

**EFEK FARMAKOLOGI DAN ANALISIS SENYAWA DARI
KRATOM (*Mitragyna speciosa* Korth) SEBAGAI
PENGOBATAN BARU**

SKRIPSI

**MUHAMMAD TAUFIQ
A183025**



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Sebagai salah satu syarat untuk memperoleh gelar Sarjana Farmasi

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September, 2020
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Kutipan atau saduran baik sebagian ataupun seluruh naskah, harus menyebut nama pengarang dan sumber aslinya, yaitu Sekolah Tinggi Farmasi Indonesia.

Lembar persembahan

Skripsi ini adalah persembahan kecil saya untuk orang tua saya. Ketika dunia menutup pintunya pada saya, ayah dan ibu membuka lengannya untuk saya. Ketika orang-orang menutup telinga mereka untuk saya, mereka berdua membuka hati untukku. Terima kasih karena selalu ada untukku.

ABSTRAK

Pohon *Mitragyna speciosa* Korth. (Rubiaceae) ditemukan di Asia Tenggara (Thailand, Indonesia, Malaysia, Myanmar, Filipina dan Papua Nugini). Secara tradisional, *Mitragyna speciosa* digunakan untuk meredakan nyeri, hipertensi, batuk, diare dan sebagai pengganti morfin untuk mengobati pecandu. *Association of Southeast Asian Nations* (ASEAN), menyebut kratom sebagai obat. Kratom mengandung lebih dari 40 jenis alkaloid diantaranya *mitraginin* sebanyak (66,2%) dan turunannya, *speciogynine* (6,6%), *speciociliatine* (0,8%), *paynantheine* (8,6%), *7-hidroksimitraginin* (2%). Artikel ini dibuat untuk memberikan informasi terkait efek farmakologis kratom, analisis senyawa kratom, dan potensi senyawa dari kratom menjadi obat baru. Metode yang digunakan dalam penelitian ini adalah review dan menganalisis artikel kratom dari makalah penelitian, review bibliografi dan laporan kasus termasuk, penelitian yang dilakukan di Indonesia dan dalam bahasa Inggris. Dari hasil review yang di dapat penggunaan kratom (*Mitragyna speciosa* Korth.) sebagai bahan baku obat dalam dunia kesehatan dianjurkan menggunakan senyawa mitraginin yang dosisnya dapat diatur dengan mudah tergantung tujuan penggunaan dan efek farmakologis yang diinginkan.

Kata Kunci : Kratom, *Mitragyna speciosa* Korth, efek farmakologi, laporan kasus, toksisitas, manfaat, obat baru.

ABSTRACT

Mitragyna speciosa Korth. (Rubiaceae) a tree found in Southeast Asia (Thailand, Indonesia, Malaysia, Myanmar, Philippines and Papua New Guinea. Traditionally, the *Mitragyna speciosa* was used to alleviate pain, hypertension, cough, diarrhea and as a substitute for morphine in treating addicts. Association of Southeast Asian Nations, refers to kratom as a drug. Kratom contains more than 40 types of alkaloids including Mitraginin, as many as (66.2%) and their derivatives, speciogynine (6.6%), speciociliatine (0.8%), paynantheine (8.6%), 7- hidroksi Mitraginin (2%). The article was created to provide information related to the pharmacological effects of kratom, kratom compound analysis, and the potential of compounds from kratom to become new drugs. The method used in this research is to review and analyze kratom articles from research papers, bibliographic reviews and case reports included, research conducted in Indonesia and in English. The main purpose of this review is not only to understand the chemical content, benefits of kratom, and analytical methodologies for analysis, but also the use of kratom secondary metabolites as therapeutic drugs and the side effects associated with their consumption, to help health professionals assess the content of compounds from kratom worthy of being new drugs.

Keywords: *Kratom, Mitragyna speciosa* Korth; effect pharmacology; case report; toxicity; benefits; new drugs.

