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Kratom Alkaloids: A Blueprint?

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Abstract

Alkaloids from the botanical *Mitragyna speciosa* (commonly referred to as “kratom”) interact with opioid, adrenergic, serotonergic, and other receptors to provide myriad reported effects, including analgesia, energy, improved mood, and relaxation, among others. These alkaloids are complex and unique and may serve as a blueprint for the development of novel molecules to treat various substance use disorders.

Keywords

Mitragyna speciosa ; kratom; natural products; substance use disorder; novel pharmacotherapy

Background

The ongoing global polydrug use epidemic is characterized in large part by use of opioids, stimulants, and alcohol. Morbidities and mortalities attributable to substance use disorders (SUDs) for these drug classes are at record highs. Although some effective pharmacotherapies have been developed for opioid use disorder (OUD) and alcohol use disorder (AUD), they are not always accessible or well-tolerated. Pharmacotherapies for stimulant use disorder (StimUD) remain evasive. Polydrug mis- and abuse are prevalent, meaning that effective interventions for one SUD drug class may have little impact on another. Moreover, psychiatric disorder comorbidities are common among people with SUD histories. This population is often also underdiagnosed and undertreated, not only for SUDs and psychiatric health, but physical comorbidities, such as chronic pain. Given the need for expanding treatment for people with multiple SUDs and the slow progress that has been made in advancing novel therapeutics for OUD, AUD, and StimUD, nonmedical natural products as forms of “self-treatment” have emerged among people with SUDs and related conditions. Use of the botanical *Mitragyna speciosa*, commonly referred to as “kratom,” has

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increased since 2007, particularly in the United States. Human self-report has converged to indicate that kratom products are being used, with some seeming effect, as a substitute for opioids, stimulants, and alcohol among people with SUD histories, including some with co-occurring chronic pain and psychiatric disorders.[1] This includes kratom use to attenuate opioid and alcohol withdrawal. Use of kratom for its mild psychostimulant effects is increasingly documented.

As a nontrivial portion of pharmaceutical drugs eventually approved by the US Food and Drug Administration (FDA) are natural products or derived from natural products, kratom's adoption, initially among people in Southeast Asia (where kratom is indigenous) and then among US adults seeking to self-treat myriad health conditions, is perhaps unsurprising. However, the therapeutic potential of kratom and its alkaloids remains speculative in the absence of adequate human data. Published pharmacokinetic/pharmacodynamic data on kratom alkaloids in humans is confined to two small studies at present. No large-scale clinical studies of safety and tolerability, human abuse potential, or drug discrimination have been published. Based on the *in vitro* and *in vivo* pharmacology of kratom that we discuss below, we envision the eventual evaluation of the effectiveness of kratom in clinical trials for reducing key symptoms of OUD, AUD, and/or StimUD either using the whole plant matter or alkaloid combinations from the over 45 indole, N(4)-oxides of indole, oxindole, and 9-hydroxylated oxindole alkaloids that have now been isolated from the kratom leaf (see Figure 1). Here, we highlight pharmacodynamics of kratom alkaloids *in vitro* focusing on opioid, adrenergic, and serotonergic receptors, and *in vivo* pharmacokinetics of several alkaloids of interest.

Kratom Pharmacodynamics

Kratom alkaloids have shown moderate binding affinity to the established CNS-drug targets of pain, anxiety, mood elevation, and OUD including opioid (μ, κ, and δ) and non-opioid (adrenergic and serotonergic) receptors. The most studied and major kratom alkaloid, mitragynine, is a partial (E_{max}, 40%) μ-opioid receptor agonist (K_i, 161 ± 10 nM), that can also bind to adrenergic receptors (α_{1A}, α_{1B}, α_{1D}, and α_{2C} receptors).[2] A metabolite of mitragynine, 7-hydroxymitragynine (7HMG), is a potent partial μ-opioid receptor agonist (K_i, 7.2 ± 0.9 nM), and it has shown indicators of opioid-induced addiction potential in rodents. 7HMG has been reported as one of the kratom alkaloids, but concentrations of 7HMG in native kratom leaves were found to be below the lower limit of quantification (LLOQ, <0.001%) in multiple analytical studies. Mitragynine does not appear to recruit the β arrestin-2 pathway and it can reduce opioid self-administration in non-human animals without any known indicators of addiction potential.[2,3] It's potential, along with other alkaloids, may also extend to decreasing alcohol intake, though more work is needed to further support this possibility.[4]

