SYSTEMATIC REVIEW

Adverse Psychological and Therapeutic Effects of Kratom (*Mitragyna speciosa*) Use: A Systematic Review

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ABSTRACT

Aims: This review aimed to comprehensively examine kratom's therapeutic potential for treatment of mental health-related issues as well as any related benefits and risks. **Design:** Systematic review. **Data sources:** Google Scholar, Web of Science, PubMed, Scopus, PsycINFO, EMBASE, Cochrane Library, and Medline. **Review methods:** Three authors carried out electronic search of articles published between 1950 to September 2022 through major databases for a duration of three months (from July to September 2022). Each author independently screened the literature for inclusion and exclusion criteria, the findings were then compared, discrepancies between authors were resolved, and the final selection of articles were reviewed. **Results:** A total of 46 articles were included in this review. A total of three in vitro and animal studies and five cross-sectional online surveys reported the therapeutic potential of kratom in opioid replacement therapy. In addition, a total of two animal studies and three cross-sectional online surveys highlighted the role of kratom as a potential antidepressant and anxiolytic. Contrastingly, two animal studies, 11 studies in human subjects, and 16 case reports documented the risk of kratom dependence, cravings, tolerance, and kratom-related substance use disorder as the major safety concern of implementing kratom use as a therapeutic agent. **Conclusion and impact:** In the absence of human clinical trial, coupled with various considerable adverse events of kratom (not limited to psychological side effects), evidence to support kratom as potential therapeutic use remains inconclusive.
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Keywords: Kratom, mental health-related safety profile, opioid replacement therapy, antidepressant, anxiolytic

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INTRODUCTION

Kratom (*Mitragyna speciosa* Korth.) belongs to the rubiaceae family and is native to Southeast Asia, especially Malaysia, Thailand, and Indonesia (1). It has been used for centuries in southern Thailand and northern peninsular Malaysia (2, 3). Its leaves are dark green and oval in shape, and are available for use as a traditional remedy for various illnesses. Due to its medicinal value, kratom leaves are often used as an antidiarrheal, analgesic, and antihypertensive. Kratom is available in various forms, such as tea, gum, and capsules, making it very convenient to use and leading users to consider it a safe psychoactive product with therapeutic potential (4). In recent years, kratom has been widely used in Europe and the United States due to its broad antidepressant, anxiolytic, and analgesic effects (5).

Current research indicates that kratom leaves contain more than 40 compounds, four of which have been identified as having pharmacological activity: mitragynine, 7-hydroxymitragynine (7-HMG), corynantheidine, and speciociliatine (6). The main pharmacologically active compound contained in kratom is mitragynine, an indole alkaloid, which is the main producer of kratom's opioid-like activity. In addition, two indole alkaloids that are frequently investigated are mitragynine and its active metabolite, 7-HMG (1, 7). As mitragynine, 7-HMG, and other psychoactive kratom-derived analogs exhibit binding affinity for various receptors, such as opioid, adrenergic, and serotonergic receptors, kratom is expected to possess various therapeutic potentials in addition to adverse effects (8).

Kratom's effects on humans are dose-dependent: low-dose intake of kratom has a stimulating effect similar

to caffeine, while higher doses can induce opioid-like effects (9). Long-term use of kratom can cause side effects, including anorexia, weight loss, insomnia, and kratom dependence (9, 10). Although kratom's toxicity is far lower than that of conventional drugs, there are still reports pointing out the negative effects and lethal risk (11). Consequently, kratom is classified as a controlled substance in various countries around the world. The consumption and possession of kratom is regulated in Malaysia's Poison Act 1952 and a ban on kratom as a dangerous substance was only recently lifted in Thailand (12, 13). The United States Food and Drug Administration classified it as an opioid with harmful effects and it is now considered a controlled substance in several states (13, 14).

