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Letters to the Editor

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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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References

1. Suwanlert S. A study of kratom eaters in Thailand. *Bull Narc* 1975; **27**: 21–7.
2. Vicknasingam B., Narayanan S., Beng G. T., Mansor S. M. The informal use of ketum (*Mitragyna speciosa*) for opioid withdrawal in the northern states of peninsular Malaysia and implications for drug substitution therapy. *Int J Drug Policy* 2010; **21**: 283–8.
3. Adkins J. E., Boyer E. W., McCurdy C. R. *Mitragyna speciosa*, a psychoactive tree from Southeast Asia with opioid activity. *Curr Top Med Chem* 2011; **11**: 1165–75.
4. Stolt A. C., Schroder H., Neurath H., Grecksch G., Hollt V., Meyer M. R. *et al.* Behavioral and neurochemical characterization of kratom (*Mitragyna speciosa*) extract. *Psychopharmacology (Berl)* 2014; **231**: 13–25.
5. Brown P. N., Lund J. A., Murch S. J. A botanical, phytochemical and ethnomedicinal review of the genus *Mitragyna* Korth: implications for products sold as kratom. *J Ethnopharmacol* 2017; **202**: 302–25.
6. Grundmann O. Patterns of kratom use and health impact in the US—results from an online survey. *Drug Alcohol Depend* 2017; **176**: 63–70.
7. Varadi A., Marrone G. F., Palmer T. C., Narayan A., Szabo M. R., Le Rouzic V. *et al.* Mitragynine/Corynantheidine pseudoindoxyls as opioid analgesics with mu agonism and delta antagonism, which do not recruit beta-arrestin-2. *J Med Chem* 2016; **59**: 8381–97.
8. Kruegel A. C., Gassaway M. M., Kapoor A., Varadi A., Majumdar S., Filizola M. *et al.* Synthetic and receptor signaling explorations of the *Mitragyna* alkaloids: mitragynine as an atypical molecular framework for opioid receptor modulators. *J Am Chem Soc* 2016; **138**: 6754–64.
9. White C. M. Pharmacologic and clinical assessment of kratom. *Am J Health Syst Pharm* 2018; **75**: 261–7.
10. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Kratom (*Mitragyna speciosa*) drug profile. Lisbon, Portugal: EMCDDA; 2015.
11. Feng L. Y., Battulga A., Han E., Chung H., Li J. H. New psychoactive substances of natural origin: a brief review. *J Food Drug Anal* 2017; **25**: 461–71.
12. Henningfield J. E., Fant R. V., Wang D. W. The abuse potential of kratom according the 8 factors of the controlled substances act: implications for regulation and research. *Psychopharmacology (Berl)* 2018; **235**: 573–89.
13. Anwar M., Law R., Schier J. Notes from the field: kratom (*Mitragyna speciosa*) exposures reported to poison centers—United States, 2010–2015. *Morb Mortal Wkly Rep* 2016; **65**: 748–9.
14. US Food and Drug Administration (FDA). *Statement from FDA Commissioner Scott Gottlieb, M.D., on the agency's scientific evidence of the presence of opioid compounds in kratom, underscoring its potential for abuse.* Silver Spring, MD, 2018: US FDA.
15. Swogger M. T., Walsh Z. Kratom use and mental health: a systematic review. *Drug Alcohol Depend* 2018; **183**: 134–40.
16. Swogger M. T., Hart E., Erowid F., Erowid E., Trabold N., Yee K. *et al.* Experiences of kratom users: a qualitative analysis. *J Psychoact Drugs* 2015; **47**: 360–7.
17. Smith K. E., Lawson T. Prevalence and motivations for kratom use in a sample of substance users enrolled in a residential treatment program. *Drug Alcohol Depend* 2017; **180**: 340–8.
18. Singh D., Narayanan S., Vicknasingam B., Corazza O., Santacroce R., Roman-Urrestarazu A. Changing trends in

the use of kratom (*Mitragyna speciosa*) in Southeast Asia. *Hum Psychopharmacol* 2017; **32**. DOI: 10.1002/hup.2582.
19. Dwyer J. T., Coates P. M., Smith M. J. Dietary supplements: regulatory challenges and research resources. *Nutrients* 2018; **10**. https://doi.org/10.3390/nu10010041.
20. Ajazuddin S. S. Legal regulations of complementary and alternative medicines in different countries. *Pharmacogn Rev* 2012; **6**: 154–60.
21. Sharma S. Current status of herbal product: regulatory overview. *J Pharm Bioallied Sci* 2015; **7**: 293–6.

