**Journal of Neonatal Surgery**
***ISSN(Online): 2226-0439***
***Vol. 14, Issue 26s (2025)***
*https://www.jneonatalsurg.com*

OPEN ACCESS

# Exploration of Alternative Therapies for the Management of Morphine Opioid Withdrawal Symptoms using Mitragyna s peciose Compound Compared with naloxone at the Mu Opioid Receptor: In Silico Approach and Molecular Docking

**Tri Puji Lestari Sudarwati[1], Muhammad Sasmito Djati[2*], Warsito Warsito[3], Sri Widyarti[4]**

[1,2,3,4]Brawijaya university, Jl. Veteran No.10-11, Ketawanggede, Kec. Lowokwaru, Kota Malang, Jawa Timur 65145, Indonesia.

Email ID: tri.puji.ls@student.ub.ac.id/tri.puji.ls@akfarsurabaya.ac.id[1], msdjati@ub.ac.id[2*], warsito@ub.ac.id[3], swid@ub.ac.id[4]

***Corresponding Author:**

Muhammad Sasmito Djati,

Email ID: msdjati@ub.ac.id

Cite this paper as: Tri Puji Lestari Sudarwati, Muhammad Sasmito Djati, Warsito Warsito, Sri Widyarti, (2025) Exploration of Alternative Therapies for the Management of Morphine Opioid Withdrawal Symptoms using Mitragyna s peciose Compound Compared with naloxone at the Mu Opioid Receptor: In Silico Approach and Molecular Docking, *Journal of Neonatal Surgery*, 14 (26s), 217-229

**ABSTRACT**

The current study elucidates the molecular pharmacodynamics of alkaloids derived from Mitragyna speciosa as candidates for mitigating opioid withdrawal symptoms, considering their interaction with the Mu Opioid Receptor (MOR). Employing an integrative in silico approach—including LC-MS/MS chemical profiling, ADMET prediction, molecular docking, and molecular dynamics simulation—we identified Corynoxine B as a lead compound exhibiting the most favorable binding affinity (-8.5 kcal/mol) relative to morphine and naloxone. Despite its superior affinity, Corynoxine B demonstrated comparatively lower structural stability in dynamic simulation, indicating the need for structural optimization. These findings suggest a differentiated interaction mechanism that could minimize conventional opioid side effects while maintaining therapeutic efficacy. Further in vivo and structure-activity relationship (SAR) studies are warranted to validate pharmacokinetics, receptor selectivity, and safety profiles. This work contributes to the rational development of plant-based modulators of MOR as novel alternatives or adjuncts in the clinical management of opioid dependence.

**Keywords**: *Mitragyna speciosa, Opioid, Molecular Docking, In Silico, Abbreviations: Mu Opioid Receptor (MOR), Delta Opioid Receptor (DOR), and Kappa Opioid Receptor (KOR), Liquid Chromatography-Mass Spectrometry/ Mass Spectrometry (LC-MS/MS), ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) Prediction*

## 1. INTRODUCTION

Opioid abuse is one of the most pressing public health problems worldwide, with significant impacts on individuals, families, and society as a whole. Opioid use has increased, both for users under supervision for therapeutic benefits for pain management but also has a high potential for dependence and abuse by its use. Opioid withdrawal symptoms will appear when individuals who use opioids stop using them . Physically it will cause unbearable pain, while psychologically it will cause excessive anxiety, depression, muscle pain, diarrhea, and insomnia. These symptoms are what trigger opioid users to return to using them to relieve discomfort, making opioid dependence difficult to break. Therefore, the development of management for opioid withdrawal symptoms needs to be attempted by exploring research from natural materials with minimal risk. One plant that has potential in managing opioid withdrawal symptoms is *Mitragyna speciose* , known as kratom.

*Mitragyna speciose* or kratom is a tropical plant from Southeast Asia that originates from Thailand, Malaysia and Indonesia in recent decades attracting global attention because has pharmacological potential especially as an alternative natural analgesic and management of opioid withdrawal symptoms. (Hassan et al., 2013; Prozialeck et al., 2012; Singh et al., 2014) . The use of kratom is increasing globally, although its legal and regulatory status varies across the world, and there is ongoing debate about its benefits and risks. (Kowalczuk et al., 2013; Raini, 2017; Ramanathan & McCurdy, 2020; Swogger & Walsh, 2018) , thus giving rise to an urgent need for comprehensive research covering the mechanisms of action, pharmacokinetics, therapeutic potential , and risks associated with kratom use. and the safety profile of its active compounds

(Váradi et al., 2016) . Compounds from kratom have the potential to interact with the same mu opioid receptor (MOR) as morphine, and are a major target in the management of pain and withdrawal symptoms. Early research suggests that compounds from kratom may provide analgesic effects similar to opioids, but with a different side effect profile. This makes kratom an interesting candidate for further exploration in the context of managing opioid dependence (Kruegel & Grundmann, 2018; Tang et al., 2021; Warner et al., 2016; Yamamoto et al., 1999) . In conditions overdose morphine so will given opioid antagonist such as naloxone for relieve . Mechanism Work naloxone with tie MOR receptors and inhibit opioid effects , so that can reduce symptom opioid withdrawal . Such as other types of opioids , the use of naloxone can also cause symptom opioid withdrawal with different effects each individuals who use . Research This will compare effect *Mitragyna speciosa* with naloxone , regarding the interaction with MOR modeled virtually so that can give outlook new about mechanism Work compound from kratom the main thing development of alternative therapies replacement naloxone in management of opioid withdrawal symptoms. In silico approaches , including molecular docking techniques that allow in-depth analysis of compounds from kratom binding to receptors, as well as evaluating therapeutic potential and mechanisms of action and identify possibility agonist effect or antagonist that can generated , thus providing efficiency in research by reducing the need for early-stage animal and human trials . In addition, this study also aims to identify the potential of kratom compounds as a safer and more effective alternative to synthetic opioids.

Pharmacokinetic and pharmacodynamic profiles of compounds from kratom includes absorption , distribution, metabolism , excretion and toxicity is matter important things to do known . Important thing other is know use effective and safe dose to minimize effect possible side arise and interaction with compound others . Analysis on the signaling pathways involved in the interaction between kratom compounds and mu opioid receptors will also provide important information regarding the mechanism of action of these compounds in overcoming opioid withdrawal symptoms . understand interaction molecular between compound active from kratom and MOR receptors , we hope can identify underlying mechanisms effect possible therapeutic owned by *Mitragyna speciosa* . In addition , research this is also expected can give contribution to development of more advanced treatment strategies effective and safe for individuals who experience opioid dependence . With increasing prevalence opioid abuse worldwide , it is important For Keep going look for solution innovative that can help overcome challenge this and improve quality life affected patients . The results of this study are expected to provide a better understanding of the function of kratom as an alternative or complementary in the management of opioid withdrawal symptoms. Thus, this study not only contributes to the development of more effective and safe opioid dependence management strategies, but also paves the way for further research into the therapeutic potential of natural compounds in modern medicine. In addition, this study can also provide a scientific basis for the use of kratom in a broader medical context, as well as provide useful information for policy makers and health practitioners in formulating guidelines for the use of kratom as an alternative therapy. Overall, this study aims to make a significant contribution to global efforts in addressing the opioid abuse crisis. Thus, this study is not only relevant in the context of opioid dependence management, but also in the broader context of the use of natural compounds in medicine and public health

