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Research Article

In Silico Study of the Potential of Endemic Sumatra Wild Turmeric Rhizomes (*Curcuma Sumatrana*: Zingiberaceae) As Anti-Cancer

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ABSTRACT
Cancer is one of the diseases that is the highest cause of death in humans. Most human cancer cells are formed as a result of over-expression of anti-apoptotic proteins. Thus, the activation of these proteins can inhibit pro-apoptotic proteins, then apoptosis will be inhibited so that other apoptotic pathways need to be activated to prevent cancer cells from developing. Current cancer treatments, such as chemotherapy using synthetic compounds, have various side effects, so research on natural based therapies can be used as an alternative in cancer treatment. *Curcuma sumatrana* is one of the plants of the Zingiberaceae family which is an endemic plant from Sumatra which is found along the Bukit Barisan. The research was carried out in silico by analyzing the potential bioactivity of the compounds, testing the bioavailability, toxicity, and molecular docking of the bioactive compounds from the ethanol extract of the rhizome of *C. sumatrana* which had been previously identified through gas chromatography-mass spectroscopy (GC-MS) analysis. The results obtained that the compound 9-Acetyl-S-octahydrophenanthrene and 3-Oxo-androsta-1,4-dien-17.beta.-spiro-2'-3'-oxo-oxetanecontained in *C. sumatrana* has the potential to be developed as an anticancer where the compound has good bioavailability value and is not toxic and potentially can trigger apoptosis. However, the results of this study need to be analyzed further with an *in vitro* or *in vivo* approach.
Key words: Anticancer, *C. sumatrana*, *In silico*.

INTRODUCTION

Cancer is a very complex disease and is ranked first as the most common cause of death worldwide.[1] In poor and developing countries, the increase in the incidence of cancer is in line with the increase in the prevalence of risk factors such as smoking, overweight, physical inactivity, and patterns of reproductive changes associated with urbanization and economic growth.[2] Cancer has become a major health burden for society because the main treatment for cancer requires surgery, chemotherapy, radiation therapy and immunotherapy which are expensive and high risk. In addition, the side effects of cancer drugs and irradiation are still a threat to cancer patients, while not all cancer patients can be cured by surgery. Therefore, it is necessary to explore alternative solutions that are effective, economical and have low side effects in suppressing cancer cases. Cancer chemoprevention is the latest rapidly developing approach using natural or synthetic agents to prevent, inhibit or reverse tumorigenesis and suppress the development of invasive cancer.[3] Considering the high diversity and potential sources of raw materials for Indonesian natural medicines, the exploration and development of medicinal materials made from natural medicines for cancer is a strategic and urgent step.

Previous reports stated that the rhizomes of plants in the genus Curcuma contain a variety of potential secondary metabolites as anticancer, especially the saponins, alkaloids, flavonoids, tannins and curcuminoids.[4] So far, the study of the medical properties of turmeric rhizome has only focused on cultivated turmeric species such as turmeric from *Curcuma domestica* and *C. longa* species.[5]

A recent study proved that the ethanol extract of *C. sumatrana* rhizome was effective in preventing brain degeneration, decreased cognitive function and accumulation of free radicals in mice induced with high doses of monosodium glutamate.[6] This efficacy is strongly suspected to be related to the content of various bioactive compounds in the rhizome of *C. sumatrana* which is dominated by the sesquisterpenoid group. In order to develop the potential of bioactive compounds in *C. sumatrana* rhizome as anticancer natural medicinal materials, extensive and in-depth studies with various approaches are needed.

Apoptosis is the most successful non-surgical therapy, targeting apoptosis effectively for all types of cancer.[7] The one way to trigger apoptosis is by extrinsic pathway, namely ligand binding and through activation of death domain receptor families, such as FAS and TNF-associated apoptosis-inducing ligand (TRAIL).[8-10] The TRAIL receptors used were TRAIL-R1 DR-4 and TRAIL-R2 (APO-2, DR-5). This will allow activation of caspase-8 or -10 by generating a death-inducing signaling complex (DISC).[11]

Cancer cells are more easily triggered to carry out apoptosis than normal cells.[12] This can be attributed to the increased sensitivity of cancer cells to apoptosis caused by environmental stress or hypoxia.[13] In addition, tumor/cancer cells are also more sensitive when apoptosis is triggered through

