Submission Manuscript Journal : Kratom (Mitragyna speciosa Korth) for a New Medicinal: A Review of Pharmacological and Compound Analysis

Inbox ×

Adang Firmansyah <adangfirmansyah@stfi.ac.id>
to review

Thu, Aug 27, 2020, 6:52 PM

Dear Admin,

I intend to submit a research journal entitled Kratom (*Mitragyna speciosa* Korth) for a New Medicinal: A Review of Pharmacological and Compound Analysis. The following manuscript, cover letter, figure folder, and the Author Agreement Form is attached. We hope to be considered, for the attention we thank you.

Best regards,
Adang Firmansyah

1. Title of Article: Kratom (*Mitragyna speciosa* Korth) for a New Medicinal: A Review of Pharmacological and Compound Analysis
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4. 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 *Mitragynine speciosa*, as many as (66.2%) and their derivatives, speciogynine (6.6%), speciociliatine (0.8%), paynantheine (8.6%), 7- hydroxy mitragynine (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.

5. Keywords: *Mitragyna speciosa Korth; effects; case report; toxicity; benefits; new drugs.*

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Alex Grumezescu <al.grumezescu@gmail.com> Fri, Aug 28, 2020, 12:34 PM
to me

Dear Author,

the paper was safely received.

We will proceed with peer-review.

Thank you for your submission.

Best regards,

Alex

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Kratom (*Mitragyna speciosa* Korth) for a New Medicinal: a Review of Pharmacological and Compound Analysis

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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 *Mitragynine speciosa*, as many as (66.2%) and their derivatives, speciogynine (6.6%), speciociliatine (0.8%), paynantheine (8.6%), 7-hydroxymitragynine (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 caused by kratom, to help health professionals assess the content of compounds from kratom worthy of being new drugs.

Keywords: Kratom; *Mitragyna speciosa* Korth; effects; case report; toxicity; benefits; new drugs.

1. Introduction

Mitragyna speciosa Korth. (Rubiaceae) a tree found in Southeast Asia (Thailand, Indonesia, Malaysia, Myanmar, Philippines, and Papua New Guinea) has proven to have medicinally relevant alkaloids within its leaves [1]. Kratom, also known as *Mitragyna speciosa*, is extracted from the leaves of evergreen, deciduous tree native to Southeast-Asia and was originally described in 1839 by botanist Pieter Willem Korthals. Kratom has been widely used in Southeast Asia for hundreds of years [2]. In Indonesia, kratom use typically involves the ingestion of the plant's raw leaves or consumption of teas that are brewed or steeped from the leaves [3]. Traditionally, the *Mitragyna speciosa* was used to alleviate pain, hypertension, cough, diarrhea, and as a substitute for morphine in treating addicts [4-5].

Mature leaves of *Mitragyna speciosa* are recognized as a rich source of alkaloids, and mitragynine was obtained as the major constituent, which is 66.2% based on the crude base and followed by its analogs speciogynine, speciociliatine and paynantheine [4-12]. Mitragynine compounds in kratom have one of the properties as an antinociceptive [13]. Mitragynine produced antinociceptive effects similar to the reference opioid agonists when administered intraperitoneal and oral routes [14]. Supported by the results of research Yue et

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al. (2018), which states that mitragynine has an affinity of 16 times greater with opioid receptors than opioids and opioid receptors, its affinity with opioid receptors is about 200 times that of morphine, so mitragynine shows its potential as an opioid analgesic [15]. Its derivative 7-hydroxymitragynine shows a much more potent antinociceptive effect in mice than does either mitragynine or morphine [7]. According to a survey conducted by Swogger et al. (2018) kratom effects similar to morphine, but the side effects it produces are smaller than other similar opioid substances [16]. Other pharmacological effects produced by kratom leaves have been studied as analgesics [4], antipyretic [17], sedatives, stimulants, and depressants [18], anti-inflammatory [19], antidiarrheal [20], antioxidant and antimicrobial [21]. Kratom has a high economic value for 5 grams kratom extract, it costs $ 34.99, while the ultra enhanced form is more expensive, at 5 grams price $ 45.99 [22].

This article aims to examine kratom plants so that they can provide information to the public and related institutions about the hidden benefits of kratom leaves, kratom abuse, content analysis of kratom compounds, the pharmacological effects, and potential as raw materials for new medicines in the pharmaceutical field.

2. Materials and Methods

A search for this review was done online at Pubmed, Google Scholar, and European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) websites. Research papers, bibliographic reviews, and case reports were included, the research done in Indonesia and in English. The search strings used were *Mitragyna speciosa*, *Mitragyna speciosa* extract, *Mitragyna speciosa* and toxicity, kratom benefit and risk, kratom pharmacology, Mitragyna abuse, kratom deaths, and kratom analysis. The search was performed between January of 2020 and July of 2020. No publishing date restrictions were used. Among the 140 papers, we selected 78 publications based on the search criteria for *Mitragyna speciosa* Korth, kratom extract, kratom, qualitative, methodology, general review, updates. Those publications comprised case reports, toxicity, dependence, pharmacology, pharmacokinetics, analysis of kratom leaves. Although there is a risk of bias because our search was intended to demonstrate mostly risks (toxicity) of kratom (*Mitragyna speciosa* Korth) use and to a lesser degree comparing benefits and risks of the leave, we did review kratom biochemical benefits that we describe in the result section where we present the most supported publications representing the most advanced and recent findings of kratom.

