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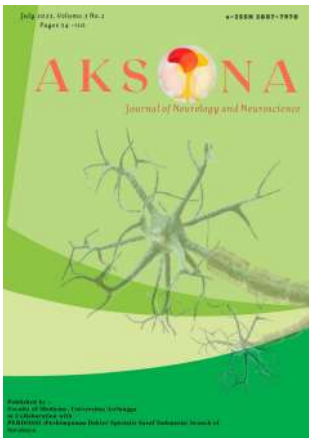

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Volume 3 Number 2, July 2023

In Silico Analysis of *Pongamia pinnata* to Inhibit Neuronal Apoptosis after Ischemic Stroke via NMDAR and Caspase-3

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ABSTRACT

Introduction: One of the cardiovascular diseases with the highest mortality rate is stroke. Stroke is the second-leading cause of death worldwide. Each year, 12.2 million new cases of stroke occur, of which 7.6 million are ischemic strokes. In ischemic stroke, there are several pathways that cause neuronal apoptosis. The activity of NMDAR and caspase-3 is one of the pathways. *Pongamia pinnata* phytochemicals have a neuroprotective function against neurological disorders. However, its use as an inhibitor of apoptosis in ischemic stroke has never been evaluated before. **Objective:** This research was designed to evaluate the phytochemicals of *Pongamia pinnata* as inhibitors of neuronal apoptosis in ischemic stroke using an in silico study. **Methods:** This study used four main phytochemicals of *Pongamia pinnata*, namely Karanjin, Karanjachromene, Pongapin, and Pongachromene. The protein targets for neuronal apoptosis were NMDAR and caspase-3. The molecular docking processes were ligand preparation, protein preparation, grid box determination, molecular docking, and visualized molecular docking. **Results:** In silico results showed that at NMDAR target proteins, Karanjin, Karanjachromene, Pongapin, and Pongachromene have binding energies of -5.12, -5.83, -5.03, and -5.13 kcal/mol. At protein targets, Caspase-3, Karanjin, Karanjachromene, Pongapin, and Pongachromene have binding energies of -4.87, -4.98, -4.88, and -5.08 kcal/mol. **Conclusion:** The phytochemicals of *Pongamia pinnata* have the potential to inhibit neuronal apoptosis via NMDAR and caspase-3 in ischemic stroke. The binding of Karanjachromene to NMDAR demonstrated the compound's best interaction.

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INTRODUCTION

Stroke is one of the cardiovascular diseases with the highest mortality rate. Stroke is the second-leading cause of death in the world. Strokes cause 6.5 million fatalities worldwide. In a year, there are 12.2 million new cases of stroke, of which 7.6 million are ischemic strokes. In ischemic stroke, there are several pathways that cause neuronal apoptosis.[1] One of the pathways is the activity of N-methyl-d-aspartate receptors (NMDAR), the main receptor that plays a role in the intrinsic apoptotic pathway. NMDAR activation causes excess Ca^{2+} influx and triggers calpain activation. Calpain converts the Bcl-2 interacting domain (BID) into a tBID that interacts with Bax. Bax forms homo-oligomers and then incorporates them into the outer mitochondrial membrane. Consequently, the pores of the mitochondrial permeability transition (mPTP) open and allow the release of apoptogen (Cytc). The released cytc combines with Apaf-1 and pro-caspase-9 and will gradually activate caspase-3. It is this caspase-3 activation that ultimately induces neuronal apoptosis.[2]

Pongamia pinnata (*P. pinnata*) is a plant originating from India and Southeast Asia. This species' phytochemical studies led to the identification of several compounds from various classes, including flavonoids and terpenoids. These plant phytochemical compounds exhibit various pharmacological activities such as antioxidant, antimicrobial, antiparasitic, anti-inflammatory, anticonvulsant, antidiabetic, cytotoxic, anthelmintic, insecticidal, and immunomodulatory activity.[3] *P. pinnata* extract contains many flavonoid compounds, namely Karanjin, Karanjachromene, Pongapin, and Pongachromene.[4] These compounds have a neuroprotective function in Alzheimer's disease.[5] However, its use as an apoptosis inhibitor in ischemic stroke has never been evaluated. Therefore, we carried out this in silico research.

