Indonesian Journal of Science & Technology

Journal homepage: http://ejournal.upi.edu/index.php/ijost/

Potential Molecular Interaction of Nutmeg's (*Myristica fragrans*) Active Compound via Activation of Caspase-3

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ABSTRACT

Myristica fragrans Houtt (belongs to the Myristicaceae family) is a Maluku Island (Indonesia) native plant. The seed of *M. fragrans* (Nutmeg) has been used for medicinal benefits. *M. fragrans* also has anti-cancer properties. The goal of this research was to use computer-aided drug design to investigate the in silico molecular docking of selected nutmeg compounds against Caspase-3. Molecular docking using Malegro Virtual Docker (MVD) software Ver 5.5 was performed to investigate binding complicated models to offer information on critical drug-receptor interactions. The most potent ligand was Licarin B, which had a docking score of -103.07 kcal/mol. The Licarin B structure formed several hydrogen bonds with Trp214 and Phe250. These findings imply that the nutmeg seed contains a prospective compound that could be a great anti-cancer agent.

ARTICLE INFO

Article History:
Submitted/Received 10 Dec 2021
First revised 19 Jan 2022
Accepted 25 Mar 2022
First available online 27 Mar 2022
Publication date 01 Apr 2022

Keyword:
Anticancer,
Caspase-3,
Molecular docking,
Myristica fragrans.

1. INTRODUCTION

Myristica fragrans Houtt. (Myristicaceae) is an evergreen tree that produces nutmeg and mace (Kusuma *et al.,* 2020; Ha *et al*., 2020). The aromatic evergreen tree (*M. fragrans*) has long been utilized as a spice in the culinary world (Ha *et al*., 2020). Nutmeg (the seed of *M. fragrans*), a Maluku Island (Indonesia) native plant, has been utilized in traditional medicine for a long time (Susianti *et al*., 2021).

M. fragrans has long piqued the interest of pharmacologists and chemists due to its widespread culinary and folk medicinal applications. Several investigations have found that *M. fragrans* contains a wide range of phytochemicals, including lignans, neolignans, terpenoids, diphenylalkanes, flavonoids, and phenylpropanoids, all of which have pharmacological effects (Fatimah *et al*., 2019; Ha *et al*., 2020; Ebulue, 2022).

M. fragrans exhibits many biological properties, including anticancer (Abourashed & El-Alfy, 2016; Le *et al*., 2017), antioxidants, antibacterial (Matulyte *et al*., 2020), analgesics (Mishra *et al*., 2018), and antidiabetic (Lestari *et al*., 2019). Extracts and a variety of chemicals from the nutmeg seed have been found to have anti-cancer and antioxidant properties in several studies (Zhang *et al*., 2015; Abbas & Baig, 2020).

Cancer is one of the most common health related search topics in the world (Yousaf *et al*., 2021). Skin cancer prevention property is caused by a flavonoid present in nutmeg that has anti-cancer properties (Chen *et al*., 2012). Skin cancer (melanoma) has been on the rise in recent years as a result of UV exposure (Ika & Hery, 2021).

Skin cancer induced by excessive UV radiation from the sun is almost as severe as skin cancer caused by others (Chavda & Bhatt, 2019). Environmental factors cause melanoma cancer to grow more quickly than non-melanoma cancer (Ika & Hery, 2021). Melanoma is a skin cancer that develops from the aberrant multiplication of melanocyte cells, which generate melanin. This cancer has a high level of aggressiveness and is potentially fatal (Linares *et al*., 2015; Davis *et al*., 2019). Melanoma skin cancer has a high proclivity for spreading to other regions of the body, making treatment challenging (Ika & Hery, 2021). The development of novel bioactive chemicals is highly important (Ebulue, 2023). Specifically, chemicals with highly specific anti-cancer action are critical important in the treatment of cancer (Ika & Hery, 2021). Myristicin's anti-cancer properties were anticipated using computer-assisted molecular docking.