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DAFTAR PUSTAKA

- Abd Razak, N.H.Z.1 bin Abdul Rahman, M.B., Ashari, S.E. 2020. "Optimization of Extraction Yield and Phytochemical Characterization of Crude Methanolic Extract and Its Fractions of *Mitragyna speciosa* Leaves" BMC Chemistry. <https://doi.org/10.21203/rs.3.rs-52121/v1>
- Aggarwal, G., Robertson, E., McKinlay, J., Walter, E. 2018. "Death from Kratom toxicity and the possible role of intralipid" Journal of the Intensive Care Society. 19(1),61-63.
- Ahmad, K., Aziz, Z. 2012. "*Mitragyna speciosa* use in the northern states of Malaysia: a cross-sectional study" Journal of Ethnopharmacology. 141(1):446-450.
- Apryani, EM., Hidayat MT., Moklas MAA., Fakurazi S., Idayu NF., 2010. "Effects of mitragynine from *Mitragyna speciosa* Korth leaves on working memory" Journal of Ethnopharmacology. 129(3):357–60.
- Azizi, J., Ismail, S., Mansor, S.M. 2013. "*Mitragyna speciosa* Korth leaves extracts induced the CYP450 catalyzed aminopyrine-N-demethylase (APND) and UDP-glucuronosyl transferase (UGT) activities in male Sprague-Dawley rat livers" Drug Metabolism and Personalized Therapy. 28:95-105.
- Azizi, J., Ismail, S., Mordi, M.N., Ramanathan, S., Said, M.I.M., Mansor, S.M. 2010. "In vitro and in vivo effects of three different *Mitragyna speciosa* Korth leaf extracts on phase II drug metabolizing enzymes—glutathione transferases (GSTs)" Molecules. 15, 432-441, <https://doi.org/10.3390/molecules15010432>.
- Badan Pengawasan Obat dan Makanan (BPOM). (2005) "Peraturan Kepala Badan Pengawasan Obat dan Makanan Republik Indonesia Nomor" HK.00.05.41.1384.
- Basilieri, S., Kerrigan, S. 2020. "Temperature and pH-Dependent Stability of *Mitragyna* Alkaloids" Journal of Analytical Toxicology. 44(4):314-324. <https://doi.org/10.1093/jat/bkz103>
- Beng, Goh Teik. 2011. "A Simple And Cost Effective Isolation And Purification Protocol Of Mitragynine From *Mitragyna speciosa* Korth (Ketum) Leaves" Universiti Sains Malaysia, Minden 11800, Penang, Malaysia.
- Boffa, L., Ghè, C., Barge, A., Muccioli, G., Cravotto, G. 2016. "Alkaloid profiles and activity in different *Mitragyna speciosa* strains" Natural Product Communications. 13.
- Carpenter, J.M., Criddle, C.A., Craig, H.K., Ali, Z., Zhang, Z., Khan, I.A., Sufka, K.J. 2016. "Comparative effects of *Mitragyna speciosa* extract, mitragynine, and opioid agonists on thermal nociception in rats" Fitoterapia. 109:87-90.

