

**STUDI LITERATUR PROSES ISOLASI, ANALISIS DAN
POTENSI SENYAWA MITRAGININ DALAM DAUN KRATOM
(*Mitragyna speciosa* Korth) UNTUK PENGEMBANGAN BAHAN
BAKU OBAT**

SKRIPSI

**NELLA NURMEILASARI
A161069**



**SEKOLAH TINGGI FARMASI INDONESIA
YAYASAN HAZANAH
BANDUNG
2020**

**STUDI LITERATUR PROSES ISOLASI, ANALISIS DAN POTENSI
SENYAWA MITRAGININ DALAM DAUN KRATOM
(*Mitragyna speciosa* Korth) UNTUK PENGEMBANGAN BAHAN
BAKU OBAT**

SKRIPSI

Sebagai salah satu syarat untuk memperoleh gelar Sarjana Farmasi

**NELLA NURMEILASARI
A161069**



**SEKOLAH TINGGI FARMASI INDONESIA
YAYASAN HAZANAH
BANDUNG
2020**

**STUDI LITERATUR PROSES ISOLASI, ANALISIS DAN POTENSI
SENYAWA MITRAGININ DALAM DAUN KRATOM
(*Mitragyna speciosa* Korth) UNTUK PENGEMBANGAN BAHAN BAKU
OBAT**

**NELLA NURMEILASARI
A161069**

Agustus, 2020
Disetujui oleh:

Pembimbing 1

Pembimbing 2

apt. Adang Firmansyah, M.Si.

apt. Melvia Sundalian, M.Si.

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

Lembar persembahan

Skripsi ini dipersembahkan untuk orang-orang yang sangat saya sayangi. Terkadang, ketika saya kehilangan kepercayaan pada diri saya sendiri, kalian disini untuk percaya pada saya.

ABSTRAK

Kratom merupakan tanaman tropis asal Asia Tenggara yang banyak disalahgunakan. Beberapa kasus penyalahgunaannya dikombinasikan dengan obat-obatan lain tanpa mempertimbangkan dosis sehingga menyebabkan 81,25% laporan kematian. Kratom mengandung mitraginin yang memiliki banyak manfaat dibidang farmakologis sehingga berpotensi menjadi bahan baku obat dalam dunia kesehatan. Tingginya potensi mitraginin menyebabkan peneliti berupaya untuk memperoleh mitraginin dengan proses yang lebih efektif dan efisien. Studi ini bertujuan untuk memberikan informasi terkait farmakologis, proses produksi dan analisis mitraginin. Hasil menunjukan bahwa penggunaan kratom dalam bentuk mitraginin lebih aman dibandingkan kratom dalam bentuk mentah karena meskipun LD₅₀ untuk ekstrak lebih tinggi daripada mitraginin namun *safety margin* mitraginin lebih luas daripada ekstrak. Hasil isolat tertinggi ditunjukan oleh metode konvensional pada suhu ekstraksi <50°C dengan pemurnian menggunakan *column flash chromatography* serta metode non konvensional dengan instrumen SFE dibantu *co-solvent* etanol pada suhu 40°C dan tekanan 5000 psi. Kedua metode diawali reaksi asam basa dan menghasilkan isolat masing-masing 0,091% dan 4,05% dari total daun kering. Mitraginin dapat dianalisis secara sederhana menggunakan KLT dibantu reagen Erlich yang dimodifikasi HClO₄, Spektrofotometer UV-Vis pada panjang gelombang 220 nm dengan bahu spektrum 247 nm, 285 nm dan 293 nm dan HPLC dengan fase gerak yang paling banyak digunakan metanol:air (80:20) menggunakan fase diam C18.

Kata Kunci: Kratom, *Mitragyna speciosa* Korth, mitraginin, farmakologis, isolasi, analisis

ABSTRACT

Kratom is a tropical plant from Southeast Asia that is widely abused with other drugs, resulted in 81.25% reported mortality. In pharmacological field, kratom contains mitraginin that has potential to become a raw material for medicine in the health sector. It causes researchers to seek to obtain mitraginin in a more effective and efficient process. This study aims to provide information related to pharmacology, production processes and mitraginin analysis. Kratom in the mitraginin form is safer than the raw form because although the LD₅₀ for extract is higher, mitraginin safety margin is wider than the extract.. The highest yield of isolates by conventional methods with purification using column flash chromatography is <50 ° C and non-conventional methods with SFE instruments assisted by ethanol co-solvent is 40 ° C and 5000 psi pressure. Both were initiated by an acid-base reaction and produced isolates, respectively 0.091% and 4.05% of the total dry leaves. Mitraginin can be analyzed simply using TLC assisted by Erlich's reagent modified HClO₄, UV-Vis spectrophotometer at a wavelength of 220 nm with a spectrum of 247 nm, 285 nm and 293 nm and HPLC with the mobile phase most widely used methanol: water (80:20) using the C18 stationary phase.

Keywords: Kratom, Mitragyna speciosa Korth, mitraginin, pharmacological, isolation, analysis.

