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Molecular Docking Analysis of Zerumbone Derivatives as XIAP-BIR3 Inhibitor for Anticancer Agent

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ABSTRACT

Cancer is the second most common cause of death worldwide. Common therapies used to treat cancer include radiation, chemotherapy, and surgery. However, resistance to treatment often gives a challenging problem, and new alternative therapies derived from natural compounds are needed. Zerumbone is terpenoid compound with various biological activities, including anti-tumor and anti-cancer. This study aims to investigate the activity of Zerumbone and its derivatives against the XIAP-BIR3 protein. The target protein used PDB ID: 4KMP as inhibitor of XIAP-BIR3. There are 21 zerumbon derivatives retrieved from published article. Docking of zerumbone derivatives was performed using Autodock 1.5.6. Molecular docking result showed derivative 6 of Zerumbone has potential as an anti-cancer agent with a binding energy of -7.84 kcal/mol; meanwhile, the reference inhibitor has a binding energy of -5.21 kcal/mol. These results of the study indicate that the development of inhibitor XIAP-BIR3 may be a potential strategy in cancer treatment and zerumbone derivatives are predicted to be potential candidates that can be analyzed further.

Keywords: In silico, zerumbone, cancer, XIAP-BIR3

Introduction

Cancer is a disease caused by uncontrolled cell growth and spread to other parts of the body (National Cancer Institute, 2021). Colorectal cancer is cancer that attacks the colon to the rectum. In 2020 colorectal cancer ranks third as the most common cancer cases in the world with 1,931,590 cases. In addition, colorectal cancer ranks second as a cancer case that causes many deaths with 935,173 deaths. In Indonesia, colorectal cancer is the second most common cancer in men (after lung cancer) at 11.9% and the fourth most common in women (after breast, uterine cervical and ovarian cancer) by 5.8% (World Health Organization, 2022).

Several previous studies reported that cancer cells are more sensitive to death due to changes in the characteristics of the apoptotic pathway. In cancer cells, there is an increase in the work of both pro-apoptotic and anti-apoptotic proteins simultaneously. Therefore, efforts to increase the inhibition of proapoptotic protein action can be a potential strategy in cancer treatment (Pfeffer & Singh, 2018). Apoptosis is also affected by Inhibitors of Apoptosis Proteins (IAP). IAP is the main inhibitory protein of both apoptotic pathways, namely intrinsic and extrinsic. The BIR3 domain of IAP binds to procaspase-9, blocking its dimerization and activation as well as triggering the activation of caspase-9 (Lalaoui & Vaux, 2018). Because caspase-9 is an important initiator caspase in the intrinsic and effector pathways caspase-3 and caspase-7 also play a key role in the execution of apoptosis, both in the extrinsic and intrinsic pathways, so that XIAP-BIR3 can effectively inhibit the intrinsic and extrinsic apoptotic pathways (Hu et al., 2014).

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Currently, natural compounds are considered as alternative in the treatment of cancer. Zerumbon from *Zingiber zerumbet* (Lempuyangan) is reported to have apoptotic, antiproliferative and antimetastatic activity in various cancer cells (Rahman et al., 2014). Apart from the zerumbon compound, several studies have carried out the synthesis of its derivative compounds to look for more potential anticancer candidates. Previous studies have found that some zerumbon derivatives have potential as anti-cancer against liver cells in vitro (Rahman et al., 2014). This study aims to conduct an initial screening by molecular docking to look for zerumbon derivatives that have anticancer potential in the XIAP-BIR3 apoptotic pathway.

Material and Methods

Tools, software, website

The software and database used are Avogadro, Gaussview 6.0, ChemDraw Ultra 12.0, Autodock Tools 1.5.7, Protein Data Bank (PDB) (https://www.rcsb.org/).

Validation of 3D protein

Macromolecules are downloaded from PDB via the website https://www.rcsb.org/ in pdb file format. The macromolecule that can be selected is if there are no mutations, the resolution is less than 3, and there are natural ligands. XIAP-BIR3 Inhibitor was used with PDB ID: 4KMP. Next, macromolecular validation was carried out using Autodock Tools 1.5.6. Macromolecules were validated using cocrystalled natural ligand data from pdb to obtain the rmsd ≤2.

