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A Review on Alkaloid Diversity in *Mitragyna speciosa* (Kratom): Influence of Strain and Geographic Origin

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Abstract - Kratom (*Mitragyna speciosa*) is a Southeast Asian herbal plant that has long been traditionally used as a stimulant, analgesic, and folk medicine. The plant contains various secondary metabolite compounds, particularly alkaloids, which are responsible for its pharmacological activities. However, the alkaloid composition of kratom varies significantly depending on strain and geographical origin, leading to inconsistencies in its pharmacological properties and potential risks. This paper reviews the phytochemical diversity of kratom, with a focus on how strain-specific and regional factors influence the alkaloid composition across different Southeast Asian countries such as Indonesia, Malaysia, and Thailand. Red vein kratom strains generally have higher concentrations of the potent 7-hydroxymitragynine alkaloid compared to green and white vein variants. Green vein strains tend to have higher overall alkaloid content, including mitragynine. White vein strains typically have relatively low total alkaloid concentrations. Kratom cultivated in Indonesia (the largest producer) often exhibits higher mitragynine content compared to kratom from other Southeast Asian nations. Malaysian kratom frequently contains higher levels of 7-hydroxymitragynine than Indonesian sources. Kratom from Thailand displays highly variable alkaloid profiles depending on the specific growth region. These variations in phytochemical profiles result in differences in the psychoactive, analgesic, and stimulant effects experienced by kratom consumers. Understanding the sources of alkaloid diversity is crucial for developing standardized kratom preparations and safe dosing guidelines. This highlights the implications of kratom's phytochemical complexity for its potential therapeutic applications and risks.

Keywords: alkaloid, geographical variation, *Mitragyna speciosa* (Kratom), phytopharmacology, strain

1 Introduction

Mitragyna speciosa, commonly known as Kratom, is a tropical tree native to Southeast Asia, renowned for its diverse alkaloid profile and varying pharmacological effects. Kratom particularly flourishing in countries such as Thailand, Indonesia, Malaysia, and Myanmar. Belonging to the Rubiaceae family, kratom has been an integral part of local culture and traditional medicine for centuries [1].

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The plant has garnered considerable interest in recent years, both for its historical applications and its growing significance in contemporary herbal medicine. In Southeast Asia, kratom leaves are utilized for their stimulant and sedative effects, which vary with the dosage. Local populations have traditionally chewed the leaves for increased energy and pain relief, especially among workers and farmers. Furthermore, kratom is involved in social and ceremonial activities, appreciated for its mood-enhancing and fatigue-reducing qualities [1], [2].

In Indonesia, this plant is known as Kratom, while in Thailand, it is referred to as tom or thom. In Malaysia, it is commonly referred to as ketum, although names like bia and biak are also used. Kratom is prevalent in Thailand, Malaysia, Indonesia (Kalimantan), the Philippines, New Guinea, and parts of Africa [3]. Around 25 alkaloids have been isolated from *M. speciosa*, with mitragynine and 7-hydroxymitragynine recognized as the main active substances. These alkaloids are known to have effects comparable to those of morphine [4].

Kratom strains are typically categorized by their vein color—red, green, and white—each associated with distinct alkaloid profiles and effects. The alkaloid profiles of kratom strains can vary significantly based on their color, origin, and cultivation practices. Understanding these differences is crucial for users seeking specific effects, whether for pain management, energy enhancement, or relaxation. As research continues, the complexity of kratom's alkaloid diversity will likely yield further insights into its therapeutic potential. The alkaloid content in kratom leaves can vary significantly based on factors like geographic location, season, and plant characteristics [5].