OBJECTIVE

This research was designed to evaluate the main phytochemicals of *Pongamia pinnata*, namely karanjin, karanjachromene, pongapin, and pongachromene, as inhibitors of neuronal apoptosis in ischemic stroke using an in silico study.

METHODS

System Configuration

This study used a 32-bit Windows 10 laptop with an Intel Core i3 processor and 2 GB of RAM. Avogadro, AutoDock 4.2, Biovia Discovery Studio 2019, and PyMol were applications employed in this in silico research.

Ligand Preparation

P. pinnata has the main phytochemical compounds, namely Karanjin, Karanjachromene, Pongapin, and Pongachromene (Figure 1).[3] The phytochemical compounds of *P. pinnata* were analyzed using the Swiss-Adme website to predict Lipinski's parameters. The compounds were downloaded from NCBI PubChem in.sdf format. All the phytochemicals were optimized using Avogadro software. Every compound's energy was minimized using the MM4 force field. After that, the polar hydrogen was added, the nonpolar hydrogen was merged, and the gasteiger charge was computed using AutoDock 4.2.

Protein Preparation

NMDAR (PDB ID: 5H8Q) and caspase-3 (PDB ID: 3DEI) were chosen as the protein targets in this study because they are key players in the pathophysiology of neuronal apoptosis following ischemic stroke in patients.[2] The protein target structure was downloaded from the Protein Data Bank (http://www.rcsb.org) in.pdb format. NMDAR has two chains, namely chains A and B. We used chain B for molecular docking because the native ligand 5YE is in chain B. Caspase-3 has four chains, namely chains A, B, C, and D. We used chain C for molecular docking because the native ligand RXB is in chain C. The proteins were then optimized by including polar hydrogens, merging nonpolar ones, and adding Kollman charges. The 3D structures of NMDAR and caspase-3 with their native ligands are shown in Figure 2.

Grid Box Determination

Using AutoDock 4.2 software, the native ligand position determined the grid box. In NMDAR, the native ligand grid 5YE was set at 30x30x30 (XYZ) point size, -14.959, -14.301, -25.150 center coordinates, and 0.375 A spacing. In the caspase-3 protein, the native ligand RXB grid was set at 30x30x30 (XYZ) point size, -46.620, 15.373, -22.195 center coordinates, and 0.375 A spacing.

Molecular Docking

Molecular docking was performed using AutoDock 4.2 software after proteins and ligands were prepared and grid boxes were defined. The ligand conformation was analyzed using the Lamarckian Genetic Algorithm. The docking parameters were left as defaults. A favorable conformation was selected based on the lowest energy binding (ΔG) and inhibitory constant (Ki). After that, the docking results were visualized using PyMol software and BIOVIA Discover Studio 2019.[6]

RESULTS

P. pinnata has around 70 phytochemical compounds. The main phytochemicals of *P. pinnata* were karanjin, karanjachromene, pongapin, and pongachromene. All these phytochemicals can be found in all parts of *P. pinnata*. All the main phytochemical compounds were screened before docking. All phytochemicals met Lipinski's parameters with no infractions (Table 1). All ligands have the ability to pass the blood-brain barrier to neuronal apoptosis inhibitory receptors in the brain.

