Analysis of Potential Poly (ADP-Ribose) Polymerase 2 (PARP2) Inhibitor in Nyale Worm (Eunice sp.) Extract for Ovarian Cancer: An In Silico Approach

by Tri Wahyu

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Abstract

Cancer is an umbrella term for a large group of diseases that are characterized by abnormal cell growth and adjacent tissue or organ invasion. One of the most common cancers in Indonesia is ovarian cancer. Recently, PARP enzyme inhibitor use as a therapy for cancer, including ovarian cancer, has become more common. Apart from the standard PARP inhibitor drug, natural resources are also found to have high potential for cancer therapy. Marine biotas are known for their capability to produce biomolecules which can inhibit the cell mitosis of their rivals or predators. One of the marine biotas that are commonly consumed in Lombok Island is Nyale worm. This research aimed to analyze the potential PARP, particularly PARP2, inhibitor compounds in Nyale worm extract for ovarian cancer by using molecular docking with *in silico* approach. Compounds identification was conducted by using gas chromatography-mass spectrometry (GC-MS) and molecular docking was done with PyRx v.0.8 software. There were three potential PARP2 inhibitor compounds, tricyclo[10.2.1.02,11]pentadeca-4,8-diene, tricyclo[8.6.0.02,9]hexadeca-3,15-diene, and linoleic acid. The binding affinity energy of these three compounds were lower compared with that of the native ligand 3-aminobenzamide. The lower value of the energy means greater molecular binding stability and PARP2 inhibition mechanism.

Key words: DNA repair, Nyale worm, ovarian cancer, PARP, PARP2 inhibitor

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Introduction

Cancer is an umbrella term for a large group of diseases that are characterized by abnormal cell growth and adjacent tissue or organ invasion[1]. One of the most common cancers in Indonesia is ovarian cancer. As of 2018, there were 14,896 new cases of ovarian cancer making it the tenth disease with the most new cases in Indonesia according to Globocan data[2]. With a total of 9,581 deaths, ovarian cancer is also the seventh cancer with the highest number of deaths[3].

Anticancer therapy targeting Poly(ADP-ribose) polymerase (PARP) enzyme was originally proposed by Mendel. PARP enzyme detects the DNA single-strand break (SSB) and causes DNA repair in cancer cells through base exicional repair (BER) mechanism[4]. PARP uses NAD^+ that is transferred to the glutamate, aspartate, and lysine residues acceptor to catalyze ADP-ribose for auto-modification. This facilitates DNA repair through the formation of chromatin structures by replacing the histone and signaling the DNA repair complex protein. There are 17 enzymes of the PARP superfamily in humans, including PARP1 and PARP2 [5, 6]. Recently, PARP enzyme inhibitor use as a therapy for cancer, including ovarian cancer, has become more common[6-8]. An orally-administered PARP inhibitor standard drug, 3-aminobenzamide, is effective in enhancing the damage of the cancer cell DNA[6, 9].

Apart from the standard drug, natural resources are also found to have high potential for cancer therapy. Marine biotas are known for their capability to produce biomolecules which can inhibit the cell mitosis of their rivals or predators[10, 11]. A marine worm, *Hermione hystrix*, is reported to have antimitotic-cytotoxic activity towards sea urchin *Paracentrotus lividus* embrio[12]. Several other marine biotas such as sponges, mollusks, and cyanobacteria are also reported to have anticancer compounds[13].

Lombok Island is rich in marine biota. One of the renowned marine biotas found in Kuta Mandalika beach, a famous tourism destination in Central Lombok, is Nyale worm. It is

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commonly consumed by the local community. Nyale worm (*Eunice sp.*) from *Eunicidae* family is a member of Polychaeta class that includes three other species, *Lysidice sp.*, *Neanthes*, and *Aphrodite* (14).

The anticancer properties of Nyale worm have not been widely researched. Therefore, this research aimed to analyze the potential PARP2 inhibitor compounds in Nyale worm extract for ovarian cancer by using molecular docking with *in silico* approach. The compounds were compared with a standard drug for inhibition target mechanism against PARP2 enzyme.

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2. Materials and Methods

2.1 sample collection and Extraction

Nyale worms were collected from the coastal waters of Kuta, Central Lombok. Dried samples were ground in a mortar and macerated in 250 mL ethanol 96% for 24 hours and n-hexane (99%) for 8 h. the residue was extracted three times with ethanol until it was colorless for ethanol extraction and removal of solvent (n-hexane) using evaporator at 68°C. A rotary vacuum evaporator used to combine and concentrate the filtrate.