## 2. METHODOLOGY

### Material

This study used leaves Mitragyna speciose as samples, some chemicals used in this research were ethanol 96% pa

Procedures

**1.Sample Preparation.**

Methods used based on (Shaik Mossadeq et al., 2009) use leaf Mitragyna speciose as much as 10000g is dried at room temperature. room for 10 days , finely ground become powder dry coarse (<1 mm) and extracted with 96% ethanol for 72 hours. Extract evaporated with a rotary evaporator until become mass semi-solid colored chocolate old and stored at room temperature temperature –20°C before used analysis Next . Next extract analyzed using LC-MS/MS ( MassLynx 4.1 SCN 884 Xevo G2-S QTof / Xevo G2-S Tof ) (Avula et al., 2015) for separating , characterizing , and profiling alkaloid chemistry contained from kratom.

**2.Profile Prediction Analysis Identified Metabolites Based on Drug bank**

Profile and structure identified metabolites obtained from PubChem CID data https://pubchem.ncbi.nlm.nih.gov where its structure in the form of SMILES (Simplified Molecular-Input Line-Entry System) then predicted use SwissADME online tool http://www.swissadme.ch/ used For explore ADME properties of metabolit identified that have been found (Daina et al., 2017). Analysis potential protein prediction use SwissProtein online tool http://www.swisstargetprediction.ch/ used For potential protein target prediction from metabolit identified . Toxicity pattern from metabolit identified analyzed use pkCSM online tool https://biosig.lab.uq.edu.au/pkcsm/, where this online device predict some toxicity parameters such as LOAEL, LD50, etc. (Pires et al., 2015).

**3. Molecular Analysis of Interactions Metabolites Potential Mitragyna speciose Against Mu Opioid Receptor (MOR)**

**Protein**

PDB protein structure https://www.rcsb.org/structure/8EF6 from MOR protein molecules have been prepared docking with remove all water molecules and hetatms (hetero atoms such as carbohydrates , substrates , ligands, solvents , and metal ions ) to molecular docking simulation to predict affinity binding between MOR proteins ( macromolecules ) and metabolites identified from plants (ligands). Structural data collection chemistry compounds found in kratom extract in 3D file shape . Then docked use Autodock vina in PyRx which is device soft virtual screening computing in the library computer against drug targets potential with perform docking of several ligands against One macromolecules . The docking results show low binding affinity value For prediction compound identified against MOR. Device soft PyRx version 8.0 and the visualization program Discovery Studio Visualizer v21.1.0.20298 were used. For pair bioactive substances (ligands) with the target protein Mu opioid receptor . The Protein Data Bank ( www.rcsb.org) database library was used. For find target protein 3D file. 3D file of protein molecule cleaned from native water molecules , ions, and ligands using Discovery Studio Visualizer v21.1.0.20298. Next , the protein files were saved with * .pdb . In PyRx version 8.0 device soft , blind docking is used For pairing ligands one by one with its target protein . The results of analysis conducted is know Binding affinity value of each compound found as well as residue from MOR bond with compound potential and compared with naloxone. The ligand bound complexes were visualized through Discovery Studio v21.1.0.20298 as well as PyMOL v3.1.3 (Wang et al., 2015).

**4. Analysis of ligand residue interactions**

Discovery Studio v21.1.0.20298 and PyMOL v3.1.3 were used. For evaluate MOR protein by analyze combined complex together with metabolit identified ( i.e. , acid chicoric , luteone, reserpine , and arginine acids rosmarinic ). Analysis structure comparative used with utilise pattern binding . In addition , the interaction molecular morphine and naloxone ( control) positive ) with the protein under study were also analyzed .

**5. Molecular dynamics study on compounds candidate against MOR**

Treatment in method This based on (Meylani et al., 2023), with A little modification namely Molecular dynamics is carried out using YASARA (Yet Another Scientific Artificial Reality Application) software with AMBER14 forcefield for 25 ns with running system customized with the situation inside cell namely pH 7.4, temperature 310 K, pressure 1atm, salt content 0.9%, and water density 0.997. The macro program that is run is md_run For operate visualization and md_analyze For analyze results simulation . Analysis results molecular dynamic to find out stability compound potential of kratom against MOR compared with morphine .

## 3. RESULT

**1. Identification of potential compounds** *of Mitragyna speciose*

**Table 1. Potential compounds of Mitragyna speciose obtained from the results of analysis using LC-MS/MS (MassLynx 4.1 SCN 884 Xevo G2-S QTof/Xevo G2-S Tof)**

| Mass spectro value (m/z) | RT | Wide spectrum | Active compounds | SMILES |
|---|---|---|---|---|
| 385.2122 | 1.19;<br>5. 303;<br>10,878 | 2.66% | Corynoxine B<br>Corynoxine | COC=C(C1CC2N(CC1CC)CCC12C(=O)Nc2c1cccc2)C(=O)OC |
| 397.2122 | 7,559 | 8.16% | Paynantheine | COC=C(C1CC2N(CC1C=C)CCc1c2[nH]c2c1c(OC)ccc2)C(=O)OC |
| 397.2123 | 7,651 | | 3-Isopaynantheine | COC=C(C1CC2c3[nH]c4c(c3CC[N+]2(CC1C=C)[O-])c(OC)ccc4)C(=O)OC |
| 399.1944 | 4,642 | 1.3% | Isospecificoleine | COC=C(C1CC2N(CC1C=C)CCC12C(=O)Nc2c1c(O)ccc2)C(=O)OC |
| 399.2276 | 10,049 | 2.11% | Mitragynine | COC=C(C1CC2N(CC1CC)CCc1c2[nH]c2c1c(OC)ccc2)C(=O)OC |

| | | | | |
|---|---|---|---|---|
| 399.2278 | 7.63 | 65.31% | Speciogynine | COC=C(C1CC2N(CC1CC)CCc1c2[nH]c2c1c(OC)ccc2)C(=O)OC |
| 401.2066 | 4.332;<br>6,048 | 1.53 % | Isorotundifoline | COC=C(C1CC2N(CC1CC)CCC12C(=O)Nc2c1c(O)ccc2)C(=O)OC |
| 415.2227 | 8.199 | 18.93% | 7-Hydroxymitragynine | COC=C(C1CC2N(CC1CC)CCC1(C2=Nc2c1c(OC)ccc2)O)C(=O)OC |