3. Results and Discussion

3.1. Case report

Kratom is consumed worldwide for stimulant effects and as a substitute for opioids (in the form of tea, chewed, sucked, or digested in capsules). Several case reports have been related to kratom related to psychosis, seizures, intrahepatic cholestasis, other medical conditions, and death [23]. Osborne et al. (2019) case report of use kratom a 47-year-old male who developed fatigue, pruritus, and abnormal liver tests approximately 21 days after beginning kratom [24]. The patient was diagnosed with drug-induced liver injury (DILI) caused by kratom. Nine months after his liver tests returned to normal, he took kratom again, and after a latency of 2 days, he developed fatigue, pruritus, and loss of appetite along with abnormal liver tests (with the same biochemical profile as previously), consistent with a positive rechallenge. Aggarwal et al. (2018) case report of a 26-year-old man who was brought into our emergency department

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in cardiorespiratory arrest, having taken kratom 24 h previously [25]. Despite multi-organ support, he deteriorated and died from cardiorespiratory failure and hypoxic brain damage 12 hour later. Lipid emulsion was given, with significant temporary improvement in the cardiorespiratory failure. Nelsen et al. (2010) also reported a case of a 64-year-old man witnessed a seizure at home after consumption of kratom. The analysis showed that the concentration of mitragynine in urine was 167 ± 15 ng/ml [26]. Case reports involving users who consumed kratom leaves in powder form, with 5 cases of kratom leaf use along with other drugs such as venlafaxine, diphenhydramine, and mirtazapine in patients who died of suspected excessive doses of kratom leaves [27]. Tungtananuwat et al. (2010) reported the case of the death of a 21-year-old man suspected of having an overdose of kratom leaves [28]. The following substances are found in blood and urine samples: mitragynine (alkaloids found in kratom; *Mitragyna speciosa* leaves), caffeine, diphenhydramine, alprazolam, nortriptyline, methadone, tramadol, methamphetamine, and some of its metabolites. In this case, the cause of death might be caused by multidrug poisoning additional side effects, especially Central Nervous System (CNS) and respiratory depression. Besides that, a case report on the use of kratom with other substances was also reported by Kronstrand et al. (2011), which found 9 cases of death from consuming mitragynine and O-desme thyltramadol [29]. From the results of the analysis in the blood found the concentration of mitragynine in the blood ranged from 0.02 to 0.18 µg/g, and O-desmethyltramadol ranged from 0.4 to 4.3 µg/g. Karinen et al. (2014) reported a case of death of a middle-aged man due to a kratom overdose with post-mortem peripheral blood results found mitragynine 1.06 mg/L, 7-hydroxymitragynine 0.15 mg/L [30]. Additionally zopiclone 0.043 mg/L, citalopram 0.36 mg/L and lamotrigine 5.4 mg/L were detected in the blood but in the therapeutic concentration range. Holler et al. (2011) found cases of death involving the abuse of propylhexedrine and mitragynine [31]. Toxicological results revealed the presence of propylhexedrine 1.7 mg/L and mitragynine 0.39 mg/L in his blood. The cause of death is propylhexedrine poisoning, and the manner of death is due to an accident. Mitragynine might have contributed as well, but because there are no published data for drug concentrations, medical examiners also did not include mitragynine toxicity in causes of death. The average case report of kratom use with the addition of other substances or just the use of kratom itself causes, among others, psychosis, seizures, intrahepatic cholestasis, other medical conditions, until death due to the use of kratom leaf doses has not been proven and standardized [32]. The reasons for using kratom include reasons for use-self-medication, recreation, relaxation, body-building, avoiding positive drug tests [33].

3.2. Toxicity

From the literature study conducted, there is still little information about the safe dosage range of using kratom leaves so that it can cause toxic effects to cause death. As in the study conducted by Moklas et al. (2008), testing the level of toxicity of the alkaloid extract of *Mitragyna speciosa* against saltwater shrimp obtained the result of moderate toxicity to the brine of 50 shrimp larvae with LC values at 62 µl/ml [18]. Azizi et al. (2010) also tested the toxicity level of the alkaloid extract of *Mitragyna speciosa* on mice reporting a lethal effect of a total of 200 mg/kg [34]. The same study also carried out by Harizal et al. (2010) reported that *Mitragyna speciosa* methanol extract increased rat blood pressure (systolic: 147.4 ± 1.01, 131.64 ± 4.94 and 137.8 ± 4.46) after each dose of 100, 500, and 1000 mg/kg, respectively [35]. No deaths were recorded after 14 days of treatment. However, it significantly increases one's blood pressure hours after administration, and the highest dose of the extract also induces

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acute severe hepatotoxicity and mild nephrotoxicity after single-dose administration. Sabetghadam et al. (2013) conducted a study on mitragynine toxicity to mice showing that mitragynine was relatively safe at lower sub-chronic doses (1-10 mg/kg) but showed toxicity at the highest dose (sub-chronic 28 days: 100mg/kg) [36]. This is confirmed by histopathological changes in the liver, kidneys, and brain, as well as hematological and biochemical changes.

