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REVIEW

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The Potential for Kratom as an Antidepressant and Antipsychotic

Lindsay E. Johnson[a], Lilian Balyan[b], Amy Magdalany[b], Fizza Saeed[b], Robert Salinas[b], Starla Wallace[b], Charles A. Veltri[b], Marc T. Swogger[c], Zach Walsh[d], and Oliver Grundmann[a,b,*]

[a]College of Pharmacy, Department of Medicinal Chemistry, University of Florida, Gainesville, FL; [b]Midwestern University, College of Pharmacy, Department of Pharmaceutical Sciences, Glendale, AZ; [c]Department of Psychiatry, University of Rochester Medical Center, Rochester, NY; [d]Department of Psychology, University of British Columbia, Kelowna, BC, Canada

Mitragyna speciosa, otherwise known as kratom, is a plant in the coffee family (Rubiaceae) native to Southeast Asia and Thailand whose leaves have been shown to cause opioid-like and stimulant responses upon ingestion. The major pharmacologically active compounds present in kratom, mitragynine and 7-hydroxymitragynine (7-HMG), are both indole alkaloids and are responsible for its opioid-like activity. While kratom is most commonly known for its affinity for mu-opioid receptors, research has shown one of its active components has effects on the same receptors to which some antipsychotics bind, such as D_2 dopamine, serotonin ($5\text{-}HT_{2C}$ and $5\text{-}HT_7$), and alpha-2 adrenergic receptors displaying possible indications of kratom to be used as both antipsychotics and antidepressants. Although studies to evaluate this effect are still lacking, several online and in-person surveys note relief of depression and anxiety symptoms among those who consume kratom products, and in fact identify it as a common reason for consumption. This then highlights the dire need for further research to be conducted on kratom, its mechanism of action and the constituents that elicit these antidepressant, anxiolytic, and antipsychotic properties.

INTRODUCTION

Mitragyna speciosa, also known as kratom, is a plant within the coffee family (Rubiaceae) native to Southeast Asia and Thailand [1]. Kratom has been used in Southeast Asia for centuries as a stimulant, treatment for diabetes, diarrhea, improved circulation within the body, and to extend the duration of sexual intercourse [2,3]. The leaves of *Mitragyna speciosa* have been shown to cause opioid-like and stimulant responses upon ingestion, and

*To whom all correspondence should be addressed: Oliver Grundmann, PhD, Department of Medicinal Chemistry, College of Pharmacy, University of Florida, 1345 Center Drive, Room P6-20, Gainesville, FL, 32611; Tel: 001-352-246-4994, Fax: 001-352-392-9455, Email: grundman@ufl.edu, ORCID iD: 0000-0003-2302-8949.

Abbreviations: 7-HMG, 7-hydroxymitragynine; 5-HT, serotonin; DEA, US Drug Enforcement Administration; CYP, cytochrome P450 enzyme; P-gp, P-glycoprotein; FST, forced swimming test; EEG, electroencephalogram; SSRI, selective serotonin reuptake inhibitor; REM, rapid eye movement; DMT, dimethyltryptamine; LSD, lysergic acid diethylamide; GI, gastrointestinal; FDA, US Food and Drug Administration.

Keywords: Kratom, Depression, Anxiety, Neurological Disorders, CNS activity, mitragynine

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in the regions of its traditional use kratom is used as a treatment for pain management and opioid withdrawal [1,4].

The observational science on the experience of kratom users indicates several reliable psychoactive effects. At lower doses, an increase in alertness, motivation, and sexual desire are commonly reported. At higher doses, opioid dependent users report improvements in opioid withdrawal symptoms and a decreased desire to use other illicit substances, suggesting kratom's potential as a harm reduction agent for people with substance use disorders. Another widely reported reason for kratom use is pain management [5-7]. Whereas fewer studies have examined kratom's use for negative mood states and conditions, a recent systematic review of 13 observational studies indicated that kratom is also being used to self-treat negative affect, most frequently anxiety and depression, with users reporting generally positive results [8]. Based on prior and recent studies involving kratom and similarities between kratom and several substances with antidepressant and antipsychotic properties, we examine literature germane to estimating kratom's potential utility as a treatment for psychiatric symptoms [9].