2.21 Chemistry

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Quantitative analysis with gas chromatography-mass spectrometry (GC-MS) Shimadzu 2010 was conducted to identify the bioactive compounds present in Nyale worm extractQuantitative analysis with gas chromatography-mass spectrometry (GC-MS) was [illegible]

2.32 Protein/Macromolecule

PARP2 (GDP: 3KCZ) structure was obtained from rscb.org in the Protein Data Bank (PDB) format. PARP2 structure consisted of two chains, chain A and chain B. Each chain contained inhibitor ligand 3-aminobenzamide. PARP2 PDB structure was prepared using PyMOL application2.5.2software (state the version).

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2.43 Ligand and drug screening

Twenty compounds were identified by GC-MS- in the Nyale worm extract were identified by GC-MS and The compounds identity were confirm through chemical n searched using PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The bioavailability of the compounds was assessed according to Lipinski's Rule of Five using SwissADME (http://www.swissadme.ch/). Assessment of human intestinal absorption (HIA) was conducted with the use of PreADMET predictor (https://preadmet.webservice.bmdrc.org/). Ligands were prepared using Avogadro 1.2software [15].

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2.54 Molecular docking

Molecular docking of the twenty compounds in Nyale worm extract to the PARP2 protein was done with PyRx v.0.8 software [16]. The molecule binding target area was X: 19.5762, Y: 2.9482, Z: 20.3313 and Dimension (A) X: 11.3241, Y: 8.1201, Z: 10.2827. This was the binding site of 3-aminobenzamide, a widely-used PARP2 inhibitor standard drug. The active binding site on PARP2 was observed in Computed Atlas of Surface Topography of Proteins (CASTp) (sts.bioe.uic.edu/castp/index.html?3kcz) [17]. The result of the protein interaction and ligand binding residue identification was visualized with PyMOL 2.5.2 and Discovery Studio R17.

3. Result and Discussion

3.1 Result

3.1PARP2 inhibitor mechanism for cancer cell

PARP2 working mechanism in Figure 3 shows that DNA repair is a potential target to kill ovarian cancer cell [18]. The SSB is often found in proliferating cells. The PARP2 inhibitor affects BER, preventing the DNA repair to occur. The SSB then turns into double-strand break (DSB) leading to inhibition of cell proliferationwhich harms the cell. It may also affects the cell recombinant if the homologous recombination deficiency (HRD) is present. This condition renders the DSB irreparable, inducing cell apoptosis [19].

Based on the PARP2 molecule structure shown in Figure 2, PARP2 was found to have NAD^+ cofactor (denoted by arrow). NAD^+ has a pivotal role in DNA repair process. NAD^+ breaks down into nicotinamide and ADP-ribose to form poly(ADP-ribose) (PAR) which binds to the DNA repair protein acceptor [20]. Previous studies reported that inhibiting NAD^+ significantly hampered the DNA repair by PARP2, leading to cell apoptosis [21, 22].

The binding affinity of 3-Aminobenzamide to the native ligand was -6.6 kcal/mol. This value indicated the energy needed to bind to the PARP2 receptor. The lower the value, the higher the possibility [illegible]

3.2 Human intestinal absorption (HIA)

Percentage of HIA (% HIA) tells the absorbability of the compounds in the small intestine. Table 1 indicates that the compounds in Nyale worm extract had high absorption level (HIA > 90%). This means that the compounds are more absorbablehave good oral absorption profile and can reach the ovarian cancer cell receptor if the extract is administered orally. Thus, oral administration can increase the efficacy of the compounds [24].

3.3 Lipinski's Rule of Five

Assessment according to Lipinski's Rule of Five parameter before docking can iensure [illegible]

3.4 Molecular docking

There were three potential PARP2 inhibitor compounds, tricyclo[10.2.1.0^{2,11}]pentadeca-4,8-diene, tricyclo[8.6.0.0^{2,9}]hexadeca-3,15-diene, and linoleic acid (Table 1). Molecular docking can predict the amount of energy generated

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among two or more interacting or binding molecules [27]. The binding affinity energy of the three compounds were lower compared with that of the native ligand 3-aminobenzamide. Figure 2 shows the visualization of PARP2 where the four compounds bound to the same active site. The lower value of the energy resulting ed from docking (kcal/mol) means greater molecular binding stability and PARP2 inhibition mechanism [28].

