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Title: Kratom exposures managed by the British Columbia poison centre 2012-2019, a descriptive analysis
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Reviewer 1: Ms. Xin Yi Lim
Institution: Institute For Medical Research Herbal Medicine Research Centre
General comments (author response in bold)

Comment #1 (p3)
(p.3) Kindly refer to good practice in writing plant botanical names

All species need to be fully validated using http://mpns.kew.org/mpns-portal/?_ga=1.111763972.1427522246.1459077346 or http://www.plantsoftheworldonline.org/ or www.theplantlist.org.

in this case it should be Mitragyna speciosa Korth.
Mitragyna speciose has been changed to Mitragenya speciosa Korth (p3) Thank you.

Comment #2 (p3)
(In regard to the statement: In Thailand Kratom has been illegal to buy, sell or possess since 1943)
Kindly check this statement again. The latest news is that it has been decriminalized.
As of August 2021, Kratom has indeed been decriminalized. The previous version was written before this date. This has now been changed in the manuscript.

Comment #3 (p6)
(In regards to research ethics) Is there a study registration number for this study?
As research ethics was not required, there is not a study registration number

Comment #4 (p11)
specific to hepatotoxicity- Is this among sole use or co-ingestion with other substances, and is there any analysis based on duration of use (acute or chronic?), as well as dose
Of the 4 cases that suggested hepatotoxicity, kratom was the only substance identified. 2 cases were considered chronic use and 2 cases were considered acute in nature. Of the 2 chronic cases, the daily doses were 15 grams and 10 grams. The dose was unknown for the 2 acute cases.

Reviewer 2
General comments (author response in bold)

This is a well written manuscript based on the aims and objectives of its title. However, being only a descriptive analysis of calls to a poison control in relation to supposed use of kratom with no laboratory confirmation of the use of kratom (mitragynine), there is no real way of knowing that the calls were in fact related to use of kratom. It is well known that what illicit drugs can be sold as drug A when in fact it is drug B.
Although it is stated on page 15; lines 13-15 that 'the DPIC record of exposure to kratom was not validated by assessment of the substances consumed or by biological sample,"

this point needs to be reinforced more as a potential pitfall to the interpretation of the results of this descriptive study
Thank you. Please see General comment above

Reviewer 3: Dr. Matthew Mink

General comments (author response in bold)

Thank you for submitting this interesting manuscript on kratom. The authors should be commended for contributing to the evolving story associated with this natural product. Thank you

The major strength of your paper is that the analysis goes beyond what many poison centre studies do, which is to solely report on NPDS mandated codes. Here, in addition to detailing who uses kratom and what effects they are experiencing, you have abstracted information on how patients are using kratom. The justification and background provided for producing the work is reasonable. Thank you

The major critique of your submission is likely known; in that we are dealing with a single poison centre's experience. The broader CMAJ readership might value a pan-Canadian perspective. Additionally, the numbers (n=32) over 7 years are relatively small (tacitly acknowledged in your title), especially when compared to papers from the United States using NPDS data.
Agree. Colleagues in other Canadian Centres report few cases, and as we note, as compared to the US, rates of exposure and of attributable effects on user health, are low.

Nonetheless, it must be acknowledged that British Columbia often serves as an early warning signal to the rest of the country when it comes to drugs of abuse. The relationship that DPIC has with the BC CDC is unique amongst the poison centre community. Importantly, no Canadian equivalent to NPDS currently exists.

Suggestions to enhance the manuscript's strength include:
1) Abstract: Would remove the final sentence. While no doubt, knowledge about kratom could be improved, clinician knowledge wasn't methodically measured in this review, nor is there enough presented in the text to make this assertion. Likewise, the opioid crisis probably does have something to do with kratom use but as only 3 patients identified that kratom was being used for opioid withdrawal, the assertion might be deemed speculative if your paper is taken in isolation.
Thank you. Done.

2) Methods: Kratom displays dose-dependent effects and to account for this, you have classified patients as stimulant, depressive, hepatotoxic or withdrawal cases. It's not clear to me in my research, or from reading your paper, at what dose these various effects occur. Sanderson and Rowe's "5 things to know" on kratom (reference 32) makes a comment about opioid toxidrome, while Wang and Walker (reference 12) suggest the exact doses where these effects occur are unknown. It would be helpful to the readership to know the average doses associated with these effects.
Our paper only included nine cases in which dosing information was available and unfortunately we would not be able to comment on the specifics of what adverse symptoms occur at which doses. From our research, it seems that low doses of 1-

5g are associated with mild stimulant effects, and higher doses of 5-15g are associated with opioid-like effects. See Prozialeck et al – Pharmacology of Kratom: An emerging Botanical Agent with Stimulant, Analgesic and Opioid-Like Effects. Journal of Osteopathic Medicine 112.12 (2012): 792-799.

