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Potential of Chemical Compounds from Coloring Plants (*Stenochlaena palutris*) as Competitors for ALK Protein Damage Due To Pesticide Exposure: In Silico Study

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Abstract:

Pesticide active ingredients have widespread toxicity effects on target and non-target organisms. Continuous exposure to pesticides causes cancer. Kelakai is thought to have potential cytotoxic activity against the growth of cancer cells. The aim of this research is to examine the potential activity of chemical compounds on Anaplastic Lymphoma Kinase (ALK) proteins exposed to organophosphate pesticides in silico. Protein and ligand preparation with the Chimera program, Docking using SwissDock, as well as virtual screening using the pkCSM web and ProTox. Ethion and neophytadiene have the most negative ΔG values of -8.62 kcal/mol and -8.39 kcal/mol, respectively. The binding site for ethion and neophytadiene compounds with the ALK protein is right at the active site of the ALK protein. Ethion is the most toxic organophosphate pesticide and has the potential to be cytogenic. Neophytadiene from kelakai compounds has the potential to act as a competitor in inhibiting the ALK protein. The similarity in the type and number of binding residues in ethion and neophytadiene in the ALK protein indicates competition between ethion and neophytadiene.

Keywords: Anaplastic Lymphoma Kinase; docking molekula; skrining virtual; ethion, neofitadiena

Introduction

Pesticides are a class of chemicals used in various fields, ranging from households, health, agriculture, and others. Apart from its benefits, pesticides also have the potential to poison and eradicate other living creatures, including plants and beneficial insects, animals and humans. [1] This is because most of the active ingredients in pesticides do not have specific toxic effects, thus affecting both target and non-target organisms, humans and the environment and ecosystem as a whole. Pesticides are cytotoxic and because they are mutagenic, they can cause mutations, cancer and are teratogenic.[2]

Currently, treatment for cancer can be done with chemotherapy, radiotherapy and surgery. However, it can cause dangerous side effects for the body such as hair loss, bone marrow suppression, and heart toxicity. The use of active compounds from herbal plants is an alternative in the search for anticancer drugs because they have minimal side effects and the availability of herbal plants is relatively easy to find.[3] Kelakai (*Stenochlaena palustris*) is a typical Kalimantan fern that lives wild in peatlands. This plant is widely consumed by the people of Kalimantan as a traditional medicine or vegetable food.

Kelakai has health benefits, it has high antioxidant content, prevents infection, and for postpartum mothers to facilitate breastfeeding by consuming it every day.[4] Dayak people also believe kelakai can treat anemia because of its high Fe content.[5] Kelakai contain secondary metabolites, i.e alkaloids, saponins, flavonoids, phenols, terpenoids, glycosides and tannins.[6]

Based on several studies, kelakai has antibacterial, anticholinergic, antioxidant, antitumor and cytotoxic activity against HepG2 cells, antibreast cancer by inhibiting ER-α.[6-10] The isolated fraction of kelakai leaves against HeLa cancer cells has cytotoxic activity with an IC50 value of less than 50%.11 The Kelakai has been widely developed for its cytotoxic activity against cancer cells and has potential as an anticancer agent.

Cancer cases are increasing day by day with population growth. Generally, cancer can be detected by mutations in the causative gene.[9] One of the causes of colorectal cancer, which is a mutation in the Anaplastic Lymphoma Kinase (ALK) gene.[12] ALK is a gene that codes for the formation of one of the receptor protein tyrosine kinases and plays a role in the signal transduction process.[13]

Molecular docking studies are a computational method as the first stage in designing new drugs. Molecular docking produces affinity energy data (ΔG) which defines the strength of the bond produced by the interaction between the ligand and the receptor.[14] This study was conducted to determine the potential of chemical compounds from the kelakai herb which have the potential to act as competitors in damaging the ALK protein due to exposure to pesticides with parameters in the form of data on Gibbs free energy (ΔG) and residue interactions with protein as well as knowing the predicted pharmacotoxicity of ten organophosphate pesticides and ten compounds. chemicals derived from Kelakai.

