Original Article

Analgesic Serotonin from Banana Fruit (*Musa paradisiaca*) on Serotonin 1 b (5-HT1b) Receptor Protein *In Silico*

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ABSTRACT

Serotonin analgesics from banana (Musa paradisiaca) fruit have been investigated to determine potential interactions with serotonin 1 b (5-HT1b) receptors at the molecular level. The study utilized an *in silico* approach to predict the interaction between serotonin analgesics and receptor proteins. The research method involved the use of Pymol, MOE 2015, Discovery Studio, and Lipinski Rule software. The use of Pymol and MOE was used for visualization of the molecular structures of serotonin analgesics and receptor proteins. Discovery Studio was used to analyze the interaction between serotonin analgesic and receptor protein, which revealed the presence of binding between the two with Binding Affinity of -5.1297 and -11.1061 and RMSD of 1.7373 and 3.7057. In addition, analysis by Lipinski Rule revealed the molecular characteristics of the serotonin analgesic, including a mass of 196, no hydrogen bond donor, two hydrogen bond acceptors, a log P of 3.023, and a molar reactivity of 56.390. These results demonstrate the analgesic potential of serotonin in interacting with serotonin 1 b (5-HT1b) receptors, which may form the basis for further research in drug development related to serotonin-based pain treatment.

Introduction

Bananas (*Musa paradisiaca*) have long been one of the most popular and widely consumed fruits around the world. In addition to its great taste and nutrient-rich content, bananas have also been recognized for their potential health properties. One of the components of interest in bananas is the analgesic serotonin [1-3].

Serotonin is a neurotransmitter that plays an important role in regulating various neurobiological and physiological functions in

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humans. One of the known types of serotonin receptors is the 5-HT1b receptor. This receptor is mainly found in the brain and is a target for the treatment of various neurological and psychiatric disorders, including pain and depression [4, 5].

Pain is one of the most common health problems experienced by humans. The development of effective and safe analgesics is a major focus in pharmaceutical research. One promising approach is through the interaction between serotonin analgesics and serotonin 1 b (5-HT1b) receptor proteins [6, 7]. Banana fruit (*Musa paradisiaca*) is known to contain serotonin compounds that have potential as analgesics. Therefore, this study aims to understand the molecular interaction between serotonin analgesics derived from banana fruit and serotonin receptor protein 1 b (5-HT1b) in silico [8-10].

Research into serotonin analgesics and interactions with serotonin 1 b (5-HT1b) receptors is still in its infancy. Some previous studies have shown that serotonin compounds have potential as analgesics, and banana fruit (*Musa paradisiaca*) is known to contain significant amounts of serotonin [11-13]. *In silico* approaches using software such as Pymol, Molecular Operation Environment 2015.10 (MOE 2015), Discovery Studio 2016, and Lipinski Rule can provide insights into the molecular interactions between serotonin analgesics and receptor proteins, which could pave the way for new drug development in serotonin-based pain treatment [14-16].

The novelty of this study is the use of an *in silico* approach to study the interaction between banana-derived serotonin analgesics and serotonin receptor protein 1 b (5-HT1b). In the context of analgesic development, previous studies have identified the analgesic potential of serotonin and serotonin content in banana fruit [17-18]. However, this study combines an *in silico* approach with the use of software such as Pymol, MOE 2015, Discovery Studio 2016 and Lipinski Rule to analyze molecular interactions in depth [19-21].

The contribution of this study is to provide a more comprehensive understanding of the analgesic potential of banana-derived serotonin and its molecular interactions with serotonin receptor protein 1 b (5-HT1b), which can serve as a foundation for the development of more effective and safe serotonin-based pain medications [22, 23]. This study aims to understand the molecular interactions between serotonin analgesics derived from banana fruit and serotonin receptor protein 1 b (5-HT1b) *in silico* to identify their analgesic potential and provide new insights in the development of serotonin-based pain medications.

