From:	Drew Wolfson
To:	supplementalcomm@surfcity-hb.org; Andrew.gruel@surfcity.hb.org; Butch.twinning@surrfcity.hb.org; Casey.McKeon@surfcity.hb.org; Chad.willams@surfcity.hb.org; Don.kennedy@surfcity.hb.org; Grace.vandermark@surfcity.hb.org; Pat.burns@surfcity.hb.org
Subject:	7Oh scheduling
Date:	Saturday, August 30, 2025 9:23:57 PM

I write to you with sincerity and deep concern. The potential banning of 7-hydroxymitragynine (7-OH) would not only be a devastating blow to countless people who rely on it, but it could create a true public crisis. Not one person has died from this. I am a vendor in the public market im a software engineer worked for some of the top companies in the world. I wanted to make a difference in the world; so I joined this space. I lost countless friends due to the pandemic and precipitation drugs, I refuse to lost any more. Follow the science please;

For many, 7-OH has been a godsend — offering relief, stability, and a lifeline where other options have failed. It has helped people step away from far more dangerous substances, giving them a chance at a healthier, safer, and more productive life.

If access is taken away, the reality is that overdose rates will rise. Those who have found safety in 7-OH will be pushed back toward street drugs and high-risk alternatives. Instead of protecting people, such a ban would expose them to far greater harm.

This is not an abstract policy decision. It is about real lives — about mothers, fathers, sons, daughters, and friends who have found hope where there once was none. To remove that is to risk undoing years of progress in harm reduction and public health.

I urge you to consider the human cost. The people who rely on 7-OH are not statistics — they are our neighbors, family members, and community. This compound has been a bridge away from danger for so many, and banning it would close that bridge at the exact moment it is most needed.

With respect and sincerity,

Thank you,

Drew

NEW YORK, NY

DREWWOLFSON1@GMAIL.COM

516-662-8519

From:	wakeup777
To:	supplementalcomm@surfcity-hb.org
Subject:	Agenda Item 25-704 - Approve for Introduction Ordinance No. 4339 Prohibiting the Sale, Distribution and Possession of Kratom
Date:	Saturday, August 30, 2025 10:28:25 PM

Hello,

I'm reaching out in regards to Agenda Item 25-704 - Approve for Introduction Ordinance No. 4339 Prohibiting the Sale, Distribution and Possession of Kratom to be discussed during the September 2, 2025 Huntington Beach City Council meeting. I wanted to provide some feedback on what negative affects that the prohibition of selling and possessing of kratom could have.

Kratom is a plant that has been used for centuries in Southeast Asia. It is related to coffee as they are both flowering, sub-tropical plants in the Rubiaceae family. This is a plant that has an alkaloid called mitragynine. Mitragynine has pain relieving properties as it is a partial agonist of the mu-opioid receptor.

Because kratom is a partial agonist of the mu-opioid receptor, it has been shown to help people get off of illicit substances such as fentanyl and heroin and there have been countless testimonies from multitudes of people who have been given their lives back and have once again been brought back to living lives that are productive to society and productive for their families after being addicted and homeless from illicit substances. Making the sale and possession of kratom illegal will rob people in the future from having the potential of being saved from a life on the streets caused by addiction.

Kratom with its pain relieving effects also helps chronic pain patient who can't afford healthcare to manage their pain with a wholistic alternative. People who pay for insurance, sometimes cannot afford the copays, prescription costs or the lack of coverage for testing that insurance refuses to cover. Some people cannot afford to pay for insurance in the first place, much less copays, prescription costs and testing costs.

It is a fact that kratom causes far less respiratory depression than even FDA approved pharmaceuticals and opioids since it is a partial mu-opioid receptor agonist.

Please consider the treatment that this plant can provide for people to get off of illicit substances and for chronic pain patients to be given relief before making its possession and sale illegal. Thank you.

From: Dakota Crocker
To: supplementalcomm@surfcity-hb.org; Andrew.gruel@surfcity.hb.org; Butch.twinning@surrfcity.hb.org; Casey.McKeon@surfcity.hb.org; Chad.willams@surfcity.hb.org; Don.kennedy@surfcity.hb.org; Grace.vandermark@surfcity.hb.org; Pat.burns@surfcity.hb.org
Subject: The Benefit of Keeping 7-hydroxymitragynine (7-OH) Legal
Date: Saturday, August 30, 2025 11:48:38 PM

7-hydroxymitragynine (7-OH) is a plant alkaloid that provides a safe and effective alternative for treating pain and various psychiatric conditions. Unlike alcohol, 7-OH does not incite violence or idiotic behavior, and an overdose on 7-OH alone cannot cause death. Additionally, 7-OH is even less toxic than mitragynine, the primary active alkaloid in kratom. Banning 7-OH while keeping mitragynine legal would be a misinformed decision, as mitragynine is metabolized into 7-OH in the liver. I believe that keeping 7-OH legal will help reduce opioid-related deaths, as people will have a safe, non-toxic alternative to potentially lethal drugs like fentanyl, heroin, and prescription painkillers.

