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Revealing of Anti-inflammatory Agent from *Garcinia mangostana* L. Phytochemical as NF-κB Inhibitor Mechanism through In Silico Study

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Rasyadan Taufiq Probojati[1], Santika Lusia Utami[2], Dora Dayu Rahma Turista[3]*, Arbi Wiguna[4], Priscilla Listiyani[1], Arini Wijayanti[5], Yuanita Rachmawati[6], Sri Wahyuningsih[2], Alyaa Farrah Dibha[7], Thobib Hasan[8], Muhammad Aldino Hafidzhah[9], Renadya Maulani Wijaya[9], Agus Mohammad Hikam[10], Muhammad Badrut Tamam[11], Ahmad Affan Ali Murtadlo[1], Sin War Naw[12]

[1]Computational Virology Research Unit, Molecular Biology and Genetics Division, Generasi Biologi Indonesia Foundation, Gresik Indonesia.
[2]Faculty of Biology, Universitas Gadjah Mada, Yogyakarta, Indonesia.
[3]Educational Biology Department, Faculty of Teacher Training and Education, Mulawarman University, Samarinda, Indonesia.
[4]Zoology Division, Generasi Biologi Indonesia Foundation, Gresik, Indonesia.
[5]Department of Ecology and Evolutionary Biology, University of California Santa Cruz, Santa Cruz, United States.
[6]Department of Biology, Faculty of Science and Technology, UIN Sunan Ampel Surabaya, Surabaya, Indonesia.
[7]Chemistry Department, Faculty of Mathematics and Natural Sciences, Brawijaya University, Malang, Indonesia.
[8]Department of Biology, Faculty of Mathematics and Natural Sciences, IPB University, Bogor, Indonesia.
[9]Department of Bioinformatics, School of Life Sciences, Indonesia International Institute for Life-Sciences, East Jakarta, Indonesia.
[10]Faculty of Mathematics and Natural Sciences, Universitas Islam Malang, Malang, Indonesia.
[11]Department of Biology, Faculty of Sciences and Technology, Universitas Muhammadiyah Lamongan, Lamongan, Indonesia.
[12]Department of Chemistry, Myitkyina University, Myitkyina, Myanmar.

*Corresponding author: doraturistaofficial@gmail.com

ABSTRACT

Immune response that occurs when a pathogen such as a virus, fungus, bacteria, & protozoa. Red color due to swelling is a characteristic of inflammation, this condition can occur due to high blood flow and increased membrane permeability in the area of infection, inflammation is also caused by tumors, cancer, and autoimmune diseases by infectious microorganisms. NF-κB regulation has

† Footnotes relating to the title and/or authors should appear here.
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also been identified to be associated with conditions for the transformation of normal cells into cancer, specific autoimmune diseases, and viral infections. Previous studies have shown the potential of *Gracinia mangostana* L. for anti-inflammatory, but the molecular mechanism of anti-inflammatory in these two compounds has not been found. This research was conducted to reveal the potential of compounds from *Garcini mangostana* L. as anti-inflammatory agents through an in silico approach. Gamma-mangostin from Garcinia mangostana L. are predicted to be anti-inflammatory agents, this compound can produce more negative binding affinity and weak bond interactions. This indicates the stability of the binding interaction that triggers the inhibitory activity.

Keywords: Anti-inflammatory, *Garcinia mangostana* L, Inhibitor, In Silico, NF-κB

INTRODUCTION

Immune response that occurs when a pathogen such as a virus, fungus, bacteria, & protozoa[1,2]. Red color due to swelling is a characteristic of inflammation, this condition can occur due to high blood flow and increased membrane permeability in the area of infection, inflammation is also caused by tumors, cancer, and autoimmune diseases by infectious microorganisms[3,4]. The cytokine storm in COVID-19 patients is also caused by the release of excess proinflammatory cytokines by immune cells which causes cases of severe inflammation that can lead to death[5,6]. Several previous studies have designed drugs with activity to inhibit the activation of proinflammatory proteins such as NF-κB through in vitro and in vivo approaches[7,8,9].

NF-κB has an important role to control the transcription process, production of specific cytokines and cell survival[10,11,12]. This protein is widely expressed in all types of animal cells and is involved in cellular responses such as the release of cytokines, free radicals, defense against ultraviolet radiation and infectious pathogens[13,14,15]. NF-κB regulation has also been identified to be associated with conditions for the transformation of normal cells into cancer, specific autoimmune diseases, and viral infections. NF-κB activation is influenced by specific enzymes such as IKK-κB which phosphorylate the NF-κB & IκBα complex[16,17,18]. The dissociated complex triggers the release of NF-κB into the nucleus for activation of the regulation of various proinflammatory genes. This indicates that IKK-B can be used as a target inhibitor to inhibit proinflammatory regulation by NF-κB[19,20,21].

