

Review

Not peer-reviewed version

# A critical Review on the Neuropharmacological Effects of Kratom: An Insight from the Functional Array of Identified Natural Compounds

Rahni Hossain , [Abida Sultana](#) , [Manit Nuinoon](#) , [Kunwadee Noonong](#) , [Jitbanjong Jitbanjong](#) <sup>\*</sup> ,  
Kazi Helal Hossain , [MD ATIAR RAHMAN](#) <sup>\*</sup>

Posted Date: 22 September 2023

doi: 10.20944/preprints202309.1502.v1

Keywords: kratom; neurological effects; mitragynine; 7-hydroxymitragynine; antioxidant and antiinflammation



Preprints.org is a free multidiscipline platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Review article

# A critical Review on the Neuropharmacological Effects of Kratom: An Insight from the Functional Array of Identified Natural Compounds

Rahni Hossain <sup>1</sup>, Abida Sultana <sup>2</sup>, Manit Nuinoon <sup>1,3</sup>, Kunwadee Noonong <sup>1,4</sup>, Jitbanjong Tangpong <sup>1,\*</sup> Kazi Helal Hossain <sup>5</sup> and Md Atiar Rahman <sup>1,3,\*</sup>

<sup>1</sup> School of Allied Health Sciences, Walailak University, Nakhon Si Thammarat, 80160, Thailand; rahni.ho@mail.wu.ac.th (R.H.); manit.nu@wu.ac.th (M.N.); kunwadee.no@wu.ac.th (K.N.)

<sup>2</sup> Department of Biochemistry & Molecular Biology, University of Chittagong, Chittagong-4331, Bangladesh; adibaabida800@gmail.com

<sup>3</sup> Hematology and Transfusion Science Research Center, Walailak University, Nakhon Si Thammarat, Thailand.

<sup>4</sup> Research Excellence Center for Innovation and Health Product (RECIHP), Walailak University, Nakhon Si Thammarat, 80160, Thailand.

<sup>5</sup> Angiogenesis and Brain Development Laboratory, Department of Neurosciences, Huntington Medical Research Institutes (HMRI), Pasadena, CA, 91105, USA

\* Correspondence: rjitbanj@wu.ac.th (J.T.); atiar@cu.ac.bd (M.A.R.); Cell: +660971174180 (M.A.R.); Tel: +88-031-2606001-10, Extension- 4334 (M.A.R.); Fax: +88-031-726310 (M.A.R.)

## Highlights

- ❖ Neuroprotective effect of Kratom is a recent development
- ❖ Possible neuroprotective mechanism of Kratom is figured out
- ❖ Antioxidative and antiinflammatory mechanism supported the observation
- ❖ Research gap has been explored through rigorous search
- ❖ Toxicological and toxicokinetics of Kratom are illustrated

**Abstract:** Kratom (*Mitragyna speciosa* Korth. Havil) has been considered a narcotic drug for years, barred by the law in many parts of the world, while extensive research over the past few decades proves its several beneficial effects some of which are still in ambiguity. In many countries, including Thailand, the indiscriminate use and abuse of Kratom have led to the loss of life. Nonetheless, researchers have isolated almost fifty pure compounds from Kratom, most of which are alkaloids. The most prevalent compounds, mitragynine and 7-hydroxy mitragynine, are reported to display agonist morphine-like effects on human  $\mu$ -opioid receptors and antagonists at  $\kappa$ - and  $\delta$ -opioid receptors with multimodal effects at other central receptors. Mitragynine is also credited to be one of the modulatory molecules for the Keap1-Nrf2 pathway and SOD, CAT, GST, and associated gene's upregulatory cascades leading to play a pivotal role in neuroprotective actions while its long-high dose is evident to cause the neuronal disorder. Additionally, the anti-inflammatory, antioxidative, antibacterial, and gastroprotective effects are well-cited. In this context, this review focuses on the research gap to resolve the ambiguities about the neuronal effects of kratom to demonstrate its prospects as a therapeutic target for neurodisorders connecting with other pharmacological effects.

**Keywords:** kratom; neurological effects; mitragynine; 7-hydroxymitragynine; antioxidant and antiinflammation

## 1. Introduction

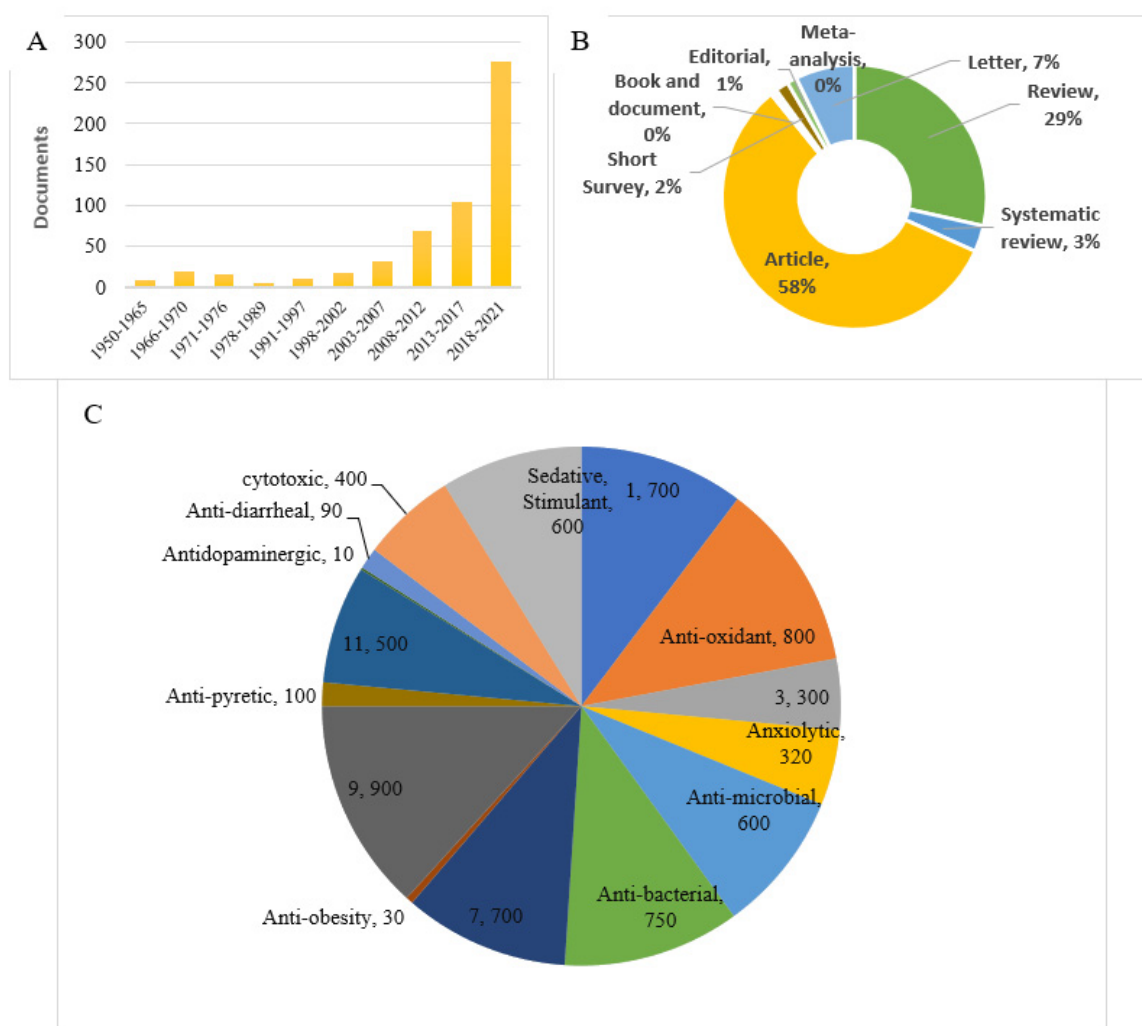
A variety of natural products have been used as medicines and are associated with traditional medicine for thousands of years. <sup>1</sup> Compounds derived from natural products have gained

substantial market share, or they serve as biochemical tools for demonstrating the role of specific pathways in disease and their potential as drugs.<sup>2</sup> Thus, natural products have historically consisted of the most successful sources of new medicines. Compounds derived from natural products serve as both drugs and templates for drugs directly, as well as leading to the discovery of novel aspects of physiology or biology that assist in better understanding disease targets and pathways.<sup>1,3</sup> By the World Health Organization, natural products are considered to be important sources of medicine because of their traditional uses or remedies, and through a few systematic approaches to exploring naturally used products or compounds that can be developed as drug leads, the world has recognized the importance of natural products as medicines.<sup>4</sup> To find drugs from natural products, it is important to know which active compound targets accurate pathways of disorders.

An indigenous Southeast Asian plant with specific medicinal benefits, *Mitragyna speciosa* Korth. (Rubiaceae) Havil. is also known as Kratom, kakuam, ithang, thom in Thailand, ketum or biak-biak in Malaysia, or krypton when combined with O-demethyltramado.<sup>5,6</sup> Thailand, Indonesia, Malaysia, Myanmar, and Papua New Guinea are among the countries that originated it.<sup>7,8</sup> Different formulations are available for kratom, including raw leaves, tea, capsules, tablets, powders, and concentrated extracts. It is widely used for anxiety, depression, pain relievers, talkativeness, sociability, sedation, mood enhancer, constipation, increase energy, appetite, sexual desire, wounds healer as a local anesthetic, and other ailments/conditions as a traditional medicine. The Ketum solution is recommended to ease opiate withdrawal symptoms by taking three 3 × 250 mL daily.<sup>9-12</sup> Due to addiction concerns and an increase in the number of young people utilizing the leaf material and developing a "hook," kratom was formerly outlawed in Thailand and the adjacent country of Malaysia.<sup>13</sup> By using a quick and reliable PCR-reverse dot blot (RDB) hybridization experiment, kratom demonstrated the presence of several narcotic specimens, such as ground leaves and Kratom's cocktail, particularly in matK sequences, a diagnostic barcode.<sup>14</sup> In a different investigation, DNA barcoding in conjunction with high-resolution melting (Bar-HRM) analysis was used to confirm the validity of kratom as a species of narcotic plant for law enforcement.<sup>15</sup> Since at least the eighteenth century, it has been employed in herbal medicine, with various therapeutic benefits, including antioxidant,<sup>16-18</sup> antimicrobial, and antibacterial,<sup>16,19</sup> antinociceptive,<sup>20</sup> and anti-inflammatory,<sup>21</sup> cytotoxic,<sup>20</sup> weight reduction,<sup>22</sup> analgesic,<sup>23-26</sup> antipyretic, sedative, stimulant, antidiabetic, anxiolytic and anti-depressant,<sup>27-32</sup> antidopaminergic<sup>33</sup> and antidiarrheal. Very recently, Salleh et al. has reported the potential neuroprotective role of Kratom on aging brain.<sup>34</sup> Zul Aznal et al., have shown that mitragynine, the major compound of kratom, exposure to adolescent animal brains causes deficits in social behavior but cognitive behavior remains unaffected.<sup>35</sup> In the controversy, Singh and his colleagues proved that a higher intake of kratom juice (>3 glasses daily) did not appear to impair the motor, memory, attention, or executive function of regular kratom users.<sup>36</sup> In this context, the review dissects the neurological role of Kratom and its phytoconstituents to disappear the research gap and ensure whether kratom could be used in neurological disorders by sketching out the underlying molecular mechanisms and relevant pharmacological action.

## 2. Methodology

In this review, the literature was searched using PubMed, Google Scholar, and Scopus from June 2010 to July 2022 to retrieve information about consumption, health effects, phytochemistry, phytoconstituent, toxicology, pharmacokinetics, case reports, and pharmacological effects of kratom using the keywords antioxidant, anti-inflammatory, neuroprotective, antidiabetic, anxiolytic, and anti-depressant. Additionally, a literature search was done to find pertinent human and animal studies. Various research papers, reviews of the literature, and case studies on kratom were also included in this review (**Figure 1**).

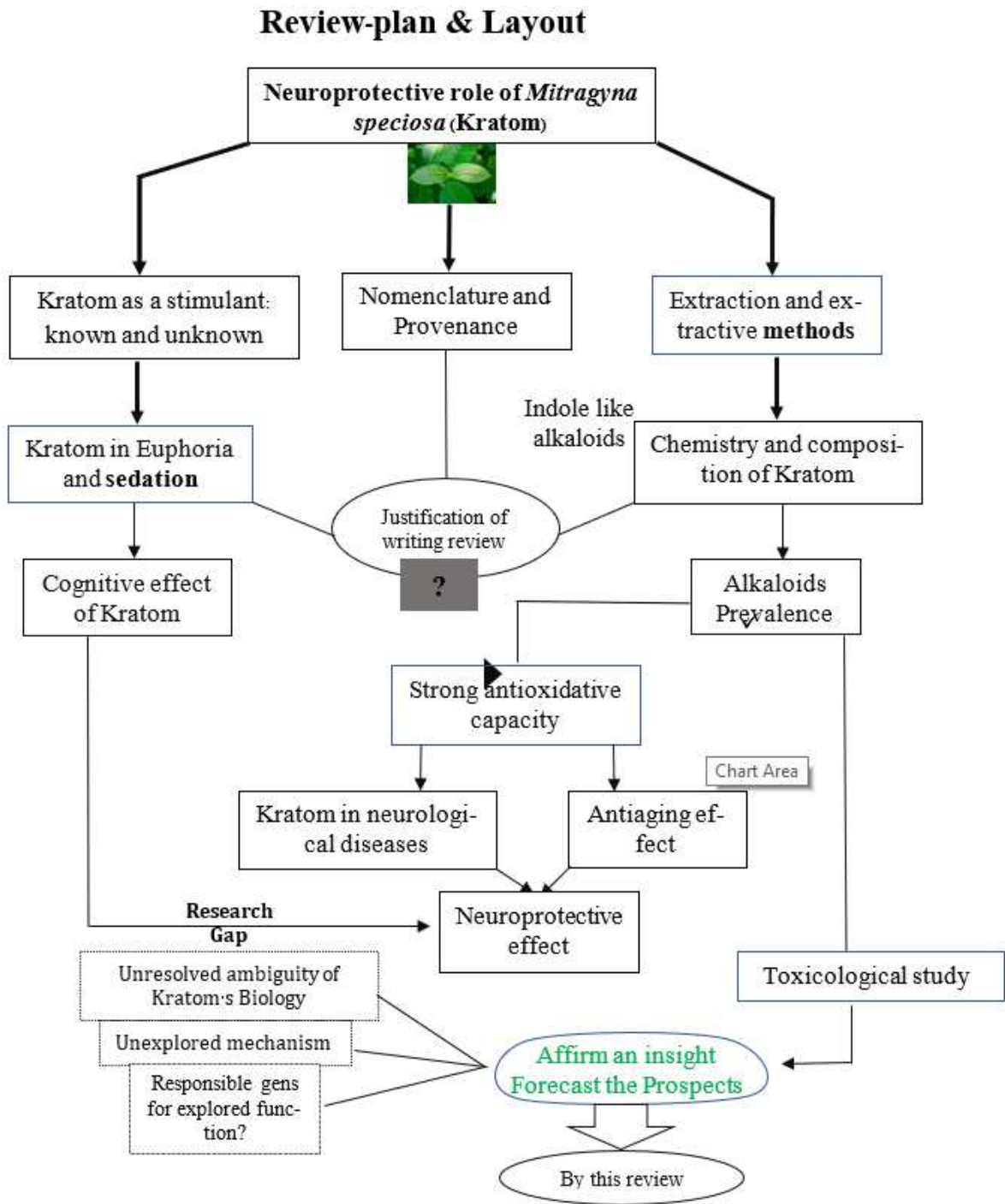


**Figure 1.** The recognized data were retrieved from the PubMed and Google Scholar databases in June 2022. (A) The yearly appearance of publications from 1950-2021. In the years 1950-1965, the publication number is 9. The number of publications numbers in the years 1966-1970, 1971-1976, 1978-1989, 1991-1997, 1998-2002, 2003-2007, 2008-2012, 2013-2017 are 19, 16, 5, 10, 17, 31, 69, 105 respectively. The highest number of publications 276 was published in 2018-2021. (B) Document-wise proportional rate of publications. Total review, Systematic review, Article, Short Survey, Editorial, Letter based documents are found 29%, 3%, 58%, 2%, 1%, and 7% correspondingly. Meta-analysis, Books, and documents are shown in only one copy individually in the PubMed database. (C) Proportional rate of publications according to pharmacological effects. According to pharmacological effects, the number of publications regained from the Google Scholars database showed Anti-inflammatory, 700; Antioxidant, 800; Anti-diabetic, 300; Anxiolytic, 320; Antimicrobial, 600; Antibacterial, 750; Antinociceptive, 700; Antibesity, 30; Analgesic, 900; Antipyretic, 100; Antidepressant, 500; Antidopaminergic, 10; Antidiarrheal, 90; Cytotoxic, 400; Sedative and Stimulant, 600 publications approximately.

### 3. Focus of this review

Kratom has been known for creating an addiction for many years. However, over the past years, scientists' extensive research on kratom has re-introduced it to people as a wonder. The CNS effects of kratom turn into a precious context of drug exploration. Almost all of the compounds analyzed in kratom are important alkaloids or their derivatives.<sup>37</sup> So far, research findings on the major compound of kratom, mitragynine, suggest its mixed and controversial effect on cognitive behavior while some other researchers reported the neuroprotective effect of kratom although the true

mysteries remain unknown. However, by combining the efficacy of kratom's alkaloids, especially the mitragynine and 7-hydroxy mitragynine, with those demonstrating neurological activity, we designed the necessary approaches and models to uncover its neurologically potential. We specifically sought to propose the mechanisms of how kratom can potentially contribute to neurological properties through the linked biochemical and pharmacological actions including antioxidative, anti-inflammatory, and related gene modulatory functions. A schematic diagram has been placed to hypothesize the neurological effects of Kratom (**Figure 2**).



**Figure 2.** Schematic design to illustrate the research question, hypothesis, and novelty of the review to make a spotlight on the insight.