KATA PENGANTAR

Bismillahirrahmanirrahim,

Alhamdulillah, puji dan syukur bagi Allah SWT yang melimpahkan rahmat dan hidayah-Nya sehingga penulis dapat menyelesaikan tugas akhir yang berjudul **“Studi Literatur Proses Isolasi, Analisis dan Manfaat Senyawa Mitraginin dalam Daun Kratom (*Mitragyna speciosa* Korth) untuk Pengembangan Bahan Baku Obat”** dengan pembimbing apt. Adang Firmansyah, M.Si. dan apt. Melvia Sundalian, M.Si. yang merupakan syarat untuk mendapatkan gelar sarjana pada jurusan Farmasi Sekolah Tinggi Farmasi Indonesia.

Pada kesempatan ini, tidak lupa penulis mengucapkan terima kasih kepada banyak pihak. Dengan keikhlasan hati, penulis mengucapkan banyak terimakasih yang sebesar – besarnya kepada :

- 1 apt. Adang Firmansyah, M.Si. selaku Ketua Sekolah Tinggi Farmasi Indonesia.
- 2 apt. Revika Rachmaniar, M.Farm. selaku Ketua Program Studi.
- 3 Nur Asni Setiani, M.Si selaku Dosen Wali yang telah banyak memberikan bimbingan dan arahan kepada penulis.
- 4 Seluruh staf dosen, staf administrasi serta karyawan Sekolah Tinggi Farmasi Indonesia atas ilmu, pengalaman, dan bantuan yang telah diberikan selama penulis menepuh penididikan.
- 5 Serta rekan angkatan 2016 dan konversi 2018 yang telah memberikan inspirasi dan kegembiraan selama penulis kuliah di Sekolah Tinggi Farmasi Indonesia.

Dalam penyusunan skripsi ini masih banyak kesalahan dan kekurangan karena pengetahuan yang masih sangat terbatas. Oleh karena itu, dengan segala kerendahan hati diharapkan masukan berupa kritik dan saran yang bersifat membangun untuk perbaikan di masa yang akan datang. Penulis berharap semoga tugas akhir ini akan memberikan manfaat bagi penulis sendiri dan juga bagi pihak lain yang berkepentingan.

Bandung, Agustus 2020

Penulis

DAFTAR ISI

LEMBAR PENGESAHAN	i
KUTIPAN	ii
PERSEMBAHAN.....	iii
ABSTRAK	iv
ABSTRACT	v
KATA PENGANTAR.....	vi
DAFTAR ISI.....	vii
DAFTAR TABEL.....	x
DAFTAR GAMBAR.....	xi
DAFTAR LAMPIRAN	xii
BAB I PENDAHULUAN	1
1.1. Latar Belakang	1
1.2. Identifikasi Masalah.....	3
1.3. Tujuan Penelitian	3
1.4. Luaran yang Diharapkan	3
1.5. Kegunaan Penelitian	3
BAB II TINJAUAN PUSTAKA	4
2.1. Kratom (<i>Mitragyna speciosa</i> Korth).....	4
2.1.1. Morfologi Tumbuhan Kratom.....	4
2.1.2. Taksonomi Kratom.....	5
2.1.3. Varietas Daun Kratom.....	5
2.1.4. Kandungan Kimia Daun Kratom	5
2.1.5. Khasiat Daun Kratom.....	6
2.2. Mitraginin	7
2.2.1. Kimia Mitraginin.....	7
2.2.2. Sifat Fisikokimia Mitraginin	8
2.2.3. Manfaat Mitraginin	8
2.3. Proses Isolasi Mitraginin.....	8
2.3.1. Ekstraksi.....	9
2.3.2. Fraksinasi dan Pemurnian	12

2.4. Proses Analisis Mitraginin	14
2.4.1. Kromatografi Lapis Tipis (KLT)	14
2.4.2. Spektrofotometer UV-Vis	16
2.4.3. <i>High Performnace Liquid Chromatography</i> (HPLC)	17
BAB III METODE PENELITIAN.....	21
3.1. Desain Penelitian.....	21
3.2. Populasi dan Sampel.....	21
3.2.1. Populasi	21
3.2.2. Sampel.....	21
3.3. Variabel Penelitian.....	22
3.3.1. Variabel Dependen.....	22
3.3.2. Variabel Independen	22
3.4. Metode Pengumpulan Data.....	22
3.4.1. Data Sekunder	22
3.4.2. Metode Kajian Pustaka	23
3.5. Metode Analisis Data	23
3.6. Publikasi.....	23
BAB IV HASIL DAN PEMBAHASAN.....	24
4.1. Laporan Kasus Penyalahgunaan Kratom.....	24
4.2. Farmakologis Mitraginin	26
4.2.1. Dosis Toksik Mitraginin	26
4.2.2. Dosis Efektif Mitraginin	26
4.3. Metode Isolasi Mitraginin	27
4.3.1. Ekstraksi.....	27
4.3.2. Metode Fraksinasi dan Pemurnian	33
4.4. Proses Analisis Mitraginin	34
4.4.1. Kromatografi Lapis Tipis	34
4.4.2. Spektrofotometer UV-Vis	35
4.4.3. <i>High Performnace Liquid Chromatography</i> (HPLC)	36
BAB V SIMPULAN DAN ALUR PENELITIAN SELANJUTNYA	39
5.1. Simpulan	39
5.2. Alur Penelitian Selanjutnya	39

