Jurnal Pertanian Terapan of JURNAL ROCE (AGROSCIENCE)
https://jurnal.rocewisdomaceh.com/index.php/roce e-ISSN : 3032-4505
Vol. 2, No. 1, Thn. 2025
https://doi.org/10.71275/roce.v2i1.73

IN SILICO ANALYSIS OF ACTIVE LIGANDS OF MITRAGYNA SPECIOSA KORTH PLANT AS ANTICOCEPTIVE

ANALISIS IN SILICO LIGAND AKTIF TANAMAN MITRAGYNA SPECIOSA KORTH SEBAGAI ANTIOSISEPTIF

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Abstract

Mitragyna speciosa Korth (MSK) plant known as Kratom is a leading export commodity from West Kalimantan Province. The leaves of this plant are processed by farmers into crumbs and flour to be sold to collectors and exported abroad, especially to the United States. The leaves of this plant have long been used by local people as a traditional herbal medicine to relieve pain and provide a calming effect if the boiled water is drunk. The purpose of this study was to evaluate the content of Kratom as an Antinociceptive, Analgesic, General Anesthetic, Vasodilator, and 5 Hydroxytryptamine Release Stimulant (5HRS). Active metabolites and most of the simplified molecular input line entry (SMILE) codes of the MSK plant were obtained from the Knapsack database. The relationship between active metabolites and proteins in the human body was analyzed using STITCH software computationally. There are 23 active metabolites in MSK leaves. Isomitraphylline, Isopaynantheine, and Paynantheine have the highest Antinociceptive bioactivity (82.8). Corynoxine and Corynoxine B have higher Analgesic bioactivity (81.5) compared to other ligands. Isomitrafoline and Speciophylline show the strongest general Anesthetic (92.2) compared to other ligands.

Keywords*: *mitragyna speciosa korth, in silico, antiocciceptive, analgesic

Abstrak

Tanaman Mitragyna speciosa Korth (MSK) atau dikenal dengan nama Kratom merupakan komoditas ekspor unggulan dari Provinsi Kalimantan Barat. Daun tanaman ini diolah oleh para petani menjadi remahan dan bentuk tepung untuk dijual kepada para pengepul dan diekspor ke luar negeri terutama ke Amerika Serikat. Daun tanaman ini sudah lama digunakan masyarakat lokal sebagai jamu tradisional untuk menghilangkan rasa nyeri dan memberikan efek tenang jika diminum air rebusannya. Tujuan dari studi ini yaitu untuk mengevaluasi kandungan Kratom sebagai Antiosiseptif, Analgesik, Anestesis Umum, Vasodilator, dan 5 Hydroxytryptamine Release Stimulant (5HRS). Metabolit aktif dan sebagian besar kode simplified molecular input line entry (SMILE) tanaman MSK diperoleh dari database Knapsack. Hubungan metabolit aktif dengan protein dalam tubuh manusia dianalisis menggunakan perangkat lunak STITCH secara komputasional.. Terdapat 23 metabolit aktif dalam daun MSK. Isomitraphylline, Isopaynantheine, dan Paynantheine memiliki bioaktivitas Antinociceptive tertinggi (82,8). Corynoxine dan Corynoxine B memiliki bioaktivitas Analgesic (81,5) lebih tinggi dibandingkanligand lain. Isomitrafoline dan Speciophylline menunjukkan Anesthetic general (92,2) paling kuat dibandingkan dengan ligand lain.