Kratom has been regarded as a beneficial herbal remedy for various issues, including diarrhea, pain relief, coughs, hypertension, and enhancing sexual performance. In Indonesia, this plant grows abundantly in Kalimantan. Now, kratom is widely available in the United States and Europe. This plant is often abused and sold in powder or extract form through online shops. Consuming kratom results in a stimulant effect at low doses and an opioid-like effect at medium to high doses. It is frequently misused and can be easily bought online [1], [2]. Given these concerns, this study aims to analyze the alkaloid diversity of kratom leaves across different regions and seasons in Southeast Asia to better understand its pharmacological properties and potential medical applications.

2 Materials and methods

This review article employs a literature review approach, involving the systematic collection and analysis of existing research and scientific articles on the topic of interest. This approach facilitates the synthesis and evaluation of existing knowledge and findings related to *Mitragyna speciosa*. The primary objective of this research study is to explore the alkaloid content of various kratom strains from Southeast Asia, particularly those found in Indonesia, Malaysia, and Thailand.

Ethnopharmacology involves investigating the use of plants as traditional medicine by various cultures. The articles referenced in this review were sourced from reputable journals and publications aligned with the research topic. Key sources mentioned include Web of Science, Sinta, and Scopus. These databases and platforms provide access to a wide range of scientific articles across different disciplines. Most of the selected journals and articles were published in the last decade, ensuring the inclusion of the latest research findings and enhancing the relevance of the information presented in this review article.

By focusing on recent publications, this research aims to provide a comprehensive overview of current knowledge regarding Kratom. In addition to journal articles, books related to the family and species associated with Kratom were also consulted. These books offer in-depth information on taxonomy, morphology, ecology, and other aspects of the plant species. By including book references,

this review article encompasses a broader range of literature sources, enriching the content and analysis.

3 Results and Discussion

3.1. Habitat and Morphology

Mitragyna speciosa (Korth.) Havil., commonly known as kratom, is a native plant of Southeast Asia, thriving in regions such as Thailand, Indonesia, Malaysia, Sumatra, Java, Bali, and Borneo [6]. Kratom flourishes in swampy areas and is indigenous to these countries. The Rubiaceae family, to which kratom belongs, is highly diverse, encompassing over 13,000 species, making it the fourth largest plant family [1], [7]. Members of this family range from small herbs to climbing vines and large trees. *Mitragyna speciosa* have a simple leaves, interpetiolar stipules, inferior ovaries, and sympetalous flowers [5], [8], [9].

This plant grows as a woody tree, reaching heights of 10 to 30 meters, either standing alone or in close proximity to other similar species. In its youth, the trunk remains straight and features greenish-gray bark; however, as it matures, this bark transforms into a brownish-gray hue. The texture of the trunk's surface also changes: when young, it is smoother, but it becomes coarser and develops more pustular lenticels with age. On a juvenile trunk, one can observe 10 to 12 paired leaves that grow in opposing and intersecting formations. Each pair of leaves emerges alongside two interpetiolar stipules, which are positioned directly above or slightly above the two petioles. Notably, flowers and fruit develop in the leaf axils, nestled between many of the leaves near the tip of the tree trunk [9] [10].

The habitat of kratom is found in river basin areas and wetlands. Kratom grows optimally in fertile, water-saturated alluvial soil (mineral deposits). This plant has the ability to survive in flooded conditions. Such conditions can be found in several regions of Indonesia, such as the Suwi wetland area, which includes the Suwi river basin (Suwi region), the Kenohan river, and Lake Mesangat in East Kalimantan, as well as the Sebangau area, traversed by the Katingan and Sebangau rivers in Central Kalimantan [11], [12]. Observations by the research team from the Health Research and Development Agency in West Kalimantan indicate that kratom is widely cultivated in home gardens, farms, and river basin areas. Generally, the planting locations are in low-lying, humid areas that also contain abundant organic material. Kratom can still grow in land conditions with acidic pH and waterlogged throughout the year [13]. In Thailand, kratom trees are primarily found in the southern regions of the country, and the leaves are readily available from teashops, often used as an alternative to alcohol and opium [14], [15].

