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ANTICANCER ACTIVITY OF SANTONIN BY MOLECULAR DOCKING METHOD

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ABSTRACT

Objective: Santonin is an active compound of sesquiterpene lactones derived from the *Artimisia sp*. Santonin has been scientifically proven to have various important pharmacological activities including: antitumor, anti-inflammatory, immunomodulatory, antimicrobial. This study aims determine the anticancer activity of Santonin through computational chemical methods using several target receptors that have a dominant role in anticancer activity: Protein Kinase B, Vascular Endothelial Growth Factor Receptor-2 (VEGFR2), and Procaspase 7. **Materials and Methods:** The computational chemistry method was carried out through molecular docking using Pyrx, Avogadro, and Discovery Studio software. The molecular docking process was carried out using Auto Dock Vina software and the results were visualized in 2D interactions with the Discovery Studio Visualizer. Docking evaluation was carried out by observing the parameters of the binding affinity score and the type of bond formed between the target receptor and the ligand compound. **Results:** Docking scores obtained by Santonin against PKB -5.9 kcal/mol, VEGFR2 -7.2 kcal/mol, and Procaspase -8.6 kcal/mol. **Conclusion:** Evaluation of the docking binding affinity value can be concluded that the Santonin compound has anticancer activity through an inhibitory mechanism of Procaspase 7.

KEYWORDS: Computational chemistry, molecular docking, santonin, *Artimisia sp*, anticancer, binding affinity, protein kinase B, VEGFR2, procaspase 7.

INTRODUCTION

Cancer is the leading cause of death and a barrier to increasing life expectancy in every country, according to data from the World Health Organization (WHO) in 2019.[1] 3 types of cancer with the highest number in the world, namely: lung cancer (11.6%), breast cancer (11.6%), and colorectal (10.2%).[2] Current cancer treatment can be done by surgery, radiotherapy, and chemotherapy. The high toxicity, and the occurrence of resistance are the main reasons for the search for active compounds from nature that are more effective and safe.[3]

Santonin derived from the *Artimisia sp* plant has been known to have important pharmacological activities such as antitumor[4], anti-inflammatory[5], immunomodulatory[6], antimicrobial[7], and anthelminthic.[8]

Molecular docking has been widely known and used by researchers for sreening the new active compound candidates through the interaction between the target compound and the receptor. Evaluation of the binding energy of the target compound and the receptor and also the type of bond formed can provide information about the activity of the compound against the desired receptor target.[9]

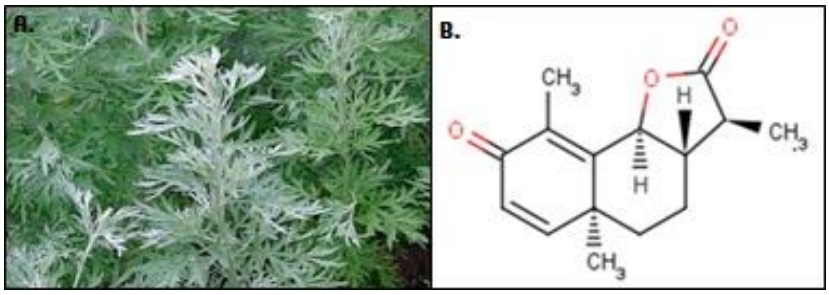

Figure 1: (a) *Artimisia sp;* (b) Santonin Structure.

Santonin compounds as targets of active compounds will interact with receptor targets responsible for cancer growth and physiology, namely: protein kinase B (PKB; PDB ID: 1GZN), Vascular Endothelial Growth Factor R2's receptor kinase (VEGFR2; PDB ID: 1VR2), and procaspase 7 (GDP ID: 1K88).

PKB is involved in the mechanism of cellular protein metabolism and phosphorylation processes, related to cell growth/apoptosis, cell differentiation and proliferation. PKB overexpression is related to information on the condition of tumor development (T-cell lymphoma) or prostate intraepithelial neoplasia.[10,11] Vascular endothelial growth factors

(VEGFs) and receptors (VEGFRs) are responsible for the vasculogenesis cycle, the process of angiogenesis.[12] VEGFR2 causes pathological processes of angiogenesis, growth of tumor angiogenesis, regulates vascular permeability, expression of cell, and also antiapoptotic effects.[13,14] Procaspase 7 is formed from 303 amino acid residues in a polypeptide chain. The formation of 175 large chain residues and 105 short chain residues through the mechanism of activation and removal of the amino acid Ile-Gln-Ala-Asp-2-Ser-Gly formed active caspase-7. Procaspase 7 is responsible for the process of cell apoptosis.[15]

MATERIALS AND METHODS

Software and Tools

AutoDock Vina 1.1.2, PyRx, MGL tools, Discovery Studio Visualizer, Avogadro.

Ligand Preparation

Scientific data on xanthonin compounds and other ligands are listed in table 1.

Table 1: Ligands used in the study.