Kata Kunci : mitragyna speciosa korth, in silico, antioksisepsi, analgesik

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INTRODUCTION

Antinociceptive substances are substances that have therapeutic effect activity in suppressing pain. (Qadir *et al*., 2020). Analgesic substances are substances that have an activity to stop or reduce pain. (Vardanyan & Hruby, 2006). General anesthetic substances are substances that can cause loss of consciousness accompanied by loss of protective reflexes. (Dodds, 1999). Vasodilators are substances that can widen blood vessels so that they can control hypertension, pain due to coronary heart disease, and cessation of blood flow that supplies the heart muscle. (Hariri & Patel, 2023). Ligands that have properties as 5 Hydroxytryptamine release stimulants are tryptophan metabolites that have activity as modulators for the development and production of nervous system cells, intestinal resistance, synthesis and release of chemical substances in the form of mucus, the body's response to injury, and the development of outer cells that cover the body. (Liu *et al*., 2021). Bioactive ligands obtained from traditional medicinal plants have been widely used to treat various diseases in humans. (Chidambaram *et al*., 2022). One of the traditional medicinal plants that has been recognized for its efficacy for decades is the Kratom plant native to West Kalimantan from Indonesia. This plant has its uniqueness with its extraordinary opioid and stimulant bioactivity (Paul *et al.*, 2023). Kratom plants are exported to America in the form of leaf flour, capsules, resin, and thick extracts with Mytragynine and 7-Hydroxymitragyninen as the main components (Sharma *et al*., 2019). People consider the leaves of this plant as herbal medicine for coughs, diarrhea, diabetes, analgesics, and inflammation. (Maharani & Prasetyo, 2022). The medicinal properties of a plant can be screened as long as the chemical ligand content is known. Chemical ligands that have bioactivity as drugs can be screened with the help of a computer. One of the software in the form of a server that can be used to screen the efficacy of several ligands in a plant is the PASS Server. (Prabhakar *et al*., 2006). The chemical ligands that are screened for their efficacy are predicted from the SMILE (Simplified Molecular Input Entry Line) code. This code is a modern chemical bond code that is converted into lines and facilitates the grouping process in the system. (Alfiyanti *et al*., 2019). The SMILE code is used in the PASS Server to screen its bioactivity so that the predicted efficacy of each ligand contained in a plant can be known. The correlation between chemical ligands and proteins in the human body can be analyzed using the STITCH server program. This study aims to evaluate the bioactivity of chemical ligands in kratom plants that have bioactivity as antiseptics, analgesics, general anesthetics, vasodilators, and 5 Hydroxytryptamine release stimulants. The method used follows the procedure of Iskandar et al. with several adaptations. (Iskandar *et al*., 2022)

RESEARCH METHODS

This study was conducted using an in silico analysis approach that was descriptive-analytical and was carried out in the Microbiology Laboratory of the Politeknik Negeri Pontianak.

Preparation of Materials

The Latin name of the MSK plant was entered along with its scientific name into the search engine at http://www.knapsackfamily.com/KNApSAcK_Family/ and the ligand names and SMILE codes were obtained.

Bioactivity Screening of Each Ligand

Each SMILE code of the ligand was screened using the PASS server (https://www.way2drug.com/PassOnline/predict.php) to determine the predicted bioactivity value indicated by the active probability (Pa) value >70%.

Relationship Between Ligands And Proteins In The Human Body

Chemical ligands in plants are predicted to interact with proteins in the human body so that the relationship between the two can be analyzed. The prediction uses the STICH program

RESULTS AND DISCUSSION

MSK plants contain 23 active ligands with various bioactivity Pa values including Antiocciceptive, Analgesic, General Anesthetic, Vasodilator, and 5 Hydroxytryptamine Release Stimulants (5HRS). More details can be seen in Table 1.

Table 1. Results of Screening Pa Bioactivity of Ligands in MSK Plants (%)

No	Ligand	Antinosiseptif	Analgesik	General Anesthesia	Vasodilator	5 HRS
1	3-Isoajmalicine	-	-	-	-	-
2	Ciliaphylline	75.3	73.1	-	-	-
3	Corynantheidine	81.4	81.3	-	-	-
4	Corynoxeine	71.1	74.0	-	-	-
5	Corynoxine A	70.4	81.5	-	-	-
6	Corynoxine B	70.4	81.5	-	-	-
7	Isocorynantheidine	81.4	81.3	-	-	-
8	Isomitrafoline	-	-	92.2	70.3	
9	Isomitraphylline	82.8	-	-	84.9	79.0
10	Isopaynantheine	82.8	-	-	84.9	79.0
11	Isorhynchophylline	74	81.4	-	-	-
12	Javaphylline	-	-	82.4	70.7	
13	Mitrafoline	73.6	71.5	-	-	-
14	Mitragynine oxindole A	75.3	73.1	-	-	-
15	Mitragynine oxindole B	75.3	73.1	-	-	-
16	Mitrajavine	-	-	87.9	94.9	
17	Paynantheine	82.8	-	-	84.9	79.0
18	Rhynchociline	75.3	73.1	-	-	-
19	Speciociliatine	-	-	-	78.1	-

