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POTENCY LIMPASU (*Baccarea lanceolata* (Miq.) Müll.Arg.) AS A CYP2C9 INHIBITOR FUNCTIONING IN XENOBIOTIC METABOLISM

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Abstract

Hepatotoxic is incident damage liver caused by substances poisonous. Poisonous substance That can caused by drugs medicine, poison industry, alcohol, and fungi poisonous. So that objective study This is CYP2C inhibitor screening 9 of compounds contained from B. lanceolata. Method used in study This is docking using PLANTS software and the compounds contained contained in *B. lanceolata* obtained of KNAPSACK, research This started with redocking ligand against CYP2C9, and obtained docking coordinates used for docking the compounds contained from *B. lanceolata* . Docking results obtained is as following Melatonin: -72.0859; Epidihydrotutin : -67.2656; Sapidolide A: -68.1767; 6'-O-Vanilloylisotachioside : -81.4806; 6'-O-Vanilloyltachioside: -92.3659. Research conclusions This is compounds contained from Spleen Two potential compounds were obtained as a CYP2C9 inhibitor 6'-O-Vanilloylisotachioside and 6'-O-Vanilloyltachioside.

Keywords: Limpasu, CYP2C9, docking

Introduction

Hepatotoxic is a term referring to damage liver caused by substances poisonous. This substance Can originate from various sources, namely: Several type medicine, like antibiotics, medicine nonsteroidal anti-inflammatories (NSAIDs), and medications anticonvulsants , can cause damage liver in some people (Wang et al., 2015) . Exposure to substance chemistry dangerous in place work , like carbon tetrachloride , can cause damage heart. Consumption alcohol excessive can damage heart. Consume mold poisonous certain can cause damage heart . Disease autoimmune: Several disease autoimmune, such as autoimmune hepatitis, can attack cells heart and cause damage (Chettri et al., 2020) .

Symptom hepatotoxic can varies depending on the level severity damage heart. Symptom general namely: fatigue, nausea and vomiting, loss lust eating, pain stomach, colored urine dark, skin and eyes colored jaundice (jaundice) fatigue, nausea and vomiting, loss lust eating, pain stomach, colored urine dark, skin and eyes colored yellow (jaundice) (Meharie et al., 2020) .

Some enzymes that can cause hepatotoxic, for example Cytochrome P450 (CYP450), NADPH-C reductase and GST. CYP450 is involved in metabolism drugs and substances chemistry other (Adebisi & Ugwah-Oguejiofor, 2021). A number of metabolites produced by CYP450 can nature reactive and capable damage cells heart. NADPH-cytochrome c reductase is involved in production radical superoxide, which is type molecule oxygen reactive that can be damage cells. Glutathione S-transferase (GST) is involved in detox Lots substance dangerous. However, GST can also catalyze formation metabolites reactive that can be damage cells heart (Idoh et al., 2018) .

Spleen (*Baccaurea lanceolata* (Miq .) Müll.Arg .), known as drug traditional For Sick headache stomach , acne , and replacement sour in food. People also use it For maintenance skin with method crushed and smeared on the exposed parts ray sun. Study scientific about benefit fruit spleen For skin Still limited. However, research on other species such as *B. ramiflora* show its potential as antioxidant. Results of isolation of 6-Ovanilloylisotachioside from *B. ramiflora* own ability antioxidant 36.9 ppm (Pan et al., 2015). Fruit *B. ramiflora* also contains total phenolics of 141.27 mg GAE/L, flavonoids of 149.2 QE/L, and flavonols of 103.2 mg QE/L. *B. motleyana* show ability antioxidant with IC50 5090.11 □g / mL (Prodhan & Mridu, 2021). *B. sapida* capable inhibit radical ions hydroxyl can degrade deoxyribose, so expected can prevent aging early with hinder damage sour nucleic (Pradhan et al., 2014). Based on background behind the Not yet Once done study regarding CYP450 enzyme inhibitors . So that study This done .

Materials and Methods

Tools and materials

Equipment used is an Acer Aspire E5-475 laptop with specifications 2 GB RAM, VGA, Pentium DualCore , 160 GB hard disk , docking software PLANT (Korb et al., 2009) , YASARA (Krieger & Vriend, 2014), Discovery studio (Biovia, 2019), Chemaxon (ChemAxon, 2016) and paymol. Materials used in study This is compounds contained in Baccaurea namely melatonin, epidihydrotutin , sapidolide A, 6'-O-Vanilloyllisotachioside, 6'-O-Vanilloyltachioside

Methods

Redocking of native ligands against CYP2C9 protein with code 4nz2. This redocking process started from protein preparation with remove any ligands that are not involved in interaction namely water, HEM, sulfate ions and glycerol . Stage furthermore is ligand preparation . Preparation This done with use chemaxon started from make from addition of hydrogen atoms, creation two- dimensional structure and manufacturing ligand conformation . After preparation finished Then done with redocking for knowing the radius and coordinates of ligands on proteins. After get coordinates Then docking is carried out . From the results of this docking obtained lowest docking score . Ligand of docking results later combined with the CYP2C9 protein using paymol For analysis more carry on .

