuricemia, research was done on it.

Until now, non-steroidal anti-inflammatory medications (NSAIDs), which are intended to treat pain, have been utilized to treat hyperuricemia. In addition, he took anti-gout medication in the form of colchicine to reduce uric acid levels and uric acid deposits. Steroids may be administered orally or by intra-articular injection if the patient is intolerant to NSAIDs or colchicine or has contraindications to their use. NSAIDs can raise the risk of major cardiovascular thrombosis, myocardial infarction, and stroke, all of which have a high mortality rate.[4,5] Patients with cardiovascular disease or those at risk

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for coronary heart disease are more likely to develop this risk over time. Additionally, it can raise the chance of deadly gastrointestinal disorders such bleeding, ulcers, and perforations of the stomach or intestines. Without any prior indications, these adverse effects can happen at any time while using the product. Patients who are older are more likely to experience major gastrointestinal adverse effects.

Without being able to demonstrate its activity on a molecular level, research on the medicinal properties of *C. asiatica* has thus far been conducted. This *in silico* research can explain the molecular cellular mechanisms that take place when the active compounds found in these plants are stimulated. Previous research could only prove whether the compounds contained in *C. asiatica* could be anti-hyperuricemia without explaining the mechanism of action of each plant compound with receptors in living things. Therefore, in this study, using the *in-silico* method on a dry-lab basis using certain applications to determine whether the ingredients of *C. asiatica* can be anti-hyperuricemia and can explain its mechanism of action. Using the *in-silico* method to determine the mechanism of action of these compounds in humans, this study was able to accurately provide recommendations for further research that the content of *C. asiatica* could be a drug candidate as an antihyperuricemia.

This research will focus on exploring the compounds contained in *C. asiatica*, which can be candidates for anti-hyperuricemia drugs, and the molecular mechanism of this plant.

The purpose of this research was to investigate the ability of centellin, madecassic acid, madasiatic acid, isothankunic acid, pomolic acid, 2alpha-hydroxyursolic acid, quercetin, and kaempferol to prevent hyperuricemia caused by an excess of uric acid.

RESEARCH METHODS

Materials

The research material was obtained from the database with the following details: Twenty five active compounds of *C. asiatica* were analyzed in this study, including 1-Cyclohexyl-11-heneicosanone (CID 129882177), Centellin (CID 163184102), Asiaticoside E (CID 102212085), Asiaticoside C (CID 101103169), Asiaticoside D (CID 102212084), Centellicin (CID 163183805), Madecassic acid (CID 73412), Madasiatic acid (CID 23132225), Isothankunic acid (CID 12302703), Madecassoside (CID 45356919), Centellasaponin D (CID 101103168), Centellasaponin C (CID 85348461), Centellasaponin B (CID 85411973), Asiaticoside B (CID 91618002), Asiaticoside (CID 11954171), Pomolic acid (CID 382831), Acetylursolic acid (CID 475119), 3-Epimaslinic acid (CID 25564831), 2alpha-Hydroxyursolic acid (CID 6918774), Quercetin (CID 5280343), Kaempferol (CID 5280863), Asiatic acid (CID 119034), alpha-Caryophyllene (obsol.) (CID 5281520) , beta-Caryophyllene (CID 5281515), and Labiatenic acid (CID 5281792). Two enzyme proteins were taken from the RCSB. PDB database, XDH (PDB ID 1JRP) and ABCG2 (PDB ID 8BHT), and the XDH enzyme used in this study.

Methods

Bioactive compound data collection

Data on *C. asiatica* bioactive chemicals were obtained from Dr. Duke's Phytochemical and Ethnobotanical Databases (https://phytochem.nal.usda.gov/phytochem/search). The data collected from the database is supplemented by data obtained by accessing the PubChem chemical compound library portal (https://pubchem.ncbi.nlm.nih.gov/). Chemical compound data completeness contains SMILES (Simplified Molecular-Input Line-Entry System) data, PubChem CID, 2D molecular structure, and 3D molecular structure.