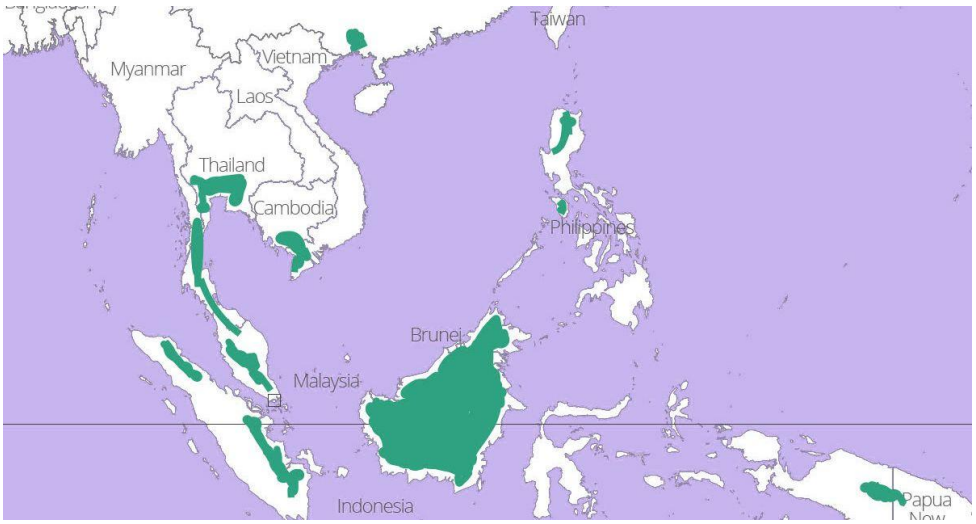

Fig. 1. Distribution of Kratom/ *Mitragyna speciosa* (Korth.) Havil in Southeast Asia. The green shaded part of the map shows where wild kratom normally grows [16]

3.2. Traditional Uses

There have been several uses for Kratom's alkaloid-containing leaves throughout history. Preparations made from the leaves have been used as traditional medicine to treat a range of ailments. Kratom has traditionally been used as medicine in Kapuas Hulu Regency, Indonesia, for centuries [14], [17]. The study showed that Kratom has the potential as an anti-diarrhea, anti-diabetic, cough, etc.[13], [18], [19], [20]. In southern Thailand, kratom leaves have been used as a traditional medicinal herb and have gained acceptance as a cultural stimulant beverage, similar to coffee and tea. Women in these villages widely use kratom leaves as a home remedy for common issues like fever, cough, hypertension, diabetes, pain, and anxiety [5], [6].

In Southeast Asia, villagers commonly consume kratom in the morning to enhance work productivity and alleviate fatigue. Its coca- and opium-like effects assist manual laborers, such as farmers, rubber tapers, machine drivers, and fishermen, enabling them to work in the intense heat without tiring [2], [26], [27], [28]. Kratom is also consumed as a recreational drink during relaxation and social gatherings, primarily among men, and is sometimes included in small religious ceremonies in certain Thai villages. Additionally, it is utilized as a wound poultice and is believed to act as a deworming agent and appetite suppressant [21], [22], [23].

In Malaysia, Thailand, and other places, farmers, laborers, and fisherman have long chewed the fresh leaves to lessen weariness during hot labor. As a stimulant and alternative to opium, dried kratom leaves or concentrated leaf extracts have been consumed or smoked. A Malaysian study noted self-reports indicating that kratom is used as an aphrodisiac to enhance sexual desire. Interestingly, the primary medical use of kratom in the West is for treating chronic pain [24], [25], [26].

The majority of male employees pick up kratom usage tips from other local users. When opium was more widely used in Malaya in the past, many who relied on it supposedly shifted to ketum when opium became scarce. Men take kratom as a drink in the evening to unwind and mingle. In rural areas, men are also offered kratom as a beverage at parties. Users of kratom are not subject to the social stigma associated with alcohol consumption since they are not viewed as alcohol users. Additionally, Kratom has gained acceptance in certain local religious rituals where it is presented to a deity or spirit as a priceless gift in exchange for their fulfilling their vows or desires.[15], [24], [27].