No	Ligand	Antinosiseptif	Analgesik	General Anesthesia	Vasodilator	5 HRS
20	Speciofoline	73.6	71.5	-	-	-
21	Speciogynine	-	-	-	78.1	-
22	Specionoxeine	72.6	-	-	-	-
23	Speciophylline	-	-	92.2	70.3	-
	Average	52.96	46.05	15.42	31.18	10.30

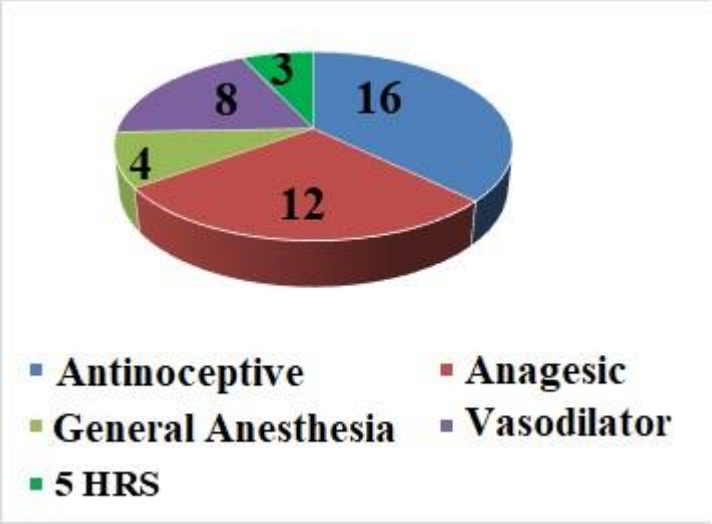

Figure 1. Number of Ligand Involvement in Each Bioactivity

Bioactivity as Antinociceptive involves 16 most chemical ligands, followed by Analgesic (12), Vasalidator (8), General anesthetic (4) and HRS (3) (Figure 1). Based on the screening of analysis results using PASS Server (Table 1), the average value of Paligand with bioactivity as Antinociceptive is 52.96%, Analgesic 46.05%, General anesthetic 15.42%, Vasodilator 31.18%, and 5 HRS 10.30%. Of the 23 active ligands, the strongest Antinociceptive bioactivity is possessed by Isomitraphylline, Isopaynantheine, and Paynantheine with a Pa value of 82.8%. The highest Analgesic bioactivity is possessed by Corynoxine A and Corynoxine B ligands with a Pa value of 81.5%. The strongest general anesthetic bioactivity is in the Speciophylline ligand with a Pa value of 92.2%. The highest Pa value of vasodilator bioactivity of 94.9% is owned by Mitrajavine. Meanwhile, Isomitraphylline, Isopaynantheine, and Paynantheine have 5HRS bioactivity with the same Pa value of 79.0%.

