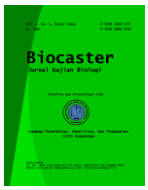

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IMMUNOMODULATORY AND ANTIDIABETIC POTENTIAL OF KRATOM (*Mitragyna speciosa*) ON ANIMAL MODELS: POTENTIALS AND FUTURE RESEARCH

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ABSTRACT: Kratom (*Mitragyna speciosa*) has been traditionally used for its analgesic and stimulant properties. Recent preclinical studies suggesting its potential as an anti-inflammatory and antidiabetic agent. A comprehensive search of PubMed, ScienceDirect, and Google Scholar (2010-2024) using keywords "Kratom", "inflammation", and "diabetes" identified 82 studies. After applying inclusion criteria (original research, English/*Bahasa* Indonesia, in vivo animal models investigating anti-inflammatory/antidiabetic effects) and excluding reviews, in vitro studies, and conference abstracts, 14 studies comprising 9 key articles on the pharmacological activities of Kratom were analyzed. Dosages ranged from 0,5 mg/g to 500 mg/kg across various extraction methods and treatment durations. Studies show that Kratom extracts can inhibit pro-inflammatory cytokines (IL-1β, TNF-α) via NF-κB, COX-2, and MAPK/ERK pathways. In diabetic models, Kratom reduced blood glucose levels by 15-45%, improved glucose tolerance, and enhanced antioxidant status. Aqueous and ethanolic extracts showed comparable efficacy, with optimal effects observed at 100-200 mg/kg doses. Despite these findings, safety concerns remain regarding toxicity, dependence, and drug interactions. Further toxicological studies and clinical trials are essential to validate its therapeutic potential. This review highlights the need for comprehensive research and regulatory evaluation to support the safe medicinal use of Kratom.

Keywords: Animal Models, Antidiabetic, Immunomodulatory, *Mitragyna speciosa*.

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INTRODUCTION

Kratom (*Mitragyna speciosa*) is a tropical tree indigenous to Southeast Asia, where it has been traditionally utilized for its medicinal properties. Historically, the leaves of Kratom have been employed for various purposes, including analgesia, treatment of diarrhea, and as a stimulant to enhance productivity among laborers (Cinosi et al., 2015; Kruegel & Grundmann, 2018; Raslina et al., 2018). The pharmacological profile of Kratom is complex, primarily due to the presence of over 40 alkaloids, with mitragynine and 7-hydroxymitragynine being the most extensively studied (Begum et al., 2024; Hanapi et al., 2021). These alkaloids interact with multiple receptors in the body, including opioid receptors, which

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contribute to both stimulant and sedative effects depending on the dosage (Henningfield et al., 2018; Kruegel et al., 2019).

Recent scientific investigations have expanded interest in Kratom beyond its traditional analgesic and stimulant roles, revealing promising anti-inflammatory and antidiabetic properties. Studies using rodents models have demonstrated that both aqueous and ethanolic extracts of Kratom exhibit significant anti-inflammatory and analgesic effects. The plant's ethanolic extract demonstrated potent antidiabetic activities in rats with type 2 diabetes, improving glucose tolerance, lipid profiles, and markers of oxidative stress (Zhang et al., 2023). Experiments conducted on Swiss albino mice revealed that Kratom extracts significantly reduced blood glucose levels during an oral glucose tolerance test. In addition, in silico investigations have identified four major alkaloids (Mitragynine, Corynantheidine, Corynoxine, and Speciociliatine) that exhibited high binding affinity to the DPP4 receptor, suggesting a potential molecular basis for antidiabetic mechanisms (Hossain et al., 2023).

Previous literature studies have examined various effects of Kratom on both animals and humans, as well as related aspects. Singh et al. (2016) discusses the differences between traditional and non-traditional uses of Mitragynine (Kratom) in Southeast Asia and Western countries. Brown et al. (2017) examined the botanical, phytochemical, and ethnomedicinal aspects of the Mitragyna genus, particularly *Mitragyna speciosa* (Kratom), and their implications for products marketed as Kratom are examined. Other reviews, including those by Chin & Lee (2018), Ni'ma (2024), and Heywood et al. (2024), focused primarily on Kratom's sedative effects, toxicity, or potential for dependence, often relying on computational predictions or anecdotal evidence. Although interest in Kratom has led to an expanding collection of research, there remains a lack of comprehensive reviews focusing specifically on its immunomodulatory and antidiabetic effects, especially those derived from animal model studies.