Molecular docking is a problem-solving or simulation approach used to aid in the early phases of drug development (Altaf *et al*., 2022; Maripul, 2017). In structural molecular biology and computer-assisted drug creation, molecular docking is an important technique (Morris *et al*., 2008). Molecular docking is a technique for determining the activity and affinity of small compounds by anticipating their binding orientation to their protein targets (Ika & Hery, 2021).

Several anti-cancer molecular docking studies using phytochemical ingredients have previously been published (Kirishnamaline *et al*., 2021; Ibrahin & El-Banna, 2021; Galal *et al*., 2011). Caspase-3 is a key player in apoptosis, cleaving a variety of protein substrates in cells and causing cell death when activated. Because several chemotherapeutics have been shown to induce apoptosis in cancer cells, promoting or activating apoptosis by targeting apoptosis regulators has been recommended as a possible technique for anticancer drug development. *M. fragrans'* anti-cancer activity via caspase-3 has not been molecularly docked before.

Based on our previous studies (Ray *et al*., 2021a; Ray *et al*., 2021b; Masuda *et al*., 2017), here in this study, we have conducted the molecular interaction selected *M. fragrans* seed constituents as anticancer

DOI: https://doi.org/10.17509/ijost.v7i1
p- ISSN 2528-1410 e- ISSN 2527-8045

agents against caspase-3. A docking score was also evaluated for investigating the anti-cancer activity.

2. METHODS

The structure of caspase 3 (was obtained from the Protein Data Bank (PDB ID: 4DCP; www.rcsb.org/structure/4DCP) (Kang *et al*., 2012) and the isolated constituents from Myristica fragrans Seeds (Matulyte *et al*., 2019) were prepared using ChemDraw ver 16.0.1.4 (61) (Cambridge Soft). The receptor-ligand interactions were identified and calculated using molecular docking.

AutoGrid was used to create the grid map, which included a grid box and a docking box. A genetic algorithm with local search was used to calculate the docking possibilities. The ligands were docked using Molegro Virtual Docker (MVD) Ver 5.5 utilizing a blind docking method to include the full potential binding site.

The binding free energy (kcal/mol) was used to calculate the binding affinity. The value of free binding energy can be determined by using Notepad++ to examine the docking "dock.dlg" file. The lowest bond energy affinity for each docking result was found by looking at the histogram for each cluster—the lower the energy, the stronger the relationship. AutoDockTools was used to visualize the conformation of molecular docking data.

The PyMOL Visualization Tool and the Molegro 5.5 program are used to visualize the bonds that occur between the ligands of each macromolecule. The ideal post-docking compound structure must have the lowest energy and the molecules must be at the same active site as the native ligand, as visible in the protein structure. For the pose with the highest score, observations of ligand-protein interactions were made, including hydrogen bond interactions, steric (van der Waals) interactions, and electrostatic interactions.

3. RESULTS AND DISCUSSION

The interaction between two molecules is anticipated using molecular docking, a technique utilized in drug discovery and medicinal chemistry. In drug development, docking is the process of connecting a small molecule (ligand) with protein (enzyme). The binding energy is calculated using molecular mechanics in most docking programs (Prieto-martinez *et al*., 2018). Virtual screening, pose prediction, calculation-ligand and binding conformation affinity are all phases in molecular docking (Guedes *et al*., 2013). Molecular docking is useful in drug design since it allows users to find the best conformation and orientation of the ligand-protein complex (Ika & Hery, 2021). The ligand must have the lowest free energy score to be effective in selecting therapeutic candidates (Gaba *et al*., 2015).

Molecular docking provides many advantages, including the ability to evaluate large compound databases at a lower cost than experiments (Vlasiou & Pafti, 2021). The optimal structure is utilized to forecast the constituent probable mode and find the direction of the ideal pose using molecular modeling (Lin *et al*., 2020). Root mean square deviation (RMSD) and visual position are used to evaluate validation parameters. The reliability and reproducibility of the new docking technique were first verified by redocking ligands at the active receptor site using the RMSD measurement.