Experimental

Materials and Methods

The research method used in this study consists of several stages. The initial stage is molecular data collection. The molecular structure of serotonin analgesic from banana (*Musa paradisiaca*) is obtained from reliable literature sources or molecular synthesis can be done using software such as ChemDraw (https://www.cambridgesoft.com/Ensemble_for_Chemistry/ChemDraw/). Data on serotonin receptor protein 1 b (5-HT1b) can be obtained from protein databases such as Protein Data Bank (PDB) (https://www.rcsb.org/) using the appropriate PDB code [24-25].

The next step is visualization and analysis of the molecular structure. Pymol (https://pymol.org/) and MOE 2015 software can be used to visualize the molecular structures of serotonin analgesics and serotonin 1 b (5-HT1b) receptor proteins. This allows researchers to understand important conformations and structural features [26, 27].

Afterwards, molecular interaction analysis was performed using Discovery Studio 2016. This software can facilitate the modeling of the interaction between serotonin analgesics and receptor proteins. The results of the analysis will provide information regarding Binding Affinity and RMSD, which indicate the strength of the bond and the stability of the interaction between the two molecules [28-32].

The last stage is Lipinski rule analysis. Lipinski rule analysis is performed to examine the molecular characteristics of serotonin analgesics. Lipinski Rule software can be used to analyze factors such as molecular mass, hydrogen bond donor, hydrogen bond acceptor, log P, and molar reactivity. Using this method, researchers can gain a

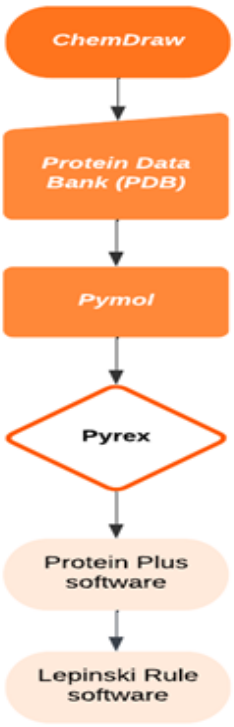

Figure 1. Flowchart research

deeper understanding of the molecular interactions between serotonin analgesics from banana fruit and serotonin 1 b (5-HT1b) receptor proteins, contributing to the interpretation of data and the development of more effective serotonin-based pain medications [33-35].

Results and Discussion

The results of this study involve several important aspects related to the molecular interaction between serotonin analgesics from banana fruit and serotonin receptor protein 1 b (5-HT1b). Molecular interaction analysis using Discover Studio 2016, this study successfully analyzed the interaction between serotonin analgesic and serotonin 1 b (5-HT1b) receptor protein. The results of this analysis revealed a binding between serotonin analgesics and serotonin receptors, which was reinforced by the Binding Affinity values found (-5.1297 and -11.1061). The docking conformation of dihydroergotamine has a hydrogen bond with Val201. On the other hand, no hydrogen bond was detected from Xanthone. However, due to the high value of RMSD (< 2 Å) on dihydroergotamine shows a poor dock conformation result [36].

This suggests that serotonin analgesics have the potential to interact with 5-HT1b receptors, which are important targets in analgesic drug development [37-39]. Table 1 indicates the molecular docking analysis result of Xanthone and ligand reference on 5-HT1b receptor protein. Analyzing molecular characteristics through Lipinski rule analysis using Lipinski Rule software, this study examined the molecular characteristics of serotonin analgesic. In this analysis, it was found that serotonin analgesic has a mass of 196, no hydrogen bond donor, two hydrogen bond acceptors, a log P of 3.023, and a molar reactivity of 56.390. These results provide a deeper understanding of the chemical properties and molecular characteristics of serotonin analgesics, which can be an important basis in the development of effective analgesic drugs [40, 41]. Molecular visualization analysis with the use of Pymol and MOE 2015 software allows visualization of the molecular structure of serotonin analgesics and serotonin 1 b (5-HT1b) receptor proteins. With the help of these visualizations, researchers can understand the conformation and relevant structural features. This visual analysis helps in understanding the interaction between the two molecules and gives a clearer picture of how serotonin analgesics can potentially bind to the 5-HT1b receptor [42, 43]. Table 2 presents the data from Lipinski and Figure 1 displays the interaction results of Serotonin and 4iaq.