More than 40 alkaloids have been identified to date from kratom leaves, of which mitragynine, corynantheidine, and 7-hydroxymitragynine (7-HMG) are known to produce a range of pharmacological effects in humans [10,11]. The proposed major pharmacologically active compounds with opioid-like activity are mitragynine and 7-HMG. These are indole alkaloids exclusive to *Mitragyna speciosa* that act as partial biased agonists at mu-opioid receptors activating only the G-protein signaling pathway [1]. Importantly, these compounds operate without recruiting beta-arrestin 2, which is associated with a range of commonly reported undesirable effects such as respiratory depression, constipation, and dependence [1,12]. The major constituent, mitragynine, is also a proposed agonist at the adrenergic alpha-2 receptor [13], a mechanism that is currently utilized in opioid withdrawal therapies with mechanism of action similar to clonidine, a selective alpha-2 receptor agonist. This activity may therefore allow for the reduction of withdrawal symptoms and have the ability to decrease opioid cravings. Unlike 7-HMG, mitragynine has been found to lack addictive properties [4]. 7-HMG is present in lower concentrations than mitragynine, but displays a higher potency. While kratom is most commonly known for its affinity to opioid receptors, it also has affinity to serotonin and dopamine receptors [13,14], signaling its potential for treating depression, anxiety, and psychosis.

METHODS

Search Strategy

This narrative literature review addresses the current scientific knowledge of kratom and its potential use as an antidepressant, anxiolytic, and antipsychotic based on structural similarities of its indole alkaloids, *in vitro* receptor binding studies, animal experiments, and human reports. Human data was obtained from surveys and observational studies since, to date, there are no clinical studies on kratom or any of its constituents. The 32 relevant articles included are from peer-reviewed journal articles obtained through electronic databases (PubMed, ScienceDirect, and Google Scholar). Keywords used to execute the searches included the following: "kratom," "Mitragynine," "*Mitragyna speciosa,*" "7-hydroxymitragynine," and "indole alkaloids." Articles included discuss the pharmacology of either kratom preparations or the isolated Mitragyna alkaloids and their potential adverse effects as it relates to stimulant, antidepressant, anxiolytic, antipsychotic, and opioid-like effects, in which approximately 70 articles were found. Once the information was identified in literature searches, more specific searches were conducted focusing on the following: (i) indole alkaloids and pharmacological activity (ii) antidepressant effects and kratom (iii) antipsychotic effects and kratom. Forty-three articles were analyzed and retained for further review. We excluded studies that did not include information directly related to the antidepressant, anxiolytic, or antipsychotic activity of *Mitragyna speciosa* or its constituents *in vitro*, in animals, or in human studies for inclusion in the review of the study methods. Finally, 32 articles met all criteria and were examined for data relevant to kratom and antipsychotic, antidepressant, or anxiolytic effects.

ANTIDEPRESSANT AND ANTIPSYCHOTIC EFFECTS OF KRATOM AND MITRAGYNINE

Indole alkaloids have been used for, and continue to show promise as, therapeutic drugs [15]. These compounds exhibit pharmacological activity through interactions with dopamine, serotonin, and norepinephrine receptors [16]. They have been developed into useful therapies for migraine, depression, and schizophrenia. *Mitragyna speciosa* contains indole alkaloids that target serotonin and dopamine signaling pathways and show promise as a treatment for depressive and psychotic disorders. While mitragynine is most prevalent in the leaves, similar indole alkaloids, such as paynantheine and speciociliatine, are also present [10].

Antipsychotics can be grouped into two major classes, typical and atypical. Typical agents such as haloperidol and chlorpromazine, are thought to work by inhibit-

ing D_2 dopamine receptors to treat the positive symptoms of psychosis such as hallucination and delusion while atypical antipsychotics treat both positive and negative symptoms, the latter including decreased motivation and ability to feel pleasure, as well as social withdrawal via inhibition of D_2 dopamine, alpha-2 adrenergic and serotonin receptors (5-HT_{2A}). While both of these classes of medications can be especially helpful in the management of psychosis, the side effects present a wide range of complications for the patient, some of which include tardive dyskinesia, dystonia, weight gain, and agranulocytosis to name a few [17]. To date, these adverse effects have not been observed with the use of kratom or its isolated alkaloid mitragynine in animals or humans.

