

## Letter to the Editor

### THE THERAPEUTIC POTENTIAL OF KRATOM

The leaves of *Mitragyna speciosa* (Korth.) Havil. (Rubiaceae), 'kratom', have been used traditionally as a relaxant, stimulant, anxiolytic and to treat minor pain [1–5]. Recent surveys also indicate that kratom may be used as a self-medication substitute for prescription and illicit opioids in the United States [6]. Research suggests that kratom may produce its effects without the respiratory suppression induced by classical opioids [7–9]. Although the therapeutic potential of kratom appears promising, pending more carefully controlled clinical studies, the risk/benefit determinations for human use depend upon accurate characterizations of available data.

The genus *Mitragyna* encompasses 10 species with documented ethnomedicinal use; however, stimulant and analgesic effects are characteristic only for *Mitragyna speciosa* [5,10]. Currently kratom is not scheduled by the United Nations Drug Conventions and has no approved medical uses, although some European Union (EU) Member states currently control *Mitragyna speciosa*, mitragynine and/or 7-hydroxymitragynine [10]. Kratom falls under narcotic law in Australia, Malaysia, Myanmar and Thailand and under the Medicines Amendment Regulations in New Zealand [2]. Kratom attracted mainstream attention in North America and Europe in the 2000s when products containing no mitragynine, but labeled as 'Kratom or mitragynine acetate', were marketed in Europe [11]. Concerns escalated, with nine fatalities in Sweden attributed to the kratom product 'krypton', although it was later found adulterated and the tramadol metabolite O-desmethyltramadol causative for the deaths [10]. As kratom has been marketed in the United States as a dietary supplement, increased consumption and demand have accelerated discussion about its legal status [5,12].

In the United States, proposed regulatory responses to kratom appear overmatched to evidence of harms. In 2016 the US Drug Enforcement Administration (DEA) announced its intention to place kratom alkaloids mitragynine and 7-hydroxymitragynine into the Controlled Substance Act Schedule 1, based on 660 poison control center calls and 30 deaths where kratom use was reported but not identified as the causative agent [13]. Following extensive public comments and bipartisan objections from the US Congress, the DEA withdrew its proposal and provided a public comment period of several months. In 2018, efforts in the United States to restrict kratom appear to be resurgent; the US Food and Drug Administration's (FDA) Commissioner recently referred to

kratom as a narcotic-like opioid with respect to 'potential for abuse, addiction, and serious health consequences; including death' [14]. This statement by the FDA is based primarily on isolated adverse event reports and an *in-silico* receptor binding model: the Public Health Assessment via Structural Elucidation (PHASE). Based on this model, the FDA statement concludes that 'we feel confident in calling compounds found in kratom, opioids' [14].

It is our opinion that the evidence does not support such conclusions regarding the risks of kratom. Although using well-defined, validated *in-silico* models in hypothesis development can provide valuable insights, an isolated receptor interaction study does not reflect the complexity of a living organism and has never been considered an acceptable replacement for experimental *in-vivo* data for FDA drug evaluations and approval. The physiological consequences of opioid receptor bindings vary widely, from the deadly effects of fentanyl to the relatively innocuous effects of the non-scheduled dextromethorphan. In the case of mitragynine, whole cell assay research shows binding to mu-opioid receptors without recruitment of beta-arrestin 2, which is linked to many adverse effects associated with classical opioids, such as respiratory depression, euphoria and tolerance development [8]. The available scientific evidence indicates that the kratom indole alkaloids mitragynine and 7-hydroxymitragynine are not functionally identical to opioids; their molecular and pharmacodynamic mechanisms of action are distinctly different. This has been shown at the molecular and cellular level, as well as with whole organisms in animal models and observational studies [12]. Further, frequency of kratom consumption and dosing are important to tolerance or risk for withdrawal, which appear mild relative to classical opioid withdrawal [15]. Further research is necessary to make a definitive and evidence-based statement that encompasses all aspects of kratom pharmacokinetics and pharmacodynamics *in vivo*.

The majority of kratom-related calls to poison control centers were categorized as minor or moderate in severity, with 49 (7%) classified as major exposure. This is consistent with recent user surveys, including a 2016 study showing that fewer than 1% of respondents sought medical or mental health treatment related to consumption [6,12]. The most common dose-dependent adverse effects reported are constipation, nausea/vomiting, stomach irritability and drowsiness, and it has been proposed that these unpleasant opioid-like effects that may lead users to self-titrate kratom intake to avoid excessive dosing [6,16]. The more precise characterization of adverse effects of kratom will require targeted studies that examine individual

differences in users and co-ingested substances, with particular attention to factors that might contribute to more severe negative reactions.

In sum, although the scientific literature and long-standing traditional use suggests an acceptable risk profile, kratom is not benign and requires regulatory oversight with regard to marketing and quality to ensure public health. Although caution regarding compounds such as kratom alkaloids that bind to opioid receptors is warranted, equating kratom with more dangerous known opioids runs the risk of casting premature judgment on a herbal product used by millions as an opioid substitute. For some consumers, decreased access to kratom has the potential to increase risk of resumption of opioid use, with potential for disordered use, overdose and death [17,18].

In light of this, we urge the FDA and regulatory bodies world-wide to reconsider recent scientific evidence regarding the effects and safety of kratom, and use flexibility in developing an approach within legal frameworks that ensures continued lawful and safe access to kratom for those using it therapeutically and as a self-treatment for opioid and prescription drug dependence [17,18]. Precedents for such regulatory approaches may be found internationally among legislative controls for herbal medicines that vary widely with respect to definition, licensing, dispensing, manufacturing and trade, based on well-established standards of evidence for safety, quality and efficacy of herbal products [19–21].

#### Declaration of interests

J.H. and M.S. have consulted for the American Kratom Association (AKA), a not-for-profit organization that is advocating for keeping kratom legal in the United States. J.H. also consults on the development of new opioid analgesics and new treatments for opioid use disorders. P.N.B. provides scientific research guidance on dietary supplement manufacture and regulatory compliance to companies, associations and government.

**Keywords** Dietary supplement, kratom, mitragyna speciosa, mitragynine, opioids, regulation.

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