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Environmental and physiological determinants of growth and phytochemical variation in Kratom (*Mitragyna speciosa*): A review

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ABSTRACT

Purpose: Kratom (*Mitragyna speciosa*) is a tropical plant native to Southeast Asia, widely used for traditional and emerging therapeutic purposes. This review investigates the environmental and physiological determinants of phytochemical variation in *Mitragyna speciosa* (kratom), with a focus on optimizing alkaloid yield and raw material quality. As kratom gains commercial traction, particularly in Western markets, the need for standardizing cultivation practices becomes increasingly urgent. **Findings:** Geographic origin significantly influences mitragynine content, with native Southeast Asian samples displaying higher and more consistent levels than those cultivated elsewhere. Environmental factors such as light exposure, temperature, soil acidity, and nutrient composition play crucial roles in modulating both plant morphology and secondary metabolite biosynthesis. Internally, leaf maturity, organ specificity, and vein color are linked to variable alkaloid profiles, reflecting genetic and developmental influences. Alkaloid biosynthesis is regulated not only by climate and geography but also at the molecular level through gene–environment interactions. Studies across continents and related species further underscore the diversity and adaptability of the genus. These findings suggest that integrated, site-specific agronomic strategies are essential to support kratom's evolution as a standardized phytopharmaceutical. **Limitations:** Most existing studies are regionally constrained, lack standardized methodology, and rarely incorporate multi-site or molecular validation, limiting their broader applicability. **Directions for future research:** Future work should prioritize field-based, multi-environment trials to validate the effects of environmental variables on alkaloid biosynthesis and biomass traits. In addition, controlled environment experiments, genetic profiling, and enzyme-specific biosynthetic studies are essential to refine cultivation protocols and support regulatory frameworks. Integrative agronomic and phytochemical modeling is also needed to guide the development of standardized and high-quality kratom production systems.

INTRODUCTION

Kratom (*Mitragyna speciosa* Korth.), a member of the Rubiaceae family, is a tropical plant traditionally used across Southeast Asia, including Indonesia, Thailand, Malaysia, the Philippines, Vietnam, and Papua New Guinea (Löfstrand et al., 2014). It is known by various local names, such as "Kratom" in Thailand, "kadamba" in Indonesia, "ketum" and "biak" in Malaysia, "giam" in Vietnam, and "mambog" in the Philippines (Chua, 2001). *Mitragyna speciosa* thrives in humid environments, particularly along rivers, swamps, and alluvial lowlands. Its natural habitat includes freshwater swamp forests, riverbanks, and peat soils (Nilus et al., 2011).

Historically, Kratom has been used by local communities to treat various ailments. In Kalimantan, Indonesia, for example, Kratom leaves are brewed like tea to relieve fatigue, enhance stamina, and alleviate pain and fever (Utomo et al., 2022). Over the past decade, global interest in this plant has grown due to its diverse pharmacological properties, including analgesic, anxiolytic, and anti-inflammatory effects in treating chronic conditions (Sitthiphon & Prakasit, 2025). Some studies have even reported its potential as an alternative therapy in opioid cessation programs (Singh et al., 2023; Tabanelli et al., 2023; Indriyanti et al., 2024). Despite its medicinal and ethnobotanical significance (Arief et al., 2025; Begum et al., 2025), Kratom remains controversial and often mischaracterized due to its association with substance misuse (Cinosi et al., 2015; Predescu et al., 2025), leading to legal restrictions in several countries (Diversion Control Division, 2024). Nevertheless, Kratom retains high popularity and increasing international market demand (Grundmann et al., 2023), with commercial products such as powders, capsules, tablets, and concentrated extracts fetching prices as high as USD 3.57 per gram of concentrated extract (Prevete et al., 2024). With Kratom's rapid expansion into international markets, especially in Western countries, commercial interest has intensified and diversified product demand. However, this accelerated growth highlights the absence of standardized cultivation protocols, which are urgently needed to ensure consistency in alkaloid yield, product quality, and regulatory compliance across different production regions.

Chemically, Kratom's pharmacological effects are primarily attributed to its alkaloid content, particularly mitragynine, which can constitute up to 66% of the total alkaloid profile (Veeramohan et al., 2018). Other alkaloids, including speciogynine, speciociliatine, and paynantheine, contribute between 1% and 9% (Ameline et al., 2024). In concentrated preparations such as resins and tinctures, mitragynine content can reach up to 40%. These alkaloids not only influence pharmacological potency but also play a critical role in determining product quality and market value (Cinosi et al., 2015; Grundmann et al., 2023).

Given that alkaloid biosynthesis and accumulation are heavily influenced by environmental conditions, a comprehensive understanding of ecological determinants such as climate, light, soil, seasonal variation, and geographic location is essential for sustainable and high-quality Kratom cultivation. Despite growing demand and commercial exploitation, there remains a lack of consolidated knowledge on how environmental variables interact with plant physiology to shape both biomass and bioactive compound profiles. To date, no integrative review has systematically examined the environmental and physiological factors affecting Kratom's growth and chemical quality in diverse cultivation contexts.