3.3. Dependence

According to a research survey conducted by Singh et al. (2014) of 293 kratom users reported that more than half of regular users (> 6 months of use) had severe kratom dependence, while 45% showed mild kratom dependence [37]. Physical withdrawal symptoms commonly experienced include muscle spasms and pain, sleeping difficulty, watery eyes/nose, hot flashes, fever, decreased appetite, and diarrhoea. Psychological withdrawal symptoms commonly reported were restlessness, tension, anger, sadness, and nervousness. McWhirter et al. (2010) study reported that kratom dependency syndrome is caused by the activity of short-acting opioid receptor agonists, and shows that dihydrocodeine and lofexidine are effective in supporting detoxification [38]. Warner et al. (2016) also revealed that stimulant and dose-dependent effects of drugs do exist, but growing concerns about the effects of drugs and safety of use have generated national and international attention mainly due to increased hospital visits and deaths in several countries that are allegedly caused by kratom plant extracts [9]. The main active alkaloid substances in kratom, mitragynine, and 7-hydroxymitragynine, present with a variety of CNS stimulant and depressant effects that are mediated mainly through monoaminergic and opioid receptors.

In the research Yusoff et al. (2016) described the profile of addiction and cognitive impairment in the administration of acute and chronic mitragynine, which is very similar to morphine [39]. Chronic mitragynine administration causes passive activity disorders and objects recognition learning. Overall, these findings provide evidence of the potential for addiction to cognitive impairment for mitragynine, which suggests classification as a dangerous drug. But the research of Hemby et al. (2019) states that mitragynine has no potential for abuse and reduces morphine intake, a desirable characteristic of pharmacotherapy candidates for opiate addiction and withdrawal, whereas 7-hydroxymitragynine should be considered a kratom constituent with a high potential for abuse that can also increase opiate withdrawal [40]. The other Other studies have also examined kratom usage patterns, reported effects, and explored their potential to cause dependence. Ahmad et al. (2012) research using face-to-face interviews was conducted using a structured questionnaire on 562 respondents [41]. The response rate is 91%. The majority of respondents (88%) reported daily kratom use. Only the level of education has a statistically significant relationship with the ability to stop or not stop using kratom. Overall, kratom user performance was compared to control participants, and high performance (> 3 glasses per day) as well as low (≤3 glasses per day) kratom used groups, comparable in all neuropsychological domains [42]. Those who consumed higher quantities of kratom tea daily (≥4 glasses) had higher odds of reporting a longer duration of kratom use history, higher frequency of daily kratom use (≥4 times), and were more likely to experience moderate symptoms of depression during kratom cessation than those who consumed between one and three glasses of kratom tea per day. Cessation from regular and long-term kratom tea consumption was not associated with symptoms of high anxiety or

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depression [43]. Regular and higher (three or more glasses) consumption of kratom decoction did not appear to cause significant constipation problems, but users were prone to severe fatigue during kratom cessation [44].

3.4. Pharmacological activities

The use of kratom or mitragynine extracts and their derivatives at certain doses will have various pharmacological effects, as summarized in Table 2.

Table 2. Research related to the pharmacological activity of kratom leaves.