Interaction between PARP2 and 3-aminobenzamide shown in Table 2 explains its the affinity for PARP2 inhibitor. The side chain residue of TYR473 formed pi-alkyl bond with the imidazole ring. The bond between GLU558 and nitrogen atom at the end of the imidazole chain formed two hydrogen bonds. The backbone of TRP427 and HIS428 bound to the nitrogen atom, also forming the hydrogen bonds. The backbone residue of GLY429 and SER470 formed hydrophobic bonds. TYR462 caused an interaction with the cyclic amine substituent (proline) in the benzamidine ring to the backbone of GLY429. The residue of LYS469, TYR462, ALA464, PHE463 formed hydrophobic bonds as well.

The low binding affinity of tricyclo[8.6.0.0^{2,9}]hexadeca-3,15-diene results from interaction could be caused by the binding of TYR473 residue to with the cyclooctane ring of the inhibitor ligand. This residue functioned as a bridge for the bond between TYR462 and inhibitor. LYS469 and ALA464 also bound to the cyclooctane ring, forming pi-alkyl bond. TYR462 residue had a key role in the binding to the side chain of cyclooctane ring and in determining the binding of the inhibitor compound. The side chain residue of SER470, GLY429, PHE463, HIS428, GLN332, and TYR455 helped with the binding to the PARP2 receptor and yielded the hydrophobic bonds.

From Similarly, the interaction between the inhibitor compound tricyclo[10.2.1.0^{2,11}]pentadeca-4,8-diene and the PARP2 receptor, it was locatedindicates that TYR473 bound to the cyclodecane ring, forming two pi-alkyl bonds. Likewise, residue

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TYR462 formed pi-alkyl bonds ~~(with what?)~~withtricyclo[10.2.1.$0^{2,11}$]pentadeca-4,8-diene causing low and stable binding affinity energy.

Residues TYR473 and TYR462 ~~had important contribution~~were actively involved in the interaction with the three inhibitors from the Nyale worm extract. The result of the interactions ~~can be made as a reference regarding the similarity~~ of the inhibitor compounds from the Nyale worm extract compares favourably with the commercially used native ligand with respect to the ~~of~~similarity of the binding domains. ~~among the inhibitor compounds contained in the extract and the commercially used native ligand. Eventually, The result of this research was able to analyze the potential inhibitor compounds based on their bonds with PARP2.~~

4. Conclusion

This research confirms the anticancer properties in Nyale worm by analyzing the potential PARP2 inhibitor compounds in the worm extract through the use of molecular docking with *in silico* approach. Future studies in developing anticancer drug from Nyale worm extract are encouraged.

~~Nyale worm is a commonly consumed marine biota in Lombok Island. This research analyzed the potentials of PARP2 inhibitor compounds in Nyale worm extract for ovarian cancer by using molecular docking with in silico approach. There were three potential PARP2 inhibitor compounds, tricyclo[10.2.1.$0^{2,11}$]pentadeca-4,8-diene, tricyclo[8.6.0.$0^{2,9}$]hexadeca-3,15-diene, and linoleic acid. The binding affinity energy of these three compounds were lower compared with that of the native ligand 3-aminobenzamide. The lower value of the energy means greater molecular binding stability and PARP2 inhibition mechanism.~~

There is no conflict of interest.

6. Acknowledgement

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Table and figure

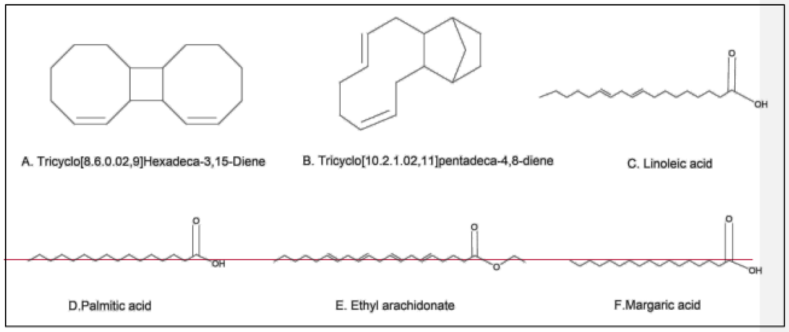

Figure 1 Some the Ccompounds contained identified in Nyale worm (*Eunice sp.*)

Table 1. Identification of the potential PARP2 inhibitor compounds contained in Nyale worm extract based on their bioavailability and HIA.