This review aims to bridge that critical gap by systematically examining the relationship between environmental factors and Kratom's phytochemical quality. It represents the first scientific effort to integrate both ecological and physiological perspectives into a unified framework, providing a foundation for developing sustainable cultivation strategies, improving raw material quality, and advancing evidence-based Kratom product development on a global scale. Given Kratom's increasing global prominence in herbal markets and its complex regulatory landscape, such insights are urgently needed to guide scientific research and industry practices.

MATERIALS AND METHODS

This study was conducted as a narrative literature review aimed at identifying and synthesizing scientific evidence regarding the environmental factors influencing the growth and phytochemical composition of *Mitragyna speciosa*. Literature searches were performed using major peer-reviewed academic databases, including PubMed, Scopus, Web of Science, Google Scholar, and the Directory of Open Access Journals (DOAJ).

Search terms were constructed using Boolean operators (AND/OR) and included combinations of relevant keywords such as: ("*Mitragyna speciosa*" OR "Kratom" OR "mitragynine") AND ("environment" OR "climate" OR "growing media" OR "light" OR "season" OR "soil") AND ("morphology" OR "plant organ" OR "phytochemistry" OR "alkaloid"). Additional keywords such as "plant nutrition," "Kratom strain," "leaf maturity"and "vegetative growth" were also used to expand the search coverage.

The literature search covered publications ranging from the oldest study published in 1983 to the most recent articles published in 2025 to ensure the inclusion of both foundational and the most recent advances in the field. Inclusion criteria were limited to original research articles and scientific reviews published in English or Indonesian, with full-text availability and direct relevance to the research topic. Editorials, commentaries, and non-scientific sources were excluded. The selection process involved screening titles, abstracts, and full texts to ensure alignment with the scope of the review. Eligible literature was then analyzed qualitatively to identify thematic patterns, trends, and correlations among environmental variables and both physiological and phytochemical responses of *Mitragyna speciosa*. The final body of evidence corresponds to the 96 publications cited in the reference list of this manuscript. Findings were synthesized narratively to establish a conceptual framework for optimizing ecophysiological determinants in sustainable Kratom cultivation.

RESULTS AND DISCUSSION

Phytochemical composition of *Mitragyna speciosa*

Wide arrays of natural compounds have been identified in *Mitragyna speciosa* as a result of extensive phytochemical investigations. These studies consistently revealed that the major classes of constituents included terpenoids, flavonoids, and most notably, alkaloids. Among these, indole-based alkaloids represent the predominant bioactive group. Some compounds are also present as oxindole derivatives with four- or five-membered ring structures, reflecting the plant's considerable chemical complexity (Takayama, 2004). A visual overview of these phytochemical classes and representative compounds is illustrated in Figure 1.

Mitragynine and its derivative, 7-hydroxymitragynine, exhibit strong affinity for opioid receptors and have demonstrated potent analgesic properties. Notably, 7-hydroxymitragynine has been reported to be up to 46 times more potent than mitragynine and 13 times stronger than morphine (Takayama, 2004). In addition to mitragynine, *M. speciosa* contains a range of structurally diverse and pharmacologically promising indole alkaloids such as ajmalicine, paynantheine, speciogynine, isopaynantheine, speciociliatine, and mitraciliatine. It also comprises oxindole-type alkaloids including isomitraphylline, isospeciofoline, speciofoline, corynoxine A, corynoxeine, and rhynchophylline. At least 19 alkaloids have been characterized in this plant (Flores-Bocanegra et al., 2020; Manwill et al., 2022). Alkaloid concentrations have been shown to vary significantly based on environmental factors. For example, in plants cultivated in the United States (University of Mississippi), mitraphylline was identified as the dominant alkaloid (León et al., 2009). In another study, mitragynine levels in Thai specimens were approximately 66% higher than those in Malaysian counterparts (Takayama et al., 1998). Numerous factors have been associated with this variation, including macronutrients (Phromchan et al., 2024), light exposure (Zhang et al., 2022), plant maturity (Veeramohan et al., 2023), seasonal and geographical conditions (Leksungnoen et al., 2022; Sengnon et al., 2023), soil characteristics (Rossalinda et al., 2024), and the other factors.

Beyond its rich alkaloid content, recent studies confirm that leaves of *Mitragyna speciosa* also contain various non-alkaloid bioactive compounds. These include at least 10 flavonoids, six terpenoids, and several phenylpropanoids, along with carboxylic acids, glycosides, phenols, and phenolic aldehydes (Veeramohan et al., 2023). Methanolic extracts of Kratom leaves contain epicatechin, and its polymeric form (condensed procyanidin tannins) exhibited notable biological activity against SARS-CoV-2, with an EC_{50} of 8.38 µg/mL. Other isolated non-alkaloid constituents include chlorogenic acid, saccharic acid 1,4-lactone, and inositol; each with distinct biological activities (Sureram et al., 2024). Ethanol extracts from red, white, and green Kratom variants have demonstrated the presence of phenolic and flavonoid compounds with antioxidant activity (Masriani et al., 2024). Furthermore, saponins such as daucosterol and triterpenoid saponins (quinovic acid 3-O-β-D-quinovopyranoside and quinovic acid 3-O-β-D-glucopyranoside) have been isolated from Kratom cultivated in the U.S. (León et al., 2009), while common phytosterols such as β-sitosterol and stigmasterol have been reported across *Mitragyna* species, including *M. speciosa* (Phongprueksapattana et al., 2008).