- Cheaha, D., Keawpradub, N., Sawangjaroen, K., Phukpattaranont, P., Kumarnsit, E. 2015 “Effects of an alkaloid-rich extract from *Mitragyna speciosa* leaves and fluoxetine on sleep profiles, EEG spectral frequency and ethanol withdrawal symptoms in rats” *Phytomedicine*. 22:1000-1008.
- Cheaha., *et al.*, (2015). Effects of an alkaloid-rich extract from *Mitragyna speciosa* leaves and fluoxetine on sleep profiles, EEG spectral frequency and ethanol withdrawal symptoms in rats. *Phytomedicine*, 22(11), 1000–1008.
- Chittrakarn, S., Keawpradub, N., Sawangjaroen, K., Kansenalak, S., Janchawee, B. 2010. “The neuromuscular blockade produced by pure alkaloid, mitragynine and methanol extract of kratom leaves (*Mitragyna speciosa* Korth.)” *Journal of Ethnopharmacology*. 129:344-349.
- Chittrakarn, S., Sawangjaroen, K., Prasetho, S., Janchawee, B., Keawpradub, N. 2008. “Inhibitory effects of kratom leaf extract (*Mitragyna speciosa* Korth.) on the rat gastrointestinal tract” *Journal of ethnopharmacology*. 116:173-178.
- Cinosi E, Martinotti G, Simonato P, Singh D, Demetrovics Z, Roman-Urrestarazu A, et al. 2015. “Following (the roots) of kratom (*Mitragyna speciosa*): The evolution of an enhancer from a traditional use to increase work and productivity in Southeast Asia to a recreational psychoactive drug in Western Countries” *BioMed Research International*. <http://dx.doi.org/10.1155/2015/968786>
Diakses : 29 Desember 2019
- Cinosi, E., Martinotti, G., Simonato, P., Singh, D., Demetrovics, Z., Roman-Urrestarazu, A., Yu, W.J. 2015. “Following “the roots” of Kratom (*Mitragyna speciosa*): the evolution of an enhancer from a traditional use to increase work and productivity in Southeast Asia to a recreational psychoactive drug in western countries” *BioMed research international*. 3:1-11.
- Compton, D. M., Garcia, C., Kamaratos, A., Johnson, B.G., Wedge, T. 2010. “An examination of the consequences of chronic exposure to *Mitragyna speciosa* during adolescence on learning and memory in adulthood” *J Phytopharmacol*. 3:300-309.
- Corkery, J.M., Streete, P., Claridge, H., Goodair, C., Papanti, D., Orsolini, L., Hendricks, A. 2019. “Characteristics of deaths associated with kratom use” *Journal of psychopharmacology*. 33(9):1102-1123.
- Depkes, RI. 2010. “Farmakope Herbal Indonesia.” Jakarta: Departemen Kesehatan Republik Indonesia.
- Devotee, Kratom. 2009. Kraom.net - *Mitragyna speciosa* Kratom: a Sedative narcotic and a Stimulant:. Kratom.net – Kratom. Net Home. 13 Nov. 2009.

- <http://www.kratom.net/content.php?50-Mitragyna-speciosa-Kratom-a-sedative-narcotic-and-a-stimulant#top> Diakses : 29 Desember 2019.
- Dey, S., Rathod, V.K. 2013. "Ultrasound assisted extraction of β -carotene from *Spirulina platensis*" *Ultrasonics Sonochemistry*. 20:271–276.
- European Monitoring Centre for Drugs and Drug Addiction [EMCDDA]. *Kratom (Mitragyna speciosa)*. <http://www.emcdda.europa.eu/publications/drug-profiles/kratom/de> Diakses : 29 Desember 2019.
- Fluyau, D., Revadigar, N. 2017. "Biochemical benefits, diagnosis, and clinical risks evaluation of kratom" *Frontiers in Psychiatry*. 8:62.
- Gandjar, I. G. dan Rohman, A., 2007. *Kimia Farmasi Analisis*, Pustaka Pelajar. Yogyakarta.
- Ginting, E. 2013. "Carotenoid extraction of orange-fleshed sweet potato and its application as natural food colorant" *J. Teknol. dan Industri Pangan*, 24.
- Hanajiri, Ruri Kikura., *et al.*, 2008 "Simultaneous analysis of mitragynine, 7-hydroxymitragynine, and other alkaloids in the psychotropic plant "kratom" (*Mitragyna speciosa*) by LC-ESI-MS" *Japanese Association of Forensic Toxicology and Springer*.
- Harizal, S.N., Mansor, S.M., Hasnan, J., Tharakan, J.K.J., Abdullah, J. 2010. "Acute toxicity study of the standardized methanolic extract of *Mitragyna speciosa* Korth in rodent" *Journal of ethnopharmacology*. 131(2):404-409.
- Harun, N., Navaratnam V., Hassan Z., Shoib M. 2015 "Discriminative stimulus properties of mitragynine (kratom) in rats" *Phycopharmacology*. 232(13):2227–28.
- Hassan, Z., Muzaimi, M., Navaratnam, V., Yusoff, N.H., Suhaimi, F.W., Vadivelu, R., Jayabalan, N. 2013. "From Kratom to mitragynine and its derivatives: physiological and behavioural effects related to use, abuse, and addiction" *Neuroscience & Biobehavioral Reviews*. 37:138-151.
- Hemby, S.E., McIntosh, S., Leon, F., Cutler, S.J., McCurdy, C.R. 2019. "Abuse liability and therapeutic potential of the *Mitragyna speciosa* (kratom) alkaloids mitragynine and 7-hydroxymitragynine. *Addiction Biology*. 24(5):874-885.
- Hidayati, A. 2013. "Sedative Effect Test of N-Hexane Extract from Kratom (*Mitragyna speciosa* Korth.) Leaves in Balb/c strain male mice" *Doctoral dissertation, Tanjungpura University*. 3.