Preparation of ligan

Derivat zerumbon which has passed the Lipinski`s rule of five were built using Chemsketch ACDLab2021, optimized using Gaussview 5.0 with Density Functional Theory (DFT) calculation and saved in pdb format using Avogadro. The prepared ligand of zerumbone derivatives was used as input for Autodock 1.5.6.

Molecular docking

Docking was carried out on Zerumbon and its derivatives against the 4KMP target protein which has been validated with coordinates x,y,z 13.422, 0.0, 1.823 spaced 0.375 and 100 runs using Autodock Tools 1.5.6 software. Then the bond energy of each ligand with macromolecules is compared with reference inhibitor.

Results and Discussion

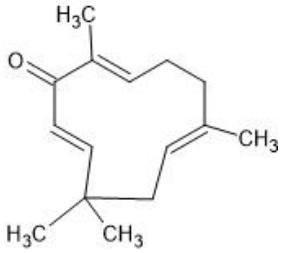
Zerumbon which isolat of *Zingiber zerumbet* has various pharmacological activity including anticancer. The mechanism of zerumbon still drawn the attention of many researchers because it can exhibit various effect on proliferation or apoptosis agains various cancer cell (Kalantari et al., 2017; Leung et al., 2017; Taha et al., 2010). Zerumbon also have proliferation effect on breast cancer specifically (Kim et al., 2016). Apoptosis is a form of cell death that multicellular organisms normally have to eliminate damaged or unwanted cells. Incorrect or abnormal regulation of apoptosis can lead to disease in humans, including inflammation, cancer, and autoimmune diseases (Barth et al., 2020). There are two apoptotic pathways, namely the intrinsic pathway (mitochondrial pathway) and the extrinsic pathway (death receptor pathway). These two pathways are interrelated and influence each other. Among the pro-apoptotic proteins, namely SMAC/DIABLO and HTRA2/OMI proteins activate the caspase signaling pathway in mitochondria by inhibiting IAP activity (Singh et al., 2022).

Apoptosis is also influenced by Inhibitors of Apoptosis Proteins (IAP). IAP is the main inhibitory protein of both apoptotic pathways, namely intrinsic and extrinsic. IAP is defined by the presence of one to three of the 70-80 amino acid Baculoviral IAP Repeat (BIR) domains.

The BIR3 domain of XIAP-BIR3 binds to pro-caspase9 and blocks its dimerization and subsequent activation, as well as triggering the activation of caspase-9 (Lalaoui &Vaux, 2018).

Because caspase-9 is an important initiator caspase in the intrinsic pathway and the effectors caspase-3 and caspase-7 also play a key role in the execution of apoptosis, both in the extrinsic and intrinsic pathways, XIAP-BIR3 can effectively inhibit both the intrinsic and extrinsic pathways of apoptosis. Therefore, the XIAP-BIR3 protein was chosen because it has great potential to be a target in anticancer therapy via the apoptotic pathway, and the BIR3 domain was chosen because this domain can inhibit three types of caspases, namely caspase-9, caspase-3, and caspase-7 (Hu et al., 2019). BIR stands for 'Baculovirus Inhibitor of apoptosis protein Repeat'. It is found repeated in inhibitor of apoptosis proteins (IAPs), and in fact it is also known as IAP repeat.

Derivat of zerumbon were retrieved from many studies (Vu & Vu, 2021; Kitayama et al., 2013; Songsiang et al., 2019), 21 zerumbone derivates was tested using molecular docking. The molecules and pharmacokinetic result are listed in Figure 1 and Table 1.



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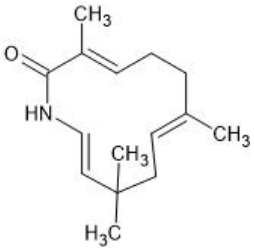

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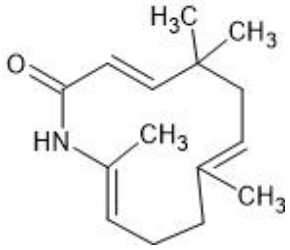

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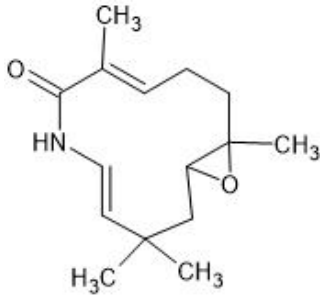