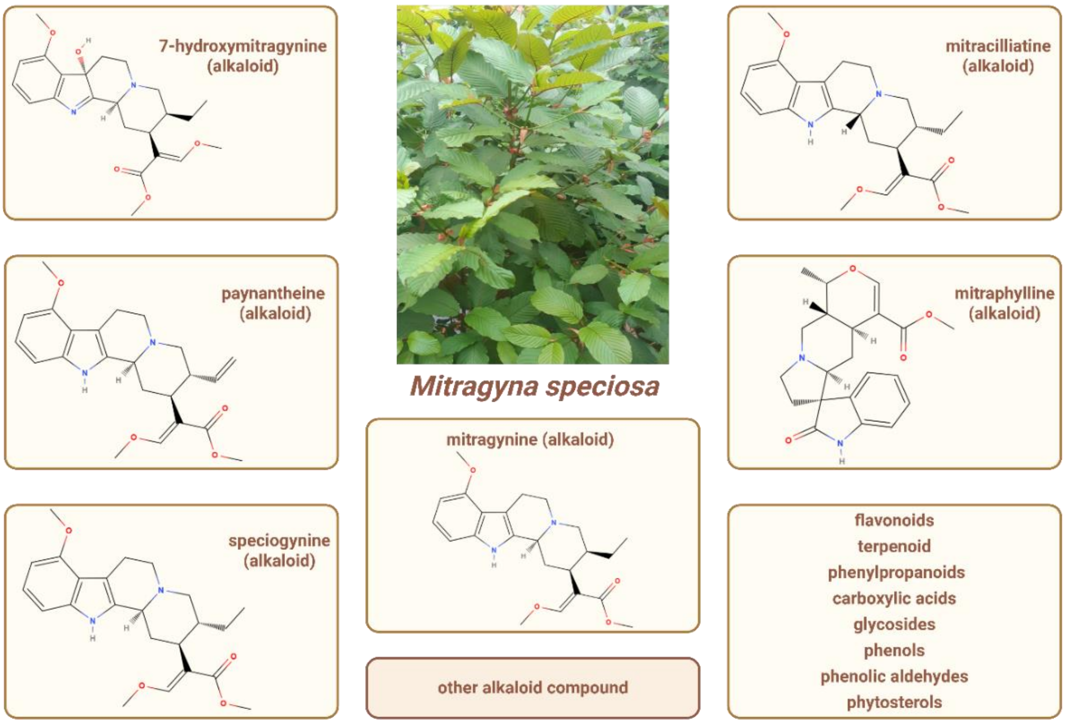

Fig. 1. Phytochemical constituents in *Mitragyna speciosa* leaves.

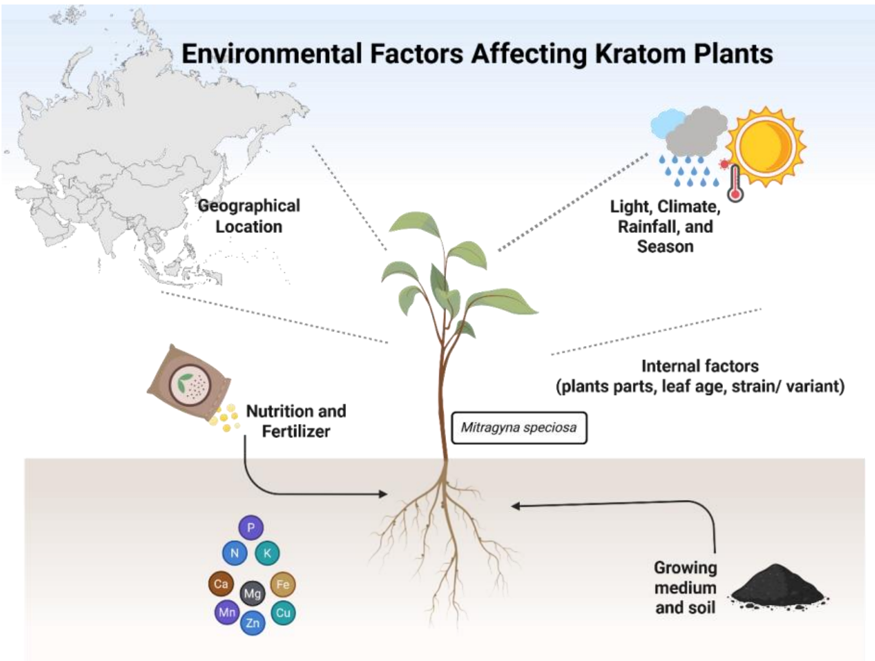

Fig. 2. Key environmental and physiological factors influencing the growth and phytochemical composition of *Mitragyna speciose.*

This rich and diverse phytochemical profile underscores *M. speciosa*'s wide-ranging pharmacological potential and the need for further exploration. It also raises important considerations regarding how environmental variables such as geography, seasonality, light intensity, and soil nutrient status shape the composition and concentration of alkaloids and other secondary metabolites in this plant (Fig. 2).