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the extrinsic pathway so that this pathway can be used as a therapeutic target in cancer cells.[14]

Exploration of potential anticancer drug materials can be carried out independently *in vivo* with test animals and *in vitro* with specific cell or tissue cultures. However, these classical approaches are expensive and time consuming. In addition, determining the specific target of a bioactive compound from medicinal herbs in intervening signaling systems related to the initiation and development of cancer *in vitro* and *in vivo* requires a very complex experimental stage. Therefore, it is necessary to do an alternative approach that is fast, specific and economical, namely through *in silico* studies. *In silico* investigation of the anticancer potential of compounds from *C. sumatrana* is very possible because data on the secondary metabolites contained therein are available (although these are only a group of volatile compounds and low molecular weight).

MATERIALS AND METHODS

Sample retrieval

Data on bioactive compounds of *C. sumatrana* rhizome ethanol extract (with GC-MS test) were isolated from PubChem (https://pubchem.ncbi.nlm.nih.gov/) in *.sdf format, 3D structure protein taken from the Protein Data Bank (PDB) is FAS/CD95 (PDB ID:3EZQ) with a resolution of 2.73Å, TRAIL protein is death receptor 4/DR-4 (PDB ID:1DG6) with a resolution of 1.30Å and death receptor 5/ DR-5 (PDB ID:1D4V) with 2.20Å. resolution in *.pdb format.

Bioactivity probability analysis

Prediction of the bioactivity of metabolites in *C. sumatrana* was carried out by entering SMILE (simplified molecular-input line entry system) canonical data into the PASS web server (http://www.way2drug.com/passonline/). The value of Probability activity (Pa) which represents the target protein and the predicted compound, the value of Pa must be greater than the value of Pi (Probability inhibition). Pa value >0.3 (medium confidence) indicates a computationally proven result and further analysis is needed.[14,22,23]

Bioavailbility analysis

Bioavailability prediction is carried out to determine the permeability and solubility of a compound in the body. Bioavailability prediction based on lipinski rule of control ligand using SCFBio web server (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp). Lipinski rules include molecular weights, hydrogen bond donors, hydrogen bond acceptors, log P and molar refractivity. Ligands that have passed the Lipinski rule are then determined for their toxicity potential.

Toxicity analysis

Analysis of the safety level of the compound was carried out using the pkCSM (https://biosig.lab.uq.edu.au/pkcsm/) web server. Ligands that had passed Lipinski's rules were then determined for their potential toxicity. Parameters analyzed included carcinogenicity (AMES), acute oral toxicity (LD50), and Human Ether A-Go-Go Related Gene (hERG), and Minnow test. The test was carried out by entering SMILES ligand data into the pkCSM web server (http://biosig.unimelb.edu.au/pkcsm/).

Analysis of ligand potential with molecular docking

This analysis was carried out through specific steps in the form of preparation of the test ligand, receptor, and molecular docking. Phytochemical data from *C. sumatrana* then inputted into the Pubchem database and isolated as a ligand in *.sdf format. Furthermore, ligand minimization was carried out using PyRx 0.8 software. Isolated proteins FAS/CD95, DR-4, and DR-5 (a protein involved in the apoptotic pathway of cancer cells) from the Protein Data Bank (PDB) as receptors. Protein model that has missing residue is completed by using Moddlop web server. Preparation by removing water molecules and minimizing energy using Yasara Dynamic and Chimera. Receptor proteins are stored in *.pdb format. After that predicted the binding site of the protein using the P2rank web server (https://prankweb.cz/). The simulation of protein and ligand binding used molecular docking using PyRx 0.8 software. Visualization of interactions between proteins and ligands was visualized using Biovia Discovery Studio and PyMol.[24-26]

RESULTS AND DISCUSSION

GC-MS data namely 22 compound ssuccessfully identified (Appendix 1) and obtained 12 compounds that are predicted to stimulate caspase-8. Data from bioactivity analysis are presented in Figure 1. The prediction results of compound bioactivity using the PASS web server indicated that 12 compounds in the rhizome of *C. sumatrana* had a high level of activation probability with a value of Pa>0.3, indicating that the prediction results were computationally proven.[16] These compounds have been computationally proven to have the potential to stimulate caspase-8, which is one of the important pathways in cancer inhibition. The activity potential inhibition (Pi) value for the 12 compounds was lower than the Pa value, this indicated that there would be no inhibition in caspase-8 stimulation if these compounds entered the human body.[17,18,27]