ADME analysis

The SwissADME program (http://www.swissadme.ch/) was used to perform ADME analysis (Absorption, Distribution, Metabolism, and Excretion) of *C. asiatica* bioactive compounds. This analysis yielded results on the bioavailability of the bioactive compound *C. asiatica* as described in radar form. Data on compound absorption and dispersion are depicted using a boiled egg illustration. In addition, there is molecular weight, human intestinal absorption, blood brain barrier, and TPSA data.

Protein Target Fishing and Network Analysis

Using the swisstargetprediction software (http://www.swisstargetprediction.ch/) and the string-db software (https://string-db.org/), a protein network analysis linked to hyperuricemia was conducted on the target proteins of the *Centella asiatica* plant. The expected outcome is an overview of connected protein networks relevant to the hyperuricemia process.

Molecular Docking for the Hyperuricemia Protein and *C. asiatica* ligands

PyRx version 8.0 software and the visualization program Discovery Studio Visualizer v21.1.0.20298 were used for pairing bioactive substances (ligands) with hyperuricemia target proteins. The RCSB. org library (www.rcsb.org) was used for finding the target protein 3D files. Protein molecules 3d files were cleaned of water molecules, ions, and native ligands using the Discovery Studio Visualizer v21.1.0.20298. Furthermore, protein files are saved with the *.pdb. In PyRx version 8.0 software, blind docking is used to couple the ligands one by one with the target protein.

RESULTS AND DISCUSSION

The most of pharmaceutical substances interact with multiple or even several molecular targets within the organism, which determines the complexity of complex biological profiles. In fact, their metabolization in the human body results in the formation of one or more metaboliteswith distinct biological activity profiles. Consequently, the reasonabledevelopment and use of novel drugs requires the analysis of their biological activity profiles, taking into consideration human metabolism. Currently, in silico methods are widely used for estimating the interactions with new drug-like compounds with therapeutictargets and predicting their metabolic transformations.[6] The first step in this research was collecting data in the form ofsearching for compounds contained in the *C. asiatica* plant usinga database-based website, namely Dr. Duke's Phytochemical and Ethnobotanical Databases, available at the link https://phytochem.nal.usda.gov/phytochem/search, after knowing the content of compounds in C. asiatica plants. Therefore, the selection of suitable compounds is carried out as candidates for anti-hyperuricemia drugs.[7] For a molecule to be effective as a therapeutic, it must reach its target in the body in sufficient quantity and remain there in bioactive form long enough for the predicted biological activities to occur. Assessment of absorption, distribution, metabolism, and excretion (ADME) occurs earlier and earlier in the drug development process, at a time when compounds under consideration are many but access to physical samples is restricted. In this situation, computer models are valid substitutes for experimentation. Here, we introduce the new SwissADME web application, which provides free access to a pool of rapid yet reliable predictive models for physicochemical properties, pharmacokinetics, drug-likeness, and medicinal chemistry friendliness, including in-house proficient methods like the BOILED-Egg, iLOGP, and Bioavailability Radar. Through a user-friendly interface on the website http://www.swissadme.ch, simple, efficient entry of data and interpretation are guaranteed. Specialists and nonspecialists in cheminformatics and computational chemistry

are able to immediately predict crucial properties for a collection of compounds to aid in the development of drugs.[8] After selecting protein candidates with SwissADME, proceed with the AdmetSAR application. As a thorough resource and open-source tool for the forecasting of chemical ADMET properties, admetSAR was created. The chemical and pharmaceutical industries have made extensive use of admeSAR since its initial release in 2012, which included 27 predictive models. With a significant increase in training data quantity and quality, AdmetSAR 2.0 focuses on extending and optimizing existing models. There are currently 47 models available for either environmental risk assessment or drug discovery. For lead optimization based on anticipated ADMET properties, we also added a new module called ADMETopt.[9] The next step will be to use the String. DB application on the website https://string-db.org/ to determine the relationship between protein sequences and hyperuricemia using proteins from the *Centalla asiatica* compound that have been chosen as anti-hyperuricemia drug candidates. The last step is to conduct interpretation by docking the protein between the ligand and the receptor using the Pyryx-based docking application and the Discovery Studio application. a description of the docking program used by Discovery Studio to analyze and model molecular sequence and structure relevant to life science researchers.

