Potential Role of Mitragynine as Lipolysis Stimulator

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Original Article

Potential Role of Mitragynine as Lipolysis Stimulator via Adrenergic Signalling: Docking Model Study

Khoirul Rista Abidin[1,2], Ronny Lesmana[3,4]*, Mas Rizky Anggun Adipurna Syamsunarno[4], Kelana Kusuma Dharma[5]

ABSTRACT

Backgrounds: Mitragynine is the most popular of the more than 50 alkaloids contained in *M.Speciosa*. In particular, the Mitragynine alkaloid has the potential to increase lipid (fats) metabolism through specific pathways such as adenylyl cyclase signaling *via* adrenergic receptors. In this case, Asp Amino acid and Ser are the types of residues that can activate adenylyl cyclase to initiate a series of activities in cells. **Methods:** This study used Mitragynine ligand and adrenergic receptors (α1b, α2a, α2b, α2c dan β1). The receptor candidates were tested using Autodock whose test results were presented in the form of tables and 3-dimensional images using the Biovia Discovery Studio. **Results:** Hydrogen bonds were formed between Mitragynine and the amino acids Asp and Ser at the β1-adrenergic receptor. The binding amino acids were found in Ser20 and Asp21 with energy bond of -5.26 kcal/mol and IC50: 111.35 ppm. Meanwhile, at the adrenergic receptor α2b there was only Asp residue that formed hydrogen bond with Mitragynine namely Asp218A. The energy bond formed between the two was -5.19 kcal/mol and IC50: 125.04 ppm. **Conclusion:** Mitragynine has the potential to stimulate lipolysis through the pathways of α2b and β1-adrenergic receptors.

Key words: Mitragynine, Adrenergic, Docking, Lipolysis.

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INTRODUCTION

Mitragyna Speciosa (*M. Speciosa*), known as Kratom, contains more than 50 alkaloids, and Mitragynine is the most popular alkaloid.[1] Various studies have investigated that Mitragynine contains alkaloid properties that provide analgesic and anti-inflammatory effects. A study by Matsumoto *et al.* explained that the analgesic effect of Mitragynine is produced through the induction of antinociception in the brain and involves part of the supraspinal opioid mechanism.[2] While the anti-inflammatory effecting of Mitragynine is produced by reducing COX-1 and 2 expressions.[3] For this reason Mitragynine is grouped into the opium group. In general, it is used to reduce pain through the opioid receptor pathway.[4] The opium long-term intake in the body can also decrease weight in its users.[5] Thus, the use of opium is applied to treat obese patients in weight loss therapy.[6] Several related studies have previously described the mechanism of action of opium use, which is through stimulation of the mesolimbic dopamine pathway that reduces appetite.[5]

Losing weight can also be optimized through other means, one of which is increasing fat metabolism.[7] One possible pathway associated with this process is through adrenergic signaling. Adrenergic receptors can be divided into two types such as α and β-adrenergic receptor. Stimulation of β-adrenergic receptor will trigger lipolysis activity and inhibit lipoprotein lipase enzyme activity. The stimulation of α-adrenergic receptor will inhibit the mobilization of fat cells.[8] Meanwhile, the stimulation pathway of β-adrenergic receptor toward the lipolysis process occurs in adipocyte which is connected to the activation of adenylyl cyclase, protein kinase (PKA) and triaglycerol lipase.[9] The stimulation of α-adrenergic receptor will also regulate the process of gluconeogenesis and cytogenesis through neurotransmitter hormones such as catecholamine. Hence, the induction of these pathways produces raw materials for energy needs when the body responds to stress.[10]

However, to be able to prove whether Mitragynine has the potential to regulate lipolysis requires a comprehensive study. It is believed that Molecular docking is an efficient method and worth employed in investigating the possible interaction between ligands and specific proteins.[11] Therefore, in this study, docking between Mitragynine and several adrenergic receptors was carried out in order to prove its potential in affecting the lipolysis process.

RESEARCH METHOD

Hardware

The hardware used in this research is a Central Processing Unit (CPU) computer equipped with an Intel(R) Core(TM) i7-10700 processor, @ 2.90GHz 2.90 GHz, 8.00 GB RAM. The operating system (OS) installed on the CPU is Microsoft Windows 10 pro.

Compound data settings

The code used for component of Mitragynine Alkaloid was Conformer3D_CID_303496, which was obtained through the National Center for Biotechnology Information (NLH) (https://pubchem.ncbi.nlm.nih.gov/compound/611919).