From the results of the bioactivity prediction analysis, it was found that 12 compounds were predicted to stimulate caspase-8 (Table 1). Predictions made with the Lipinski server showed that the metabolites (as ligands in this study) in the rhizome of C. sumatrana complied with Lipinski's rules, namely molecular weight (MW) < 500 Daltons, lipophilicity (LogP) < 5, hydrogen donor bond (HBD) <10, and molar refracticity (MR) 40-130.[19] These compounds are predicted to have good absorbivity and can trigger biological responses when interacting with target proteins.

The results of the toxicity prediction analysis that have been carried out are presented (Table 2). Ligand toxicity based on AMES mutagenic parameters indicates the potential of chemicals that cause mutations in the DNA structure, while hERG 2 inhibitors show potential chemical inhibitors against human ether-a-go-go-related gene receptors, and Oral Rat Acute Toxicity (LD50) represents the dose. the lowest level of a substance under certain conditions that can kill 50% of the exposed test sample. While hepatotoxicity represents the level of liver damage due to exposure to chemicals, and the Minnow test represents the level of toxicity of chemicals in a solution.[20,28,29]

The results of the predictive toxicity analysis found that most of the secondary metabolites in the rhizome of *C. sumatrana* were non-toxic (safe). However, there is one compound, namely boldenone which is predicted to be toxic which can specifically elicit an inhibitory effect on the hERG 2 receptor. Thus, boldenone does not meet the criteria for further analysis regarding its anticancer potential.

The proteins that are used as ligand targets in the analysis are the main proteins that play a role in the apoptosis signaling system in cancer cells, namely FAS/CD95 protein, DR-4 protein, and DR-5. The binding affinity values for each ligand and protein are presented in Table 3.

The results of molecular docking between the ligand and FAS/CD95 protein showed that the compound 9-Acetyl-S-octahydrophenanthrene had the lowest binding affinity value of -9.3 kcal/mol. The interactions between ligands and proteins are hydrogen bonds (Gln E:311), hydrogen pi-donor bonds (Gln G:311, Gln A:311), alkyl bonds (Ala G:307, Ile E:310, Ile G:310, Ala E:307, Leu A:315, Ala C:307, Ile G:314, Leu G:315), and the van der walls bond (Ile E:314, Gln C:311, Ala A:307, Ile A: 314) (Figure 1). The results of molecular docking between the ligand and DR-5 protein also showed that the compound 3-Oxo-

Table 1: Bioavailbility analysis based on Lipinski's rule.

Compounds (Ligans)	Criteria Based on Lipinski's Rule				
	MW (Dalton)	LogP (<5)	Hydrogen Donor (<5)	Hydrogen Acceptor (<10)	Molar Refracticity (40-130)
α-selinene	204	4.72	0	0	66.74
Curzerene	216	3.84	0	1	66.52
α-Guajene	204	4.72	0	0	66.74
Cycloisolongifolene, 8,9-dehydro-9-formyl	230	3.59	0	1	67.4
Boldenone	286	3.65	1	2	82.62
Spathulenol	220	3.38	1	1	65.97
Viridiflorol	222	3.46	1	1	65.99
(3E,7E)-10-prop-1-en-2-ylcyclodeca-3,7-dien-1-one	190	3.43	0	1	60.05
3-Oxo-androsta-1,4-dien-17.beta.-spiro-2'-3'-oxo-oxetane	326	3.26	0	3	98.15
Isovelleral	232	2.77	0	2	65.36
9-Acetyl-S-octahydrophenanthrene	228	3.64	0	1	69.73
5,6-Azulenedimethanol,1,2,3,3a,8,8a-hexahydro-2,2,8-trimethyl-,(3a.alpha.,8.beta.,8a.alpha.)-	236	2.52	2	2	69.5
Methyl 2-[2,4a-epidioxy-3,4,5,6,7,8-hexahydro-5,5,8a-trimethyl-2H-	284	2.72	0	5	70.62

Table 2: Toxicity analysis secondary metabolite *Curcuma sumatrana* rhizome.