ANALGESIC			
Comparative effects of *Mitragyna speciosa* extract, mitragynine, and opioid agonists on thermal nociception in rats.	Kratom Extract	Test articles were vehicle, 6 mg/kg oxycodone, 300 mg/kg *Mitragyna speciosa* extract, or 100 mg/kg mitragynine with hotplate tests conducted 30 and 60 min after administration. Mitragynine produced antinociceptive effects similar to the reference opioid agonists when administered IP and PO routes.	[14]
Effects of the extracts from *Mitragyna speciosa* Korth. leaves on analgesic and behavioral activities in experimental animals	Kratom Extract	The alkaloid extract from *Mitragyna speciosa* also increased response latency with a dose of 20 mg/kg but was less strong than methanol extract (100 mg/kg) in mice (compare 5-10 mg/kg of alkaloid extract with those corresponding to 200 mg/kg of methanol extract). These results indicate that the methanol and alkaloid extracts of *Mitragyna speciosa* leaves have the most important analgesic activity on opioid receptors in the supraspinal opioid system.	[4]
Chemistry and Pharmacology of Analgesic Indole Alkaloids from the Rubiaceous Plant, *Mitragyna speciosa*	Mitragynine	The activity of mitragynine opioid agonists, with the mechanism underlying analgesic activity clarified, shows potent antinociceptive activity in rats.	[6]
Antinociceptive Action of Isolated Mitragynine from *Mitragyna speciosa* through Activation of Opioid Receptor System.	Mitragynine	In this study, 35 mg/kg of mitragynine showed a significant increase in latency time, and this dose was used in antagonist receptor studies (antinociceptive effect).	[13]
Anti-Inflammatory and Antinociceptive Effects of *Mitragyna speciosa* Korth Methanolic Extract.	Kratom Extract	Results showed that intraperitoneal administration of the extract at doses of 100 and 200 mg/kg produced significant dose-dependent activity in all of the nociceptive models evaluated. With the formalin test, the antinociceptive activity in mice was inhibited only at the highest dose of the extract (200 mg/kg).	[19]
SEDATIVE			
Effects of an alkaloid-rich extract from *Mitragyna speciosa* leaves and fluoxetine on sleep profiles, EEG spectral frequency and ethanol with drawal symptomsin rats.	Kratom Extract	Alkaloid extract from Kratom (60 mg/kg) was found to significantly attenuate ethanol withdrawal-induced hyperexcitability (increases gamma activity) in both cortices and to reduce locomotor activity (sedative).	[45]
Test of Sedative Effects of N-Hexane Extract from Kratom (*Mitragyna speciosa* Korth) Leaves on Male Mice.	Kratom Extract	The results showed that *n*-hexane extract had a sedative effect contained the compound group of alkaloids, glycosides, steroids, and flavonoids. The dosage 4 (96 mg/kg BW) of *n*-hexane extract of kratom leaves gave sedative effects better than diazepam.	[46]
The Test On The Sedative Effect Of Kratom (*Mitragyna speciosa* Korth.) Leaves Infusa To Male Balb/C Strain Mice	Kratom Extract	Based on the result, all of kratom leaves infusa dosages has a sedative effect, which is the most effective dose kratom leaves infusa at a dose of 7.80 g/Kg BW. But the sedative effect still below diazepam.	[47]
Sedative Effect Test of Kratom (*Mitragyna speciosa* Korth) Ethanolic Extract Extract Leaves on Balb/C strain male mice	Kratom Extract	The results show, there are sedative effects at doses of 27.20 mg/20g BW, 54.39 mg/20g BW, and 108.78 mg/20g BW, which the all dose are greater potential than the positive control group	[48]

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		(diazepam). The effective dose of fraction ethanol of kratom leaf is 27.20 mg/20g BW.	
ANTIOBESITY			
Acute and long-term effects of alkaloid extract of *Mitragyna speciosa* on food and water intake and body weight in rats	Kratom Extract	Acute administration of *Mitragyna speciose* extract (45 and 50 mg/kg) significantly resulted in dose-dependent decreases in food and water intakes (Pb0.05) in rats. Prolonged suppressing effects were observed following administration of the *Mitragyna speciose* extract (40 mg/kg) for 60 consecutive days. Moreover, the long-term administration also significantly suppressed weight gaining.	[49]
MEMORY			
An examination of the consequences of chronic exposure to *Mitragyna speciosa* during adolescence on learning and memory in adulthood	Kratom Extract	In this experiment, adolescent rats were given repeated saline injections, 15 mg/kg, or 50 mg/kg extract of *Mitragyna speciosa*. After animals reach 107 days, they are assessed for general activity. The results of the study show that chronic exposure to alkaloids during adolescence can produce subtle changes but affect memory performance and work in adulthood, long after exposure to Kratom has ended.	[50]
BREAST ANTICANCER			
Characterization of cytotoxic compounds from the ethrat acetate fraction of Kratom (*Mitragyna speciosa* Korth) leaves and their activity on T47d breast cancer cells	Kratom Extract	Based on the research that has been done, it can be concluded that the cytotoxic compounds obtained from the ethyl acetate fraction are classified as moderate cytotoxic against T47D breast cancer cells with an IC_{50} value of 161.67 µg/mL.	[51]
ANTINOSISEPTIVE			
Fos-like immunoreactivity in rat dorsal raphe nuclei induced by alkaloid extract of *Mitragyna speciosa*.	Kratom Extract	The results showed that a single injection (dose of 60 or 90 mg/kg) significantly decreased the time of immobility in FST. These findings indicate that *Mitragyna speciose* extract has a stimulating effect on the dorsal raphe nucleus and antidepressant activity. Stimulation of this area of the brain has been known to cause antinosisepsi.	[52]
The evaluation of antinociceptive activity of alkaloid, methanolic, and aqueous extracts of Malaysian *Mitragyna speciosa* Korth leaves in rats.	Kratom Extract	Results showed that oral administration of the alkaloid (20 mg/kg), methanolic (200 mg/kg), and aqueous (400 mg/kg) extracts significantly prolonged the latency of nociceptive was blocked by naloxone. In conclusion, these results suggest the presence of an antinociceptive effect in various extracts of Malaysian *Mitragyna speciosa* leaves.	[53]
Antinociceptive Activity of Aqueous Fraction of Kratom Leaves *Mitragyna speciosa* Korth.) on Male Swiss Albino Mice	Kratom Extract	The result showed that the aqueous fraction at the dose of 140, 280, and 560 mg/kgBW significantly differentiate with the negative control group and positive control group. The antinociceptive effect increases with increasing doses. The three doses showed that the antinociceptive effect was no better than the positive control (morphine).	[54]
Antinociceptive Activity of Dichloromethane Fraction of Kratom Leaves (*Mitragyna speciosa* Korth.) by Oral Route In Male Swiss Mice	Kratom Extract	The purpose of this research was to investigate the antinociceptive effect of dicholoromethane fraction from kratom leaf and determine the percentage of antinociceptive activity on male Swiss mice. Result data were analyzed using One Way ANOVA and Post Hoc Test LSD. It showed the antinociceptive effect of dichloromethane fraction at dose 70, 140, and 280 mg/kgBW were significantly difference ($p<0.05$) with the normal group. The conclusion of this study is the dichloromethane fraction of kratom leaf has antinociceptive activity. The percentage of antinociceptive from the fraction group at dose 280 mg/kgBW was higher than the other two dose-groups (140 and 70 mg/kgBW).	[55]
Comparative effects of *Mitragyna speciosa* extract, mitragynine, and	Kratom Extract	Mitragynine produced antinociceptive effects similar to the reference opioid agonists when administered IP and PO routes.	[14]