#### 4. Nomenclature and Provenance

A notable example of a new psychoactive drug (NPS) of natural origin is kratom (Korth.) Havil (Figure 3), a tropical tree that may reach heights of 4 to 16 meters and is found in both Asia and Africa.<sup>13</sup> In various regions of Southeast Asia, manual laborers have traditionally made tea or chewed on the tree's chopped fresh or dried leaves to reduce weariness and boost productivity.<sup>38</sup> Kratom compounds have also been used for thousands of years in ceremonial social rites and to cure a wide range of diseases, including opium addiction in Malaya and morphine dependence in Thailand.<sup>39</sup>



**Figure 3.** The specimen of the kratom plant from the Walailak University campus, in Thailand.

The name "*Mitragyna*" for the genus is thought to have been given by the Dutch botanist Korthals because the stigmas and leaves of the plant's flowers have the same shape as a bishop's miter.<sup>40</sup> Though it might be inferred that the word derives from "Mithraic cults" which have long been regarded as a source of spiritual transcendence, given its broad variety of applications.<sup>41</sup> The Kratom tree, which is utilized as an alternative to alcohol and opium in Thailand, is primarily found in the southern part of the nation and is easily bought from teashops. Two different types of Kratom can be distinguished by the color of the leaf vein, which can be either red or green. The crimson vein, which is renowned for its abrasiveness and lasting effects, is often preferred by the locals.<sup>13</sup> Although fresh leaves are often chewed and taken as a powder at a dosage of 10 to 30 fresh leaves per day, they can be smoked or used to make tea.<sup>42</sup>

The Kratom Act was passed in Thailand in 1943, and it was thought that this action was taken more for economic reasons than out of concern for the general welfare of the population. Taxes were levied on the opium trade at the time, and since it was so expensive, people began switching to Kratom as a replacement, which had an impact on the Thai government's revenue. The Thai

government categorized Kratom under Category V of a narcotics categorization in the Narcotics Act later in 1979, among cannabis, opium, and hallucinogenic mushrooms (the least restrictive and punitive level).<sup>42-44</sup>

Kratom has been on the Poison Schedule List since the 1952 passage of the Poison Act. According to the First and Third Schedules of Malaysia's Poison Act 1952, which was amended in 2003, mitragynine, which is found in kratom leaves, is toxic. As a result of Section 30 (3) of the Poison Act of 1952, anyone who violates subsection (3) or any regulations under this Act pertaining to psychotropic substances faces a fine of up to ten thousand ringgit or imprisonment for up to four years. Using kratom improperly can result in a 4-year jail sentence or fines not exceeding RM10,000 or both.<sup>45</sup>

In the beginning, Kratom was mostly utilized for its therapeutic benefits in treating minor medical issues like fever, diarrhea, diabetes, and discomfort as a wound poultice, as well as to alleviate the strain and tiredness of physical labor. But because it is readily available and inexpensive, it has also gained recognition for its use in the suppression of opiate withdrawal symptoms.<sup>9,43,44,46</sup> Kratom tea has recently become a popular base for the "4 × 100" drink, which combines Coca-Cola, cough syrup, ice cubes, and Kratom tea. This eventually became a concern because these users were enhancing the effects with substances such as benzodiazepines.<sup>42</sup> A study assessed the cognitive function of 70 regular kratom users and 25 control participants using the Cambridge Neuropsychological Test Automated Battery. Six neuropsychological tests on the participants' motor, learning and memory, attention, and executive functions were administered. Higher consumption of kratom tea (more than three glasses per day or mitragynine levels between 72.5 mg and 74.9 mg) was specifically linked to subpar performance on the Paired Associates Learning task, which reflects deficiencies in visual episodic memory and new learning. Overall, the performance of kratom users was equivalent to that of control participants, and both high (>3 glasses per day) and low (3 glasses per day) use groups performed similarly across all neuropsychological domains. Regular users of kratom did not appear to experience any negative effects from consuming more kratom juice (>3 glasses per day).<sup>36</sup>

The main causes of Kratom use, as well as the sociodemographic traits of its users, were researched by Vicknasingam et al.<sup>9</sup> 136 active users were included in the study, and 76.5% of them had previously used narcotics. Utilizing Kratom had advantages over heroin, including reducing dependence on other drugs, easing opiate withdrawal symptoms, and being more affordable. Many both short-term and long-term users claimed to feel more energetic, and capable of working hard to have a higher sexual desire.<sup>9,47</sup>

In the USA, an anonymous cross-sectional online survey was carried out in 2006. Through the use of social media and internet resources provided by the American Kratom Association, 8049 users were studied.<sup>48</sup> The results of this study showed that middle-aged (31–50 years) and middle-income (over \$35,000) people are the main users of Kratom, with the main uses being the treatment of pain (68%) and emotional or mental conditions (66%).

As a relatively affordable opiate substitute that doesn't require a prescription from a doctor, kratom is still readily available for purchase online.<sup>49,50</sup> Since the beginning of the new millennium, kratom-branded goods have been sold in Europe under the names "Kratom acetate" or "mitragynine acetate".<sup>2</sup> Due to its psychoactive qualities, Kratom products have recently been advertised as "incense" albeit the levels of these active compounds differ depending on the type of Kratom utilized, the environment, and the time of harvest. Along with khat and *Salvia divinorum*, Kratom was one of the top three plant-based substances according to the United Nations Office of Drugs and Crime's questionnaire on NPS.<sup>51</sup> Because Kratom was infrequently observed in national drug abuse surveys, information on its prevalence is scarce. The 1961 and 1971 Conventions do not identify Kratom or its active alkaloids, but numerous nations have established regulations for its management, which also cover mitragynine and 7-hydroxymitragynine (7-HMG).<sup>3</sup>

Kratom was one of the most commonly given NPS, according to internet surveys conducted by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in 2008 and 2011.<sup>4</sup> It is

not currently prohibited in the USA or the majority of Europe. Kratom and mitragynine, as well as 7-HMG, are restricted substances in numerous EU nations, including Denmark, Latvia, Lithuania, Poland, Romania, and Sweden, due to their significant potential for abuse. They are regulated under drug legislation in other nations, including Australia, Malaysia, Myanmar, and Thailand (which legalized the use of Kratom and cannabis plants for medicinal use in December 2018). Kratom and mitragynine are regulated in New Zealand by the Medicines Amendment Regulations.<sup>4</sup>

## 5. Extraction and extractive of kratom

Researchers concurred that solvent type, which also influences the number of plant extracts, dictates the kind of phytochemicals recovered from plant sources. The leaf of kratom, which is extracted with methanol, has been the subject of most research. And to obtain alkaloid extract, the methanol extract was produced in acid, followed by alkaline, and chloroform extraction. Using the accelerated solvent extraction (ASE) method on Kratom leaves, water, ethanol, and ethyl acetate were employed instead of methanol, the most used extraction solvent because of their lower toxicity, safety, and environmental friendliness.<sup>52,53</sup>

Utilizing UHPLC-ESI-QTOF-MS/MS analysis, it was possible to determine how the ASE technique affected the extraction yield, total phenolic content (TPC), total flavonoid content (TFC), and phytochemical profiling of kratom leaf; however, there was no discernible change in the dry yield or mitragynine content following water extraction at various extraction times. The dry yield of the extract and its associated mitragynine content varied between 0.53 and 2.91 g when Kratom leaves were extracted using organic solvents of various polarities, such as methanol, ethanol, and ethyl acetate. The ethyl acetate ASE extract of Kratom leaf had the greatest TPC ( $459.78 \pm 5.47$  GAE mg/g) compared to other ASE extracts when the TPC and TFC for Kratom leaf extracts were evaluated. In comparison to other ASE extracts, TFC was noticeably greater in the ASE ethanol Kratom leaf extract ( $194.00 \pm 5.00$  QE mg/g).<sup>20</sup>

In a different investigation, adding heat and an Ultra sonicator to the acetic acid extraction process increased the amount of mitragynine that was extracted. By extending the time, increasing the temperature, and using an ultrasonicator, the % yield of mitragynine increased. The best extract of mitragynine was discovered to be acetic acid, which produced the maximum yield of mitragynine at  $2.69 \pm 0.12$  % when heated to  $80^\circ\text{C}$  for 30 min. After being extracted with hexane, dichloromethane, ethyl acetate, ethanol, and 50 % acetic acid, purified mitragynine from the Kratom extract showed antibacterial action. Extracting using boiling water is another facile extraction method, which used boiling water followed by dichloromethane partitioning. The three primary indole alkaloids—mitragynine (MG), paynantheine (PAY), and speciogynine (SG)—were isolated by boiling fresh leaves in water and then partitioning them with dichloromethane. The extraction yield was 1.0 % (w/w) under ideal conditions, which was ten times lower than the yield of methanol. The *Stephania venosa* extract produced by this approach was rich in alkaloids. The technique was simple to carry out, affordable, safe for the environment, and quickly scaled up from a laboratory to an industrial scale.<sup>54</sup>

In some other studies, the conventional approach of extraction was used starting with non-polar (hexane), followed by medium polar (chloroform), and polar (methanol), however, no yield is accounted for in this experiment. The evidence on the use of multiple solvents for extraction and variation of yield content unresolved the intrigue of why not hydroalcoholic extract or Soxhlet apparatus is yet to use for kratom extraction. The consequence of their use in biological function may lead to creating a new question.

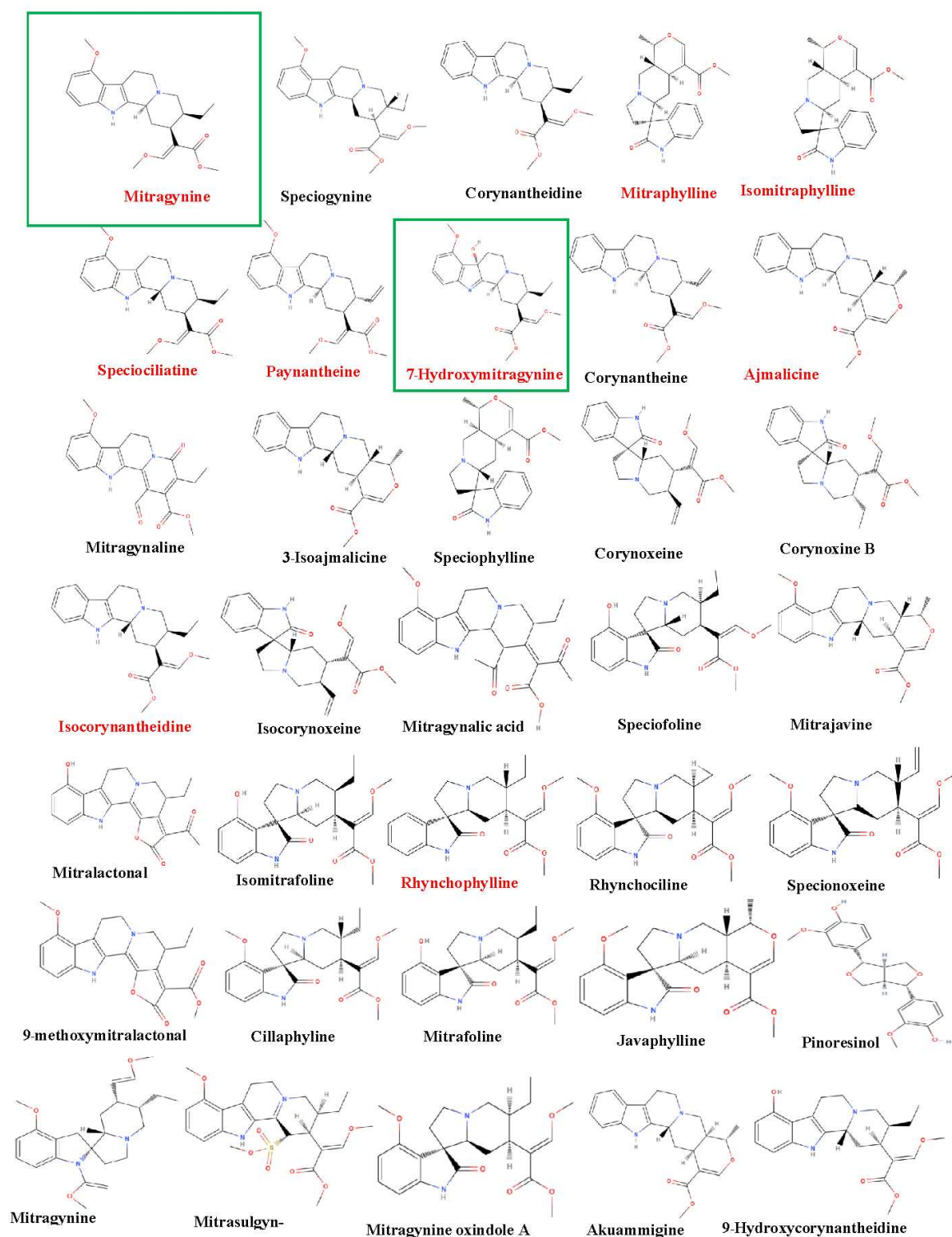
## 6. Chemistry and Composition-linked actions of kratom

The phytochemical properties of kratom have been extensively reported for many years. kratom consists of 79 secondary metabolites, a high number of alkaloids, flavonoids, polyphenols, terpenoids, triterpenoids, saponins, and secoirids.<sup>16,55-57</sup>



More than 50 alkaloids from kratom leaves have been isolated during the previous 87 years, and six of them are pharmacologically active as a psychoactive substance through testing. These six alkaloids are mitragynine (66-67%), paynantheine (PAY)-(8-9%), speciogynine (SG)-(6-7%), 7-hydroxymitragynine (7-HMG)-2%, speciociliatine (SC)-0.8%, and mitraphylline- <0.1% approximately (**Figure 4**).<sup>5,51,58,59</sup> Other substances that kratom covers likewise have various pharmacological effects ajmalicine (cerebro-circulant, anti-aggregant, anti-adrenergic, sedative, anti-convulsant, smooth muscle relaxant),<sup>60,61</sup> akuammigine (stimulant, analgesic, anti-malarial),<sup>62</sup> ciliaphylline (anti-tussive, analgesic, mild sedative and anti-diarrheal),<sup>63</sup> corynantheidine (anti-hypertensive,  $\alpha$ -1 and  $\alpha$ -2 Adrenergic),<sup>64</sup> corynoxine (calcium channel blocker, anti-locomotive, anti-Parkinson's effect),<sup>65</sup> epicatechin (antioxidant, anti-bacterial, anti-diabetic, anti-inflammatory),<sup>66,67</sup> 9-Hydroxycorynantheidine (partial opioid agonist),<sup>68</sup> isomitraphylline (immune-stimulant, anti-leukemic),<sup>69</sup> isomitrafoline (auxiliary immune-stimulant), isopteropodine (immune-stimulant, anti-bacterial),<sup>70</sup> isospeciofoline (analgesic, anti-tussive), mitrafoline (anti-hypertensive, anti-amnesic, anti-leukemic), mitraciliatine, mitraphylline (strong muscle relaxant, vasodilator, diuretic), mitraversine, rhynchophylline (calcium channel blocker),<sup>71</sup> isorhynchophylline, speciofoline, speciophylline (anti-leukemic), stipulatine, tetrahydroalstonine (hypoglycemic, anti-adrenergic) (**Figure 4**).<sup>10,36,72-75</sup> The primary alkaloid in Kratom, mitragynine, a corynanthine-like indole alkaloid, was initially isolated by Field in 1921 and has subsequently shown opioid receptor affinity and partial agonist activity. It makes up roughly 1–2 % of the dried leaf material.<sup>76</sup> The structure of mitragynine a white amorphous powder was first fully determined in 1965 through X-ray crystallography<sup>77</sup> and it is found to be soluble in alcohol, chloroform, and acetic acid. Some other indole and oxindole moiety-based major alkaloids possessed by Kratom are speciociliatine, speciogynine, paynantheine, and minor alkaloids are isopaynantheine, 7-hydroxy mitragynine (7OH), corynoxine A, corynoxine B, mitraciliatine, corynantheidine.<sup>30,37,78-82</sup>

Apart from a high number of alkaloid components, kratom also has some secondary metabolites various saponins, iridoids, and other monoterpenoids, triterpenoids such as ursolic acid, and oleanic acid, as well as various polyphenols including apigenin, apigenin 7-glycosides, quercitrin, isoquercitrin, rutin, and quercetin type flavonoids. The list of kratom metabolites also includes hyperoside, quercetin-3-galactoside-7-rhamnoside, kaempferol, kaempferol 3-glucoside, epicatechin, caffeic acid, chlorogenic acid, 1-O-feruloyl- $\beta$ -D-glucopyranoside, benzyl- $\beta$ -D-glucopyranoside, quinic acid and its derivatives, monoterpenes 3-oxo- $\alpha$ -ionyl-O- $\beta$ -D-glucopyranoside, roseoside, secoiridoid, vogeloside, epigeloside etc.<sup>16,83-86</sup>



**Figure 4.** Structural diversity of the chemical compounds from kratom. Red color names signify active compounds with reported pharmaceutical properties.

#### *Nature of alkaloids from kratom*

The majority of alkaloids found in kratom are indole alkaloids, including 7-OH, anjmalicine, paynantheine, mitragynine, speciogynine, isopaynantheine, and mitraciliatine. Six other oxindole alkaloids also appear in it: rhynchophylline, isomitrabrylline, isospeciiofoline, speciofoline, and corynoxine A.<sup>87</sup> Speciogynine, paynantheine, isopaynantheine, and speciociliatine are diastereoisomers of mitragynine that are found in these alkaloids.<sup>88</sup> 7-OH is a well-known terpenoid

indole alkaloid that descended from mitragynine in 1994. According to Azizi et al.<sup>89</sup> the three Corynanthe alkaloids found in kratom, mitragynine, paynantheine, and speciogynine, all have a distinctive 9-methoxy group that contributes to their biological effect on the central nervous system. An indole alkaloid known as akuammigine, ciliaphylline, epicatechin, and isopteropodine (a hetero yohimbine-type oxindole alkaloid), mitraversine (an indole derivative), rhynchophylline (an indole alkaloid), and tetrahydroalstonine (a yohimban alkaloid, an organic heteropentacyclic compound, and a methyl ester). The remaining kratom components are either alkaloids or polyphenolic chemicals. Understanding the nature of these alkaloids is critical for understanding the mechanisms underlying kratom's purported neuroprotective benefits.

## 7. Toxicology and toxicokinetics of kratom

As of yet, nothing is known about the toxicokinetics of Kratom in humans, including the metabolic half-life, protein binding characteristics, and elimination rates.<sup>90,91</sup> On the other hand, moderate to high dosages (5 to 15 g) produced opioid-like effects. It has been demonstrated experimentally that low to moderate dosages (1 to 5 g) provide modest stimulant effects to aid employees in overcoming weariness.<sup>9</sup> High dosages (>15 g) are associated with reports of anxiety, irritation, and increased aggression, which have been linked to several unusual consequences.<sup>9,38,51</sup> For some users, the Kratom withdrawal effect is quite unpleasant, making it difficult to maintain abstinence similar to opioid withdrawal. In a study on animals, Trakulsrichai et al.<sup>92</sup> discovered that the main unfavorable consequences of ingesting Kratom "mitragynine tea" were the onset of numbness and an increase in blood pressure and heart rate, which both occurred eight hours after consumption. Using 200 mg/kg of kratom whole alkaloid extract caused rats to die, according to a study.<sup>89</sup> However, 129 Kratom users in the USA were found to use 1-3 grams of Kratom each dose regularly.<sup>93</sup> Of the 129 regular users, 37% consumed kratom as a no optimum dose of kratom is still set a safe dose. A case report of a young kratom user showed that approximately 10–14 days after consumption has stopped kratom metabolites could still be detected in urine. Saturation of enzymatic pathways or high plasma protein binding could account for this situation, but none was proven to be right.<sup>94</sup> A significant rise in blood pressure (one hour after administration), acute severe hepatotoxicity, and mild nephrotoxicity were noted in a 14-day intervention of toxicity evaluation using 100, 500, and 1000 mg/kg BW of kratom methanolic extract, even though spontaneous behavior, food, and water consumption, absolute and relative organ weight, and hematological parameters were normal.<sup>95</sup> Kratom was discovered to damage the kidneys and the lungs, resulting in emphysema, over-inflation of the alveoli, and an increase in blood urea and serum creatinine levels.<sup>96</sup> Neither the Kratom extract nor the mitragynine displayed any genotoxicity toward human brain cells in the mouse lymphoma gene mutation assay. The Ames test was used in research, but no mutagenic effects were discovered.<sup>97</sup>

Although numerous toxicities and fatal results following the use of mitragynine or Kratom have been reported, the fundamental causes are still unknown. Mitragynine is a glycoprotein-P inhibitor, which Rusli et al.<sup>98</sup> demonstrated interacts with significant residues at the nucleotide-binding domain site of glycoprotein-P but not with residues from the substrate binding site (a multidrug transporter for modulating xenobiotic pharmacokinetics mediation of drug-drug interactions). As a result, it is okay to use mitragynine-containing Kratom products concurrently with medications that alter the way Glycoprotein-P behaves, but not with residues that are involved in substrate binding. As a result, taking mitragynine-containing Kratom products at the same time as psychoactive medications that are Glycoprotein-P substrates may cause toxicity, which may have therapeutic implications.