Compounds (Ligan)	Toxicity Criteria				
	AMES Toxicity	hERG 2 Inhibitor	Oral Rat Acute Toxicity (LD50) (mol/kg)	Hepatotoxicity	Minnow Toxicity (Log Mm)
α-selinene	No	No	1.543	No	0.353
Curzerene	No	No	1.836	No	-0.194
α-Guajene	No	No	1.679	No	0.366
Cycloisolongifolene, 8,9-dehydro-9-formyl	No	No	1.753	No	0.707
Boldenone	No	**Yes**	2.118	No	0.635
Spathulenol	No	No	1.687	No	1.266
Viridiflorol	No	No	1.615	No	1.063
(3E,7E)-10-prop-1-en-2-ylcyclodeca-3,7-dien-1-one	No	No	1.815	No	1.397
3-Oxo-androsta-1,4-dien-17.beta.-spiro-2'-3'-oxo-oxetane	No	No	1.848	No	0.279
Isovelleral	No	No	1.694	No	0.857
9-Acetyl-S-octahydrophenanthrene	No	No	1.998	No	0.109
5,6-Azulenedimethanol,1,2,3,3a,8,8a-hexahydro-2,2,8-trimethyl-,(3a.alpha.,8.beta.,8a.alpha.)-	No	No	1.464	No	1.318
Methyl 2-[2,4a-epidioxy-3,4,5,6,7,8-hexahydro-5,5,8a-trimethyl-2H-	No	No	2.584	No	1.209

Table 3: Potential anticancer ligands based on molecular docking analysis.

Senyawa (ligan)	Binding Affinity (Kcal/mol)		
	Protein FAS/CD95	Protein DR-5	Protein DR-4
α-selinene	-5,6	-5,1	-5,4
Curzerene	-3,6	-5,0	-4,9
α-guajene	-4,2	-5,5	-5,5
Cycloisolongifolene, 8,9-dehydro-9-formyl	-0,6	-5,6	-5,5
Spathulenol	-3,5	-5,3	-5,1
Viridiflorol	-5,3	-5,4	-4,9
(3E,7E)-10-prop-1-en-2-ylcyclodeca-3,7-dien-1-one	-5,3	-4,8	-4,8
3-Oxo-androsta-1,4-dien-17.beta.-spiro-2'-3'-oxo-oxetane	-5,3	**-7,0**	**-7,1**
Isovelleral	-5	-5,4	-5,2
9-Acetyl-S-octahydrophenanthrene	**-9,3**	-6,2	-6,1
5,6-Azulenedimethanol,1,2,3,3a,8,8a-hexahydro-2,2,8-trimethyl-,(3a.alpha.,8.beta.,8a.alpha.)-	-5	-5,6	-5,4
Methyl 2-[2,4a-epidioxy-3,4,5,6,7,8-hexahydro-5,5,8a-trimethyl-2H-	-5	-5,4	-5,4