Pharmacological effects and uses of Mitragyna speciosa

Mitragyna speciosa is widely recognized for its complex pharmacological profile, primarily attributed to its key alkaloids, mitragynine and 7-hydroxymitragynine. These compounds exhibit notable affinity for opioid receptors, particularly the μ-opioid receptor, which accounts for the plants reported analgesic and mild euphoric effects (Takayama, 2004; Chear et al., 2021). Notably, 7-hydroxymitragynine has demonstrated significantly higher agonist potency than morphine, positioning it as a promising candidate for the development of plant-derived analgesics (Kruegel et al., 2019).

Historically, *Mitragyna speciosa* has been widely utilized in ethnomedicinal practices across Southeast Asia, particularly in Thailand, Malaysia, and Indonesia. In Thailand, Kratom leaves are traditionally chewed by laborers to enhance energy and stamina during fieldwork. In Malaysia and West Kalimantan, Indonesia, the leaves are brewed as tea to relieve pain, fatigue, and symptoms of diarrhea. Additionally, Kratom has been used as a traditional remedy for opioid withdrawal and as a natural sedative alternative (Cinosi et al., 2015). Thai folk medicine also employs *M. speciosa* leaves to treat cough, diarrhea, hyperglycemia, and pain (Nakaphan et al., 2016).

Table 1. Geographical variation in Kratom phytochemistry.

No	Location/ Country	Sample Type	Cultivation	Mitragynine Content	Notes	Reference
1	Kedah & Penang Malaysia	Fresh leaves	Cultivated	9.38-18.85 mg g^{-1}	Other alkaloids: corynoxine; corynoxine B; isospeciofoline; mitragynine oxindole B; corynantheidine; speciogynine; paynantheine; speciociliatine; speciociliatine N(4)-oxide; 7-hydroxymitragynine; isocorynantheidine; ajmalicine; mitraphylline	(Chear et al., 2021)
2	Malaysia	Mature leaves	Not specified	318.3 mg (± 12%) of total alkaloid	other alkaloids: 7α-hydroxy-7h-mitragynine; speciogynine; (+)-pinoresinol; mitralactonal; speciociliatine; paynantheine; mitragynaline; 3,4, 5,6-dehydromitragynine; mitrasulgynine	(Takayama et al., 1998)
3	United States	Young plants (<5 years)	Cultivated	8 mg (0.044%)	Dominant alkaloid: mitraphylline (24 mg) Other alkaloids: ajmalicine; corynantheidine; 7-hydroxymitragynine; isomitraphylline; paynantheine; isocorynantheidine	(León et al., 2009)
4	Kalimantan, Indonesia	Mature leaves	Wild	13.94-17.69 mg g^{-1} (leaf powder), 15.87-48.52 mg g^{-1} (ethanolic extract)	High mitragynine content observed in wild plants	(Novianry et al., 2024)
5	Kalimantan, Indonesia	Mature leaves	Not specified	1.4% (leaf powder) 4.5%-5.03% (crude extract) 38.56%-45.86% (alkaloid extract)	Includes paynantheine, speciogynine, speciociliatine	(Bayu et al., 2024)
6	Indonesia	Not specified	Not specified	0.37%-1.70% (leaf powder)	-	(Tanti et al., 2021)
7	Thailand	Mature leaves Plant age 5 to 25	Cultivated	7.5-26.6 mg g^{-1}	-	(Leksungnoen et al., 2022)

		years				
8	Thailand	Plant age 3 to 60 years	Cultivated	0.39%-3.46%	Includes paynantheine, speciogynine	(Sengnon et al., 2023)

Numerous studies have explored the pharmacological potential of Kratom leaves through in vitro, in vivo, and ethnographic approaches. While these studies confirm diverse activities such as anti-inflammatory and analgesic most evidence derives from preclinical models (Kafo et al., 2024; Rahmawati et al., 2024; Tuntiyasawasdikul et al., 2024; Alford et al., 2025; Mahaprom et al., 2025; Sornsenee et al., 2025). Kratom has also demonstrated sedative properties, as evidenced by experimental studies that reported central nervous system, depressant effects and traditional uses supporting its calming potential (Prasetya & Sudarwati, 2023; Obeng et al., 2024). In addition, several investigations have highlighted its anti-obesity activity, showing that Kratom extracts may influence metabolic regulation and body weight control in preclinical models (Janthongkaw et al., 2023; Pansai et al., 2024; Tampanna et al., 2025). Evidence of anti-cancer potential has also emerged, with in vitro and in silico studies demonstrating cytotoxic and antiproliferative effects against selected cancer cell lines, including those derived from lung cancer and brain cancer (Viwatpinyo et al., 2023; Bayu et al., 2024; Priatna et al., 2025) . Finally, Kratom has been increasingly studied in the context of opioid cessation, where observational and early clinical studies suggest its possible role as a harm-reduction tool, though methodological limitations and regulatory concerns still constrain firm conclusions (Romeu et al., 2020; Singh et al., 2020, 2023). This wide-ranging pharmacological activity reflects the plant's intricate phytochemical composition. Consequently, understanding the environmental factors influencing the synthesis and concentration of bioactive compounds is essential for elucidating the variability in *M. speciosa*'s biological effects and ensuring consistency in its quality and efficacy as a medicinal plant.