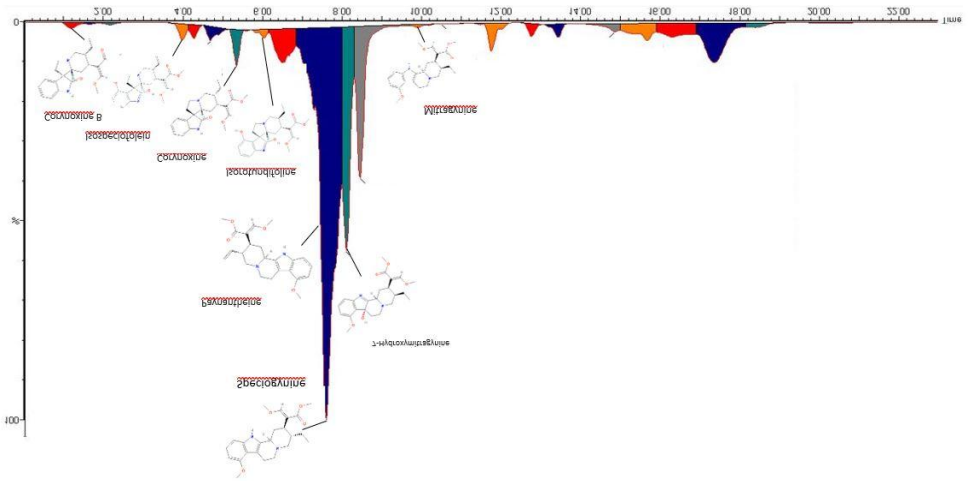


**Figure 1. LCMS/MS *curve* spectra of compounds contained in *Mitragyna* speciosa**

Analysis results LC-MS/MS (MassLynx 4.1 SCN 884 Xevo G2-S QTof/Xevo G2-S Tof) from maceration 96% ethanol of kratom leaves with the aim of separating, characterizing, and chemical profiling the alkaloids that can be identified . is speciogynine , paynantheine , 7 hydroxymitragynin , isorotundifoline , corynoxine , corynoxine B, isospeciofoleine , 3 isopaynantheine and mitragynine . The largest spectral area in the compound speciogynine namely 65.31% and the lowest is group corynoxine and corynoxine B. Compounds found furthermore analyzed using ADMET and Lipinski criteria online devices .

**2. Analysis Prediction of Identified Metabolite Profiles Based on Drug bank**

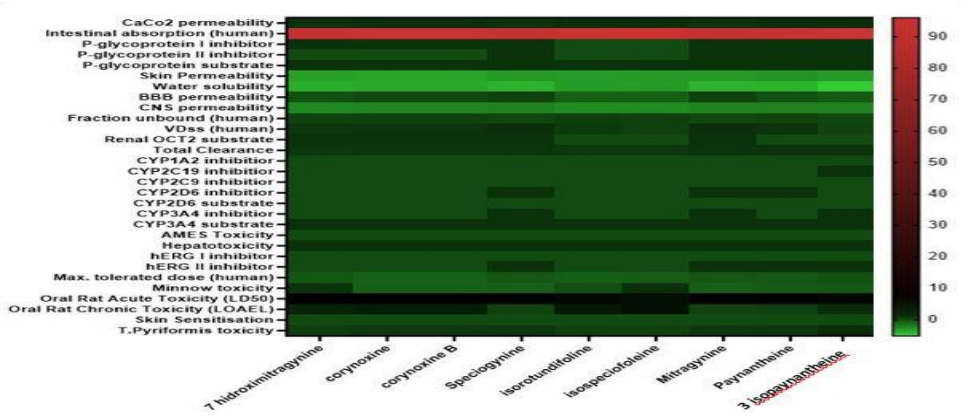



**Figure 2. ADME heatmap diagram of 9 identified compounds .**

**Table 2. Lipinski**

| Compound Name | Molecular Weight (g/mol) | Log P (Partition Coefficient) | Number of Bond Donors Hydrogen | Number of Hydrogen Bond Acceptors | TPSA |
|---|---|---|---|---|---|
| Corynoxine B | 384.47 | 2.02 | 1 | 5 | 67.87 Å² |
| Corynoxine | 384.47 | 2.02 | 1 | 5 | 67.87 Å² |
| Paynantheine | 396.48 | 1.94 | 1 | 5 | 63.79 Å² |
| Mitragynine | 398.50 | 2.02 | 1 | 5 | 63.79 Å² |
| Speciogynine | 398.50 | 2.02 | 1 | 5 | 63.79 Å² |
| Isorotundifoline | 400.47 | 1.49 | 2 | 6 | 88.10 Å² |
| 7-Hydroxymitragynine | 414.49 | 1.3 | 1 | 7 | 80.5 9 Å² |

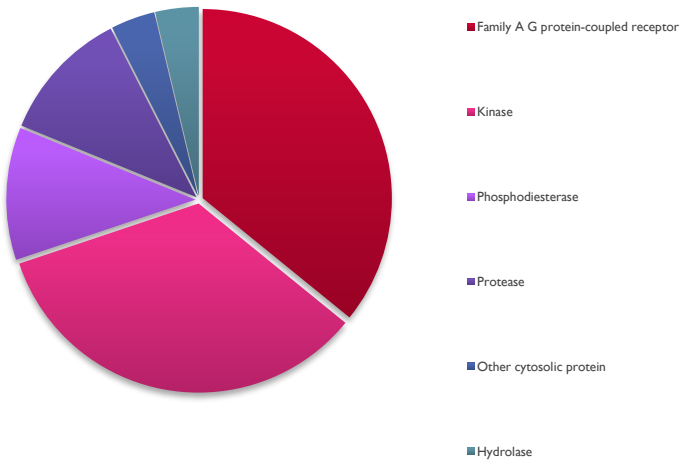



**Figure 3. Potential Target Protein Diagram *of Mitragyna speciose***

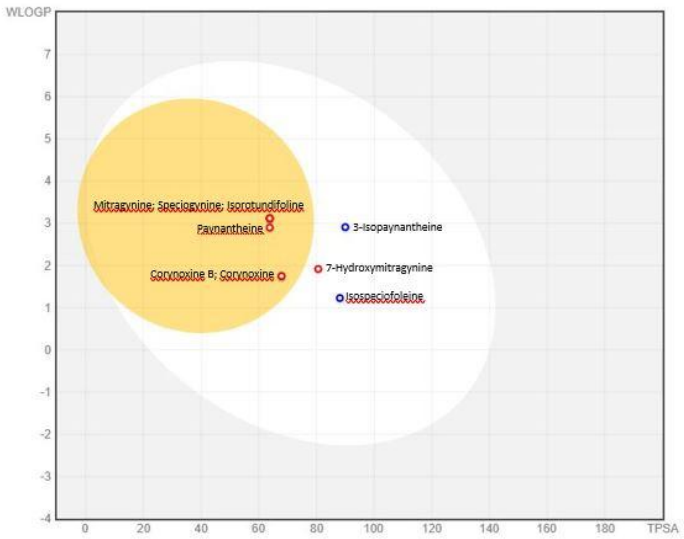



**Figure 4. Distribution compound based on absorption body , some the compound that is Corynoxine B; Corynoxine ; Paynantheine ; Mitragynine ; Speciogynine ; Isorotundifoline < 3-Isopaynantheine < Isospeciofoleine < 7-Hydroxymitragynine absorbed with both by human intestine , but There are 6 compounds that is Corynoxine B; Corynoxine ; Paynantheine ; Mitragynine ; Speciogynine ; Isorotundifoline is capable penetrate barrier blood brain .**