In Indonesia, the resurgence of Kratom's popularity followed a controversial statement by the Minister of Home Affairs expressing support for the export of kratom as an herbal plant. Prior to this,

Indonesia held the distinction of being the largest exporter of kratom to the United States, primarily in the form of simplicial powder [29]. Concurrently, within Indonesia, the regulation of kratom falls under the purview of the National Agency of Drug and Food Control (BPOM), as outlined in Circular No. HK.04.4.42.421.09.16.1740 of 2016. This circular pertains to the prohibition of the use of Kratom in registered traditional medicines [30]. However, the regulation pertaining to individual consumption remain unregulated. Therefore, this review article endeavors to expound upon both the benefits and risks associated with kratom usage as traditional medicine. The elucidation of these facets serves as a crucial consideration for governmental deliberations regarding the liberalization or restriction of kratom use in Indonesia.

Over the past ten years, the availability of these leaves has expanded to a global market through e-commerce. Nowadays, *M. speciosa* is used by those seeking relaxation, spiritual experiences, or a "legal high," as well as by those searching for a natural substitute for prescription antidepressants and painkillers. It is also used to help with opiate withdrawal [1], [9], [21], [28]

3.3. Bioactive compounds and pharmacological properties

Previous research has shown that Kratom includes a wide range of secondary metabolites, including indole alkaloids, flavonoids, triterpenoids, saponins, and glycosides [31]. The primary constituents of the kratom plant are identified as indole alkaloid compounds, which also contain mitragynine and 7-hydroxymitragynine (7-HMG) [9]. Furthermore, investigations conducted both in vitro and in vivo have demonstrated that kratom possesses a range of pharmacological characteristics, including anti-inflammatory, antibacterial, anti-analgesic, and antioxidant effects [4], [32]. There is currently a paucity of scientific data regarding the mechanism and inhibitory effects of enzymatic activities, despite earlier studies reporting that kratom leaves exhibit activities that affect metabolism and diabetes [23]. [24], [33], [34].

Fig. 2. Kratom in West Kalimantan (Putussibau), Indonesia

3.4. Alkaloids in Kratom

Numerous phytochemical studies have demonstrated that indole alkaloids naturally occur in the *Mitragyna* genus. Mitragynine, an indole alkaloid that makes up over 66% of the total alkaloidal content, is the main component of Kratom [18], [35]. The concentration of mitragynine varies between younger and older plants, with older plants exhibiting significantly higher levels than their younger counterparts. The existence of alkaloids in different species can be explained by environmental conditions; also, the contents of some alkaloids vary from month to month. The concentration of mitragynine in a Thai specimen is approximately 66% greater than in Malaysian specimens. Similarly, the alkaloidal contents of *M. speciosa* in other sites, such as London, England, change, possessing alkaloids previously not documented in Southeast Asian species[21].

Four alkaloid—mitragynine, 7-hydroxymitragynine, corynantheidine, and speciociliatine—of the more than 40 alkaloids found in Kratom currently appear to function on opioid receptors [36], [37]. More than 25 distinct alkaloids have been found in Kratom leaves. Paynantheine, speciogynine, 7-hydroxymitragynine, and speciociliatine are some further significant alkaloids [7].

Mitragynine is the predominant alkaloid found only in Kratom, making up approximately 66% of all alkaloids. Its molecular structure is more akin to that of a psychedelic than an opiate, although it does not seem to have any psychedelic activity. More mitragynine is present in the leaves, though the amount varies substantially depending on the growing environment. Kratom from Thailand contains approximately 66% mitragynine, whereas Malaysian samples contain around 12%, and Indonesian samples, particularly from Kapuas Hulu, contain 54%. One study found that 7-hydroxymitragynine, which makes about 1.6% of all alkaloids, is present in Thai kratom leaves [38].