Based on the result of molecular docking, karanjachromene has the potential to inhibit neuronal apoptosis via NMDAR inhibitors. Karanjachromene has the strongest binding energy of the other ligand and the native ligand 5YE with NMDAR. Karanjachromene has a binding energy of -5.83 kcal/mol, an inhibition constant of 53.64 µM, and amino acid bonds with ILE128, PRO141, LYS143, TYR144, SER249, GLY250, and HIS273. While the native ligand 5YE has a binding energy of -5.50 kcal/mol with an inhibition constant of 93.10 µM. The other ligands have inhibitory activity against NMDAR. It is shown by the negative energy binding value. Karanjin (ΔG -5.12 kcal/mol and Ki 176.24 µM), Pongapin (ΔG -5.03 kcal/mol and Ki 206.90 µM), and Pongachromene (ΔG -5.13 kcal/mol and Ki 174,27 µM) have a lower relative energy binding value than the native ligand 5YE (Table 2). The molecular docking visualization of *P. pinnata* phytochemical compounds with NMDAR is shown in Figure 3.

At the caspase-3 receptor, the phytochemical of *P. pinnata* that has the strongest binding energy is Pongachromene, with a binding energy of -5.08 kcal/mol, an inhibition constant of 189.85 µM, and an amino acid bond with THR166, GLU167, LEU168, CYS170, TYR204, THR255, PHE256, and LYS259. The other ligands, Karanjin, Karanjachromene, and Pongapin, have binding energies of -4.87, -4.98, and -4.88 kcal/mol with inhibition constants of 269.40, 223.26, and 266.27 µM. Meanwhile, the native ligand RXB has a binding energy of -5,82 kcal/mol with inhibition constant of 54.30 µM (Table 2). The molecular docking visualization of *P. pinnata* phytochemical compounds with caspase-3 is shown in Figure 4.

DISCUSSION

Prior to molecular docking, Lipinski's parameters screened the phytochemical compounds of *P. pinnata*. Lipinski's parameters include molecular weight, log P, H-bond donor, and H-bond acceptor.[7] All the phytochemicals of *P. pinnata* met Lipinski's parameters. According to the molecular docking results, all the phytochemicals of *P. pinnata* have negative bonds with NMDAR and caspase-3. Through NMDAR and caspase-3, these phytochemicals can inhibit neuronal apoptosis in ischemic stroke. Karanjachromene inhibits NMDAR better than other ligands and native ligands due to its best binding interaction. Stronger ligand-receptor interactions result from ligands with greater negative binding energy, and those ligands are more effective in inhibiting the receptors.[8]

GluN1 and GluN2 subunits combine to form NMDAR (PDB ID: 5H8Q), a glutamate-gated ion channel. In the CNS, NMDAR functions in both neuronal survival and neuronal death.[9] NMDAR plays an important role in synaptic plasticity and initiates cellular responses in the CNS, such as learning, brain development, and memory. However, NMDAR also has a harmful side for neurons. When the brain is in ischemia or hypoxia, there is a rapid increase in glutamate levels in the ischemic area, which can destroy neurons.[10,11] 5H8Q has a structure weight of 65.92 kDa, a modeled residue count of 557, a deposited residue count of 578, an atom count of 4786, two unique protein chains, and a native ligand 5YE that binds to LYS140, PRO141, PHE142, LYS143, TYR144, ARG248, SER249, GLY250, LEU270, and HIS273.[12] Caspase-3 (PDB ID: 3DEI) is a cysteine protease that plays a critical role in human apoptotic cell death. Caspase-3 is a key mediator of neuronal death in the acute stage of ischemic stroke because it involves the final common pathway of apoptosis. Caspase-3 is a major executioner caspase, and it will trigger when it is activated by other caspases.[13,14,15] 3DEI has a structure weight of 114.63 kDa, 933 modeled residue, 966 deposited residue, 7672 atom count, 1 unique protein chain, and a native ligand RXB that binds to THR166, GLU167, LEU168, CYS170, TYR204, THR255, and LYS259.[16]