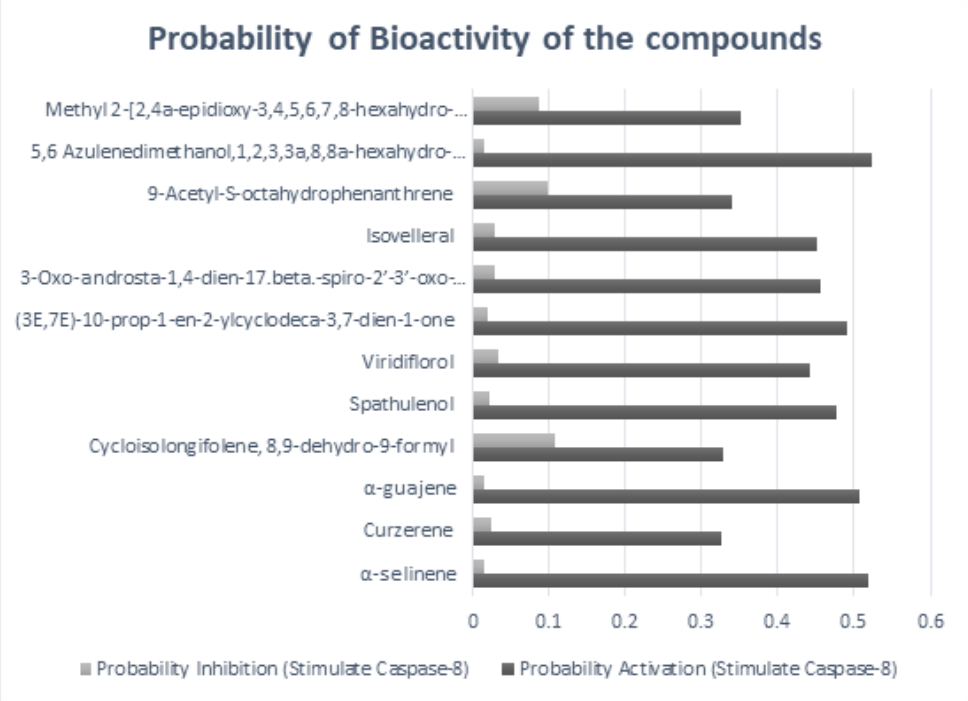

Figure 1: Probability of bioactivity from the rhizome *Curcuma sumatrana.*

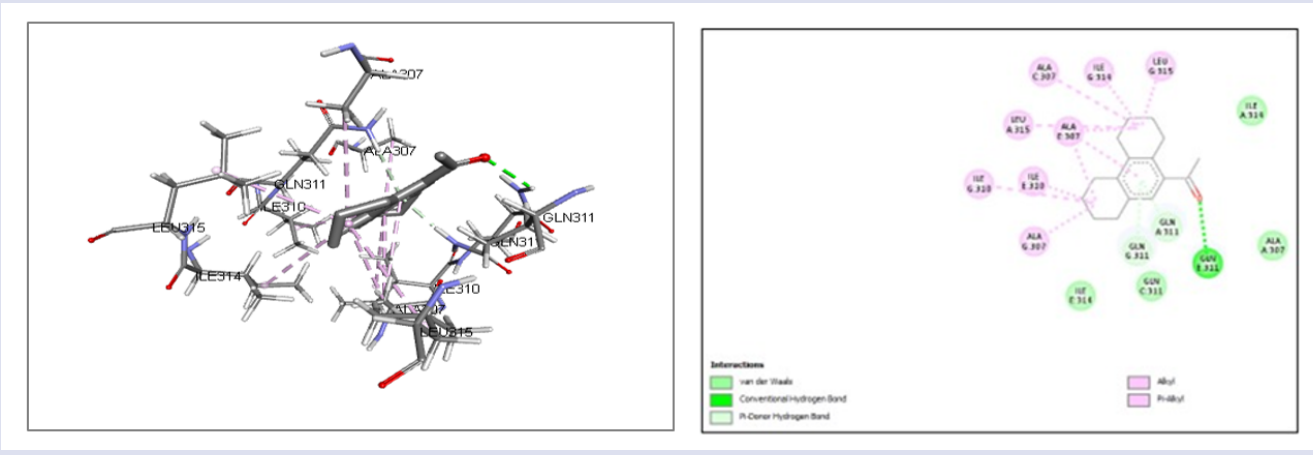

Figure 2: Visualization of the interaction between 9-Acetyl-S-octahydrophenanthrene compound and FAS/CD95 protein.