Kratom grown in America contains a higher level of the oxindole alkaloid compound mitraphylline, accounting for 45% of the total alkaloids. León et al. (2009) revealed that kratom from America has different chemical properties compared to kratom from Southeast Asia. Isomemitraphylline, speciophylline, speciofoline, isospeciofoline, mitrafoline, isomitrafoline, rotundifoleine, isorotundifoleine, ciliaohylline, rhynchociline, specionoxeine, iso-specionoxeine, corynoxine, isocorynoxine, rhynchophylline, isorhynchophylline, corynoxeine, and isocorynoxeine are additional oxindole alkaloid compounds found in kratom. In contrast, heteroyohimbine-type alkaloid compounds are uncommon in kratom. Another substance that has been effectively extracted from kratom is ajmalicine, which is also sold under the trade names lamuran and circolene. This substance acts as an α-adrenergic receptor antagonist [10], [39].

3.5. Strains Characteristics

All kratom products are derived from the kratom tree, which is indigenous to Southeast Asia. Kratom is primarily classified into three types based on the color of the central vein in the leaves: red, green, and white. Further classifications are made according to their country of origin, such as Green Malay from Malaysia and Red Thai from Thailand), White Borneo or Bali Red (Indonesia), as well as the techniques used for drying and processing them [13], [33].

Red kratom, sourced from mature red-veined leaves, is the most popular variety among kratom users. Red kratom is versatile and can help manage low energy and pain, depending on the individual's dosage and tolerance. Among the strains, Red Maeng Da is the strongest variety, providing effects akin to those of opioids. Red Borneo and Bali Red are also favored options among kratom enthusiasts. Red kratom is known for its rapid onset and is frequently used to alleviate migraines, arthritis, and other chronic pain conditions. It is often consumed in the evening due to its strong sedative properties. Because the experience with red kratom is highly sought after and closely resembles opioid effects, it comes with an extensive list of potential side effects and a significant risk of dependence and addiction. Red vein strains generally have higher levels of 7-hydroxymitragynine, associated with increased sedative and pain-relieving effects, and the mitragynine content typically ranges from 1.0%

to 1.4%. Users often report these red strains as more relaxing and effective for pain relief and sleep. In southern Thailand, locals believe that red-veined leaves possess medicinal qualities, while green-veined leaves are seen as more stimulating. However, the genetic differences between these leaf types have not been extensively researched. Natives usually prefer the red vein for its longer half-life and stronger effects, despite its unpleasant taste. Fresh leaves can be dried for smoking or brewed into tea, with a typical dosage being 10 to 30 leaves per day, either chewed or consumed as a powder [14], [15].

Green vein kratom is sourced from leaves that have not fully matured and is subjected to minimal processing. This results in an incomplete development of alkaloids, creating a balanced profile that provides a combination of energizing and relaxing effects. Unlike red strains, known primarily for their sedative properties, and white strains, associated with stimulation, green kratom is considered a more moderate homeopathic supplement. Once a Kratom leaf reaches its full potential, it turns a dark green color. The stage of a Green vein Kratom leaf that has achieved its primary condition is indicated by the peak concentration of chlorophyll in the Kratom. Green vein kratom strains typically contain 1.3–1.8% mitragynine, indicating a more balanced alkaloid profile. As a result, in comparison to red and white strains, green strains have a more moderate, "middle-of-the-road" impact profile. The traditional way to consume kratom involves preparing tea from powders such as Green Bali and Green Maeng Da. The most popular strains of green vein kratom include Green Maeng Da, Green Sundanese, Green Borneo, and Green Malay [5].