Big kratom companies have sought to make 7-OH a banned substance. They are merely trying to protect their market share, which has been threatened by 7-OH recently. If public health were the primary concern, then tobacco and alcohol would be targeted, as they are much more dangerous substances. An overdose on 7-OH alone has yet to cause a single death, and it is non-toxic to the body.

Thank you for reading.

From: S Eppard
To: supplementalcomm@surfcity-hb.org
Subject: My son died from Kratom powder, not 7oh
Date: Monday, September 1, 2025 7:54:02 AM

My 22 year old son Matthew died from Kratom POWDER (the least potent form of Kratom available in the United States). He did NOT die from 7oh/7hydroxymitragynine. Kratom caused him to have a seizure, go into cardiac arrest and die. His toxicology showed he died from the "TOXIC effects of Mitragynine" an alkaloid found only in krat0m. He had no prescription drugs, no street drugs nor alcohol in his system when he died, and his autopsy showed he had no underlying health conditions.

Please email me if you would like his toxicology and autopsy results. Susan Eppard (Matthew's Mom)

Sent from my iPad

From: Jared Beam
To: supplementalcomm@surfcity-hb.org
Subject: Agenda Item 25-704: Please Delay or Reconsider Kratom Ban
Date: Tuesday, September 2, 2025 8:27:56 AM

Dear city council,

I urge you to please delay or reconsider the banning of kratom and its alkaloids (agenda item 25-704). The current push of misinformation against its major alkaloids is driven by lobbying against a safe alkaloid for market interests, not because of any real danger.

The safety profile of 7-OH is demonstrated by over 500 million doses of 7-OH and no confirmed deaths from it alone. Studies also show it’s a partial-agonist that doesn’t bind to the receptors that cause respiratory depression. Kratom, which likewise does not affect those receptors, has been safely used by millions for much longer.

Removing access to these safe harm reduction tools will put people at risk. There is no emerging public health threat from kratom or its alkaloids that justifies a ban.

Thank you for your time. I pray you'll keep the public’s safety in mind and protect safe harm reduction options.

Best,

Jared beam

From: Matthew Weicberger
To: supplementalcomm@surfcity-hb.org
Subject: Matthew An advocate for kratom and 7oh
Date: Tuesday, September 2, 2025 8:28:20 AM
Attachments: icon.png
icon.png

Hello my name is Matthew. I am reaching out to you in regards to the upcoming hearing that you have regarding the action to ban kratom in Huntington Beach California. I oppose to this idea. The thought that our political leaders want to take away and alkaloid / medicine that provides relief as well as harm reduction and so many benefits that range from pain relief to emotional relief to anxiety relief and others; In my opinion the idea of banning kratom is nonsensical and will only bring harm to many who are trying to live a decent life. I'm attaching below a document and a written article that is written by the national library of medicine. I welcome you to please read through this information I would like to bet that after doing so there would be a change of heart and this would not come from sympathy or compassion but from scientific proof from studies and due diligence being done on this beautiful plant and alkaloid that millions of us on this planet use so that we can live a normal decent life. Thank you kindly for your time and I hope that the right decision is made; that the decision for the people is made; one that is for the people and not for the money.

Kind regards
Matthew.

Hello my name is Matthew. I am reaching out to you in regards to the upcoming hearing that you have regarding the action to ban kratom in Huntington Beach California. I oppose to this idea. The thought that our political leaders want to take away and alkaloid / medicine that provides relief as well as harm reduction and so many benefits that range from pain relief to emotional relief to anxiety relief and others; In my opinion the idea of banning kratom is nonsensical and will only bring harm to many who are trying to live a decent life. I'm attaching below a document and a written article that is written by the national library of medicine. I welcome you to please read through this information I would like to bet that after doing so there would be a change of heart and this would not come from sympathy or compassion but from scientific proof from studies and due diligence being done on this beautiful plant and alkaloid that millions of us on this planet use so that we can live a normal decent life. Thank you kindly for your time and I hope that the right decision is made; that the decision for the people is made; one that is for the people and not for the money.

Kind regards
Matthew.

Pharmaceuticals logo

Pharmaceuticals (Basel). 2025 Feb 6;18(2):222.
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Exploring the Therapeutic Potential of Mitragynine and Corynoxeine: Kratom-Derived Indole and Oxindole Alkaloids for Pain Management

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Editor: Réjean Couture[1]