Phytochemical variation of *Mitragyna speciosa* across geographical regions

Comparative analysis across various geographical regions reveals substantial variation in the mitragynine content of *Mitragyna speciosa* leaves. As summarized in Table 1, samples originating from Southeast Asia such as Thailand and Malaysia generally exhibited higher and more consistent levels of mitragynine. In contrast, cultivated specimens from the United States showed markedly lower concentrations, averaging approximately 0.044%. In these samples, mitraphylline was reported as the dominant alkaloid, which differs significantly from the mitragynine, dominant profiles typically found in Asian specimens. Notably, wild-harvested plants from Kalimantan, Indonesia, demonstrated relatively high mitragynine content, suggesting that natural tropical conditions may play a pivotal role in promoting the biosynthesis of mitragynine, as opposed to cultivated environments outside the species' native habitat.

Beyond Asia, the genus *Mitragyna* is also found across the African continent, although represented by distinct species. For instance, *M. stipulosa*, *M. ciliata*, and *M. inermis* are native to West Africa, and their alkaloid profiles include compounds such as rotundifoline, isorotundifoline, rhynchophylline, isorhynchophylline, mitraphylline, ciliaphylline, and speciophyllin. In East Africa, *M. robustipulata* has also been identified, with its leaves containing rotundifoline, isorotundifoline, rhynchophylline, isorhynchophylline, mitraphylline, and isomitraphylline (Shellard, 1983). This species diversity emphasizes that while the *Mitragyna* genus is pantropical in distribution, its phytochemical profile is highly species-specific and environmentally dependent.

Table 2. Effects of light exposure, climate, and seasonal factors on the alkaloid content and growth of *Mitragyna speciose.*

No	Environmental Factor	Condition / Treatment	Impact	Location	Reference
1	Season	Comparison between rainy and dry seasons	Highest mitragynine (MG) content (up to 4.94% w/w) at end of dry season; broader and greener leaves; rainy season reduces MG content (to 0.74%)	Thailand	(Sengnon et al., 2023)
2	Rainfall and precipitation	Seasonal variation	Ideal rainfall <800 mm; mitragynine content decreases with high precipitation; June identified as optimal period	Thailand	(Sengnon et al., 2023)
3	Sunlight exposure	Medium to full sunlight	Cool and dry season leads to lower alkaloid content	Thailand	(Sengnon et al., 2023)
4	Light intensity	18 MJ $m2^{-1}$ per jam	Larger stem circumference and plant height; broader leaves; mitragynine content 18–21 mg g^{-1}	Thailand	(Leksungnoen et al., 2022)
		Greenhouse shaded (~40% light, ~25% full sunlight) vs. non-shaded vs. direct sun	Mitragynine content 31-40% higher under GH-shaded conditions; highest total chlorophyll, plant height, leaf size under GH-shaded; 35% higher paynantheine; 2x corynoxine concentration vs. other conditions	United States	(Zhang et al., 2022)
5	High light intensity	1200 µmol m^{-2} s^{-1}	Highest total dry mass (incl. stems: 23.83 ± 6.92 g); higher leaf thickness (0.20 ± 0.03 mm)	Thailand	(Leksungnoen et al., 2025)
6	Average temperature	25°C to 28°C	Highest mitragynine content recorded within this temperature range	-	(Leksungnoen et al., 2022; Zhang et al., 2022)

Light exposure, climate, and seasonal factors

Referring to Table 2, the analysis of various environmental conditions highlights the central role of climatic dynamics in influencing the variability of alkaloid content in *Mitragyna speciosa*. The plant's differential responses to seasonal shifts, temperature fluctuations, and variations in light intensity have been consistently observed across multiple study locations. These significant environmental effects are reflected not only in the accumulation of mitragynine but also in key morphological traits such as leaf area, stem height, and total biomass. The interplay among these environmental parameters appears to modulate the physiological efficiency of the plant in synthesizing secondary metabolites. Notably, variations in light treatment (whether through natural intensity or artificial shading) produce measurable effects on both the primary and secondary alkaloid concentrations. Taken together, these findings underscore the critical importance of controlled environmental conditions in optimizing alkaloid production in Kratom cultivation.

Table 3. Effects of nutritional and growing media factors on growth and alkaloid content in *Mitragyna speciose.*

No	Nutritional / Growing Media Factor	Condition / Treatment	Impact on Plant and Alkaloids	Reference
1	Soil type	Mineral soil (alluvial, red-yellow podzolic soil) vs peat soil	Peat soil has high porosity and elevated N and P content, supporting superior vegetative growth. Addition of dolomite lime and chicken manure improves plant height, leaf number, and dry weight.	(Edi et al., 2024; Rossalinda et al., 2024)
2	Soil element content	High Ca and Mg content	Increases mitragynine content	(Leksungnoen et al., 2022; Sengnon et al., 2023)
3	Soil pH	pH 4-6 (acidic)	Optimal zone for growth and alkaloid accumulation	(Edi et al., 2024; Leksungnoen et al., 2022; Sengnon et al., 2023)
4	Soil water content (volumetric & retention)	High	Positively associated with increased mitragynine levels	(Leksungnoen et al., 2022; Sengnon et al., 2023)
5	Soil water potential	−0.03 MPa vs −0.7 MPa	High water potential (−0.03 MPa) improves plant height and stem biomass. Medium potential (−0.4 MPa) yields highest MG content (0.63% w/w)	(Leksungnoen et al., 2025)
6	NPK fertilizer dosage	Application of Osmocote Plus (N, P, K) 15-9-12 (doses: 0, 46, 74, and 96 g per container)	High doses increase mitragynine content (up to 2.58% per plant); enhance plant height, leaf number, leaf area, SPAD value*, and photosynthetic efficiency; minor alkaloids highest at low to moderate doses	(Zhang et al., 2020)
7	Nutrient composition	Macronutrients (N, P, K, Ca, Mg) and micronutrients (Fe, Mn, Zn, Cu)	Increases mitragynine, paynantheine, and total alkaloid content	(Sengnon et al., 2023)
8	Liquid organic fertilizer	150 ml L^{-1}	Enhances leaf number, root and shoot dry weight; no significant effect on plant height, leaf area, and chlorophyll content	(Antoni et al., 2023)