Indonesia is an archipelagic country that has 40,000 endemic plant species including 6000 types of medicinal plants. People in Indonesia use a lot of specific medicinal plants to treat a disease[22,23]. *Garcinia mangostana* L. or Mangosteen consists of 400 species which are widely used in traditional medicine of a disease in the world[24,25]. Mangosteen has been reported to have bioactive compounds consisting of alpha-mangostin, beta-mangostin and gamma-mangostin[26,27]. Previous studies have shown the potential of *Gracinia mangostana* L. for anti-inflammatory, but the molecular mechanism of anti-inflammatory in these two compounds has not been found[28,29,30]. This research was conducted to reveal the potential of compounds from *Garcini mangostana* L. as anti-inflammatory agents through an in silico approach.

METHOD

Ligand-protein preparation

This study used a compound from *Gracinia mangostana* L. which consisted of alpha-mangostin (CID: 5281650), beta-mangostin (CID: 5495925) and gamma mangostin (CID: 5464078) with file structure data format (sdf) obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) IKK-B protein was used in this study to target the binding of chemical compounds from *Garcinia mangostana* L, the target was obtained through the RCSB PDB database (https://www.rcsb.org/). Ligand minimization is done through the OpenBabel v2.3.1 plugin with the aim of converting sdf files to pdb. The removal of water molecules on the target protein was carried out in this study through PyMol v2.5 software with the aim of increasing the effectiveness of binding energy formation during docking simulations[31,32].

Molecular docking simulation

Molecular docking aims to determine the activity or binding strength of a ligand in the target domain. Simulation of inhibitor activity produced by compounds from *Gracinia mangostana* L. with IKK-B was carried out using the blind docking method to determine compounds that have potential as drug candidates. PyRx v0.9.9 software was used in this study for blind docking with autogrid covering the entire protein domain[33,34]. 3D visualization of docked molecular complexes is displayed with PyMol v2.5 software through cartoons, surfaces, and sticks structures[35,36].

Ligan-protein interaction analysis

The molecular complex identified the positions and types of chemical bond interactions formed through LigPlus v2.2.4 software. The software can display the position and type of chemical bond interactions such as hydrogen and hydrophobicity that contribute to triggering the activity of the target protein[37,38].

RESULT AND DISCUSSION

Revealing of IKK-B inhibitor from *Garcinia mangostana* L. compound

Garcinia mangostana L. has potential as anti-inflammatory, antioxidant, antiviral, antimicrobial, antidiabetic, and prevention of free radical production[39,40,41]. *Garcinia mangostana* L. has the main chemical compounds consisting of alpha-mangostin, beta-mangostin, and gamma-mangostin (Table 1). Compounds from *Garcinia mangostana* L. were used in this study to predict potential anti-inflammatory candidates through inhibition of IKK-B activity. The blind docking simulation is performed with reference to the grid positions center (Å) X:-1.292 Y:-12.270 Z:-93.627, dimensions (Å) X:137.336 Y:91.096 Z:177.507.

Table 1. *Garcinia mangostana* L. chemical compound from PubChem

Compound	CID	Formula	SMILE Canonical
alpha-mangostin	5281650	C24H26O6	CC(=CCC1=C(C2=C(C=C1O)OC3=C(C2=O)C(=C(C(=C3)O)OC)CC=C(C)C)O)C
beta-mangostin	5495925	C25H28O6	CC(=CCC1=C(C=C2C(=C1O)C(=O)C3=C(O2)C=C(C(=C3CC=C(C)C)OC)O)OC)C
gamma mangostin	5464078	C23H24O6	CC(=CCC1=C(C2=C(C=C1O)OC3=C(C2=O)C(=C(C(=C3)O)O)CC=C(C)C)O)C

Gamma-mangostin has a binding affinity of -9.3 kcal/mol more negative than other compounds when it binds to E6 protein (Table 2), gamma-mangostin is predicted to inhibit the activity of IKK-B because it has more negative binding than other compounds. The molecular docking simulation aims to determine the activity of the ligand binding on the protein domain by referring to the binding affinity value[42]. The binding affinity value indicates the inhibitory ability of a ligand on the target protein[43,44]. Visualization of molecular docking results is displayed through cartoons structure and sticks with selected coloring (Figure 1).

Table 2. The comparison of compound binding affinity

Compound	Molecular Weight (g/mol)	RCSB Target ID	Minimize Energy (kcal/mol)	Binding Affinity (kcal/mol)
alpha-mangostin	410.5	4KIK	+453.57	-8.9
beta-mangostin	424.5	4KIK	+530.63	-7.9
gamma mangostin	396.4	4KIK	+415.98	-9.3