**Table 3. Binding Affinity and Residue Binding Compound Potential *Mitragyna speciosa* Against MOR Compared With Morphine And Naloxone**

| Ligand | Binding Affinity (kcal/mol) | Interac ti on (bond) | Residue |
|---|---|---|---|
| **Corynoxine B** | **-8.5** | Van der Waals | GLN126; TRP320; LYS235; MET153; TRP295; GLY237; VAL302 |
| | | Conventional Hydrogen Bond | ASP149 |
| | | Pi-Sigma | HIS299 |
| | | Pi-Pi Stacked | TYR328 |
| | | Alkyl | LEU234; VAL238 |
| | | Pi-Alkyl | ILE298; ILE324; TYR150 |
| **Corynoxine** | **-7.1** | Van der Waals | TYR130; HIS321; TYR77; VAL145; LYS305; CYS219 |
| | | Conventional Hydrogen Bond | ASP218; GLN126 |
| | | Carbon Hydrogen Bond | GLN126; ASP149 |
| | | Alkyl | ILE324 |
| | | Pi-Alkyl | TRP320 |
| **Paynantheine** | **-7.7** | Van Der Wals | THR220; TRP295; GLY327; CYS219; ASN129; TYR328; GLN126 |
| | | Carbon Hydrogen Bond | TYR150 |
| | | P i -Anion | ASP149 |
| | | Pi-Sigma | ILE298 |

| | | | |
|---|---|---|---|
| | | Alkyl<br>Pi-Alkyl | ILE324; IL146; MET153; IL298<br>ILE324; TYR150; HIS299; TRO320; HIS321 |
| **Mitragynine** | **-7.9** | Van Der Wals<br>Conventional Hydrogen Bond<br>Carbon Hydrogen Bond<br>P i -Anion<br>Pi-Sigma<br>Alkyl<br>Pi-Alkyl | ASN129; GLY327; TRP295; GLN126<br>TRP320<br>TY150; TYR77<br>ASP149<br>ILE298<br>ILE324; MET153; ILE298<br>ILE324; TYR77; HIS299; TRP320; HIS321 |
| **Speciogynine** | **-8.1** | Van Der Wals<br>Conventional Hydrogen Bond<br>Carbon Hydrogen Bond<br>Pi-Donor Hydrogen Bond<br>Pi- Sigma<br>Alkyl<br>Pi-Alkyl | VAL302; MET153; IL146; TYR130; TYR77; TRP320; GLY327; ILE298; ASP149<br>ASN129; TYR328<br>ILE234<br>GLN126<br>TYR150<br>ILE324<br>TRP135; TYR150; TRP295; TYR328 |
| **Isorotundifoline** | **-8.2** | Van der Waals<br>Conventional Hydrogen Bond<br>Carbon Hydrogen Bond<br>Unfavorable Donors<br>Alkyl<br>Pi-Alkyl | TRP320; ILE298; HIS321; TYR77; THR220; ASP218; VAL145; IL146; TYR328<br>ASP149; ASN129; TYR150<br>CYS219<br>GLN126<br>CYS219<br>ILE324; TRP135 |
| **7-Hydroxymitragynine** | **-7.6** | Van Der Wals<br>Conventional Hydrogen Bond<br>Carbon Hydrogen Bond<br>Alkyl<br>Pi Alkyl<br>Pi-Pi Stacked | PHE239; CYS 219; LEU234; LYS305; LEU221<br>TYR150; THR220<br>LYS235<br>MET153; VAL238<br>ILE146; TYR150<br>TYR150 |
| **Morphine** | **-8** | Van der Waals<br>Pi-Sigma<br>Pi-Sulfur<br>Pi-Pi T-Shaped | TYR150; TRP320; ASP149; GLY327; TRP295; VAL302; VAL238<br>TYR328<br>MET153 |

| | | | |
|---|---|---|---|
| | | Alkyl<br>Pi-Alkyl | HIS299<br>ILE298; ILE324; MET153<br>ILE298; TYR328 |
| **Naloxone** | **-8** | Van Der Wals<br>Carbon Hydrogen Bond<br>P i -Anion<br>Alkyl<br>Pi-Alkyl | MET153; TRP320<br>GLN126; TYR328<br>ASP149<br>ILE298; LYS235; VAL238; VAL302<br>ILE298; ILE324; TYR150 |