*SPAD value = an index of relative chlorophyll concentration using SPAD device meter.

Nutritional and growing media factors

Table 3 demonstrates that both growing media and nutrient availability significantly influence vegetative growth and alkaloid accumulation in *Mitragyna speciosa*. Plants cultivated in peat-based media exhibit superior vegetative performance, characterized by increased plant height, leaf number, root volume, and total dry biomass. This advantage is attributed to the physical and chemical properties of peat soils, such as high porosity and abundant nitrogen and phosphorus content. Soil pH within the mildly to moderately acidic range (pH 4–6) was shown to support both optimal growth and alkaloid accumulation. Additionally, soil water potential and its moisture retention capacity contributed to higher mitragynine content. Fertilization (both organic and inorganic) enhanced biomass parameters and physiological efficiency. Although alkaloid concentration per unit leaf weight did not always increase proportionally, total alkaloid content per plant improved as biomass increased under moderate to high fertilization regimes. Furthermore, minor alkaloids such as paynantheine and corynantheidine also increased depending on nutrient composition and dosage. These findings underscore the importance of nutrient and substrate management as key strategies in optimizing high-quality Kratom raw material production.

Table 4. Internal factors affecting *Mitragyna speciosa.*

No	Internal Factor	Treatment	Part / Condition Analyzed	Results	Reference
1	Plant part	Leaves, stems, and twigs	Phytochemical content by plant part	Leaves and stems contain alkaloids, steroids, quinones, saponins, tannins; twigs contain alkaloids, quinones, saponins	(Sofia et al., 2022)
		Roots and stems	Phytochemical content by plant part	Roots contain alkaloids, phenols, terpenoids, flavonoids, tannins, saponins; stems contain alkaloids, phenols, steroids, terpenoids, flavonoids, tannins	(Putri et al., 2023)
		Leaves, stems, bark, and roots	Alkaloid profile by plant organ (via LC-MS)	Mitragynine, speciogynine, paynantheine, speciociliatine dominant in leaves; lower in stems and bark; not detected in roots	(Schotte et al., 2023)
2	Leaf age	Young vs. mature leaves	Top 2 leaves vs. 7-10th leaves from shoot tip	Mature leaves had 1.2x higher mitragynine and 3.3x higher 7-hydroxymitragynine; 86 metabolites shared, 5 unique to each leaf type	(Veeramohan et al., 2023)
		Five developmental stages (S1–S5)	S1 (7-15 days) S2 (15-30 days) S3 (30-45 days) S4 (45-60 days) S5 (60-75 days)	Highest mitragynine in S1-S2; highest chlorophyll, carotenoids, stomatal density in S5; antioxidant activity increased with age	(Phromchan et al., 2024)
3	Variety/strain	Strain comparison/ vein leaf colors	Red Malay, Red Bali, Red Thai, Green Malay, White Borneo	Green Malay had highest mitragynine (59.7%) and total alkaloids (94.9%); White Borneo had highest extract yield (12.2 mg g^{-1})	(Boffa et al., 2018)
			Red, green, white Indonesia	White strain had highest ethanol extract yield (18.74%); all contained alkaloids, flavonoids, tannins, saponins, phenols, triterpenoids	(Masriani et al., 2023)
			Red dan green Thai	Green Thai had highest mitragynine (63.60 mg g^{-1}); both contained rutin and quercetin	(Janthongkaw et al., 2023)
			Red vein vs White vein (Pho Thong strain)	White strain had higher mitragynine (39.79 mg g^{-1} ± 1.81); both had rutin and quercetin	(Nawaka et al., 2025)
			Green vein Bali, Maeng Da, Red Indo, Red Borneo	Green strains had higher mitragynine (42.29-52.81 mg g^{-1}) than red strains (26.68%-33.84 mg g^{-1})	(Ng & Ha, 2024)

In addition to external environmental influences, alkaloid content in *Mitragyna speciosa* is also determined by internal factors, including anatomical structure, organ maturity, and genetic variation. Different plant organs (roots, stems, and leaves) exhibit uneven distribution of alkaloids. Leaf maturity further influences the concentration of active compounds, with specific developmental stages linked to peak alkaloid levels. Genetic factors, such as strain or variety, also shapen the alkaloid profile; plants with different leaf vein colors (e.g., red, green, or white) have been reported to contain varying ratios of mitragynine and other alkaloids. These phenotypic differences reflect the complex interplay between genetic background and environmental conditions, which ultimately influence the plant's phytochemical composition and pharmacological potential. Therefore, precise selection of plant parts and varietal identification are essential steps for standardizing and developing evidence-based Kratom products. A summary of these internal determinants and their phytochemical implications is presented in Table 4.