Table 1. Molecular docking analysis result

Ligand	Binding Affinity (Kcal/mol)	RMSD (Å)	Hydrogen bond	Van der Waals interaction	Carbon hydrogen bond	Amino acid residue (hydrogen bond)
Dihydroergotamine (Ligand reference)	-11.1061	3.7057	1	16	1	Val201
Xanthone	-5.1297	1.7373	0	9	0	-

Not available

Table 2. Lipinski data

Mass	Hydrogen bond donor	Hydrogen bond acceptor	LOGP	Molar reactivity
196.000000	0	2	3.023299	56.390488

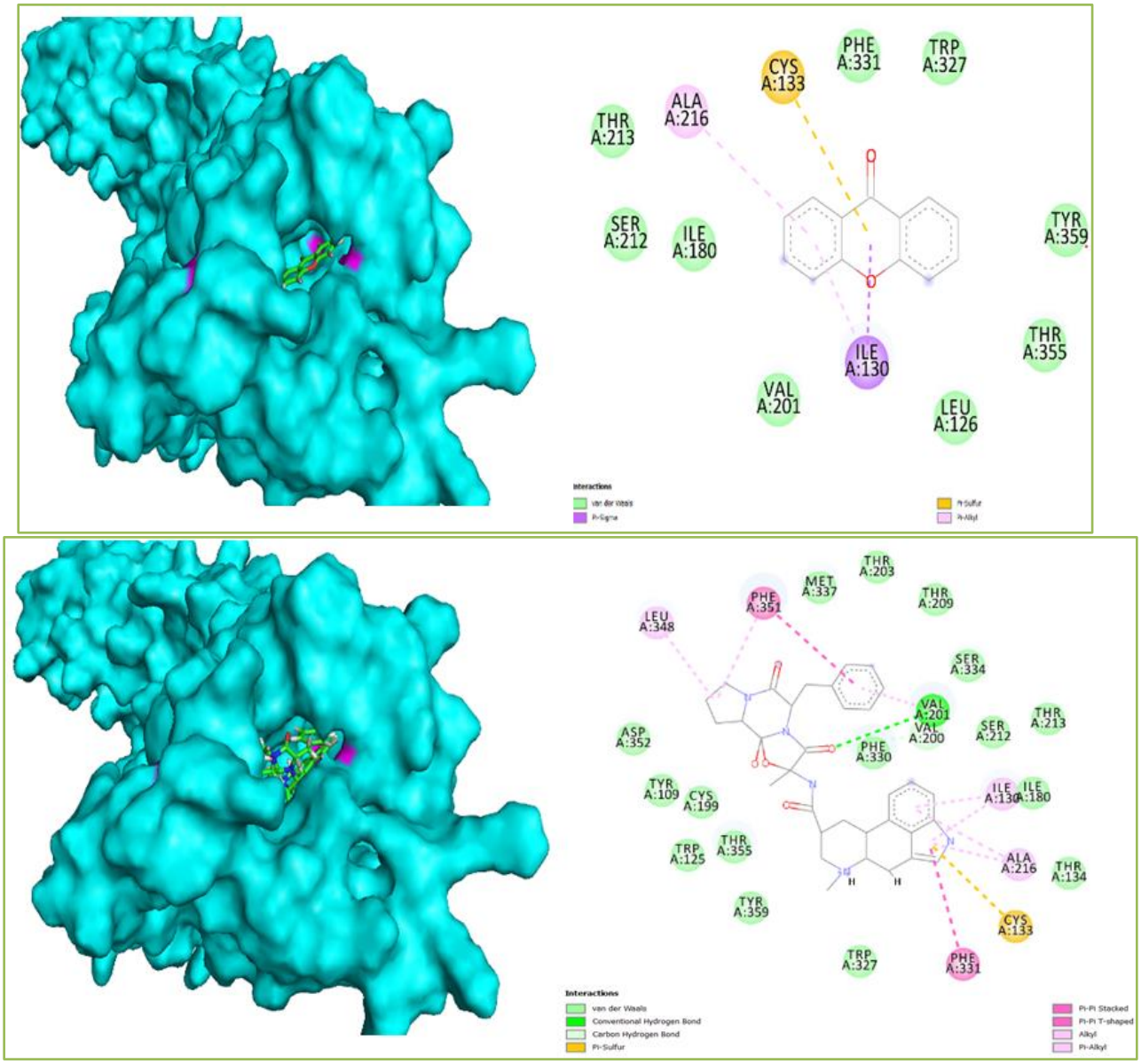

Figure 2. Xanthone (above) and dihydroergotamine (below) visual and interactions

Overall, this analysis provides valuable insights into the molecular interactions between serotonin analgesics from banana fruit with serotonin receptor protein 1 b (5-HT1b). These findings may make important contributions to the development of new serotonin-based analgesic drugs, with a better understanding of the molecular characteristics, interactions, and therapeutic potential of serotonin analgesics in pain relief [4-7].

The interpretation of this research led to an important understanding of the analgesic potential of banana (*Musa paradisiaca*) fruit-derived serotonin in binding to the serotonin 1 b (5-HT1b) receptor protein [2,6,10]. Using *in silico* approaches and software such as Pymol,

MOE 2015, Discovery Studio, and Lipinski Rule, this study revealed the presence of interactions between serotonin analgesics and receptor proteins, with Binding Affinity indicating significant binding strength. These results suggest that serotonin analgesics from banana fruit have the potential to function as pain-relieving agents through interaction with the 5-HT1b receptor [44, 45].

In addition, analysis of the molecular characteristics of serotonin analgesics showed that these compounds have physicochemical properties that conform to the requirements of the Lipinski rule, such as adequate molecular mass, optimal log P, and the presence of hydrogen bond acceptors that facilitate interaction with receptors. This suggests that serotonin analgesics from banana fruit have favorable pharmacokinetic potential to be developed as analgesic drugs [46, 47].