The target protein receptors were obtained from the Research Collaborator for Structural Bioinformatics Protein Data Bank (RSCB PDB) (https://www.rcsb.org/).[12] In this study, the authors analyzed the energy

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Table 1: Model of binding and energy between mitragynine and adrenergic receptors.

Name of Target Protein	Free Energy of Binding, FEB (kcal/mol)	IC50 (ppm)	Hydrogen Bond	Hydropobhic Interaction
β1- Adrenergic	-5,26	111,35	Asn1A; Ser20A*; Asp21A*	Trp3A
α2b-Adrenergic	-5,19	125,04	Arg41R; Asp218A*; Pro46R	Ile28A; Ala31A; Pro126R; Leu55B; Arg44R
α2a-Adrenergic	-4,34	528,6	Cys188A	Tyr394A; Phe390A; Phe391A; Phe412A; Val114A;
α2c-Adrenergic	-4,14	739	Glu1186B; Lys1190B; Glu1009B	Not detected
α1b-Adrenergic	-2,88	6.280,36	Not detected	Ile67A; Leu68A

*Amino acids that can potentially activate the adrenergic receptors

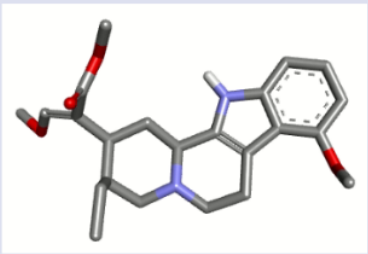

Figure 1: Mitragynine structure 3D, one of the alkaloids, *Mitragyna speciosa*, which was retrieved from https://pubchem.ncbi.nlm.nih.gov/compound/611919 (Conformer3D_CID_303496).

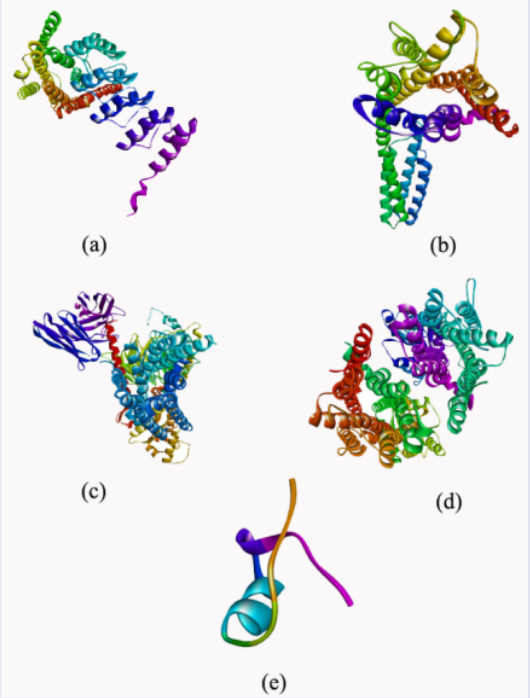

Figure 2: Molecule Structure (a) α1b- adrenergic (PDB ID 7b6w; DOI: http://doi.org/10.2210/pdb7B6W/pdb); (b) α2a- adrenergic (PDB ID 6kux; DOI: http://doi.org/10.2210/pdb6KUX/pdb; (c) α2b-adrenergic (PDB ID 6k41; DOI: http://doi.org/10.2210/pdb6K41/pdb); (d) α2c- adrenergic (PDB ID 6kuw; DOI: http://doi.org/10.2210/pdb6KUW/pdb); (e) β1-adrenergic (PDB ID 2lsq; DOI: http://doi.org/10.2210/pdb2LSQ/pdb).

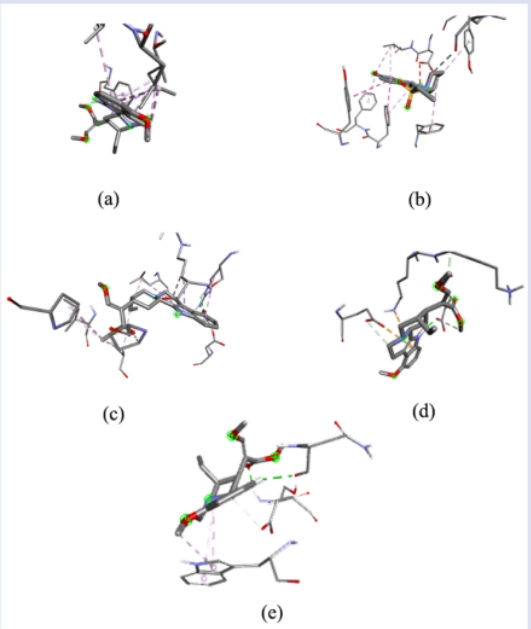

Figure 3: Interaction docking results 3D (a) Mitragynine and α1b- adrenergic (b) Mitragynine and α2a- adrenergic (c) Mitragynine and α2b- adrenergic (d) Mitragynine and α2c- adrenergic (e) Mitragynine and β1-adrenergic.

bond between Mitragynine and several adrenergic receptors that have the potential to regulate lipolysis ((α1b, α2a, α2b, α2c and β1).