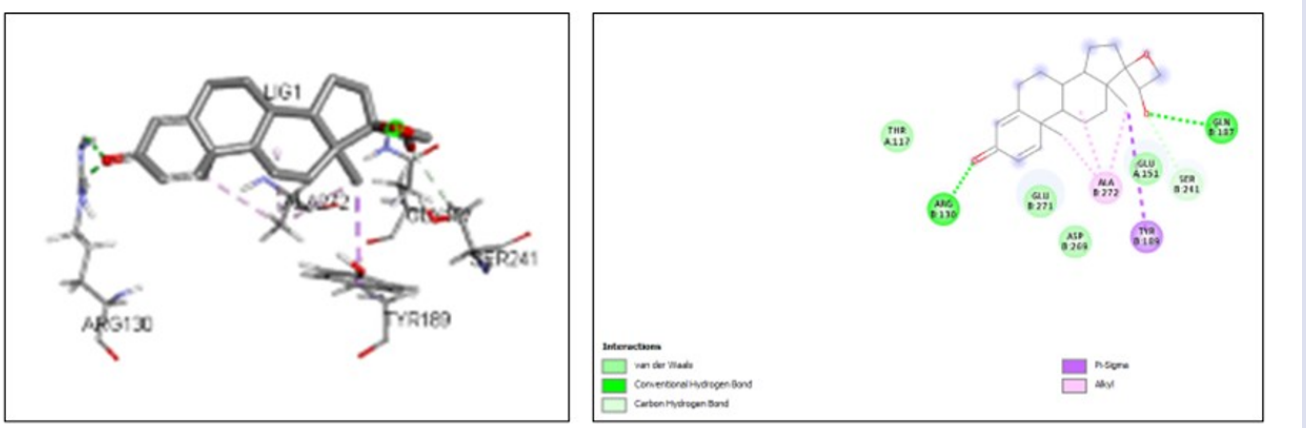

Figure 3: Visualization of interaction between 3-Oxo-androsta-1,4-dien-17.beta.-spiro-2'-3'-oxo-oxetane compound and DR-5 protein.

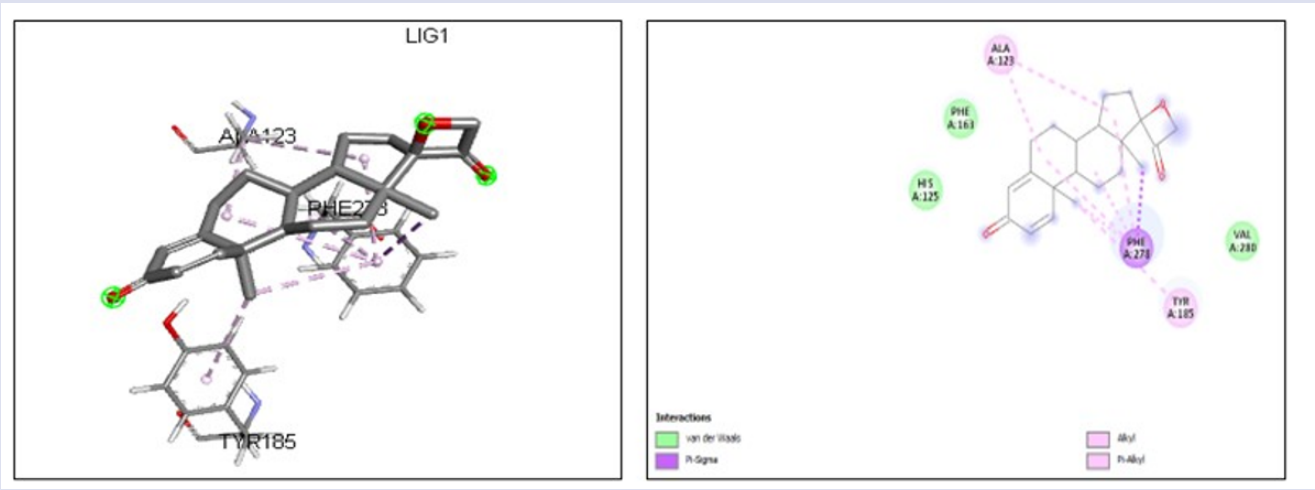

Figure 4: Visualization of the interaction between 3-Oxo-androsta-1,4-dien-17.beta.-spiro-2'-3'-oxo-oxetane compound and DR-4 protein.

androsta-1,4-dien-17.beta.-spiro-2'-3'-oxo-oxetane had the lowest binding affinity value -7.0 kcal/mol with interactions between ligands and proteins in the form of hydrogen bonds (Arg B:130, Gln B:187), pi-sigma bonds (Tyr B:189), alkyl bonds (Ala B:272), hydrogen- carbon (Ser B:241), and van der walls bonds (Thr A:117, Glu A:151, Glu B:271, Asp B:269) (Figure 2). While the results of molecular docking between the ligand and DR-4 protein showed that the compound 3-Oxo-androsta-1,4-dien-17.beta.-spiro-2'-3'-oxo-oxetane had the lowest binding affinity value, namely -7.1 kcal/mol. The interactions between ligands and proteins are in the form of pi-sigma bonds (Phe A:278), alkyl bonds (Ala A:123, Tyr A:185), and van der walls bonds (Phe A:163, His A:125, Val A: 280) (Figure 3).