Hyperuricemia is an abnormal metabolic trait characterized by serum uric acid levels greater than 6 and 7 mg/dL for women and men, respectively, and is associated with cardiometabolic risk factors including obesity, diabetes, hypertension, and dyslipidemia. The progression of kidney disease and impaired kidney functions can both be predicted by hyperuricemia. Serum uric acid levels are influenced by a variety of variables, including genetic predisposition, diet, sex, lifestyle, and alcohol consumption. In fact, some purine or urate metabolism-related genes have variants that seem to predispose to hyperuricemia. A few of these include the ABCG2 gene, which codes for a membrane transporter that transports urates to the kidney and intestine, and the SLC2A9 gene, which codes for the kidney protein GLUT9, which is crucial for controlling the flow of urates in the proximal tubules. Similar to this, the hypoxanthine-xanthine-urate conversion pathway, which breaks down purines from nucleic acids, is broken down by the xanthine dehydrogenase enzyme that is produced by the XDH gene.[12]

Inhibitors of xanthine oxidase are increasingly utilized in the medical treatment and prevention of gout caused by hyperuricemia. Allopurinol, the prototypical xanthine oxidase inhibitor, has demonstrated additional beneficial effects, including a reduction in vascular reactive oxygen species and mechano-energetic uncoupling. This chapter examines these properties and their relevance to human pathophysiology, focusing on Allopurinol and newer xanthine oxidase inhibitors including Febuxostat and Topiroxostat. Xanthine oxidase (XO) and xanthine dehydrogenase (XDH) are known as xanthine oxidoreductase collectively (XOR). XDH is initially synthesized as a 150-kDa protein from which XO is derived, e.g., under ischemia/hypoxia conditions, either reversibly by conformational changes (calcium or SH oxidation) or irreversibly by proteolysis, the latter leading to formation of a 130-kDa form of XO. Both XO and XDH catalyze the conversion of hypoxanthine to uric acid *via* xanthine, the former by producing superoxide and hydrogen peroxide while the latter by implementing NAD+.[13]

There are three proteins known to be linked with ligand compounds derived from *C. asiatica* and nuclear receptor-specific proteins in the hyperuricemia process. ABCG2, SLC22A12, and XDH are the nuclear receptor proteins that make up these receptors. ABCG2 is known to play a role in both renal and extrarenal urate excretion. Mediates the export of protoporhyrin IX (PPIX) from mitochondria to cytosol and cytosol to extracellular environment, as well as the extract of hemin and heme from the cell. SLC22A12 is a known blood-level component. Mediates saturable urate absorption by facilitating urate exchange with organic anions. XDH catalyzes the transformation of hypoxanthine into xanthine. catalyzes xanthine's oxidation to uric acid. The results indicated that XDH with a greater affinity could be a potential drug candidate in hyperuricemia.[12]

Based on the results of an analysis using an online database-based computerized application, there are 8 active compounds *C. asiatica* that have a Pa value (predictive probability of being an active compound) above 0.05 as an anti-hyperuricemia. Based on Table 1, it is known that there are 8 compounds, of which 2 can be absorbed through the blood-brain barrier, and all of them are expected to be absorbed passively by the digestive tract, which means that the predicted results will have a high probability value similar to laboratory tests.

Analysis using the SwissADME application, Discovery Studio, and Pyrx can provide sufficient analytical results because they produce valid data. *In silico* research using a computerized model continues to increase, along with the increasing number of digital data inputs related to testing the activity of drug compounds.