Overall, the interpretation of this research suggests that banana fruit has potential as a natural source of serotonin analgesics that can interact with serotonin 1 b (5-HT1b) receptors. This discovery provides an important foundation for continued research in the development of more effective and safe serotonin-based drugs in the treatment of pain. With a better understanding of the molecular interactions and molecular characteristics of serotonin analgesics, this research provides a valuable contribution in the search for better treatment solutions to address the pain problems that humans often face [48, 49].

Comparisons of this research from several perspectives and reviews can provide a deeper understanding of the contributions and uniqueness of this research. In terms of research methods, this research utilizes *in-silico* approaches and software such as Pymol, MOE 2015, Discovery Studio 2016, and Lipinski Rule. This approach enables efficient analysis of molecular interactions and molecular characteristics of serotonin analgesics. Compared to *in vitro* or *in vivo* experimental studies, *in silico* approaches have advantages in terms of cost and time, as well as allowing efficient preliminary testing before conducting further experiments. However, it is also important to remember that in silico findings need to be verified with actual experiments to validate the results [50-51].

This study shows the potential application of serotonin analgesics from banana fruit in the development of serotonin-based pain medications. These findings can serve as a foundation for the development of new analgesic drugs that are potentially more effective and safe. The utilization of natural sources such as banana fruit as a basic ingredient for analgesics can also be an attractive alternative in the pharmaceutical industry. However, further research is needed to understand the efficacy, bioavailability, and safety of serotonin analgesics from banana fruit before they can be used clinically [2,8,10].