- Holler, J.M., Vorce, S.P., McDonough-Bender, P.C., Magluilo Jr,J., Solomon, C.J., Levine, B. 2011. "A drug toxicity death involving propylhexedrine and mitragynine" *Journal of analytical toxicology*. 35(1):54-59.
- Ichwan, R., Rais. 2014. "Ekstraksi Andrografolid dari *Andrographis paniculata* (Burm.f.) Nees Menggunakan Ekstraktor Soxhlet"
- Ikhwan, D., Harlia, W.A. 2018. "Characterization of cytotoxic compounds from ethyl acetate fraction of Kratom leaves (*Mitragyna speciosa* Korth.) And their activity against T47D breast cancer cells" *Jurnal Kimia Khatulistiwa*. 7:18-24.
- Jessica, E., Adkins, E.W. 2011. "*Mitragyna speciosa*, A Psychoactive Tree from Southeast Asia with Opioid Activity" *Current Topics in Medicinal Chemistry*. 11:1165-1175.
- Karinen, R., Fosen, J.T., Rogde, S., Vindenes, V. 2014. "An accidental poisoning with mitragynine" *Forensic science international*. 245:e29-e32.
- Kikura-Hanajiri, R., Kawamura, M., Maruyama, T., Kitajima, M., Takayama, H., Goda, Y. 2009. "Simultaneous analysis of mitragynine, 7-hydroxymitragynine, and other alkaloids in the psychotropic plant "kratom"(*Mitragyna speciosa*) by LC-ESI-MS" *Forensic toxicology*. 27, 67-74.
- Kowalczyk, AP., Łozak A., Zjawiony JK. 2013 "Comprehensive methodology for identification of Kratom in police laboratories" *J Forsciint*. 1-20.
- Kronstrand, R., Roman, M., Thelander, G., Eriksson, A. 2011. "Unintentional fatal intoxications with mitragynine and O-desmethyltramadol from the herbal blend Krypton" *Journal of analytical toxicology*, 35(4):242-247.
- Kumarnsit, E., Keawpradub, N., Nuankaew, W. 2006. "Acute and long-term effects of alkaloid extract of *Mitragyna speciosa* on food and water intake and body weight in rats" *Fitoterapia*. 77:339-345.
- Leon, Francisco., Eman Habib., Jessica E., Adkins., Edward B. Furr., Christopher R., McCurdy and Stephen J. Cutler. 2009. "Phytochemical Characterization of the Leaves of *Mitragyna speciosa* Grown in USA" Department of Medicinal Chemistry & National Center for Natural Products Research, School of Pharmacy University of Mississippi University. MS 38677. USA.
- Limsuwanchote, S., Wungsintaweekul, J., Keawpradub, N., Putalun, W., Morimoto, S., Tanaka, H. 2015. "Development of indirect competitive ELISA for quantification of mitragynine in Kratom (*Mitragyna speciosa* Korth.) *Forensic Sci. Int*. 244, 70-77.