The RMSD is a measure of precision with reliable findings for repeated assays. It is the difference between the expected and observed experimental values. When compared to the crystallographic structure, an RMSD value less than 2.0 indicates that the algorithm is viable (Osman *et al*., 2020). This research might continue utilizing our verified docking approach (Sargolzaei, 2021), as can be shown from the comparison of our RMSD with the RMSD indicated above. The creation of the best-quality docking

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mechanism is indicated by an RMSD of less than 2.0 (Ghosh *et al*., 2021).

A molecular docking study was performed using Malegro Virtual Docker (MVD) software version 5.5. Criteria of acceptance are set with the value of RMSD less than 2.0 Å (**Figure 1**) The docking program is used to look into the inhibitor's potential binding mechanism to the nutmeg constituents. Nutmeg seed essential oil contains anticarcinogenic effects. The nutmeg seed oil has a wide range of compositions depending on where it's sourced (Ika & Hery, 2021, Nikolic *et al*., 2021).

Ten compounds of nutmeg seed were docked to the binding site with the stimulant caspase-3. Caspase-3 activation as an apoptosis effector is one of the apoptosis signaling pathways (Li & Yuan, 2008). Apoptosis is a type of cell death that can be induced by both endogenous and external triggers (Sharifi-Rad *et al.,* 2017). Extrinsic and intrinsic apoptosis are the two basic types of apoptosis signaling mechanisms. Intrinsic apoptosis pathways are activated by most anticancer actions (Lu *et al.,* 2017; Wicaksono *et al.,* 2015; Rizal & Sandra, 2016).