This review aims to systematically evaluate and synthesize current evidence from in vivo studies using animal models investigating the potential immunomodulatory and antidiabetic effects from Kratom. This study seeks to clarify Kratom's therapeutic prospects, highlight existing safety concerns, and identify knowledge gaps that warrant further research. By focusing on preclinical models, this study offers novel insights into Kratom's potential role in managing metabolic and inflammatory conditions, a perspective requiring further research to support its safe and effective application in modern medicine.

METHODS

A comprehensive literature review was conducted to examine the potential of Kratom (*Mitragyna speciosa*) as an immunomodulator and antidiabetic agent. This literature review was conducted in accordance with the PRISMA 2020 guidelines to evaluate the immunomodulatory and antidiabetic potential of *Mitragyna speciosa* (Kratom) based on preclinical evidence in animal models. The literature search encompassed national and international articles published between 2015 and 2025, accessed through the Google Scholar, SINTA, Research Gate, PubMed, and Science Direct databases. These sources provide current information

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on findings related to antidiabetic and anti-inflammatory properties, particularly in animal models. The key search terms included "Kratom", "*Mitragyna speciosa*", "anti-inflammatory", "immunomodulatory", "cytokines activity", "antidiabetic", "blood glucose" and "animal models". During the literature search phase, articles were selected based on the presence of relevant keywords in the title, abstract, and content in accordance with predetermined criteria for inclusion in this literature review.

The inclusion criteria were as follows: original research articles published in English or *Bahasa* Indonesia, utilizing in vivo animal models, and investigating the anti-inflammatory or antidiabetic effects of *Mitragyna speciosa*. Excluded materials comprised reviews, in vitro or in silico studies, conference abstracts, and publications unrelated to inflammation or diabetes. Data extraction was performed to collect relevant details from each study, including study design, animal species, Kratom extract type and dosage, administration route, treatment duration, and primary outcomes related to cytokine expression or glycemic regulation. A critical analysis was conducted to compare the effective doses from prior studies in animal models with those found in Kratom natural compounds. The extracted data were systematically organized into summary tables to facilitate cross-study comparisons. This process helped highlight similarities and differences between the studies. PRISMA flow chart shown in Figure 1.