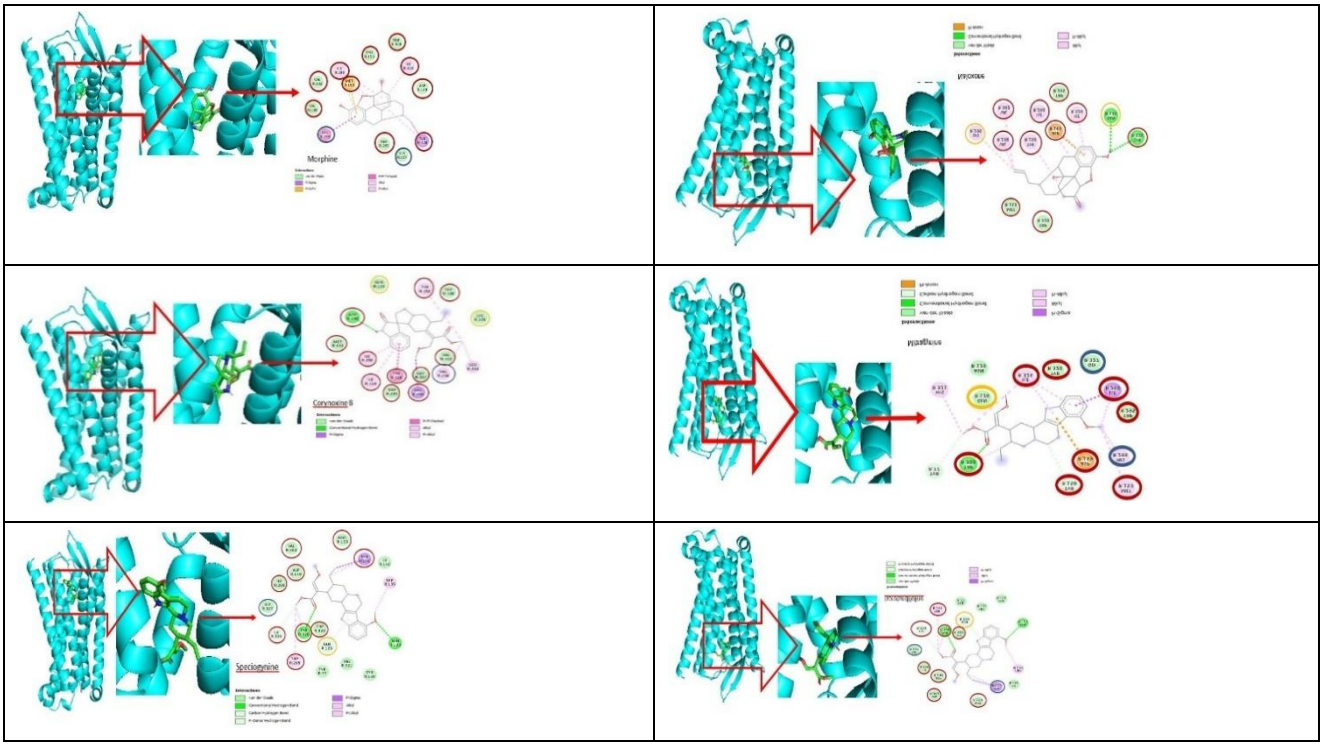
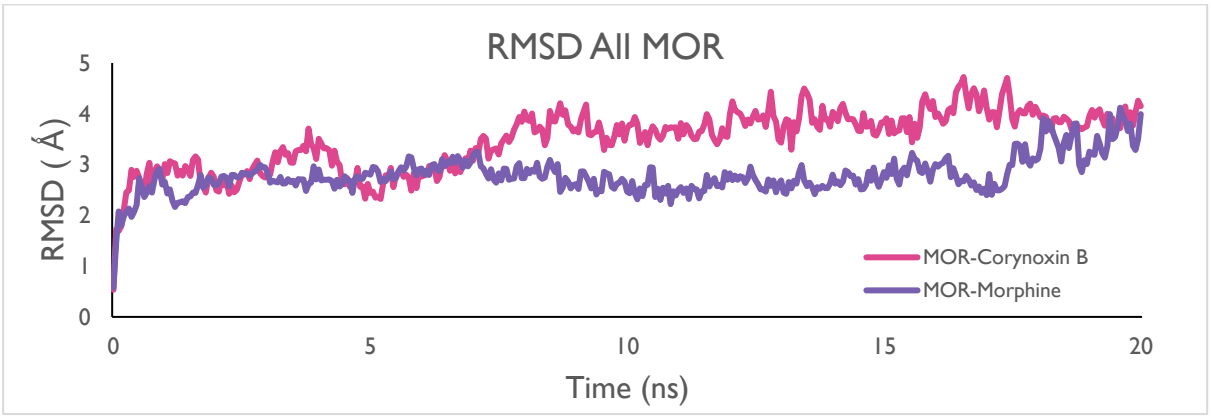


**Figure 5. Molecular interactions and Ligand-amino acid interaction mode of compounds potential *Mitragyna speciosa* against MOR**



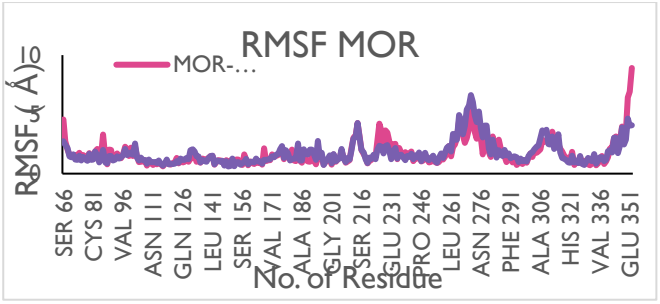



**Figure 6. Molecular dynamics of Corynoxine B ligand with Morphine comparison to MOR Protein**

## 4. DISCUSSION

Analysis LC-MS/MS (MassLynx 4.1 SCN 884 Xevo G2-S QTof/Xevo G2-S Tof) to maceration 96% ethanol kratom leaves can identify kratom compounds based on detected m/z pattern Then identified results compared to with the database. The parameters covering rate flow , temperature and composition phase motion and stationary phase for separate component based on characteristic chemical and physical from extract kratom ethanol . After the separation process to be continued with ionization that can change compound into ions, then ions detected by Xevo G2-S QTof based on ratio mass to charge (m/z) so that results served in form ion fragmentation . Analysis identification compound using LC-MS/MS with MassLynx 4.1 SCN 884 on Xevo G2-S QTof / Xevo G2-S Tof is very effective and efficient in analyze compounds contained in kratom extract as well show results accurate and information deep about composition chemistry from sample extract kratom leaves ( Veeramohan et al., 2018) . Fractionation of the resulting ions from extract 96% ethanol of kratom leaves in research This as many as 9 compounds . The results of the analysis in study This dominated by speciogynine (65.31%), paynantheine and 7 hydroxymitragynine . Speciogynine is diastomers from mitragynine contained in shift at position C20 from group methoxyl become group hydroxyl (-OH), the occurrence of configuration stereochemistry the can influence interaction with receptor biological (Karunakaran et al., 2022) . Beside Existence compound dominant also exists minor compounds such as corynoxine B and isorotundifoline even though pregnant not enough of 5%. Alkaloid content in *Mitragyna speciose* can due to geographic area as place growth , where type land , level nutrition , intensity ray sun , humidity , rainfall rain , and temperature Can influence synthesis and concentration alkaloid compounds in plant . (Boffa et al., 2018; Wahyono et al., 2019)

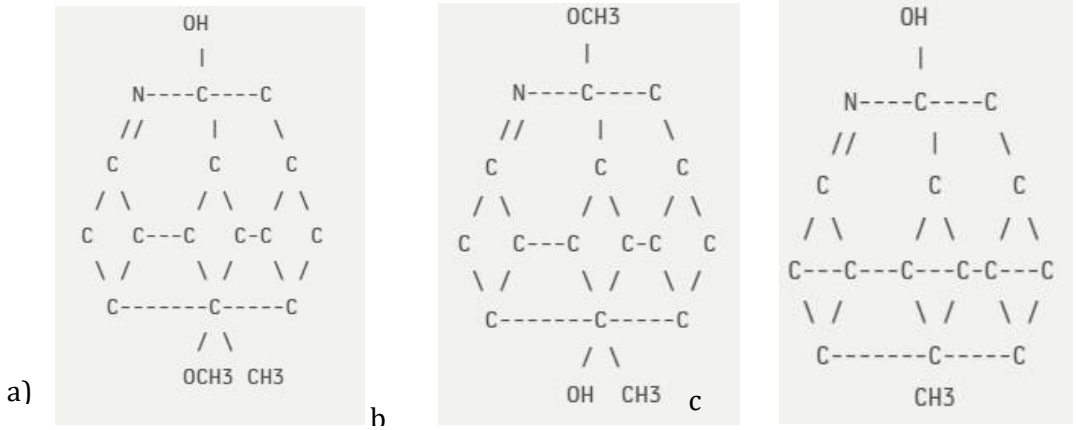



**Figure 7. Structure chemistry a) Speciogynine , b) Mitragynine , c) Morphine**

Interaction specific speciogynine in vivo and in vitro based on study ( Hanapi et al., 2021; León et al., nd) show that speciogynine own affinity tall against 5-HT1AR and 5-HT2BR which causes effect antinociceptive in mice No through mechanism interaction to opioid receptors , so that produce effect analgesic light with minimal depression breathing and the risk of euphoria is also greater low compared to with classic opioid alkaloids like morphine , naloxone (Takayama et al., 2002) . Beside Existence compound dominant also exists minor compounds such as corynoxine B and isorotundifoline even though contained not enough from 5% , compound minorities This No can ignored also because compound the own effect addictive or antagonists that arise from interaction synergistic between alkaloids. Based on study previously known that compounds in *Mitragyna speciose* can bound with mu opioid receptors , where receptor the is the same receptor with receptor responsive morphine , so that can cause effect analgesic like morphine and even more strong than morphine (Boffa et al.,

2018; Matsumoto et al., 2005; Suhaimi et al., 2016) .

