Case Report

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Kratom-induced acute liver injury: A case study and the importance of herbal supplement regulation

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Summary

Alternative medicine supplements have become the second most common cause of drug-induced liver injury (DILI) in the US. Kratom is a herbal supplement that is popular for its psychotropic and opioid-like activity. It has become increasingly available in western countries, which often have no specific regulations on its use. However, reports of adverse events linked to kratom use have been increasing; it has been implicated in acute liver injury (mostly cholestatic), acute liver failure, organ dysfunction, toxicity, coma, seizures, and death. Herein, we aim to increase healthcare provider and public awareness of the risks posed by kratom and ultimately support increased regulation of its use.

Introduction

Drug-induced liver injury (DILI) and drug-induced liver failure due to alternative medicine supplements have increased in the US. Alternative medicine supplements have become the second most common cause of DILI.[1] Kratom is a herbal supplement that is derived from the leaves of *Mitragyna speciosa* trees in Southeast Asia. Kratom is popular for its psychotropic and opioid-like activity. In addition to its addictive potential, kratom has been shown to cause acute liver injury and, in a rare case, acute liver failure resulting in the need for liver transplantation.

Kratom has become increasingly available in western countries.[2] This has led to an increasing number of calls to the US poison center due to kratom ingestion. There were reportedly over 1,800 total calls from 2011-2017.[3] Unfortunately, it is currently banned in only six states (Rhode Island, Indiana, Alabama, Arkansas, Wisconsin, and Vermont), regulated in eight states, and completely unregulated in the remaining states (Fig. 1).

This paper provides a report of a patient who presented with cholestatic liver injury due to kratom use, which highlights the dangers of poorly regulated herbal supplements domestically and globally. The purpose of our paper is to review the shortcomings of regulatory practices, to increase healthcare provider and public awareness, and to provide support for Food and Drug Administration (FDA) regulation of kratom.

Case report

A 47-year-old male with a past medical history of peripheral neuropathy and hypertension presented to the emergency department complaining of jaundice for the past 5 days and an unintentional 6.8 kg weight loss in the past month. He had a history of heavy alcohol use, drinking about 750 ml of vodka per day for 1 year but had quit 2 years ago. On questioning regarding new medications or supplements, he reported starting kratom for neuropathy and hip pain for 3 weeks prior to presentation. His physical exam was notable for jaundice, and his lab results were significant for cholestatic injury with an R-ratio of 1.8, and urine drug screen was positive for tetrahydrocannabinol and benzodiazepines (Table 1). The patient tested negative for acetaminophen toxicity, viral hepatitis, and human immunodeficiency virus infections.

A computed tomography of the abdomen and pelvis with intravenous contrast showed normal liver and portal veins with an incidental finding of a pancreatic tail mass. Further imaging with the magnetic resonance of the abdomen with and without contrast showed a complex cystic mass in the pancreatic tail. Endoscopic ultrasound with fine-needle aspiration of the cyst was performed, with findings consistent with a well-differentiated neuroendocrine tumor. While waiting for the fine-needle aspiration results, the patient's liver function continued to improve. The patient was discharged to follow-up with his primary care provider and outpatient gastroenterology and oncology departments. Since discharge, the patient

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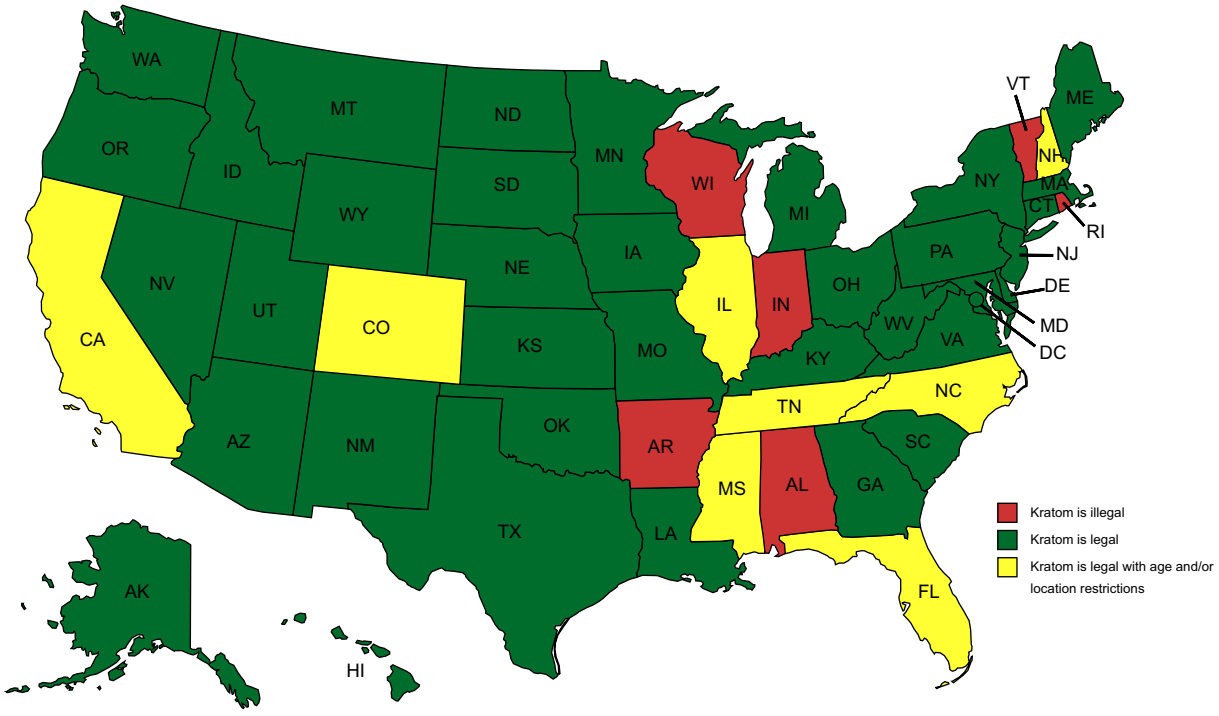