Prior to docking, receptor preparation was carried out using the Biovia Discovery Studio version 4.0 application (Accelrys, Inc., USA). The receptors which were downloaded from the RSCB PDB website were then cleared from unneeded water molecules and ligands. Afterwards, the receptor groups were then docked with Mitragynine using Autodock 4.2.6 software.[13]

Molecular docking

Receptor files and ligands to be docked were prepared using AutoDockTools (ADT) version 1.5.6 Sep_17_14. A grid map with a size of 60 x 60 x 60 was placed at the center on the ligand and receptor. The search for ligand conformation was carried out by adding the *Lamarckian Genetic Algorithm* (LGA) and the docking process, which was run within 1000 repetitions.

The results of the docking conformation were then learned based on the values of energy binding, which were sorted by cluster from the smallest to the largest energy binding values. In this regard, the lowest energy

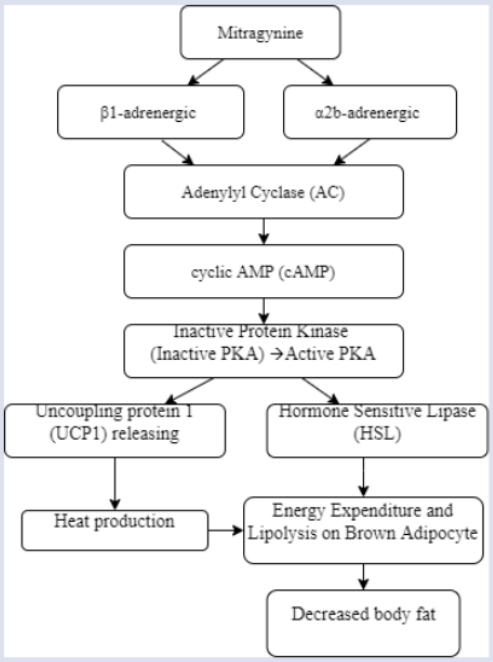

Figure 4: The prediction of lipolysis pathway in brown adipocyte is stimulated by mitragynine *via* α2b-adrenergic receptor and β1-adrenergic. Both activated adrenergic receptors will then activate adenylyl cyclase pathway.

conformation was chosen as the most optimal binding conformation. The energy conformation was translated in the form of Free Energy Binding (FEB) with the units of kcal/mol and the estimated inhibition constant value (Ki).[10] The final result of total energy was expressed in a unit of IC50 (ppm). The intermolecular interactions were then reanalyzed using Biovia Discovery Studio 4.0. Other parameters were presented in the forms of energy bond such as hydrogen bonding and hydrophobicity. The docking results that did not show the inhibition values were not included in the subsequent analysis.

RESULTS

The results of energy calculations and amino acid binding between Mitragynine and adrenergic receptors are presented in table 1. Meanwhile, the interaction between them is presented in 3-dimensional images (Figure 3). In this study, the hydrogen binding between Mitragynine and amino acid Asp and Ser occurred in β1-adrenergic receptor. The binding amino acids occurred in Ser20 and Asp21 with energy binding of -5.26 kcal/mol and IC50: 111.35 ppm. While in the α2b-adrenergic receptor there was only Asp residue that formed hydrogen binding toward Mitragynine, which was Asp218A. The energy binding occurring between the two molecules was -5.19 kcal/mol and IC50: 125.04 ppm.

DISCUSSIONS

Asp residues on adrenergic receptors have the potential to activate receptors when initiated by all ligands.[14] Specific amino acids that have the potential are Asp121, Ser211 and Ser215.[15] Therefore, the results indicate that Mitragynine can potentially activate β1 and α2b-adrenergic receptors.

The lower the energy is, the more stable the complex is formed between the ligand and the receptor.[16] Adrenergic receptors can naturally be activated by catecholamine ligands (epinephrine and norepinephrine).[17] Ligand bindings toward serine (Ser), at least S208 and S211, play an important role in the activation of β1-adrenergic receptor.[18] Another study also explained that the amino acids Aspartate (Asp) and Ser belong to residue types that can activate adenylyl cyclase initiating a series of activities in cells.