Due to the activation of drug-metabolizing enzymes such as CYP450s and UDP-glucuronosyl transferase, Kratom metabolism is primarily hepatic, and there is some evidence that this can alter the metabolism and effectiveness of other medicines (UGT).<sup>99</sup> Inhibition of CYP3A4, CYP2D6, and CYP2C9 was discovered to be caused by kratom alkaloid extract, according to several studies that examined the effects of kratom on human recombinant CYP450 enzyme activities.<sup>100</sup> Mitragynine was

substantially degraded in liver microsomes, largely to O-demethylated and mono-oxidated metabolites, according to Kamble et al.<sup>101</sup> Some other investigations that assessed the effects of kratom on human recombinant CYP450 enzyme activity have confirmed that these enzymes partially account for inter-individual variability in drug metabolism and toxicity due to cytochrome-related genetic variants in humans.<sup>100,102</sup> This finding implies that mitragynine should be administered concurrently with herbal or contemporary medications that follow the same metabolic pathway as herb-drug interactions.<sup>103</sup> Particularly in the case of medications with limited therapeutic windows as carbamazepine, theophylline, digoxin, warfarin, and phenytoin, such combinations may cause severe adverse drug responses.<sup>104</sup> Ulbricht et al.<sup>105</sup> reviews found that kratom is likely to be dangerous if used by individuals with neurologic problems or who are using neurologic medications like alcohol, sedatives, benzodiazepines, opioids, or goods containing opium, or stimulant drugs like caffeine, caffeine-containing products, cocaine, yohimbine, or related substances. Additionally, it is not recommended to co-administer monoamine oxidase inhibitors (MAOIs). A recent tragic case involving a 27-year-old male who had deadly levels of both mitragynine and quetiapine in his blood was reported.<sup>106</sup> While Yohimbe (*Pausinystalia johimbe*) in combination with kratom has been observed to produce overstimulation and elevated blood pressure, other herbs have also been documented to exhibit drug-drug interactions with kratom.<sup>105</sup> After all, in an inconclusive safety profile of Kratom, the overweigh benefits on toxicity and risk can open the window to the use of Kratom in respective cases.<sup>107</sup>

8. Neurological effects of kratom

The neurological effects have been defined in the context of the following spectrum of biological events that appeared to be approached by kratom:

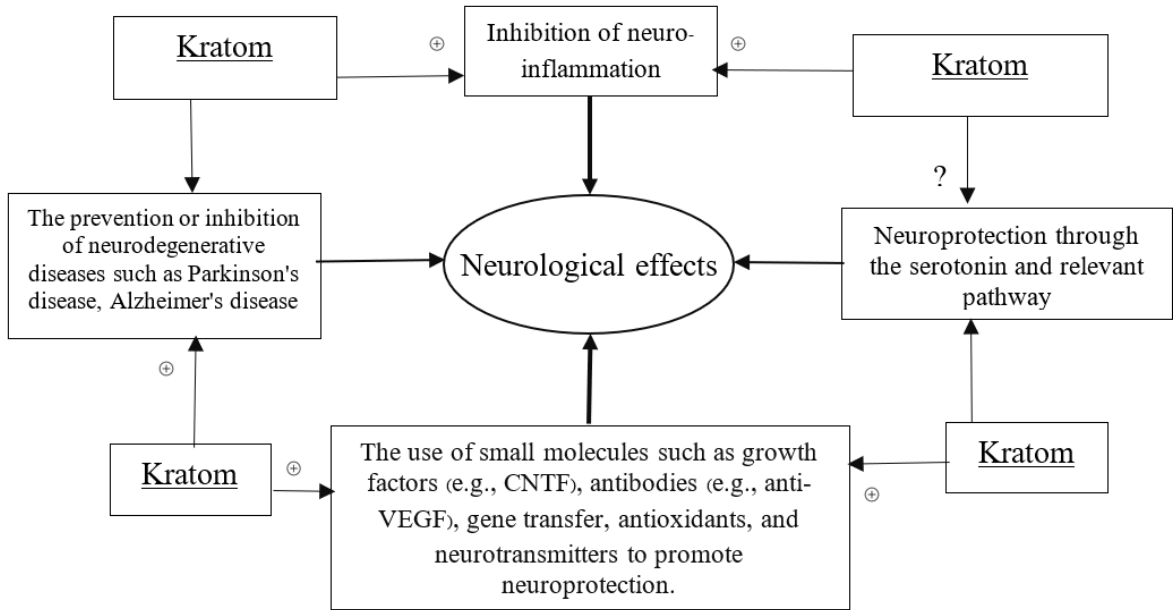


Diagram 1. Schematic diagram to define neurological effects.

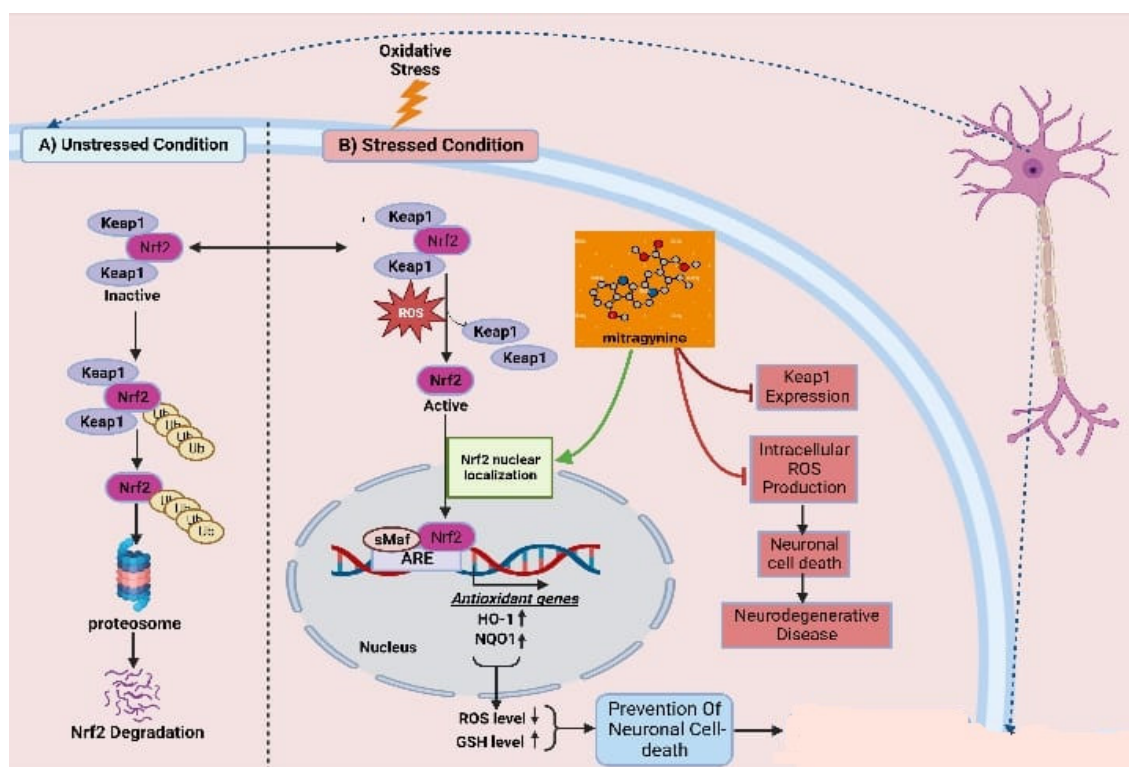
The central nervous system actions of kratom's alkaloids and their derivatives are the subject of growing scientific interest. Two ways that mitragynine's effects on the nervous system were revealed in 1932 were effects on the autonomic nervous system, which included facilitation of impulse passage affecting both the cranio-sacral and sympathetic divisions, and another effect on the central nervous system, which included excitation of the medulla, likely the motor centers.<sup>108</sup> Kratom was found to show an anti-depressant activity at the behavioral level.<sup>27</sup> Mitragynine, the major compound of kratom, was found to activate the GABA<sub>B</sub> receptor in a mitragynine-induced conditioned place preference test in rats.<sup>109</sup> Mitragynine is also found to show a weak functional AMPA as well as



NMDA receptor antagonist action of mitragynine.<sup>110</sup> However, the neuroendocrine-hypothalamic-pituitary-adrenal axis is overactive, as evidenced by the excess production of monoamine neurotransmitters including serotonin, noradrenaline, and dopamine. Nonetheless, the complex pharmacological profile of raw kratom extracts may be explained by the Mitragyna alkaloids' apparent diverse activities at other brain receptors, such as adrenergic, serotonergic, and dopaminergic receptors.<sup>111</sup> Chronic mitragynine (5-15 mg/kg; i.p.) injection for 28 days before a working memory test in mice markedly decreased locomotor activity in an open-field test and object identification.<sup>28</sup> Acute oral administration to kratom extract had no discernible effects on mice's short-term memory or their ability to coordinate their movements when tested with the rota-rod and the Y-maze, but it did increase their exploratory activity in the Y-maze.<sup>112</sup> A human study published in 2018 found that frequent Kratom users' motor, memory, attention, and executive function were unaffected by consuming more than three glasses of Kratom juice per day.<sup>36</sup> Chronic morphine,  $\Delta$ -9-tetrahydrocannabinol, or Kratom administration impaired spatial learning and memory processing.<sup>113</sup> The methanolic extract of kratom (100-1000 mg/kg) was reported to promote learning by demonstrating the latency as a deficiency in memory consolidation of a passive avoidance test. In a two-way active avoidance task, the methanolic extract of kratom had no discernible effects on long-term memory consolidation. The methanolic extract inhibited long-term potentiation (LTP) induction but promoted short-term potentiation in hippocampal field excitatory postsynaptic potentials (fEPSP), demonstrating the impact of extract constituents on the brain's learning and memory pathways.<sup>114</sup>

### 8.1. *Kratom, an indole-like alkaloid for neurological effects*

As one of the most abused plant psychotic drug sources, kratom possesses a powerful psychoactive compound in the form of mitragynine, which demonstrates opioid-like behavioral effects and results in neuroplasticity of the reward system in the brain. There are evident and reported cognitive impairments associated with its chronic administration. By combining increased efficacy with better tolerability and a sparing of opioids, multimodal analgesic strategies are paving the way for major improvements in the management of pain. The association of analgesics with different mechanisms of action has proven to be a successful strategy for the treatment of a wide range of pain conditions, minimizing side effects and maximizing the advantage of additive and synergistic effects of the individual agents. Mitragynine, the most common and concentrated indole alkaloid of kratom, is postulated to be involved in the regulation of the Keap-1/Nrf-2 pathway to ensure neuroprotection. The mechanism by which mitragynine exerts its complex effects adrenergic, serotonergic, and opioid-like is structurally and pharmacologically distinct from that of traditional opioids. In addition to mitragynine and many of this category's alkaloids, many of them may play a pivotal role in regulating the overproduction of intracellular ROS, which contributes to neuronal cell death via H<sub>2</sub>O<sub>2</sub> exposure. It has been shown that the activation of antioxidative genes of Nrf2, such as HO-1 and NQO1, is primarily dependent upon the nuclear translocation of Nrf2 (**Figure 5**).<sup>115</sup> This implies that Nrf2 translocation from the cell cytosol to the nucleus plays an important role, while indole-like alkaloids (e.g., prenylated alkaloids) inhibit Keap1, resulting in Nrf2 nuclear translocation. By activating Nrf2, HO-1, and NQO1 were expressed, resulting in a decreased level of ROS and an increased level of GSH, thereby protecting neurons from oxidative damage.

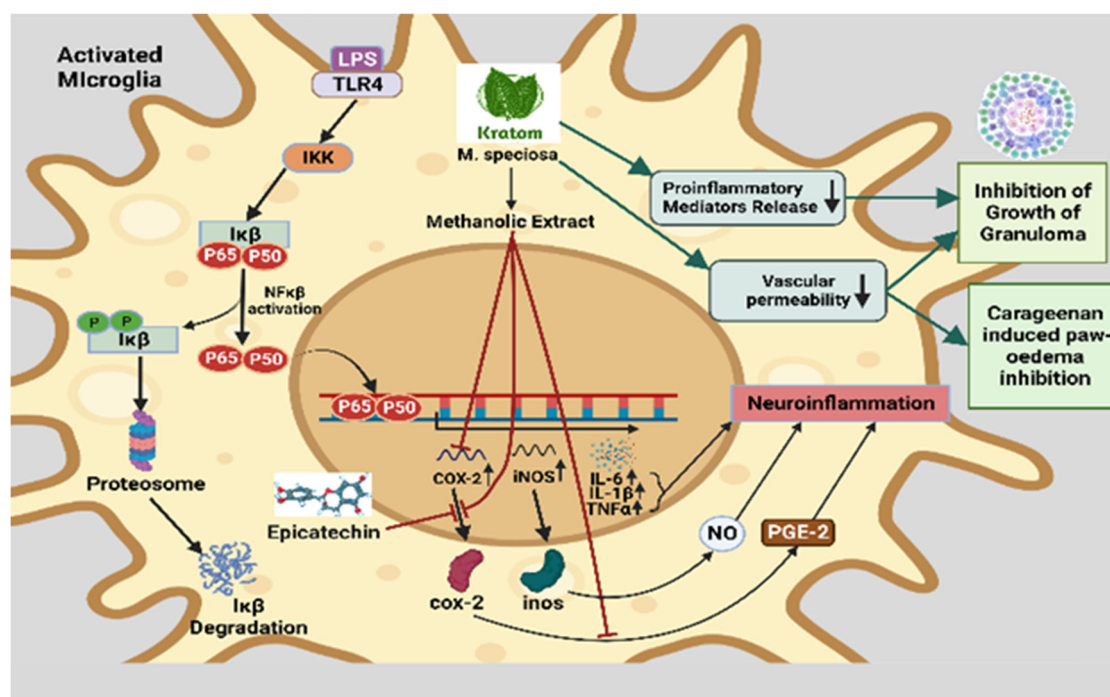


**Figure 5.** Keap1-Nrf2 linked neuroprotective effects of Kratoms' major compound mitragynine. Oxidative stress leads to dissociation of the Keap1-Nrf2 conjugation, homeostatic condition, and releases the Nrf2. The resulting Nrf2 becomes translocated to the nucleus and upregulates the expression of antioxidative genes. Mitragynine is proposed to facilitate the translocation of Nrf2 to the nucleus. While Keap1 expression seems responsible for neuronal cell death and other neurodegenerative diseases (Figure is drawn by BioRender, Registered version).

## 8.2. Anti-inflammatory effects leading to neuroprotective effects

In a recent study, Kratom has been shown to inhibit release of proinflammatory mediators and reduce vascular permeability and can enhance immunity.<sup>107</sup> Activated inflammatory cells at the site of infection release inflammatory mediators like cytokines, arachidonic acid, and chemokines, which in turn trigger signal transduction cascades and changes in transcription factors like nuclear factor kappa B (NF- $\kappa$ B), signal transducer and activator of transcription 3, activator protein-1, NF-E2 related factor-2, nuclear factor of activated T cells, and hypoxia-inducible factor-1 $\alpha$  (HIF1- $\alpha$ ). Initiation of cyclooxygenase-2 (COX-2) (**Figure 6A**), inducibility of nitric oxide synthase (iNOS), and high expression of inflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-6, and chemokines (CXC chemokine receptor 4).<sup>116,117</sup> Epicatechin has effective anti-inflammatory effects. One of the most potent inflammatory mediators is PGE2. Prostaglandin PGE2 is produced by COX-1 and COX-2, which are cyclooxygenases involved in the inflammatory pathway. Previous research demonstrates that the methanolic extract of kratom inhibits COX-2 mRNA and protein expression in RAW264.7 macrophage cells, as well as PGE2 production.<sup>118</sup> The A $\beta$  plaque comprises A $\beta$  peptides derived from APP through enzymatic cleavage *via* ( $\alpha$ ,  $\beta$ , and  $\gamma$ ) secretases. A $\beta$ <sub>1-42</sub> readily aggregates and forms the plaque that activates calpain and deregulates p35 into p25, which hyperactivates CDK5 and leads to hyperphosphorylation of tau and the formation of NFTs.  $\beta$  amyloid plaques promote neurotoxicity or activation of microglia by upregulating NF- $\kappa$ B and AP-1 transcription factors, which in turn release ROS and pro-inflammatory cytokines like NO, PGE2, IL-1, IL-6, COX-2, and TNF- $\alpha$  that damage cholinergic neuron (**Figure 6B**). These pro-inflammatory cytokines also directly stimulate astrocytes, which create their cytokines to increase inflammatory signals, leading to neuroinflammation and neurodegeneration. Daily intraperitoneal injection of 100-

200 mg/kg kratom methanolic extract also had a significant inhibitory effect on the development of granuloma tissue, as demonstrated by the proliferation of modified macrophages, fibroblasts, and highly vascularized, reddish mass tissue, as well as a significant inhibitory effect on the progression of carrageenan-induced paw oedema. In spite of some question marks, inflammation response mechanism, inflammatory cytokines, activation of the inflammasome, and metabolic syndrome as a cause of inflammation in neurotoxicity show that antiinflammation and neuroprotection are strongly correlated.<sup>119</sup> In the study, the authors suggested that kratom's anti-inflammatory properties could be attributed to its inhibition of the release of proinflammatory mediators and its effect on vascular permeability, as well as enhanced immunity and stimulation of tissue repair and healing processes.<sup>21</sup>



**Figure 6. A.** Speculated neuroprotective mechanism of kratom showed that inhibit COX-2 activity. In the neuroinflammation pathway, microglial cells get activated by LPS. As a result of oxidative stress, and inflammatory cytokines, some proteins get phosphorylated and activated which end up in the phosphorylation and ubiquitination of NF-κB. Then NF-κB is secreted to the nucleus where it can bind to a specific binding site to activate the transcription and translation of inflammatory cytokines (TNF-α and IL1-β) and proteins (COX-1, COX-2, and iNOS), that are released from the microglia. Kratom inhibits COX-2 activity. **B.** Antiinflammatory action-based neuroprotective effect of Kratom. Inflammatory status in activated microglia is initiated through LPS-mediated TLR, IKK, IκB, and NFκB activation leading to the synthesis of interleukin and TNFα which are thought to be neuroinflammatory modulators. While Kratom and its alkaloids are postulated to inhibit COX-2, Proinflammatory mediators and decrease vascular permeability implying the contribution of Kratom in neuroprotection (Figure is drawn by BioRender, Registered version).