DAFTAR PUSTAKA	40
LAMPIRAN.....	50

DAFTAR TABEL

Tabel	Halaman
4.1 Laporan Kasus Penyalahgunaan Daun Kratom.....	25
4.2 Dosis Toksik Mitraginin	26
4.3 Metode Isolasi Menggunakan Reaksi Asam Basa	30
4.4 Metode Isolasi Tanpa Menggunakan Reaksi Asam Basa	31
4.5 Proses Isolasi Non Konvensional.....	32
4.6 Metode Identifikasi Menggunakan KLT.....	35
4.7 Metode Identifikasi Menggunakan HPLC	37

DAFTAR GAMBAR

Gambar	Halaman
2.1 Struktur Kimia Alkaloid Daun Kratom.....	6
2.2 Struktur Kimia Mitraginin.....	7

DAFTAR LAMPIRAN

Lampiran	Halaman
1. Efek Farmakologi Mitraginin.....	50
2. Bukti Submit Jurnal <i>Publisher JAPS</i>	52
3. Bukti Submit Jurnal <i>Publisher TJPR</i>	53

DAFTAR PUSTAKA

- Apryani, E., Taufik, M., Moklas, M.A.A., Fakurazi, S., Idayu, N.F. 2010. "Effects of Mitraginin From *Mitragyna speciosa* Korth Leaves on Working Memory". *Journal of Ethnopharmacology*, 12(9): 357–360.
- Avula, B., Satyanarayananaraju, S., Yan-Hong, W., Wang, M., Zulfiqar, A., 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". *J AOAC Int*, 98(1):13-21.
- Azizi, J., Ismail, S., Mordi, M.N., Ramanathan, S., Ikram, M., Said, 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*, 1(5): 432–441.
- Azizi, J., Sabariah, I., Mansor, S.M. 2013. "*Mitragyna speciosa* Korth Leaves Extracts Induced The CYP 450 Catalyzed Aminopyrine-N-Demethylase (APND) and UDP-Glucuronosyl Transferase (UGT) Activities in Male Sprague-Dawley Rat Livers". *Drug Metab Drug Interact*, 28(2): 95–105.
- Barceloux, D.G. 2012. "Kratom [*Mitragyna speciosa* (Korth.) Havil.]. In Medical Toxicology of Drug Abuse: Synthesized Chemicals and Psychoactive Plants". *John Wiley & Sons Inc*. 3(1): 880-885.
- Basiliere, S., Brower, J., Winecker, R., Friederich, L., & Kerrigan, S. 2020. "Identifcation of fve mitragyna alkaloids in blood and tissues using liquid chromatography-quadrupole/time-of-fight mass spectrometry". *Forensic Toxicology*, 3(8): 420–435.
- Beng, GT., Mohamad, RH., Siddiqui, M.J., Mordi, M.N., Mansor, S.M. 2011. "A Simple and Cost Effective Isolation and Purification Protocol of Mitraginin from *Mitragyna speciosa* Korth (Ketum) Leaves". *The Malaysian Journal of Analytical Sciences*, 1(5): 54 – 60.
- Boffaa, L., Ghèb, C., Bargea, A., Mucciolib, M., and Cravottoa, G. 2018. "Alkaloid Profiles and Activity in Different *Mitragyna speciosa* Strain". *Natural Product Communications* 13(9): 1111-1116.
- Boyer, E.W., Kavita, M.B., Jessica, E., Adkins., Christopher, R., McCurdy, and John H. Halpern. 2008. " Self-Treatment of Opioid Withdrawal Using Kratom (*Mitragynia speciosa* Korth)". *Adiction*, 10(3): 352-356.
- Carpenter, Jessica, M, Helaina, K.C., Zulfiqar, A., Zhihao, Z., Khan, I.A., Kenneth, J.S. 2016. "Comparative Effects of *Mitragyna speciosa* Extract, Mitraginin,