Lipolysis process carried out *via* the adrenergic pathway through β1-adrenergic receptor begins with the activation of adenylyl cyclase (AC). This is normally mediated by catecholamine hormones against adrenergic receptors. AC activation then induces cAMP. The role of activated cAMP is to convert inactive PKA to active.[19] This will then induce *Sensitive Lipase Hormone* (HSL) to carry out the lipolysis process in adipocytes.[20] Other studies also support that AC activation by β1-adrenergic will initiate a series of specific fat breakdown processes in the adipocytes brown adipose tissue.[21] The regulatory pathway of lipolysis by Mitragynine is briefly depicted in figure 4 as follows.

Another process that can result from the activation of β1 is the production of thermogenesis. The stimulation of β1-adrenergic receptor plays an important role in maintaining body-heat during cold exposure by increasing cAMP activity and activation of brown adipose tissue.[22] The heat that arises is part of the work of uncoupling protein 1 (UCP1) as a thermogenic protein located in the inner mitochondria of adipocytes. These proteins have the ability to separate proton gradient potentials through a series of electron transports.[23] Meanwhile, several studies have shown that thermogenesis is mostly produced through the activation of β1 and β3-adrenergic receptors. Both work by targeting UCP1 as an intermediate protein. However, what distinguishes them is the limited receptor quantity of β3-adrenergic receptor compared to β1-adrenergic receptor with a percentage ratio of around 9:28, and the rest is β2-adrenergic receptor.[23] Thus, β1-adrenergic receptor will have a greater role in the activation of thermogenesis process when stimulated by ligand activators. Especially, the resulted thermogenesis will eventually result in the reduction of the amount of fat in body.[24]

If adrenergic receptors are stimulated by Mitragynine in large quantities, the possibility of thermogenesis production in the body will be maximized. This is in line with the simultaneous production of thermogenesis during exercises.[25] Thus, the development of studies through *in vivo* is needed to prove that Mitragynine can positively activate adrenergic receptors.

CONCLUSION

Based on the results of this study, Mitragynine has a stronger interaction with β1 and α2b-adrenergic receptors. Therefore, it can be concluded that Mitragynine has the potential to stimulate lipolysis through adrenergic receptors which will then activate adenylyl cyclase. However, further studies such as *in vivo* are needed to prove whether Mitragynine can stimulate the activity of these two adrenergic receptors. This study can be an additional reference to understand the potential of Mitragynine as a stimulator of lipolysis.

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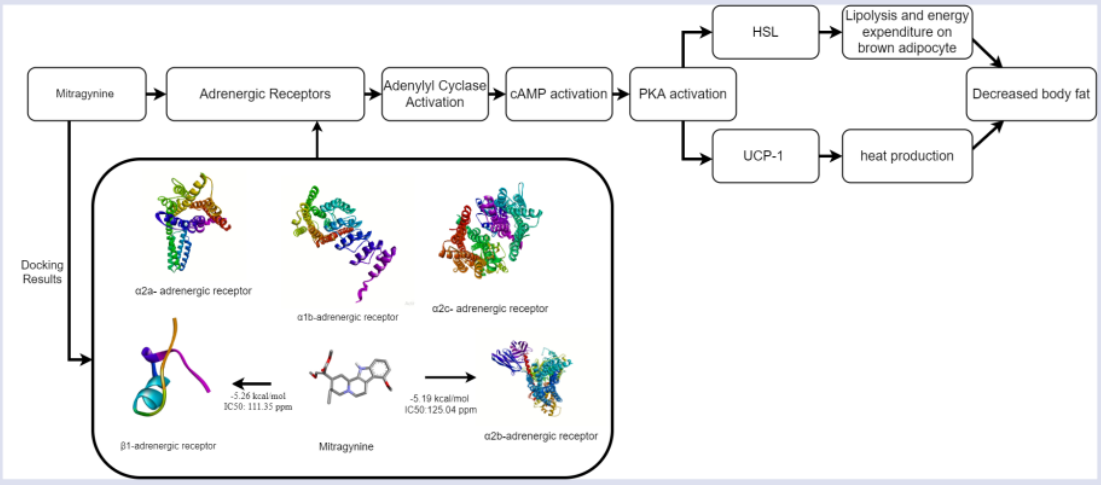
GRAPHICAL ABSTRACT



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