No	Compound Name	Molecular Formula	Da	H-donor	H-acceptor	LogP	HIA (%)	Binding Affinity (kcal/mol)
1	Tricyclo[8.6.0.$0^{2,9}$]hexadeca-3,15-diene	$C_{16}H_{24}$	202.34	0	0	4.02	100	-8.8
2	3-Aminobenzamide (native ligand)	$C_7H_8N_2O$	136.15	2	1	0.32	90.98	-6,6
3	Margaric acid	$C_{17}H_{34}O_2$	270,45	1	2	5,57	98,40	-6,2
4	9-Octadecenal	$C_{18}H_{34}O$	266,46	0	1	5,94	100	-6,1
5	Myristic acid	$C_{14}H_{28}O_2$	228,37	2	1	4,45	978.483	-5,9
6	Pentadecylic acid	$C_{15}H_{30}O_2$	242,40	1	2	4,84	98,11	-5,9
7	Stearic acid	$C_{18}H_{36}O_2$	284,48	1	2	5,93	98,44	-6,2
8	Linoleic acid	$C_{18}H_{32}O_2$	280,45	1	2	5,45	98,37	-6,7
9	Palmitic acid	$C_{16}H_{32}O_2$	256,42	1	2	5,20	98,29	-6.1
10	Methyl myristate	$C_{15}H_{30}O_2$	242,40	2	0	4,81	100	-5,8

11	Ethyl arachidonate	$C_{22}H_{36}O_2$	332,52	0	2	6,42	100	-5,9
12	Octadec-9-enoic acid	$C_{18}H_{34}O_2$	282.46	1	2	5,71	98.43	-6.6
13	Benzene, 1,2-dimethyl-	$C_6H_4(CH_3)_2$	106.17	0	0	2.83	100	-5.6
14	Hexadecanoic acid	$C_{18}H_{36}O_2$	284,48	0	2	5,79	100	-6.0
15	Tricyclo[10.2.1.0^{2,11}]pentadeca-4,8-diene	$C_{15}H_{22}$	202.34	0	0	4.02	100	-8.4
16	Methyl palmitate	$C_{17}H_{34}O_2$	270.45	0	2	5.54	100	-5.9
17	Ethyl myristate	$C_{16}H_{32}O_2$	256,42	0	2	5,17	100	-6.0
18	Ethyl palmitate	$C_{18}H_{36}O_2$	284.48	2	0	5.90	100	-5.9
19	Methyl stearate	$C_{19}H_{38}O_2$	298.50	0	2	6.24	100	-6,3
20	Ethyl stearate	$C_{20}H_{40}O_2$	312,53	0	2	6,71	100	-5,9
21	Dythol	$C_{27}H_{46}O$	386,65	1	1	6,67	100	-3.1

Table 2 Interaction between compounds contained in Nyale worm extract and PARP2 ~~Compounds interaction~~

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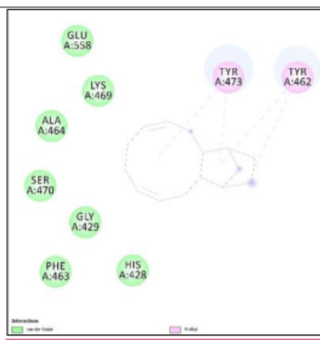
No.	Compound Name	Molecular Visualization	Interaction
1.	Tricyclo[10.2.1.0^{2,11}] pentadeca-4,8-diene		TYR473, TYR462, GLU558, LYS 469, ALA 464, SER 470, GLY 429-, PHE 463, HIS 428

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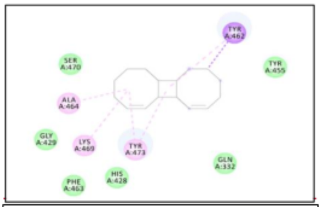
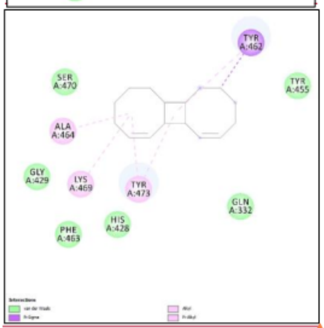
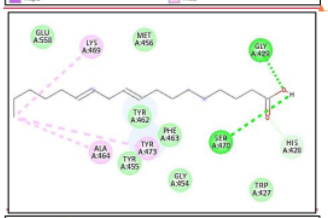
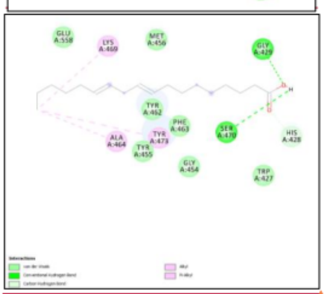
2	Tricyclo[8.6.0.0^{2,9}]hexadeca-3,15-diene	 	TYR462, TYR473, LYS469, ALA464, TYR455, GLN332, HIS428, PHE463, GLY429, SER470
3	Linoleic acid	 	ALA464, TYR473, GLY429, HIS470, MET429, SER470, TRP427, GLY454, PHE463, TYR462, TYR455,