Fig. 1. A map of the US and locations of Kratom restrictions as of 2022. California: Kratom is legal, except in San Diego and Oceanside; Colorado: Kratom is legal, except in the towns of Monument and Parker; Florida: Kratom is legal, except in Sarasota country; Illinois: Kratom is legal for adults 18 years and older, except in Jerseyville and Alton; Mississippi: Kratom is legal, except in several counties; New Hampshire: Kratom is legal, except in Franklin city; North Carolina: Kratom is legal for adults 18 years and older; Tennessee: Kratom is legal for adults 21 and older.

Table 1. Laboratory test results.

Variable (normal range)	Day of admission	Day of discharge
Total bilirubin, mg/dl (0.0-1.2)	10.7	5.0
Direct bilirubin, mg/dl (≤0.5)	6.7	
AST, U/L (8-34)	64	53
ALT, U/L (10-49)	168	87
ALP, U/L (46-116)	265	279
GGT, U/L (12-64)	376	
INR (0.80-1.2)	1.04	
Prothrombin time (9.3-12.4 seconds)	10.9	
Lipase, U/L (<78)	36	
CA 19-9, U/ml	<5.30	
Acetaminophen, μg/ml (0.0-10.0)	5.6	
Ferritin, ng/ml (11.0-307.0)	410.2	
Iron, μg/dl (65-175)	140	
Ceruloplasmin, mg/dl (16.0-31.0)	31.3	
Copper, μg/dl (72-166)	120	
Antinuclear antibody	Negative	
Smooth muscle antibody, units (0-19)	20	
Anti-mitochondrial antibody, units (0.0-20.0)	<20.0	
Alpha-1 antitrypsin, mg/dl (90.0-200.0)	186.0	

ALP, alkaline phosphatase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin; AST, aspartate aminotransferase; CA 19-9, carbohydrate antigen 19-9; GGT, gamma-glutamyltransferase; INR, international normalization ratio.

reported resolution of all of his symptoms following the discontinuation of kratom.

Discussion

The use of kratom has been increasing in the US. This is likely in part a response to the opioid epidemic, as healthcare policies have shifted toward discouragement of prescribed opioids for non-cancer pain.[4] The raw leaves can be smoked, chewed, or boiled in water. In western countries, kratom is sometimes dried into powder, capsules, and extracts.[2] The FDA has recently performed extensive biochemical analysis of kratom.[6] The plant from which kratom is derived contains more than 40 psychoactive alkaloids including mitragynine, 7-hydroxymitra-gynine (7-MHG), speciociliantine, and corynantheidine.[2,5] The most prevalent alkaloid is mitragynine (about 66%) with 7-MGH present in lower amounts (0.02%).[2] These active ingredients have been shown to partially bind and activate mu-opioid receptors as well as kappa receptors, though with less affinity. It may also be a partial antagonist of delta-opioid receptors.[2,5] While 7-MHG seems to be 13 times more potent than morphine, mitragynine seems to have less affinity to opioid receptors than morphine.[2] Additionally, mitragynine is structurally like yohimbine. Similarly to yohimbine, it binds to alpha-2 adrenergic postsynaptic receptors modulating descending pain pathways.[2] The pharmacology of the remaining trace alkaloids are complex, with a combination of stimulant and opiate-like activities.[2]