NEW ZEALAND COURT DISMISSES MINISTRY OF HEALTH CASE AGAINST 'HEAT-NOT-BURN' TOBACCO PRODUCTS, HIGHLIGHTING THE NEED TO FUTURE-PROOF TOBACCO CONTROL LAWS

In recent years tobacco multi-nationals have invested billions of dollars in developing 'lower-risk' alternatives to cigarettes [1,2]. 'Heat-not-burn' (HNB) tobacco products are one outcome of this innovation [2]. HNB work by heating tobacco in an electronic device at temperature lower than the combustion point of cigarettes and thus, according to the producers, reduce exposure to toxic substances [3]. However, findings about the precise level of risks posed by HNB are inconclusive [4–8]. In view of this uncertainty, policymakers are divided in how best to respond.

In the United Kingdom, a notification to Public Health England is required for any 'novel tobacco product' such as HNB [9]. In the United States, the Food and Drug Agency recently extended its authority to regulate new products, including the authorization of reduced-risk marketing claims [10]. Singapore has explicitly banned emerging tobacco products in the 2016 amendment to the Tobacco Act [11]. In many other countries, however, there are no legal provisions regulating new tobacco products, and hence their legal status remains uncertain. A recent landmark case from New Zealand illustrates the challenges in clarifying the legal status of HNB through the courts, and highlights the need for future-proofing tobacco legislation.

The New Zealand District Court recently dismissed a charge by the Ministry of Health (MOH) against Philip Morris International (PMI) for selling HNB products called *Heets* [12]. *Heets* are tobacco sticks which are heated at 350 degrees in an electronic device called *IQOS* [3]. The MOH argued that *Heets* are prohibited under s29(2) of the Smoke-free Environments Act which bans the sale of tobacco 'for chewing, or for any other oral use (other than smoking)'.

PMI argued successfully that the ban in s29(2) was originally enacted to control the sale of chewing and other forms of tobacco when it is placed in the users' mouth, and it was never meant to capture inhalation-based products [12]. They brought an expert witness (from the 'Scientific and Public Communications' unit within PMI) who presented evidence on the reduced risks of HNB. The MOH argued this was irrelevant, but the judge disagreed. The judge applied the legal rule *ejusdem generis* (i.e. if particular words describe a class of things, then the general words that follow are limited to the same class of things), resulting in a narrow interpretation of the ban.

The case sets a precedent which may be used by tobacco corporations in other countries. PMI won using the argument that HNB are safer than cigarettes, based on the evidence from an internal expert witness. Not only does this (again) demonstrate the litigation powers of the industry but also threatens future attempts to limit the sale and marketing of new products, when there is insufficient evidence of their safety. The judgement highlights the need for future-proofing tobacco legislation, including reconsideration of legal language. For example, the use of narrowly defined terms (e.g. 'cigarettes') as opposed to general language (e.g. 'tobacco or vaping products') may mean that existing advertising and tax regulations will not apply to novel products. Ultimately, modern tobacco legislation needs to account for a range of future tobacco innovations.

Declaration of interests

None.

Keywords Heat-not-burn tobacco, IQOS, New Zealand, Smoke-free Environments Act, tobacco industry, tobacco legislation, tobacco litigation.

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References

1. Kennedy R. D., Millstein R. A., Rees V. W., Connolly G. N. Tobacco industry strategies to minimize or mask cigarette smoke: opportunities for tobacco product regulation. *Nicotine Tob Res* 2013; **15**: 596–602.
2. Gillette F., Kaplan J., Chambers S. Big tobacco has caught startup fever (8 March 2017). Available at: https://www.bloomberg.com/news/features/2017-03-08/big-tobacco-has-caught-startup-fever (accessed 30 April 2018) (Archived at http://www.webcitation.org/6yoKmlO0q).
3. Philip Morris International (PMI). Tobacco meets technology. Undated. Available at: https://www.pmi.com/smoke-free-products/iqos-our-tobacco-heating-system (accessed 30 April 2018) (Archived at http://www.webcitation.org/6swdh1LfB).