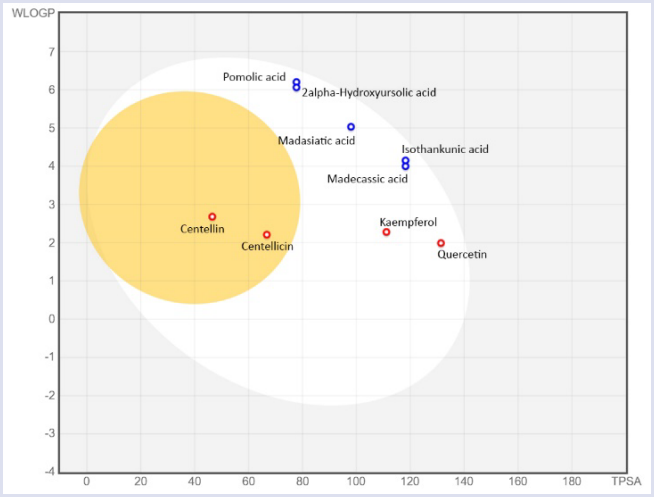


Figure 1: Distribution of compounds based on body absorption, Some of the compounds, namely Centellin and Centellicin < Pomolic acid < 2alpha-Hydroxyursolic acid < Madasiatic acid < Madecassic acid < Isothankunic acid < quercetin < Kaempferol are well absorbed by human inestine, but only about 2 compounds, namely Centellin and Centellicin, are able to penetrate the blood-brain barrier.

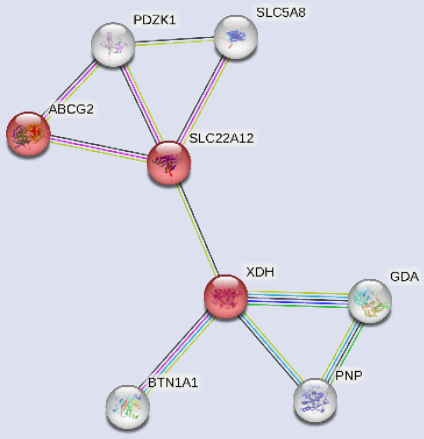


Figure 2: Protein network associated with hyperuricemia disease results of analysis using string-db. The three proteins are labeled red.

Table 1: Table of results of the absorption, distribution, metabolism, and excretion (ADME) analysis of the *C. asiatica* plant The table shows that nine compounds have a high degree of drug similarity. All of these compounds meet the famous Lipinsky criteria according to the rule of five. In addition, the table also presents radar bioavailability, which can explain more concisely the bioavailability of each compound.

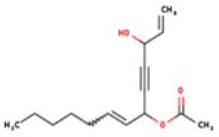
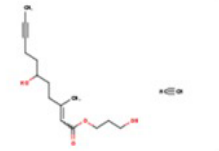
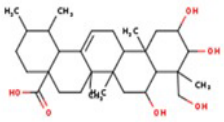
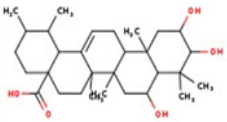
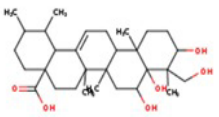
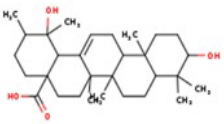
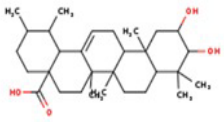
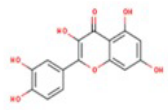
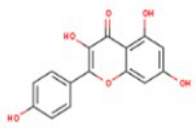
Metabolit	Compound Structure	Bioavailability Radar	PUBCHEM CID	MW	LD50	HIA	BBB	TPSA
Centellin			163184102	250.33 g/mol	2,6913	0.9523	0.9512	46.53
Centellicin			163183805	294.39 g/mol	1,7712	0.8658	0.7161	66.76
Madecassic acid			73412	504.70 g/mol	2,0501	0.9442	0.7483	118.22
Madasiatic acid			23132225	488.70 g/mol	2,1021	0.9770	0.6631	97.99
Isothankunic acid			12302703	504.70 g/mol	2,0501	0.9442	0.7483	118.22
Pomolic acid			382831	472.70 g/mol	2,3866	0.9918	0.7488	77.76
2alpha-Hydroxyursolic acid			6918774	472.70 g/mol	2,1021	0.9770	0.6631	77.76
Quercetin			5280343	302.24 g/mol	3,02	0.9650	0.5711	131.36
Kaempferol			5280863	286.24 g/mol	3,0825	0.9855	0.6286	111.13

Table 2: Result of docking XDH with Centellin, Madecassic acid, Pomolic acid, 2alpha-Hydroxyursolic acid, Quercetin, and Kaempferol.