Research Method

Instrument

The hardware used was an Acer Aspire 3 laptop with Windows 11 specifications, 64 bit, Intel Celeron N5100 processor RAM 4 GB SSD 256 GB 14 inch. The software used in this research is the Windows 11 64-bit operating system, Chimera 1.16

(https://www.cgl.ucsf.edu/chimera/download.html), Protein Data Bank (https://www.rcsb .org/) PubChem (https://pubchem.ncbi.nlm.nih.gov/) Swiss ADME (http://www.swissadme.ch/), SwissDock (http://www.swissdock.ch/), pkCSM web server (http://biosig.unimelb.edu.au/pkcsm/prediction), and Protox online tool (https://tox-new.charite.de/protox_II/).

The research materials consist of compounds, 3D structure data of the target protein Anaplastic lymphoma kinase (ALK) along with its original ligand 8LY, 2D structures of ten pesticide 2D structures (Table 1), namely diazinon, parathion, ethion, profenofos, malathion, chloropyrifos, fenitrothion, carbophenothion, dichlorvos, and dicapthon; ten 2D structures of Kelakai test compounds (Table 2) namely hexadecanoic acid ethyl ester, neophytadiene, phenethyl alcohol, hexadecanoic acid, pentadecanoic acid, linalool, linoleic acid, 3-methyl acetate, 3-methyl-2,5-furandion, and 5 -hydroxymethyl-2- furancarboxaldehyde.[15]

Table 1. Active ingredient compounds of organophosphate pesticides

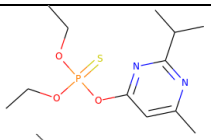
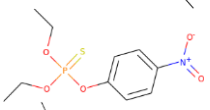
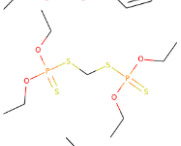
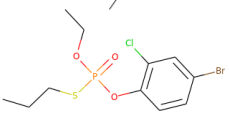
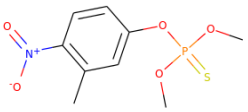
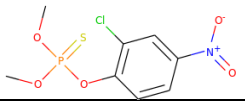
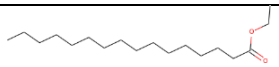
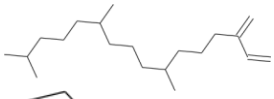
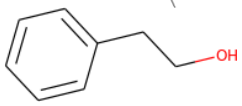
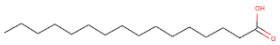
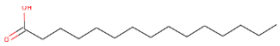
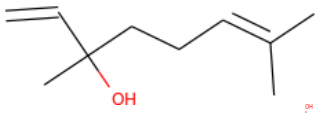
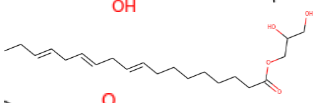
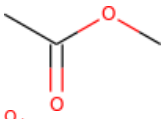
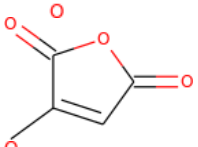
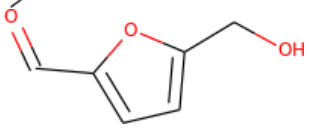
No	Ligand	Pubchem CID	Smile's Formula	Structure
1	Diazonin	3017	CCOP(=S)(OCC)OC1=NC(=NC(=C1)C)C(C)C	
2	Parathion	991	CCOP(=S)(OCC)OC1=CC=C(C=C1)[N+](=O)[O-]	
3	Ethion	3286	CCOP(=S)(OCC)SCSP(=S)(OCC)OCC	
4	Profenofos	38779	CCCSP(=O)(OCC)OC1=C(C=C(C=C1)Br)Cl	
5	Malation	4004	CCOC(=O)CC(C(=O)OCC)SP(=S)(OC)OC	
6	Kloropirifos	2730	CCOP(=S)(OCC)OC1=NC(=C(C=C1Cl)Cl)Cl	
7	Fenitrothion	31200	CC1=C(C=CC(=C1)OP(=S)(OC)OC)[N+](=O)[O-]	
8	Carbo-phenothion	13081	CCOP(=S)(OCC)SCSC1=CC=C(C=C1)Cl	
9	Dichlorvos	3039	COP(=O)(OC)OC=C(Cl)Cl	
10	Dicap-thon	17168	COP(=S)(OC)OC1=C(C=C(C=C1)[N+](=O)[O-])Cl	