Mitragynine has shown low binding affinity (5-HT_{1A}, 5.9 ± 0.8 μM) to serotonergic receptors, but two other major kratom alkaloids, speciogynine and paynantheine, have demonstrated high binding affinity to 5-HT_{1A} and 5-HT_{2B} serotonergic receptors. Both speciogynine and paynantheine can produce 5-HT_{1A} mediated non-opioid hot-plate antinociception and lower lip retraction without activating 5-HT_{2B} receptors. Apart from

speciogynine, two other diastereomers of mitragynine, speciociliatine and mitraciliatine, are partial agonists at μ-opioid receptors. These have shown robust antinociceptive effects in rodents. Antinociceptive effects were also observed during the hotplate or warm-water tail-withdrawal assay after i.c.v. administration of other minor kratom alkaloids, specifically corynoxine, corynantheidine and isopaynantheine.[2]

Kratom Pharmacokinetics

According to the *in vitro* metabolism studies in human liver microsomes, mitragynine is metabolized to *O*-demethylated and mono-oxidative metabolites primarily by CYP3A4, with a minor contribution by CYP2D6, CYP2C9, and CYP2C19. A secondary glucuronide and/or sulfate conjugation of a few *O*-demethylated and mono-oxidative metabolites of mitragynine were also identified. Among the 22 identified metabolites of mitragynine, 9-hydroxycorynantheidine and mitragynine acid are two major metabolites. Mitragynine exhibits high human plasma protein binding (f_u, 0.02) and it can readily cross the blood brain barrier.[2,3]

Pharmacokinetics of mitragynine have been studied in rodents, dogs and, to a lesser degree, in humans. Oral bioavailability in rats varies from 3.0 −52.7%, while 69.6% oral bioavailability was observed in female beagle dogs. Mitragynine is the most studied kratom alkaloid although pharmacokinetics of other kratom alkaloids have recently also been investigated following oral dosing (7HMG, corynantheidine and speciociliatine) or as complex alkaloid extracts. Systemic exposure of kratom alkaloids depends upon the type of kratom formulation (individual alkaloid, traditional whole plant matter versus organic extract).[2,3] Following an oral dose of a well characterized kratom product (2 g) to healthy adult participants, a fast absorption of kratom alkaloids (mitragynine, speciogynine, speciociliatine, paynantheine, T_{max}, ≤ 2.5 hr) was observed, except for isopaynantheine and mitraciliatine (T_{max}, 4.5 hr). Among the kratom alkaloids that have been studied, dose normalized exposure of mitraciliatine was highest followed by isopaynantheine, speciociliatine, speciogynine, paynantheine, and mitragynine. 7HMG content in the dosed kratom product was below the LLOQ, but 7HMG formed after metabolism of mitragynine was quantified in plasma samples and metabolite to parent exposure ratio ((AUC_{7HMG}/ $AUC_{mitragynine}$) * 100) was 26.5%.[5] Corynantheidine was not specifically investigated in this clinical study, but it was one of four alkaloids (mitragynine, 7-hydroxymitragynine, and speciociliatine) available systemically after oral doses of either lyophilized kratom tea or a commercial kratom product (OPMS) in male rats.[2]

Conclusion and Future Directions

Kratom alkaloids may offer a novel structural approach to the treatment of several SUDs, including alcohol, opioids, and stimulants, given their binding to multiple receptor systems that have been identified as targets. In this instance, the relative lower potency at opioid receptors, the partial agonist activity, and interaction with adrenergic and serotonergic receptors may provide an advantage over selective opioid-targeting molecules. Especially in the development of kratom as pharmacotherapy for SUDs, a concomitant benefit of kratom alkaloids appears to be some putative anti-depressant and anxiolytic effects,

reported by many human users and evinced in preclinical models. A closer look at structure-activity principles at the various targets and metabolic activation may yield derivatives that present with favorable pharmacodynamic and pharmacokinetic properties sufficient to justify clinical trials and eventual FDA approval.