- and Opioid Agonists on Thermal Nociception in Rats". *Fitoterapia*, 10(9): 87–90.
- Catherine, A.C., Helaina, K.C., Zulfiqar, A., Zhihao, Z., Khan, I.A., Kenneth, J.S. 2015. "A Comparison of *Mitragyna speciosa* and Mitraginin Against Opioids On Thermal Nociception In Rats". *University of Mississippi*, 7:170-175.
- Cheaha, A., Niwat, K., 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 with Drawal Symptomsin Rats". *Phytomedicine*, 2(2): 1000–1008.
- Chittrakarn, S., Sawangjaroen, K., Prasettho, S., Janchawee, B. 2009. "Inhibitory Effects of Kratom Leaf Extract (*Mitragyna speciosa* Korth.) on The Rat Gastrointestinal Tract". *J Ethnopharmacol*, 11(6): 173–178.
- Chittrakarn, S., Pimpimol, P., Keawpradub, N. 2012. "Quantitative Analysis of Mitraginin, Codeine, Caffeine, Chlorpheniramine and Phenylephrine in a Kratom (*Mitragyna speciosa* Korth.) Cocktail Using High-Performance Liquid Chromatography". *Forensic Sci Int*, 21(7): 81-86.
- Chittrakarna, S., Niwat, K., Sawangjaroen, K., Kansenakal, S., Janchawee, B. 2010. "The Neuromuscular Blockade Produced by Pure Alkaloid, Mitraginin and Methanol Extract of Kratom Leaves (*Mitragyna speciosa* Korth.)". *Journal of Ethnopharmacology*, 12(9): 344–349.
- Christine, R., Heise, A., Conley, T., Thomas, T. 2016. "Quantitative and Qualitative Analysis of Mitraginin in Kratom (*Mitragyna speciosa*) by GC-MS, LC-MS/MS and UPLC-PDA". *Journal of Ethnopharmacology*, 12(9): 344–349.
- Cinosi, E., Giovani, M., Simonato, P., Singh, D., Demetrovics, Z., Roman-Urrestarazu, A., Bersani, F.S., Vicknasingam, B., Piazzon, G., Jih-Heng, L., Wen-Jing, Y. 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): 1-11.
- Compton, D.M., Corina, G., Annamaria, V., Kamaratos., Brittany, G., Johnson, T.W. 2014. "An Examination of The Consequences of Chronic Exposure to *Mitragyna speciosa* During Adolescence on Learning and Memory in Adulthood". *The Journal of Phytopharmacology*, 3(5): 300-309.
- Dey, S., Rathod, V.K. 2013. "Ultrasound assisted extraction of β-carotene from *Spirulina platensis*" *Ultrasonics Sonochemistry*, 20(2): 271 – 276.
- Fakurazi, S., Shamima, AR., Hidayat, M.T., Ithnin, H., Moklas, M.A.M., Arulselvan, P. 2013. "The Combination of Mitraginin and

- Morphine Prevents the Development of Morphine Tolerance in Mice". *Molecules*, 1(8): 666-681.
- Ginting, E. 2013. "Carotenoid extraction of orange-fleshed sweet potato and its application as natural food colorant" *J. Teknol. dan Industri Pangan*, 2(1): 2-4.
- Hanajiri, R.K., Kawamura, M., Maruyama, T., Kitajima, M., Takayama, H., Yukihiro, G .2009. "Simultaneous analysis of mitraginin, 7-hydroxymitraginin, and other alkaloids in the psychotropic plant "kratom" (*Mitragyna speciosa*) by LC-ESI-MS". *Forensic Toxicology*, 27(2): 67-74.
- Hanzhuo, F., Frank X. Cid., Dworkin, N., Cocores J., Shore, Gloria. 2015. "Screening and Identification of Mitraginin and 7-Hydroxymitraginin in Human Urine by LC-MS/MS". *Chromatography*, 2(1): 253-264.
- Harizal, S.N., Mansor, S.M., Hasnan, J., Tharakan J.K.T., Abdullah, J. 2010. "Acute Toxicity Study of The Standardized Methanolic Extract of *Mitragyna speciosa* Korth in Rodent". *J Ethnopharmacol*, 131(2): 404–409.
- Harun, N., Zurina, H., Navaratnam, V., Sharif M.M., Shoaib, M. 2014. "Discriminative Stimulus Properties of Mitraginin (Kratom) in Rats". *Psychopharmacology*, 232(13): 2227-2238.
- Hassan, Z., Muzaimi, M., Navaratnam, V., Nurul, H., M, Yusoff., Suhaimi, F.W., Vadivelu, R., Balasingam, K., Vicknasingam, Davide, M., Hörsten, S.V., Nurul, I., W. Ismail. 2013. "From Kratom to Mitraginin and its Derivatives: Physiological and Behavioural Effects Related to Use, Abuse, and Addiction". *Neuroscience and Biobehavioral Reviews* 3(7): 138–151.
- Hazim, A.I, Ramanathan, S., Parthasarathy, S., Muzaimi, M., Mansor, S.M. 2014. "Anxiolytic-Like Effects of Mitraginin in The Open-Field and Elevated Plus-Maze Tests in Rats". *J Physiol Sci*, 64(3): 161-169.
- Herero, M., Cifuentes, A., Ibañez, E. 2006. "Sub- and supercritical fluid extraction of functional ingredients from different natural sources: Plants, food-byproducts, algae, and microalgae: A review". *Food Chemistry*, 98(1): 136 – 148.
- Hidayati. Anna. 2013. "Test of Sedative Effects of Extract of n-Hexane from Kratom (*Mitragyna speciosa* Korth.) Leaves in Male Mice". *Journal of UNTAN Medical Faculty Students*, 3(1): 1-9.
- Holler, J.M, Shawn, P., Vorce, P.C., Donough-Bender, M., Magluilo, J., Carol, J., and Levine, B. 2011. "A Drug Toxicity Death Involving Prophyhexidine and Mitraginin". *J. Anal Toxicol*, 3(5): 54-59.
- Ichwan, R. 2014. "Ekstraksi Andrographolid dari Andrographis paniculata (Burm.f.) Nees Menggunakan Ekstraktor Soxhlet". *Pharmaciana*, 4(1): 85-92.