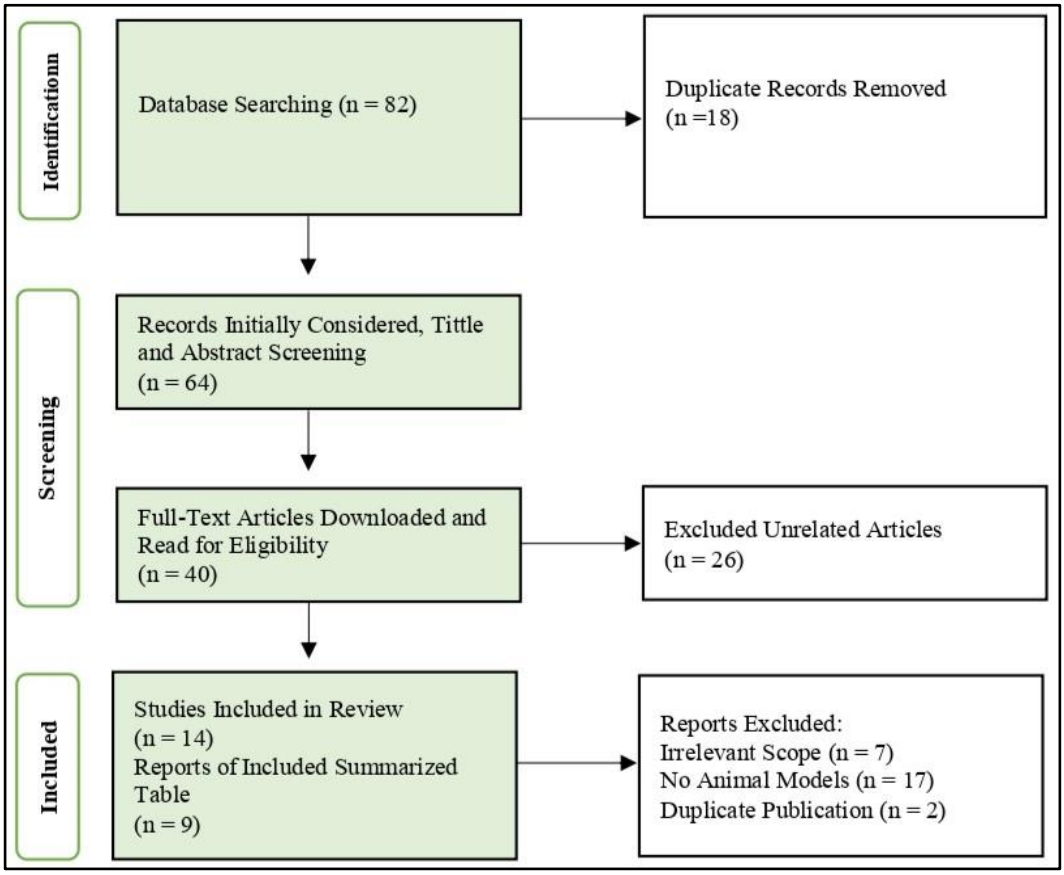

Figure 1. PRISMA Flow Chart. Reference Selection Focused on Pharmacological Potential of *Mitragyna speciosa*.

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The search yielded a total of 82 records. After the removal of 18 duplicate entries, 64 articles were screened based on titles and abstracts. Of these, 26 articles were excluded for not meeting the inclusion criteria. The full texts of 40 articles were assessed for eligibility, all of which were successfully retrieved. 26 full-text articles were excluded during this phase due to irrelevant scope (n = 7), absence of animal models (n = 17), or duplicate publication (n = 2). Ultimately, 14 articles met all eligibility criteria, with 9 key articles discussed in greater depth and their data systematically summarized in tables.

RESULTS AND DISCUSSION

Phytochemical Composition and Pharmacological Properties of *Mitragyna speciosa*

Kratom, scientifically known as *Mitragyna speciosa*, encompasses various psychoactive substances, with mitragynine being the principal alkaloid. In the United States, individuals typically consume the plant's leaves as powders or tea for medicinal purposes, including potential opioid withdrawal management. Additional significant alkaloids in Kratom include speciogynine, speciociliatine, paynantheine, and corynantheidine (Melchert et al., 2023). Despite Kratom's increasing prevalence for its potential therapeutic applications, concerns exist regarding the heavy metal content in Kratom products. Research examining 27 Kratom products revealed that certain Kratom tea samples contained manganese levels up to 20 times the acceptable upper intake limit, potentially causing manganism, a condition characterized by Parkinsonian Symptoms (Fleming et al., 2023). This finding underscores the necessity for more stringent regulations on Kratom products to address public health concerns. Structural arrangements of specific indole alkaloids present in Kratom extracts shown in Figure 2.

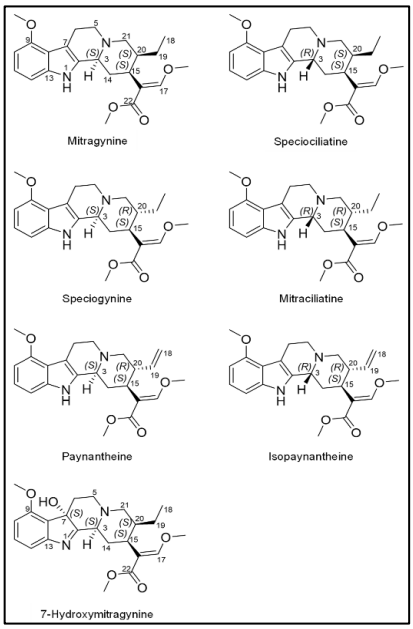

Figure 2. Structural Arrangements of Specific Indole Alkaloids Present in Kratom Extracts. The Compound 7-Hydroxymitragynine Functions as an Essential Active Breakdown Product of Mitragynine (Tanna et al., 2023).