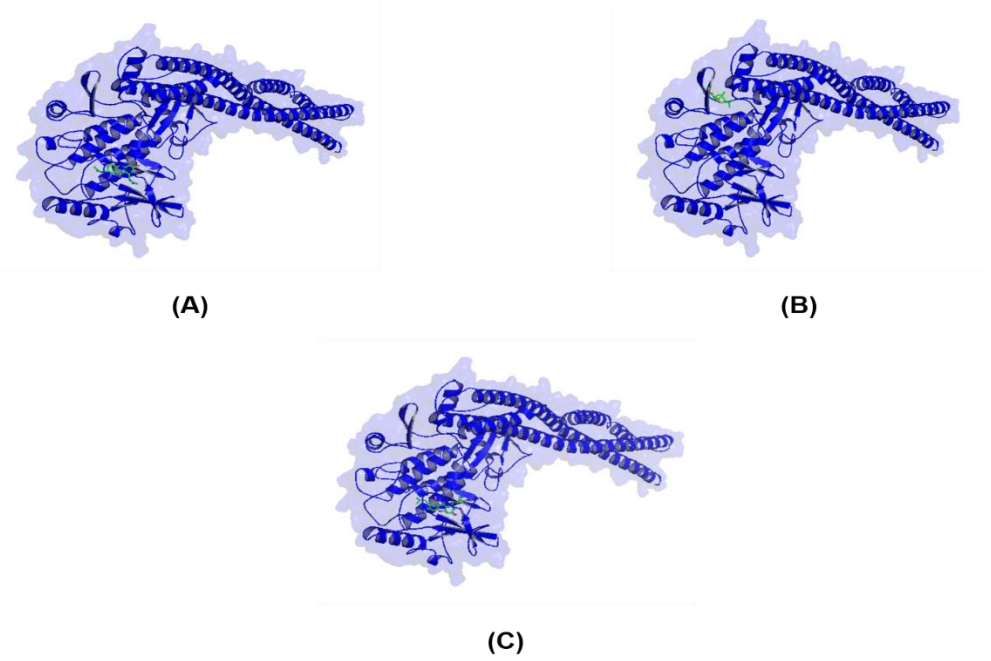

Figure 1. 3D Visualization from the docking results. (A) IKK-B_alpha-mangostin (B) IKK-B_beta-mangosting (C) IKK-B_gamma-mangostin.

Molecular interaction of *Garcinia mangostana* L. compounds at IKK-B

The inhibitory activity on the target protein is triggered by weak binding interactions of the formed ligands. these interactions are played by hydrogen bonds, hydrophobicity, van der Waals, and pi[45]. Unfavourable interactions are unstable bonds formed in the molecular complex (ligand-protein) a stable ligand must have at least two unfavourable interactions[46]. Hydrogen bond interactions have an important role in triggering a specific response to the target protein and are used as an indicator of the effectiveness of a drug's performance, the more types of hydrogen bonding interactions on the target protein, the stronger the effect of the drug[47]. Identification of molecular interactions and binding positions on the protein-ligand complex (Figure 2) showed that the bonding gamma-mangostin in IKK-B resulted in non-covalent bond interactions consisting of Van der Waals, pi, hydrogen, and one unfavourable interaction. All the weak binding interactions produced by gamma-mangostin can contribute to the formation of stable ligand-protein complexes and initiate an inhibitory activity response in IKK-B.

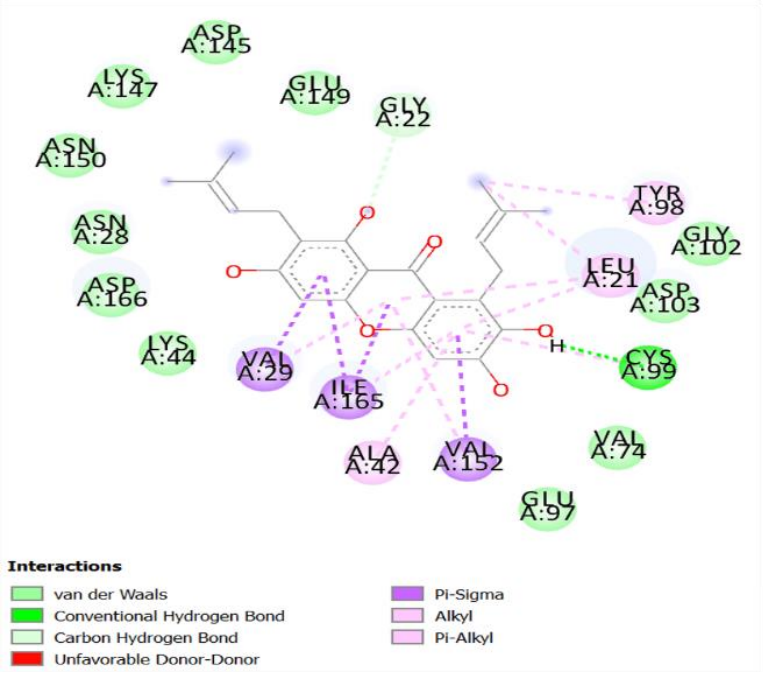

Figure 2. Positions and types of chemical bond interactions on IKK-B_gamma-mangostin

CONCLUSION

Gamma-mangostin from *Garcinia mangostana* L. are predicted to be anti-inflammatory agents, this compound can produce more negative binding affinity and weak bond interactions. This indicates the stability of the binding interaction that triggers the inhibitory activity. We recommend the IKK-B binding domain and gamma-mangostin from *Garcinia mangostana* L. for further research as a target for anti-inflammatory drug design and the results of this study are yet to be verified through wet lab analysis.

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