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Abstract

The search for effective pain management solutions remains a critical challenge, especially amidst growing concerns over the use of conventional opioids. In the US, opioid-related mortality rates have surged to as many as 80

deaths per 100,000 people in some states, with an estimated economic burden of USD 1.5 trillion annually—exceeding the gross domestic product (GDP) of most US industrial sectors. A remarkable breakthrough lies in the discovery that indole and oxindole alkaloids, produced by several genera within the plant Tribe Naucleeae, act on opioid receptors without activating the beta-arrestin-2 pathway, the primary driver of respiratory depression and overdose deaths. This systematic review explores the pharmacological properties, mechanisms of action, dosing considerations, interactions, and long-term effects of mitragynine and corynoxeine, alkaloids from the Southeast Asian plant Mitragyna speciosa (kratom) and others in the Tribe Naucleeae. Mitragynine, a partial opioid receptor agonist, and corynoxeine, known for its anti-inflammatory and neuroprotective effects, demonstrate significant therapeutic potential for managing diverse pain types—including neuropathic, inflammatory, nociceptive, visceral, and central pain syndromes—with a focus on cancer pain. Unlike traditional opioids, these compounds do not recruit beta-arrestin-2, avoiding key adverse effects such as respiratory depression, severe constipation, and rapid tolerance development. Their distinct pharmacological profiles make them innovative candidates for safer, non-lethal pain relief. However, challenges persist, including the unregulated nature of kratom products, inconsistencies in potency due to crude extract variability, potential for misuse, and adverse drug interactions. Addressing these issues requires establishing standardized quality control protocols, such as Good Manufacturing Practices (GMP), to ensure consistent potency and purity. Clear labeling requirements with dosage guidelines and warnings should be mandated to ensure safe use and prevent misuse. Furthermore, the implementation of regulatory oversight to monitor product quality and enforce compliance is essential. This review emphasizes the urgency of focused research to optimize dosing regimens, characterize the pharmacodynamic profiles of these alkaloids, and evaluate long-term safety. By addressing

these gaps, the mitragynine- and corynoxeine-related drug classes can transition from promising plant-derived molecules to validated pharmacotherapeutic agents, potentially revolutionizing the field of pain management.
Keywords: mitragynine, corynoxeine, pain management, *Mitragyna speciosa*, systematic review, pharmacology, β-arrestin, opioids

1. Introduction

The search for effective pain management solutions remains a critical challenge, especially amidst growing concerns over the side effects and dependency risks associated with conventional opioids. In the United States, opioid misuse has led to significant mortality and economic burden, with opioid-related deaths estimated at 80 per 100,000 individuals in some states and an annual cost of approximately USD 1.5 trillion [1]. Amid this crisis, certain indole and oxindole alkaloids from the plant tribe Naucleeae have emerged as promising alternatives due to their ability to engage opioid receptors without activating the β-arrestin-2 pathway, a key mediator of respiratory depression and other severe opioid side effects [2].

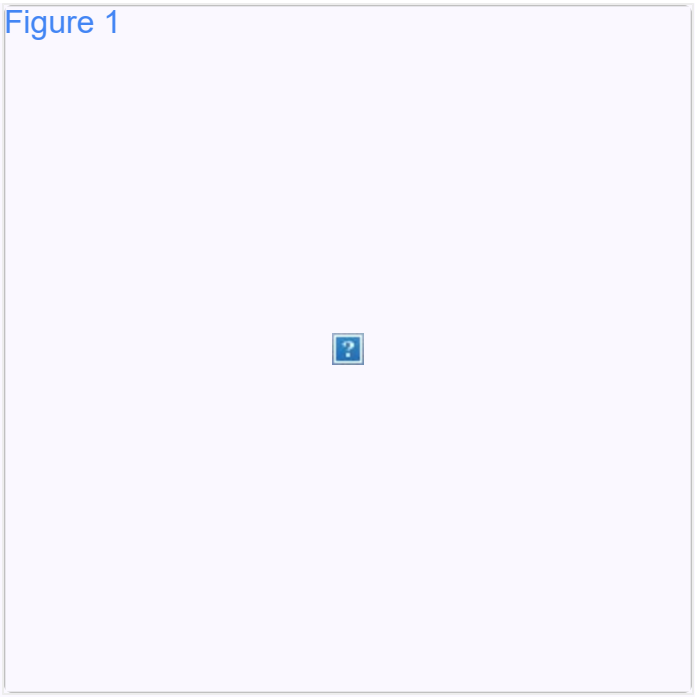
The alkaloid composition of *Mitragyna speciosa* (kratom) is dominated by mitragynine, which constitutes approximately 66.2% of the total alkaloid content in commercial kratom products. In contrast, 7-hydroxymitragynine, despite its higher potency at opioid receptors, is a minor component, accounting for only 0.01–0.03% of the total alkaloids. Other significant alkaloids include speciociliatine (8.6–16.6%), paynantheine (9.0–16.0%), and speciogynine (6.6–8.6%), with trace amounts of additional alkaloids such as corynoxeine, isocorynoxeine, and speciophylline. These secondary alkaloids may also contribute to kratom's pharmacological profile but in a less pronounced manner. The variability in alkaloid composition across kratom products is influenced by factors such as genetic differences, environmental conditions,

and processing methods, resulting in inconsistencies that affect their pharmacological effects and safety profiles.