The kratom plant is a member of the coffee family, and white vein kratom delivers energizing and uplifting effects comparable to coffee. It contains a specific blend of natural compounds that are not found in mature leaves. Grinding of white kratom leaves begins as soon as the leaves start to germinate. White vein kratom is nearly as popular as red kratom. White kratom provides an energy boost akin to caffeine, enhancing alertness and stamina, making it a favored choice for morning or daytime use. White vein kratom strains generally have the highest mitragynine content, around 1.3-1.8%. This makes white strains more stimulating and energizing compared to the other vein colors. White kratom products include White Thai (originating from Thailand), White Maeng Da, and White Borneo. Among these, Maeng Da is often regarded as the best due to its superior quality and consistency [39].

A

B

C

Fig. 3. Strains of Kratom, A=Red vein; B=Green Vein; C=White Vein

3.6. Geographical source in Southeast Asia

In Myanmar, Thailand, Malaysia, and Indonesia, kratom is a native plant[2]. There are several red- and green-veined kratom plants in the region. Southeast Asia's kratom distribution, which includes countries like Thailand, Malaysia, the Philippines, Cambodia, Vietnam, Papua New Guinea, and Indonesia. Kratom is available in Indonesia on the islands of Papua, Kalimantan, and Sumatra [12].

The effects of mitragyna leaves can vary significantly in intensity and type based on factors such as location, maturity stage, and the specific concentrations of alkaloid chemicals present, as well as the ecotype. Research has shown that the proportion of kratom as a fraction of total alkaloids can range from 66% in Thai-origin plants to 12% in Malaysian plants, and 54% in Indonesian plants. A study found the mitragynine content ranged from 0.35-4.94% w/w across different regions and seasons in Thailand [1][2]. Soil nutrients, especially calcium and magnesium, were found to play an important role in promoting alkaloid production in kratom plants. Geographical location also influenced mitragynine levels, but did not affect the leaf vein color [29], [37], [39], [40].

3.7. Pharmacological Effect

At larger doses, the unique narcotic characteristics of Kratom mix opiate-like effects with psychostimulant effects [4], [36]. The plant variety, which includes red and white-veined leaves, plays a significant role in determining its effects. Due to its potency, red vein leaf is valued in Thailand [25]. The kratom plant yields a variety of phytochemicals, including around 40 structurally related alkaloids, with mitragynine serving as the main alkaloid and 7-hydroxymitragynine serving as a minor ingredient (exhibiting potencies up to 13 and 46 times greater than that of morphine and mitragynine, respectively). It is said that Mitragyna speciosa has effects similar to those of morphine Although there is evidence that both of these alkaloids have dose-dependent antinociceptive effects and are associated with the increasing usage of these compounds for pain relief in the West [4], [2], [4].

Although regular kratom use has the potential to be addictive, it does not carry the same negative stigma as opium smoking. Over time, habitual users are more likely to increase their consumption of kratom than individuals who use it infrequently. [2], [27], [28]. Even among long-term users, no negative physical or psychological symptoms were reported. Additionally, only minimal withdrawal symptoms were recorded when the drug was stopped. Most people who have used or consumed kratom reported feeling happy, powerful, and energetic after doing so. Vicknasingam et al. (2020) note that kratom users reported higher levels of physical activity, heightened sexual desire, and

increased work capability. In a similar vein, Ahmad and Aziz (2012) documented statements from ketum users describing feelings of being attentive, calm, happy, energized, and dizzy. Other effects reported by users included feeling hot and sweating, better sexual performance, and exhilaration. Typically, these effects last anywhere from one to six hours [8].

