Statement on the science of kratom products and their US regulation

Kratom (*Mitragyna speciosa* Korth.), refers to a tree with a long use history in its native Malaysia, Thailand, Indonesia, and other parts of Southeast Asia.[1] Kratom has received increased attention in the United States since US consumers first began using kratom in the early 2000s for the self-treatment of a variety of health conditions, including pain and some psychiatric symptoms. Since this time, kratom products have proliferated and are used not only to address pain or as a substitute for licit and illicit substances with high-risk profiles, but also to improve general well-being, increase energy, mood, and productivity, as well as for recreation.[2] In its native Southeast Asia, kratom has been used by chewing freshly picked leaves or brewing tea immediately after leaf harvest. The first written reports of kratom use in scientific literature appeared over 150 years ago stating the traditional medicine use to alleviate pain, decrease fatigue/increase stamina, and self-treat other ailments.[3] To this day, fresh kratom leaf is widely used. More recently in Southeast Asia, the fresh leaf has been used to ameliorate withdrawal symptoms from a substance use disorder, most commonly related to opioid, alcohol, or stimulants.[4] In the US, primarily dried leaf material (not freshly harvested) is used in a number of preparations and products.

The known science of kratom is centered on the presence of alkaloids (chemicals) which act on a variety of neurotransmitter systems to elicit a complex pharmacological profile. Mitragynine is the major alkaloid in kratom and because of this, it has been the subject of most scientific reports. There is a much smaller body of science around whole leaf kratom preparations and other individual alkaloids. Mitragynine acts on opioid, adrenergic, and serotonergic receptors, which is different than classical opioids, like morphine, that only act on opioid receptors.[5] As such, mitragynine is not a classical opioid, like morphine, but rather is unique in that it has partial agonist activity and relatively low abuse liability. To date, mitragynine and lyophilized kratom tea have not been shown to cause respiratory depression in animal models, which is a major concern of licit and illicit opioids consumed in the US.[6,7] The potential for mitragynine and kratom to serve as a medical blueprint for the treatment of substance use disorders has

been recognized by the National Institute on Drug Abuse.[2,8] Other kratom alkaloids exert diverse actions that may further explain the complex effects that kratom consumers report.

The native kratom leaf contains varying amounts of alkaloids that usually are present in amounts of 2-4% by weight. The primary alkaloid in many leaf materials is mitragynine, which is present on a percent weight basis ranging from <1.0% but usually not exceeding 2.5%.[9,10] The other alkaloids are present in major and minor amounts with paynantheine, speciogynine, speciociliatine, and mitraciliatine, all of which do present with pharmacological activity, accounting for most of the remaining alkaloids.

Mitragynine is metabolized in the human body to some degree into the active metabolite, 7-hydroxymitragynine.[11] This 7-hydroxymitragynine metabolite has been shown to be associated with relatively greater abuse liability than its parent mitragynine, as it is more potent than mitragynine and 3-22 times more potent than morphine at opioid receptors.[12–14] The pharmacology of 7-hydroxymitragynine appears to differ from mitragynine in that is only acts on opioid receptors, rather than multiple systems in the human body. It has been proposed that the amount of 7-hydroxymitragynine should be limited in products as it is found in very low levels in the native kratom leaf material and, indeed, many US products do not contain 7-hydroxymitragynine in detectable amounts. From a safety perspective, limiting the amount of both mitragynine, 7-hydroxymitragynine, and other alkaloids as has been done in most kratom-related state legislation, ensures that consumers are unlikely to experience adverse effects at commonly reported amounts of kratom ingestion.