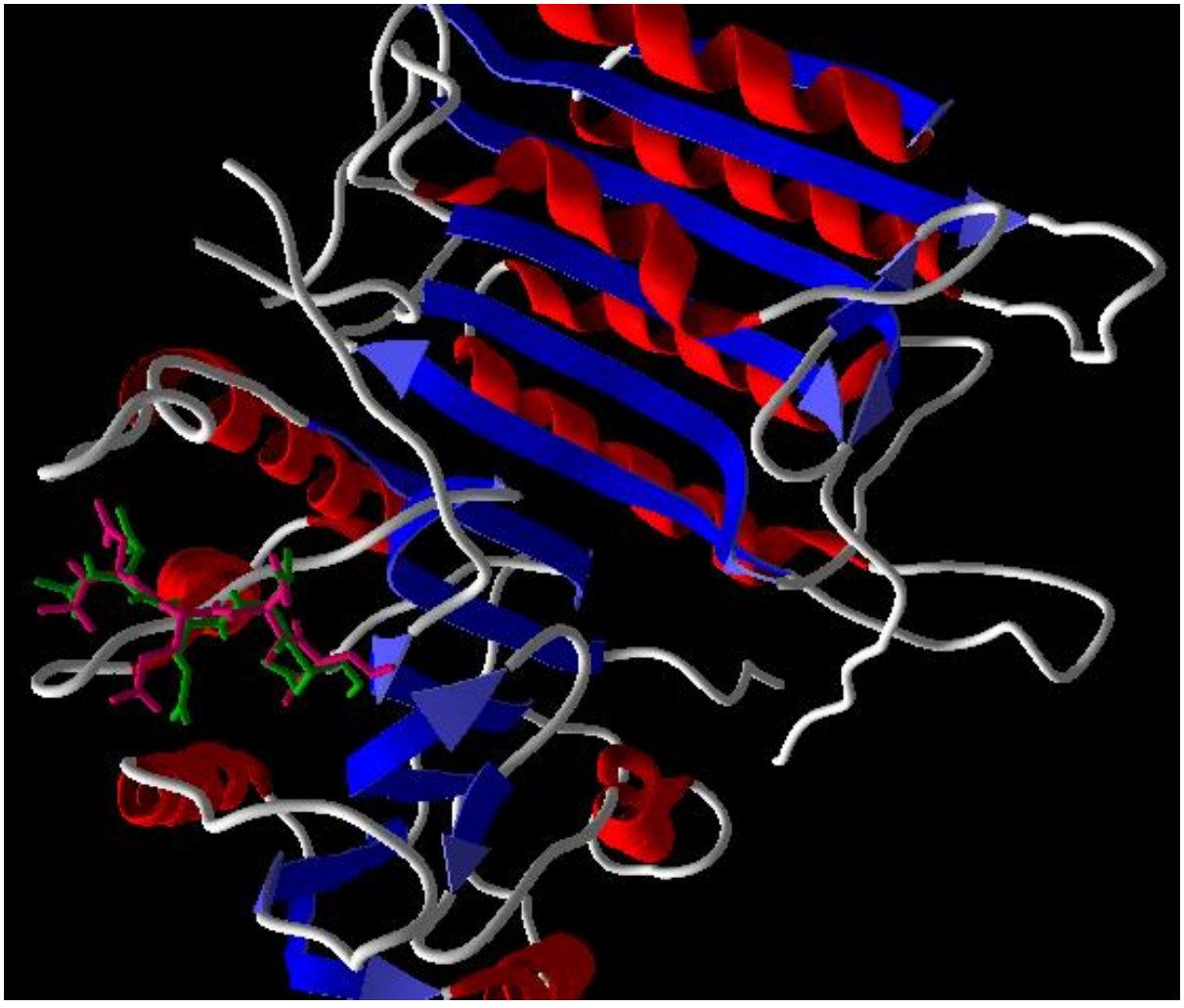

Figure 1. The binding orientation between the native ligand (green) and the docking result simulation (purple) by MVD. The RMSD is 1.24Å.

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p- ISSN 2528-1410 e- ISSN 2527-8045

The Pass online and molecular docking results were presented in **Table 1**. It indicates that the compounds from nutmeg are Piperitol, Myristicin, Licarin B, Isoelemicin, and Methylisoeugenol showed the best anti-cancer activity with a Probably active (Pa) value above 0.7, the compounds were believed to play a role in preventing the proliferation of cancer cells via the stimulant caspase-3 pathway. With pass online software, the findings in silico are also linear; five compounds have a rank score of less than 0.7.

The compound expected to actively block Caspase 3 production enzymes has a score ranging from -65.70 to -103.07 kcal/mol. As shown in **Table 1**, all nutmeg seed compounds performed significantly better as active substances of nutmeg. The anti-cancer activity correlates to the predicted binding energy (Rahman *et al.,* 2021)

The docking score between caspase-3 and compound of Methylisoeugenol, Isoelemicin, Myristicin, Piperitol, and Licarin B was -65.79, -69.10, -74.80, -91.71, -103.07, respectively. The docking score is a prediction of the inhibitory activity based on the binding affinity between receptor and ligand as determined by the optimal algorithm. The docking score's major importance is the evaluation index for quick preliminary steps and inhibitors (Ika & Hery, 2021). The docking score for the protein-ligand complex is used to estimate the free binding free energy. The highest protein affinity with the strongest powerful ligand equals the best docking scores (Rahman *et al.,* 2021).

Table 1 shows the interaction of nutmeg compound and stimulant caspase-3. **Table 1** shows the interacting hydrogen bond and steric interaction (non-hydrogen bond) from the nutmeg compound. Docking simulation colored 2D-binding mode representation between caspase-3 and compound of nutmeg shown in **Figure 2**. The binding interaction between the bioactive compound of nutmeg and stimulant caspase-3 was verified by molecular docking.

Figure 2 shows the two-dimensional interaction of the bioactive compound of nutmeg and stimulant caspase-3. There is no hydrogen bond interaction formed in Isogermacrene, Sylvestrene, Bergamotene, and Cubebol. This component has a low Pa score of less than 0.6.

This is thought to be a molecule that plays a little function in cancer cell proliferation prevention. On other hand, five others (Piperitol, Myristicin, Licarin B, Isolemicin, and Methylisoeugenol) have great potency as inhibitor caspase-3 according to the higher Pa value. Specifically, Licarin B has the greatest Pa value of all the active nutmeg compounds, and it has hydrogen bonds with Trp214 and Phe250.