### 8.3. Analgesic and Anti-nociceptive Effects

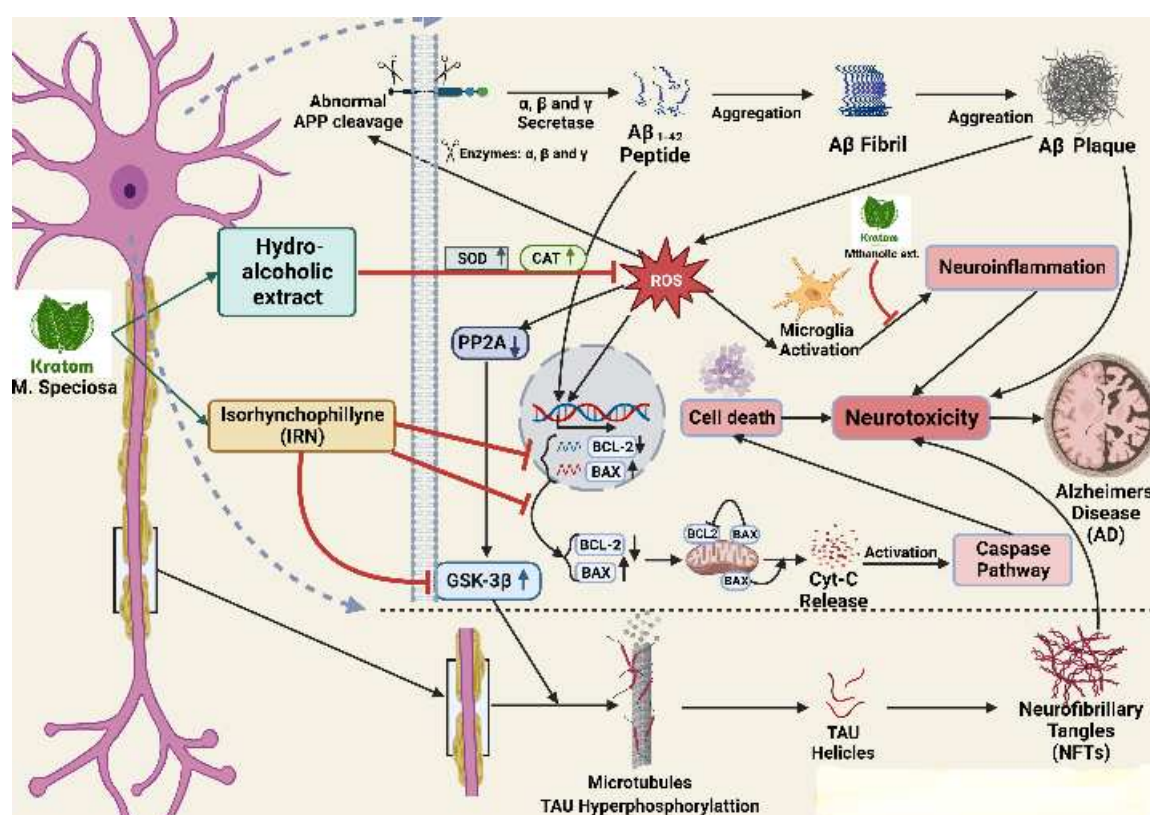
The first case of using kratom as an anesthetic by a patient with chronic pain.<sup>120</sup> In both a concentration-dependent and a time-dependent manner, indole alkaloids such as mitragynine and other derivatives (7-HMG, SC, PAY, and SG) isolated from kratom inhibited electrically induced contractions. Naloxone reverses the opioid receptor agonistic action of electrical stimulation on the guinea pig ileum using the switch contraction of the ileum, which is measured by the opioid receptor agonist action of electrical stimulation.<sup>78,121,122</sup> There was a delay in nociceptive responses to noxious stimulation by both methanolic and alkaloid kratom leaves extracts in mice in the hot-plate test, but

not in the tail-flick test.<sup>123</sup> Furthermore, a methanolic extract of kratom was shown to possess antinociceptive activity when it significantly reduced writhing responses and pain sensations when acetic acid was used as the writhing stimulus and the formalin test was administered.<sup>21</sup> Comparing the antinociceptive effects of various oral kratom extracts with morphine in rats, researchers concluded that alkaloids (20 mg/kg), methanolic extracts (200 mg/kg), and aqueous extracts (100-400 mg/kg) all prolonged the latency of nociceptive responses in both, the hot plate and the tail flick-tests. Administering naloxone before the administration of morphine blocks its effects, suggesting that the opioid receptor may play a partial role in mediating those effects.<sup>124</sup> In comparison to 5 mg/kg morphine, these effects were less pronounced, but they were more evident than after 100 mg/kg paracetamol.<sup>125</sup> The anti-nociceptive activity of the alkaloid extract of kratom was potentiated by co-administration of caffeine (25 mg/kg, p.o.) and codeine (3 mg/kg, p.o.) in a hot plate test in rats.<sup>90,126</sup> 7-HMG exhibits more potent antinociceptive activity in the tail-flick and hot-plate tests than morphine when administered subcutaneously or orally. The ability of 7-HMG to penetrate the blood-brain barrier (BBB) and exert a more rapid effect than morphine has been attributed to its higher potency and rapid effect.<sup>68,122</sup> The 7-HMG also confirmed a high level of potency at opioid receptors. The analgesic properties of mitragynine are 13 times greater than those of 7-HMG, while 3-4 times higher for mitragynine.<sup>23,127</sup> There was also evidence that 7-HMG, a minor constituent of kratom, was 46 times more potent as an analgesic than mitragynine in another study.<sup>122</sup> In humans, it exerts sedative and analgesic effects at higher doses and stimulant effects at low doses.<sup>38</sup> Due to this characteristic of the plant, drug addicts have been highly tempted to abuse it.<sup>128</sup> In the tail-flick test in mice, intracerebroventricular administration of mitragynine and mitragynine pseudoindoxyl had an antinociceptive effect with an ED<sub>50</sub> estimate of 60.22 nM and 6.51 nM, respectively. The antinociceptive effects of mitragynine and mitragynine pseudoindoxyl were blocked by naloxone, indicating that they are mediated by opioid receptors.<sup>78,121</sup> By blocking  $\mu$ -opioid receptors, the antinociceptive effect of 7-HMG was eliminated in both tail-flick and hot-plate tests since its antinociceptive action is dose-dependent and predominantly mediated through these receptors.<sup>129</sup> It has been shown that mitragynine binds strongly to the  $\mu$ -opioid receptors and has analgesic, respiratory depression, and euphoric effects.<sup>130,131</sup> A part of the antinociceptive activity of 7-HMG has also been attributed to the supraspinal- $\mu$  and  $\delta$ -opioid receptors.<sup>6,130,131</sup> In addition to alleviating withdrawal symptoms, kratom can be used to diminish the effects of opium addiction. However, it has a lower affinity for the  $\kappa$ -receptor.<sup>131</sup> Through presynaptic dopamine actions, the  $\kappa$ -receptor exhibited analgesic and depressive effects on locomotor activity.<sup>132</sup> 7-HMG's supportive actions are partially mediated by  $\mu$  and  $\delta$ -opiate receptors.<sup>133</sup> In contrast, a study revealed that kratom powder has less affinity for the  $\mu$ -opioid receptor than morphine.<sup>134</sup> In mice, the head-twitch reaction brought on by activating postsynaptic 2-adrenoceptors can be reduced by mitragynine and the 5-HT<sub>2A</sub> receptor antagonist ritanserin. Mitragynine and 7-hydroxymitragynine may produce antinociceptive synergism with adrenergic- $\alpha$ 2 (A $\alpha$ 2R) and  $\mu$ -opioid receptor agonists, according to Obeng, S.<sup>135</sup> Mitragynine may potentially generate hypothermic synergism when paired with A $\alpha$ 2R agonists. The improvement of positive and negative psychotic symptoms by the methanolic extract of kratom may be attributable to the inhibition of D<sub>2</sub> and 5-HT<sub>2</sub> receptors.<sup>23,136</sup> Mitragynine may inhibit NG108-15 cell adenylyl cyclase via opioid receptors. Mitragynine can limit neurotransmitter release by reversibly inhibiting neuronal Ca<sup>2+</sup> channels, which may lead to a reduction in neurotransmitters and an inhibition of pain transduction.<sup>122</sup> In the heart, kratom inhibits hERG-mediated K<sup>+</sup> currents and prolongs action duration, constituting a major risk of cardiotoxicity due to blockage of the human Ether-a-go-go-Related Gene (hERG) channel.<sup>137</sup>



#### 8.4. Neurological effects by gene regulation

Figure 7 has been summarized to show the gene-cascade for neuroprotection by Kratom. An interesting finding has been that two alkaloids, bufanidrine (2) and buphanisine (3), have a high affinity for the serotonin reuptake transport protein (SERT). The neuroprotective effects of the Amarylridaceae alkaloids were considered to be associated with the 1,3-dioxole moiety in those alkaloids, which was thought to be responsible for their neuroprotective effects in AD.<sup>138-140</sup> According to previous studies on MAO inhibitory effects of some plant alkaloids, bitter leaf alkaloid-rich extract (BLAE) might produce these effects as a result of its constituent alkaloids.<sup>141,142</sup> Several amine neurotransmitters, such as noradrenaline, dopamine, and serotonin, are oxidized by the MAO enzyme, which is a strategic neuronal enzyme.<sup>141</sup> Furthermore, elevated MAO activity has been directly linked to AD and Parkinson's disease (PD) because of excessive enzymatic depletion of neuroactive amines and the generation of free radicals which initiate and propagate oxidative stress in AD brains.<sup>141,143-145</sup> As a result, inhibiting MAO activity is a valuable restorative methodology for AD and PD.<sup>146</sup>



**Figure 7.** Cascade of gene regulation by Kratom to control neuroinflammation. Abnormal APP cleavage eventually assists the formation of A $\beta$  plaque which is stimulated by ROS and increases the neuroinflammation in many ways including BCL-2 decrease, BAX increase, microglia activation, and PP2A activation leading to GSK-3B activation. The activation of GSK-3B finally increases the NFTS formation. Kratom's alcoholic extract inhibits ROS production and its products (IRN) inhibit GSK-3B to substantially inhibit the NFTs formation (Figure is drawn by BioRender, Registered version).

As a potential treatment for AD, it has been reported that repression of acetylcholine esterase (AChE), butylcholine esterase (BChE), ATPase, ADPase, and MAO activity may be effective in combination. The enzymes superoxide dismutase (SOD) and catalase (CAT) are also important antioxidant enzymes that serve to prevent the toxicity of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>). They were observed to be markedly increased in the brain tissue with the treatment of kratom hydroalcoholic extract in an animal model.<sup>147</sup> It has been discovered that elevated amounts of A $\beta$  oligomers promote the development of oxidative stress, neuroinflammation, synapse loss, and nerve cell death. In

another current study, mitragynine has been shown to inhibit the enzyme acetylcholinesterase (AChE) involved in AD.<sup>148</sup> The  $\alpha$ -synuclein expression is established to increase in PD and several alkaloids such as physostigmine are reported to attenuate the expression of the  $\alpha$ -synuclein gene. ROS, which is also the primary cause of the aberrant aggregation of A $\beta$  peptides that causes the progression of AD, is particularly sensitive to the brain.<sup>149</sup> The alkaloid **Isorhynchophylline** is beneficial for treating AD because of its neuroprotective properties through lowering the levels of Bcl-2/Bax gene expression by reducing A $\beta$ -tempted neuronal apoptosis of neurons in the hippocampus as a result of its neuroprotective properties. In the A $\beta$ -transgenic CL2006 and CL4176 strains, **palmatine**, a naturally occurring isoquinoline alkaloid, greatly reduced A $\beta$ -induced paralysis and showed neuroprotective benefits. A variety of antioxidant defense mechanisms, which include the involvement of antioxidant enzymes like SOD and CAT, mediate the removal of excessive ROS. In wild-type nematodes, **palmatine** increased the expression of heat shock genes (*shsp*), such as *hsp-16.11*, *hsp-16.2*, and *hsp-16.49*, and it increased the intensity of *hsp-16.2p*: GFP fluorescence in transgenic CL2070 nematodes. As a result, it's probable that sHSP's enhanced expression reduced protein aggregation and reduced A $\beta$  toxicity, indicating that sHSP is crucial to **Palmatine**'s neuroprotective benefits. Heat shock factor (HSF-1) is a transcription factor that is known to have a major role in regulating the production of sHSP. Its decreasing activity has been linked to several detrimental processes that occur in neurodegenerative diseases.<sup>150,151</sup> The results are from previous studies that suggest HSF-1 is involved in the inhibition of A $\beta$  toxicity.<sup>151,152</sup> As a result, the regulator HSF-1, and modulation of the expression of its target genes, including *hsp-16.11*, *hsp-16.2*, and *hsp-16.49*, are involved in palmatine-mediated suppression of A $\beta$  toxicity. In comparison to morphine, speciociliatine, and mitragynine had DNA protection capacities that were respectively 1200- and 20-fold higher. In a dose-dependent manner, mitragynine, the main component of the alkaloid extracted from kratom, was administered at concentrations ranging from 0.5 to 20 g/mL. This resulted in a significant inhibition of the mRNA expression of COX-2 induced by LPS, which was followed by a decrease in PGE 2 production, implying mitragynine's anti-inflammatory effects.<sup>118</sup> The contribution of all these alkaloids is hypothesized to impact the neuroprotective effect of alkaloids of alkaloid-rich plant products kratom either in a direct or in a cascade mechanism of neuroprotection.

### 8.5. Antioxidative effects

By limiting the start or growth of oxidative chain reactions, antioxidants are those substances that can delay or hinder the oxidation of lipid or auxiliary molecules.<sup>153</sup> They can extend shelf life and neutralize free radicals by postponing the oxidation of lipids. Antioxidants are available in both natural and synthetic forms. While synthetic antioxidants are produced using synthetic chemicals, natural antioxidants are obtained by extracting natural substances that can snare free radicals.<sup>154</sup> However, numerous types of research on the potential of naturally occurring antioxidants produced from plants have been conducted due to worries about the adverse effects of utilizing synthetic antioxidants. These can prevent degenerative illnesses and food-based fat oxidation.<sup>155</sup> Kratom exhibits antioxidant action, which has primarily been attributed to the presence of polyphenolic substances such as flavonoids and alkaloids (**Table 1**). DPPH free radical scavenging, lipid protection of DNA, and prevention of metal-induced protein oxidation against H<sub>2</sub>O<sub>2</sub>-induced oxidative stress were all used to assess antioxidant capabilities.<sup>156</sup> According to reports, the polar nature of the antioxidant biomolecules may be seen in the fact that aqueous and methanol extracts from several of plant sources have better free radical scavenging action than dichloromethane or ethyl acetate extracts.<sup>154</sup> By using several techniques, including the 2, 2'-diphenyl-1-picrylhydrazyl (DPPH), reducing power, oxygen radical absorption capacity test (ORAC), FRAP, and CUPRAC procedures, the relevance of antioxidant activity in kratom was revealed.<sup>157</sup> Additionally, 100 mg/kg of the kratom aqueous extract significantly increased the specific activity of glutathione-S transferase (GSTs) by 129% compared to the control.<sup>89</sup> Another study showed the ethanolic extract of kratom exposed antioxidant

effects on DPPH, and phytochemical screening.<sup>16,18</sup> Kratom is already mentioned to inhibit the release of proinflammatory mediators, especially NF- $\kappa$ B, interleukins, and cytokines. And antioxidants exert a regulatory effect on the expression of pro-inflammatory cytokines.<sup>158</sup> The comprehensive pathways and links associated with the antioxidative potential of Kratom are presented in **Figure 8**.

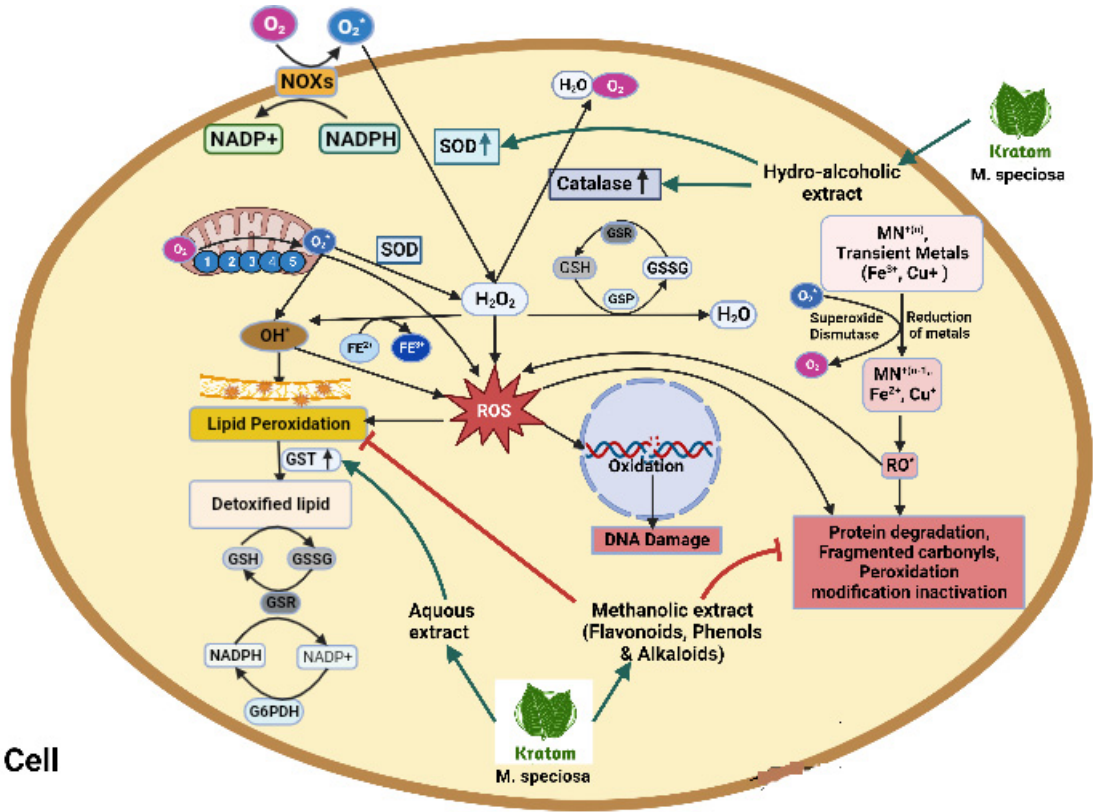
**Table 1.** Comprehensive pre-clinical studies for the physiological effects of kratom.