Binding affinity refers to the binding energy formed when one molecule interacts with another molecule. Thus it can produce a number of affinities that affect the activity of the target molecule.[21,16,30] Molecular complexes can be formed from weak bond interactions, hydrogen bond interactions have an important role in drug molecules, which play a role in maintaining molecular complexes so that they can trigger biological responses to protein targets.[16,31,32]

CONCLUSION

From the results of an *in silico* study on the potential of secondary metabolites in the rhizome of wild turmeric endemic to Sumatra (*C. sumatrana*) as anticancer, the following conclusions can be drawn:

There are 12 compounds in the rhizome of *C. sumatrana* which have potential bioactivity in stimulating caspase-8 (an enzyme involved in the apoptotic pathway/programmed death of cancer cells).

The compounds in the rhizome of *C. sumatrana* have good bioavailability according to the Lipinski rule criteria so that they are predicted to have high absorbivity and trigger a biological response when interacting with target proteins in body tissues.

Most of the compounds in the rhizome of *C. sumatrana* that have bioactivity in stimulating caspase-8 are non-toxic except for boldenone which is predicted to have an inhibitory effect on the hERG 2 receptor.

Compound 9-Acetyl-S-octahydrophenanthrene and 3-Oxo-androsta-1,4-dien-17.beta.-spiro-2'-3'-oxo-oxetane in the rhizome of *C. sumatrana* are the main candidates as anticancer with good binding affinity. strong against specific proteins (FAS/CD95, DR-5 and DR-4) proteins involved in the apoptotic pathway of cancer cells.

DISCLOSURE STATEMENT

The authors have no conflicts of interest to declare.

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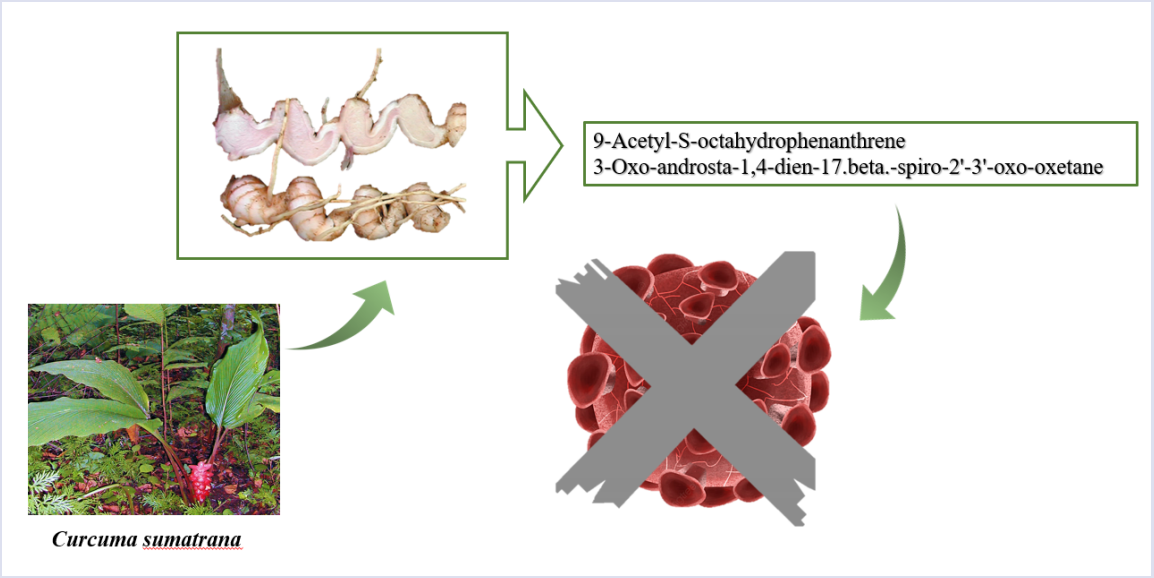
GRAPHICAL ABSTRACT



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