Ligand and Receptor	Binding affinity (kcal/mol)	interaction (bond)	Residue
XDH vs Centellin	-6,2	Van der waals	VAL A:339, LEU A:305, ILE A:285, ARG A:331, GLY A:282, GLU A:334
		Conventional Hydrogen Bond	GLU A:337, SER A:338
		PI-Sigma	TYR A:193
		Alkyl	LEU A:307, PHE A:321, ALA A:245, PHE A:335, LEU A:225, LEU A:189
		PI-Alkyl	LEU A:307, PHE A:321, ALA A:245, PHE A:335, LEU A:225, LEU A:189
XDH vs Madecassic acid	-8,9	Van der waals	PRO A:261, LEU A:348, GLU A:449, ARG A:349, GLU A:459, TYR A:351, ALA A:456, VAL A:457, LEU A:458, ARG A:269, ARG A:268, GLY A:265, LEU A:266
		Conventional Hydrogen Bond	CYS A:350
		Unfavorable Donor-donor	ALA A:262
XDH vs Pomolic acid	-8,6	Van der waals	TYR A:351, ALA A:456, GLU A:449, ALA A:262, ARG A:349, PRO A:261, ARG A:269, CYS A:350, LEU A:458, GLU A:459, GLY A:265
		Unfavorable Donor-donor	ARG A:445
XDH vs 2alpha-Hydroxyursolic acid	-9,4	Van der waals	LEU A:252, ALA A:254, ILE A:234, VAL A:247, GLY A:246, THR A:248, SER A:226, LYS A:229, ALA A:55
		Conventional Hydrogen Bond	PHE A:255, ALA A:251, ALA A:232
		Unfavorable Donor-donor	GLN A:233
XDH vs Quercetin	-8,5	Van der waals	ASP A:329, LEU A:305, ILE A:285, ALA A:245, GLU A:337, GLY A:282, LEU A:225, LEU A:189, LEU A:189, TYR A:193, LEU A:307
		Conventional Hydrogen Bond	GLN A:328, GLU A:334, ARG A:331
		PI-Sigma	PHE A:335
		PI-PI T-Shaped	PHE A:321
XDH vs Kaempferol	-8,0	Van der waals	GLU A:25, SER A:22, THR A:213, LEU A:64, ASN A:61, GLU A:37, GLU A:41, GLY A:131
		Conventional Hydrogen Bond	THR A:48, ALA A:62, ALA A:46
		PI-Donor Hydrogen Bond	ALA A:46
		PI-Sigma	LEU A:24

SwissADME was additionally utilized for ADME prediction. ADME parameters are essential for reducing the time required to obtain drug candidates that are effective in terms of absorption, distribution, metabolism, and excretion. Compounds with high bioactive components and low toxicity alone are insufficient for drug candidate selection, but a thorough pharmacokinetic profile will help save time and money. Due to the high absorption capacity of the gastrointestinal tract, the results of the ADME analysis revealed that a few of the compounds had the potential to be used as drugs in oral preparations. However, only a small number of molecules can cross the blood-brain barrier. Complete results can be discovered in Figure 2.[8]

The results of the *in-silico* analysis of biological activity in this study showed that of the 25 selected *C. asiatica* metabolites, only eight were closely related to the XDH receptor, as shown in Figure 2. The eight metabolites were: Centellin, Madecassic acid, madasiatic acid, Isothankunic acid, Pomolic acid, 2alpha-Hydroxyursolic acid, Quercetin, and Kaempferol. Of the eight metabolites, six compounds (Centellin, Madecassic acid, Pomolic acid, 2alpha-Hydroxyursolic acid, Quercetin, and Kaempferol) interact with the XDH enzyme. The results can be seen in Figure 3.