Response in a way physiology from The alkaloid compounds in kratom, morphine and naloxone are different against the mu opioid receptor (MOR). MOR is a group G protein coupled receptor ( GPCR ) and one of the from the main subtype from opioid receptors , which have role central in management pain and function physiological other through mechanism binding with opioid compounds ( Waldhoer et al., 2004) . Morphine is phenanthrene alkaloids -classic opioids that are responsive to MOR because arranged on the classic opioid phenanthrene which has framework pentacyclic with group phenol and hydroxyl alilik , have framework pentacyclic rigid with group phenol (C3-OH) and hydroxyl critical allylic (C6-OH) For MOR binding . While naloxone is a derivative morphine with N-allyl group works as antagonist against MOR through binding competitive to the same site with morphine . Kratom alkaloids have complex interactions against MOR where after binding MOR can allow selective GPCR incorporation without recruits β-arrestin-2, so that can minimize risk depression breathing and tolerance that is usually associated with full agonist like morphine , as well as involving non-opioid pathways , such as system serotonergic and adrenergic , because structure its flexible indole . Monoterpenoid indole alkaloids with ring Indo fused and β- methoxy ester substituent acrylate this is what can increase interaction hydrophobic with non-polar residues in the MOR active site as in speciogynine which can to form bond allosteric partial so that produce activation receptor become more selective . While in minor alkaloids such as corynoxine B which can show interaction to group methylene dioxide and stereochemistry C3- *R* (Karunakaran et al., 2022) . Polypharmacology This is what contributes to the effect addition like modulation atmosphere heart and reduce symptom separated drug from opioids ( Hanapi et al., 2021; Syahida , 2024) . That matter in accordance with prediction potential target protein in figure 3 where of the 9 ligand compounds have potential the biggest against the AG protein family of receptor couple proteins and Kinases, and potential light against phosphodiesterase, protease, other cytosolic proteins and hydrolases. GPCR ligands are transmission signal from various stimulus external such as hormones, neurotransmitters and signals sensory ( light and smell ), with the occurrence activation of the GPCR ligand then will activates G protein so that happen exchange of GDP for GTP on the alpha subunit, which causes 2 lines active signaling from cAMP as a second messenger and pathway signaling related phosphatidylinositols with mobilization of calcium ions and protein kinase C (PKC) (Yang et al., 2021) . The group of GPCRs that are the targets of interaction for good opioid compounds endogenously (endorphin) or exogenous ( morphine ) which regulates pain , mood and function physiology other There are 3 subtypes namely mu opioid receptors (MOR), delta opioid receptors (DOR) and kappa opioid receptors (KOR) ( Waldhoer et al., 2004) . Use morphine which is opioid compounds will interact active with MOR which is receptor main in management to painful (Martini & Whistler, 2007) . In addition to potential protein targets , an in silico approach was carried out. in study It also predicts the ADMET of 9 identified compounds .

Based on ADMET for prediction reviewed from TPSA value which shows polarity compounds and WLOGP shows mark lipophilicity compound , depicted in the egg diagram interpreted with ability compound absorbed in the intestinal organs and occurs penetration of the barrier blood brain (BBB) in the section yellow egg diagram (Daina et al., 2017) . There is six Kratom compounds are Corynoxine B, Corynoxine , Paynanthein , Mitragynine , Speciogynine , Isorotundifoline capable penetrate barrier blood brain (BBB) is shown with compounds – compounds the located in the section yellow with point red from the egg diagram as well as absorbed both by intestinal organs. In the section white shown 7- hydroxymitragynine , isospesiofolein and 3-isopaynantheine only can absorbed both by intestinal organs but No can happen penetration of the barrier blood brain (BBB). Compound with higher TPSA value low score not enough of 79.38 Å² and high lipophilicity (>2-3 ) can diffuse more easy through the endothelial membrane in the nervous system center (Cornelissen et al., 2023; Spielvogel et al., 2025) whereas molecule compound more big or polar requires a special transporter so that can pass through the BBB so that influence Work from the nervous system center (de Sá et al., 2010) . For know prediction interaction from compound potential from ADMET prediction then docking is done so that obtained mark affinity and interaction residue against MOR.

Docking was performed on the ligands Corynoxine B, Corynoxine , Paynanthein , Mitragynine , Speciogynine , Isorotundifoline against the MOR protein then compared to with morphine and naloxone as control. The affinity value of morphine and naloxone is -8 and the compound that has higher affinity value from morphine and naloxone namely corynoxine B, speciogynine , isorotundifoline as well as mitragynine which is approaching affinity value of the control. A higher affinity value low ( to minus) indicates that happen binding between ligand and protein more strong and stable , thing the become important in a way pharmacology to assess potential and efficacy drug against a specific protein target (Rodarte et al., 2023) . So corynoxin B has more bond strong and stable against MOR compared with morphine and naloxone. Active site of morphine ligand interactions with MOR are TYR150, TRP320, ASP149, GLY327, TRP295, VAL302, VAL238, TYR328, MET153, HIS299, ILE298, ILE324, MET153, ILE298, TYR328. The active site of The ligand interactions of naloxone with MOR are MET153, TRP320, GLN126, TYR328, ASP149, ILE298, LYS235, VAL238, VAL302, ILE298, ILE324, TYR150. Table 3 shows that corynoxine B has equality residue with morphine and naloxone in almost all bond in structure the chemistry compared to with mitragynine , speciogynine and also isorotundifoline , then For know stability and flexibility from corynoxine B is necessary done molecular dynamics analysis .

Based on the molecular diagram dynamic of the corynoxine B ligand against MOR ( red line ) compared with morphine against MOR ( purple line ) shows that morphine stable relatively fast , reach point peak about 2-3 Å. Relative fluctuations

small during simulation and can maintained conformation that approaches structure initially , compared to corynoxin B reaches point peak about 3-4 Å and shows more fluctuations big during simulation . So in stability The MOR-Morphine complex is more stable (areas Gln124 and Tyr148) than MOR- Corynoxine B complex (Lys233 area).