A 2016 study using *in vivo* and *ex vivo* models showed that mitragynine has inhibitory effects on the same receptors to which atypical antipsychotics bind. Mitragynine has inhibitory effects on receptors similar to current medications that are used to treat psychosis which also inhibit D_2 dopamine receptors [17]. This study also conducted research on the effect of mitragynine as an antipsychotic in mice in whom psychosis was induced by using apomorphine, a dopamine agonist, which manifested in abnormal cage-climbing behavior. It was then determined that 75 to 100 mg/kg of a methanolic kratom leaf extract containing 4.4% mitragynine was able to significantly decrease psychotic symptoms. While mitragynine has affinity to dopamine receptors assisting in the alleviation of positive symptoms (auditory, visual, and tactile hallucinations, delusions), it is suggested that mitragynine would also have the ability to reduce negative symptoms (alogia, avolition) through antagonism at serotonin 5-HT_{2A} and 5-HT_{2C} receptors.

In the screening of antidepressant compounds, two methods are commonly used to assess the effectiveness of compounds in mice: the forced swimming test (FST) and the tail suspension test. The forced swimming test is used to assess the absence of escape-oriented behaviors which is timed when the mouse becomes immobile, defined as motionless except for the mouse keeping their head above water. The tail suspension test involves attaching tape on the mouse's tail to keep it suspended above the ground. Immobility is again tested by the time the mouse is completely immobile and motionless [3]. In a study in which two different doses of mitragynine and a control were injected intraperitoneally, both the forced swimming test and the tail suspension test indicated that both the 10 mg/kg and 30 mg/kg doses of mitragynine significantly reduced immobility time when compared to the control. In addition, like fluoxetine and amitriptyline, two common antidepressant drugs, mitragynine produced similar responses in immobility time indicating that in this context mitragynine may be effective as an antidepressant. It was also found that mitragynine decreased levels of blood cortisol similar to the effects of fluoxetine and amitriptyline in these tests [3]. Clinical research indicates a positive correlation between cortisol levels as a representation of stress and the risk of developing major depressive disorders [18].

A separate animal study conducted in 2006 on mitragynine in adult male Wistar rats and male ICR mice, found a single intraperitoneal administration of the alkaloid-rich fraction of kratom (containing 60% mitragynine) in doses of 60 mg/kg and 90 mg/kg to mice also resulted in significantly decreased immobility time in the FST [19] without affecting locomotor activity, which is an indicator of stimulant effects. The same study identified that both the antinociceptive and antidepressant effects of kratom may in part be mediated through activation of the c-Fos pathway and higher FOS protein levels in the dorsal raphe nuclei [19]. The Dorsal raphe nucleus presents with a high density of serotonin nuclei and innervations to the forebrain which has been linked to its central role in depression. A major limitation of these two studies is the intraperitoneal route of administration of mitragynine and kratom circumventing the gastrointestinal tract thus excluding potential metabolism by CYP enzymes and intestinal bacteria.

Two other animal studies in rats and mice investigated the effect of orally administered kratom on mitigation of ethanol withdrawal symptoms compared to fluoxetine [20,21]. Ethanol withdrawal in previously ethanol-dependent animals is a commonly employed model for the induction of depression and subsequent evaluation of antidepressant activity of new drugs [22]. The proposed neuropathological changes leading to reductions in monoamine neurotransmitters as well as other pathways associated with depressive disorders are reproducible in this model. In both studies, the alkaloid fraction of kratom reduced ethanol withdrawal symptoms in a similar manner to fluoxetine by reducing locomotor hyperactivity. A distinction between the alkaloid fraction of kratom and fluoxetine was observed via EEG in rats. While fluoxetine and other selective serotonin reuptake inhibitors (SSRIs) are known to suppress REM sleep, the alkaloid fraction of kratom did not affect any REM parameters following oral administration. As shown in [3], mitragynine may have similar impact on animal behavior to that of fluoxetine in studies using both the forced swimming test and tail suspension test. This similarity in action suggests the potential value of kratom as an antidepressant. While mitragynine is primarily recognized for its action on opioid receptors, it does not structurally resemble other medications in the opioid family. This indicates mitragynine may have a broader receptor specificity than originally expected [23]. Mitragynine, fluoxetine, DMT, LSD, and psilocybin all interact with serotonin receptors, while LSD also has an affinity to D_2 receptors. The affin-

ity of mitragynine to the 5-HT_{2C} receptor, and affinity to D_2 receptors may indicate how this compound could be an effective antidepressant, as fluoxetine is an inhibitor at this receptor subtype as well.