- Idayu, N., Hidayat, M.T., Moklas, M A M., Sharida, F., Raudzah, A.R.N., Shamima, A.R., Apryani, E. 2011. "Antidepressant-Like Effect of Mitraginin Isolat Ofed From *Mitragyna speciosa* Korth in Mice Model of Depression". *Phytomedicine*, 1(8): 402–407.
- Ikhwan, D., Harlia, A.W., Widiyantoro, A. 2018. "Characterization of Cytotoxic Compounds from The Fraction of Ethyl Acetate of Kratom Leaves (*Mitragyna speciosa* Korth.) And Its Activity Against T47d Breast Cancer Cells". *Journal of Equatorial Chemistry*, 7(2): 18-24.
- Jessica, E.A., Boyer, E.W., McCurdy, C.R. 2011. *Mitragyna speciosa*, A Psychoactive Tree from Southeast Asia with Opioid Activity . *Current Topics in Medicinal Chemistry*, 1(1): 1165-1175.
- Kai, Y., Kopajtic, T.A., Jonathan L.K. 2018. "Abuse Liability of Mitraginin Assessed With A Self-Administration Procedure In Rats". *Psychopharmacology*, 10(2): 2823-2829.
- Karinen, R., Fosen, J.T., Rogde, S., Vindenes, V. 2014. "An Accidental Poisoning With Mitraginin". *Forensic Sci Int*, 24(5): 29–32.
- Khor, B.S, Fadzly, M., Jamil, A., Adenan, I.M., Shu-Chien, A.C . 2011. "Mitraginin Attenuates Withdrawal Syndrome in Morphine" *Withdrawn Zebrafish. PloS ONE*, 6(12): 2834-2840.
- Kowalcuk, A.P, Łozak, A., Zjawiony, J.K. 2013. "Comprehensive Methodology For Identification Of Kratom In Police Laboratories". *Forensic Sci Int*, 23(3): 238-243.
- Kresnanugraha. 2012. "Uji Penghambatan Aktivitas Enzim Xantin Oksidase dari Ekstrak Daun Belimbing Wuluh (*Averrhoa bilimbi* L.) dan Identifikasi Golongan Senyawa dari Fraksi Aktif". Depok : Farmasi UI. Hal. 21.
- Kronstrand, R, Roman, M., Thelander, G., Eriksson, A. 2011. "Unintentional Fatal Intoxications with Mitraginin and O- Desmethyltramadol from the Herbal Blend Krypton". *Journal of Analytical Toxicology*, 3(5): 242-247.
- Kruegel, Gassaway, M.M., Kapoor, A., Váradi, A., Majumdar, S., Filizola, M., Jonathan A.J; Sames, D. 2016. "Synthetic And Receptor Signaling Explorations of The *Mitragyna* Alkaloids: Mitraginin as an Atypical Molecular Framework For Opioid Receptor Modulators". *J Am Chem Soc*, 138(21): 6754-6764.
- 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*, 7(7): 339–345.