Preparation of derived ligands from spleen . Ligands contained in spleen obtained from the knapsakfamily database (Afendi et al., 2012) . Ligand of spleen before used for docking is prepared use chemaxon and made 10 conformers. From redocking that has been done previously obtained coordinates and radius used for docking, this data Then next used for docking the compounds contained in Limpasu

Data analysis

Analyze data with see score docking with ANN and comparative algorithms residues involved in interaction from ligands and native ligands

Results and Discussion

This section may each be divided by subheadings or may be combined. A combined Results and Discussion section is often appropriate. This should explore the significance of the results of the work, don't repeat them. Avoid extensive citations and discussion of published literature only, instead discuss recent literature for comparing your work to highlight novelty of the work in view of recent development and challenges in the field.

CYP2C9 is one enzyme cytochrome P450 plays a role role key in metabolism medicine in the liver man. Enzyme This especially involved in phase oxidation, which involves breaking and changing structure chemistry drug. CYP2C9 has role important in change a number big compound medication , incl nonsteroidal anti- inflammatory drugs (NSAIDs), anticoagulants such as warfarin, and some drug antihypertensive (Banskota et al., 2000) .

metabolic processes carried out by CYP2C9 increase polarity medicine , make it more easy excreted by the kidneys or eliminated through bile. Activity enzyme This can varies between individual Because exists variation genetic in population. A number of variant genetic in the CYP2C9 gene can influence speed metabolism medicine, so influence response to treatment (Adnyana et al., 2001) **.**

Based on the redocking carried out obtained docking coordinates as following bindingsite_center X:- 62.7888; Y:-44.6719; Z: -22.4533 with bindingsite radius 12.6191 is visible in Figure 1. for validate docking results are carried out RMSD examination of native ligands. With use method superpose object obtained RMSD value 1.728 Å (Ångström) (Sharma & Malla, 2020) so that can used for docking from compounds contained from Spleen .

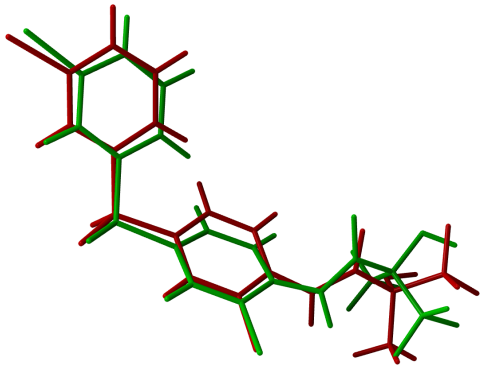
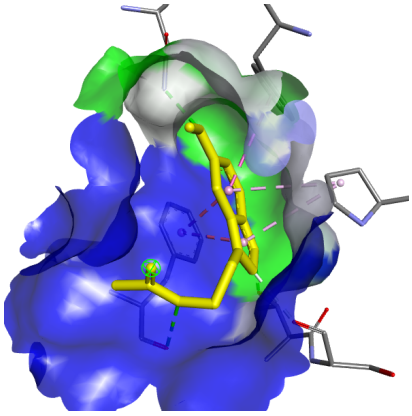
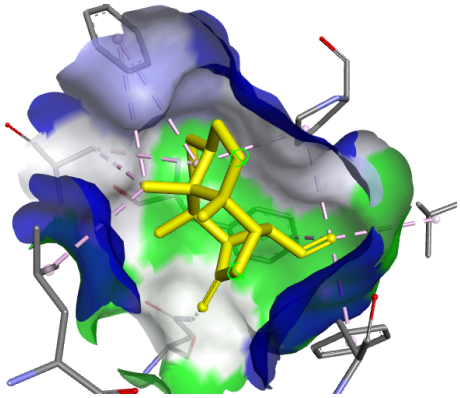


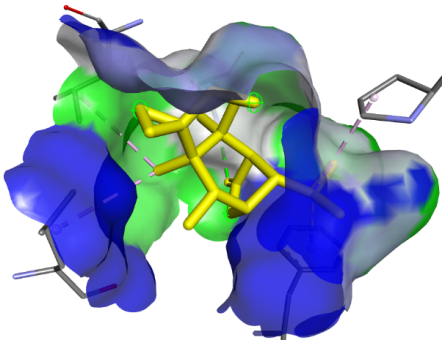
Figure 1. Redocking results of native ligands. The colors are native ligand green and red redocking results