- Lu, S., *et al.*, 2009. “Quantitative analysis of mitragynine in human urine by high performance liquid chromatography–tandem mass spectrometry”. *J. Chromatogr. B* 877 2499–2505.
- Luliana, S., Robiyanto, R., Islamy, M.R. 2018. “Antinociceptive Activity of Kratom Leaf Dichloromethane Fraction (*Mitragyna speciosa* Korth.) Oral Route in Swiss Male Mice” *Pharmaceutical Sciences and Research*. 5:58-64,
- Manda, V.K., Avula, B., Ali, Z., Khan, I.A., Walker, L.A., Khan, S.I. 2014. “Evaluation of in vitro absorption, distribution, metabolism, and excretion (ADME) properties of mitragynine, 7-hydroxymitragynine, and mitraphylline” *Planta Med.* 80:568-576.
- Mandal, V., Dewanjee, S., Mandal, S. C. 2009. “Microwave-assisted extraction of total bioactive saponin fraction from *Gymnema sylvestre* with reference to gymnemagenin: a potential biomarker” *Phytochemical Analysis: An International Journal of Plant Chemical and Biochemical Techniques*, 20(6):491-497.
- Masturoh, I., N. Anggita. 2018. “Metodologi Penelitian Kesehatan” Kementerian Kesehatan RI. Jakarta.
- Matsumoto, K., Takayama, H., Narita, M., Nakamura, A., Suzuki, M., Suzuki, T., Tashima, K. 2008. “MGM-9 [(E)-methyl 2-(3-ethyl-7a, 12a-(epoxyethoxy)-9-fluoro-1, 2, 3, 4, 6, 7, 12, 12b-octahydro-8-methoxyindolo [2, 3-a] quinolizin-2-yl)-3-methoxyacrylate], a derivative of the indole alkaloid mitragynine: A novel dual-acting μ - and κ -opioid agonist with potent antinociceptive and weak rewarding effects in mice” *Neuropharmacology*. 55:154-165.
- McIntyre, I.M., Trochta, A., Stolberg, S., Campman, S.C. 2015. “Mitragynine ‘Kratom’ related fatality: a case report with postmortem concentrations” *Journal of analytical toxicology*. 39(2):152-155.
- McWhirter, L., Morris, S. 2010. “A case report of inpatient detoxification after kratom (*Mitragyna speciosa*) dependence” *European addiction research*. 16(4):229-231.
- Menkes Republik Indonesia. 2017. Peraturan Menteri Kesehatan RI Nomor 2 Tahun 2017 Tentang Perubahan Penggolongan Narkotika. Jakarta.
- Moklas, M.A.M. Nurul Raudzah, A.R., Taufik, H.M., Sharida, F., Farah, I.N., Zulkhairi, A., Shamima, A.R. 2008. “A preliminary toxicity study of mitragynine, an alkaloid from *Mitragyna speciosa* Korth and its effects on locomotor activity in rats” *Adv. Med. Dent Sci*. 2:56-60,
- Mossadeq, W.S., Sulaiman, M.R., Mohamad, T.T., Chiong, H.S., Zakaria, Z.A., Jabit, M.L., Israf, D.A. 2009. “Anti-inflammatory and antinociceptive effects of

- Mitragyna speciosa* Korth methanolic extract” Medical Principles and Practice. 18:378-384, <https://doi.org/10.1159/000226292>.
- Mudge, E.M., Brown, P.N. 2017. Determination of mitragynine in *Mitragyna speciosa* raw materials and finished products by liquid chromatography with UV detection: Single-laboratory validation. J. AOAC Int. 2017, 100, 18–24.
- Murple. 2006. Kratom. <http://www.murple.net/yachay/index.php/kratom> Diakses : 29 Desember 2019.
- Nelsen, J.L., Lapoint, J., Hodgman, M.J., Aldous, K.M. 2016. “Seizure and coma following Kratom (*Mitragyna speciosa* Korth) exposure” Journal of Medical Toxicology. 6(4):424-426.
- Notoatmodjo, S. 2002. “Metodologi Penelitian Kesehatan” Rineka Cipta, Jakarta
- Novindriani, D. 2014. “Kratom leaf infusion (*Mitragyna speciosa*) sedative effect test on Balb/C strain male mice” Doctoral dissertation, Tanjungpura Universit. 3.
- Nugraha, W.I., Robiyanto, R., Luliana, S. 2018. “Antinociceptive Activity of Aqueous Fraction of Kratom Leaves (*Mitragyna speciosa* Korth.) on Male Swiss Albino Mice” Traditional Medicine Journal. 23:91-96.
- Orio, L., Alexandru, L., Cravotto, G., Mantegna, S., Barge, A. 2012. “UAE, MAE, SFE-CO₂ and classical methods for the extraction of *Mitragyna spesiosa* leaves” Ultrasonics Sonochemistry. 19:591-595.
- Orio, Laura., Lavinia Alexandru., Giancarlo Cravotto., Stefano Mantegna., Alessandro Barge. 2012. “UAE, MAE, and classical methods for the extraction of *Mitragyna speciosa* leaves. Ultrasonics Sonochemistry 19, 591–595.
- Osborne, C.S., Overstreet, A.N., Rockey, D.C.; Schreiner, A.D. 2019. “Drug-induced liver injury caused by kratom use as an alternative pain treatment amid an ongoing opioid epidemic” Journal of investigative medicine high impact case reports. 7.
- Parthasarathy, S., Bin, A.J., Ramanathan, S., Ismail, S., Sasidharan, S., Said, M.I.M., Mansor, S.M. 2009. “Evaluation of antioxidant and antibacterial activities of aqueous, methanolic and alkaloid extracts from *Mitragyna speciosa* (Rubiaceae family) leaves” Molecules. 14:3964-3974.
- Ponglux, D., *et al.*, (1994) ”A new indole alkaloid, 7 alpha-hydroxy-7H-mitragynine, from *Mitragyna speciosa* in Thailand” Planta Med 60:580–581.
- Prutipanlai, S., Botpiboon, O., Janchawee, B., Theanchaiwattana, S. 2017. “Solid phase extraction method for determination of mitragynine in urine and its application