Docking was performed to further examine the mode of interaction between Centellin, Madecassic acid, Pomolic acid, 2alpha-Hydroxyursolic acid, Quercetin, and Kaempferol to XDH. As shown in Table 2, the docking results revealed that all proteins and ligands had binding affinities lower than -6,2 kcal/mol. This indicated that the ligands had strong interactions with their respective target proteins. Fascinatingly, the protein ligand-binding profiles of Centellin-XDH, Madecassic acid-XDH, Pomolic acid-XDH, 2alpha-Hydroxyursolic

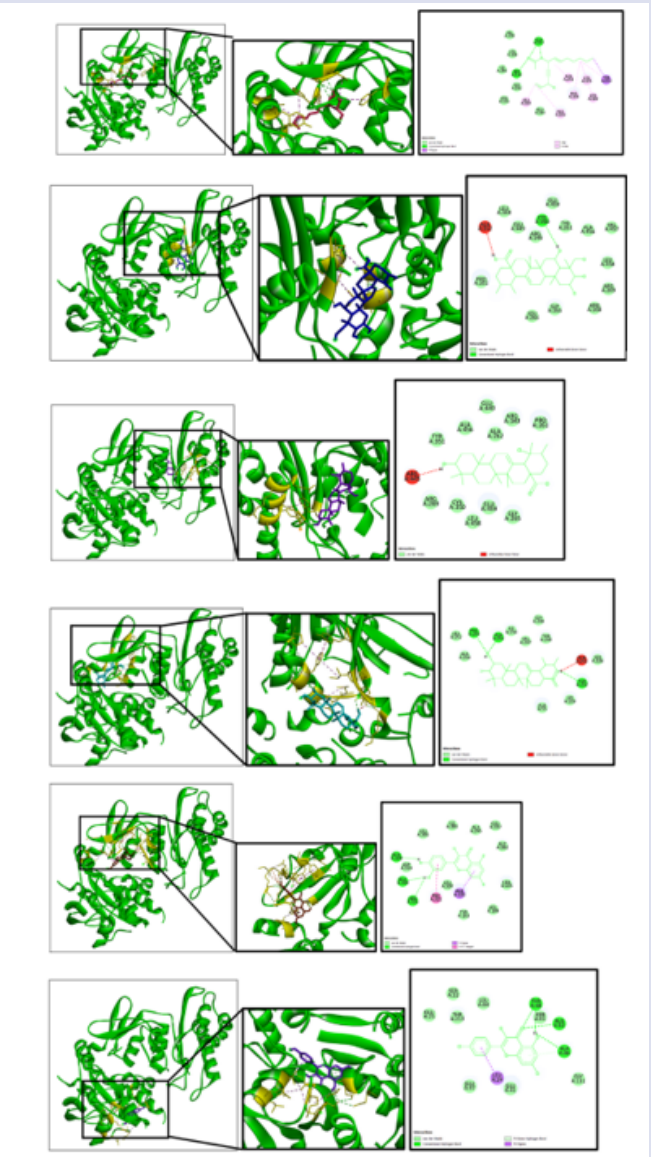


Figure 3: Results of docking XDH with Centelin, Madecassic acid, Pomolic acid, 2alpha-Hydroxyursolic acid, Quercetin, and Kaempferol. The yellow color each protein is the active site.

acid-XDH, Quercetin-XDH, and Kaempferol-XDH are in contact with the active sites on each of these protein enzymes, suggesting that they have antihyperuricemic potential.[14]

CONCLUSION

Based on the results of the above-mentioned *in silico* analysis, it is known that Centellin, Madecassic acid, Madasiatic acid, Isothankunic acid, Pomolic acid, 2 alpha-Hydroxyursolic acid, Quercetin, and Kaempferol, which are found in the *Centella asiatica* plant, have the potential to be anti-hyperuricemia and to inhibit the activity of XDH enzymes in humans because the metabolites of the *Centella asiatica* plant can interact by binding to receptors in the form of XDH.

SUGGESTION

Further research is needed regarding the content of the *Centella asiatica* plant, which is suitable as a candidate for antihyperuricemia drugs.

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