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Abbreviation:

BLLOQ	below the lower limit of quantification (<0.001%, w/w)

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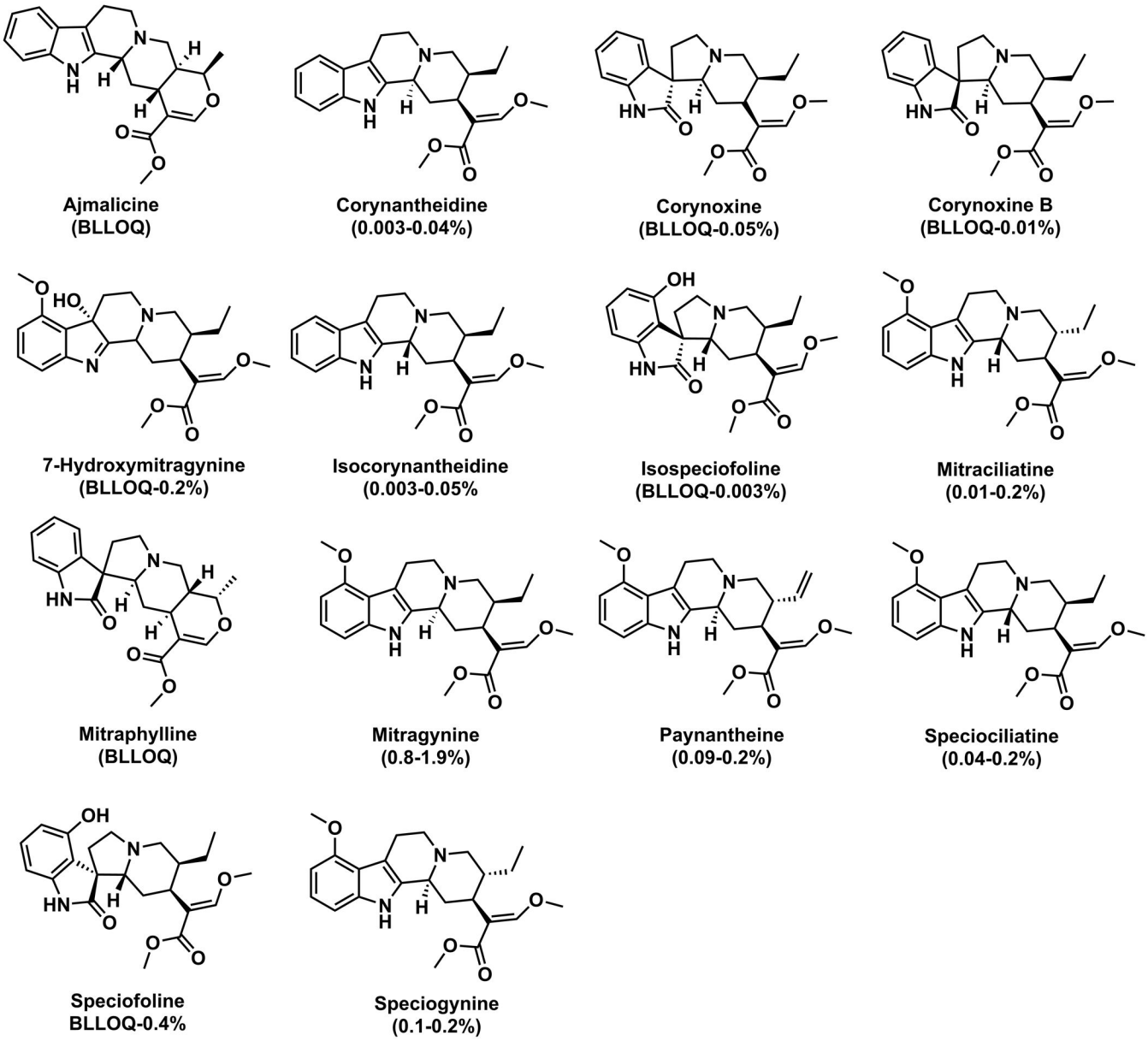

Figure 1.

Chemical structures of major and minor kratom alkaloids. Values represent % alkaloidal content in mitragynine rich (≥0.8%) dried kratom leaves.