Constipation, weight loss, sleeplessness, mouth dryness, frequent micturition, dehydration (increased thirst), fatigue, skin darkening, and reduced sexual drive have also been linked to long-term kratom usage. Nonetheless, it seems that Southeast Asian kratom consumers can generally withstand the side effects of frequent ketum consumption. Numerous research have found a connection between the manufacture of Kratom and the administration of mitragynine and increased blood pressure, hepatotoxicity, and nephrotoxicity in rats. There have been reports of human toxicity, fatalities, unpleasant withdrawal symptoms, and impaired cognitive and behavioral function [35], [2], [26]. Kratom was initially utilized mainly for its medicinal properties to address minor health issues such as fever, diarrhea, diabetes, pain, and as a poultice for wounds. Due to its accessibility and affordability, it also gained popularity as a means of squelching the symptoms of opiate withdrawal. Young customers have been using kratom tea as the foundation for a drink, which consists of ice cubes, Coca-Cola, cough syrup, and kratom tea, in recent years. This later got problematic since these users were enhancing the effects with substances like benzodiazepines [30], [39].

Vicknasingam et al. (2020) investigated the sociodemographic traits of kratom users in addition to the main drivers of kratom intake. 136 current users participated in the study, and 76.5% of them had previously used drugs. The benefits of using kratom over heroin were improved symptoms of withdrawal from opiate addiction, less addiction to other substances, and its lower cost. Both short- and long-term users have reported increased energy levels, improved work performance, and heightened libido. Animal models have demonstrated the potential for addiction to kratom when mitragynine and 7-HMG are administered orally for five days.

3.7.1. Analgesic Properties

Mitragynine binds to mu-opioid receptors with great affinity. Analgesia, pleasure, and respiratory depression are all mediated by these receptors. It has been demonstrated that the supraspinal mu- and delta-opioid receptor subtypes mediate most of its antinociceptive activity, designating it as the alkaloid accountable for kratom's analgesic effects. This supports the idea that kratom can be used as a less painful alternative to opium or to lessen the effects of opium addiction by easing the discomfort associated with withdrawal symptoms. It has a significantly reduced affinity for kappa-receptors. Stolt et al. (2014) identified that kratom has analgesic properties through kappa receptors and depresses locomotor activity via presynaptic dopamine. The reinforcing effects of 7-HMG are partially driven by mu and delta opiate receptors. Furthermore, kratom can act as an anesthetic; Vermaire et al. (2019) reported a case where a patient used kratom for chronic pain management [41], [42].

Additionally, 7-HMG showed strong opioid receptor activity. Research has shown that both mitragynine and 7-HMG are more potent than morphine for analgesic effects, with mitragynine being roughly 13 times more effective and 7-HMG around 4 times more effective. Additionally, a recent study found that kratom powder has a weaker affinity for the mu-opioid receptor compared to morphine. By reversibly inhibiting neuronal Ca2+ channels, mitragynine can restrict the release of neurotransmitters at the cellular level. The authors suggest that the suppression of pain transduction is caused by a reduction in neurotransmitters. Via opioid receptors, mitragynine also reduced the activity of adenylyl cyclase in NG108-15 cells [43].

3.7.2. Anti-Inflammatory Properties

Research has also explored kratom's anti-inflammatory properties. Prostaglandin PGE2, a key inflammatory mediator, is produced through an inflammatory pathway catalyzed by the cyclooxygenase isoforms COX-1 and COX-2. Mitragynine inhibits the expression of COX-2 mRNA and protein, thereby reducing the production of PGE2. Caution is advised when using higher doses, as lower concentrations do not affect COX-1 mRNA and protein expression. Beyond enhancing immunity, kratom may promote tissue repair and healing, and decrease the production of pro-inflammatory mediators and vascular permeability [42], [43].

3.7.3. Gastrointestinal Effects

Kratom has demonstrated gastrointestinal effects as well. In vivo studies indicate that the methanolic extract of kratom leaves lowers both defecation frequency and fecal weight in rats subjected to castor oil-induced diarrhea. A single dose of the extract was effective in reducing intestinal transit, but further reductions were not observed with extended use. Additionally, pre-treatment with naloxone did not impact defecation frequency, implying that kratom may operate through mechanisms that extend beyond opioid receptors [20], [40], [41].