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opioid agonists on thermal nociception in rats.			
Antinociception, tolerance and withdrawal symptoms induced by 7-hydroxymitragynine, an alkaloid from the Thai medicinal herb *Mitragyna speciosa*	7-hydroxymitragynine	In the present study, investigates the opioid receptor subtype responsible for the analgesic effect of this compound. Subcutaneous (s.c.) administration of 7-hydroxymitragynine (10 mg/kg, twice daily for 5 days) produced a potent antinociceptive effect mainly through activation of A-opioid receptors. Tolerance to the antinociceptive effect of 7-hydroxymitragynine developed as occurs to morphine. 7-Hydroxymitragynine exhibited a potent antinociceptive effect based on the activation of A-opioid receptors and its morphine-like pharmacological character, but 7-hydroxymitragynine is structurally different from morphine.	[56]
Central antinociceptive effects of mitragynine in mice: contribution of Descending noradrenergic and serotonergic systems	Mitragynine	This study investigated the roles of central monoaminergic systems in the antinociceptive action of mitragynine. Mitragynine (1.0–10 μg) injected i.c.v. exerted a dose-dependent antinociceptive activity in both tests. in this study, it was revealed that mitragynine causes antinociception by stimulating α_2-adrenoceptor and / or blocking 5-HT receptors in mice but has lower antinociceptive activity than morphine.	[57]
Involvement of μ-opioid receptors in antinociception and inhibition of gastrointestinal transit induced by 7-hydroxymitragynine, isolated from Thai herbal medicine *Mitragyna speciosa*.	7-hydroxymitragynine	The present study investigated the mechanism of antinociception 7-hydroxymitragynine, and compared its effects with those of morphine. When administered subcutaneously to mice, 7-hydroxymitragynine produced antinociceptive effects about 5.7 and 4.4 times more potent than those of morphine in the tail-flick (ED50 = 0.80 mg/kg) and hotplate (ED50 = 0.93 mg/kg) tests, respectively.	[58]
Antinociceptive effect of 7-hydroxymitragynine in mice: Discovery of an orally active opioid analgesic from the Thai medicinal herb *Mitragyna speciosa*	7-hydroxymitragynine	When orally administered, 7-hydroxymitragynine (5–10 mg/kg) showed potent antinociceptive activities in tail-flick and hotplate tests. In contrast, only weak antinociception was observed in the case of oral administration of morphine at a dose of 20 mg/kg. It was found that 7-hydroxymitragynine is a novel opioid agonist that is structurally different from the other opioid agonists, and has potent analgesic activity when orally administered.	[59]
MGM-9 [(E)-methyl 2-(3-ethyl-7a,12a-(epoxyethanoxy)-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 m- and k-opioid agonist with potent antinociceptive and weak rewarding effects in mice.	MGM-9	Pemberian MGM-9 secara subkutan dan oral menghasilkan antinosiseptif yang kuat efek dalam tes ekor tikus, hot-plate, dan menggeliat. Ketika diberikan secara oral, efek antinociceptive dari MGM-9 adalah tujuh hingga 22 kali lebih kuat daripada morfin.	[60]
NEUROMUSCULAR			
The neuromuscular blockade produced by pure alkaloid, mitragynine and methanol extract of kratom leaves (*Mitragyna speciosa* Korth.).	Kratom Extract	Kratom methanolic extract present at 0.1–1 mg/mL and mitragynine (0.0156 mg/mL) decreased the muscle twitch on the isolated phrenic nerve–hemidiaphragm and hemidiaphragm preparation. Muscle relaxation caused by kratom extract (1 mg/mL) was greater than the effect of mitragynine. High concentrations of kratom extract (10–40 mg/mL) and mitragynine (2 mg/mL) blocked the nerve conduction, amplitude, and duration of a compound nerve action potential.	[61]
Inhibitory effects of kratom leaf extract (*Mitragyna speciosa*	Kratom Extract	Kratom extract reduces muscle contraction in phrenics, which reduces phrenic nerve-hemidiaphragm causing muscle relaxation at	[62]