The nutmeg components and inhibitor binding mechanism were clearly understood and visualized as a result of the molecular docking studies (Ika & Hery, 2021). Inhibition may be mediated by the same binding location and manner (Zou *et al.,* 2018). The most extensively used approach for structure-based drug design is molecular docking, which offers a wide range of applications, including binding energies and interactions (Zhang *et al.,* 2017).

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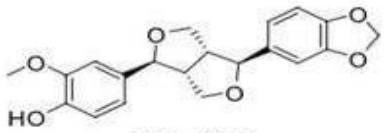
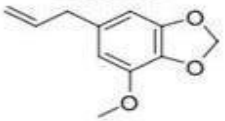
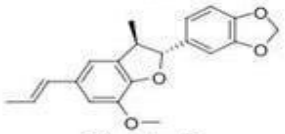
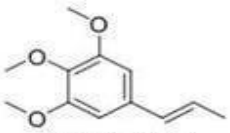
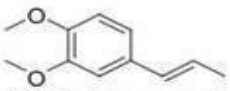
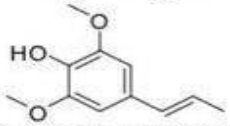
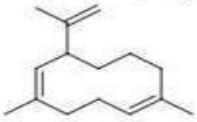
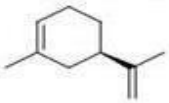
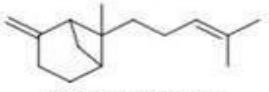
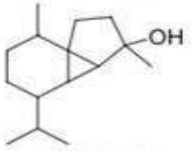
p- ISSN 2528-1410 e- ISSN 2527-8045

Table 1. Pass online and molecular docking result.

Compound	Pa (Caspase-3 stimulant)	Re-rank Score (kcal/mol)	Hydrogen Bond Interaction	Steric Interaction
 Piperitol	0,923	-91,71	Arg 64; Ser 120; Arg 207; Ser 251	His 121; Gln 161; Ser 205; Arg 207; Trp 251
 Myristicin	0,911	-74,80	Arg 207	Tyr 204
 Licarin B	0,897	-103,07	Trp 214; Phe 250	Gly 161; Ser 205; Trp 206; Arg 207;
 Isoelemicin	0,751	-69,10	Cys 163; Arg 207	Arg 64; Ser 120; Cys 163; Tyr 204; Ser 205; Arg 207
 Methylisoeugenol	0,732	-65,79	Cys 163; Arg 207	Gln 161; Cys 163; Ser 205
 4-Propenyl syringol	0,688	-58,71	His 121; Cys 163; Arg 207	Gln 161; Cys 163; Ser 205; Trp 206
 Isogermacrene	0,545	-55,55	-	Ser 205 Arg 207
 Sylvestrene	0,537	-52,14	-	Gln 161 Ser 205 Arg 207
 Bergamotene	0,361	-31,37	-	Gln 161; Ser 205; Arg 207
 Cubebol	0,272	-20,19	-	His 121; Gln 161; Cys 163; Ser 205; Arg 207