Kratom is a substance exhibiting an increasing usage trend as a self-prescribed agent amid an emerging epidemic of opioid abuse and dependence in the United States due to stricter access to prescription opioids which led to an increased use of heroin and illicit fentanyl since 2015 (15). Hence, it is of the utmost importance to gather data on kratom's therapeutic potential as well as any safety concerns and risk of toxicity, to allow treating clinicians and researchers to gauge the benefits versus the risk of kratom use. Hence, we conducted a systematic review to comprehensively examine kratom's therapeutic potential when treating mental health-related issues as well as any related benefits and risks.

METHODOLOGY

Search strategies

Three authors (MFILA, BY, and SY) independently carried out an electronic search of published literature from 1950 to September 2022 using the major databases, such as Google Scholar, Web of Science, PubMed, Scopus, PsycINFO, EMBASE, Cochrane Library, and Medline. The electronic search was carried out from July 2022 to September 2022 (for a duration of 3 months). Initially, a preliminary search was performed using Mitragyna, *Mitragyna speciosa*, and kratom as the terms and keywords. Then, a refined search was carried out with additional keywords, such as psychological effects, therapeutic effects for mental health, depression, anxiety disorders, psychotic disorders, affective disorders, obsessive compulsive disorder, stress, acute stress disorder, posttraumatic stress disorder, anxiolytic effects, antidepressant effects, sedative effects, attention deficit hyperactive disorder, kratom addiction, kratom dependence, kratom withdrawal, kratom tolerance, cross-tolerance, bipolar mood disorder, and drug replacement therapy. The terms in this string were combined with 'OR'. This search led to a total of 2,140 hits. In addition, hand searching was carried out in this review, resulting in a page-to-page perusal of the key journals that may have published studies on the psychological effects of kratom use. Hand searching was also carried out for conference proceedings. After the three authors completed their independent searches, the findings were compared, discrepancies were resolved, and final selection of articles were reviewed.

Inclusion and exclusion criteria

Literature was eligible for review if they fulfilled the following inclusion criteria: [1] published in English language peer review journals, including in-press articles; [2] research articles, case reports, and case series; and [3] literatures related to mental health and psychological impact of kratom use, including treating kratom dependence. Literatures were excluded if: [1] they were published in non-English language journals (the reason for exclusion being the authors did not have access to expertise to interpret the content and findings of the studies published in languages other than English); [2] systematic review, narrative review, letters to the editor and editorials, commentaries, correspondence, unpublished articles, and thesis; and [3] literatures which dealt with adverse effects and toxicity of kratom use other than mental health or psychological impact, such as epidemiology, physical adverse effects and toxicity of kratom use, and therapeutic effects of kratom other than for psychiatric or mental health purposes.

Data extraction

The three authors coded the study characteristics and findings into a database. The coded data contained information, including methodological characteristics (study design, participants' socio-demographic characteristics such as age and gender, sampling method, sample size estimation, study objectives, and outcome measures), study findings, and limitations. Then, the review was organized into the following categories: kratom therapeutic potential for substance withdrawal and dependence, kratom therapeutic potential as an antidepressant and anxiolytic, and mental health drawbacks on kratom use as a therapeutic agent.

RESULTS

Characteristics of the studies

An initial database search for titles and abstracts yielded 2,140 articles, but 1,900 articles were excluded as duplicates. Careful screening of the abstracts of 240 articles resulted excluding another 140 articles as they were not specific to kratom use and/or were systematic review, narrative review, letters to the editor and editorials, commentaries, correspondence, and unpublished articles. Then, 100 full-texted articles were screened for eligibility criteria, and another 64 articles were excluded as they described Mitragyna genus other than *Mitragyna speciosa*, focused on adverse effects and toxicity other than mental health or psychological impacts, and did not present enough information. Hence, 46 articles were finally selected for review after another 10 additional articles were discovered through hand searching. The flow of search findings is illustrated in Fig 1.