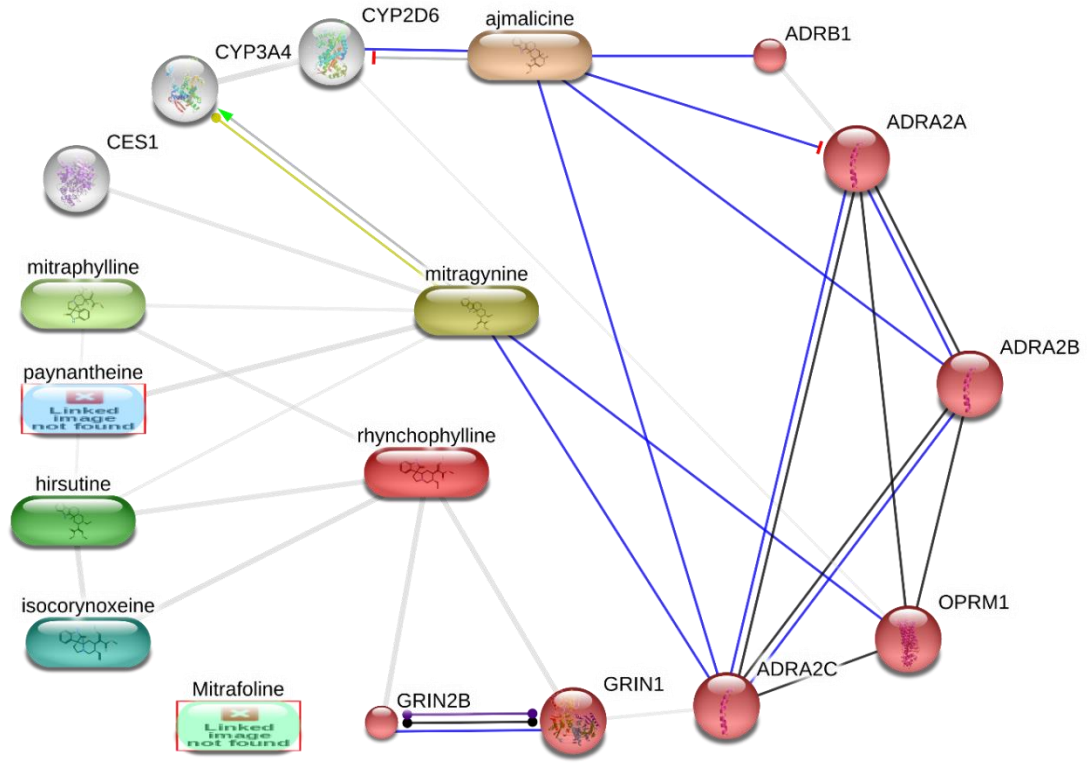

Figure 2. Relationship of Active Ligands to Proteins

The relationship between proteins involved in the human body with active ligands from MSK plants is described in Figure 2. Ligands detected by the STITCH program database include Mitraphylline, Paynantheine, Hirsutine, Isocorynoxeine, Ajmalicine, Mitragynine, Rhynchophylline, and Mitrafoline. Other ligands have not been detected because the data from the study of the related ligands have not been updated by the STITCH program database.

Molecular Mechanism

The molecular mechanism of the interaction between ligands from MSK plants with proteins in the human body that has been analyzed through the STITCH program in Figure 2 shows that the KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway with the type of Neuroactive Ligand-Receptor Interaction (NLRI) with a false discovery rate value of 5.08×10^{-7}. NLRI is a combination of receptors and ligands on the plasma membrane that correlate with intracellular and extracellular signals. (Lauss *et al*., 2007). The NLRI mechanism is related to pain caused by a disease, the severity of the pain, time, and pain relief (Su *et al*., 2017). NLRI also involves 5 HRS related to depression due to pathogenesis (Wen *et al*., 2022). Seven proteins involved in the NLRI mechanism are Adrenoceptor alpha 2A (ADRA2A), Adrenoceptor alpha 2B (ADRA2B), Adrenoceptor alpha 2C (ADRA2C), Adrenoceptor beta 1 (ADRB1), Cytochrome P450 Family 2 Sub Family D polypetide 6 (CYP2D6), Cytochrome P450 Family 3 Sub Family A Polypetide 4 (CYP3A4), Opioid Receptor Mu1 (OPRM1), Glutamate Receptor Ionotropic N-Methyl D-Aspatate 1 (GRIN1), and Glutamate Receptor Ionotropic N-Methyl D-Aspatate 2B

(GRIN2B). Mitragynine activates CYP3A4 by 70%. CYP3A4 is an enzyme that can break down drugs in the liver, control the oxidation of drugs that have been clinically prescribed, and influence toxicity, pharmacokinetics, and clinical results of drug treatment (Mulder *et al*., 2021). CYP3A4 plays a role in the metabolism of drugs, pollutants, plant toxins, and carcinogens to protect against environmental toxicity which is then excreted through urine or bile (Shayeganpour *et al*., 2006; Kumagai *et al*., 2012).