Table 2. Ligand compounds from Kelakai extract

No	Ligand	Pubchem CID	Smile's Formula	Structure
11	Asam heksadekanoat etil ester	12366	CCCCCCCCCCCCCCCC(=O)OCC	
12	Neofitadiena	10446	CC(C)CCCC(C)CCCC(C)CCCC(=C)C=C	
13	Fenetil alkohol	6054	C1=CC=C(C=C1)CCO	
14	Asam heksadekanoat	985	CCCCCCCCCCCCCCCC(=O)O	
15	Asam pentadekanoat	13849	CCCCCCCCCCCCCCC(=O)O	
16	Linalool	6549	CC(=CCCC(C)(C=C)O)C	
17	Asam linoleat	5280450	CCC=CCC=CCC=CCCCCCCCC(=O)OCC(CO)O	
18	3-Metil asetat	6584	CC(=O)OC	
19	3-metil-2,5-furan dion	12012	CC1=CC(=O)OC1=O	
20	5-hidriksimetil-2furan Karbok saldehid	237332	C1=C(OC(=C1)C=O)CO	

Ligand and protein preparation

The ALK protein (PDB ID: 5USQ) was downloaded via the protein data bank site in the form of *.pdb. Then, it was prepared using the UCSF Chimera 1.16 program by removing residues. Isolate the natural ligand from the target protein by removing all ALK protein groups other than the 8LY group, then prepare and store it in mol2 form. Preparation of ten pesticide and laxative test compounds using the UCSF Chimera 1.16 program was carried out by entering the PubChem CID of each ligand which had previously been viewed via the PubChem web server, then saving it in mol2 form.

Molecular Docking between proteins and test compounds and natural ligands

Docking is carried out using Swissdock. The docking results are expressed by the Gibbs free energy value (ΔG).

Visualization of Docking Results

Visualization was carried out using the USCF Chimera 1.16 program by entering target protein data in *.pdb format and docking results in *.pdb format. The visualization will show the type of bond interaction formed and the amino acid at the binding site. The visualization results are saved in *.png format.

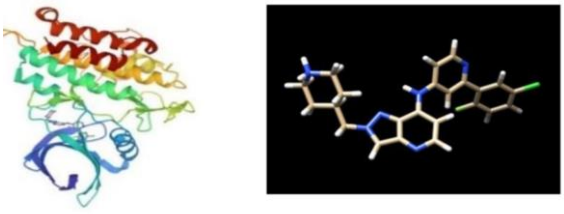
Analysis of Pharmacotoxicity in Silico

Ames toxicity, hepatotoxicity, and skin sensitization were analyzed using the pkCSM web server. LD_{50} and toxicity class were predicted from the Protox online tool site.

Results

Molecular Docking

Preparation of target proteins and ligands for molecular docking using UCSF Chimera 1.16. The target protein is Anaplastic Lymphoma Kinase (ALK) which is located on the short arm of chromosome 2 (2p23) and exchanges chromosome segments with other genes. 16 The 3D structure of ALK can be seen in Figure 1a. The 3D structure of the 8LY A 500 ligand can be seen as in Figure 1b.