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Korth.) on the rat gastrointestinal tract.		concentrations greater than 0.1 mg / mL, and at the highest concentration used (1 mg / mL), causes perfect contraction, about 15 minutes.	
INDUKSI CYP450			
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.	Kratom Extract	The assessment of the enzyme activity was conducted using spectrophotometric methods. *In vitro*, the IC_{50} value could only be obtained for the methanolic extract in APND study (595.30±30.78 µg/mL) and not in other studies due to the enzyme percentage inhibitions being <70%. In contrast to the *in vitro* study, the oral treatment of male Sprague-Dawley rats for 14 days with 50, 100, and 200 mg/kg of methanolic and aqueous extracts and with 5, 10, and 20 mg/kg of total alkaloid extract showed a profound increment on the APND and UGT activities.	[63]
ANTIINFLAMATION			
Anti-Inflammatory and Antinociceptive Effects of *Mitragyna speciosa* Korth Methanolic Extract.	Kratom Extract	The study showed that intraperitoneal administration of the methanol extract of *M. speciosa* (10 0 and 200 mg/kg) significantly and dose-dependently suppressed the development of carrageenan-induced rat paw edema.	[19]
Chemical constituents and nitric oxide inhibitory activity of supercritical carbon dioxide extracts from *Mitragyna speciosa* leaves	Kratom Extract	Extract *Mitragyna speciosa* possessed the strongest activity without cytotoxic effect 60.08 ± 10.02% and cell viability, 91,98 ± 5.58%). It is noteworthy that M5S1 was constituted largely by a fatty acid, in particular palmitic acid (34.90%), which has been claimed as an anti-inflammatory compound.	[64]
OPIATE			
A Psychoactive Tree from Southeast Asia with Opioid Activity	Kratom Extract	This study reports that date, more than 40 compounds have been isolated from the leaves. The major alkaloid found within the crude extract, mitragynine, has been the subject of many pharmacological studies. In addition to the pharmacological studies, two total syntheses of mitragynine have been published as well as general structure-activity relationships (SARs) with respect to the opioid activity.	[1]
OPIATE WITHDRAWAL			
Kratom to mitragynine and its derivatives: Physiological and behavioural effects related to use, abuse, and addiction.	Kratom leaf	It was found that kratom consumed in a systematic manner aims to increase tolerance for hard work or as a substitute for self-medication for opioid addiction. There is also evidence from animal models that support analgesics, muscle relaxants, anti-inflammatory and strong anorectic effects. Mitragynine and its derivatives actions in the central nervous system involve µ-opioid receptors, neuronal Ca^{2+} channels, and descending monoaminergic projections.	[11]
Kratom use and mental health: A systematic review.	Kratom leaf	This study reports that kratom's potential as a harm reduction tool, most notably as a substitute for opioids among people who are addicted. Kratom also enhances mood and relieves anxiety among many users. For many, kratom's negative mental health effects – primarily withdrawal symptoms – appear to be mild relative to those of opioids. For some users, however, withdrawal is highly uncomfortable, and maintaining abstinence becomes difficult.	[16]
The informal use of ketum (*Mitragyna speciosa*) for opioid withdrawal in the northern states of peninsular Malaysia and implications for drug substitution therapy.	Kratom leaf	This study reports that kratom users were relatively older (mean 38.7 years) than the larger substance-using group. Nearly 77% (104 subjects) had previous drug use history, whilst urine screening confirmed 62 subjects were also using other substances. Longer-term users (use >2 years) had higher odds of being married, of consuming more than the average three glasses of ketum a day, and reporting better appetite. Short-term users had higher odds of having ever used heroin, testing	[65]