## 5. CONCLUSION

This study demonstrates the pharmacological promise of Mitragyna speciosa alkaloids, notably Corynoxine B, in targeting the Mu Opioid Receptor (MOR) as part of a therapeutic strategy for opioid withdrawal. Computational docking results indicate that several kratom-derived ligands exhibit receptor affinities comparable to or exceeding those of morphine and naloxone, with distinct residue interaction profiles. Among them, Corynoxine B emerged as the most potent binder; however, its reduced conformational stability during molecular dynamics underscores the necessity for further optimization. To advance these findings toward translational application, future research should integrate in vivo validation, detailed SAR modeling, and bioavailability enhancement strategies. This investigation reinforces the relevance of natural indole alkaloids as structurally and mechanistically novel candidates in opioid detoxification paradigms.

## ACKNOWLEDGEMENTS

Study This funded by the Indonesian Education Scholarship (BPI), Education Fund Management Institute (LPDP), Republic of Indonesia

## REFERENCES

[1] Alkassabi OY, Al- Sobayel H, Al-Eisa ES, Buragadda S, Alghadir AH, Iqbal A. Job satisfaction among physiotherapists in Saudi Arabia: Does the leadership style matter? BMC Health Serv Res. 2018;18(1):1–9.

[2] Alva R. Job and career satisfaction among Indian physiotherapists: A preliminary survey. Int J Ther Rehabil . 2016;23(2).

[3] Arif F. THE RELATIONSHIP BETWEEN ORGANIZATIONAL CITIZENSHIP BEHAVIOR AND JOB SATISFACTION AMONG PHYSIOTHERAPIST OF HOSPITALS OF KARACHI, PAKISTAN [Internet].

[4] Avula, B., Sagi, S., Wang, Y. H., Wang, M., Ali, Z., Smillie, T. J., Zweigenbaum, J., & Khan, I. A. (2015). Identification and characterization of indole and oxindole alkaloids from leaves of Mitragyna speciosa Korth using liquid chromatography - Accurate QToF mass spectrometry. Journal of AOAC International , 98 (1), 13–21. https://doi.org/10.5740/jaoacint.14-110

[5] Boffa, L., Ghè, C., Barge, A., Muccioli, G., & Cravotto, G. (2018). Alkaloid profiles and activity in different Mitragyna speciosa strains. Natural Product Communications , 13 (9), 1111–1116. https://doi.org/10.1177/1934578x1801300904

[6] Brattig B, Scabbard A, The House A, Peter C. Occupational accident and disease claims, work related stress and job satisfaction of physiotherapists. Journal of Occupational Medicine and Toxicology. 2014 Jan;9(1)

[7] Cornelissen, F.M.G., Markert, G., Deutsch, G., Antonara, M., Faaij, N., Bartelink, I., Noske, D., Vandertop, W.P., Bender, A., & Westerman, B.A. (2023). Explaining Blood-Brain Barrier Permeability of Small Molecules by Integrated Analysis of Different Transport Mechanisms. Journal of Medicinal Chemistry , 66 (11), 7253–7267. https://doi.org/10.1021/acs.jmedchem.2c01824

[8] Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific Reports , 7 (October 2016), 1–13. https://doi.org/10.1038/srep42717

[9] de Sá, M. M., Pasqualoto, K. F. M., & Rangel-Yagui, C. de O. (2010). A 2D-QSPR approach to predict blood-brain barrier penetration of drugs acting on the central nervous system. Brazilian Journal of Pharmaceutical Sciences , 46 (4), 741–751. https://doi.org/10.1590/s1984-82502010000400016

[10] Dixit A, Madan M, Goswami SK, Professor A, Deendayal P, Delhi N, et al. DIFFICULTIES EXPERIENCED BY OCCUPATIONAL THERAPISTS AND PHYSICAL THERAPISTS AT THE BEGINNING OF THEIR CAREER

[11] Frenny FC, Balaji S, Anusuya A. A SURVEY ON LEVEL OF JOB SATISFACTION AMONG DIFFERENT

[12] Gupta N, Joshi S. Predictors of Job Satisfaction among Physiotherapy Professionals. Indian Journal of Physiotherapy and Occupational Therapy - An International Journal. 2013;7(3):146.

[13] Hanapi, NA, Chear, NJY, Azizi, J., & Yusof, SR (2021). Kratom Alkaloids: Interactions With Enzymes, Receptors, and Cellular Barriers. Frontiers in Pharmacology , 12 (November), 1–21. https://doi.org/10.3389/fphar.2021.751656

[14] Hassan, Z., Muzaimi, M., Navaratnam, V., Yusoff, NHM, Suhaimi, FW, Vadivelu, R., Vicknasingam, BK, Amato, D., von Hörsten, S., Ismail, NIW, Jayabalan, N., Hazim, AI, Mansor, SM, & Müller, CP (2013). From Kratom to mitragynine and its derivatives: Physiological and behavioral effects related to use, abuse, and addiction. Neuroscience and Biobehavioral Reviews , 37 (2), 138–151. https://doi.org/10.1016/j.neubiorev.2012.11.012

[15] Iliopoulos E, Morrissey N, Baryeh K, Polyzois I. Correlation between workplace learning and job satisfaction of NHS healthcare professionals [Internet]. Vol. 24, English Journal of Healthcare Management. 2018. Available from: www.bjhcm.co.uk

[16] IN INDIA-A CROSS SECTIONAL STUDY [Internet]. Peers Reviewed and Referee Journal. 2021. Available from: http://ijmer.in/pdf/e-Certificate%20of%20Publication-IJMER.pdf

[17] International Research Journal of Modernization in Engineering Technology and Science www.irjmets.com @International Research Journal of Modernization in Engineering. 2032. p. 2582–5208. Available from: www.irjmets.com

[18] Karunakaran, T., Ngew, KZ, Zailan, AAD, Mian Jong, VY, & Abu Bakar, MH (2022). The Chemical and Pharmacological Properties of Mitragynine and Its Diastereomers: An Insight Review. Frontiers in Pharmacology , 13 (February), 1–11. https://doi.org/10.3389/fphar.2022.805986

[19] Kowalczuk, A.P., Lozak, A., & Zjawiony, J.K. (2013). Comprehensive methodology for identification of Kratom in police laboratories. Forensic Science International , 233 (1–3), 238–243. https://doi.org/10.1016/j.forsciint.2013.09.016

[20] Kruegel, A.C., & Grundmann, O. (2018). The medicinal chemistry and neuropharmacology of kratom: A preliminary discussion of a promising medicinal plant and analysis of its potential for abuse. In Neuropharmacology (Vol. 134). Elsevier Ltd. https://doi.org/10.1016/j.neuropharm.2017.08.026

[21] Latzke M, Putz P, Kulnik ST, Schlegl C, Sorge M, Mériaux -Kratochvila S. Physiotherapists' job satisfaction according to employment situation: Findings from an on line survey in Austria. Physiotherapy Research International. 2021 Jan;26(3).