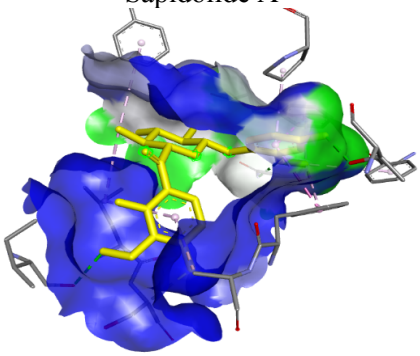
Melatonin



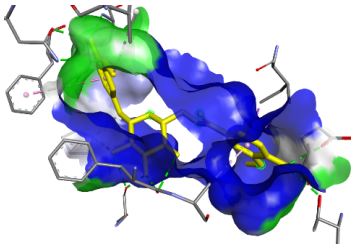
Sapidolide A



Epidihydrotutin



6'-O-Vanilloylisotachioside



6'-O-Vanilloyltachioside

Figure 2. Display interaction between CYP2C9 compounds and enzymes

Table 1. Docking scores between CYP2C9 ligands and enzymes

Compound Name	Docking Score
Native ligands	-90.5038
Melatonin	-72.0859
Epidihydrotutin	-67.2656
Sapidolide A	-68.1767
6'-O-Vanilloylisotachioside	-81.4806
6'-O-Vanilloyltachioside	-92.3659

Table 1. Residues CYP2C9 enzyme interacting amino acids with ligands

Compound Name	Bond		
	Hydrogen	Hydrophobe	Halogen
Native ligands	ASN217	LEU208; PHE100; PHE476; ALA103; VAL113; PRO367; LEU388; PHE100; PHE114; PHE476	ASP293
Melatonin	ASN217; THR364; PHE476; SER365	PHE100; PHE476; PRO367	-
Epidihydrotutin	ASN217	PRO367; LEU102; LEU208; PHE476	-
Sapidolide A	ASN217	ALA103; PRO367; LEU208; LEU388; PHE 100; PHE114; PHE476	-
6'-O-Vanilloylisotachioside	ASN217; THR364; IL105; SER209	PHE100; PHE476; LEU208; PHE69; PHE114; PRO367; ALA477	-
6'-O-Vanilloyltachioside	ALA103; ASN217; THR304; SER365; PHE 476; GLU300; PRO367	IL205; PHE100; ILE213; ALA103; ALA477	-

Based on the docking of the compounds contained in from spleen obtained docking scores with a minimum of 80% are 6'-O-Vanilloylisotachioside and 6'-O-Vanilloyltachioside with respective docking scores : -81.4806 and -92.3659 can be seen in Table 1 and Figure 2. based on comparison of native ligands bound with residue that has the value of 80% is Sapidolide A in Table 2.

CYP2C9 is enzyme Cytochrome P450 plays an important role in metabolism compound xenobiotics and endogenous via oxidation . About 18% of cytochrome P450 proteins in microsomes heart is CYP2C9 (Rajalingam et al., 2016) . This protein especially expressed in the liver , duodenum, and small intestine . The role of CYP2C9 in Drug Metabolism : About 100 drugs therapeutic metabolized by CYP2C9, including warfarin, phenytoin , acenocoumarol , tolbutamide, losartan, glipizide, and some drug nonsteroidal anti-inflammatory. Metabolism of Polyunsaturated Fatty Acids by CYP2C9: Extrahepatic CYP2C9 metabolize fatty acids don't fed up double like sour arachidonic and docosahexaenoic acids become various active product in a way biological. Products This including sour eicosatrienoic epoxides (EETs), acids epoxydocosapentaenoic acids (EDPs), and acids epoxyeicosatetraenoic (EEQs) (Chukwuma et al., 2023) .

Effect Biological EETs, EDPs, and EEQs: EETs, EDPs, and EEQs have various effect biological , including : Regulating pressure blood , Protect from infarction myocardium and disorders heart other (Vermeulen et al., 1992), Encourage cancer growth and metastasis , Inhibit inflammation , Stimulate formation vessels blood, Modulate release of neurohormones, Blocking perception pain , Comparison of EDPs and EEQs with Other CYP450 Products : EDPs and EEQs have frequent effects against product other CYP450 enzymes like 20-Hydroxyeicosatetraenoic acid (20-HETE). EDPs and EEQs more powerful compared to EET in lower hypertension and perception painful (Nofal et al., 2021) .

EDPs and EEQs more strong or The same its potential with EET in push inflammation . EDPs and EEQs inhibit angiogenesis, migration cell endothelium, proliferation cell endothelium , and growth as well as cell line metastasis cancer breast and prostate humans , while EET has effect stimulation. Consumption Foods rich in omega -3 fatty acids dramatically improve Serum and tissue EDP and EEQ levels in animals and humans . An increase in EDP and EEQ is most prominent change in profile metabolites fatty acids don't fed up double caused by omega-3 fatty acids (Kumar et al., 2020) .

Conclusion

Based on research conducted to compounds contained from Spleen two potential compounds were obtained as a CYP2C9 inhibitor 6'-O-Vanilloylisotachioside and 6'-O-Vanilloyltachioside.

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Declaration of Interest Statement

The authors declare that they have no conflict of interests.

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