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		positive for heroin, and of using ketum to reduce addiction to other drugs.	
Mitragynine reduced morphine-induced conditioned place preference and withdrawal in rodents	Mitragynine	This study aimed to provide an evaluation of abuse liability and the potential of mitragynine in the treatment for opioid addictions. The results showed after being given morphine to rat, 10 mg/kg mitragynine could reduce jumping behavior to the same level as chronic treatment of 10 mg/kg mitragynine alone, and 30 mg/kg mitragynine could reduce Straub tail reaction. This study indicates that mitragynine had low abuse liability and could attenuate the acquisition and expression of morphine-induced conditioned place preference and precipitated withdrawal symptoms.	[66]
ANTIMICROBA			
Evaluation of Antioxidant and Antibacterial Activities of Aqueous, Methanolic and Alkaloid Extracts from *Mitragyna speciosa* (Rubiaceae Family) Leaves	Kratom Extract	In this study, the antimicrobial of kratom showed activity against Salmonella typhi and Bacillus subtilis. The minimum inhibitory concentrations (MICs) of extracts determined by the broth dilution method ranged from 3.12 to 6.25 mg/mL. The alkaloid extract was found to be most effective against all of the tested organisms.	[21]
Antibacterial activities of kratom leaf extract *Mitragyna speciosa* korth) against bacteria propionibacterium Acnes causes acne.	Kratom Extract	The results showed that the thick extract of kratom leaf had an inhibitory effect on the growth of Escherichia Coli bacteria and the kratom leaf extract was able to inhibit the growth of Propionibacterium acnes at a concentration of 5% with a diameter of inhibition of 8.6 mm± 0,20.	[67]
ANTIOXIDANT			
Evaluation of Antioxidant and Antibacterial Activities of Aqueous, Methanolic and Alkaloid Extracts from *Mitragyna speciosa* (Rubiaceae Family) Leaves	Kratom Extract	The extracts showed antioxidant activities were correlated with the total phenolic content. This result suggests that the relatively high antioxidant activity of the methanolic extract compared to aqueous and alkaloid extract could be possibly be due to its high phenolic content.	[21]
Characterization, Phytochemical Screenings and Antioxidant Activity Test of Kratom Leaf Ethanol Extract (*Mitragyna speciosa* Korth) Using DPPH Method	Kratom Extract	The results showed phytochemical screening containing kratom leaf ethanol extract containing chemical composition: alkaloids, flavonoids, triterpenoids/steroids, saponins, and tannins. The results of antioxidant activity testing showed that ethanol extract had an IC_{50} value of 38.56 µg/ml. These results indicate that the kratom ethanol extract has strong antioxidant activity.	[68]
Glutathione Transferase (GSTs) OBLIGATOR			
In Vitro and in Vivo Effects of Three Different *Mitragyna speciosa* Korth Leaf Extracts on Phase II Drug Metabolizing Enzymes-Glutathione Transferases (GSTs)	Kratom Extract	At the highest concentration used, the methanolic extract showed the highest GSTs specific activity inhibition (61%), followed by aqueous (50%) and total alkaloid extract (43%), respectively. In in vivo study, three different dosages; 50, 100, and 200 mg/kg for methanolic and aqueous extracts and 5, 10, and 20 mg/kg for total alkaloid extract were given orally for 14 days. An increase in GST specific activity was generally observed. However, only *Mitragyna speciosa* aqueous extract with a dosage of 100 mg/kg showed significant results: 129% compared to control.	[34]

3.5. Pharmacokinetics

The use of mitragynine is relatively safe at lower sub-chronic doses (1-10 mg/kg) but shows toxicity at the highest dose (sub-chronic 28 days: 100 mg/kg) [8]. But there is no literature related to the use of safe doses of kratom in humans. Trakulsrichai et al. (2015) conducted a study of pharmacokinetic parameters in mitragynine showing time to reach maximum plasma concentrations (0.83 ± 0.35 hours), terminal half-life (23.24 ± 16.07 hours), and clear volume distribution (38, 04 ± 24.32 L/kg) [69]. Prutipanlai et al. (2017) conducted a determination of mitragynine in urine, which showed mitragynine recovery ranged from 92.75-

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100.83% [70]. Mitragynine concentration-time data showed two peak plasma concentrations (Cmax). The first Cmax 457.2 ± 42.3 (ng/mL) occurred within 1.5 h postdose, while the second Cmax 335.0 ± 34.3 (ng/mL) occurred between 2.8 to 3.8 h post-dose [71]. Research Manda et al. (2014) conducted in vitro research showing mitragynine, 7-hydroxymitragynine, and mitraphylline were unstable in gastric fluid simulation but stable in intestinal fluid simulation, 7-hydroxymitragynine decomposed 27% in gastric fluid simulation, 23% were converted to mitragynine, and 6% decompose in intestinal fluid simulation [72]. Meanwhile, mitraphylline is stable in gastric fluid simulation but is not stable in intestinal fluid simulation. Mitragynine, 7-hydroxymitragynine, and mitraphylline have high plasma bonds (> 90%). Mitragynine is stable in the human liver microsome. Instead, 7-hydroxymitragynine, and mitraphylline are metabolized by human liver microsome with a half-life of 24 and 50 minutes. Mitragynine and 7-hydroxymitragynine inhibit P-glycoprotein with EC50 values of 18.2 ± 3.6M and 32.4 ± 1.9 M, respectively, determined by the fluorescent calcein-AM test, while no inhibition was seen with mitraphylline. These data indicate the possibility of drug interaction if mitragynine and 7-hydroxymitragynine are coadministered with drugs that are P-glycoprotein substrates.