- Kumarnsit, E., Vongvatcharanon, U., Keawpradub, N., Intasaro, P. 2007. "Fos-Like Immunoreactivity in Rat Dorsal Raphe Nuclei Induced by Alkaloid Extract of *Mitragyna speciosa*". *Neuroscience Letters* 41(6): 128–132.
- León, F., Eman, H., Jessica, E.A., Edward, B.F., Christopher, R.M., Stephen, J.C. 2009. "Phytochemical characterization of the leaves of *Mitragyna speciosa* grown in U.S.A". *Nat Prod Commun*, 4(7): 907-910.
- Lesiak, A.D, Robert, B.C., Dane, J.A., Musah, R.A. 2014. "Rapid Detection by Direct Analysis in Real Time-Mass Spectrometry (DART-MS) of Psychoactive Plant Drugs of Abuse : The case of *Mitragyna speciosa* aka "Kratom" . *Forensic Science International*, 24(2): 210–218.
- Limsuwanchote, L., Wungsintawekul, J., Keawpradub, N., Putalun, W., Morimoto, S., Tanaka, M. 2014. "Development of Indirect Competitive ELISA for Quantification of Mitraginin in Kratom (*Mitragyna speciosa* (Roxb.) Korth.)". *Forensic Sci Int*, 24(4):70-77.
- Luliana, S., Robiyanto., Nugraha, W.I. 2018. "Antinociceptive Activity of Dichloromethane Fraction of Kratom Leaves (*Mitragyna speciosa* Korth.) by Oral Route In Male Swiss Mice". *Pharmaceutical Sciences and Research (PSR)*, 5(2):58 – 64.
- Matsumoto, K, Yamamoto, L.T., Watanabe, K., Yano, S., Shan, J., Peter, K.T.P., Ponglux, D., Takayama, H., Horie, S. 2005. "Inhibitory Effect of Mitraginin, an Analgesik Alkaloid From Thai Herbal Medicine, on Neurogenic Contraction of The Vas Deferens". *Life Sciences*, 7(8): 187–194.
- Matsumoto, K., Mizowaki, M., T, Suchitra., Y, Murakami, Takayama, H., Sakai, S., N, Aimi., H, Watanabe. 1996. "Central Antinociceptive Effects of Mitraginin In Mice: Contribution of Descending Noradrenergic and Serotonergic Systems". *European Journal of Pharmacology*, 31(7): 75-81.
- Matsumoto, K., Hatori, Y., Murayama, T., Tashima, K., Wongseripipatana, S., Misawa, K., Kitajima, M., Takayama, H., Horie, S. 2006. "Involvement of M-Opioid Receptors in Antinociception and Inhibition of Gastrointestinal Transit Induced By 7-Hydroxymitraginin, Isolat Ofed From Thai Herbal Medicine *Mitragyna speciosa*". *European Journal of Pharmacology*, 54(9): 63–70.
- Matsumoto, K., Horie, S., Takayama, H., Ishikawa, H., Aimi, N., Ponglux, D., Murayama, T., Watanabe, K. 2005. "Antinociception, tolerance and withdrawal symptoms induced by 7-hydroxymitraginin, an alkaloid from the Thai medicinal herb *Mitragyna speciosa*". *Life Sci*, 78(1): 2-7.
- Matsumoto, K., Mizowaki, M., Takayama, H., Sakai, S., Aimi, N., Watanabe, H. 1997. "Suppressive Effect of Mitraginin on the 5-methoxy-N,N-

- dimethyltryptamine-induced Head-Twitch Response in Mice". *Pharmacol Biochem Behav*, 57(1-2): 319-323.
- Matsumoto, K., Takayama, H., Narita, M., Nakamura, A., Suzuki, M., Suzuki, T., Murayama, T., Wongseripipatana, S., Misawa, K., Kitajima, M., Tashima, K., Horie, S. 2008. "A Derivative Of The Indole Alkaloid Mitraginin: A Novel Dual-Acting M- And K-Opioid Agonist With Potent Antinociceptive And Weak Rewarding Effects In Mice". *Neuropharmacology*, 5(5): 154–165.
- McIntyre., Iain, M., Trochta, A., Stolberg, S., Campman, S.C. 2014. "Mitraginin 'Kratom' Related Fatality: A Case Report with Postmortem Concentrations". *Journal of Analytical Toxicology*, 10(1): 1–4.
- Mossadeq, W.M., Sulaiman, M.R., T.A Tengku Mohamad., H.S Chiong., Z.A Zakaria., M.L, Jabit., M.T.H, Baharuldin., D.A, Israf. 2009. "Anti-Inflammatory and Antinociceptive Effects of *Mitragyna speciosa* Korth Methanolic Extract". *Med Princ Pract*, 1(8): 378–384.
- Mudge, E.M., Paula, N.B. 2017. "Determination of Mitraginin in *Mitragyna speciosa* Raw Materials and Finished Products by Liquid Chromatography With UV Detection: Single-Laboratory Validation". *J AOAC Int*, 100(1): 18-24.
- Nahazima, M.Z., Ikram, M.S., Normah , M.N., Zainal, Z., Chew, J.K., Ismail, I. 2013. "Induction and Analysis of the Alkaloid Mitraginin Content of a *Mitragyna speciosa* Suspension Culture System upon Elicitation and Precursor Feeding". *Scientific World Journal*, 2(6): 2094-2114.
- Neerman, M.F., Randall, E.F., Deking, J. 2013. "A Drug Fatality Involving Kratom". *J Forensic Sci*, 2(1): 278-279.
- Nelsen, J.L., Lapoint, L., Hodgman, M.J., Kenneth, M.A. 2010. "Seizure and Coma Following Kratom (*Mitragynina speciosa* Korth) Exposure". *J. Medical Toxicology*, 6(4): 424–426.
- Novindriani, D., Bambang, W. 2013. "The Test on The Sedative Effect Of Kratom (*Mitragyna speciosa* Korth.) Leaves Infusa To Male Balb/C Strain Mice". *Journal of UNTAN Medical Faculty Students*, 3(1): 1-9.
- Novindriani, D., Mohammad, A. 2013. "Sedative Effect Test of Kratom (*Mitragyna speciosa* Korth) Ethanolic Extract Extract Leaves on Balb / C strain male mice". *Journal of UNTAN Medical Faculty Students*, 1(1): 1-9.
- Nugraha, W.I., Luliana, R.S. 2018 . "Antinociceptive Activity of Aqueous Fraction of Kratom Leaves (*Mitragyna speciosa* Korth.) on Male Swiss Albino Mice". *Trad. Med. J*, 23(2): 91-96.