- to mitragynine excretion study in rats receiving caffeine” *Tropical Journal of Pharmaceutical Research*. 16:1675-1682.
- Reanmongkol, W., Keawpradub, N., Sawangjaroen, K. 2007. “Effects of the extracts from *Mitragyna speciosa* Korth. leaves on analgesic and behavioral activities in experimental animals” *J. Sci. Technol.* 29:39-48.
- Ridayani, Y. 2013. “Test the sedative effect of the ethanol fraction of kratom leaves (*Mitragyna speciosa* Korth.) In male BALB / c mice” *Doctoral dissertation*, Tanjungpura University. 3.
- Ridayani, Y. 2013. Test the sedative effect of the ethanol fraction of kratom leaves (*Mitragyna speciosa* Korth.) In male BALB / c mice” *Doctoral dissertation*, Tanjungpura University 3, 1,
- Sabetghadam, A., Navaratnam, V., and Mansor, SM. 2013. “Dose-response relationship, acute toxicity, and therapeutic index between the alkaloid extract of *Mitragyna speciosa* and its main active compound mitragynine in mice” *Drug Development Reseach*. 23–30.
- Sabetghadam, A., Ramanathan, S., Mansor, S.M. 2010. “The evaluation of antinociceptive activity of alkaloid, methanolic, and aqueous extracts of Malaysian *Mitragyna speciosa* Korth leaves in rats” *Pharmacognosy research*. 2.
- Sabetghadam, A., Ramanathan, S., Sasidharan, S., Mansor, S.M. 2013. “Subchronic exposure to mitragynine, the principal alkaloid of *Mitragyna speciosa*, in rats” *Journal of ethnopharmacology* 146(3):815-823.
- Sanagi., Wan Aini Wan Ibrahi., *et al.*, 2013. “Determination of mitragynine for the identification of *Mitragyna* species in Kedah (Malaysia) by gas chromatography-mass spectrometry.” *Der Pharma Chemica*, 5(5):131-138.
- Sapkale, G. N., Patil, S. M., Surwase, U. S., Bhatbhage, P. K. 2010. “Supercritical fluid extraction” *Int. J. Chem. Sci*, 8(2):729-743.
- Shamima, Abdul Rahman., *et al.*, 2012. “Antinociceptive Action of Isolated Mitragynine from *Mitragyna speciosa* through Activation of Opioid Receptor System” *Int. J. Mol. Sci*. 13, 11427-11442.
- Shargel, L., Yu, A., and Wu, S. 2005. “Biofarmasetika dan Farmakokinetika Terapan Edisi kedua” *Airlangga University Press*, Surabaya. 167 – 187.
- Singh, D., Damodaran, T., Prozialeck, W.C., Grundmann, O., Karunakaran, T., Vicknasingam, B. 2019. “Constipation prevalence and fatigue severity in regular kratom (*Mitragyna speciosa* Korth.) users” *Journal of Substance Use*. 24(3):233-239.