DOI: https://doi.org/10.17509/ijost.v7i1
p- ISSN 2528-1410 e- ISSN 2527-8045

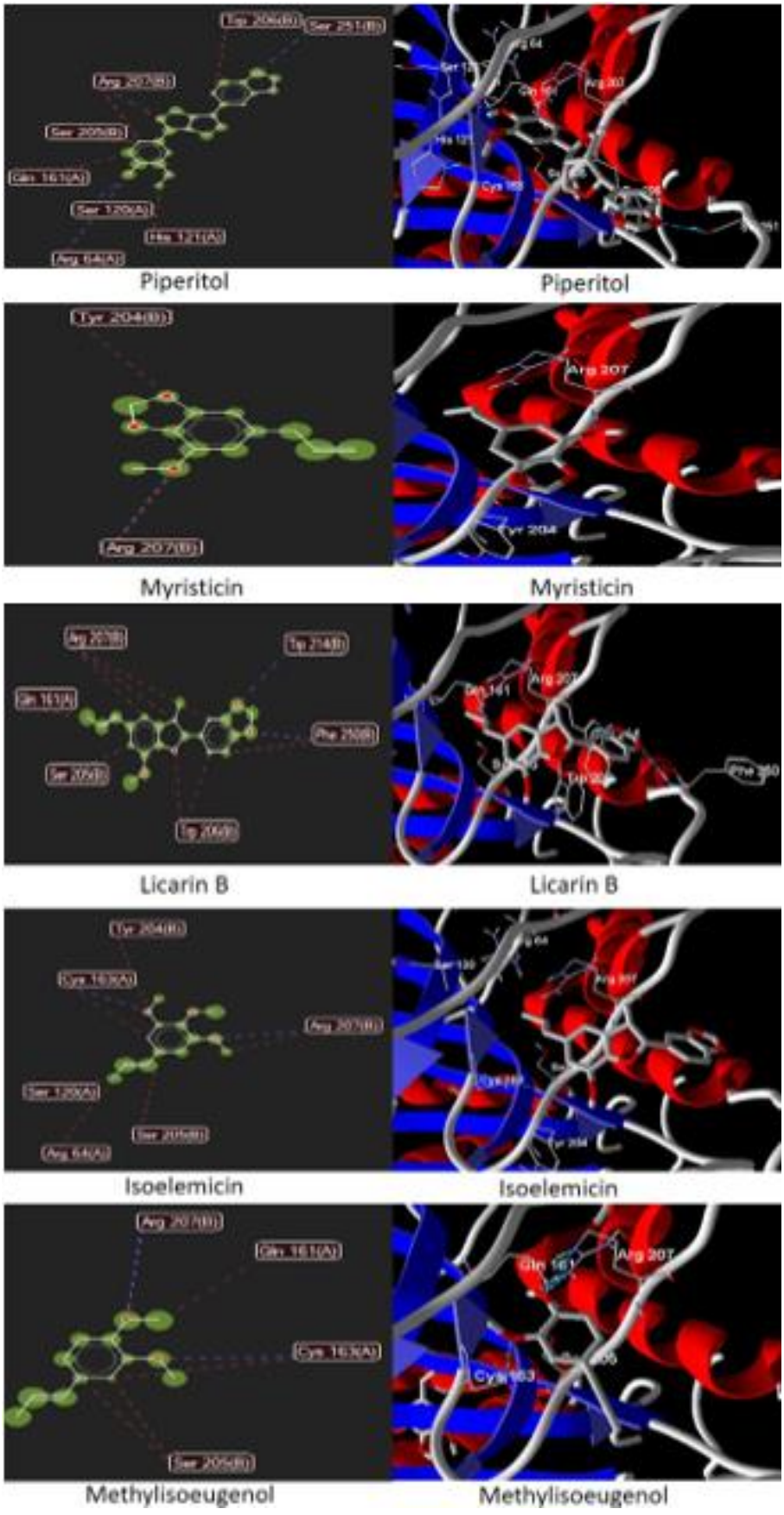


Figure 2. The binding interaction between the bioactive compound of nutmeg and stimulant caspase-3.

DOI: https://doi.org/10.17509/ijost.v7i1
p- ISSN 2528-1410 e- ISSN 2527-8045

4. CONCLUSION

Molecular docking of selected compounds from nutmeg (*M. fragrans*) exhibit that five constituents have great potency as an inhibitor of caspase-3. The best interaction model of the nutmeg compound was shown by Licarin B with a binding energy score of -103.07 kcal/mol. Licarin B has the greatest Pa value of all the active nutmeg compounds, and it has hydrogen bonds with Trp214 and Phe250. These findings implicated that nutmeg contains great compounds which could actively block the caspase-3 activity, and could be further developed as a potent compound against cancer (potential as anti-cancer).

5. AUTHORS' NOTE

The author(s) declare(s) that there is no conflict of interest regarding the publication of this article. The authors confirmed that the data and the paper are free of plagiarism.

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DOI: https://doi.org/10.17509/ijost.v7i1
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