Mitragynine interacts by binding with ADRA2C and OPRM1 with scores of 30.2% and 70.4%, respectively. OPRM1 is a gene that encodes the main receptor for opioid action (Vieira et al., 2019). OPRMI is predicted to be used shortly to adjust opioid therapy, avoid opioid side effects and disease progression (De Gregori *et al*., 2015). Opioids are a type of drug group that produces analgesic properties that can relieve pain in the human body. (Ramos-Matos et al., 2023). 3-Isoajmalicine interacts by binding with ADRA2C, ADRA2B, CYP2D6, and ADRB1 with scores of 99.5%; 97.2%; 95.3% and 30.9% respectively. On the other hand, 3-Isoajmalicine inhibits ADRA2A by 80.0%. ADRA2A is one type of adrenergic receptor (for adrenaline or epinephrine). In general, this adrenergic receptor has the property of inhibiting adenylate cyclase (AS) (Durkee *et al*., 2019). These receptors include 3 highly homologous subtypes: alpha2A, alpha2B, and alpha2C (Gallaway *et al*., 2022; Zhu *et al.*, 2019; Maaliki *et al*., 2019; *MacKillop et al*., 2019; Wang *et al*., 2018). AS inhibition can relieve pain and reduce behaviors associated with opioid dependence (Giacoletti *et al*., 2022). AS inhibition plays an important role in treating pain due to nerve disorders in the body and pain due to inflammation (Haddad *et al*., 2023).

CONCLUSION

This study is far from perfect because it only relies on the in silico approach method. This method is used to save costs with a simple procedure to evaluate and analyze the potential bioactivity of active ligands in the MKS Plant as a herbal pain reliever. This plant contains 23 ligands that are predicted as substances that have Antiocclusive, Analgesic, General Anesthetic, Vasodilator, and 5 Hydroxytryptamine Release Stimulant bioactivity. Although this study was conducted using a basic computational approach and was not equipped with in vitro and in vivo tests, the results of this study are basic studies so further evidence is needed regarding ligands related to dosage, safe consumption limits, and negative effects of using the MKS plant as a herbal pain reliever therapy.

ACKNOWLEDGEMENTS

Thank you very much to the Politeknik Negeri Pontianak for providing free WIFI internet facilities.

https://jurnal.rocewisdomaceh.com/index.php/roce e-ISSN : 3032-4505
Vol. 2, No. 1, Thn. 2025
https://doi.org/10.71275/roce.v2i1.73

REFERENCES

Alfiyanti, Y. D., Ratnawati, D. E., & Anam, S. (2019). Klasifikasi Fungsi Senyawa Aktif Data Berdasarkan Kode Simplified Molecular Input Line Entry System (SMILES) menggunakan Metode Modified K-Nearest Neighbor. *Jurnal Pengembangan Teknologi Informasi Dan Ilmu Komputer*, *3*(4 SE-), 3244–3251. https://j-ptiik.ub.ac.id/index.php/j-ptiik/article/view/4902.

Chidambaram, K., Alqahtani, T., Alghazwani, Y., Aldahish, A., Annadurai, S., Venkatesan, K., Dhandapani, K., Thilagam, E., Venkatesan, K., Paulsamy, P., Vasudevan, R., & Kandasamy, G. (2022). Medicinal Plants of Solanum Species: The Promising Sources of Phyto-Insecticidal Compounds. *Journal of Tropical Medicine*, *2022*, 1–22. https://doi.org/10.1155/2022/4952221.

De Gregori, M., Diatchenko, L., Belfer, I., & Allegri, M. (2015). OPRM1 receptor as a new biomarker to help the prediction of post-mastectomy pain and recurrence in breast cancer. *Minerva Anestesiologica*, *81*(8), 894–900. http://www.ncbi.nlm.nih.gov/pubmed/25300626

Dodds, C. (1999). General Anaesthesia. *Drugs*, *58*(3), 453–467. https://doi.org/10.2165/00003495-199958030-00006.

Durkee, C. A., Covelo, A., Lines, J., Kofuji, P., Aguilar, J., & Araque, A. (2019). G i/o protein-coupled receptors inhibit neurons but activate astrocytes and stimulate gliotransmission. *Glia*, *67*(6), 1076–1093. https://doi.org/10.1002/glia.23589.