(a) (b)

Figure 1. The 3D structure: (a) ALK protein; and (b) Ligand 8LY A 500

Table 3. Results of molecular docking of Anaplastic Lymphoma Kinase (ALK) ligands and proteins

Ligands Number	ΔG (kkal/ mol)	Residu Asam Amino	
		Ikatan Hidrogen	Interaksi Hidrofobik
1	-8.16	-	LEU260, GLY286, LEU340, ALA230, VAL219, SER280, ALA350, TYR249, PHE262, ASP351, LYS232, ILE211, ALA 230, GLU245.
2	-7.68	-	TYR249, LEU260, ASP351, LEU340, GLY286, ASP281, TYR282, ALA230, SER280, VAL 219, LYS232, LEU278
3	-8.62	-	TYR282, GLY286, SER287, LEU340, ILE211, ALA230, VAL279, LYS232, LEU278, GLU245, ASP351, LEU260, SER280, VAL231, TYR282
4	-8.05	-	SER280, LEU340, LEU260, TYR282, ALA230, ALA350, VAL219, LYS232, ILE 211, ASP281, ASP351, GLY286, LYS337.
5	-7.95	-	SER280, LEU340, LEU260, TYR282, TYR249, PHE262, ALA230, VAL219, LYS232, VAL231, LEU278, GLU245, PHE262.
6	-7,63	-	GLY286, LEU340, TYR282, ALA350, ASP351, ILE211, VAL219, LYS232
7	-7.59	ASP351 (2.261 Å)	SER280, LEU340, TYR282, ALA230, ALA350, VAL219, LYS232, ILE 211, ASP281, ASP351, GLY286, LY232, TYR249.
8	-8.24		SER280, LEU278, TYR282, ALA230, VAL219, LYS232, ILE 211, PHE262, GLY286, TYR249, LEU260, LEU340.
9	-7.40	ALA380 (2.129 Å)	ALA403, ALA399, ASP400, LEU334, TYR378, THR375, ASP333, GLY374, VAL373, ARG332, VAL383, MET379
10	-8.16	ASP351 (2.426 Å)	ALA350, LEU340, GLY286, LEU260, ASP281, TYR282, ILE211, VAL219, ALA230, LYS232, TYR249.
11	-7.08	LYS337 (1.878 Å)	ILE211, ALA230, ASP351, LEU340, ASN338.

Ligands Number	ΔG (kkal/ mol)	Residu Asam Amino	
		Ikatan Hidrogen	Interaksi Hidrofobik
12	-8.39	-	ILE211, VAL219, LYS232, LEU278, ALA278, ALA230, TYR282, SER280, PHE262, TYR249, GLU284, LEU260, ASP351, GLY286, ALA350, LEU 340.
13	-6.55	ARG332 (2.011 Å)	MET379, VAL383, THR375, ALA399, GLY374, VAL373, ASP400, LEU334, ALA403, TYR378.
14	-8.09	-	SER280, PHE262, TYR249, LEU360, ASP351, ASP290, GLY286, ALA350, LEU 340, ARG294.
15	-8.00	-	ILE211, VAL219, LYS232, LEU278, ALA330, ALA230, TYR249, GLU245, LEU260, ASP351, SER280, GLY286, TYR282.
16	-6.90	TYR378 (1.853 Å)	THR375, GLY374, ASP333, MET379, VAL383, ASP400, ALA403, ALA380, ALA399, ILE388, ARG372, VAL373.
17	-8.01	-	LEU260, PHE262, GLY286, LEU340, TYR249, SER287, ASP290, PHE289, LYS337.
18	-5.88	-	MET379, VAL383, THR375, ALA399, ARG332, ASP333, LEU334, ALA403, TYR378.
19	-6.54	THR375 (2.210 Å)	MET379, VAL383, THR375, ALA399, ARG332, ASP400, LEU334, ALA403, TYR378, GLY374, ASP333.
20	-6.58	VAL373 (2.196Å) dan ALA403 (2.196 Å)	MET379, VAL383, THR378, ALA399, ARG332, ASP400, LEU334, TYR378, GLY374.
8LY A 500	-9.19	-	*ILE211, VAL219, VAL231, VAL279, LYS232, LEU278, ALA230,* TYR282, SER280, LEU340, ASP281, PHE262, GLY286, ASP351, TYR249, GLU284, GLY286, ARG294.