In scientific terms, this study contributes to broadening the understanding of the molecular interactions and molecular characteristics of serotonin analgesics. Through the analysis of molecular interactions and characteristics, this study provides important insights into the potential and uniqueness of serotonin analgesics from banana fruit. These findings may encourage further research in the field of pain medicine development and enrich the scientific literature related to molecular interactions between serotonin analgesics and serotonin 1 b (5-HT1b) receptors (Figure 2) [6, 7,44].

Overall, this research has comparative value in terms of research methods, potential applications, and scientific contributions. In the context of serotonin-based analgesic drug development, this research provides an important contribution in understanding the molecular interactions and molecular characteristics of serotonin analgesics from banana fruit. However, further research and experimental validation are needed to strengthen these findings and encourage practical application in pain treatment [52, 53]. Figure 3 and Figure 4 demonstrate the Xanthone ligand and 4iaq protein.

The recent research on serotonin receptor 1B (5-HT1B) has provided significant insights into its structure and function, which can be compared with findings from previous studies. The study by Xu *et al.*, published in Nature, has revealed crucial details about the molecular underpinnings of 5-HT receptor activation and

modulation. This study highlights the importance of cholesterol in the function and organization of G Protein-Coupled Receptors (GPCRs), including the 5-HT1B receptor. Cholesterol was found to make direct contact with the receptor and contribute to the high affinity of ligands, indicating its vital role in receptor activity. In addition, the study discussed the importance of palmitoylation at the receptor's C-terminal cysteine residues for efficient signaling, pointing towards the synergistic effects of cholesterol and palmitoylation on receptor structure and function [54].

Another study focused on the crystal structure of the human 5-HT1B serotonin receptor bound to an inverse agonist, providing detailed insights into the receptor's structural aspects that facilitate drug binding and receptor modulation. The use of the fusion partner OB1 to improve crystallization was highlighted, showcasing the technical advancements in understanding receptor-ligand interactions at the molecular level. These findings underline the complex interplay of structural modifications and their impact on the receptor's pharmacological properties [54].

Comparing these findings with previous research underscores the evolution of our understanding of 5-HT1B receptors. The detailed structural insights from recent studies, such as those on cholesterol's role and the effect of palmitoylation and crystallization techniques, offer a more nuanced understanding of receptor function and its implications for drug development and therapeutic interventions. This represents a significant advancement over earlier studies that might not have had the benefit of such detailed molecular and structural insights [54].

The recent advancements in research on the serotonin receptor 1b (5-HT1b) have highlighted the intricate mechanisms of receptor activation and the structural basis for ligand recognition and receptor modulation. A study detailed the structural insights into the lipid and ligand regulation of serotonin receptors, focusing on the functional importance of specific interactions between lipids and G protein-coupled receptors (GPCRs). This research emphasized the role of membrane-lipid interactions in regulating GPCR dynamics and functions, with particular attention to how phospholipids like phosphatidylinositol 4-phosphate (PtdIns4P) enhance the activity of the receptor-G protein complex, acting as positive allosteric modulators. The study further explored the contribution of cholesterol to receptor activity, highlighting the need for additional experiments to understand its role in the structure of the ligand-binding pocket of 5-HT receptors (Signal Transduction and Targeted Therapy) [55,56].

Another study focused on the engineering of a BRIL fusion partner to facilitate the crystallization of the 5-HT1B receptor in complex with an inverse agonist. This research aimed to improve the diffraction quality of the crystals by optimizing the sequence of BRIL, introducing mutations to reduce surface entropy and enhance specific polar interactions. The study successfully obtained a crystal structure that provided insights into the receptor's ligand-binding affinity and the effects of specific mutations on crystallization efficiency (Cell Discovery) [54].