- 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.
- Singh, D., Narayanan, S., Müller, C.P., Swogger, M.T., Rahim, A.A., Leong Bin Abdullah, M.F.I., Vicknasingam, B.K. 2018. "Severity of kratom (*Mitragyna speciosa* Korth.) psychological withdrawal symptoms" *Journal of psychoactive drugs*. 50(5):445-450.
- Singh, D., Narayanan, S., Müller, C.P., Vicknasingam, B., Yücel, M., Ho, E.T.W., Mansor, S.M. 2019. "Long-term cognitive effects of Kratom (*Mitragyna speciosa* Korth.) use" *Journal of psychoactive drugs*. 51(1):19-27.
- Sudjadi. 1988. "Metode Pemisahan. Kanisius" Yogyakarta
- Sugiyono. 2007. "Metode Penelitian Kuantitatif Kualitatif dan R&D" Bandung: Alfabeta
- Sugiyono. 2015. "Metode Penelitian Kombinasi (Mix Methods)" Bandung: Alfabeta.
- Suhaimi, S., Puspasari, H., Husnani, H., Apriani, M. 2019. "Test of concentrated extract of kratom leaves (*Mitragyna speciosa* Korth) on *Propionibacterium acnes* bacteria as cause of acne" *Medical Sains*. 4:1-6.
- Swogger, M.T., Walsh, Z. 2018. "Kratom use and mental health: A systematic review" *Drug and Alcohol Dependence*. 183:134-140.
- Taguay, 2011. "Kratom in Thailand Decriminalisation and Community Control?" *Series on Legislative Reform of Drug Policies* N r .13.
- Tjay, T. H., Rahardja, K. 2007. "Obat-obat penting: khasiat, penggunaan dan efek-efek sampingnya" *Elex Media Komputindo*.
- Tohar, N., Devi, R.S. 2007. "Supercritical Carbon Dioxide Extraction of *Mitragyna speciosa* Korth" *Journal of Pharmacology and Experimental Therapeutics*. 46:251-271,
- Tohar, Norsita., Devi Rosmy Syamsir., Khalijah Awang. 2007. SUPERCRITICAL CARBON DIOXIDE EXTRACTION of *Mitragyna speciosa*. Department of Chemistry, Faculty of Science, University of Malaya, 50603.
- Trakulsrichai, S., Sathirakul, K., Auparakkitanon, S., Krongvorakul, J., Sueajai, J., Noumjad, N., 2015. "Wananukul, W. Pharmacokinetics of mitragynine in man" *Drug design, development and therapy*. 9:2421.

- Tungtananuwat, W., and Lawanprasert. 2010 “Fatal 4x100: Home-made kratom juice cocktail. J Helth Res 24(1): 43-47.
- Tungtananuwat, W., Lawanprasert, S. 2010. “Fatal 4x100; home-made kratom juice cocktail” Journal of Health Research. 24(1):43-47.
- Vicknasingam, B., Narayanan, S., Beng, G.T., Mansor, S.M. 2010. “The informal use of ketum (*Mitragyna speciosa*) for opioid withdrawal in the northern states of peninsular Malaysia and implications for drug substitution therapy” International Journal of Drug Policy. 21:283-288.
- Vinatoru, M. 2001. “An overview of the ultrasonically assisted extraction of bioactive principles from herbs” Ultrasonics sonochemistry, 8(3):303-313.
- Warner, ML., Kaufman NC., and Grundmann O. 2016. “The pharmacology & toxicology of kratom. from traditional herb to drug of abuse” International Journal of Legal Medicine. 130(1):127-138.
- Wirasuta dan Niruri. 2006. “Toksikologi Umum” Bandung: Universitas Udayana.
- Yue, K., Kopajtic, T.A., Katz, J.L. 2018. “Abuse liability of mitragynine assessed with a self-administration procedure in rats” Psychopharmacology. 235, 2823-2829, <https://doi.org/10.1007/s00213-018-4974-9>.
- Yusoff, N.H., Suhaimi, F.W., Vadivelu, R.K., Hassan, Z., Rümmler, A., Rotter, A., Müller, C.P. 2016. “Abuse potential and adverse cognitive effects of mitragynine (kratom)” Addiction biology. 21(1):98-110.