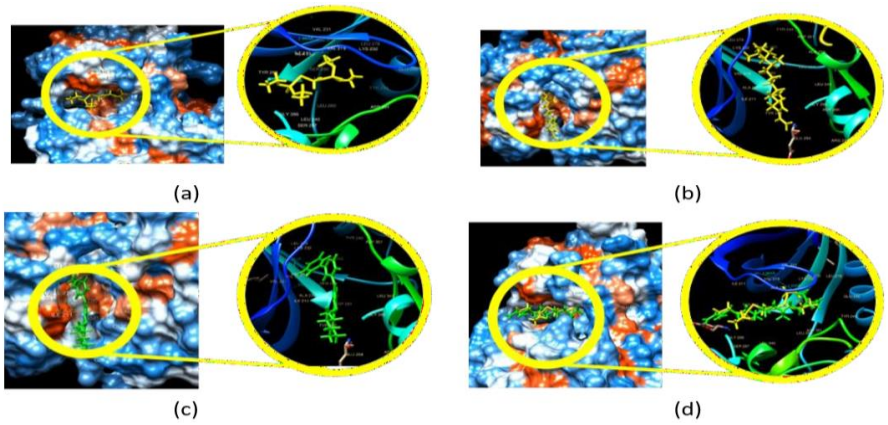


Figure 2. Molecular docking results with Anaplastic Lymphoma Kinase (ALK) protein (a) Ethion; (b) Neophytadiene (c) 8LY A 500; (d) Neophytadiene and ethion

Pharmacotoxicity Test in Silico

Virtual pharmacotoxicity test using the pkCSM and Protox web servers with Ames Toxicity, Hepatotoxicity, Skin Sensitisation, LD50Acute (mg/kg) and Class parameters. The analysis results are as in Table 4.

Table 4. Results of pharmacokinetic and toxicity prediction analysis of ligands

No.	Substance	*Ames Toxicity**	*Hepatotoxicity**	*Skin Sensitisation**	LD50Acute** (mg/kg)	*Class***
1	Diazonin	No	Yes	No	17	2
2	Parathion	No	No	No	19	1
3	Ethion	No	No	No	13	2
4	Profenofos	No	No	No	162	3
5	Malation	No	No	No	190	3
6	Kloropirifos	No	No	No	60	3
7	Fenitrothion	Yes	No	No	229	3
8	Carbopheno-thion	No	No	No	7	2
9	Dichlorvos	Yes	No	Yes	17	2
10	Dicapthon	Yes	No	No	284	3
11	Asam heksadekanoatetil ester	No	No	Yes	5000	5
12	Neofitadiena	No	No	Yes	5050	6
13	Fenetil alkohol	No	No	Yes	800	4
14	Asam heksadekanoat	No	No	Yes	900	4
15	Asam pentadekanoat	No	No	Yes	900	4
16	Linalool	No	No	Yes	2200	5
17	Asam linoleat	No	No	Yes	10000	6
18	3-Metil asetat	No	No	No	5000	5
19	3-metil-2,5-furandion	No	No	Yes	2600	5
20	5-hidriksimetil-2-furankarbok-saldehid	No	No	No	2500	5
8LY A 500	Ligan alami	No	Yes	No	200	3

Discussion

Molecular Docking

Docking between the ALK receptor protein (PDB ID: 5USQ) with 10 (ten) pesticide and Kelakai ligand compounds as well as the natural ligand 8LY was carried out using the Swissdock web server (http://www.swissdock.ch/). The parameters obtained from the docking results are the Gibbs free energy value (ΔG), the type of bond interaction formed and the amino acid at the binding site. Gibbs free energy (ΔG) shows how strong the bond between the protein and the ligand is, where a more negative (lower) ΔG value indicates that the compound requires less energy when binding, so it can be interpreted that the compound has a greater potential to interact and forms strong bonds with target proteins.[14]