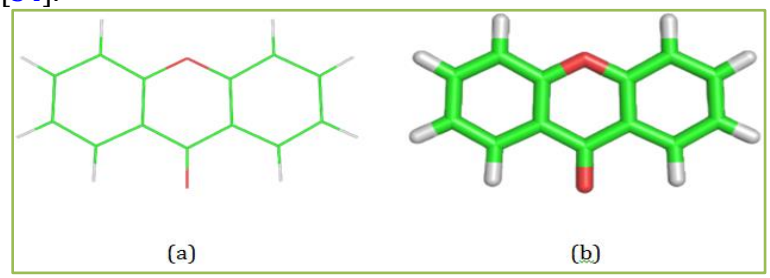

Figure 3. (a) 2D Visualization of xanthone ligand (b) 3D visualization of xanthone ligand

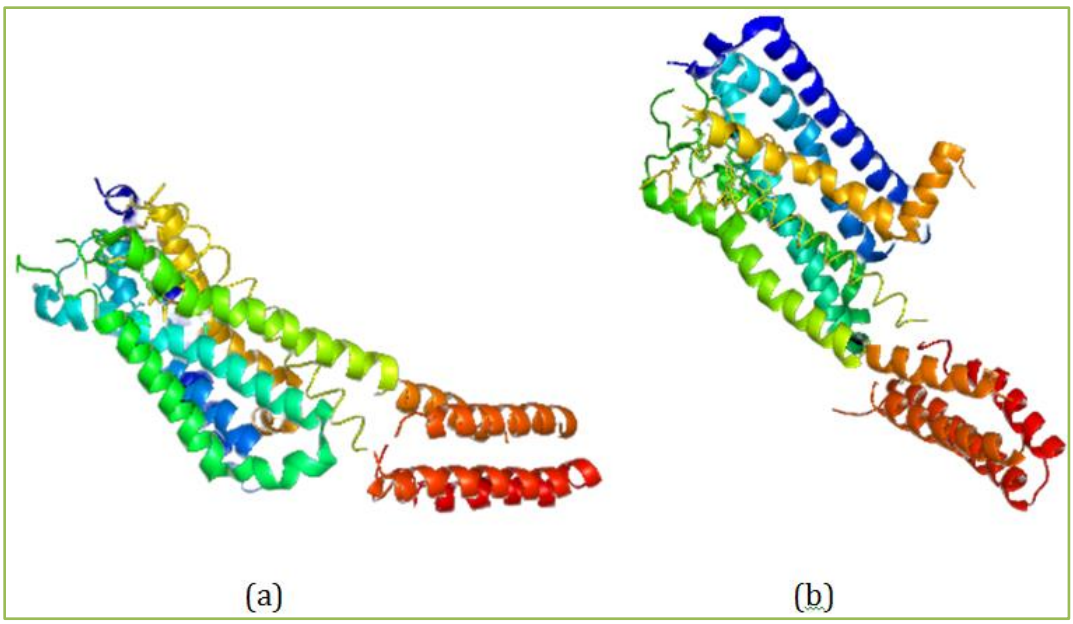

Figure 4. (a) Net protein serotonin 1b (5-HT1b) receptor (b) P net protein serotonin 1b (5-HT1b) receptor

Furthermore, cryo-electron microscopy (cryo-EM) has been employed to elucidate the structure of the 5-HT1B receptor coupled to heterotrimeric Go, offering a detailed view of the receptor's architecture and its interaction with G proteins. This approach has opened new avenues for understanding the dynamic processes involved in receptor activation and signal transduction, highlighting the receptor's conformational changes upon ligand binding and G protein coupling (Nature) [57].

Conclusion

The conclusion of this study is that serotonin analgesics derived from banana fruit (*Musa paradisiaca*) show potential in interacting with serotonin 1 b (5-HT1b) receptor protein in silico. This study provides a deeper understanding of the molecular interactions and molecular characteristics of serotonin analgesics, as well as their potential application in the development of serotonin-based analgesic drugs. These findings make an important contribution to pain research and drug development, but further research and experimental validation are needed to verify the results and understand the therapeutic potential and safety of serotonin analgesics from banana fruit before they can be applied clinically.

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Disclosure Statement

The authors have declared that there is no competing interest in this article

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