Among these compounds, mitragynine and corynoxeine, derived from the Southeast Asian plant *Mitragyna speciosa* (Figure 1), commonly known as kratom, stand out as potentially safer alternatives to traditional opioids. While kratom contains a range of bioactive alkaloids, the oxindoles, including corynoxeine and its stereoisomer isocorynoxeine, are minor yet significant tetracyclic oxindole alkaloids. Kratom also contains other active compounds, such as flavonoids, polyphenols, and terpenoids, which contribute to the pharmacological effects of the raw plant products and crude plant extract. These oxindoles also occur in higher concentrations in other plants, such as species within the *Uncaria* genus, further highlighting their pharmacological importance [3]. Mitragynine, an indole alkaloid, is recognized as a partial agonist of the mu-opioid receptor (MOR), whereas corynoxeine demonstrates notable anti-inflammatory and neuroprotective properties. Unlike conventional opioids, both mitragynine and corynoxeine lack β-arrestin recruitment, which reduces risks of adverse effects such as respiratory depression, constipation, and tolerance development [4]. This unique pharmacological profile positions them as promising candidates for managing various types of pain—including neuropathic, inflammatory, nociceptive, visceral, and central pain syndromes—with a particular focus on cancer-related pain.

Figure 1.

Figure 1



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Mitragyna speciosa, commonly known as kratom, contains bioactive secondary metabolites, specifically indoles (e.g., mitragynine) and oxindoles (e.g., corynoxeine).

This review focuses specifically on mitragynine and corynoxeine as representative compounds of the indole and oxindole alkaloid classes, respectively. Although kratom is traditionally consumed in its whole form (e.g., crude leaves or powdered leaves), isolating and examining these two compounds allows for a targeted analysis of their unique therapeutic potential, mechanisms of action, and safety profiles. By focusing on mitragynine and corynoxeine, this review seeks to reflect the broader pharmacological potential of indole and oxindole alkaloids, addressing their potential applications in pain management without the confounding factors present in whole-plant kratom formulations. For reference, Table 1 and Table 2 present the principal structures of the oxindole and indole alkaloids derived from *Mitragyna speciosa*, providing an overview of these compounds' structural diversity relevant to their pharmacological profiles.

Table 1.

Principal structures of oxindole alkaloids of *Mitragyna speciosa*.

Compound	R_1	3	7	15	20	R_2
Corynoxeine	H	S	R	S	R	$CHCH_2$
Corynoxine A	H	S	S	S	S	CH_2CH_3
Corynoxine B	H	S	R	S	S	CH_2CH_3
Mitrafoline	OH	S	S	S	S	CH_2CH_3
Speciofoline	OH	R	R	S	S	CH_2CH_3
Specionoxeine	OCH_3	S	R	S	R	$CHCH_2$
Rhynchophylline	H	S	R	S	R	CH_2CH_3
Rotundifoline	OH	S	S	S	R	CH_2CH_3
Rotundifoleine	OH	S	S	S	R	$CHCH_2$

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Table 2.

Principal structures of indole alkaloids of *Mitragyna speciosa*.

Compound	R_1	3	15	20	R_2
Mitragynine	OCH_3	S	S	S	CH_2CH_3
Speciogynine	OCH_3	S	S	R	CH_2CH_3
Speciociliatine	OCH_3	R	S	S	CH_2CH_3
Mitraciliatine	OCH_3	R	S	R	CH_2CH_3
Paynantheine	OCH_3	S	S	R	$CHCH_2$
Corynantheidine	OH	S	S	S	CH_2CH_3

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Despite these promising pharmacological profiles, challenges remain, particularly around the unregulated nature of kratom products, variability in dosage, and potential for abuse. This review aims to identify and critically assess relevant studies to provide an in-depth understanding of the current evidence surrounding mitragynine, corynoxeine, and other kratom-derived alkaloids. While no clinical trials have yet defined therapeutic doses or established guidelines, the preclinical and observational data reviewed here may offer preliminary insights that could inform future research. This synthesis is intended to support clinicians and researchers in gaining a foundational understanding of these compounds' potential pharmacological profiles and mechanisms, and to encourage further investigation into their role in pain management and other therapeutic areas. Policymakers and the general public may also find this review beneficial in understanding the complex landscape of kratom's benefits and risks as they relate to public health considerations.

2. Results

2.1. Pharmacodynamics

Corynoxeine's mechanisms of action suggest significant potential in the treatment of pain through several pathways:

Anti-Inflammatory Agent: Corynoxeine's role as an anti-inflammatory agent is critical in managing pain linked to inflammation, a common cause in conditions such as arthritis and autoimmune diseases. Through inhibition of vascular smooth muscle cell (VSMC) proliferation, particularly by blocking the extracellular signal-regulated kinase (ERK1/2) phosphorylation pathway, corynoxeine reduces inflammatory processes in vascular and tissue contexts. This anti-inflammatory activity can

help mitigate pain by lessening the release of pro-inflammatory cytokines and mediators that typically heighten pain sensitivity. By targeting inflammation pathways, corynoxeine supports tissue health and reduces the potential for chronic pain development [5,6].