Karanjin is a bioactive furoflavanoid. This phytochemical was first isolated from *P. pinnata*. Karanjin can be isolated from the seed, flower, root, leaf, and stem bark of *P. pinnata*.[3,17,18] Karanjin has multiple health benefits, including anti-diabetic, anti-cancer, antioxidant, anti-colitis, anti-ulcer, gastroprotective, anti-inflammation, and antibacterial. Karanjin is a phytochemical with anti-Alzheimer activity and is also a neuroprotective agent.[5,17,19] Karanjachromene is a bioactive chromenoflavone. Pongaflavone is another name for Karanjachromene. This phytochemical is isolated from *P. pinnata* seed.[3,20] Karanjachrome has some pharmacological activities, such as antibacterial, antioxidant, and anti-aging. However, research on this phytochemical is still limited.[3,21] Pongapin is a bioactive furanoflavone isolated from the root bark, seed, and stem bark of *P. pinnata*.[3,22] This phytochemical has not yet been evaluated. According to a recent study, pongapin has anticancer and antidiabetic activity via alpha-glucoside

inhibitors.[23,24,25] Pongachromene is a bioactive chromeneflavone. The first chromeneflavone from *P. pinnata* to be reported was this phytochemical. Pongachromene was isolated from the root and stem of *P. pinnata*.[24,26] The pharmacological activities of pongachromene are still limited. This phytochemical has been reported as antibacterial, antidiabetic, and antioxidant.[24,27]

P. pinnata with its main phytochemical compounds Karanjin, Karanjachromene, Pongapin, and Pongachromene, has the neuroprotective potential to inhibit neuronal apoptosis after ischemic stroke. It is shown from the molecular docking of the compounds that they can inhibit NMDAR and caspase-3. Through this mechanism, neuronal death can be prevented in ischemic stroke patients.[2]

CONCLUSION

Molecular docking of *P. pinnata* compounds has the potential to inhibit neuronal apoptosis via NMDAR and caspase-3 in ischemic stroke. The binding of Karanjachromene to NMDAR with a binding energy of -5.83 demonstrated the best interaction of the compound. This bond is slightly stronger than the native ligand to NMDAR (ΔG: -5.50). More in vitro and in vivo studies are needed to prove the potency of *P. pinnata* in inhibiting neuronal apoptosis after ischemic stroke, especially the Karanjachromene compound in inhibiting NMDAR.

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Conflict of Interest
All authors have no conflict of interest in this article

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Author Contribution
The first and second authors designed the concept, collected and analyzed the data, and wrote the manuscript. The third and fourth authors provided independent consultations for the review and revision of the manuscript.

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TABLES AND FIGURES

Table 1. ADME Analysis of *P. pinnata* Phytochemical Compounds

Phytochemical Compounds	CID	Lipinski's Rule of Five					BBB Permeant
		Molecular Weight (g/mol)	Log P	H-bond donor	H-bond acceptor	Violations	
Karanjin	100633	292.29	3.43	0	4	0	Yes
Karanjachromene	14033983	334.37	3.94	0	4	0	Yes
Pongapin	3083586	105,6336.37	3.25	0	6	0	Yes
Pongachromene	14033985	378.37	3.80	0	6	0	Yes

Table 2. Molecular Docking Results of *P. pinnata* Phytochemical with Protein Target

Protein Target	Ligand	ΔG (kcal/mol)	K_i (μM)	Amino Acid Bond
NMDAR	Native Ligand (5YE)	-5.50	93.10	LYS140, PRO141, PHE142, LYS143, TYR144, ARG248, SER249, GLY250, LEU270, HIS273
	Karanjin	-5.12	176.24	ILE128, PRO141, PHE142, LYS143, TYR144, GLY250, HIS273
	Karanjachromene	-5.83	53.64	ILE128, PRO141, LYS143, TYR144, SER249, GLY250, HIS273
	Pongapin	-5.03	206.90	ILE128, PRO141, PHE142, LYS143, TYR144, SER249, GLY250, HIS273
	Pongachromene	-5.13	174.27	ILE128, PRO141, TYR144, SER249, GLY250, HIS273
Caspase-3	Native Ligand (RXB)	-5.82	54.30	THR166, GLU167, LEU168, CYS170, TYR204, THR255, LYS259
	Karanjin	-4.87	269.40	THR166, GLU167, LEU168, CYS170, THR255, PHE256 LYS259
	Karanjachromene	-4.98	223.26	THR166, LEU268, TYR204, TRP206, THR255, PHE256
	Pongapin	-4.88	266.27	THR166, GLU167, LEU168, CYS170, TYR204, THR255, LYS259
	Pongachromene	-5.08	189.85	THR166, GLU167, LEU168, CYS170, TYR204, THR255, PHE256, LYS259

