THE OPTIMIZATION OF α- MANGOSTIN AS A NEW DRUG CANDIDATE THROUGH MOLECULAR DOCKING AND DYNAMIC SIMULATIONS

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ABSTRACT

α-mangostin has a strong pharmacological effect in both in vitro and in vivo testing. It is examined by targeting several cellular targets with various mechanisms of action. Various approaches have been made to determine the efficacy of α-mangostin. One of them is a molecular modelling technique in which it alters the structure of a compound using the computational technique. This well-known technique is conducted through studies of molecular docking and Molecular dynamics as a part of new drug development. This review study aimed to show the role of the application of the molecular modelling approach of α-mangostin as a new drug candidate.

Keyword: *α* - Mangosteen, Molecular Docking, Molecular Dynamics, Drug Candidate

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INTRODUCTION

Mangosteen (*Garcinia mangostana*) is a fruit grown in tropical regions, such as Southeast Asia, India, and Sri Lanka. The pericarp (skin) of this fruit has been used empirically from time to time as a traditional medicine for some diseases treatment.[1]

Ever since ancient times, mangosteen has been known as hereditary medicine to cure chronic diarrhea, wound infections, skin infections, and dysentery. Several studies have been proved that mangosteen pericarp has a major compound of xanthone derivate that is α-mangostin This xanthone derivative has demonstrated a few pharmacological activities such as antifungal, antioxidant, antibacterial[2], anti-tumor, anti-inflammatory, and anti-allergic.[1,3,4]

Besides having pharmacological properties, α-mangostin also has several disadvantages such as low solubility and low bioavailability. Various studies have been conducted to determine the effects of α-mangostin both in vitro, in vivo and silico. This review explains the Molecular dynamic simulations and Molecular Docking as assisting α-mangostin as an inhibitor of some diseases.

Molecular Docking and Dynamic Simulations of α -Mangostin
α-Mangostin as Inhibitor α/β-Amyloid Aggregation

Alzheimer, a neurodegenerative disease, is caused by the plaque in the intraneuronal neurofibrillary tangles, neurons and synapses degradation and extracellular senile in the brains of a person with the disease. The β-amyloid peptides (αβ) consist 39-43 residual amino acids is the main constituent of amyloid plaques that is crucial to the neuropathogenesis of Alzheimer's disease.[5] A structure of αβ*/β-Amyloid Aggregation* was taken from Protein Data Bank (PDB) with ID: 1BA4.[6] The structure of α-mangostin, novel breast cancer drug, was docked to αβ-*amyloid*. α-mangostin as the potential molecule comprising antagonist properties toward hERα. α-mangostin is the active secondary metabolite primarily derived from the pericarp part of *Garcinia mangostana* containing antiproliferative properties associated with suppression of tumor growth; it inhibits the proliferation of MCF-7 cell lines through inhibiting of hERα activity.[7] Anti-proliferative activity of α-mangostin against MCF-7 cell lines observed with IC_{50} by 20 μg/mL.[8] The IC_{50} value observed was categorized in the less active category ranging from 10 to 100μg/Ml.[9] Thus, this study was performed to modify the α-mangostin as a parent structure and investigated its molecular interactions to enhance its antagonistic activity toward hERα through molecular

docking and molecular dynamics simulation utilizing MOE's (Molecular Operating Environment) automatic docking algorithm was used. The top thirty poses from α-mangostin were determined over the conformational search, and further the all poses were docked into a receptor where the grid box was set due to binding site evaluation and energy minimization. The binding mode result was determined from the superior ligand pose. Based on the results, it has been found the potential energy and interactions between ligand and receptor. MOE was employed in this study that gives hydrophobic surfaces and a diagram of the interaction between the ligands and the receptors. Molecular Dynamics (MD) of complex α-mangostin and αβ helix was achieved at 20 ns using the Amber v.11on GPU-based workstations produced by Hewlett-Packard, USA. The general model in macromolecular simulations is preferred to water. During the simulation, the temperature was set at 300K and the cut-off distance was set at 12 Å. During the minimization phase and simulation, the ff99SB force field was set as the force field for this simulation. As polyphenols, α-mangostin has a similar effect to curcumin and resveratrol as in neuroprotective effects by leading the conformation of β-helix and a transition conformation between α-helix and β-sheets.[7] Thus, it retains αβ on a conformational α-helix. Firstly, the molecular docking analysis is performed in the PDB complex of 1BA4, 13-40 residues were obtained and conservatively estimated form with α-helix. Therefore, the helix αβ includes 13-40 residues were used in docking analysis.