No	Ligand	Molecular Formula	References
1	Santonin	$C_{15}H_{18}O_3$	[4]
2	RPRTSSF	RPRTSSF	[9]
3	Cilengitide	$C_{15}H_{27}N_7O_8$	[14]
4	RGDS	$C_{36}H_{59}N_{13}O_{11}$	[13]

Target Receptor and Ligan Preparations

The target receptor proteins related to cancer growth conditions were obtained from a protein data bank (http://www.rcsb.org); protein kinase B (PDB ID: 1GZN), receptor kinases R2 growth factor Endothelial Factor R2 (PDB ID: 1VR2), and procaspase 7 (PDB ID: 1K88).

The 3D ligand structure can be downloaded via https://pubchem.ncbi.nlm.nih.gov/. The obtained ligand file was then energy minimised, and converted into PDBQT file format.

Process and Evaluation of Docking Parameters

The docking process for santonin compounds and native ligands was carried out using AutoDock Vina 1.1.2 software. The use of grid boxes was set with a distance of 1 Å which makes the ligand movement space remain flexible to find the best position in the formation of bonds with the target receptor.

The evaluation of the docking results was carried out by analyzing the binding affinity score and also the type of bond formed.

RESULTS AND DISCUSSION

Ligand and Protein Preparation

Santonin and native ligands from each receptor were carried out in the first step of energy minimization, then the file format was changed to PDBQT. Physicochemical properties, 3D structure of ligands are summarized in table 2, and figure 2.

Table 2: Physiochemical properties of ligand.

No	Ligand	Molecular Weight (g/mol)	Hydrogen Bond Donor	Hydrogen Bond Acceptor	XLogP3-AA	Minimize Energy
1	Santonin	246.30	0	3	2.3	346.10
2	RPRTSSF	849.9	14	14	-7.7	1277.93
3	Cilengitide	588.65	7	8	-1.0	1216.28
4	RGDS	433.42	9	10	-7.3	390.38

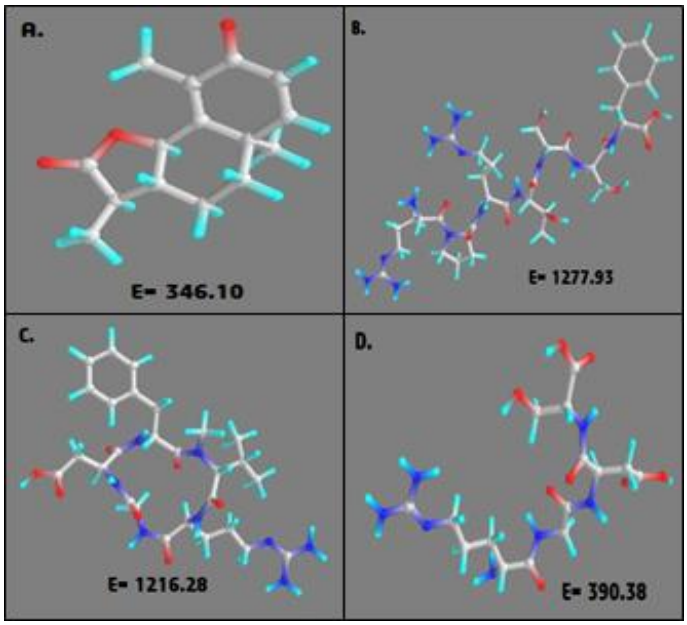

Figure 2: 3D ligand structure and energy minimized results: (A) Santonin, (B). RPRTSSF, (C) Cilengitide, (D) RPRTSSF.

The receptor protein was converted to PDBQT format, and docking simulations were performed for each native ligand and the binding affinity score was compared with the active compound santonin against the target of each receptor. 3D structure of the target receptor protein in figure 3.

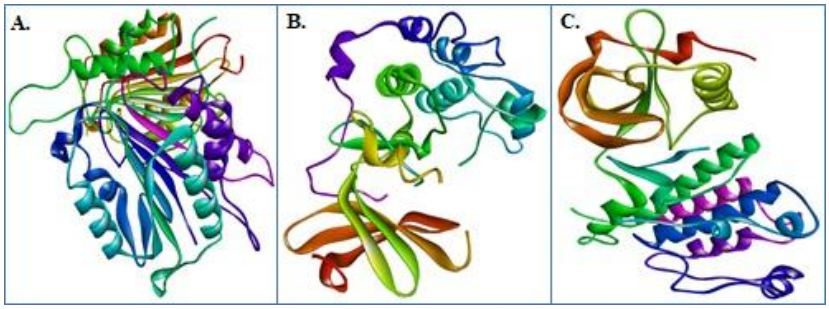

Figure 3: 3D structure of receptor, (A) Procaspase 7, (B) Protein Kinase B, (C) VEGFR2.