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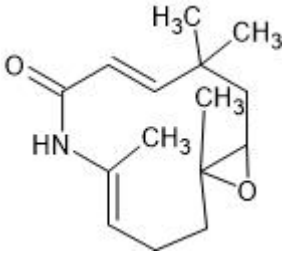

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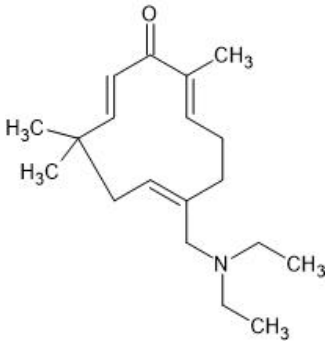

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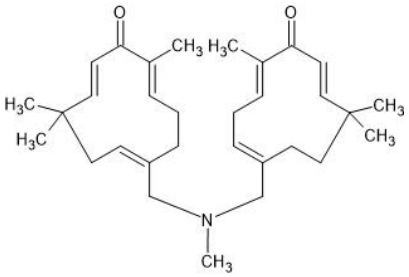

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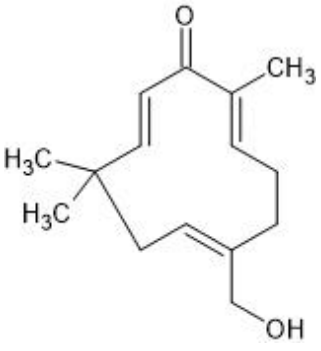

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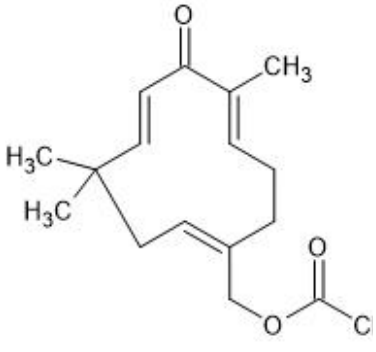

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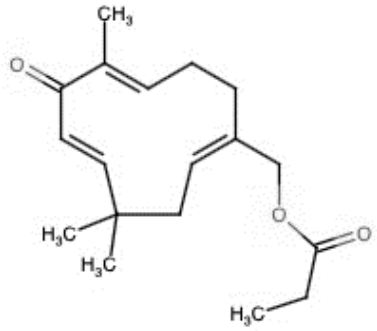

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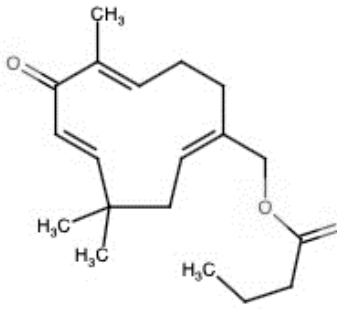

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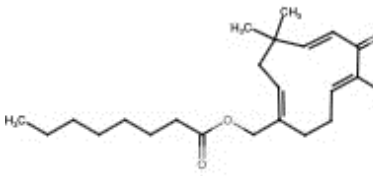

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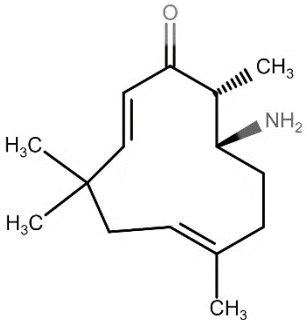

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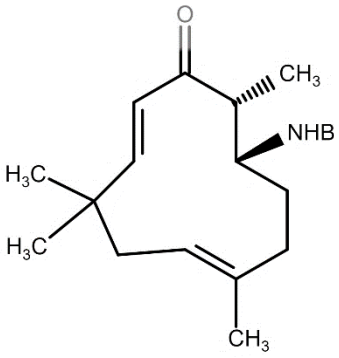

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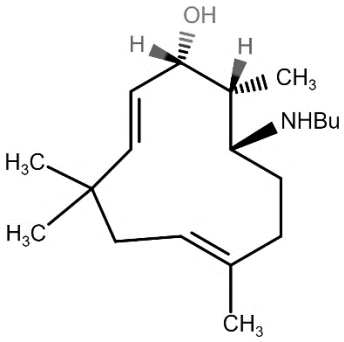

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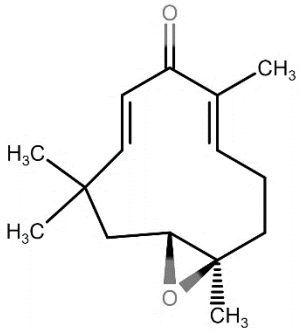