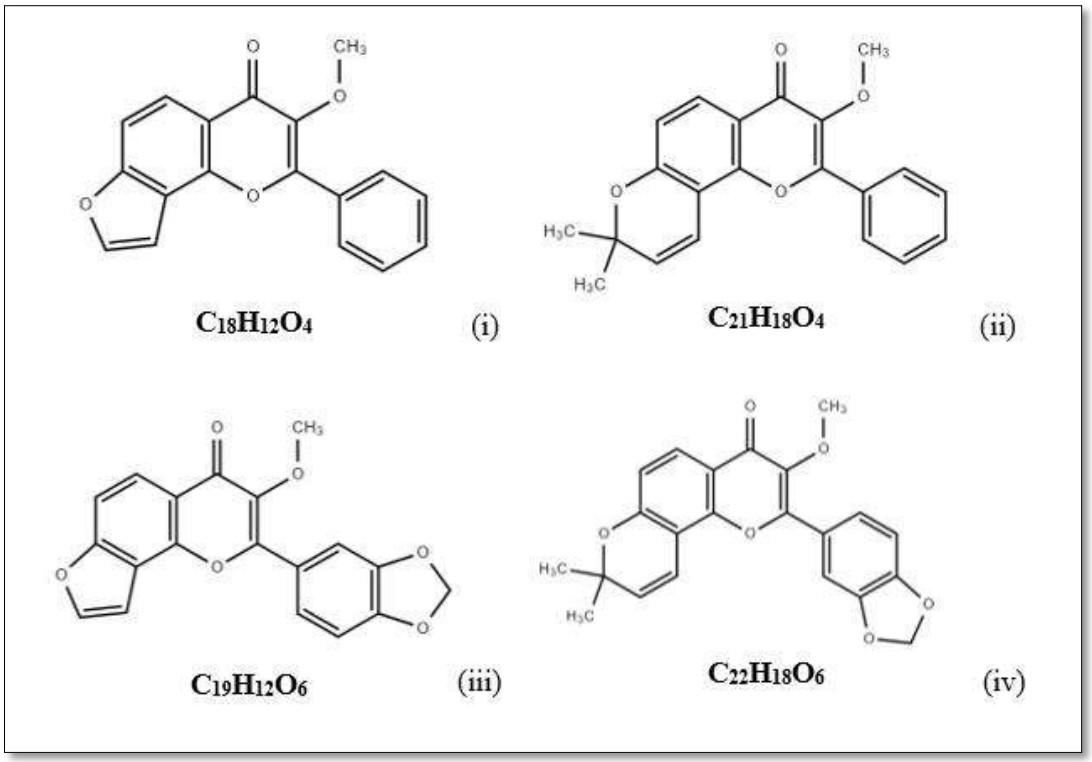

Figure 1. Chemical Structure of *P. pinnata* Phytochemical Compounds (i) Karanjin, (ii) Karanjachromene, (iii) Pongapin, and (iv) Pongachromene