Neuroprotective Actions and Autophagy Enhancement: Corynoxeine serves as a neuroprotective agent, offering significant potential in conditions associated with neuropathic pain where nerve cell damage or dysfunction contributes to pain perception. Through the enhancement of autophagy, corynoxeine helps clear neurotoxic protein aggregates such as alpha-synuclein, which can otherwise accumulate and cause neural stress and degeneration. By engaging pathways like Akt/mTOR to induce autophagy, corynoxeine may reduce neuronal death and maintain nerve function, effectively lowering pain signals associated with damaged or impaired nerves. This neuroprotective mechanism could be beneficial in conditions like peripheral neuropathy and neurodegenerative diseases, where nerve protection aligns with pain mitigation [6,7].

Calcium Channel Blockade and Vasorelaxation: Corynoxeine induces vasorelaxation by blocking L-type calcium channels in vascular smooth muscle cells, thus preventing the influx of calcium ions. Calcium ions play a critical role in smooth muscle contraction; by limiting their entry, corynoxeine reduces smooth muscle tone and relaxes blood vessels. This vasodilation effect is particularly beneficial in conditions where vascular constriction is linked to pain, such as migraines and certain vascular pain syndromes. Enhanced blood flow from reduced vascular resistance can alleviate symptoms by improving oxygenation and nutrient delivery to affected tissues, thus reducing ischemic or tension-induced pain [6,7,8].

Adrenergic Receptor Antagonism: By inhibiting

α1A adrenergic receptors, corynoxeine further promotes vasodilation, countering the effects of adrenergic-mediated vasoconstriction. Adrenergic receptors, when activated, increase vascular tone, which can exacerbate pain in conditions like tension headaches and hypertension-related discomfort. Corynoxeine's antagonism of these receptors allows for relaxation of blood vessels, which can ease pain by reducing the stress and pressure within the vascular system. This mechanism adds a layer of vascular relief in pain conditions where adrenergic activity contributes to vascular tightness and discomfort [9,10].

Potassium Channel Activation and Vascular Smooth Muscle Relaxation: As a potential potassium channel opener, corynoxeine hyperpolarizes vascular smooth muscle cells, further reducing cellular excitability and promoting vasodilation. The activation of potassium channels encourages the efflux of potassium ions, stabilizing the cellular membrane potential away from depolarization thresholds that trigger contraction. This action complements calcium channel inhibition, creating a dual mechanism for smooth muscle relaxation. By decreasing vascular resistance and enhancing blood flow, corynoxeine's potassium channel activation may help alleviate pain from vascular sources, as seen in migraine and other vascular pain disorders [6,7].

Prevention of Vascular Smooth Muscle Cell Proliferation: Corynoxeine also inhibits the proliferation of vascular smooth muscle cells (VSMCs), an effect particularly relevant in conditions like atherosclerosis and restenosis, where abnormal cell growth contributes to vascular narrowing and pain. By blocking the ERK1/2 pathway, corynoxeine disrupts the signaling required for VSMC proliferation, which can prevent or slow down the progression of vascular blockages. This mechanism is essential in managing chronic pain linked to vascular diseases, as maintaining healthy,

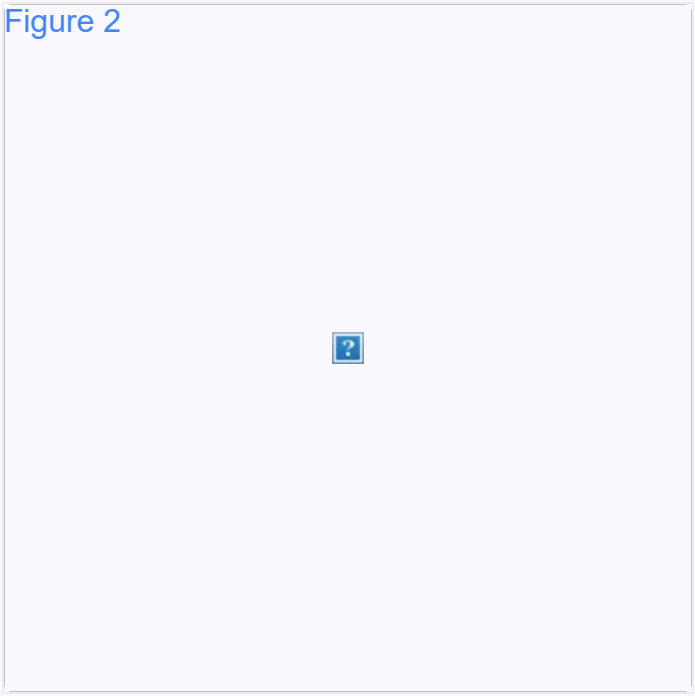
unobstructed vessels can reduce ischemic pain and improve blood circulation to affected regions [7,8].

In summary, corynoxeine's multi-faceted mechanisms—including its roles as an anti-inflammatory agent, neuroprotective agent, calcium channel blocker, adrenergic receptor antagonist, and potassium channel opener—highlight its potential in effectively managing and treating various types of pain.