USER EXPERIENCE AND CLINICAL REPORTS WITH KRATOM

A range of personal experiences have been described by kratom users at varying doses. Low doses generally provide a motivational and stimulant effect and may thus be helpful in work settings. Higher doses are reported to increase relaxation and calm. Users describe increased sociability and empathy. While visual alterations, gastrointestinal (GI) upset, dizziness, and vomiting have been reported as common side effects, GI upset and dizziness are most commonly observed if kratom is taken concomitantly with other substances [24,25]. Users from various backgrounds have reported feeling happiness, well-being, mellowness, being able to relax, a mental calm with no loss of clarity, having more energy, increased desire to work, and a strong desire to communicate with loved ones [25]. Users have reported the kratom experience as akin to a mild psychedelic experience, including close-eye visual patterns, a mild expansion consciousness relative to visual and auditory stimuli. These experiences [25] may indicate a similarity in the mechanisms (*i.e.* 5-HT) of kratom to that of psychedelic substances such as LSD and DMT.

Although no clinical study has evaluated the antidepressant effects of kratom, or any of its constituents to date, several online and in-person surveys document the reasons and benefits that kratom users report [7,8,24,26,27]. In a 2016 online survey conducted among 8,049 current kratom users, 58% reported use for self-treatment of a mental or emotional disorder [24]. Among those taking kratom to self-treat a mental or emotional disorder, females were more likely to take kratom for such conditions, while those aged 41 or older were less likely to consume for these reasons. In a subsequent analysis of the data, 66.5% of users who consumed kratom to self-treat a mental or emotional disorder rated their health as "good" or "very good" [7]. In the same publication, the correlation between a reported diagnosis of depression and the use of kratom for self-treatment of a mental or emotional disorder was significantly higher for women and inversely related with age. Income was found to have a negative correlation with a diagnosed depressive disorder and with the use of kratom for self-treatment.

In another 2019 online survey including 3,024 former and current kratom users, similar demographics were reported with 66.4% of current kratom users selecting anxiety or depression as one of the impelling causes for the use of the product, while 20.2% disclose it as the main motivation [27]. In contrast, only 14.5% of current users listed relief of withdrawal symptoms as one reason, and 2.2% chose it as the main reason for consuming kratom products. The most common reason for consuming kratom was pain relief in both current and past kratom users.

A 2017 anonymous survey of 500 kratom users and a 2015 quantitative analysis of experiences of 161 kratom users indicated that kratom products are used as a mitigation strategy to reduce opioid withdrawal symptoms, which often involve states of depression and anxiety [25,26]. In general, people with recent harmful opioid use are more likely to use kratom as a harm reduction strategy than those who use other illicit drugs. A third of the respondents in this survey who had used kratom to mitigate withdrawal symptoms indicated that they would take the product again [26]. From these initial survey studies kratom is primarily used to prevent opioid withdrawal effects and as a self-treatment of a mental or emotional disorder which include depression and anxiety.

PHARMACOKINETICS

Of all *Mitragyna speciosa* alkaloids, mitragynine makes up 66% of them while paynantheine accounts for 9%, followed by speciociliatine at 7%, and 7-HMG at 2% of the total alkaloid content. The additional alkaloids are only found in miniscule amounts [28]; however, of the raw leaf material, mitragynine only accounts for about 2%, illustrating the differentiation between the alkaloid fraction often reported in the literature and actual total leaf material amount that is ingested [29].

Mitragynine has a low oral bioavailability of 3% [28-30], which may be a result of high first-pass metabolism via cytochrome P450 (CYP) enzymes in the intestines and the liver, as well as low solubility in the intestinal lumen leading to reduced absorption. Mitragynine has a short half-life of approximately 3 hours after injection of the compound but presents with a long terminal half-life of approximately 29 hours following oral administration, suggesting a biphasic distribution model [31,32]. The pharmacokinetics in a small study of 10 chronic users show kratom, more specifically the major constituent mitragynine, has a two-compartment model with a half-life of approximately one day [2]. Metabolism of mitragynine mainly occurs in the liver where *in vitro* experiments indicate that mitragynine interacts with other medications and substances via CYP enzymes [9]. Mitragynine and 7-HMG may inhibit the activity of CYP2D6 and CYP3A4. Moderate inhibitory effects are seen with CYP1A2 and mild inhibition of CYP2C19. *In vitro*, it has been shown that mitragynine and 7-HMG also act as inhibitors of P-glycoprotein (P-gp). Although the clinical significance of the inhibitory effect on CYP enzymes by kratom and its alkaloids has not been determined, kratom