Antioxidative effect				
Treatment with doses	Nature of kratom product	Experimental model	Major findings (molecular changes)	Reference
<b>Kratom</b>	Methanolic, water, alkaloids	<i>In vitro</i>	The high content of phenolic, flavonoid compounds and the result of DPPH, high antioxidant activity in methanolic extract	(Parthasarathy, Bin Azizi et al. 2009) <sup>16</sup>
	Ethanolic extract	<i>In vitro</i> (DPPH)	The IC <sub>50</sub> value of 38.56 $\mu$ g / mL	(Yuniarti, Nadia et al. 2020) <sup>18</sup>
	Aqueous extract (100 mg/kg)	Male Sprague Dawley rats	↑Glutathione transferase (GSTs) activity	(Azizi, Ismail et al. 2010) <sup>89</sup>
Neurophysiological				
<b>Kratom</b>	Mitragynine (5, 10 and 15 mg/kg)	Male ICR mice	Mitragynine neither altered locomotor activity nor its high or low dose	(Apriyani, Hidayat et al. 2010) <sup>28</sup>
	Methanolic extract (0.008%)	Male Sprague Dawley rats	↓ Field excitatory post-synaptic potentials (fEPSP) in the CA1 region concentration-dependently, and blocked long-term potentiation (LTP)	(Senik, Mansor et al. 2012) <sup>114</sup>
Anti-inflammatory				
<b>Kratom</b>	Methanolic extract (100-200 mg/kg)	Male Sprague Dawley rats	Dose-dependently suppressed the development of carrageenan-induced rat paw edema, and ↓ granulomatous tissue formation at 200 mg/kg	(Mossadeq, Sulaiman et al. 2009) <sup>21</sup>
	Methanolic extract (10 and 20 g/mL)	RAW264.7 macrophage cells	↓mRNA expression of COX-2, ↓PGE2 production, and ↓COX-1 expression	(Utar, Majid et al. 2011) <sup>118</sup>
Analgesic/Anti-nociceptive				
<b>Kratom</b>	7-hydroxymitragynine (ED <sub>50</sub> = 0.80 mg/kg, and ED <sub>50</sub> = 0.93 mg/kg)	Male ddY-strain mice, and male albino guinea-pigs	4.4-5.7 times more potent as $\mu$ -opioid agonist than morphine in tail-flick and hot-plate test	(Matsumoto, Hatori et al. 2006) <sup>68</sup>

	7-hydroxymitragynine (100 nM), speciociliatine (30 $\mu$ M)	Male Albino Dunkin-Hartley guinea-pigs	$\downarrow$ Twitch contraction and 7-hydroxymitragynine showed most potent opioid effect on the electrically stimulated contraction ( $pD_2 = 8.38 \pm 0.12$ )	(Horie, Koyama et al. 2005) <sup>121</sup>
	Methanolic and alkaloid extract (100 mg/kg)	Male Swiss mice and Wistar rats	Prolong the latency of nociceptive response in the hot plate test	(Reanmongkol, Keawpradub et al. 2007) <sup>123</sup>
	Mitragynine alkaloid (10 nM-1 $\mu$ M)	Male Albino guinea pigs	Block the reversible $Ca^{2+}$ channel that activates neurotransmitters	(Matsumoto, Yamamoto et al. 2005) <sup>122</sup>
	Alkaloid (20 mg/kg), methanolic (200 mg/kg), and aqueous extract (400 mg/kg)	Male Sprague Dawley rats	Both hot plate and tail-flick tests showed prolonged nociceptive responses	(Sabetghadam, Ramanathan et al. 2010) <sup>124</sup>
	Mitragynine alkaloid (100 mg/kg), co-administration of caffeine (25 mg/kg, p.o.) and codeine (3 mg/kg, p.o.)	Male Wistar rats	$\uparrow$ Latency period in a hot plate test after 30 minutes	(Botpiboon 2010) <sup>126</sup>
	Mitragynine (2.0 mg/kg) and paynantheine (0.1 mg/kg)	Male wild-type mice (+/+) and $\mu$ opioid receptor (MOR) knockout mice (-/-)	Exert analgesic effects predominantly via $\kappa$ opioid receptors	(Stolt, Schröder et al. 2014) <sup>132</sup>
<b>Anti-depressant</b>				
<b>Kratom</b>	Mitragynine (10 mg/kg and 30 mg/kg)	Male mice from the ICR strain	$\downarrow$ Corticosterone in forced swim test (FST) and tail suspension test (TST)	(Idayu, Hidayat et al. 2011) <sup>29</sup>
	Aqueous extract (100, 300, and 500 mg/kg)	Male Swiss albino mice	Effects on serotonin or noradrenaline neurotransmissions	(Kumarnsit, Keawpradub et al. 2006) <sup>22</sup>
	Mitragynine or alkaloid extract (20, 40, and 80 mg/kg)	Male Swiss albino mice	$\uparrow$ Total number of arm entries, rearing frequency and $\downarrow$ grooming, and immobility time in the Y-maze test,	(Ammar, Muzaimi et al. 2011) <sup>112</sup>



			Alkaloid extract exhibits more potent opioid agonistic effects than mitragynine	
	Mitragynine (5, 15, 20, and 25 mg/kg)	Male Swiss albino mice	Chronic mitragynine treatment impaired spatial learning and memory	(Ismail, Jayabalan et al. 2017) <sup>113</sup>
	Mitragynine (72.5 mg and 74.9 mg) of Kratom tea or >3 glasses daily	Human	Executive function, memory, and attention were not impaired	(Singh, Narayanan et al. 2019) <sup>36</sup>
Anti-psychotic/ Anti-dopaminergic				
Kratom	Methanolic extract (75 and 100 mg/kg)	Male Swiss albino mice	Apomorphine-induced cage climbing behavior↓, ↓dopamine-induced contractile response	(Vijeeppallam, Pandey et al. 2016) <sup>136</sup>



**Figure 8.** Activation of NADPH oxidase, dual oxidase, and nitric oxidase subsequently reduces SOD, CAT, and GPX producing huge free radicals in a biological system. Hydrogen peroxide produces ROS which ultimately activates lipid peroxidation, protein degradation, DNA damage, and fragmented carbohydrate. Kratom upregulates SOD, CAT, and GST and detoxifies lipids through an oxidoreductase cascade. Kratom and its hydroalcoholic extract inhibit lipid peroxidation and inhibit protein degradation and fragmented carbohydrate (Figure is drawn by BioRender, Registered version).

9. Other pharmacological effects

The preceding pharmacological effects of kratom for controlling the disease with several animal and human case studies are shown in **Table 2**.

Table 2. Other biological and pharmacological effects of kratom.

Treatment with doses	Nature of kratom product	Experimental model	Major findings (molecular changes)	Reference
<b>Anti-bacterial</b>				
<b>Kratom</b>	Methanolic extract (3.12 to 6.25 mg/mL)	<i>Salmonella typhi</i> and <i>Bacillus subtilis</i>	Minimum inhibitory concentrations (MICs) by the broth dilution method	(Parthasarathy, Bin Azizi et al. 2009) <sup>16</sup>
	Mitragynine (40 mg/kg), alkaloid extract (100 mg/kg)	Adult male Wistar rats	Detoxification and elimination of permethrin	(Srichana, Janchawee et al. 2015) <sup>19</sup>
<b>Gastrointestinal effects</b>				
<b>Kratom</b>	Methanolic extract (50, 100, 200 and 400 mg/kg)	Adult Wistar rats	Protection against castor oil-induced diarrhea, ↓ intestinal transit	(Chittrakarn, Sawangjaroen et al. 2008) <sup>165</sup>
	mitragynine (3-30 µg)	Male Wistar rats	↓ 2-deoxy-d-glucose-stimulated gastric acid secretion	(Tsuchiya, Miyashita et al. 2002) <sup>166</sup>
	7-hydroxymitragynine (ED <sub>50</sub> = 1.19 mg/kg)	Male ddY-strain mice	↓ Gastrointestinal transit and significantly antagonized by β-funaltrexamine hydrochloride (β-FNA) pretreatment, but slightly antagonized by naloxonazine	(Matsumoto, Hatori et al. 2006) <sup>68</sup>
<b>Muscle relaxant</b>				
<b>Kratom</b>	Methanolic extract (10-40 mg/mL), mitragynine (2 mg/mL)	Wistar rats	Blockade of nerve conduction, amplitude, and duration	(Chittrakarn, Keawpradub et al. 2010) <sup>172</sup>
<b>Potential to inhibit enzyme activity</b>				
<b>Kratom</b>	Methanolic extract	Three main CYP450 enzymes CYP2C9, CYP2D6, and CYP3A4	Most potent effect on CYP2D6 at IC <sub>50</sub> (3.6 ± 0.1 µg/mL)	(Hanapi 2010) <sup>173</sup>
	Alkaloid extract	CYP450 enzymes, Quinidine (CYP2D6), ketoconazole (CYP3A4),	Most potent inhibitory effect on CYP3A4 and CYP2D6 at IC <sub>50</sub> values of 0.78 µg/mL and 0.636 µg/mL	(Kong, Chik et al. 2011) <sup>100</sup>

		tranylcypromine (CYP2C19), and furafylline (CYP1A2)		
<b>Anti-diabetic</b>				
<b>Kratom</b>	Water extract 0.6 mg mL <sup>-1</sup>	L8 muscle cells	↑ Glucose transporters (GLUT1)	(Purintrapiban, Keawpradub et al. 2011) <sup>174</sup>
<b>Anti-hypertensive</b>				
<b>Kratom</b>	Methanolic extract (100, 500, and 1000 mg/kg)	Male Albino rats	Blood pressure (diastolic: 102.7 ± 0.72, 98.74 ± 7.95 and 86.85 ± 3.34), and ↑ ALT, AST, albumin, triglycerides, cholesterol, albumin levels	(Harizal, Mansor et al. 2010) <sup>95</sup>
<b>Weight reduction</b>				
<b>Kratom</b>	Mitragynine (45 and 50 mg/kg)	Male Wistar rats	↓ Food and water intakes	(Kumarnsit, Keawpradub et al. 2006) <sup>22</sup>
	Mitragynine (100 mg/kg)	Male and female Sprague-Dawley rats	↓ Food intake, ↓ Body weight of female rats, and ↑ liver weight of both male and female rats	(Sabetghadam, Ramanathan et al. 2013) <sup>164</sup>

### 9.1. Antibacterial effects

Antioxidants are compounds that resist ROS and free radicals to prevent carcinogenesis, cardiovascular, and aging.<sup>156</sup> Kratom's antibacterial properties may protect the brain from bacterial infection and bacterial components such as LPS. LPS, a component present in the outer membrane of some bacteria, has the potential to cause an inflammatory reaction in the body. The core saccharides in all gram-negative bacteria with LPS are identical and mostly composed of N-acetylglucosamine, glucose, galactose, heptose, phosphate, and ethanolamine. Kratom can also influence the immune system's response to bacterial infections. LPS's inflammatory action is caused by the lipid A.<sup>159</sup> LPS causes the production of a wide range of inflammatory cytokines from human peripheral mononuclear blood cells, including IL-1, IL-6, IL-8, and TNF- $\alpha$  on endothelial cells.<sup>160</sup> Excessive or uncontrolled inflammation can harm the brain. The processes through which LPS activates cells and triggers inflammatory responses have received a great deal of attention. The methanolic extract of kratom shows a high content of phenolic and flavonoid compounds, and the result of DPPH and microbial test against *Salmonella typhi* and *Bacillus subtilis* displayed antioxidant and antibacterial effects respectively,<sup>16</sup> while *Salmonella typhi* outbreak is historically reported to cause Malawi-Mozambique in 2009.<sup>161</sup> According to the study, epicatechin (a kratom's phytoconstituent) performs against the bacteria *H. Pylori* which is responsible for the progression of neurological disorders.<sup>162</sup> At a dose of 100 mg/kg, kratom aqueous extract significantly increased glutathione-S-transferase (GSTs) specific activity at various levels, demonstrating its antibacterial actions to treat intestinal infections.

9.2. Gastrointestinal effects

The bidirectional gut-brain axis connects the gastrointestinal system and the brain, facilitating communication between the stomach and the central nervous system and impacting different physiological processes, moods, and behavior. This connection encompasses neuronal pathways, neurotransmitters, hormones, immunological responses, and the gut microbiome, emphasizing the significance of gut health for general brain function and mental well-being.<sup>163</sup> Kratom extract-treated rats showed immediate and long-term effects of lower food and water intake, as well as less tendency to acquire weight.<sup>22,164</sup> By reducing defecation frequency, the overall diarrheal score, intestinal transit (by a single dosage), and faecal weight in rats with castor oil-induced diarrhea, methanolic kratom extract demonstrated anti-diarrheal benefits. However, because pretreatment with naloxone did not affect the frequency of feces, repeated treatments with this extract did not result in any appreciable alteration in the intestinal transit and fluid. Excitatory and inhibitory impulses from the enteric nervous system are the primary mechanisms by which the small intestine's gastrointestinal motility is regulated. Since parasympathetic and sympathetic fibers directly link the central nervous system with the digestive tract and the local neural system with gastrointestinal hormones, kratom extract may have an impact on pathways other than opioid receptors.<sup>165</sup> Mitragynine administration into the fourth ventricle of anesthetized rats caused a dose-dependent inhibition of 2-deoxy-D-glucose-stimulated gastric acid secretion, though its effects were reversed by naloxone, indicating the involvement of opioid receptors. Mitragynine administration centrally did not affect the basal gastric acid secretion into the lateral ventricle. In addition to having an impact on anorexia and weight loss, mitragynine also has a direct inhibitory effect on neurons in the lateral hypothalamus.<sup>166</sup> In addition, subcutaneous administration of 7-HMG to mice inhibited their gastrointestinal transit.<sup>68</sup> Ciliaphylline is a minor alkaloid and also showed anti-diarrheal effects.

10. Adverse effects/ Abuse of kratom

Studies on animals and humans have demonstrated the toxic properties of kratom preparations. A total of 428 cases of Kratom use were recorded from 2011 to 2015, according to the Centers for Disease Control and Prevention, USA.<sup>167</sup> According to The Food and Drug Administration, 44 people died from Kratom use in 2018, with mitragynine being a contributing factor.<sup>168</sup> Kratom withdrawal symptoms and side effects are described in some case reports shown in **Table 3**.<sup>169</sup> Adverse effects of kratom are nausea, vomiting, tremor, diaphoresis, tachycardia, hypertension, hypothyroidism, elevated creatinine phosphokinase concentrations, dry mouth, headaches, intrahepatic cholestasis, dizziness, itching, fatigue, weight loss, sweating, and heart palpitation.<sup>6,46,170,171</sup> Due to these findings, 15 businesses that were illegally selling kratom were issued warning letters by the institution. Because in many cases other products are consumed along with Kratom, it isn't always clear which substances can produce the effects.

**Table 3.** Cases reported for adverse effects of kratom.

Uses pattern	Side effects of Kratom	Condition	History	Reference
For 1 month, kratom leaf tea is brewed with Datura stramonium	4-5 mm pupils, minimally reactive, roving conjugate gaze, spasticity of lower extremities with manipulation	Chronic pain after post-colostomy surgery	64 years male	(Nelsen, Lapoint et al. 2010) <sup>175</sup>



Powder of leaf 4.6-7 to 8.6-14 g/day for 2 weeks	Loss of appetite, fever and chills, slight abdominal discomfort, concomitant brown discoloration of the urine, jaundice, and pruritus	Intrahepatic cholestasis	25 years male	(Kapp, Maurer et al. 2011) <sup>176</sup>
Kratom tea 4 times a day for 3.5 years	A generalized tonic-clonic seizure lasting 5 min, pulse 123 beats per min	Tonic colonic seizure	43 years male	(Boyer, Babu et al. 2008) <sup>128</sup>
1 tablespoon of powder daily for 3 months	Jaundice, dark urine, mild confusion, liver injury	Cholestatic hepatitis	58 years male	(Dorman, Wong et al. 2015) <sup>177</sup>
6 g Kratom capsules daily for 2 weeks	Palpation of the right upper quadrant (RUQ) in the presence of vomiting, fatigue, abdominal pain, and brown urine	Hepatomegaly	21 years male	(Griffiths, Gandhi et al. 2018) <sup>170</sup>
Sixty tablets over 1 week	A yellowish appearance to the skin, usually associated with nausea, fatigue, joint pains, night sweats, pale stools and dark urine	Hepatitis	32 years male	(Tayabali, Bolzon et al. 2018) <sup>171</sup>
Herbal drug Kratom	Distention, mass, tenderness, rebound, sternal pleuritic chest pain, mild shortness of breath, mild cough, mild coughing, and mild chest pain	Intrahepatic cholestasis	38 years male	(Riverso, Chang et al. 2018) <sup>178</sup>
A tablespoon of crushed leaves (<1.5 g/d)	Yellow discoloration of eyes and skin, mild fatigue, jaundice	Intrahepatic cholestasis	52 years male	(Fernandes, Iqbal et al. 2019) <sup>179</sup>

Green-colored herbal powder supplement for a few weeks with increasing daily dosage	Pupils were pinpoint and not reactive to light and cool peripheries, the abdomen and pelvis revealed cholestasis without cholecystitis	Intrahepatic cholestasis	36 years male	(Palasamudram Shekar, Rojas et al. 2019) <sup>180</sup>
Kratom tea for 2 weeks	Tea-colored urine, malaise, fatigue, and intermittent subjective fever	Acute hepatitis	31 years male	(Mousa, Sephien et al. 2018) <sup>181</sup>
Kratom capsules for 3 weeks	Dark urine, pruritus, subjective fevers, fatigue, nonbloody, nonbilious emesis, nonicteric sclera, and sublingual jaundice	Hepatitis	47 years male	(Osborne, Overstreet et al. 2019) <sup>182</sup>

## 11. Critical Remarks and insights

Why kratom, the abusive plant, has been turned into one of the widely-used plant sources are partially answered through its undeniable window of valuable compounds. How narcotics become the proposal for neuroprotection has been figured out through the definitive and coordinated mode of neurodegeneration could be pondered. Whether and to what extent the toxicity of kratom could matter for future drug discovery is inclusively architected in this review. Why the alkaloids, not all but some of them due to their nature, target selective genes to help neuroprotection is answered to some extent for the future direction of using alkaloids in neuronal abnormality. Nonetheless, unraveled potential of mitragynine and 7-OH, might be the pivotal issues to be explored for the best use of kratom. Research on the interaction between neuroprotection-related genes and mitragynine as well as 7-OH needs to be unfolded through a network-pharmacological assessment. Molecular dynamics simulation could be another spotlight proposal to evaluate the biological stability of their interaction for future drug discovery.

## 12. Conclusions and Future prospective

In spite of both unsafe and beneficial effects of kratom, a very recent report on kratom as neuroprotective as well as other neuro supportive including antioxidant and anti-inflammatory potential, a very new prospect will undoubtedly be allured for its neuroprotective effects. However, all the isolated compounds, except mitragynine and 7-OH mitragynine, are yet to be studied for their biological activities to conclude an unambiguous use of kratom as neuroprotective. Further dose-response preclinical and clinical studies are demanded to ensure the neuroprotective effects of kratom affirming its advanced toxicity study.

**Authors Contribution:** Rahni Hossain: Data curation, first draft, writing; Abida Sultana: Data Curation, Editing and Reviewing; Md Atiar Rahman: Conceptualization, Project Administration, resources, Study management, reviewing and editing; Jitbanjong Tangpong: Conceptualization, resources, validation; Manit Nuinoon: Validation, Visualization, and Reviewe; Kunwadee Noonong: Review, Editing, Resources; Kazi Helal Hossain:

Reviewing & Editing, resources, critical analysis. All authors have gone through the manuscript and agreed to submit it to the special issue of “**Molecules**”.

**Funding:** This research is supported by Walailak University graduate research fund.

**Acknowledgments:** The authors wish to thank the School of Allied Health Sciences, Walailak University, Thailand and Laboratory of Alternative Medicine and Natural Product Research, Department of Biochemistry and Molecular Biology, University of Chittagong for serving necessary resources for this study.