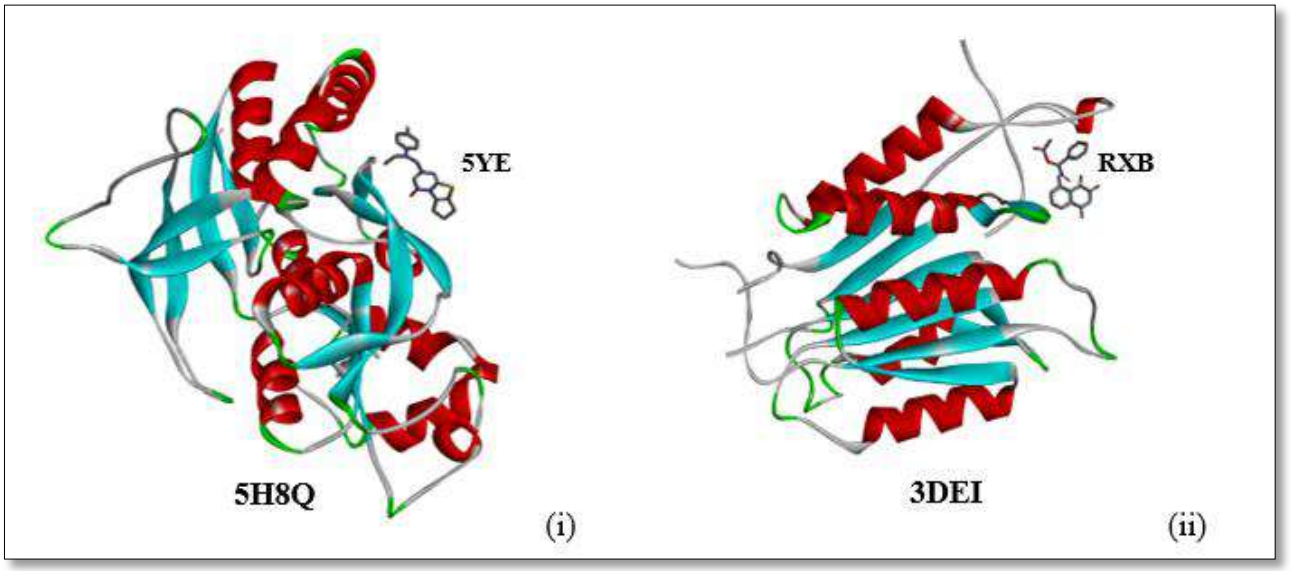

Figure 2. 3D Structure of Protein Target (i) NMDAR (5H8Q) with Native Ligand (5YE) and (ii) Caspase-3 (3DEI) with Native Ligand (RXB)