α-mangostin interacts with the helix αβ through the hydrophobic surface. The phenolic hydroxyl group α-mangostin forms a hydrogen bond with some amino acid residue (Lys16 and Asp23 of αβ with bond length 2.68 Å and 2.29 Å). Phe19 of αβ has pi-pi cation interaction (3,45 Å) with the aromatic ring of α-mangostin. This molecule interacts with Glu22 of αβ. The binding energy of α –mangosteen with the α-helix conformation of αβ is -68.76 kcal/mol. Molecular docking result provides information about molecular interactions and direct interactions between α-mangostin and αβ-amyloid at the level of atomic. To learn more about the α-mangostin function in the interaction, MD simulations were performed. RMSD of αβ helix spine is calculated to show the entire process of conformation changes in the helix. The RMSD plot shows severe conformation variations in a short period.[8]

RMSD for αβhelix is highly fluctuating. The fluctuation of the RMSD plot starts within 3 Å until 8 Å for 7ns, and also within 6 Å until 10 Å for 13 ns. It showed that the changes of conformation of helical αβ are still in a steady-state or unstable for 20 ns of MD simulation. As for the α-mangostin and αβ helix complex, RMSD starts at 3Å and reaches the equilibrium state at 8 Å, and 7 ns after MD simulation. The softer plot of the complex shows that the complex has a more stable conformation than helical αβ. On the other hand, the hydrogen bond analysis of the simulated pathway of MD shows that hydrogen bonds are stable at α-mangostin and Glu22 (Glutamine), also Asp23 and helical αβ. MD simulation and molecular docking result showed that α-mangostin binds to αβ strongly, which shows stabilized conformations, indicating that α-mangostin may disrupt with αβaggregation. 3D structure of fibrils αβ (PDB ID: 2BEG) showed before [9]. αβ represents a-b-strand turn into b-strand consisting of two intermolecular, b-sheet registers by 18-26 residual amino acids (b1) and 31-42 residual amino acids (b2. The structure-activity relationships study shows that every efficient polyphenol inhibitor at least consists of two phenolic rings containing at least two to six atomic connectors and three hydroxyl groups in an aromatic ring. It is central to the inhibition of fibrils by strengthening hydrophobic interactions between aromatic rings with a β-sheet structure by hydrogen bonding.[10] According to the molecular docking results in the study, the corresponding form of two molecules makes the α-mangostin feasible to fall into αβ binding site, hydrophobic interactions between Phe19 amino acid residue of αβ and α-mangostin aromatic ring, and enhancing the formation of hydrogen bond interactions between amino acid residues of Lys16, Glu22, and Asp23 of the hydroxyl group αβ and phenolics of α-mangostin. It can be seen that α-mangostin is also polyphenolic inhibitor. The RMSD value of the MD simulation is generally used as an indicator of the conformation variation from the structure to the equilibrium phase in comparison to the library confirmation.[11] The MD simulation further demonstrates a smooth movement of RMSD change from helical αβ when the complex compounds with α-mangostin as compared to αβ alone, thereby indicating that α-mangostin is attached to the αβhelix as expected, resulting in the more stable conformation of the αβ. There is stable hydrogen bond interactions between Glu22, Asp23, and α-mangostin. The hydrogen bond between α-mangostin and Lys16 that is absent in MD simulations can persist, thus stabilizing helical