Gallaway, K. A., Skaar, T. C., Biju, A., Slaven, J., & Tillman, E. M. (2022). A pilot study of ADRA2A genotype association with doses of dexmedetomidine for sedation in pediatric patients. *Pharmacotherapy*, *42*(6), 453–459. https://doi.org/10.1002/phar.2684.

Giacoletti, G., Price, T., Hoelz, L. V. B., Shremo Msdi, A., Cossin, S., Vazquez-Falto, K., Amorim Fernandes, T. V., Santos de Pontes, V., Wang, H., Boechat, N., Nornoo, A., & Brust, T. F. (2022). A Selective Adenylyl Cyclase 1 Inhibitor Relieves Pain Without Causing Tolerance. *Frontiers in Pharmacology*, *13*. https://doi.org/10.3389/fphar.2022.935588.

Haddad, M., Cherchi, F., Alsalem, M., Al-saraireh, Y. M., & Madae'en, S. (2023). Adenosine Receptors as Potential Therapeutic Analgesic Targets. *International Journal of Molecular Sciences*, *24*(17), 13160. https://doi.org/10.3390/ijms241713160.

Hariri, L., & Patel, J. B. (2023). Vasodilators. In *StatPearls*. http://www.ncbi.nlm.nih.gov/pubmed/27092479.

Iskandar, D., Widodo, N., Warsito, W., Masruri, M., Rollando, R., Warsidah, W., & Antang, Y. P. P. (2022). Proposed Functional Activity of Bioactive Compounds from Spatholobus littoralis Hassk in LC-MS-MS and Silico Studies. *Materials Science Forum*, *1061*, 181–186. https://doi.org/10.4028/p-0uei8m.

Kumagai, T., Suzuki, H., Sasaki, T., Sakaguchi, S., Miyairi, S., Yamazoe, Y., & Nagata, K. (2012). Polycyclic Aromatic Hydrocarbons Activate CYP3A4 Gene Transcription

through Human Pregnane X Receptor. *Drug Metabolism and Pharmacokinetics*, *27*(2), 200–206. https://doi.org/10.2133/dmpk.DMPK-11-RG-094.

Lauss, M., Kriegner, A., Vierlinger, K., & Noehammer, C. (2007). Characterization of the drugged human genome. *Pharmacogenomics*, *8*(8), 1063–1073. https://doi.org/10.2217/14622416.8.8.1063.

Liu, N., Sun, S., Wang, P., Sun, Y., Hu, Q., & Wang, X. (2021). The Mechanism of Secretion and Metabolism of Gut-Derived 5-Hydroxytryptamine. *International Journal of Molecular Sciences*, *22*(15), 7931. https://doi.org/10.3390/ijms22157931.

Maaliki, D., Issa, K., Al Shehabi, T., El-Yazbi, A., & Eid, A. H. (2019). The role of α2-adrenergic receptors in hypertensive preeclampsia: A hypothesis. *Microcirculation (New York, N.Y. : 1994)*, *26*(1), e12511. https://doi.org/10.1111/micc.12511.

MacKillop, J., Gray, J. C., Weafer, J., Sanchez-Roige, S., Palmer, A. A., & de Wit, H. (2019). Genetic influences on delayed reward discounting: A genome-wide prioritized subset approach. *Experimental and Clinical Psychopharmacology*, *27*(1), 29–37. https://doi.org/10.1037/pha0000227.

Maharani, A. R., & Prasetyo, H. (2022). Legality of the Legal Status of Kratom Plants in Indonesia. *UNIFIKASI : Jurnal Ilmu Hukum*, *9*(1), 27–38. https://doi.org/10.25134/unifikasi.v9i1.5502.

Mulder, T. A. M., van Eerden, R. A. G., de With, M., Elens, L., Hesselink, D. A., Matic, M., Bins, S., Mathijssen, R. H. J., & van Schaik, R. H. N. (2021). CYP3A4∗22 Genotyping in Clinical Practice: Ready for Implementation? *Frontiers in Genetics*, *12*. https://doi.org/10.3389/fgene.2021.711943.

Paul, B., Sribhashyam, S., & Majumdar, S. (2023). *Opioid signaling and design of analgesics* (pp. 153–176). https://doi.org/10.1016/bs.pmbts.2022.06.017.