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Regarding pharmacological characteristics, Kratom alkaloids have demonstrated the potential for drug-drug interactions by inhibiting cytochrome P450s (CYPs) and Carboxylesterase-1 (CES1) (Melchert et al., 2023). Mitragynine and 7-hydroxy-mitragynine as seen on Figure 1, the primary psychoactive components, are responsible for Kratom's opioid-like effects (Fleming et al., 2023). Research has also indicated that the dopaminergic system plays a role in mediating Kratom reward and drug-seeking behavior, with the dopamine D1 receptor being crucial in the development of mitragynine-induced conditioned place preference in rats (Japarin et al., 2023). Although regular Kratom use may pose a risk for drug dependence and withdrawal symptoms, long-term traditional consumption of fresh Kratom leaves has not been associated with an increase in common health issues (Saingam et al., 2023).

Immunomodulatory Effects

Recent studies using an in vitro inflammation model specifically LPS-induced inflammation in RAW 264.7 cells have demonstrated that mitragynine, one of the primary alkaloids found in Kratom leaves, is capable of reducing the activity of pro-inflammatory cytokines (TNF-α and IL-6), inflammation-related enzymes (COX-2 and 5-LOX), as well as the production of reactive oxygen and nitrogen species (ROS and RNS) (Rahmawati et al., 2024). However, there is still a significant lack of studies exploring the anti-inflammatory potential of Kratom using animal models. In silico studies have identified mitragynine as the compound most likely responsible for the anti-inflammatory activity, demonstrating strong binding to human 5-lipoxygenase protein (Arief & Kurnianto, 2022). Although Kratom extracts have demonstrated efficacy in alleviating withdrawal symptoms in preclinical studies, concerns remain regarding their potential for dependence and cognitive side effects with prolonged use (Suhaimi et al., 2016).

Several studies have demonstrated the significant anti-inflammatory potential of Kratom through various doses on animal models which are summarized in Table 1. These investigations employed different animal models, such as *Rattus norvegicus*, *Mus musculus* (Balb/c) and Sprague-Dawley rats using carrageenan-induced inflammation and other immune-stimulating methods to induce inflammatory responses (Marampa et al., 2022; Mat et al., 2023; Salim et al., 2021). The dosage of Kratom extract varied across studies, ranging from 0,5 mg/g to 200 mg/kg, administered orally or intraperitoneally (i.p.). Different extraction methods were utilized, including methanolic, ethanolic extracts, and purified mitragynine. Findings indicate that Kratom significantly reduces inflammation and paw swelling through cytokine modulation (Marampa et al., 2022; Salim et al., 2021). Comparison of studies on inflammatory cytokines by Kratom revealed in Table 1.

Table 1. Comparison of Studies on Inflammatory Cytokines by Kratom on Animal Models.

Animal Models	Dose/Route	Major Findings	References
Male Rats (*Rattus norvegicus*)	75, 150, and 200 mg/kg of Kratom methanol extract, administered orally	Treatment with EMS (75, 150, and 200 mg/kg) led to a dose-dependent reduction in edema. Histological analysis demonstrated preserved skin	(Salim et al., 2022)

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Animal Models	Dose/Route	Major Findings	References
		thickness, indicating anti-inflammatory effects.	
Male Mice (*Mus musculus*) balb/c	0.5, 1, 2 mg/gr of Kratom exract administered orally	The 2 mg/g body weight dose of *Mitragyna speciosa* ethanol extract optimally inhibited mouse ear edema.	(Marampa et al., 2022)
Male and Female Sprague-Dawley Rats (250-300 g),	Mitragynine (1, 5, 10, 13, 15, 30 mg/kg i.p.)	Dose-dependent analgesic effect; ED50 = 3.62 mg/kg, ED95 = 20.84 mg/kg; 30 mg/kg mitragynine resulted in 99.5% writhing inhibition and reduced withdrawal behavior.	(Mat et al., 2023)
Male ICR Mice (*Mus musculus*) and Wistar Rats (*Rattus norvegicus*)	Kratom administered orally in doses of 125**,** 250, and 500 mg/kg for systemic effects.	Oral Kratom at 125–500 mg/kg demonstrated dose-dependent anti-inflammatory effects by decreasing carrageenan-induced paw edema in rats.	(Mahaprom et al., 2025)

Moreover, Kratom exerts anti-inflammatory effects on the Central Nervous System (CNS). Specifically, mitragynine has been shown to downregulate Transient Receptor Potential Vanilloid-1 (TRPV1) expression in the thalamus, somatosensory cortex, and periaqueductal gray, suggesting a role in pain modulation and thermoregulation. These analgesic effects are dose-dependent, with 99.5% pain inhibition at high doses (30 mg/kg) (Mat et al., 2023). Additionally, in *Nile tilapia*, Kratom exhibited potential as an alternative antibiotic, though higher doses negatively affected adaptive immune responses (Paankhao et al., 2024). These findings from several study with animal models suggest that Kratom possesses strong anti-inflammatory through the modulation of key inflammatory mediators and oxidative stress, making it a promising candidate for the treatment of chronic inflammation and antidiabetic properties.