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αβ, may be short-lived as the hydrogen bonds examined in the MD simulation should be at least 5% of the total life span. Natrium or Sodium connecting Asp23 and Lys28 is crucial to the process of fibrils αβ growth. Blocking the salt bridge formation stabilizes the helical αβ and restrains the fiber growth process of αβ.[12] Despite some differences, the docking result is validated by these data. The hydrogen bond between α-mangostin and Asp23 can inhibits the sodium bridge between Asp23 and Lys28. Another interaction among helical αβ and α-mangostin can stabilize the complex. Thus the researcher hypothesizes that the binding of α-mangostin to αβ ends up in the lack of nucleation competent core formation, thereby inhibiting and separating aggregation of αβ. Still, *in silico* energy docking and MD simulation results are only of the estimated activity indicators, hence it needs further research to explain more precisely the mechanism. α-mangostin is generally acknowledged as an effectual antioxidant and ROS scavenger.[13] Although the researchers demonstrate their anti-amyloidogenic properties, the anti-oxidants effects of α-mangostin cannot be completely excluded in their neuroprotective properties against oligomers αβ. Nonetheless, α-mangostin shows ROS flushing properties in the level of micromolar[4,14], which is much higher than the molar nanoscale concentration used in the present study. On top of that, undetectable oxidative species in the neurons dealing with oligomers αβ (data are not provided) that resonates with the previous studies show that oxidative stress properties of the αβ are not involved in its oligomeric cytotoxicity of αβ.[15] Therefore, the effect of α-mangostin anti-neurotoxicity on αβ oligomers significantly depends on the direct dissociation of oligomers αβ. In this research, it is apparent that α-mangostin has strong protection against the neurotoxicity caused by αβ aggregates as a toxic form. The involving mechanism can be linked to its ability in redirecting the toxic αβ cascade by separating its oligomers accumulated with the β-sheet-rich and fibrils of the later stages, and the fibril formation inhibition. α-Mangostin is a fat-soluble molecule (<600 Da) with a possibility to pass the barrier of the central nervous system,[16] thus it holds potential as a treatment for patients with Alzheimer's disease.

α -Mangostin against MRSA As An Outcome of Membrane Targeting
The molecular interaction model of the α-mangostin and the model of the bacterial membrane using water as solvent water was simulated into the molecular docking and examined using molecular dynamics (MD). Even though the composition of lipids from different bacterial membranes varies, the main component of the membrane is POPE (1-Palmitoyl-2-oleoyl-sn-glycerol-3-phosphoethanolamine) and POPG (1-palmitoyl-2-oleoyl -n- glycerol-3-phosphoglycerol).[17] As result, this study uses 128 mixed lipids with a scale of POPG : POPE in a comparison of 3 : 1 to depict and draw a common membrane model [17]. Lipid molecules and α-mangostin is model using the strengths column of Gromos53a6 [18,20], while solvent-soluble molecules use the SPC model.[21] The parameters of α-mangostin are made by the Topology Builder column (ATB).[22] Two simulations using a molecule of α-mangostin, similar α-mangostin in high concentration. Within those simulations, a randomized α-mangostin molecule is attached to the membrane model of the bacteria. Subsequently, the system is dissolved with 7200 molecules of water and neutralized with sodium ions. Before MD simulation production phase, the system is composed of 500 times minimizing energy by employing steep linear algorithms, set up at 10 NVT simulations. The simulation of MD ns 250 can be finished in that case, which corresponds to different α-mangostin concentrations. To add a conformation sample of α-mongostin at a specific range from the center of the bilayer, a series of determining distance simulations was performed by overcoming the distance between a bilayer center and an α-mangostin; the process relied on a program named gromacs pull module. During all the process of MD simulations, 1.2 nm distance was utilized for two kind interactions consist LJ and real space electrostatic, and the algorithm of Ewald-particle mesh was utilized for calculating the interactions of long-distance electrostatic in the repeated space. The method of Nose-Hoover was applied to keep the target temperature at 310°K. The Parrinello-Rahman method with a mode of semi-isotropic coupling was then applied in keeping up the pressure at 1 atm in the gamma NPT.[23] To understand membrane disturbance at the atomic level, the author uses MD simulation to provide information about α-mangostin membrane penetration pathways using bacterial membrane models. They determine the penetration of α-mangostin into POPE / POPG (75/25) bilayers using simulations of all MD atoms. The observation of the absorption of molecules in the membrane was performed once α-mangostin was placed in the membrane. In the ratio of low drug/lipid (1/128).[24]