As a member of the Rubiaceae family, *Mitragyna speciosa* (Kratom) exhibits significant potential as a high-value agricultural commodity. Over the past decade, global demand for Kratom products has increased substantially, particularly in markets such as the United States and Europe, positioning this plant as an emerging botanical commodity. Its derivatives are now widely available in various forms, including powders, capsules, teas, and liquid concentrates, reflecting diversified usage driven by its unique physiological effects, acting as a stimulant at low doses and as a sedative-analgesic at higher doses (Singh et al., 2019). This trend presents strategic opportunities for tropical Kratom-producing countries, such as Indonesia, Thailand, and Malaysia, to advance cultivation systems and product development. Nevertheless, the industry continues to face challenges, notably the variability in active compound content caused by environmental factors, genetic diversity, and the lack of established quality standards and regulatory frameworks.

The chemical composition of *Mitragyna speciosa* reflects the complexity of tropical secondary metabolism, which generates not only a dominant bioactive compound but a synergistic phytochemical profile (Hassan et al., 2013). Mitragynine, the primary alkaloid, is recognized for its major pharmacological activities (Utar et al., 2011; Suhaimi et al., 2016; Yunusa et al., 2023; Obeng et al., 2024). However, the presence of other alkaloids such as 7-hydroxymitragynine, speciogynine, paynantheine, and speciociliatine contributes complementary biological effects. For instance, speciogynine has been shown to significantly reduce mechanical allodynia in cancer-induced bone pain models (Ortiz et al., 2024), while mitraphylline and rhynchophylline exhibit mild modulatory activity on the opioid system (Sudmoon et al., 2025). In vivo studies have further revealed that 7-hydroxymitragynine possesses strong analgesic potential at doses of 17.8 mg/kg, acting as a partial μ-opioid receptor agonist with 41% efficacy in [^{35}S]GTPγS binding assays (Calvache et al., 2021). In addition to alkaloids, the presence of flavonoids, phenols, tannins, and saponins also supports antioxidant and immunomodulatory functions. These synergistic interactions align with the polycomponent pharmacodynamics principle in phytopharmaceutical development (Saleh et al., 2012; Zailan et al., 2022; Masriani et al., 2024; Phromchan et al., 2024; Sornsenee et al., 2025).

The distribution of bioactive compounds in Kratom is spatially regulated, with leaves serving as the principal site of accumulation. This pattern is supported by studies on other plant species. In *Pterocarpus erinaceus*, phytochemical analysis revealed that leaf tissues contain significantly higher levels of bioactive compounds such as proteins, flavonoids, phenols, and saponins, compared to stems and roots (Alagbe et al., 2024). Separately, methanolic leaf extracts of *Moringa oleifera* have demonstrated the strongest antipyretic activity relative to extracts from stems and roots, with efficacy that approached or even exceeded that of the positive control (Jamil et al., 2025). In Kratom, metabolomic profiling confirms the presence of mitragynine, speciogynine, paynantheine, and speciociliatine in leaf tissue, while roots and stems predominantly contain biosynthetic precursors like strictosidine. The biosynthesis of mitragynine follows a monoterpenoid indole alkaloid pathway originating from strictosidine aglycone, catalyzed by stereospecific enzymes such as MsDCS1, MsDCS2, and MsEnolMT. Rational enzyme modifications have been shown to alter biosynthetic outputs, although mitragynine remains the predominant product due to its structural stability and efficient conversion (Schotte et al., 2023).

Leaf maturity also plays a crucial role in alkaloid accumulation. Studies have demonstrated that fully developed leaves, particularly in developmental stages S2 to S4 (15–60 days), exhibit the highest mitragynine concentrations, with stage S3 (30–45 days) identified as the optimal harvest window (Phromchan et al., 2024). Similar trends are observed in *Mangifera indica*, where bioactive content (mangiferin) declines with leaf aging (Nguyen et al., 2024). Additionally, vein color, a common phenotypic trait used to classify Kratom strains into red, green, and white has been linked to distinct alkaloid profiles. This variation is likely associated with inherited pigmentation traits and underlying differences in metabolic activity and biosynthetic capacity (Deng & Harbaugh, 2006; Kan et al., 2021). Differences in *Mitragyna speciosa* strains or varieties are also utilized by users to achieve specific pharmacological effects. Red vein Kratom is commonly used for its relaxing properties, green vein for pain relief, and white vein for its stimulant effects. However, analyses of several commercial Kratom products have reported no significant differences in mitragynine content across these strains (Huisman et al., 2023). This observation aligns with findings from previous studies, which also showed that the variation in mitragynine levels among red, green, and white strains was relatively minor (Boffa et al., 2018; Smith et al., 2024).