[22] León, F., Obeng, S., Mottinelli, M., Chen, Y., King, T.I., Berthold, C., Kamble, S.H., Restrepo, L.F., Patel, A., Gamez-jimenez, L.R., Lopera-londoño, C., Hiranita, T., Sharma, A., & Hampson, A.J. (nd). Supplemental Materials Activity of .

[23] Martini, L., & Whistler, J. L. (2007). The role of mu opioid receptor desensitization and endocytosis in morphine tolerance and dependence. Current Opinion in Neurobiology , 17 (5), 556–564. https://doi.org/10.1016/j.conb.2007.10.004

[24] Matsumoto, K., Yamamoto, L.T., Watanabe, K., Yano, S., Shan, J., Pang, PKT, Ponglux, D., Takayama, H., & Horie, S. (2005). Inhibitory effect of mitragynine, an analgesic alkaloid from Thai herbal medicine, on neurogenic contraction of the vas deferens. Life Sciences , 78 (2), 187–194. https://doi.org/10.1016/j.lfs.2005.04.042

[25] Meylani, V., Rizal Putra, R., Miftahussurur, M., Sukardiman, S., Eko Hermanto, F., & Abdullah, A. (2023). Molecular docking analysis of Cinnamomum zeylanicum phytochemicals against Secreted Aspartyl Proteinase 4–6 of Candida albicans as anti-candidiasis oral. Results in Chemistry , 5 (December 2022), 100721. https://doi.org/10.1016/j.rechem.2022.100721

[26] Pires, DEV, Blundell, T.L., & Ascher, D.B. (2015). pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. Journal of Medicinal Chemistry , 58 (9), 4066–4072. https://doi.org/10.1021/acs.jmedchem.5b00104

[27] Prozialeck, W. C., Jivan, J. K., & Andurkar, S. V. (2012). Pharmacology of Kratom: An emerging botanical agent with stimulant, analgesic and opioid-like effects. Journal of the American Osteopathic Association , 112 (12), 792–799.

[28] Raini, M. (2017). Kratom (Mitragyna speciosa Korth): Benefits, Side Effects and Legality. Health Research and Development Media . https://doi.org/10.22435/mpk.v27i3.6806.175-184

[29] Ramanathan, S., & McCurdy, C.R. (2020). Kratom (Mitragyna speciosa): Worldwide issues. Current Opinion in Psychiatry , 33 (4), 312–318. https://doi.org/10.1097/YCO.0000000000000621

[30] Rodarte, J.V., Baehr, C., Hicks, D., Liban, T.L., Weidle, C., Rupert, P.B., Jahan, R., Wall, A., McGuire, A.T., Strong, R.K., Runyon, S., Pravetoni, M., & Pancera, M. (2023). Structures of drug-specific monoclonal antibodies bound to opioids and nicotine reveal a common mode of binding. Structure , 31 (1), 20-32.e5. https://doi.org/10.1016/j.str.2022.11.008

[31] Shahida, N. (2024). Indonesian Journal of Chemical Science Kratom (Mitragyna speciosa): Medicinal Marvel or Menace? Assessing Potency, Risk, and Future Prospect of Herbal Medicine . 13 (1).

[32] Shaik Mossadeq, WM, Sulaiman, MR, Tengku Mohamad, TA, Chiong, HS, Zakaria, ZA, Jabit, ML, Baharuldin, MTH, & Israf, DA (2009). Anti-inflammatory and antinociceptive effects of Mitragyna speciosa Korth methanolic extract. Medical Principles and Practice , 18 (5), 378–384. https://doi.org/10.1159/000226292

[33] Singh, D., Müller, C. P., & Vicknasingam, B. K. (2014). Kratom (Mitragyna speciosa) dependence, withdrawal symptoms and craving in regular users. Drug and Alcohol Dependence , 139 , 132–137. https://doi.org/10.1016/j.drugalcdep.2014.03.017

[34] Spielvogel, C.P., Schindler, N., Schröder, C., Stellnberger, S.L., Wadsak, W., Mitterhauser, M., Papp, L., Hacker, M., Pichler, V., & Vraka, C. (2025). Enhancing Blood-Brain Barrier Penetration Prediction by Machine Learning-Based Integration of Novel and Existing, In Silico and Experimental Molecular Parameters from a Standardized Database. Journal of Chemical Information and Modeling . https://doi.org/10.1021/acs.jcim.4c02212

[35] Suhaimi, F.W., Yusoff, N.H.M., Hassan, R., Mansor, S.M., Navaratnam, V., Müller, C.P., & Hassan, Z. (2016). Neurobiology of Kratom and its main alkaloid mitragynine. Brain Research Bulletin , 126 , 29–40. https://doi.org/10.1016/j.brainresbull.2016.03.015

[36] Swogger, M. T., & Walsh, Z. (2018). Kratom use and mental health: A systematic review. Drug and Alcohol Dependence , 183 (October 2017), 134–140. https://doi.org/10.1016/j.drugalcdep.2017.10.012

[37] Takayama, H., Ishikawa, H., Kurihara, M., Kitajima, M., Aimi, N., Ponglux, D., Koyama, F., Matsumoto, K., Moriyama, T., Yamamoto, L.T., Watanabe, K., Murayama, T., & Horie, S. (2002). Studies on the synthesis and opioid agonistic activities of mitragynine-related indole alkaloids: Discovery of opioid agonists structurally different from other opioid ligands. Journal of Medicinal Chemistry , 45 (9), 1949–1956. https://doi.org/10.1021/jm010576e

[38] Tang, F., Ng, C.M., Bada, H.S., & Leggas, M. (2021). Clinical pharmacology and dosing regimen optimization of neonatal opioid withdrawal syndrome treatments. Clinical and Translational Science , 14 (4), 1231–1249. https://doi.org/10.1111/cts.12994

[39] Váradi, A., Marrone, GF, Palmer, TC, Narayan, A., Szabó, MR, Le Rouzic, V., Grinnell, SG, Subrath, JJ, Warner, E., Kalra, S., Hunkele, A., Pagirsky, J., Eans, SO, Medina, JM, Xu, J., Pan, YX, Borics, A., Pasternak, GW, McLaughlin, J. P., & Majumdar, S. (2016). Mitragynine/Corynantheidine Pseudoindoxyls As Opioid Analgesics with Mu Agonism and Delta Antagonism, Which Do Not Recruit β-Arrestin-2. Journal of Medicinal Chemistry , 59 (18), 8381–8397. https://doi.org/10.1021/acs.jmedchem.6b00748

[40] Veeramohan, R., Azizan, KA, Aizat, WM, Goh, HH, Mansor, SM, Yusof, NSM, Baharum, SN, & Ng, CL (2018). Metabolomics data of Mitragyna speciosa leaf using LC-ESI-TOF-MS. Data in Brief , 18 , 1212–1216.

[41] WORKING ORGANIZATIONS. IJRAR19J1702 International Journal of Research and Analytical Reviews (IJRAR) www.ijrar.org [Internet]. 2019;334. Available from: www.ijrar.org

.