Due to kratom's opioid and euphoric effects, its use has become more popular in recent years, as demonstrated by an increase in the number of calls to the US poison center. About 65% of these calls were due to isolated exposure to kratom, and 35% were with additional substances (ethanol, benzodiazepines, other herbal supplements, narcotics, acetaminophen).[3] In 2016, the Drug Enforcement Administration (DEA) noted that about 30 deaths have been reported since 2009.[7] There were 807 reported cases of kratom-induced adverse effects found by the FDA Adverse Event Reporting System (FAERS). Although, exact measures of kratom use in the US are not available,[8] data from the National Survey on Drug Use and Health estimated that about 0.7% of people in the US used kratom in 2019 (approximately 2.3 million).[9] Risk factors for kratom use included age younger than 50-years old, a past-year diagnosis of prescription opioid-use disorder, and history of recreational drug use. About 10.4% of those with opioid-use disorder reported use.[9] Unfortunately, there has been a rapid diffusion of kratom throughout western countries and it is widely available with minimal regulation.[10] The increase in kratom use in western countries correlates with availability via internet sales.[11]

In most countries, including the US, herbal medications are unregulated, and products are often unregistered. Thus, there is no assurance for the safety, quality, and efficacy of these products.[12] This makes it difficult for physicians and consumers to be informed. Only 64 of the World Health Organization's (WHO)'s 191 countries regulate herbal medications.[13] Over the years, the WHO has published guidelines for herbal medicines.[14] These guidelines were published to help improve quality, limit contamination, include herbal medicines in the national drug safety monitoring systems, and establish guidelines to register and regulate herbal medicines. Unfortunately, scientific studies on herbal products and their uses can be complicated, as many products contain more than one herb. Regardless, the WHO has stressed a need for further study of the pharmacological and clinical effects of herbal medicines.[13] In the US, rigorous evaluation of one herbal product, sinecatechins, led to its re-classification as a therapeutic drug; it was thus subjected to FDA oversight in production and marketing. Unfortunately, such events are a rare occurrence. Additionally, the ways herbal medicinal products are made, licensed, dispensed, manufactured, and traded differ between countries. Furthermore, the cultural significance of herbal medical products varies from one country to another.[12] As these products can be purchased overseas, it is difficult to harmonize regulations internationally. Due to a high volume of reports of harm, however, the FDA has issued multiple import alerts to consumers recommending against the use of kratom.[15]

In 2016, the DEA attempted to place mitragynine and 7-HMG as a schedule I drug. This resulted in a public backlash. Organized efforts by the American Kratom Association and the Botanical Education Alliance led to phone calls and petitions with over 100,000 signatures sent to the White House. Advocates maintained that kratom was safer than prescription opiates, and thus can reduce opiate deaths. Due to this reaction, the DEA withdrew their intent to place mitragynine and 7-HMG as a schedule I drug.[16] Currently, kratom is not scheduled under the US Controlled substance act, although the DEA advises against its use as an alternative to prescription opioids. The FDA has issued multiple statements describing kratom as unsafe.[17] Kratom is not listed as a schedule 1 controlled substance under the UK's Psychoactive Substance Act, which was passed in 2016. It does, however, classify it as a controlled substance.[18] The legal status of kratom greatly varies between countries, but currently it is illegal in Denmark, Finland, Ireland, Latvia, Lithuania, Poland, Romania, and Sweden.[19]

Kratom (mitragynine and 7-HMG) supplementation has been implicated in acute liver injury, largely characterized by cholestatic injury, acute liver failure, organ dysfunction, toxicity, coma, seizures, and even death. Mitragynine also appears to inhibit hepatic demethylases and transferases, and UDP-glucuronosyltransferases. For this reason, kratom can interact with many common prescription medications.[2] Kratom also has addictive potential due to its action on mu-opioid receptors.

In the US, herbal supplements are marketed as dietary supplements. Manufacturers therefore cannot claim the products are therapeutic. Since kratom's popularity is due to its opioid-like effects, we argue that it is consumed as a therapeutic, and therefore should be regulated as such. Without regulatory oversight, it is difficult to ensure authentic and pure quality and potency of commercially available kratom products. Healthcare professionals and patients need to be made aware of the potential harm kratom poses due to a lack of regulation in the US. To avoid further serious adverse events associated with kratom use, we see a strong indication for more extensive and specific guidelines on this product.

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Abbreviations

7-MHG, 7-hydroxymitra-gynine; DEA, Drug Enforcement Administration; DILI, drug-induced liver injury; FAERS, adverse event reporting system; FDA, Food and Drug Administration; FNA, fine-needle aspiration; WHO, World Health Organization.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions

K.R. - initial draft, study design, data collection, revision of the article, and approval of the final draft submitted. S.M. - data collection, revision of the article, and approval of the final draft submitted. B.S. - data collection, revision of the article, and approval of the final draft submitted. K.N. - study design, revision of the article, and approval of the final draft submitted. S.W. - revision of the article and approval of the final draft submitted. Guarantor of the article: K.R., D.O.

Data availability statement

All relevant data are within the paper.

Disclaimer

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Supplementary data

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