3.5. Analysis

Kratom contains more than 40 types of alkaloids including *Mitragyna speciosa*, as many as (66.2%) and their derivatives, speciogynine (6.6%), speciociliatine (0.8%), paynantheine (8.6%), 7- hydroxy mitragynine (2%, 0%). The number of compounds in *Mitragyna speciosa* can be influenced by geographical factors. As in Boffa et al. (2018) research studied five different strains of *Mitragyna speciosa* that have different vein colors and geographic origin; Red Thai, Red Malay, Red Bali, White Borneo and Green Malay, showed the Green Malay variety highest w/w percentages for mitragynine and total alkaloids in its extracts [73]. In addition to geographical factors that affect the compound content of mitragyna speciosa, temperature and pH factors greatly affect the stability of the compound. In the study of Basilieri et al. (2020) found that mitragynine was completely stable for eight hours at pH 2-10 at 4, 20 and 40°C [74]. In contrast, the drug was significantly acid-labile at elevated temperature (60-80°C).

Kratom alkaloid extract can be obtained through a withdrawal process with conventional and nonconventional methods because each method has its advantages and disadvantages. As in research of Idayu et al. (2011) carried out the withdrawal of kratom alkaloid extract compounds conventionally by using absolute methanol for 72 hours [75]. The methanol extract was dissolved in a 10% acetic acid solution, left for 24 hours, and filtered to produce acid filtrate. The acid filtrate is washed with petroleum ether, made into a base (pH 9) with 25% ammonia solution, and extracted with chloroform. The combined chloroform extract was washed with distilled water, dried with anhydrous sodium sulfate, and evaporated to produce 0.73% (w/w) crude alkaloid extract. The main alkaloids were isolated by silica gel eluting column chromatography with diethyl ether identified as mitragynine by standard spectroscopic methods. Overall, mitragynine yields around 0.087% (w/w) of fresh leaf weight. The same study was also carried out by Azizi et al. (2010), *Mitragyna speciosa* (5 kg) dry powder soaked in methanol for several days at room temperature [34]. The extraction and evaporation procedures were repeated three times. Next, one part of methanol extract was mixed with 35 parts 90% acetic acid. The suspension is filtered, and the filtrate is washed with petroleum ether. The acid layer is refined with sodium carbonate to pH 9 and extracted with

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chloroform several times. The combined chloroform extract was dried over sodium sulfate and evaporated to produce 5 g (yield of 0.5%) of the crude alkaloid mixture. In the research, Parthasarathy et al. (2013) produced mitragynine in plant extracts ranging from 0.8 to 25 mg/g monitored using the High Performance Liquid Chromatography with Diode Array Detector (HPLC-DAD) system with Inertsil C8 (4.6 mm 150 mm, 5 mm) as the column and mixture of acetonitrile and formic acid, 50:50 (v/v) as the mobile phase [10]. Whereas other studies conducted extracts of alkaloid extracts from kratom using nonconventional methods such as in the study of Tohar et al. (2007) kratom powder was saturated with NH_3, Supercritical Carbon Dioxide Extraction (ethanol 20) at 40ºC and 5000 psi pressure [76]. Overall, the yield of kratom alkaloids is around 4.05% (w/w) of the weight of fresh leaves. The study of Orio et al. (2012) also withdrew alkaloid extracts from kratom using ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE), and SFE-CO_2 supercritical carbon dioxide extraction, using a mixture of methanol, ethanol, water, and binary mixtures [77]. Of the several methods tested, MAE in a closed vessel at 110 C (60 W, methanol/water 1:1) gave the highest kratom alkaloid extract 16.6 ± 0.41 mg/g dried leaves, while UAE with an immersion horn at 25 C (21.4 kHz, 50 W, methanol) showed the best yield for mitragynine. Another study was also conducted by Abd Razak et al. (2020) to optimize the results of the crude methanol extract of *Mitragyna speciosa* leaves using extraction with the help of USG (UEA) [78]. The results showed the maximum yield of 49.72% at the optimal conditions (temperature, 34 °C; time, 25 min; and volume of solvent, 166 mL). Withdrawal of kratom alkaloid extract compounds using nonconventional methods results in relatively higher yields and faster processing than using conventional methods but has the disadvantages of using high technology and high costs.

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4. Conclusions

In general, kratom leaves have the potential to become the raw material for new drugs because kratom leaves contain mitragynine compounds that have many benefits of pharmacological effects. However, the use of kratom leaves directly in the form of powder or fresh leaves can increase the risk of toxicity because the quality and dosage of kratom in leaf form have not been scientifically standardized. Therefore the recommended use as a drug raw material in the world of health is isolated from the compound mitragynine whose dosage can be adjusted easily depending on the intended use and desired pharmacological effects.

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Conflicts of Interest

The authors declared no conflict of interest.

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