**Conflicts of Interest:** The authors declare that there is no conflict of interest.

**Data availability:** All data are enclosed in this review. Additional information may be supplied on request.

## Abbreviations

AChE = Acetylcholinesterase  
 AD = Alzheimer's disease  
 ALT = Alanine aminotransferase  
 ASE = Accelerated solvent extraction  
 AST = Aspartate aminotransferase  
 BBB = Blood-brain barrier  
 CAT = Catalase  
 COX-2 = Cyclooxygenase-2  
 CUPRAC = Cupric ion reducing antioxidant capacity  
 CYPs = Cytochromes P50  
 ED<sub>50</sub> = Median effective dose  
 ESI = Electrospray ionization  
 FRAP = Ferric reducing ability of plasma  
 fEPSP = field Excitatory postsynaptic potentials  
 HSP = Heat shock proteins  
 HSF = Heat shock Factors  
 HT2A = Hydroxy-Tryptamine receptor  
 IC<sub>50</sub> = Half maximal inhibitory concentration  
 I. P = Intraperitoneal  
 Keap1 = Kelch-like ECH-Associating protein 1  
 Kg = Kilogram  
 LD<sub>50</sub> = Median lethal dose  
 LPS = Lipopolysaccharides  
 LTP = Long-term potentiation  
 MAO = Monoamine oxidase  
 Mg = Milligram  
 µg = Microgram  
 MIC = Minimum inhibitory concentration  
 Nrf2 = Nuclear factor erythroid 2-related factor 2  
 Nm = Nanometer  
 PD = Parkinson's disease  
 P. O = Per Oral  
 QTOF-MS = Quadrupole time-of-flight mass spectrometry  
 SOD = Superoxide dismutase  
 TPC = Total phenolic content  
 TFC = Total flavonoid content  
 UDP = Uridine diphosphate

UGT = UDP-glucuronosyl transferase

UHPLC = Ultra high-performance liquid chromatography

w/w = Weight for weight

## References

- Butler, M. S. The role of natural product chemistry in drug discovery. *Journal of natural products*. 2004; 67(12): 2141-2153. doi: /10.1021/np040106y
- Newman, D. J. and G. M. Cragg. Natural products as sources of new drugs over the 30 years from 1981 to 2010. *Journal of natural products*. 2012; 75(3): 311-335. doi: /10.1021/np200906s
- Koehn, F. E. and G. T. Carter. The evolving role of natural products in drug discovery. *Nature reviews Drug discovery*. 2005; 4(3): 206-220. doi: /10.1038/nrd1657
- Patwardhan, B. and R. A. Mashelkar. Traditional medicine-inspired approaches to drug discovery: can Ayurveda show the way forward? *Drug discovery today*. 2009; 14(15-16): 804-811. doi: /10.1016/j.drudis.2009.05.009
- Arndt, T., U. Claussen, B. Güssregen, S. Schröfel, B. Stürzer, A. Werle and G. Wolf. Kratom alkaloids and O-desmethyiltramadol in urine of a "Krypton" herbal mixture consumer. *Forensic science international*. 2011; 208(1-3): 47-52. doi: /10.1016/j.forsciint.2010.10.025
- Michael White, C. Pharmacologic and clinical assessment of kratom. *The Bulletin of the American Society of Hospital Pharmacists*. 2018; 75(5): 261-267. doi: /10.2146/ajhp161035
- Gong, F., H.-p. Gu, Q.-t. Xu and W.-y. Kang. Genus *Mitragyna*: Ethnomedicinal uses and pharmacological studies. *Phytopharmacology*. 2012; 3(2): 263-272.
- Rech, M. A., E. Donahey, J. M. Cappiello Dziedzic, L. Oh and E. Greenhalgh. New drugs of abuse. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2015; 35(2): 189-197. doi: /10.1002/phar.1522
- Vicknasingam, B., S. Narayanan, G. T. Beng and S. M. Mansor. 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*. 2010; 21(4): 283-288. doi: /10.1016/j.drugpo.2009.12.003
- Hassan, Z., M. Muzaimi, V. Navaratnam, N. H. Yusoff, F. W. Suhaimi, R. Vadivelu, B. K. Vicknasingam, D. Amato, S. von Hörsten and N. I. Ismail. From Kratom to mitragynine and its derivatives: physiological and behavioural effects related to use, abuse, and addiction. *Neuroscience & Biobehavioral Reviews*. 2013; 37(2): 138-151. doi: /10.1016/j.neubiorev.2012.11.012
- Eisenman, S. W. The botany of *Mitragyna speciosa* (Korth.) Havil. and related species. *Kratom and other Mitragynines: The chemistry and pharmacology of opioids from a non-opium source*. 2014; 57: 57-76.
- Warner, M. L., N. C. Kaufman and O. Grundmann. The pharmacology and toxicology of kratom: from traditional herb to drug of abuse. *International journal of legal medicine*. 2016; 130(1): 127-138. doi: /10.1007/s00414-015-1279-y
- E Adkins, J., E. W Boyer and C. R McCurdy. *Mitragyna speciosa*, a psychoactive tree from Southeast Asia with opioid activity. *Current topics in medicinal chemistry*. 2011; 11(9): 1165-1175. doi: /10.2174/156802611795371305
- Jaipaew, J., T. Padungchareon and S. Sukrong. PCR-reverse dot blot of the nucleotide signature sequences of matK for the identification of *Mitragyna speciosa*, a narcotic species. *Plant Gene*. 2018; 14: 46-54. doi: /10.1016/j.plgene.2018.04.005
- Tungphatthong, C., S. K. J. Urumarudappa, S. Awachai, T. Sooksawate and S. Sukrong. Differentiation of *Mitragyna speciosa*, a narcotic plant, from allied *Mitragyna* species using DNA barcoding-high-resolution melting (Bar-HRM) analysis. *Scientific reports*. 2021; 11(1): 1-9. doi: /10.1038/s41598-021-86228-9
- Parthasarathy, S., J. Bin Azizi, S. Ramanathan, S. Ismail, S. Sasidharan, M. I. Said and S. M. Mansor. Evaluation of antioxidant and antibacterial activities of aqueous, methanolic and alkaloid extracts from *Mitragyna speciosa* (Rubiaceae family) leaves. *Molecules*. 2009; 14(10): 3964-3974. doi: /10.3390/molecules14103964
- Meireles, V., T. Rosado, M. Barroso, S. Soares, J. Gonçalves, Â. Luís, D. Caramelo, A. Y. Simão, N. Fernández and A. P. Duarte. *Mitragyna speciosa*: clinical, toxicological aspects and analysis in biological and non-biological samples. *Medicines*. 2019; 6(1): 35. doi: /10.3390/medicines6010035



18. Yuniarti, R., S. Nadia, A. Alamanda, M. Zubir, R. Syahputra and M. Nizam. Characterization, phytochemical screenings and antioxidant activity test of kratom leaf ethanol extract (*Mitragyna speciosa* Korth) using DPPH method. *Journal of Physics: Conference Series*, IOP Publishing. 2020. doi: 10.1088/1742-6596/1462/1/012026
19. Srichana, K., B. Janchawee, S. Prutipanlai, P. Raungrut and N. Keawpradub. Effects of mitragynine and a crude alkaloid extract derived from *Mitragyna speciosa* Korth. on permethrin elimination in rats. *Pharmaceutics*. 2015; 7(2): 10-26. doi: /10.3390/pharmaceutics7020010
20. Goh, Y. S., T. Karunakaran, V. Murugaiyah, R. Santhanam, M. H. Abu Bakar and S. Ramanathan. Accelerated solvent extractions (ASE) of *Mitragyna speciosa* Korth.(Kratom) leaves: Evaluation of its cytotoxicity and antinociceptive activity. *Molecules*. 2021; 26(12): 3704. doi: /10.3390/molecules26123704
21. Mossadeq, W. S., M. Sulaiman, T. T. Mohamad, H. Chiong, Z. Zakaria, M. Jabit, M. Baharuldin and D. Israf. Anti-inflammatory and antinociceptive effects of *Mitragyna speciosa* Korth methanolic extract. *Medical Principles and Practice*. 2009; 18(5): 378-384. doi: /10.1159/000226292
22. Kumarnsit, E., N. Keawpradub and W. Nuankaew. Acute and long-term effects of alkaloid extract of *Mitragyna speciosa* on food and water intake and body weight in rats. *Fitoterapia*. 2006; 77(5): 339-345. doi: /10.1016/j.fitote.2006.04.006
23. Watanabe, K., S. Yano, S. Horie and L. T. Yamamoto. Inhibitory effect of mitragynine, an alkaloid with analgesic effect from Thai medicinal plant *Mitragyna speciosa*, on electrically stimulated contraction of isolated guinea-pig ileum through the opioid receptor. *Life sciences*. 1997; 60(12): 933-942. doi: /10.1016/S0024-3205(97)00023-4
24. Pathak, L., Y. Agrawal and A. Dhir. Natural polyphenols in the management of major depression. *Expert opinion on investigational drugs*. 2013; 22(7): 863-880. doi: /10.1517/13543784.2013.794783
25. Carpenter, J. M., C. A. Criddle, H. K. Craig, Z. Ali, Z. Zhang, I. A. Khan and K. J. Sufka. Comparative effects of *Mitragyna speciosa* extract, mitragynine, and opioid agonists on thermal nociception in rats. *Fitoterapia*. 2016; 109: 87-90. doi: /10.1016/j.fitote.2015.12.001
26. Kruegel, A. C., R. Uprety, S. G. Grinnell, C. Langreck, E. A. Pekarskaya, V. Le Rouzic, M. Ansonoff, M. M. Gassaway, J. E. Pintar and G. W. Pasternak. 7-Hydroxymitragynine is an active metabolite of mitragynine and a key mediator of its analgesic effects. *ACS central science*. 2019; 5(6): 992-1001. doi: /10.1021/acscentsci.9b00141
27. Kumarnsit, E., N. Keawpradub and W. Nuankaew. Effect of *Mitragyna speciosa* aqueous extract on ethanol withdrawal symptoms in mice. *Fitoterapia*. 2007; 78(3): 182-185. doi: /10.1016/j.fitote.2006.11.012
28. Apriyani, E., M. T. Hidayat, M. Moklas, S. Fakurazi and N. F. Idayu. Effects of mitragynine from *Mitragyna speciosa* Korth leaves on working memory. *Journal of Ethnopharmacology*. 2010; 129(3): 357-360. doi: /10.1016/j.jep.2010.03.036
29. Idayu, N. F., M. T. Hidayat, M. Moklas, F. Sharida, A. N. Raudzah, A. Shamima and E. Apriyani. Antidepressant-like effect of mitragynine isolated from *Mitragyna speciosa* Korth in mice model of depression. *Phytomedicine*. 2011; 18(5): 402-407. doi: /10.1016/j.phymed.2010.08.011
30. Obeng, S., S. H. Kamble, M. E. Reeves, L. F. Restrepo, A. Patel, M. Behnke, N. J.-Y. Chear, S. Ramanathan, A. Sharma and F. León. Investigation of the adrenergic and opioid binding affinities, metabolic stability, plasma protein binding properties, and functional effects of selected indole-based kratom alkaloids. *Journal of medicinal chemistry*. 2019; 63(1): 433-439. doi: /10.1021/acs.jmedchem.9b01465
31. Johnson, L. E., L. Balyan, A. Magdalany, F. Saeed, R. Salinas, S. Wallace, C. A. Veltri, M. T. Swogger, Z. Walsh and O. Grundmann. Focus: Plant-based Medicine and Pharmacology: The Potential for Kratom as an Antidepressant and Antipsychotic. *The Yale Journal of Biology and Medicine*. 2020; 93(2): 283.
32. Ahmad, I., W. C. Prabowo, M. Arifuddin, J. Fadraersada, N. Indriyanti, H. Herman, R. Y. Purwoko, F. Nainu, A. Rahmadi and S. Paramita. *Mitragyna* species as pharmacological agents: From abuse to promising pharmaceutical products. *Life*. 2022; 12(2): 193. doi:/10.3390/life12020193
33. Vijeppallam, K., V. Pandey, D. D. Murugan and M. Naidu. Methanolic extract of *Mitragyna speciosa* Korth leaf inhibits ethanol seeking behaviour in mice: Involvement of antidopaminergic mechanism. *Metabolic brain disease*. 2019; 34(6): 1713-1722. doi: /10.1007/s11011-019-00477-2
34. NASM Salleh, S Halim, PM Ridzuan, MM Uzid, MD Ramli. The Potential Role of Neuroprotective Effects of Kratom (*Mitragyna Speciosa*) On Brain Aging. *Journal of Cellular & Molecular Anesthesia*. 2021; 6 (4): 352-353.

35. Zul Aznal AN, Mohamad Nor Hazalin NA, Hassan Z, Mat NH, Chear NJ, Teh LK, Salleh MZ, Suhaimi FW. Adolescent kratom exposure affects cognitive behaviours and brain metabolite profiles in Sprague-Dawley rats. *Front Pharmacol.* 2022; 28(13): 1057423. doi: /10.3389/fphar.2022.1057423
36. Singh, D. P., S. P. Narayanan, C. P. P. Müller, B. P. Vicknasingam, M. P. Yücel, E. T. W. P. Ho, Z. P. Hassan and S. M. P. Mansor. Long-Term Cognitive Effects of Kratom (*Mitragyna speciosa* Korth.) Use. *J Psychoactive Drugs.* 2019; 51(1): 19-27. doi: /10.1080/02791072.2018.1555345
37. Flores-Bocanegra, L., H. A. Raja, T. N. Graf, M. Augustinović, E. D. Wallace, S. Hematian, J. J. Kellogg, D. A. Todd, N. B. Cech and N. H. Oberlies. The Chemistry of Kratom [*Mitragyna speciosa*]: Updated Characterization Data and Methods to Elucidate Indole and Oxindole Alkaloids. *Journal of Natural Products.* 2020; 83(7): 2165-2177. doi: /10.1021/acs.jnatprod.0c00257
38. Suwanlert, S. A study of kratom eaters in Thailand. *Bull Narc.* 1975; 27(3): 21-27.
39. Ahmad, K. and Z. Aziz. *Mitragyna speciosa* use in the northern states of Malaysia: a cross-sectional study. *Journal of Ethnopharmacology.* 2012; 141(1): 446-450. doi: /10.1016/j.jep.2012.03.009
40. Cinosi, E., G. Martinotti, P. Simonato, D. Singh, Z. Demetrovics, A. Roman-Urrestarazu, F. S. Bersani, B. Vicknasingam, G. Piazzon and J.-H. Li. 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.* 2015. doi: /10.1155/2015/968786
41. Ruck, C. Mushrooms, Myth and Mithras: The drug cult that civilized Europe, City Lights Books. 2021.
42. Tanguay, P. Kratom in Thailand: Decriminalisation and community control? Series on legislative reform of drug policies, Vol. 13. Transnational Institute (TNI). *International Drug Policy Consortium (IDPC).* 2011.
43. Saingam, D., S. Assanangkornchai, A. F. Geater and Q. Balthip. Pattern and consequences of krathom (*Mitragyna speciosa* Korth.) use among male villagers in southern Thailand: a qualitative study. *International Journal of Drug Policy.* 2013; 24(4): 351-358. doi: /10.1016/j.drugpo.2012.09.004
44. Singh, D., S. Narayanan and B. Vicknasingam. Traditional and non-traditional uses of Mitragynine (Kratom): A survey of the literature. *Brain Research Bulletin.* 2016; 126: 41-46. doi: 10.1016/j.brainresbull.2016.05.004
45. Khalil, S., S. A. J. Abdullah and R. Ahmad. Enforcement status of the poison act 1952 against offences related to kratom (*Mitragyna speciosa* korth) misuse in Malaysia. *UUM Journal of Legal Studies (UUMJLS).* 2020; 11(1): 75-93.
46. Swogger, M. T., E. Hart, F. Erowid, E. Erowid, N. Trabold, K. Yee, K. A. Parkhurst, B. M. Priddy and Z. Walsh. Experiences of kratom users: a qualitative analysis. *Journal of psychoactive Drugs.* 2015; 47(5): 360-367. doi: /10.1080/02791072.2015.1096434
47. Assanangkornchai, S., A. Muekthong, N. Sam-Angsri and U. Pattanasattayawong. The use of *Mitragynine speciosa* (“Kratom”), an addictive plant, in Thailand. *Substance use & misuse.* 2007; 42(14): 2145-2157. doi: /10.1080/10826080701205869
48. Grundmann, O. Patterns of Kratom use and health impact in the US-Results from an online survey. *Drug Alcohol Depend.* 2017; 176: 63-70. doi: /10.1016/j.drugalcdep.2017.03.007
49. Hillebrand, J., D. Olszewski and R. Sedefov. Legal highs on the Internet. *Subst Use Misuse.* 2010; 45(3): 330-340. doi: /10.3109/10826080903443628
50. Schmidt, M. M., A. Sharma, F. Schifano and C. Feinmann. "Legal highs" on the net-Evaluation of UK-based Websites, products and product information. *Forensic Sci Int.* 2011; 206(1-3): 92-97. doi: /10.1016/j.forsciint.2010.06.030
51. Feng, L. Y., A. Battulga, E. Han, H. Chung and J. H. Li. New psychoactive substances of natural origin: A brief review. *J Food Drug Anal.* 2017; 25(3): 461-471. doi: /10.1016/j.jfda.2017.04.001
52. Mustafa, A., L. M. Trevino and C. Turner. Pressurized hot ethanol extraction of carotenoids from carrot by-products. *Molecules.* 2012; 17(2): 1809-1818. doi: /10.3390/molecules17021809
53. Mohamed, H. M. Green, environment-friendly, analytical tools give insights in pharmaceuticals and cosmetics analysis. *TrAC Trends in Analytical Chemistry.* 2015; 66: 176-192. doi: /10.1016/j.trac.2014.11.010
54. Chimnoi, N., N. Khunnawutmanoam, P. Feungfuloy, K. Chatrewongwan and S. Techasakul. Facile isolation and purification of thailandine, a biologically active oxoaporphine alkaloid, from *Stephania venosa* leaves using ion-pair liquid-liquid extraction. *Research Journal of Medicinal Plant.* 2013; 7(1): 68-76.
55. Fatima, N., L. A. Tapondjou, D. Lontsi, B. L. Sondengam, R. Atta Ur and M. I. Choudhary. Quinovic acid glycosides from *Mitragyna stipulosa*-first examples of natural inhibitors of snake venom phosphodiesterase I. *Nat Prod Lett.* 2002; 16(6): 389-393. doi: /10.1080/10575630290033169