Mitragynine administered centrally into the fourth ventricle of anesthetized rats caused a dose-dependent suppression of the stomach acid secretion triggered by 2-deoxy-d-glucose; naloxone, however, abolished this effect, suggesting that opioid receptors were involved. The injection of mitragynine into the lateral cerebroventricular ventricle did not affect the secretion of acid. Its ability to directly inhibit neurons in the lateral hypothalamus may be responsible for its effects on anorexia and weight loss. Regarding 7-HMG, gastrointestinal transit inhibition was seen in mice following a subcutaneous injection [20], [44].

Reduction of food and water consumption is one of the acute and long-term effects of Kratom. Additionally, the weight acquired also tended to decrease.Research on how L8 muscle cells' glucose transport mechanism is regulated revealed that kratom can boost glucose absorption rates and protein levels associated with glucose transport, supporting its anti-diabetic properties [19], [44].

3.7.4. Anti-Depressant Activity

Kratom has been found to possess antidepressant properties as well. The overactivation of the hypothalamic-pituitary-adrenal axis, which is a sign of depression, is characterized by elevated corticosterone levels. Mitragynine seems to demonstrate antidepressant effects by significantly reducing corticosterone levels in mice subjected to the forced swim test and tail suspension test [19].

Ismail et al. (2017) observed learning deficits similar to those caused by chronic morphine or α-9-tetrahydrocannabinol therapy, noting impairments in spatial learning and memory processing with chronic kratom administration. However, a study assessing the immediate effects of both kratom extract and mitragynine on mice's short-term memory and motor coordination found no statistically significant impact from either compound. In 2018, a human study corroborated these findings, demonstrating that habitual kratom users did not experience negative effects on motor skills, memory, attention, or executive function even with high intakes of kratom juice (more than three glasses per day) [45].

3.7.5. Antioxidant and Anti-Bacterial Properties

Kratom demonstrated to have both antioxidant and antibacterial effects. Nonetheless, there is insufficient evidence to support the use of Mitragyna speciosa for clinical indications, which is made even clearer by the inconsistent information available on the subject [13]. Kratom's effects have been discussed extensively. There are conflicting accounts on Kratom's psychoactive effects. There are reports that it has stimulant and narcotic properties, which are generally considered to be opposite effects. It's still unknown what physiological foundation stimulants and opioids have for these effects.

The antinociceptive characteristics of mitragynine and 7-hydroxymitragynine, the two main ingredients in Kratom, have been shown to operate through μ- and δ-supraspinal opioid receptors [43]. On the other hand, while there are many anecdotal reports of kratom's stimulating effects, scientific data remains insufficient. Kratom appears to be a unique plant, and understanding the mechanism of its action is crucial for enhancing our comprehension of its psychoactive qualities and addressing the ongoing controversies surrounding its use [15], [22], [23].

The epidemiology of Kratom use is unknown, despite the fact that it is a plant with psychotropic properties. Veltri et al. (2005) estimated that approximately ten million people globally use Kratom on a regular basis, however there is little published evidence on the prevalence of Kratom use. According to a cross-sectional nationwide survey of Malaysian teens, Kratom accounts for 0.5% of all narcotics consumed, with the majority of abuse occurring in Peninsula Malaysia's northern states. Kratom appears to remain a substance linked with rural areas [46], [47].

4 Conclusion

Kratom's primary bioactive compounds are alkaloids, notably mitragynine and 7-hydroxymitragynine, which can produce effects ranging from stimulation to analgesia based on dosage and strain. The diversity of these alkaloids is influenced by geographic origin, strain characteristics, and environmental factors like soil composition and climate. While different kratom strains—distinguished by color such as red, green, and white—offer varying medicinal benefits, it is essential to recognize the potential risks associated with kratom use, including dependence and adverse effects. Understanding these factors is crucial for the responsible and effective use of kratom for medicinal purposes.

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