Mitragynine's mechanisms of actions also suggest significant potential in the treatment of pain but through unique polypharmacology pathways (summarized in Figure 2).

Figure 2.

Figure 2



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Polypharmacology of mitragynine, the principal indole alkaloid derived from *Mitragyna speciosa*.

Mu-Opioid Receptor (MOR) Partial Agonist: Mitragynine acts as a partial agonist at mu-opioid receptors (MOR), which are primary

targets for traditional opioid analgesics. With a binding affinity of approximately 0.233 μM, mitragynine can activate MOR to produce analgesic effects but with limited efficacy compared to full agonists like morphine. This partial agonism allows mitragynine to provide pain relief while significantly reducing the side effects typically associated with opioid receptor activation, including respiratory depression and high potential for addiction. The decreased ability to fully activate MOR is linked to a reduced risk of tolerance development, meaning that patients are less likely to need increasing doses over time to achieve the same level of pain relief. Additionally, the partial agonism at MOR may result in lower risks of gastrointestinal side effects, such as constipation, which is a common issue with traditional opioids [9,10,11].

Kappa-Opioid Receptor (KOR) Antagonist: In contrast to its partial agonism at MOR, mitragynine functions as an antagonist at kappa-opioid receptors (KOR). KOR activation is often associated with dysphoria, hallucinations, and a reduction in reward-seeking behaviors. By antagonizing KOR, mitragynine reduces these adverse effects, potentially providing mood-stabilizing effects and lessening dysphoric reactions. KOR antagonism also contributes to pain relief, as KOR can play a role in modulating pain perception, especially in conditions where stress and mood are exacerbated by pain. This dual MOR agonism and KOR antagonism may offer a balanced analgesic effect while avoiding some of the psychological side effects of KOR agonists [12].

Competitive Antagonist at Serotonin Receptors (5-HT2A): Mitragynine acts as a competitive antagonist at the 5-HT2A serotonin receptor, which modulates the release of various neurotransmitters involved in mood, cognition, and pain perception. By blocking 5-HT2A receptors, mitragynine can reduce serotonin-related neurotransmission, which may help in

stabilizing mood and controlling pain perception, particularly in individuals with anxiety or depression-related pain. This antagonism is also thought to reduce anxiety and prevent overstimulation of neural pathways, contributing to an improved quality of life for those with chronic pain [9,10].

Partial Agonist at 5-HT1A: As a partial agonist at the 5-HT1A receptor, mitragynine can enhance serotonin signaling to some extent, particularly in ways that are anxiolytic and mood-enhancing. The 5-HT1A receptor is linked to improved mood and anxiety reduction, both of which are beneficial in chronic pain management, as pain can be exacerbated by psychological stress and anxiety. By partially activating this receptor, mitragynine may improve the psychological state of individuals suffering from chronic pain, which indirectly aids in pain management by reducing pain perception linked to stress and anxiety [9,10].

Binding to 5-HT2B and 5-HT2C Receptors: Mitragynine has weaker interactions with 5-HT2B and 5-HT2C serotonin receptors, binding with a Ki of approximately 1260 nM. While these interactions are less pronounced than its actions on other receptors, they may have subtle modulatory effects on mood and cognition. Since 5-HT2B and 5-HT2C receptors are involved in the regulation of mood and appetite, the slight binding affinity could contribute to mitigating symptoms like irritability or loss of appetite in individuals with chronic pain, although the impact is likely minor compared to its effects on other receptors [9,10].

Alpha-2 Adrenergic Receptor Agonist: Acting as an agonist at alpha-2 adrenergic receptors, mitragynine engages mechanisms similar to clonidine, a drug used to manage opioid withdrawal symptoms. Alpha-2 agonism can reduce norepinephrine release, which calms the sympathetic nervous system and provides a sense of relaxation and reduced arousal. This

agonism is particularly useful for managing symptoms of opioid withdrawal, including cravings, irritability, and heightened pain sensitivity. The activity at alpha-2 receptors may also contribute to the overall analgesic effect of mitragynine by reducing sympathetic responses that can intensify pain perception in stressful situations [9,13].

Dopamine D2 Receptor Affinity: Mitragynine's affinity for dopamine D2 receptors suggests potential antipsychotic effects, which may alleviate symptoms of psychosis in vulnerable individuals. By interacting with D2 receptors, mitragynine could theoretically reduce excessive dopamine activity, which is linked to conditions such as schizophrenia and bipolar disorder. For chronic pain patients, this dopaminergic modulation might help in managing pain perception and emotional responses, as well as in mitigating the negative psychological symptoms sometimes associated with chronic pain, such as anhedonia and low motivation [14].

β-Arrestin Activity: Unlike traditional opioids, mitragynine does not recruit β-arrestin 2 at the mu-opioid receptor, which is significant because β-arrestin 2 recruitment is linked to several adverse effects of opioids, including respiratory depression, constipation, and tolerance [15]. The absence of β-arrestin 2 recruitment in mitragynine's mechanism suggests a potentially safer side effect profile, offering effective pain relief without the heightened risks associated with conventional opioids. This property is a crucial factor in its unique pharmacological safety, making it a promising candidate for further research in pain management settings.