- Orio, L., Alexandru, L., Cravotto, G., Mantegna, S., Barge, A. 2011. "UAE, MAE, SFE-CO₂ and Classical Methods for The Extraction of *Mitragyna speciosa* Leaves". *Ultrasonics Sonochemistry*, 19(3): 591-595.
- Parthasarathy S, Ramanathan, S., Ismail, S., Adenan, M.I., Mansor, S.M., Murugaiyah, V. 2010. "Determination of Mitraginin in Plasma With Solid-Phase Extraction and Rapid HPLC–UV Analysis of, and its Application to A Pharmacokinetic Study in Rat". *Anal Bioanal Chem*, 39(7): 2023–2030.
- Parthasarathy, S., Juzaili, B.A., Ramanathan, S., Ismail, S., Sasidharan, S., I.S, Mohd ., Mansor, S.M. 2014. "Evaluation of Antioxiatndt and Antibacterial Activities of Aqueous, Methanolic and Alkaloid Extracts from *Mitragyna speciosa* (Rubiaceae Family) Leaves". *Molecules*, 1(4): 3964-3974.
- Parthasarathy, S., Ramanathan, S., Murugaiyah, V., Hamdan, M.R. 2013. "A Simple HPLC–DAD Method For The Detection And Quantification Of Psychotropic Mitraginin In *Mitragyna speciosa* (Ketum) and Its Products For The Application In Forensic Investigation". *Forensic Sci Int*, 22(6): 183-187.
- Ponglux, D., Wongseripatana, S., Takayama, H., M. Kikuchi., Kurihara, M., Kitajima, M., N. Aimi., S, Sakai. 1994. "A New Indole Alkaloid, 7 alpha-Hydroxy-7H mitraginin, From *Mitragyna speciosa* in Thailand". *Planta Med*, 60(6): 580-581.
- Prutipanlai, S., Ornchuma, B., Benjamas, J., Sittipoom, T. 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 (7): 1675-1682
- Putra, A. A. B., Bogoriani, N. W., Diantariani, N. P., Sumadewi, N. L. U. 2014. "Ekstraksi zat warna alam dari bonggol tanaman pisang (*Musa paradisiaciaca* L.) dengan metode maserasi, refluks, dan sokletasi". *Jurnal Kimia*, 8(1): 113 – 119
- Rabani, F.D., Mufligliati. 2017. "Inhibition of Fungal Growth *Schizophillum Commune* Fries by Ethanol Extract of Leaves of Kratom (*Mitragyna speciosa* Korth)". *Jurnal Hutan Lestari*, 5(3): 831 – 839.
- Reanmongkol, W., Sawangjaroen, K., Niwat, K. 2007. "Effects of The Extracts from *Mitragyna speciosa* Korth. Leaves on Analgesik and Behavioral Activities in Experimental Animals". *Songklanakarin J. Sci. Technol*, 2(9): 39-48.
- Riani, M. 2017. "Kratom (*Mitragyna speciosa* Korth):Benefits, Side Effects and Legality". *Media Litbangkes*, 2(7): 175–184.
- Ridayani, Y., Andrie, M. 2013. "Test of The Sedative Effect of Kratom (*Mitragyna speciosa* Korth.) Ethanol Fraction on Male Mice Strain BALB / c. IPI". *Journal of UNTAN Medical Faculty Students*, 3(1): 1–9.

- Rittinarong, M., Sooksawate, T. 2019. "Mitraginin Reduced Morphine-Induced Conditioned Place Preference and Withdrawal in Rodents". *Thai Journal Pharmaceutical Sciences*, 4(3): 1-5
- Sabetghadam, A., Ramanathan, S., Sasidharan, S., Mansor, S.M. 2013. "Subchronic Exposure to Mitraginin, The Principal Alkaloid of *Mitragyna speciosa*, in Rats". *Journal of Ethnopharmacology*, 14(6): 815–823.
- 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(3): 181–185.
- Sanagi, M.N., Omar, M.F.M., Ayob, Ibrahim, W.A.W. 2013. "Determination of Mitraginin for The Identification of *Mitragyna species* in Kedah (Malaysia) by Gas Chromatography-Mass Spectrometry". *Der Pharma Chemica*, 5(1): 131–138.
- Senik, M.H., Mansor, S.M., Rammes, G., Tharakan, J. 2012. "Mitragyna speciosa Korth Standardized Methanol Extract Induced Short-Term Potentiation of CA1 Subfield in Rat Hippocampal Slices". *Journal of Medicinal Plants Research*, 6(7): 1234-1243.
- Shamima, A.R., Fakurazi, S., Hidayat, M.T., Hairuszah, I., Moklas, M.A.M., Arulselvan, P. 2012. "Antinociceptive Action of Isolat ofed Mitraginin from *Mitragyna speciosa* through Activation of Opioid Receptor System". *Int. J. Mol. Sci*, 1(3): 11427-11442.
- Shijun, L., Tran, B.N., Nelsen, J.L., Aldous, K.M. 2009. "Quantitative Analysis of Mitraginin In Human Urine By High Performance Liquid Chromatography-Tandem Mass Spectrometry". *J Chromatogr B Analyt Technol Biomed Life Sci*, 877(24): 2499-2505.
- Smith, K.E., Lawson, T. 2017. "Prevalence and Motivations For Kratom Use in A Sample of Substance Users Enrolled in A Residential Treatment Program". *Drug And Alcohol Dependence*, 180(1): 340–348.
- Suhaimi, Heny, P. 2019. "Antibacterial Activities of Kratom Leaf Extract *Mitragyna speciosa* Korth) Against Bacteria Propionibacterium Acnes Causes Acne". *Medical Sains*, 4(1): 2541-2548.
- Sun, Y., Liu, D., Chen, J., Ye, X., Yu, D. 2011. "Effects of different factors of ultrasound treatment on the extraction yield of the all-trans-β-carotene from citrus peels". *Ultrasonics Sonochemistry*, 18(1): 243 – 249.
- Surash, R., Parthasarathy, S., Murugaiyah, V., Magosso, E., Tan, S.C., Mansor, S.M. 2015. "Understanding the Physicochemical Properties of Mitraginin, a Principal Alkaloid of *Mitragyna speciosa*, for Preclinical Evaluation". *Molecules*, 20(3): 4915–4927.