Beyond internal factors, phytochemical accumulation is profoundly influenced by geography and environmental conditions. Variables such as temperature, rainfall, light intensity, and photoperiod collectively shapen ecophysiological dynamics and gene expression (Kumar et al., 2017; Georgescu et al., 2022; Saravanakumar et al., 2022). In Southeast Asia, stable tropical climates with average temperatures of 25–28°C, high humidity, and filtered sunlight are optimal for alkaloid biosynthesis. In contrast, plants cultivated in subtropical regions such as the United States exhibit lower mitragynine levels and higher concentrations of alternative alkaloids like mitraphylline (León et al., 2009). A comparative study of *Euphorbia hirta* from Ethiopia and India revealed that, although both samples contained similar phytochemical constituents, the ethanolic extract from the Indian specimen exhibited greater compound diversity, with GC-MS identifying 15 compounds in the Indian sample compared to 12 in the Ethiopian one (Saravanakumar et al., 2022). Another comparative study on eight types of berries showed that specimens from Romania consistently exhibited higher total phenolic content (TPC) and radical scavenging activity (RSA) than those from Russia (Georgescu et al., 2022). These findings underscore the critical role of geographic factors, including agroclimatic conditions and local growing environments, in influencing the synthesis and accumulation of secondary metabolites, the overall phytochemical composition, and the biological activity of plants. Nevertheless, controlled greenhouse environments can offset ecological limitations, enabling competitive mitragynine yields even outside the native habitat (Zhang et al., 2022).

Climatic variables not only serve as environmental inputs but also as molecular signals regulating biosynthetic gene expression. For instance, light influences both photosynthesis and secondary metabolite synthesis through photoreceptors and redox signaling pathways (Thoma et al., 2020; Borbély et al., 2022). In *Aloe vera*, plants grown in highland semi-arid agroclimates exhibit antioxidant activity 10–12% higher than those from humid tropical zones, supporting the impact of light and temperature on metabolite production (Kumar et al., 2017). Precision agronomic strategies, including light and temperature management, thus become essential for maximizing alkaloid biosynthesis in Kratom.

The availability of nutrients and the characteristics of the growing medium are key agronomic determinants that influence the efficiency of secondary metabolism in *Mitragyna speciosa*. Nutritional imbalance not only affects morphological parameters but also disrupts the biosynthetic pathways of alkaloids involving specific enzymes such as strictosidine synthase and cytochrome P450 monooxygenase (Nguyen & Dang, 2021; Kim et al., 2023). Both macro- and micronutrients including nitrogen, phosphorus, magnesium, and calcium support alkaloid biosynthesis by serving as precursors and essential enzymatic cofactors (Hank et al., 2003; Qi et al., 2024). Soil pH further influences nutrient availability, with acidic soils impeding the uptake of key elements like phosphorus and iron (Huang et al., 2023; Yang et al., 2024). Peat-based soils, characterized by high porosity, elevated organic matter, and strong water-holding capacity, provide ideal microecological conditions for Kratom growth. Studies in Kapuas Hulu, Indonesia, showed that Kratom grown near peatlands (580–650 meters from riverbanks) exhibited higher mitragynine content (15.49%) and improved morphological traits compared to plants near water sources (Pramulya et al., 2024). These outcomes are attributed to low pH, high C-organic content, and superior cation exchange capacity (Hikmatullah & Sukarman, 2014; Cao, 2019).

Considering the diverse endogenous and exogenous factors influencing the alkaloid biosynthetic pathways, standardizing Kratom quality requires a systemic approach that integrates plant genetics, physiology, and environmental management. Genetic diversity has been shown to contribute to chemotypic variation and differential alkaloid accumulation across populations of *Mitragyna speciosa* (Leksungnoen et al., 2022; Manwill et al., 2022). Moreover, leaf developmental stage and harvesting phase significantly influence the phytochemical profile, with mature leaves generally containing higher levels of mitragynine and related alkaloids compared to younger tissues (Veeramohan et al., 2023; Phromchan et al., 2024). Findings from multiple studies suggest that a combination of superior cultivars, optimal harvesting phases, and favorable edaphoclimatic conditions such as stable temperatures, moderate light intensity, and growing media with high cation exchange capacity (e.g., managed peat) can maximize the accumulation of mitragynine and other supporting bioactive compounds (Hikmatullah & Sukarman, 2014; Zhang et al., 2020; Edi et al., 2024; Chongdi et al., 2025). Therefore, an adaptive agroecological cultivation strategy serves as a critical foundation for developing *Mitragyna speciosa* into a sustainable and evidence-based global phytopharmaceutical commodity.

CONCLUSION

The phytochemical profile of *Mitragyna speciosa* is determined by the interplay of intrinsic factors such as organ type, leaf maturity, and genetic variability, together with extrinsic variables including light exposure, temperature, soil characteristics, and nutrient availability. Mitragynine remains the dominant alkaloid underpinning its pharmacological activity, while synergistic contributions from minor alkaloids and non-alkaloid metabolites reinforce the plant's multicomponent bioactivity. These findings emphasize the need for precision cultivation strategies guided by ecophysiological data to achieve consistent quality in Kratom leaf biomass as raw material for phytopharmaceutical development. Nevertheless, challenges such as high genetic variability and regulatory heterogeneity may hinder large-scale consistency. Future studies should therefore focus on controlled cultivation systems that integrate optimized environmental parameters, multi-location and cross-country cultivation trials to assess genotype, environment interactions, and standardized post-harvest protocols to ensure reproducible phytochemical outcomes. Collectively, these efforts could strengthen the scientific basis for the sustainable cultivation and global utilization of *M. speciosa* as a strategic herbal commodity.

Conflict of interest

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