Table 3 shows the results of molecular docking of 10 pesticide ligands, 10 chemical compounds and natural ligands for the ALK protein. It was found that ethion and neophytadiene had the most negative ΔG values, namely -8.62 kcal/mol and -8.39 kcal/mol respectively. The more negative the value of ΔG, the stronger the target protein-ligand complex bond will be due to the stability and strength of noncovalent interactions.[17] Ethion is allegedly to have the potential to damage the ALK protein receptor more than other pesticides. Even though the ΔG value of neophytadiene is still greater than the natural ligand (8LY A 500) of the target

protein, this ΔG value shows a value that is not too different which still allows neophydiene to be a substitute for the natural ligand and as a competitive inhibitor.

Figure 2 shows a visualization of the molecular docking results. The ethion ligand binds to 15 residues of the ALK protein, namely: TYR282, GLY286, SER287, LEU340, ILE211, ALA230, VAL279, LYS232, LEU278, GLU245, ASP351, LEU260, SER280, VAL231, TYR282. Neophytadeien binds to 16 ALK residues, namely ILE211, VAL219, LYS232, LEU278, ALA278, ALA230, TYR282, SER280, PHE262, TYR249, GLU284, LEU260, ASP351, GLY286, ALA350, LEU 340. The binding location for ethion and neophytadiene compounds with the ALK protein is right at the active site which has similar interactions with the amino acid residues of the natural ligand 8LY A 500 with the ALK protein. The binding site (active site) is an area on the protein that will be the place where the ligand and protein bind. The similarity in the type and number of residues in the binding complex between ethion and neophytadiene ligands and the ALK protein indicates the potential for competition between ethion and neophytadiene when binding to the ALK protein.

Pharmacotoxicity Test in Silico

Toxicity Prediction aims to predict the level of toxicity of compounds to the human body. Toxicity analysis parameters use Ames toxicity, hepatotoxicity, skin sensitization and LD_{50}. The Ames toxicity test is analyzed to see the mutagenic potential of compounds with bacteria. If a compound is positive for Ames toxicity then it is mutagenic and can act as a carcinogen. LD_{50} is the amount of a given compound that can cause 50% mortality.[18]

Table 4 shows the toxicity test using pkCSM Online Tools where ethion and neophytadiene were proven to have no toxicity in Ames toxicity and hepatotoxicity. Neophytadiene in the skin sensitization analysis showed positive, so it is considered to cause skin sensitization. The natural ligand (8LY A 500) has no toxicity in the Ames toxicity and skin sensitization analysis but has hepatotoxicity so it can be predicted that the natural ligand is toxic to the target protein (ALK). Lethal dose 50 (LD50) toxicity analysis shows that the Ethion compound has an LD50 value of 13 mg/kg, so it is classified in class 2 (fatal if swallowed): 5 < LD50 ≤ 50 mg/kg) which means the compound has a high toxicity effect. Therefore, Ethion has activator activity against the ALK protein. The natural ligand (8LY A 500) has an LD50 value of 200 mg/kg, so it is classified in class 2 (toxic if swallowed): 50 < LD50 ≤ 300 mg/kg) which means the compound has a fairly high toxicity effect. Meanwhile, the neophytadiene compound has an LD50 value of 5050 mg/kg, so the compound is classified in class 6 class VI (non-toxic): LD50 > 5000 mg/kg, which means it has a very low toxicity effect. The LD50 value is indicated by the greater the toxic value, the less toxic a compound is, and vice versa.[19]

Conclusion

Ethion is the most toxic and potentially cytogenic organophosphate pesticide with ΔG= -8.6 2 kcal/mol. Neophytadiene from kelakai has the potential as a competitor in the inhibition of the Anaplastic Lymphoma Kinase (ALK) protein with ΔG = -8.39 kcal/mol. The similarity in the type and number of binding residues in ethion and neophytadiene in the ALK protein indicates competition between ethion and neophytadiene.

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