56. Asase, A., T. Kokubun, R. J. Grayer, G. Kite, M. S. Simmonds, A. A. Oteng-Yeboah and G. T. Odamtten. Chemical constituents and antimicrobial activity of medicinal plants from Ghana: *Cassia sieberiana*, *Haematostaphis barteri*, *Mitragyna inermis* and *Pseudocedrela kotschy*. *Phytother Res.* 2008; 22(8): 1013-1016. doi: /10.1002/ptr.2392
57. Phongprueksapattana, S., W. Putalun, N. Keawpradub and J. Wungsintaweekul. *Mitragyna speciosa*: hairy root culture for triterpenoid production and high yield of mitragynine by regenerated plants. *Z Naturforsch C J Biosci.* 2008; 63(9-10): 691-698. doi: /10.1515/znc-2008-9-1014
58. Ponglux, D., S. Wongseripipatana, H. Takayama, M. Kikuchi, M. Kurihara, M. Kitajima, N. Aimi and S. Sakai. A New Indole Alkaloid, 7  $\alpha$ -Hydroxy-7H-mitragynine, from *Mitragyna speciosa* in Thailand. *Planta Med.* 1994; 60(6): 580-581. doi: 10.1055/s-2006-959578
59. León, F., E. Habib, J. E. Adkins, E. B. Furr, C. R. McCurdy and S. J. Cutler. Phytochemical characterization of the leaves of *Mitragyna speciosa* grown in U.S.A. *Nat Prod Commun.* 2009; 4(7): 907-910. doi: /10.1177/1934578X0900400705
60. Jaleel, C. A., R. Gopi, A. Kishorekumar, P. Manivannan, B. Sankar and R. Panneerselvam. Interactive effects of triadimefon and salt stress on antioxidative status and ajmalicine accumulation in *Catharanthus roseus*. *Acta Physiologiae Plantarum.* 2008; 30(3): 287-292. doi: /10.1007/s11738-007-0119-1
61. Gajalakshmi, S., S. Vijayalakshmi and R. V. Devi. Pharmacological activities of *Catharanthus roseus*: a perspective review. *International Journal of Pharma and Bio Sciences.* 2013; 4(2): 431-439.
62. Duwiejua, M., E. Woode and D. D. Obiri. Pseudo-akuammigine, an alkaloid from *Picralima nitida* seeds, has anti-inflammatory and analgesic actions in rats. *J Ethnopharmacol.* 2002; 81(1): 73-79. doi: /10.1016/S0378-8741(02)00058-2
63. Trager, W. F., C. M. Lee, J. D. Phillipson, R. E. Haddock, D. Dwuma-Badu and A. H. Beckett. Configurational analysis of rhynchophylline-type oxindole alkaloids. The absolute configuration of ciliaphylline, rhynchociline, specionoxeine, isospecionoxeine, rotundifoline and isorotundifoline. *Tetrahedron.* 1968; 24(2): 523-543. doi: /10.1016/0040-4020(68)88002-0
64. Roquebert, J. and P. Demichel. Inhibition of the  $\alpha$  1 and  $\alpha$  2-adrenoceptor-mediated pressor response in pithed rats by raubasine, tetrahydroalstonine and akuammigine. *Eur J Pharmacol.* 1984; 106(1): 203-205. doi: /10.1016/0014-2999(84)90698-8
65. Chen, L. L., J. X. Song, J. H. Lu, Z. W. Yuan, L. F. Liu, S. S. Durairajan and M. Li. Corynoxine, a Natural Autophagy Enhancer, Promotes the Clearance of Alpha-Synuclein via Akt/mTOR Pathway. *J Neuroimmune Pharmacol.* 2014; 9(3): 380-387. doi: /10.1007/s11481-014-9528-2
66. Gutierrez-Salmean, G., T. P. Ciaraldi, L. Nogueira, J. Barboza, P. R. Taub, M. C. Hogan, R. R. Henry, E. Meaney, F. Villarreal, G. Ceballos and I. Ramirez-Sanchez. Effects of (-)-epicatechin on molecular modulators of skeletal muscle growth and differentiation. *J Nutr Biochem.* 2014; 25(1): 91-94. doi: 10.1016/j.jnutbio.2013.09.007
67. Escandón, R. A., M. del Campo, R. López-Solis, E. Obreque-Slier and H. Toledo. Antibacterial effect of kaempferol and (-)-epicatechin on *Helicobacter pylori*. *European Food Research and Technology.* 2016; 242(9): 1495-1502. doi: /10.1007/s00217-016-2650-z
68. Matsumoto, K., Y. Hatori, T. Murayama, K. Tashima, S. Wongseripipatana, K. Misawa, M. Kitajima, H. Takayama and S. Horie. Involvement of  $\mu$ -opioid receptors in antinociception and inhibition of gastrointestinal transit induced by 7-hydroxymitragynine, isolated from Thai herbal medicine *Mitragyna speciosa*. *European journal of pharmacology.* 2006; 549(1-3): 63-70. doi: /10.1016/j.ejphar.2006.08.013
69. Shukla, A. and B. P. Srinivasan. 16,17-Dihydro-17b-hydroxy isomitraphylline alkaloid as an inhibitor of DPP-IV, and its effect on incretin hormone and  $\beta$ -cell proliferation in diabetic rat. *Eur J Pharm Sci.* 2012; 47(2): 512-519. doi: 10.1016/j.ejps.2012.07.012
70. García, R., C. Cayunao, R. Bocic, N. Backhouse, C. Delporte, M. Zaldivar and S. Erazo. Antimicrobial activity of isopteropodine. *Z Naturforsch C J Biosci.* 2005; 60(5-6): 385-388. doi: /10.1515/znc-2005-5-603
71. Wang, X. L., L. M. Zhang and Z. Hua. Blocking effect of rhynchophylline on calcium channels in isolated rat ventricular myocytes. *Zhongguo Yao Li Xue Bao.* 1994; 15(2): 115-118.
72. Kocialski, A. B., F. J. Marozzi, Jr. and M. H. Malone. Effects of certain nonsteroid anti-inflammatory drugs, tolbutamide, and tetrahydroalstonine on blood glucose and carrageen in-induced pedal edema in rats. *J Pharm Sci.* 1972; 61(8): 1202-1205. doi: /10.1002/jps.2600610805

73. Kang, T. H., Y. Murakami, K. Matsumoto, H. Takayama, M. Kitajima, N. Aimi and H. Watanabe. Rhynchophylline and isorhynchophylline inhibit NMDA receptors expressed in *Xenopus* oocytes. *Eur J Pharmacol.* 2002; 455(1): 27-34. doi: /10.1016/S0014-2999(02)02581-5
74. Philipp, A. A., D. K. Wissenbach, A. A. Weber, J. Zapp and H. H. Maurer. Metabolism studies of the Kratom alkaloids mitraciliatine and isopaynantheine, diastereomers of the main alkaloids mitragynine and paynantheine, in rat and human urine using liquid chromatography-linear ion trap-mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2011; 879(15-16): 1049-1055. doi: /10.1016/j.jchromb.2011.03.005
75. Kruegel, A. C., M. M. Gassaway, A. Kapoor, A. Váradi, S. Majumdar, M. Filizola, J. A. Javitch and D. Sames. Synthetic and Receptor Signaling Explorations of the *Mitragyna* Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators. *J Am Chem Soc.* 2016; 138(21): 6754-6764. doi: /10.1021/jacs.6b00360
76. Joshi, B. and W. Taylor. Structure of mitragynine (9-methoxycorynantheidine). *Chemistry and Industry.* 1963; 54: 573.
77. Zacharias, D., R. Rosenstein and G. Jeffrey. The structure of mitragynine hydroiodide. *Acta Crystallographica.* 1965; 18(6): 1039-1043. doi: /10.1107/S0365110X65002499
78. Takayama, H., H. Ishikawa, M. Kurihara, M. Kitajima, N. Aimi, D. Ponglux, F. Koyama, K. Matsumoto, T. Moriyama, L. T. Yamamoto, K. Watanabe, T. Murayama and S. Horie. Studies on the synthesis and opioid agonistic activities of mitragynine-related indole alkaloids: discovery of opioid agonists structurally different from other opioid ligands. *J Med Chem.* 2002; 45(9): 1949-1956. doi: /10.1021/jm010576e
79. Sharma, A., S. H. Kamble, F. León, N. J. Chear, T. I. King, E. C. Berthold, S. Ramanathan, C. R. McCurdy and B. A. Avery. Simultaneous quantification of ten key Kratom alkaloids in *Mitragyna speciosa* leaf extracts and commercial products by ultra-performance liquid chromatography-tandem mass spectrometry. *Drug Test Anal.* 2019; 11(8): 1162-1171. doi: /10.1002/dta.2604
80. Ellis, C. R., R. Racz, N. L. Kruhlak, M. T. Kim, A. V. Zakharov, N. Southall, E. G. Hawkins, K. Burkhart, D. G. Strauss and L. Stavitskaya. Evaluating kratom alkaloids using PHASE. *PLoS One.* 2020; 15(3): e0229646. doi: 10.1371/journal.pone.0229646
81. Gutridge, A. M., M. T. Robins, R. J. Cassell, R. Uprety, K. L. Mores, M. J. Ko, G. W. Pasternak, S. Majumdar and R. M. van Rijn. G protein-biased kratom-alkaloids and synthetic carfentanil-amide opioids as potential treatments for alcohol use disorder. *Br J Pharmacol.* 2020; 177(7): 1497-1513. doi: /10.1111/bph.14913
82. Chear, N. J., F. León, A. Sharma, S. R. R. Kanumuri, G. Zwolinski, K. A. Abboud, D. Singh, L. F. Restrepo, A. Patel, T. Hiranita, S. Ramanathan, A. J. Hampson, L. R. McMahon and C. R. McCurdy. Exploring the Chemistry of Alkaloids from Malaysian *Mitragyna speciosa* (Kratom) and the Role of Oxindoles on Human Opioid Receptors. *J Nat Prod.* 2021; 84(4): 1034-1043. doi: /10.1021/acs.jnatprod.0c01055
83. Houghton, P. J. and I. M. Said. 3-dehydromitragynine: An alkaloid from *Mitragyna speciosa*. *Phytochemistry.* 1986; 25(12): 2910-2912. doi: /10.1016/S0031-9422(00)83771-1
84. Houghton, P. J., A. Latiff and I. M. Said. Alkaloids from *Mitragyna speciosa*. *Phytochemistry.* 1991; 30(1): 347-350. doi: /10.1016/0031-9422(91)84152-I
85. Limsuwanchote, S., J. Wungsintaweeikul, N. Keawpradub, W. Putalun, S. Morimoto and H. Tanaka. Development of indirect competitive ELISA for quantification of mitragynine in Kratom (*Mitragyna speciosa* (Roxb.) Korth.). *Forensic Sci Int.* 2014; 244: 70-77. doi: /10.1016/j.forsciint.2014.08.011
86. Ramanathan, S., F. León, N. J. Y. Chear, S. R. Yusof, V. Murugaiyah, L. R. McMahon and C. R. McCurdy. Kratom (*Mitragyna speciosa* Korth.): A description on the ethnobotany, alkaloid chemistry, and neuropharmacology. 2021. doi: /10.1016/B978-0-12-819487-4.00003-3
87. Manwill, P. K., L. Flores-Bocanegra, M. Khin, H. A. Raja, N. B. Cech, N. H. Oberlies and D. A. Todd. Kratom (*Mitragyna speciosa*) Validation: Quantitative Analysis of Indole and Oxindole Alkaloids Reveals Chemotypes of Plants and Products. *Planta Medica.* 2022; 88: 838 - 857. doi: 10.1055/a-1795-5876
88. Wang, M., E. J. Carrell, Z. Ali, B. Avula, C. Avonto, J. F. Parcher and I. A. Khan. Comparison of three chromatographic techniques for the detection of mitragynine and other indole and oxindole alkaloids in *Mitragyna speciosa* (kratom) plants. *J Sep Sci.* 2014; 37(12): 1411-1418. doi: /10.1002/jssc.201301389
89. Azizi, J., S. Ismail, M. N. Mordi, S. Ramanathan, M. I. M. Said and S. M. Mansor. In vitro and in vivo effects of three different *Mitragyna speciosa* Korth leaf extracts on phase II drug metabolizing enzymes—glutathione transferases (GSTs). *Molecules.* 2010; 15(1): 432-441. doi: /10.3390/molecules15010432
90. Raffa, R. B. Kratom and other mitragynines: the chemistry and pharmacology of opioids from a non-opium source, *CRC Press.* 2014.



91. Veeramohan, R., K. A. Azizan, W. M. Aizat, H.-H. Goh, S. M. Mansor, N. S. M. Yusof, S. N. Baharum and C. L. Ng. Metabolomics data of *Mitragyna speciosa* leaf using LC-ESI-TOF-MS. *Data in brief*. 2018; 18: 1212-1216. doi: /10.1016/j.dib.2018.04.001
92. Trakulsrichai, S., K. Sathirakul, S. Auparakkitanon, J. Krongvorakul, J. Sueajai, N. Noumjad, C. Sukasem and W. Wananukul. Pharmacokinetics of mitragynine in man. *Drug design, development and therapy*. 2015; 9: 2421. doi: 10.2147/DDDT.S79658
93. Smith KE, Rogers JM, Dunn KE, Grundmann O, McCurdy CR, Schriefer D, Epstein DH. Searching for a Signal: Self-Reported Kratom Dose-Effect Relationships Among a sample of US adults with regular Kratom use histories. *Front Pharmacol*. 2022; 1(13): 765917. doi: /10.3389/fphar.2022.765917
94. Manda VK, Avula B, Ali Z, Khan IA, Walker LA, Khan SI. Evaluation of in vitro absorption, distribution, metabolism, and excretion (ADME) properties of mitragynine, 7-hydroxymitragynine, and mitraphylline. *Planta Med*. 2014; 80(7): 568-76. doi: 10.1055/s-0034-1368444
95. Harizal, S., S. Mansor, J. Hasnan, J. Tharakan and J. Abdullah. Acute toxicity study of the standardized methanolic extract of *Mitragyna speciosa* Korth in rodents. *Journal of Ethnopharmacology*. 2010; 131(2): 404-409. doi: /10.1016/j.jep.2010.07.013
96. Ilmie, M. U., H. Jaafar, S. M. Mansor and J. M. Abdullah. Subchronic toxicity study of standardized methanolic extract of *Mitragyna speciosa* Korth in Sprague-Dawley Rats. *Frontiers in Neuroscience*. 2015; 9: 189. doi: /10.3389/fnins.2015.00189
97. Saidin, N. A., T. Randall, H. Takayama, E. Holmes and N. J. Gooderham. Malaysian Kratom, a phyto-pharmaceutical of abuse: studies on the mechanism of its cytotoxicity. *Toxicology*. 2008; 1(253): 19-20. doi: 10.1016/j.tox.2008.07.024
98. Rusli, N., A. Amanah, G. Kaur, M. I. Adenan, S. F. Sulaiman, H. A. Wahab and M. L. Tan. The inhibitory effects of mitragynine on P-glycoprotein in vitro. *Naunyn-Schmiedeberg's archives of pharmacology*. 2019; 392(4): 481-496. doi: /10.1007/s00210-018-01605-y
99. Azizi, J., S. Ismail and S. M. Mansor. *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 drug interactions*. 2013; 28(2): 95-105. doi: /10.1515/dmd-2012-0039
100. Kong, W. M., Z. Chik, M. Ramachandra, U. Subramaniam, R. E. R. Aziddin and Z. Mohamed. Evaluation of the effects of *Mitragyna speciosa* alkaloid extract on cytochrome P450 enzymes using a high throughput assay. *Molecules*. 2011; 16(9): 7344-7356. doi: /10.3390/molecules16097344
101. Kamble, S. H., A. Sharma, T. I. King, F. León, C. R. McCurdy and B. A. Avery. Metabolite profiling and identification of enzymes responsible for the metabolism of mitragynine, the major alkaloid of *Mitragyna speciosa* (kratom). *Xenobiotica*. 2019; 49(11): 1279-1288. doi: /10.1080/00498254.2018.1552819
102. Uno, Y., S. Uehara, N. Murayama and H. Yamazaki. Cytochrome P450 1A1, 2C9, 2C19, and 3A4 polymorphisms account for interindividual variability of toxicological drug metabolism in cynomolgus macaques. *Chemical research in toxicology*. 2018; 31(12): 1373-1381. doi: /10.1021/acs.chemrestox.8b00257
103. Hanapi, N., S. Ismail and S. Mansor. Inhibitory effect of mitragynine on human cytochrome P450 enzyme activities. *Pharmacognosy research*. 2013; 5(4): 241. doi: 10.4103/0974-8490.118806
104. Showande, S. J., T. O. Fakeye, M. Kajula, J. Hokkanen and A. Tolonen. Potential inhibition of major human cytochrome P450 isoenzymes by selected tropical medicinal herbs—Implication for herb–drug interactions. *Food science & nutrition*. 2019; 7(1): 44-55. doi: /10.1002/fsn3.789
105. Ulbricht, C., D. Costa, J. Dao, R. Isaac, Y. C. LeBlanc, J. Rhoades and R. C. Windsor. An evidence-based systematic review of kratom (*Mitragyna speciosa*) by the Natural Standard Research Collaboration. *Journal of Dietary Supplements*. 2013; 10(2): 152-170. doi: /10.3109/19390211.2013.793541
106. Hughes, R. L. Fatal combination of mitragynine and quetiapine—a case report with discussion of a potential herb-drug interaction. *Forensic Science, Medicine and Pathology*. 2019; 15(1): 110-113. doi: /10.1007/s12024-018-0049-9
107. Fluyau, D. and N. Revadigar. Biochemical benefits, diagnosis, and clinical risks evaluation of kratom. *Frontiers in psychiatry*. 2017; 8: 62. doi: /10.3389/fpsyt.2017.00062
108. Grewal, K. S. Observations on the Pharmacology of Mitragynine. *J. Pharmacol*. 1932; 46(3): 251-271.
109. Mohammad Yusoff NH, Mansor SM, Visweswaran N, Muller CP and Hassan Z. GABA<sub>B</sub> receptor system modulates mitragynine-induced conditioned place preference in rats. *Conference Abstract: 14<sup>th</sup> Meeting of the Asian-Pacific Society for Neurochemistry*. 2016. doi: 10.3389/conf.fncel.2016.36.00090

110. Effendy MA, Yunusa S, Mat NH, Has ATC, Müller CP, Hassan Z. The role of AMPA and NMDA receptors in mitragynine effects on hippocampal synaptic plasticity. *Behav Brain Res.* 2023; 13(438): 114169. doi: /10.1016/j.bbr.2022.114169
111. Kruegel AC, Grundmann O. The medicinal chemistry and neuropharmacology of kratom: A preliminary discussion of a promising medicinal plant and analysis of its potential for abuse. *Neuropharmacology.* 2018; 15;134(Pt A): 108-120. doi: /10.1016/j.neuropharm.2017.08.026
112. Ammar, I. H., M. Muzaimi and M. M. Sharif. The effects on motor behaviour and short-term memory tasks in mice following an acute administration of *Mitragyna speciosa* alkaloid extract and mitragynine. *Journal of Medicinal Plants Research.* 2011; 5(24): 5810-5817.
113. Ismail, N. I. W., N. Jayabalan, S. M. Mansor, C. P. Müller and M. Muzaimi. Chronic mitragynine (kratom) enhances punishment resistance in natural reward seeking and impairs place learning in mice. *Addiction biology.* 2017; 22(4): 967-976. doi: /10.1111/adb.12385
114. Senik, M., S. Mansor, G. Rammes, J. Tharakan and J. Abdullah. *Mitragyna speciosa* Korth standardized methanol extract induced short-term potentiation of CA1 subfield in rat hippocampal slices. *Journal of Medicinal Plants Research.* 2012; 6(7): 1234-1243. doi: 10.5897/JMPR11.1283
115. Raymond-Hamet, A. Les alcaloïdes du *Mitragyna speciosa* Korthals [The alkaloids of *Mitragyna speciosa* Korthals–French]. *Ann Pharm Fr.* 1950; 8: 482-490.
116. Federico, A., F. Morgillo, C. Tuccillo, F. Ciardiello and C. Loguercio. Chronic inflammation and oxidative stress in human carcinogenesis. *International journal of cancer.* 2007; 121(11): 2381-2386. doi: /10.1002/ijc.23192
117. Perwez Hussain, S. and C. C. Harris. Inflammation and cancer: an ancient link with novel potentials. *International journal of cancer.* 2007; 121(11): 2373-2380. doi: /10.1002/ijc.23173
118. Utar, Z., M. I. A. Majid, M. I. Adenan, M. F. A. Jamil and T. M. Lan. Mitragynine inhibits the COX-2 mRNA expression and prostaglandin E2 production induced by lipopolysaccharide in RAW264.7 macrophage cells. *Journal of Ethnopharmacology.* 2011; 136(1): 75-82. doi: /10.1016/j.jep.2011.04.011
119. Otero-Losada, M., Capani, F., & Perez Lloret, S. Neuroprotection - New Approaches and Prospects. *IntechOpen.* 2020; 77918.
120. Vermaire, D. J., D. Skaer and W. Tippetts. Kratom and general anesthesia: a case report and review of the literature. *A&A Practice.* 2019; 12(4): 103-105. doi: 10.1213/XAA.0000000000000857
121. Horie, S., F. Koyama, H. Takayama, H. Ishikawa, N. Aimi, D. Ponglux, K. Matsumoto and T. Murayama. Indole alkaloids of a Thai medicinal herb, *Mitragyna speciosa*, that has opioid agonistic effect in guinea-pig ileum. *Planta medica.* 2005; 71(03): 231-236. doi: 10.1055/s-2005-837822
122. Matsumoto, K., H. Takayama, H. Ishikawa, N. Aimi, D. Ponglux, K. Watanabe and S. Horie. Partial agonistic effect of 9-hydroxycorynantheidine on mu-opioid receptor in the guinea-pig ileum. *Life Sci.* 2005; 78(19): 2265-2271. doi: /10.1016/j.lfs.2005.09.030
123. Reanmongkol, W., N. Keawpradub and K. Sawangjaroen. Effects of the extracts from *Mitragyna speciosa* Korth. leaves on analgesic and behavioral activities in experimental animals. *Songklanakarin J. Sci. Technol.* 2007; 29(Suppl 1): 39-48.
124. Sabetghadam, A., S. Ramanathan and S. M. Mansor. The evaluation of antinociceptive activity of alkaloid, methanolic, and aqueous extracts of Malaysian *Mitragyna speciosa* Korth leaves in rats. *Pharmacognosy research.* 2010; 2(3): 181. doi: 10.4103/0974-8490.65514
125. Idid, S., L. Saad, H. Yaacob and M. Shahimi. Evaluation of analgesia induced by mitragynine, morphine and paracetamol on mice. *ASEAN Review of Biodiversity and Environmental Conservation (ARBEC).* 1998; 4: 1-7.
126. Botpiboon, O. Effects of Caffeine and Codeine on Pharmacokinetics and Antinociceptive Activity of Alkaloid Extract from Leaves of Kratom (*Mitragyna speciosa* Korth.), *Prince of Songkla University.* 2010.
127. Matsumoto, K., M. Mizowaki, T. Suchitra, H. Takayama, S.-i. Sakai, N. Aimi and H. Watanabe. Antinociceptive action of mitragynine in mice: evidence for the involvement of supraspinal opioid receptors. *Life Sciences.* 1996; 59(14): 1149-1155. doi: /10.1016/0024-3205(96)00432-8
128. Boyer, E. W., K. M. Babu, J. E. Adkins, C. R. McCurdy and J. H. Halpern. Self-treatment of opioid withdrawal using kratom (*Mitragynia speciosa* korth). *Addiction.* 2008; 103(6): 1048-1050. doi:10.1111/j.1360-0443.2008.02209.x
129. Takayama, H. Chemistry and pharmacology of analgesic indole alkaloids from the rubiaceous plant, *Mitragyna speciosa*. *Chemical and Pharmaceutical Bulletin.* 2004; 52(8): 916-928. doi: /10.1248/cpb.52.916