- Swoggera, M.T, Walsh, Z. 2018. "Kratom use and mental health: A Systematic Review". *Drug and Alcohol Dependence*, 183(1): 134–140.
- Takayama, H. 2004. "Chemistry and Pharmacology of Analgesik Indole Alkaloids from The Rubiaceous Plant, *Mitragyna speciosa*". *Chem. Pharm. Bull*, 52(1): 916—928.
- Takayama, H., Takayama, H., Kurihara, M., Kitajima, M., Said, I.M., Aimi, N. 1998. "New Indole Alkaloids From The Leaves of Malaysian *Mitragyna speciosa*". *Tetrahedron*, 54(29): 8433-8440.
- Tanguay, P. 2011. "Kratom in Thailand". *Legislative Reform of Drug Policies*, 1(3): 1–16.
- Taufik, H.M., Apryani, E., Nabishah, M., Moklas, M.A.A. 2010. "Determination of Mitraginin Bound Opioid Receptors. Adv. in Med". *Dent. Sci*, 10(3): 65-70.
- Tohar, N., Rosmy, D.S., Awang, K. 2007. "Supercritical Carbon Dioxide Extraction of *Mitragyna speciosa* Korth". *Journal of Pharmacology and Experimental Therapeutics*, 4(6): 251-271.
- Tsuchiya, S., Miyashita, S., Yamamoto, M., Horie, S., Shin-Ichiro, S., Aimi, N., Takayama, H., Watanabe, K. 2002. "Effect of Mitraginin, Derived From Thai Folk Medicine, on Gastric Acid Secretion Through Opioid Receptor in Anesthetized Rats". *European Journal of Pharmacology*, 44(3): 185– 188.
- Váradi, A., Gina, F., Marrone, T.C., Palmer, Narayan, A., Márton R.S., Valerie, L.R., Steven, G., Grinnell, J.J., Warner, S.E., Sanjay, K. 2016. "Mitraginin/Corynantheidine Pseudoindoxyls As Opioid Analgesiks with Mu Agonism and Delta Antagonism, Which Do Not Recruit β -Arrestin-2". *J. Med. Chem*, 5(9): 8381–8397.
- Verdiana, M, I Wayan R. 2018. "The Effect of Solving Type on Using Extractions Ultrasonic Wave on Activities Antioxidant of Lemon Fruit Skin Extract (*Citrus Limon* (Linn.) Burm F.)". *Journal of Food Science and Technology*, 7(1): 213-222.
- Vicknasingama, B., Suresh, N. 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*, 2(1): 283–288.
- Wang, M., Carrell, E. J., Ali, Z., Avula, B., Avonto, C., Parcher, J. F., & Khan, I. A. 2014. "Comparison of three chromatographic techniques for the detection of mitragynine and other indole and oxindole alkaloids in *Mitragyna speciosa* (kratom) plants". *J. Sep. Sci.* 1(2): 1–8.

- Warner, M.L., Nellie, C.K., Grundmann, O. 2016 . “The Pharmacology And Toxicology of Kratom: From Traditional Herb to Drug of Abuse”. *Int J Legal Med*, 130(1): 127–138.
- Wijngaard, H., Hossain, M. B., Rai, D. K., Brunton, N. 2012. “Techniques to extract bioactive compounds from food byproducts of plant origin”. *Food Research International*, 4(6): 505 – 513.
- Zhao, W., Yu, Z., Liu, J., Yu, Y., Yin, Y., Lin, S., Chen, F. 2011. “Optimized extraction of polysaccharides from corn silk by pulsed electric field and response surface quadratic design”. *J Sci Food Agric*, 9(1): 2201 – 2209.
- Zulfiqar, A., Demiray, D., Ikhlas, A.K. 2014. “Isolation, characterization, and NMR Spectroscopic Data of Indole and Oxindole Alkaloids From *Mitragyna speciosa*”. *Tetrahedron Letters*, 55(8): 369-372.