Docking Analysis Simulation

Molecular docking of Santonin compound with PKB receptor

The results of 2-D molecular docking visualization provide information that an interaction was formed between the RPRTSSF ligand and santonin against PKB receptor targets on the same amino acid, namely Asn 88, Val 86, Thr 90. Arg 87, Ala 186, Arg 187, Tyr 229, and Ser 231.

The RPRTSSF ligand and the PKB receptor form 3 hydrogen bonds in the amino acids Thr 199, Val 198, and Lys 181, while the santonin ligand has 3 hydrogen bonds in the amino acids Asn 88, Thr 90, Arg 87.

The docking value of the RPRSSF ligand to the PKB receptor was -6.6 kcal/mol, while the santonin ligand to the PKB receptor was -5.9 kcal/mol.

Molecular docking of Santonin compound with VEGFR2 receptor

The results of the docking study on the VEGFR2 receptor showed that santonin and cilengitide ligands had the same interaction at the amino acid receptor Ser 275. The cilengitide ligand formed 6 hydrogen bonds at the receptor, while santonin had no hydrogen bonds. The docking score showed the binding affinity value of cilengitide was -8.2 kcal/mol, and santonin was -7.2 kcal/mol.

Molecular docking of Santonin compound with Procaspase 7 receptor

The simulation results of the docking of the RGDS and santonin ligands to the procaspase 7 receptor showed that the two ligands had the same amino acid interactions at the receptors in Val 848, Cys 1045, Asp 1046. The RGDS ligand formed 6 hydrogen bonds with the receptor

on the amino acids Ser 231, Arg 187, Asp 93, Ser 239, Arg 233, and Arg 87. The santonin ligand forms 3 hydrogen bonds with receptors on the amino acids Lys 868, and Cys 919.

The docking score showed that the santonin ligand had a better binding affinity value of -8.6 kcal/mol and the RGDS ligand -6.9 kcal/mol.

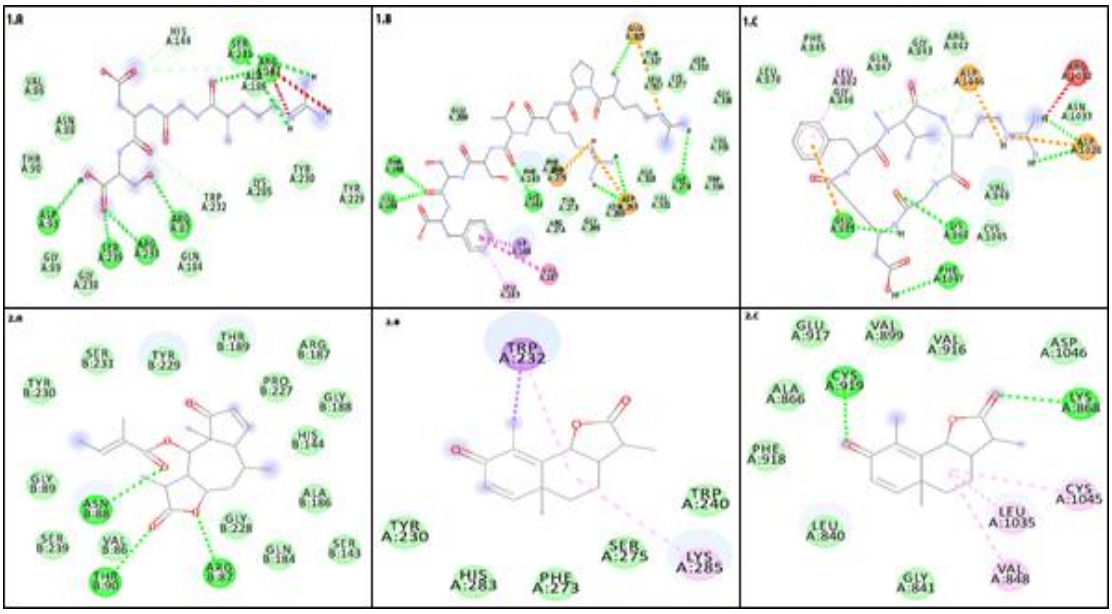

Figure 4. Interaction of ligands and target receptors. (1.a) RPRTSSF interaction with PKB, (1.b) Cilengitide interaction with VEGFR2, (1.c) RGDS interaction with Procaspase 7, (2.a) Santonin with PKB, (2.b) Santonin with PKB, (2.c) Santonin with Procaspase 7.

Table 4: Comparative binding affinity of different ligands with receptors.

No.	Receptor	Ligand	Binding Affinity (kcal/mol)
1	Vascular Endothelial Growth Factor R2	Cilengitide Santonin	-8.2 -7.2
2	Procaspase 7	RGDS Santonin	-6.9 -8.6
3	Protein Kinase B	RPRTSSF Santonin	-6.6 -5.9

CONCLUSIONS

The data from the docking simulation showed that santonin compounds had a better binding affinity value than the native RGDS ligand on the Procaspase 7 receptor target. It can be concluded that the santonin compound had a dominant activity with the mechanism of inhibition of the procaspase 7 receptor.

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