The distance between lipid bilayers and α-mangostin is changed to 100 ns but reaches 1.5 nm equilibrium, which indicates that α-mangostin could get toward lipid bilayer immediately, located under the group of lipid molecule heads. In addition to α-mangostin molecules, some α-mangostins penetrate the bacterial membrane at the lower region that is modeled above the simulation.[24]

It is accompanied by a disorder of the membrane-defective integrity (filled with water molecules) because of α-mangostin's hydrophobic interaction and bacterial membrane enhances the permeability of bacteria lipid membrane and also helps the penetration process of α-mangostin. Moreover, it also accommodates hydrophobic interactions between α-mangostin and lipid-tails part of phospholipid since α-mangostin can reach lower leaflets of lipid bilayers. The observation indicates that membrane perturbation performed by the α-mangostin tends to amplify biophysical studies data and SEM results reported.[24]

The research showed that α-mangostin is at a different range from the center of the bilayer. In the process of penetration, the isoprenyl group, driven by hydrophobic interactions, incorporates the hydrophobic area of the membrane. After that α-mangostin is induced by the entropy as the long axis is swirled with lipid tail.[13]

Molecular dynamics simulation shows that a strong α-mangostin hydrophobic association with an alkyl lipid chain is a powerful boosting for α-mangostin's penetration. The isoprenyl group is bound to xanthone structure as a short lipid tail that is found, thus triggering the penetration toward hydrophobic area of the membrane. Specifically, it could be stated that the isoprenyl group has a function to lower the free energy barrier from penetration. On top of that, the presence of the isoprenyl group improves hydrophobicity of α-mangostin, thereby increasing the possibility to split into membranes. Altogether, the isoprenyl groups produce stronger antibacterial properties. The result shows that hydrophobicity of α-mangostin is more soluble by hydrophobic lipids. Less than one isoprenyl group contained in SZ-1 region and SZ-5 region has lower anti-microbial activities as a free energy barrier to the penetration of great bacterial membranes. The results also correspond to the new reports which indicate that at least two isoprenyl groups that conjugate with xanthone scaffolding are essential for conducting strong antimicrobial properties.[1,2] Besides, during the simulation, it is found many water defects. Regardless of the inactivity of some defects, some disabilities develop into the translocation of water through the membrane. In the long-term, higher permeability can also cause large molecules to spread across membranes that cause intracellular components leakage. It is certain that a forceful α-mangostin affinity for the hydrophobic chain in the alkyl group, produces packing density and integrity, thus forming intracellular components leakage. MD simulations and biophysical studies reveal a rapid disruption of the integrity of internal membrane bacteria as the main rider of the cell even though α-mangostin is renowned for its interaction with the precursor of transmembrane proteins through hydrogen bonding.[8] An observation should be taken regarding the coefficients of the α-mangostin partition using the High-Performance Liquid Chromatography (HPLC) method following guidelines of OECD for chemical testing[25] in supporting the role of α-mangostin hydrophobic interaction in the membrane of bacteria. The log P value of the given α-mangostin is 6.4, signifying a strong hydrophobic property of α-mangostin and explaining the strong tendency to split into bacterial membranes through hydrophobic interactions. On that ground, the current data draws that hydrophobic interaction is very important for harmful bacteria. In conclusion, this study shows that bacterial membrane layers are the main target for α-mangostin activity towards Gram-positive bacterials. α-Mangostin is straightforwardly extracted from common tropical fruits. The indications of α-mangostin cause membrane disorders and intracellular content leakage in five to ten minutes. The α-mangostin hydrophobic associations with lipid membranes cause membrane deformation and water molecule diffusion across the membrane. On the other hand, the resistance is not created in laboratory simulations utilizing MRSA and *E. faecalis*. Further, α-mangostin is more effective against bacterial cell membranes rather than mammalian cell membranes in MIC and bacterial concentrations. These outcomes claim that α-mangostin, as a basic-structure molecule, is a potential object for further studies and development.