is often reported together with drugs that are substrates for CYP3A4 (alprazolam, carbamazepine, phenobarbital, phenytoin, quetiapine, oxycodone), CYP2D6 (amitriptyline, fluoxetine, haloperidol, codeine), and CYP1A2 (theophylline, clozapine) [2,9,33].

P-gp is a drug transporter expressed in the endoplasmic reticulum with very broad specificity. This protein has the ability to pump xenobiotics out of the cell to reduce absorption of the substances into the systemic circulation or from crossing the blood-brain barrier. A 2019 study determined mitragynine to be an inhibitor of P-gp, which could lead to significant drug-drug interactions between kratom and other substances [33].

TOXICITY

The toxicity of kratom has been studied for total alkaloid extracts in mice which found an LD_{50} of 173 mg/kg [34] and 592 mg/kg [35], and for methanolic extracts in mice, an oral LD_{50} of 4,900 mg/kg was reported [34]. In a study of rats receiving mitragynine at various doses for 5 days per week for 6 weeks, minor changes in body weight and liver and kidney weights were observed, but no other behavioral or physiological effects were noted. In dogs, no adverse effects were observed after 3 weeks; however, there were changes in blood chemistry, liver cell morphology, and lymphatic hyperplasia after an additional 3-week dosing period [35]. A 2013 study in rats produced similar results with low and intermediate doses showing little sign of toxicity, but induced hematological and liver and brain histopathological changes suggestive of toxicity at a higher dose [36].

In very high doses of mitragynine administered to various animal species (the human equivalent of more than 15 g/dose), there were no acute deaths or significant effects of toxicity, however in humans [37], unlike opioids, there have been no reported effects of respiratory depression or opioid toxic syndrome with the use of kratom alone. Hypothyroidism and intrahepatic cholestasis have been reported co-existent with kratom use, but these data are from case studies and thus provide little evidence that kratom caused the events due to limits on internal validity [1,36,38]. When taken orally in single doses up to 5 g, the main side effects were nausea, itching, loss of appetite, and increased urination [25,38]. When taken at increased doses of 8g or more, adverse effects included constipation, sedation, hypotension, sweating, dry mouth, and tachycardia [24].

CONCLUSIONS

Kratom as a traditional medicine has become widely known and used as a supplement for the self-treatment of a variety of disorders. Because of its proposed stimulant effects and self-reported benefits, kratom might induce increased behavioral activation among people with depression, anxiety, and psychosis, leading to the improvements of mental health conditions. The low toxicity of kratom and its constituents indicate this may be beneficial for the development of a safe and tolerable antidepressant/antipsychotic. One potential drawback of the use of kratom is dependency and addiction to the product. Because there is currently no accepted medical indication for kratom or its alkaloids and a potential for dependency, the US Drug Enforcement Administration (DEA) regards it as a "drug of concern" [5]. The US Food and Drug Administration (FDA) furthermore has classified mitragynine and alike indole alkaloids as opioids which complicates clinical trial approval to evaluate effects of kratom and its constituents in humans [5]. However, kratom as well as mitragynine require more research to determine the most effective dosing for its psychoactive properties, while reducing addiction liability.

In conclusion, the research conducted on kratom, especially its major constituent mitragynine, shows promise for the possible future use of kratom as an antidepressant and antipsychotic. Additional research needs to be conducted on the mechanism of action of kratom and its constituents to analyze the mechanism in which it elicits antidepressant and antipsychotic effects. We suggest the interaction of kratom on both dopamine and serotonin receptors may lead to a decrease in psychosis, especially due to the interaction of the dopamine receptor, as demonstrated by other antipsychotic medications interaction with this receptor. Depression is likely decreased due to the interaction on serotonin receptors, as seen with the interaction of other antidepressants on serotonin receptors. Due to mitragynine's affinity to dopamine and serotonin receptors this compound shows significant promise as a lead drug or treatment for psychiatric disorders.

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