With a diverse kratom product marketplace in the US, it is important to distinguish between products comprised predominantly of native kratom leaf material, which contains at a maximum 2.5% mitragynine as part of a total of 4% of alkaloids by weight, and kratom extract products with enriched alkaloids. Extracts products that contain multiple times the amount of mitragynine and other kratom alkaloids than are present in the native leaf material may produce a higher risk profile of adverse effects than whole-leaf products although there is currently limited clinical evidence supporting this claim. Likewise, kratom products that are pre-mixed with other substances would confer a higher risk profile than kratom leaf

alone. Further, any semi-synthetic, isolated kratom alkaloid, and selective alkaloid rich fraction would, we believe, pose considerable risk in an unregulated product, and would no longer be considered as “kratom” in any meaningful sense of the term. Because native kratom leaf has a long use history in Southeast Asia, there are very few instances of major adverse effects reported, which is the basis for the differentiation between native leaf and kratom extract materials. In the years that kratom whole leaf and extract products have been sold in the US, there have been, to date, few clinical case reports of adverse effects. These include reports related to kratom-related morbidities, toxicities, mortalities, and those related to kratom physical dependence or substance use disorder. This is noteworthy given that US kratom consumers now number in the millions.[15–17] Of the cases that do exist, many are confounded by a variety of factors, including other health conditions and polysubstance exposure.

Surveys, case reports, ecological momentary assessment, and other forms of self-report indicate that the primary use of kratom products among US consumers is for relieving pain, anxiety, or mood-related symptoms (and improving mood generally), increasing focus and energy, and for a sizable subset of consumers as a short- and long-term replacement for substances which they believed caused them problems, primarily opioids and alcohol, and to a lesser extent stimulants.[18–21]

Like many psychoactive products (e.g., caffeine), kratom products can be habit-forming as indicated by users who consume large quantities of kratom with greater frequency over an extended period of time. The severity of physical dependence is mild to moderate, and substance use disorder for kratom has been assessed as mild-moderate for those who meet criteria according to the Diagnostic and statistical Manual of Mental Disorders (DSM-5) criteria.[22] Note that a majority of kratom users do not develop a use disorder; those that use kratom regularly and develop physical dependence can manage this and their kratom consumption despite a lack of proper dosing instructions on most kratom product labels. Indeed, we have not seen clinically concerning hallmarks of addiction in the samples of consumers we and others have assessed.[23]

Because of the various kratom products on the market without Federal regulation or appropriate oversight of the US Food and Drug Administration (FDA), it is important to ensure consumers have access to kratom products that are adequately labeled to inform their consumption. As such, legislatures should require adequate labeling of kratom products according to the FDA and the US Federal Trade Commission (FTC) guidances for dietary supplements. Such labeling should include at a minimum: address and name of manufacturer or distributor, a list of all ingredients, the total amount of kratom material per serving, how many servings per container, an expiration or best before date, a statement about how products may be habit-forming with frequent or heavy use, a statement that consumers should consult a healthcare professional prior to kratom consumption, a statement that kratom use is not advised during pregnancy and lactation or by a person who is taking prescription medications. Sales of kratom products should be limited to consumers 18 years and older. The amount of mitragynine, 7-hydroxymitragynine, and total alkaloids per serving should be included on the label as well as a statement that the product contains no semi-synthetic kratom-derived alkaloids. Lastly, the FDA has established guidance documents on proper labeling and good manufacturing practices for dietary supplements that can be adapted for kratom products. Good manufacturing practices (GMP) encompasses adequate documentation of sourcing of materials, adherence to established analytical principles, and organization of facilities and personnel to adhere to regulatory requirements. All kratom products should adhere to GMP.

To conclude, we write this with the recognition that considerably more investment in scientific research is needed to better understand kratom, both as the naturally growing botanical and kratom-derived product formulations. Likewise, more research is needed on kratom's effects on humans. Our statement is based only on data to date. However, based on the currently available scientific and public health knowledge about kratom, we believe that US adults should have access to kratom products that are regulated, ideally along the lines we have noted above, and that investments are made by state legislatures not only in

passing kratom regulations, but enforcing them. Finally, this statement does not necessarily reflect the views of any institution that we work for.

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