Antidiabetic Effects

Various studies collectively indicate that Kratom exhibits differing levels of effectiveness in diabetes management depending on the experimental model used as summarized on table 2. Fitriyanti & Wati (2017) reported that ethanol extract of Kratom stem (EBMS) at 225 mg/kg BW did not significantly reduce blood glucose levels in streptozotocin-induced diabetic mice, contrasting with the positive control glibenclamide. However, subsequent studies showed more promising results. Diana & McClain (2021) found that extract *Mitragyna ciliata*, which belongs to the same genus as Kratom exhibited significant antihyperglycemic effects in alloxan-induced diabetic rats. Their research demonstrated dose-dependent (500 mg/kg and 1000 mg/kg) and time-dependent glucose reduction over 21 days, comparable to glibenclamide (0,5 mg/kg). The proposed mechanisms included decreased intestinal glucose absorption, enhanced peripheral glucose utilization, and improved glycogenesis and glycolysis. The proposed mechanisms included

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decreased intestinal glucose absorption, enhanced peripheral glucose utilization, and improved glycogenesis and glycolysis. Antidiabetic studies by Kratom are summarized in Table 2.

Table 2. Antidiabetic Studies by Kratom on Animal Models.

Animal Models	Dose/Route	Major Findings	References
Male Mice (*Mus musculus*) BALB/c Induced Streptozotocin (STZ Model).	Ethanol extract of Kratom stem (EBMS) at 225 mg/kg BW orally for 1 week.	EBMS at 225 mg/kg BW did not significantly lower fasting blood glucose levels.	(Fitriyanti & Wati, 2017)
Albino Rats (Alloxan-Induced Diabetes)	*Mitragyna ciliata* extract at 500 mg/kg and 1000 mg/kg BW, orally for 3 weeks	A significant antihyperglycemic effect was observed at both doses, 500 mg/kg and 1000 mg/kg, on blood glucose levels in hyperglycemic rats.	(Diana & McClain, 2021)
Diabetic Rats (High-Fructose + STZ Model)	Kratom extract (50 mg/kg, 200 mg/kg, oral) for 5 weeks	Administration of Kratom extract (50 and 200 mg/kg) significantly reduced elevated blood glucose levels as well as depressive and anxiety-like behaviors in diabetic rats, while enhancing antioxidant enzyme activities and suppressing TNF-α, IL-1β, and IL-6 cytokine levels.	(Chen et al., 2022)
Sprague-Dawley Rats (Fructose + STZ Model)	Kratom extract (100 mg/kg, 400 mg/kg, oral) for 5 weeks	Kratom administration in diabetic rats significantly improved body weight, blood glucose levels, glucose tolerance, dyslipidemia, hepatorenal biomarkers, and oxidative stress indices.	(Zhang et al., 2023)
Swiss Albino Mice (Alloxan-Induced Diabetes)	Kratom extract (200 mg/kg, 400 mg/kg, oral) at 60, 90, and 120 minutes post-glucose induction	Both doses of Kratom extract significantly lowered blood glucose, but showed no greater effect than glibenclamide (control).	(Hossain et al., 2023)

More recent studies have expanded our understanding of Kratom's therapeutic potential. Chen et al. (2022) investigated its effects in a high-fructose + STZ diabetic rat model, reporting that Kratom extract (50 mg/kg, 200 mg/kg) reduced blood glucose, oxidative stress, and inflammatory cytokines while improving antioxidant status in the brain. Zhang et al. (2023) corroborated these findings, demonstrating significant improvements in glucose tolerance, dyslipidemia, and hepatorenal biomarkers at doses of 100 mg/kg and 400 mg/kg. Notably, Hossain et al. (2023) combined in vivo and in silico approaches, revealing that Kratom extract (200 mg/kg, 400 mg/kg) significantly reduced blood glucose in alloxan-induced diabetic mice. Their molecular docking studies suggested that compounds like mitragynine, corynantheidine, corynoxine, and speciociliatine might act as DPP4 inhibitors, providing potential mechanistic insights into the plant's anti-diabetic properties. Additionally, Kratom extract demonstrated

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anxiolytic and antidepressant-like effects in diabetic rats, potentially by suppressing pro-inflammatory cytokines and improving brain oxidative status (Chen et al., 2022).