Cannabinoid Receptor Modulation: Mitragynine also interacts with cannabinoid receptors, particularly CB1 and CB2, which play roles in modulating pain and inflammation. Research indicates that mitragynine's analgesic effects, particularly in neuropathic pain, may be

mediated through these cannabinoid pathways. For instance, in models of chemotherapy-induced peripheral neuropathy, the analgesic effect of mitragynine was lessened when cannabinoid receptors were blocked, suggesting that these receptors are instrumental in its effect on neuropathic pain. This cannabinoid receptor interaction provides a unique avenue for pain relief, especially in complex pain conditions involving both central and peripheral mechanisms [16].

TRPV1 Modulation: Recent studies have shown that mitragynine may modulate the Transient Receptor Potential Vanilloid 1 receptor (1), a non-opioid pathway involved in sensing noxious stimuli, such as heat and inflammation. By affecting TRPV1 receptors, mitragynine can potentially reduce pain signaling in inflammatory and neuropathic pain conditions. TRPV1 modulation is particularly relevant for pain states where peripheral sensitization occurs, as blocking or modulating these receptors decreases the activation of pain pathways. This pathway represents an additional analgesic mechanism that can complement its opioid-like effects [17].

The absence of significant Delta-Opioid Receptor (DOR) activity in both mitragynine and corynoxeine indicates that their analgesic and neuroprotective effects are mediated through other pathways [12]. DORs are involved in modulating pain, mood, and neuroprotection, but DOR agonists are associated with the risk of convulsions and other adverse effects.

2.2. Pharmacokinetics

Mitragynine, the principal indole alkaloid in Mitragyna speciosa (kratom), exhibits distinctive pharmacokinetic properties that are crucial to its therapeutic applications. It is a lipophilic weak base (pKa ~8.1) with high plasma protein binding (85–95%) and undergoes extensive hepatic metabolism through both phase I

(oxidation, demethylation) and phase II (glucuronidation, sulfation) pathways.

The pharmacokinetics of mitragynine demonstrate dose-dependent variations, with key parameters providing insights into its behavior. After a single dose, the Cmax ranged from 17.1 ng/mL (6.65 mg dose) to 125 ng/mL (53.2 mg dose), while at steady-state (Cmax,ss), it ranged from 21.4 ng/mL to 143 ng/mL. The Tmax remained consistent across both single and multiple doses, ranging from 1.0 to 1.7 h. The elimination half-life (t1/2) increased significantly with dose, ranging from 8.5 h at the lowest dose to 43.4 h at the highest dose for single dosing, and from 25.7 to 67.9 h at steady state. Systemic exposure, measured as AUC0–∞, increased proportionally with dose, ranging from 52.8 h·ng/mL to 908 h·ng/mL after a single dose, while steady-state AUC (AUC0–τ,ss) ranged from 85.1 h·ng/mL to 958 h·ng/mL. Clearance (CL) decreased with increasing doses, ranging from 278 L/h at lower doses to 94 L/h at higher doses, indicating nonlinear pharmacokinetics. The volume of distribution (Vd) also increased with dose, from 1349 L to 3788 L for single doses and from 2980 L to 6020 L at steady-state, reflecting extensive tissue distribution [18]. These findings highlight the importance of dose adjustments to account for significant changes in clearance and half-life at higher doses.

A significant factor influencing the pharmacokinetics of mitragynine is the variability between administering pure mitragynine versus raw kratom products. Raw kratom contains a complex mixture of alkaloids and bioactive compounds that can alter absorption, metabolism, and clearance, resulting in greater variability in pharmacokinetic parameters. For instance, other alkaloids in raw kratom may competitively inhibit or enhance mitragynine metabolism, affecting Cmax, Tmax, and t1/2. Furthermore, no standardization of kratom formulations or dosing exists, making it

challenging to establish predictable therapeutic outcomes or mitigate potential adverse effects.

The pharmacokinetics of corynoxeine exhibit notable differences between normal physiological conditions and CUMS-induced depression models, which are essential to consider for therapeutic applications. In normal rats, the maximum plasma concentration (Cmax) of corynoxeine was 407.48 ± 10.87 ng/mL, with a time to reach Cmax (Tmax) of 1.67 ± 0.24 h. In contrast, CUMS-induced depression rats demonstrated a lower Cmax of 306.83 ± 18.72 ng/mL and a delayed Tmax of 2.33 ± 0.47 h, indicating reduced absorption under pathological conditions. The elimination half-life (t1/2) was slightly longer in CUMS-induced depression rats (2.68 ± 0.30 h) compared to normal rats (2.40 ± 0.12 h), while the clearance rate (CL) was faster in the depression model (18.06 ± 1.36 L/h/kg versus 14.48 ± 0.61 L/h/kg in normal rats), suggesting a reduced systemic exposure to the compound [14].