130. Thongpradichote, S., K. Matsumoto, M. Tohda, H. Takayama, N. Aimi, S.-i. Sakai and H. Watanabe. Identification of opioid receptor subtypes in antinociceptive actions of supraspinally-administered mitragynine in mice. *Life Sciences*. 1998; 62(16): 1371-1378. doi: /10.1016/S0024-3205(98)00075-7
131. Yamamoto, L. T., S. Horie, H. Takayama, N. Aimi, S.-i. Sakai, S. Yano, J. Shan, P. K. Pang, D. Ponglux and K. Watanabe. Opioid receptor agonistic characteristics of mitragynine pseudoindoxyl in comparison with mitragynine derived from Thai medicinal plant *Mitragyna speciosa*. *General Pharmacology: The Vascular System*. 1999; 33(1): 73-81. doi: /10.1016/S0306-3623(98)00265-1
132. Stolt, A.-C., H. Schröder, H. Neurath, G. Grecksch, V. Höllt, M. R. Meyer, H. H. Maurer, N. Ziebolz, U. Havemann-Reinecke and A. Becker. Behavioral and neurochemical characterization of kratom (*Mitragyna speciosa*) extract. *Psychopharmacology*. 2014; 231(1): 13-25. doi: /10.1007/s00213-013-3201-y
133. Hemby, S. E., S. McIntosh, F. Leon, S. J. Cutler and C. R. McCurdy. Abuse liability and therapeutic potential of the *Mitragyna speciosa* (kratom) alkaloids mitragynine and 7-hydroxymitragynine. *Addiction biology*. 2019; 24(5): 874-885. doi: /10.1111/adb.12639
134. Havemann-Reinecke, U. P01-50-Kratom and alcohol dependence: Clinical symptoms, withdrawal treatment and pharmacological mechanisms-A case report. *European Psychiatry*. 2011; 26(S2): 50-50. doi: 10.1016/S0924-9338(11)71761-8
135. Obeng, S., F. Leon, A. Patel, J. D. Zuarth Gonzalez, L. Chaves Da Silva, L. F. Restrepo, L. R. Gamez-Jimenez, N. P. Ho, M. P. Guerrero Calvache, V. L. C. Pallares, J. A. Helmes, S. K. Shiomitsu, P. L. Soto, C. R. McCurdy, L. R. McMahon, J. L. Wilkerson and T. Hiranita. Interactive Effects of  $\mu$ -Opioid and Adrenergic- $\alpha$  (2) Receptor Agonists in Rats: Pharmacological Investigation of the Primary Kratom Alkaloid Mitragynine and Its Metabolite 7-Hydroxymitragynine. *J Pharmacol Exp Ther*. 2022; 383(3): 182-198. doi: 10.1124/jpet.122.001192
136. Vijeepallam, K., V. Pandey, T. Kunasegaran, D. D. Murugan and M. Naidu. *Mitragyna speciosa* leaf extract exhibits antipsychotic-like effect with the potential to alleviate positive and negative symptoms of psychosis in mice. *Frontiers in pharmacology*. 2016; 7: 464. doi: /10.3389/fphar.2016.00464
137. Lu, J., H. Wei, J. Wu, M. F. A. Jamil, M. L. Tan, M. I. Adenan, P. Wong and W. Shim. Evaluation of the cardiotoxicity of mitragynine and its analogues using human induced pluripotent stem cell-derived cardiomyocytes. *PloS one*. 2014; 9(12): e115648. doi: /10.1371/journal.pone.0115648
138. Sandager, M., N. D. Nielsen, G. I. Stafford, J. van Staden and A. K. Jäger. Alkaloids from *Boopha disticha* with affinity to the serotonin transporter in rat brain. *Journal of Ethnopharmacology*. 2005; 98(3): 367-370. doi: /10.1016/j.jep.2005.01.037
139. Elgorashi, E. E., G. I. Stafford, A. K. Jäger and J. van Staden. Inhibition of [3H] citalopram binding to the rat brain serotonin transporter by Amaryllidaceae alkaloids. *Planta medica*. 2006; 72(05): 470-473. doi: 10.1055/s-2005-916251
140. Neergaard, J., J. Andersen, M. Pedersen, G. Stafford, J. Van Staden and A. Jäger. Alkaloids from *Boopha disticha* with affinity to the serotonin transporter. *South African Journal of Botany*. 2009; 75(2): 371-374. doi: /10.1016/j.sajb.2009.02.173
141. Kong, L., C. H. Cheng and R. Tan. Inhibition of MAO A and B by some plant-derived alkaloids, phenols and anthraquinones. *Journal of Ethnopharmacology*. 2004; 91(2-3): 351-355. doi: /10.1016/j.jep.2004.01.013
142. Oboh, G., S. Oyeleye and A. Ademiluyi. The food and medicinal values of indigenous leafy vegetables. *African Vegetables Forum*. 2017; 1238. doi: 10.17660/ActaHortic.2019.1238.15
143. Nwanna, E., S. Oyeleye, O. Ogunsuyi, G. Oboh, A. Boligon and M. Athayde. In vitro neuroprotective properties of some commonly consumed green leafy vegetables in Southern Nigeria. *NFS journal*. 2016; 2: 19-24. doi: /10.1016/j.nfs.2015.12.002
144. Oboh, G., A. J. Akinyemi, B. Adeleye, S. I. Oyeleye, O. B. Ogunsuyi, A. O. Ademosun, A. O. Ademiluyi and A. A. Boligon. Polyphenolic compositions and in vitro angiotensin-I-converting enzyme inhibitory properties of common green leafy vegetables: a comparative study. *Food Science and Biotechnology*. 2016; 25(5): 1243-1249. doi: /10.1007/s10068-016-0197-1
145. Oboh, G., O. O. Ogunruku, S. I. Oyeleye, T. A. Olasehinde, A. O. Ademosun and A. A. Boligon. Phenolic extracts from *Clerodendrum volubile* leaves inhibit cholinergic and monoaminergic enzymes relevant to the management of some neurodegenerative diseases. *Journal of Dietary Supplements*. 2017; 14(3): 358-371. doi: /10.1080/19390211.2016.1237401

146. Lühr, S., M. Vilches-Herrera, A. Fierro, R. R. Ramsay, D. E. Edmondson, M. Reyes-Parada, B. K. Cassels and P. Iturriaga-Vásquez. 2-Arylthiomorpholine derivatives as potent and selective monoamine oxidase B inhibitors. *Bioorganic & medicinal chemistry*. 2010; 18(4): 1388-1395. doi: /10.1016/j.bmc.2010.01.029
147. Chen, L., S. Fei and O. J. Olatunji. LC/ESI/TOF-MS Characterization, Anxiolytic and Antidepressant-like Effects of *Mitragyna speciosa* Korth Extract in Diabetic Rats. *Molecules*. 2022; 27(7): 2208. doi: /10.3390/molecules27072208
148. Innok W, Hiranrat A, Chana N, Rungrotmongkol T, Kongsune P. In silico and in vitro anti-AChE activity investigations of constituents from *Mytragyna speciosa* for Alzheimer's disease treatment. *J Comput Aided Mol Des*. 2021; 35(3): 325–36. doi: /10.1007/s10822-020-00372-4
149. Tsuji, M., T. Takeuchi, K. Miyagawa, D. Ishii, T. Imai, K. Takeda, M. Kitajima and H. Takeda. Yokukansan, a traditional Japanese herbal medicine, alleviates the emotional abnormality induced by maladaptation to stress in mice. *Phytomedicine*. 2014; 21(3): 363-371. doi: /10.1016/j.phymed.2013.08.025
150. Neef, D. W., A. M. Jaeger and D. J. Thiele. Heat shock transcription factor 1 as a therapeutic target in neurodegenerative diseases. *Nature reviews Drug discovery*. 2011; 10(12): 930-944. doi: /10.1038/nrd3453
151. Gomez-Pastor, R., E. T. Burchfiel and D. J. Thiele. Regulation of heat shock transcription factors and their roles in physiology and disease. *Nature reviews Molecular cell biology*. 2018; 19(1): 4-19. doi: /10.1038/nrm.2017.73
152. Steinkraus, K. A., E. D. Smith, C. Davis, D. Carr, W. R. Pendergrass, G. L. Sutphin, B. K. Kennedy and M. Kaerberlein. Dietary restriction suppresses proteotoxicity and enhances longevity by an hsf-1-dependent mechanism in *Caenorhabditis elegans*. *Aging cell*. 2008; 7(3): 394-404. doi: /10.1111/j.1474-9726.2008.00385.x
153. Gülçin, İ., M. Elmastaş and H. Y. Aboul-Enein. Antioxidant activity of clove oil—A powerful antioxidant source. *Arabian Journal of Chemistry*. 2012; 5(4): 489-499. doi: /10.1016/j.arabjc.2010.09.016
154. Sadeli, R. A. Uji Aktivitas Antioksidan Dengan Metode DPPH (1, 1-Diphenyl-2-Picrylhydrazyl) Ekstrak Bromelain Buah Nanas (*Ananas Comosus* (L.) Merr.). *Fakultas Farmasi, Universitas Sanata Dharma, Yogyakarta*. 2016.
155. Rusmarilin, H., Z. Lubis, L. Lubis and Y. Barutu. Potential of natural antioxidants of black cumin seed (*Nigella sativa*) and sesame seed (*Sesamum indicum*) extract by microencapsulation methods. *IOP Conference Series: Earth and Environmental Science, IOP Publishing*. 2019. doi: 10.1088/1755-1315/260/1/012097
156. Suhaling, S. Uji Aktivitas Antioksidan Ekstrak Metanol Kacang Merah (*Phaseolus vulgaris* L.) Dengan Metode DPPH, *Universitas Islam Negeri Alauddin Makassar*. 2010.
157. Ikhlas, N. Uji Aktivitas Antioksidan Ekstrak Herba Kemangi (*Ocimum americanum* Linn) dengan Metode DPPH (2, 2-Difenil-1-Pikrilhidrazil). 2013.
158. Chae HS, Park HJ, Hwang HR, Kwon A, Lim WH, Yi WJ, Han DH, Kim YH, Baek JH. The effect of antioxidants on the production of pro-inflammatory cytokines and orthodontic tooth movement. *Mol Cells*. 2011; 32(2): 189-96. doi: /10.1007/s10059-011-0071-1
159. Nau, R., & Eiffert, H. Modulation of release of proinflammatory bacterial compounds by antibacterials: potential impact on course of inflammation and outcome in sepsis and meningitis. *Clinical microbiology reviews*. 2002; 15(1): 95-110. doi: /10.1128/cmr.15.1.95-110.2002
160. Lüderitz, O., Tanamoto, K., Galanos, C., McKenzie, G. R., Brade, H., Zähringer, U., ... & Shiba, T. Lipopolysaccharides: structural principles and biologic activities. *Clinical Infectious Diseases*. 1984; 6(4): 428-431. doi: /10.1093/clinids/6.4.428
161. Sejvar J, Lutterloh E, Naiene J, Likaka A, Manda R, Nygren B, Monroe S, Khaila T, Lowther SA, Capewell L, Date K, Townes D, Redwood Y, Schier J, Barr BT, Demby A, Mallewa M, Kampondeni S, Blount B, Humphrys M, Talkington D, Armstrong GL, Mintz E. Neurologic manifestations associated with an outbreak of typhoid fever, Malawi—Mozambique, 2009: an epidemiologic investigation. *PLoS One*. 2012; 7(12): e46099. doi: /10.1371/journal.pone.0046099
162. Alvarez-Arellano L, Maldonado-Bernal C. *Helicobacter pylori* and neurological diseases: Married by the laws of inflammation. *World J Gastrointest Pathophysiol*. 2014; 15;5(4):400-4. doi: 10.4291/wjgp.v5.i4.400
163. Arneth, B. M. Gut–brain axis biochemical signalling from the gastrointestinal tract to the central nervous system: gut dysbiosis and altered brain function. *Postgraduate medical journal*. 2018; 94(1114): 446-452. doi: /10.1136/postgradmedj-2017-135424
164. Sabetghadam, A., S. Ramanathan, S. Sasidharan and S. M. Mansor. Subchronic exposure to mitragynine, the principal alkaloid of *Mitragyna speciosa*, in rats." *Journal of Ethnopharmacology*. 2013; 146(3): 815-823. doi: /10.1016/j.jep.2013.02.008



165. Chittrakarn, S., K. Sawangjaroen, S. Praseththo, B. Janchawee and N. Keawpradub. Inhibitory effects of kratom leaf extract (*Mitragyna speciosa* Korth.) on the rat gastrointestinal tract. *Journal of ethnopharmacology*. 2008; 116(1): 173-178. doi: /10.1016/j.jep.2007.11.032
166. Tsuchiya, S., S. Miyashita, M. Yamamoto, S. Horie, S.-I. Sakai, N. Aimi, H. Takayama and K. Watanabe. Effect of mitragynine, derived from Thai folk medicine, on gastric acid secretion through opioid receptor in anesthetized rats. *European journal of pharmacology*. 2002; 443(1-3): 185-188. doi: /10.1016/S0014-2999(02)01588-1
167. Anwar, M., R. Law and J. Schier. Notes from the field: kratom (*Mitragyna speciosa*) exposures reported to poison centers—United States, 2010–2015." *MMWR Morb Mortal Wkly Rep*. 2016; 65(29): 748-749.
168. Scott Gottlieb, M. D. Agency's Scientific Evidence on the Presence of Opioid Compounds in Kratom, Underscoring Its Potential for Abuse, Food and Drug Administration Statement from FDA Commissioner.
169. Sethi, R., N. Hoang, D. A. Ravishankar, M. McCracken and A. M. Manzardo. Kratom (*Mitragyna speciosa*): friend or foe?" The Primary Care Companion for CNS Disorders. 2020; 22(1): 27410.
170. Griffiths, Carrie L., Nidhi Gandhi, and Jacqueline L. Olin. Possible kratom-induced hepatomegaly: a case report. *Journal of the American Pharmacists Association*. 2018; 58(5): 561-563. doi: /10.1016/j.japh.2018.05.006
171. Tayabali, K., C. Bolzon, P. Foster, J. Patel and M. O. Kalim. Kratom: a dangerous player in the opioid crisis. *J Community Hosp Intern Med Perspect*. 2018; 8(3): 107-110. doi: /10.1080/20009666.2018.1468693
172. Chittrakarn, S., N. Keawpradub, K. Sawangjaroen, S. Kansanalak and B. Janchawee. The neuromuscular blockade produced by pure alkaloid, mitragynine and methanol extract of kratom leaves (*Mitragyna speciosa* Korth.). *Journal of Ethnopharmacology*. 2010; 129(3): 344-349. doi: /10.1016/j.jep.2010.03.035
173. Hanapi, N., et al. Evaluation of Selected Malaysian Medicinal Plants on Phase I Drug Metabolizing Enzymes, CYP 2 C 9, CYP 2 D 6 and CYP 3 A 4 Activities in vitro. *International Journal of Pharmacology*. 2010; 6(4): p. 494-499.
174. Purintrapiban, J., N. Keawpradub, S. Kansanalak, S. Chittrakarn, B. Janchawee and K. Sawangjaroen. Study on glucose transport in muscle cells by extracts from *Mitragyna speciosa* (Korth) and mitragynine. *Nat Prod Res*. 2011; 25(15): 1379-1387. doi: /10.1080/14786410802267627
175. Nelsen, J. L., J. Lapoint, M. J. Hodgman and K. M. Aldous. Seizure and coma following Kratom (*Mitragynina speciosa* Korth) exposure. *J Med Toxicol*. 2010; 6(4): 424-426. doi: /10.1007/s13181-010-0079-5
176. Kapp, F. G., H. H. Maurer, V. Auwärter, M. Winkelmann and M. Hermanns-Clausen. Intrahepatic cholestasis following abuse of powdered kratom (*Mitragyna speciosa*). *J Med Toxicol*. 2011; 7(3): 227-231. doi: /10.1007/s13181-011-0155-5
177. Dorman, C., M. Wong and A. Khan. Cholestatic hepatitis from prolonged kratom use: a case report. *Hepatology*. 2015; 61(3): 1086-1087. doi: 10.1002/hep.27612
178. Rivero, M., M. Chang, C. Soldevila-Pico, J. Lai and X. Liu. Histologic Characterization of Kratom Use-Associated Liver Injury. *Gastroenterology Res*. 2018; 11(1): 79-82. doi: 10.14740/gr990e
179. Fernandes, C. T., U. Iqbal, S. P. Tighe and A. Ahmed. Kratom-Induced Cholestatic Liver Injury and Its Conservative Management. *J Investig Med High Impact Case Rep*. 2019. doi: /10.1177/2324709619836138
180. Palasamudram Shekar, S., E. E. Rojas, C. C. D'Angelo, S. R. Gillenwater and N. P. Martinez Galvis. Legally Lethal Kratom: A Herbal Supplement with Overdose Potential. *J Psychoactive Drugs*. 2019; 51(1): 28-30. doi: /10.1080/02791072.2018.1562591
181. Mousa, M. S., A. Saphien, J. Gutierrez and C. O'Leary. N-Acetylcysteine for Acute Hepatitis Induced by Kratom Herbal Tea. *Am J Ther*. 2018; 25(5): e550-e551. doi: 10.1097/MJT.0000000000000631
182. Osborne, C. S., A. N. Overstreet, D. C. Rockey and A. D. Schreiner. Drug-Induced Liver Injury Caused by Kratom Use as an Alternative Pain Treatment Amid an Ongoing Opioid Epidemic. *J Investig Med High Impact Case Rep*. 2019. doi: /10.1177/2324709619826167

**Disclaimer/Publisher's Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.