I assume not all of these might be mutually exclusive in nature – you could have a hepatotoxic patient who was also displaying stimulant effects (although it doesn't look like it from Table 2).
A stimulant/depressive effect could absolutely coincide with hepatotoxicity. In the four cases in our study labelled hepatoxic however, the signs/symptoms were all in keeping with hepatoxicity (each of them presented with abdominal pain and elevation in liver enzymes), and did not exhibit stimulant symptoms (anxiety, tremors, nausea etc.) nor depressive symptoms (drowsiness, respiratory depression, coma). Based on available information, it seemed the basis for the call to DPIC was hepatotoxicity.

3) Results – Figure 1 is problematic in that while reading the text, readers will expect to see the steady increase seen in Figure 2 and Figure 4. Additionally, figure 1 appears to be missing a case (likely a case of "unknown age" from 2017). Suggest re-drafting the information into a table.
Thank you. Figure 1 has been removed as above. Please also note the formatting changes to previous figures 2, 3, and 4 (now figures 1, 2, 3)

4) Results - Information on poison centre follow up calls are presented without discussion of this in the methods. Suggest either removing this or expanding on it the method section.
NOW in methods

5) Results – Circumstances of use: 15/32 is 47%, not 57%.
Thank you for catching this. Corrected.

6) Discussion: There are a number of uncited papers that would be useful in considering:
a. In terms of limitations, how would your work stand up to the critiques of Reference 30 (Eggleston et al)? See Pharmacotherapy 2019;39(11):1119–1120.
Grundmann posits that kratom is much safer than what is described by the original study, although the supporting literature for this argument is somewhat sparse
The critiques includes:
1. That the authors of the original study ignore that kratom has been used for centuries in southeastern Asia and there has never been a kratom-related death in the region (no reference is provided for this fairly significant statement)
2. That the paper fails to cite the peer-reviewed literature describing experiences of kratom users that suggest kratom is a safe and effective substance to wean off opioids (this was a qualitative study)
3. That the authors have no way of establishing cause and effect of kratom causing the adverse outcomes (which the original authors acknowledge)
4. The number of cases requiring medical intervention was not reported
5. That they fail to acknowledge that the majority of deaths associated with kratom exposure are accompanied by polysubstance use

As far as the application of these critiques to our own study, these points are either beyond the scope of our work, or have been acknowledged and discussed by us. At this point we have not included a reference to the critique but would be happy to revisit this if reviewers deem relevant.

b. Ng et al. Substance Abuse Treatment, Prevention and Policy (2021) 16:23 recently published on the quality of information on websites targeting Canadian kratom consumers.
Ng's study used a 16-question tool to assess the quality of consumer health information provided by online vendors selling Kratom to consumers in Canada. They concluded that the overall quality of 78% of websites was poor and that individuals seeking to purchase kratom online are not provided with the critical information necessary to make an informed decision on the impacts of Kratom on the body. We have included this information in interpretation (p.11).

c. Graves et al. in J American Geriatric Society 2021 Aug;69(8):2176-2184 looked at NPDS data to show that seniors are using kratom, albeit very few.
Of 3484 kratom-related exposures from 2014-2019, 162 (4.6%) were among adults over 60 years. These numbers were similar to our study finding of 1 case (3.1%). This paper did show an increase in annual kratom-related exposures, in the age group >60 years and that the distribution of gender amongst this age group is much more evenly split than in the 18-59 age group. Adverse outcomes were more frequent amongst older adults >70 years (21.9%) compared to 9.6% among ages 18-59 and there was concern for medication interaction. We have added a statement in our interpretation (p.11) regarding this paper although it should be noted that our primary demographic in BC was young males.

7) Discussion – describing hepatotoxicity as "frequent" at 13% in your work may be over-reaching. Suggest choosing a different descriptor.
Thank you, we have changed to "occasionally"(p.11)

8) Figure 4 – Labelling both vertical axes could be considered (opioid cases, kratom cases)
Done, thank you. Now Figure 3 (p.15)

9) Appendix : Valuable to include in supplementary information in order to illustrate methodology; would be improved by labelling the codes.
The substances that are encompassed by these codes are now in methods rather than included in an appendix (p.5). Editor please advise if would prefer it another way.