In vitro studies revealed that Kratom extracts, particularly the ethanol extract, inhibited α-glucosidase and pancreatic lipase activities. Mitragynine, the major constituent of Kratom, showed potent α-glucosidase inhibition and synergistic effects when combined with acarbose (Limcharoen et al., 2022). Increasing doses of Kratom from several related studies on diabetic animal model was correlate with reduced blood glucose levels. Kratom at high doses effectively reduces blood glucose levels in test animals (Chen et al., 2022; Diana & McClain, 2021; Hossain et al., 2023; Zhang et al., 2023). This systematic analysis reveals while early studies showed limited efficacy, more recent research suggests Kratom possesses significant anti-diabetic potential, acting through multiple mechanisms including glucose regulation, antioxidant effects, and potential DPP4 inhibition at the right dosage. These result suggest that Kratom may exert antidiabetic effects through multiple pathways including inhibition of digestive enzymes, modulation of pro-inflammatory cytokines, and enhancement of antioxidant defense.

Therapeutic Potential Direction and Future Research

Animal studies have demonstrated that mitragynine, the principal active constituent of Kratom, may have therapeutic potential. Research has elucidated its interaction with dopamine-related reward pathways, indicating its potential application in addiction treatment and pain management (Japarin et al., 2023). This research suggests that alkaloids derived from Kratom can elicit significant physiological effects in animal models, potentially including anti-inflammatory and antidiabetic effects. To eliminate redundancy, this section consolidates recommendations and emphasizes key priorities. Future research should focus on evaluating the specific anti-inflammatory and antidiabetic effects of Kratom extracts and their alkaloids in appropriate animal models. In addition, it is necessary to find the right and effective dose to increase the potential of Kratom as anti-inflammatory and anti-diabetic. This may involve examination of inflammatory markers, glucose metabolism, and insulin sensitivity in rodents with diabetes or inflammatory conditions. Furthermore, investigating the mechanisms of action, such as modulation of inflammatory mediators or glucose regulation pathways, is essential (Yuandani et al., 2024). It is imperative to acknowledge that, while Kratom exhibits promise (Figure 3**)**, careful consideration must be given to potential drug interactions and safety implications. Studies have demonstrated that Kratom extracts and alkaloids can inhibit enzymes such as Carboxylesterase-1 (CES1), which may influence drug metabolism (Melchert et al., 2023).

Consequently, comprehensive toxicological and pharmacokinetic studies in animal models are necessary to determine the therapeutic potential and safety profile of Kratom for anti-inflammatory and anti-diabetic effects, and clinical trials in humans are crucial to assess the efficacy and safety of Kratom-derived compounds for potential therapeutic applications. These trials should include rigorous evaluations of the dosage, administration routes, and long-term effects to establish a comprehensive understanding of the medicinal potential of the plant. Moreover, regulatory considerations and ethical implications must be carefully

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addressed before advancing Kratom -based treatments to human subjects given the plant's current legal status in many jurisdictions.