Additionally, the volume of distribution (Vd) was significantly higher in CUMS-induced depression rats (69.15 ± 3.25 L/kg) compared to normal rats (50.09 ± 2.11 L/kg), implying greater tissue penetration in the pathological state. The area under the concentration–time curve (AUC), representing overall drug exposure, was reduced in CUMS-induced rats, with AUC0-t values of 1202.97 ± 39.79 ng·h/mL versus 1495.62 ± 55.23 ng·h/mL in normal rats and AUC0-∞ values of 1614.48 ± 119.62 ng·h/mL versus 1914.65 ± 95.66 ng·h/mL, respectively [14]. These findings highlight a significant impact of depression on corynoxeine's pharmacokinetics, including reduced absorption, faster clearance, and greater distribution into tissues.

The altered pharmacokinetic parameters in the depression model underscore the influence of pathological conditions on the behavior of

corynoxeine within the body. These differences emphasize the need for tailored dosing regimens in clinical applications to ensure therapeutic efficacy and safety in patients with underlying conditions. Understanding these variations provides a foundation for optimizing the use of these compounds in different physiological and pathological contexts. Furthermore, these disparities underscore the necessity of further research to optimize standardization, characterize dose–response relationships, and establish regulatory frameworks for the safe and effective clinical use of mitragynine and kratom products.

3. Discussion

3.1. Summary of Findings

Mitragynine and corynoxeine exhibit significant potential in effectively managing and treating various types of pain through their multifaceted mechanisms of action. When addressing pain management, there is a large basis of pharmacotherapy because of the vastly diverse pathophysiology. While these compounds hold significant potential in neuropathic pain (chemotherapy-induced peripheral neuropathy (CIPN), diabetic neuropathy, postherpetic neuralgia), inflammatory pain, nociceptive pain (post-surgical, musculoskeletal), visceral pain (IBS, endometriosis), and central pain syndromes (MS, spinal cord injury), cancer pain is the most notable for effective management.

Cancer pain presents a unique challenge in pain management due to its complex and multifaceted nature, often involving a combination of nociceptive, neuropathic, and inflammatory components. Traditional opioids like morphine have long been the mainstay for cancer pain management; however, their use is associated with significant drawbacks, including the risk of tolerance, dependence, respiratory depression, and constipation. Furthermore, recent studies have suggested that morphine

and other opioids may promote tumor growth and metastasis by enhancing angiogenesis and suppressing immune function [19,20]. This potentially adverse effect on cancer progression highlights the need for alternative analgesics that do not compromise cancer treatment outcomes.

Mitragynine and corynoxeine offer promising alternatives to traditional opioids for cancer pain management. Mitragynine, a partial agonist at mu-opioid receptors, provides effective analgesia while reducing the risk of severe side effects associated with full opioid agonists [16]. Its lack of beta-arrestin 2 recruitment minimizes the risks of respiratory depression, constipation, and tolerance development. Additionally, mitragynine's partial agonist activity at 5-HT1A receptors and antagonist activity at 5-HT2A receptors may offer mood-enhancing and anxiolytic benefits, which are crucial for the overall well-being of cancer patients [10,21].

Corynoxeine, with its potent anti-inflammatory and neuroprotective properties, can further enhance pain relief in cancer patients. Its ability to reduce inflammation and protect neurons from damage is particularly beneficial in managing pain caused by tumor growth and metastasis [8,22]. Corynoxeine's vasorelaxant effects, mediated through calcium channel blocking and adrenergic receptor antagonism, can help alleviate pain associated with tumor-induced vascular tension and improve blood flow to affected tissues [6,22].

Moreover, neither mitragynine nor corynoxeine has been shown to promote tumor growth, making them safer options for cancer patients compared to traditional opioids [23,24]. By offering effective analgesia without the risk of enhancing tumor progression, these compounds represent a significant advancement in the management of cancer pain. The combined pharmacological actions of mitragynine and corynoxeine, including their opioid receptor

modulation, anti-inflammatory effects, and neuroprotective properties, position them as superior alternatives to traditional opioids like morphine for cancer pain management. Their potential to provide comprehensive pain relief while minimizing adverse effects and supporting overall patient health underscores their importance in the evolving landscape of cancer pain therapeutics.

3.2. β-Arrestin Activity

G-protein-coupled receptors such as the opioid receptors are transmembrane receptors that are capable of recruiting proteins β-arrestins to initiate separate cellular signal transduction pathways [12]. One of the most promising aspects of the major alkaloids found in *Mitragyna speciosa* is their lack of beta-arrestin 2 recruitment. Traditional opioids like morphine and fentanyl not only activate G-protein signaling pathways to provide pain relief but also recruit beta-arrestin 2. This recruitment is associated with many adverse effects, such as respiratory depression, constipation, and the development of tolerance and dependence. Beta-arrestin 2 mediates these effects by desensitizing the receptors, internalizing them, and initiating altern

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