Prabhakar, K. R., Veerapur, V. P., Bansal, P., Vipan, K. P., Reddy, K. M., Barik, A., Reddy, B. K. D., Reddanna, P., Priyadarsini, K. I., & Unnikrishnan, M. K. (2006). Identification and evaluation of antioxidant, analgesic/anti-inflammatory activity of the most active ninhydrin–phenol adducts synthesized. *Bioorganic & Medicinal Chemistry*, *14*(21), 7113–7120. https://doi.org/10.1016/j.bmc.2006.06.068.

Qadir, S., Bashir, S., & John, R. (2020). Saffron—Immunity System. In *Saffron* (pp. 177–192). Elsevier. https://doi.org/10.1016/B978-0-12-818462-2.00015-2.

Ramos-Matos, C. F., Bistas, K. G., & Lopez-Ojeda, W. (2023). Fentanyl. In *StatPearls*. http://www.ncbi.nlm.nih.gov/pubmed/30551090.

Sharma, A., Kamble, S. H., León, F., Chear, N. J. -Y., King, T. I., Berthold, E. C., Ramanathan, S., McCurdy, C. R., & Avery, B. A. (2019). Simultaneous quantification of ten key Kratom alkaloids in Mitragyna speciosa leaf extracts and commercial products by ultra-performance liquid chromatography−tandem mass spectrometry. *Drug Testing and Analysis*, *11*(8), 1162–1171. https://doi.org/10.1002/dta.2604.

Shayeganpour, A., El-Kadi, A. O. S., & Brocks, D. R. (2006). Determination Of The Enzyme(S) Involved In The Metabolism Of Amiodarone In Liver And Intestine Of Rat: The

Contribution Of Cytochrome P450 3a Isoforms. *Drug Metabolism and Disposition*, *34*(1), 43–50. https://doi.org/10.1124/dmd.105.006742.

Su, S., Shao, J., Zhao, Q., Ren, X., Cai, W., Li, L., Bai, Q., Chen, X., Xu, B., Wang, J., Cao, J., & Zang, W. (2017). MiR-30b Attenuates Neuropathic Pain by Regulating Voltage-Gated Sodium Channel Nav1.3 in Rats. *Frontiers in Molecular Neuroscience*, *10*. https://doi.org/10.3389/fnmol.2017.00126.

Vardanyan, R. S., & Hruby, V. J. (2006). Analgesics. In *Synthesis of Essential Drugs* (pp. 19–55). Elsevier. https://doi.org/10.1016/B978-044452166-8/50003-0.

Vieira, C. M. P., Fragoso, R. M., Pereira, D., & Medeiros, R. (2019). Pain polymorphisms and opioids: An evidence-based review. *Molecular Medicine Reports*, *19*(3), 1423–1434. https://doi.org/10.3892/mmr.2018.9792.

Wang, Q.-F., Sun, Z., Zheng, F.-R., Zhang, G.-W., & Liu, Z. (2018). Association of Adrenergic Receptor α2A (α2A-AR) Gene rs1800544 Polymorphism with Bone Mineral Density and Bone Turnover Markers in an Elderly Chinese Population. *Medical Science Monitor : International Medical Journal of Experimental and Clinical Research*, *24*, 5102–5109. https://doi.org/10.12659/MSM.908376.

Wen, L., Fan, Y., Xiong, W., Liu, Y., Zhang, T., Wei, G., Altamirano, A., Zhang, T., & Yan, Z. (2022). Exploring the Mechanism of Action of Trachelospermi Caulis et Folium for Depression Based on Experiments: Combining Network Pharmacology and Molecular Docking. *Computational and Mathematical Methods in Medicine*, *2022*, 1–17. https://doi.org/10.1155/2022/3945063.

Zhu, S.-J., Wang, K.-R., Zhang, X.-X., & Zhu, S.-M. (2019). Relationship between genetic variation in the α2A-adrenergic receptor and the cardiovascular effects of dexmedetomidine in the Chinese Han population. *Journal of Zhejiang University. Science. B*, *20*(7), 598–604. https://doi.org/10.1631/jzus.B1800647.