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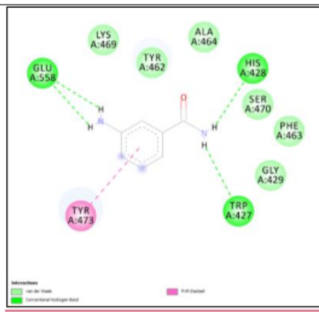
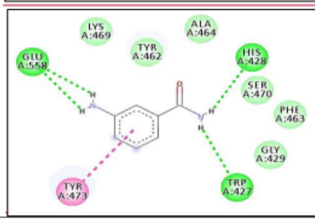
4	3-Aminobenzamide		TYR473, GLU558, HIS428, TRP427, LYS469, TYR462, ALA464, SER470,

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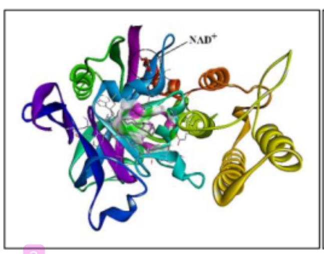
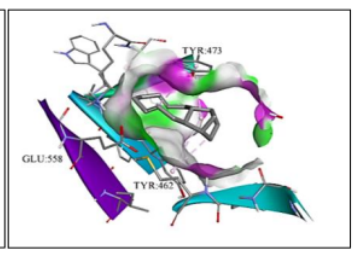
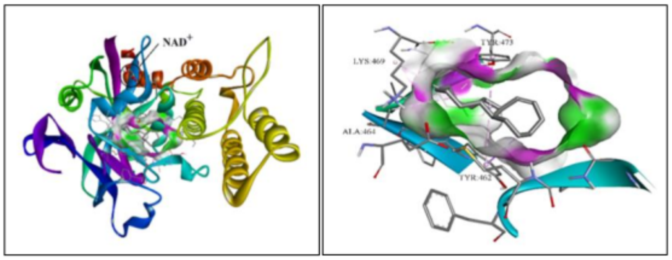
Protein Visualisation	Active Site Visualisation

A.Tricyclo[10.2.1.0^{2,11}]pentadeca-4,8-diene

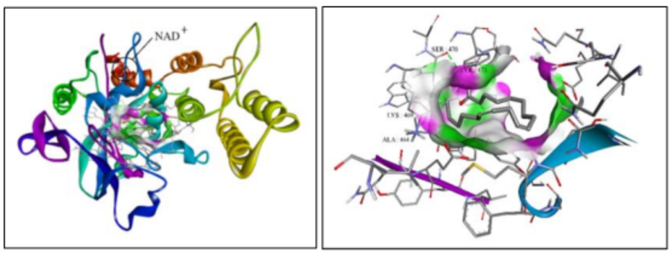




B. Tricyclo[8.6.0.0^{2,9}]hexadeca-3,15-diene



C. Linoleic acid



D. 3-Aminobenzamide

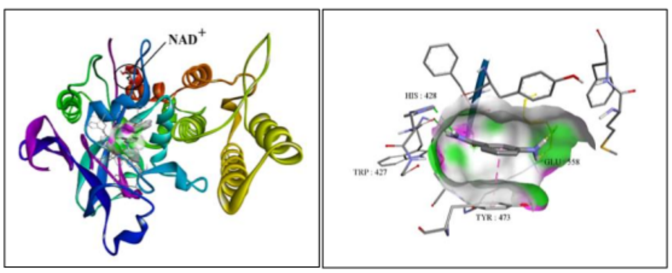


Figure2. Visualization of the inhibitor compounds against PARP2

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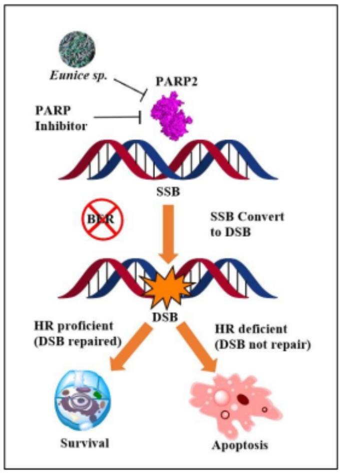

Figure 3. PARP2 inhibitor working mechanism

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