α -Mangostin against Estrogen As An Outcome of Breast Cancer Targeted

Of the common cancers among women in Asia is breast cancer. The prevalence of breast cancer has seen a steady rise over the past decades.[26] Based on data GLOBOCAN (IARC) in 2012, cancer causes the

death of about 8.2 million people. Cancer rates are expected to increase annually and, by 2030, are expected to reach 23.6 million new cases per year.[27] As based on several experiments and clinical and epidemiological evidence, the development and progression of breast cancer are heavily determined by ovarian hormones; these hormones are central to the normal breast tissues' growth and differentiation.[28] Estrogens function in enhancing the growth in estrogen-responsive target tissues, including the breast. For this reason, estrogens are the risk factor for developing cancer. Studies have examined different non-steroidal compounds other than estradiol (the natural ligand, including tamoxifen;[29] the results reveal that the compounds have different effects as agonists or antagonists; this is determined by the particular organ system or gene.[30] ERα is a ligand-activated transcription factor; its functions are crucial to many tissues and it is also significant to the etiology of breast cancer.[31,32] Considering that ERα is essential for treating and preventing breast cancer, numerous molecules have been designed to bind ERα and evoke distinct pharmacological profiles. Hence, it is essential to examine compounds of natural products that serve as antagonists of estrogen in breast tissue and as agonists in bone and cardiovascular tissues.[3] Other than estradiol (the natural ligand), various nonsteroidal compounds, including tamoxifen[29], have been studied. The compounds have different effects as agonists or antagonists; it depends on the particular organ system or gene.[30]

ERα refers to a ligand-activated transcription factor with key functions to many tissues and the etiology of breast cancer.[31, 32] Various molecules have been designed to bind ERα and elicit distinct pharmacological profiles given that ERα is essential in the treatment and prevention of breast cancer. Hence, it is of paramount importance to identify compounds of natural products that act as antagonists of estrogen in breast tissue and as agonists in bone and cardiovascular tissues.[3]

In the antagonist mechanism of estrogen, the restrained Helix-11 would forceHelix-12 to be set in the "mousetrap" like no other preferable (antagonist) conformation is found on the surface of the hERα ligand-binding site. The network zipping H3 and H11 in estrogen stabilized conformation of agonists. This zipper network proves that H12 is set in the "mousetrap", and consequently, it is unable to get into the antagonist position on the hER LBD surface when H11 is prohibited to relax. However, this network zipper is lost once an antagonist (4-OHT) is placed[33]. Mechanism of natural product compounds against human estrogen is studied by Muchtaridi et al.[13,33,35] As anti-breast cancer, α-mangostin serves as an anti-proliferative associated with inhibiting the growth of breast cancer cells MCF-7 through a reduced function of hERα receptors (most common breast cancer subtype).[36] Apoptosis of cancer cells is induced by α-mangostin through mitochondrial pathways and Aktdephosphorylation on the breast cancer cell. α-mangostin inhibits invasion also an exodus of cancer cells in the breast gland. MCF-7 adenocarcinoma cell apoptosis is inhibited by α-mangostin thus it shows as an anti-proliferative activity with an IC_{50} value of 20 Mm.[37, 38]

It is essential to examine the molecular interactions and the pharmacophore-fit of alpha mangostin and its derivatives with estrogen receptor α (ERα) using molecular docking simulation and pharmacophore modeling approaches. This is to find out the new anti-breast cancer.[39]

CONCLUSION

Mangosteen has been used for the treatment of many diseases empirically from year to year. Besides, much research proves that the compound from mangosteen called α–mangostin is effective in use for disease treatment in animal testing. The structure α–mangostin that has phenolic rings, proves that α–mangostin could penetrate the lipid membrane of bacteria. Furthermore, all of the different possesses of α-mangostin in molecular modeling is a potential candidate for a new drug. In the end, it is expected that this research can open up new avenues to find and design a new drug candidate or contributes to further development and studies.

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