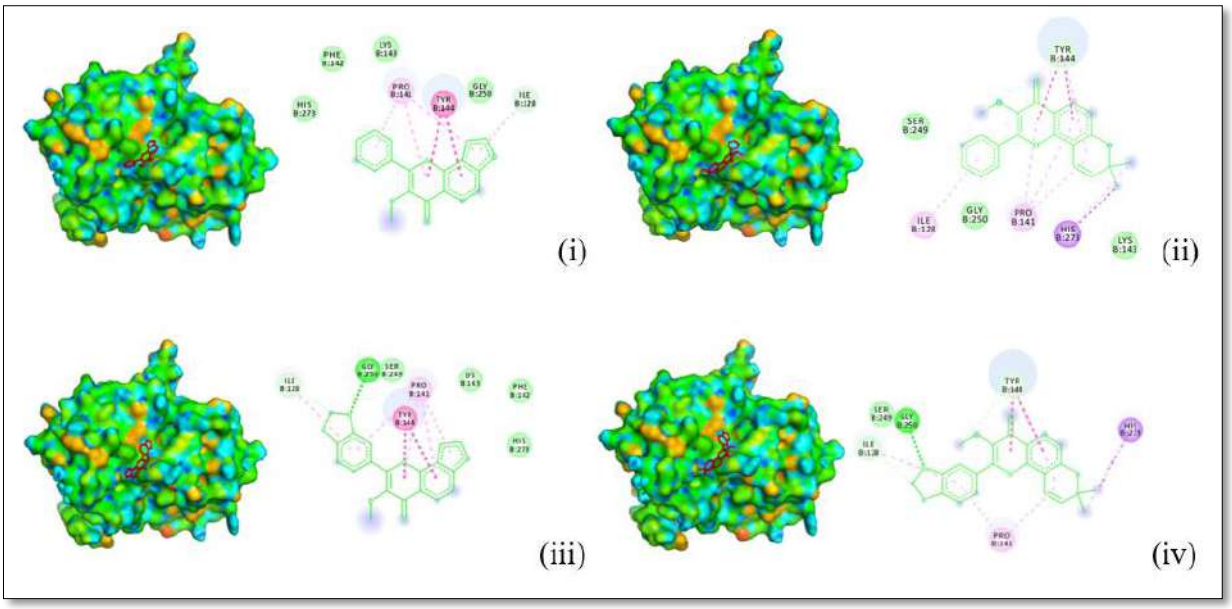

Figure 3. Visualization of *P. pinnata* phytochemical compounds (i) Karanjin, (ii) Karanjachromene, (iii) Pongapin, and (iv) Pongachromene with NMDAR

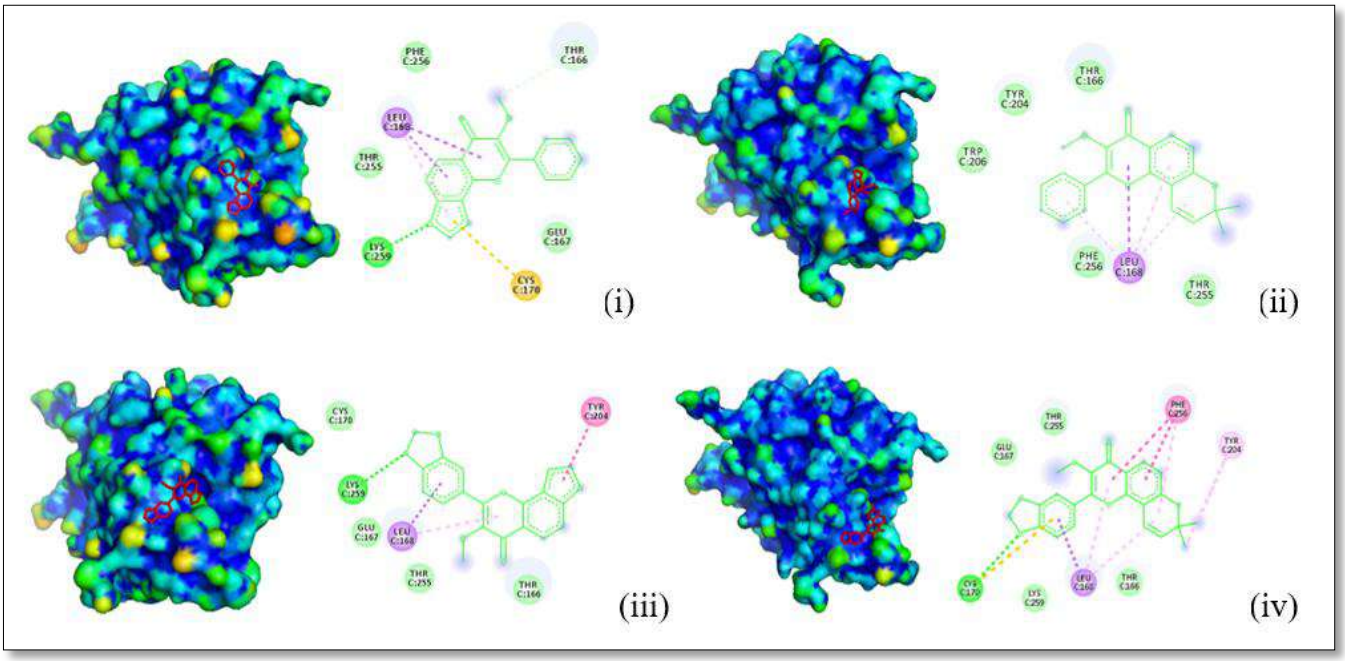

Figure 4. Visualization of *P. pinnata* phytochemical compounds (i) Karanjin, (ii) Karanjachromene, (iii) Pongapin, and (iv) Pongachromene with Caspase-3

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