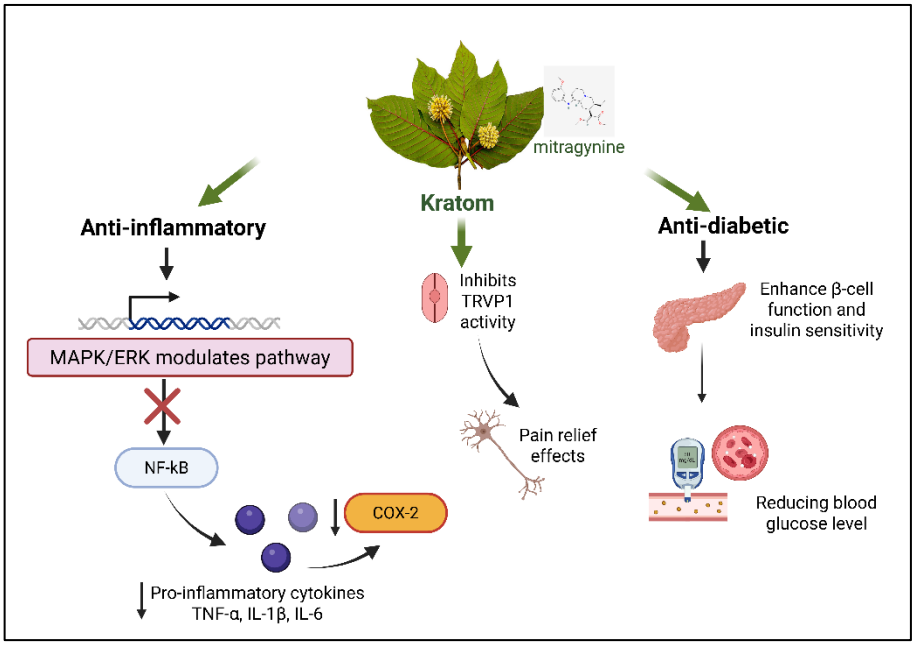

Figure 3. Multitargeted Effects of Kratom.

Additionally, clinical trials in humans are crucial to assess the efficacy and safety of Kratom -derived compounds for potential therapeutic applications. These trials should include rigorous evaluation of dosage, administration routes, and long-term effects to establish a comprehensive understanding of the plant's medicinal potential. Moreover, regulatory considerations and ethical implications must be carefully addressed before advancing Kratom -based treatments to human subjects, given the plant's current legal status in many jurisdictions. Clinical trials in humans are crucial to assess the efficacy and safety of Kratom-derived compounds for potential therapeutic applications. These trials should include rigorous evaluation of dosage, administration routes, and long-term effects to establish a comprehensive understanding of the plant's medicinal potential. Such studies should encompass a diverse range of participants to account for potential variations in responses based on factors such as age, gender, ethnicity, and pre-existing health conditions. Furthermore, researchers should investigate potential drug interactions and contraindications to ensure safe use of Kratom-derived treatments in combination with other medications. Ethical considerations should include addressing potential concerns related to addiction, abuse potential, and the impact on traditional communities that have historically used this plant.

Furthermore, comprehensive pharmacokinetic and pharmacodynamic studies should clarify the metabolic pathways and mechanisms of action of Kratom's active compounds. This knowledge is critical for predicting drug interactions, optimizing dosing regimens, and identifying biomarkers of response. This knowledge will be invaluable for predicting potential drug interactions, optimizing dosing regimens, and identifying potential biomarkers for treatment

response. Finally, as research progresses, it will be crucial to engage in public education and awareness campaigns to disseminate accurate information about Kratom and its potential therapeutic applications. This will help address misconceptions, reduce stigma, and foster informed discussions about the plant's role in modern medicine.

CONCLUSIONS

Mitragyna speciosa (Kratom) shows promising anti-inflammatory and anti-diabetic effects due to its alkaloid content. The plant extract suppresses pro-inflammatory cytokines through NF-κB, COX-2, and MAPK/ERK pathways, while mitragynine affects TRPV1 expression, contributing to its pain-relieving properties. In diabetic models, Kratom improves glucose tolerance, lowers blood sugar, and reduces oxidative stress. While these findings suggest potential therapeutic applications, currents evidence is limited to animal and *in vitro* studies. However, current evidence remains limited to preclinical studies. Safety concerns, including toxicity, dependence, and potential drug interactions, must be thoroughly addressed. Therefore, comprehensive toxicological assessments and well-designed clinical trials. With cautious advancement, Kratom may offer clinical value in managing inflammatory and metabolic disorders, however validating Kratom's therapeutic potential and ensuring its safe use in humans require careful evaluation supported by strong scientific evidence.

SUGGESTIONS

Although preclinical results are promising, further toxicological and clinical research is needed to evaluate safety, addiction potential, and drug interactions to better understand their specific molecular mechanisms. Standardization of extract dosage and formulation is essential, alongside long-term toxicological and drug interaction assessments. Kratom's traditional use is supported by its pharmacological complexity, highlighting the need for public education and careful therapeutic development. Considering all findings, Kratom's traditional use is supported by its complex pharmacological properties, with public education needed to discuss its future therapeutic potential.

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