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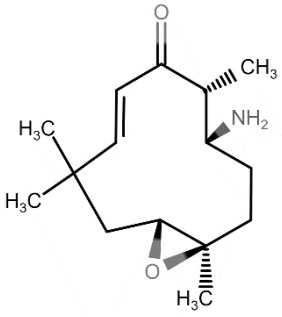

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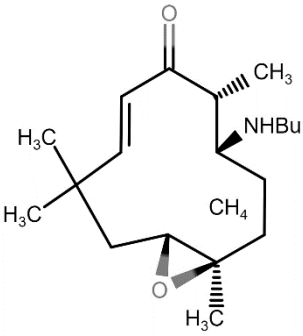

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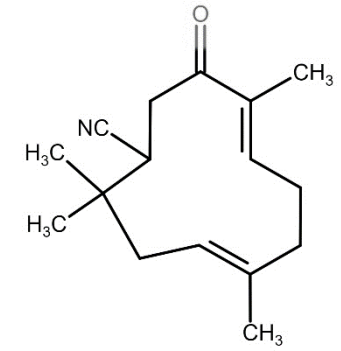

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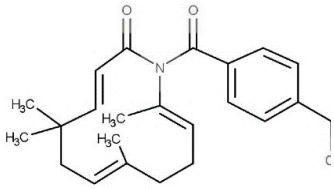

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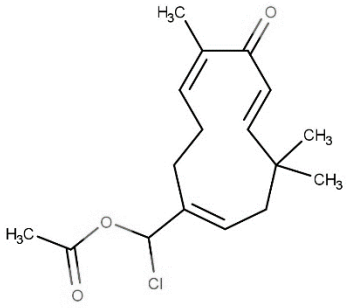

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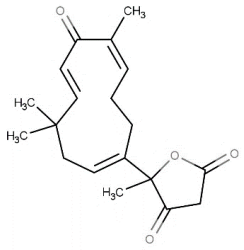

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Figure 1. Derivate of zerumbone

Docking was carried out on Zerumbon and its derivatives on the target protein XIAP-BIR3 (PDB ID: 4KMP) which was obtained using Autodock Tools 1.5.6 software. The binding energy of each ligand with the macromolecule is compared with the reference inhibitor. The RMSD values calculated between the redocked pose and the co-crystallized pose are 2, demonstrating the efficiency and effectiveness of the docking process (Chtita et al., 2021).

After the docking process was completed, the protein-ligand with differet zerumbone derivates was analyzed to investigate the nature of the interaction. The highest scoring binding energy (kcal/mol) from the AutoDock dlg output file was taken as the response for each run. The best docking binding energies of the derivatives were obtained in Table 1.

Table 1. binding energy of each zerumbone derivates with XIAP-BIR3

Molecules	Binding Energy (kcal/mol)
Reference Inhibitor	-5.21
ZER	-6.04
1	-6.05
2	-6.26
3	-6.15
4	-6.11
5	-6.6
6	-7.84
7	-5.98

To be continued…

8	-6
9	-6.18
10	-6.16
11	-5.87
12	-7.5
13	-5.88
14	-5.57
15	-5.98
16	-6.21
17	-5.38
18	-7.27
19	-6.9
20	-6.83
21	-7.56

The parameter seen from molecular docking is free binding energy (ΔG). Free binding energy (ΔG) is the result of the sum of the final intermolecular energy, final total internal energy, and torsional free energy. The sum result is reduced by the unbound system energy to produce free energy (ΔG). An increasingly negative ΔG value indicates a good level of bond stability between the ligand and receptor so that the bond formed between the ligand and receptor is stronger (Bender et al., 2021). Differences in ΔG values can be caused by differences in binding between ligands and amino acids in the target protein (Malmstrom & Watowich, 2021). The results of the docking that has been carried out (Table 1) show that derivative 6 has the best or best binding energy when compared to other derivatives. Derivate 6 showed the lowest energy binding with XIAP-BIR3, indicating the best candidate for breast cancer therapy.

Conclusion

A molecular docking study showed that derivate 6 showed better energy than reference inhibitor as inhibitor XIAP-BIR3 in anticancer therapy through the apoptosis pathway.

Acknowledgments

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