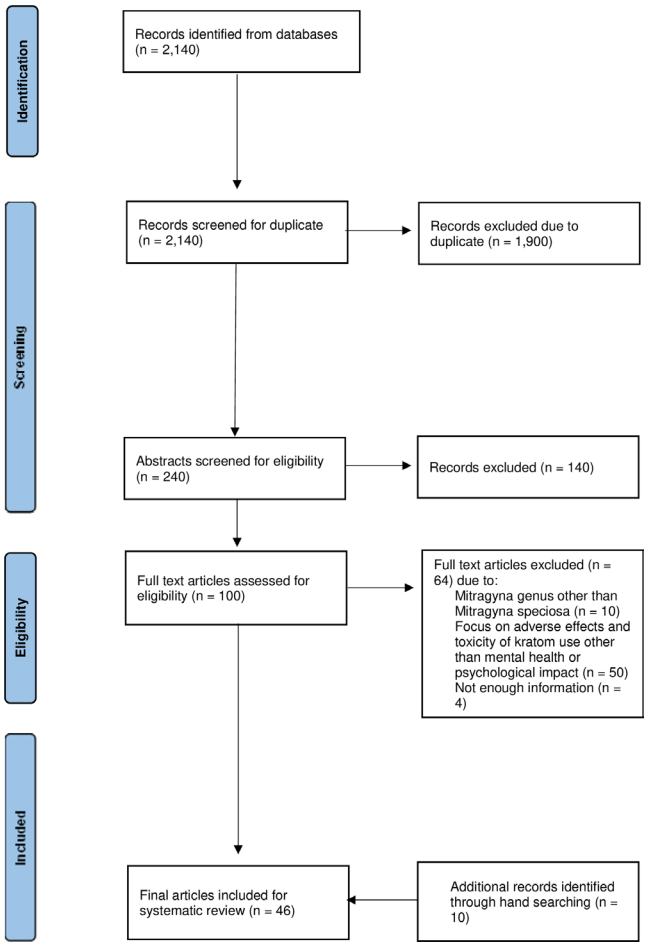

Figure 1: PRISMA flowchart illustrating the selection process of articles in this systematic review which resulting in the final selection of 46 articles for review

The studies selected for review included 10 in vitro and animal studies, 20 studies with human subjects, and 16 case reports. The sample size of the 20 studies in human subjects varied from being as low as 30 subjects to as high as 32,893 subjects (17-35). No clinical trial was found from the database search. The characteristics, findings, and limitations of the selected studies are summarized in Table I. The selected cross-sectional surveys in this systematic review was critically appraised using the Appraisal tool for Cross-Sectional Studies (AXIS). The findings of the critical appraisal are summarized in Table II.

Kratom's therapeutic potential for substance withdrawal and dependence

Kratom has long been reported to exhibit opiate-like effects and has therapeutic potential to be used for opioid replacement therapy. The most common psychoactive alkaloid of kratom extract, such as mitragynine, has been described as a possible candidate as three in vitro and/or animal studies demonstrated this therapeutic potential (7, 36, 37). Both mitragynine and 7-HMG act as partial agonist at the μ opioid receptors and as competitive antagonist at the δ and κ opioid receptors (36). Despite being an agonist at the μ opioid receptors, mitragynine failed to recruit β-arrestin 2, thereby establishing that mitragynine develops analgesic tolerance slower than morphine, and documented minimal respiratory depression, physical dependence, constipation, and display no aversion and reward effects in condition place preference (CPP) assays (37). Although 7-HMG exerts a more potent μ opioid agonist effect than mitragynine, the latter has been reported to reduce morphine intake, while 7-HMG contrastingly increases morphine intake in rats (7). A more recent animal study on the therapeutic potentials of two kratom-derived alkaloids (paynantheine and speciociliatine) and four novel kratom-derived analog (7-hydroxypaynantheine, paynantheine pseudoindoxyl, 7-hydroxyspeciogynine, and speciogynine pseudoindoxyl) revealed that paynantheine produced an aversion in a limited CPP paradigm, while 7-hydroxypaynantheine and 7-hydroxyspeciogynine—which exhibited potency at δ opioid receptors but not in μ opioid receptors—decrease voluntary alcohol consumption in wild type mice, but not in δ receptor knock-out mice. These findings suggested the potential of 7-hydroxypaynantheine and 7-hydroxyspeciogynine as therapeutic agents for alcohol use disorder, which is mediated through δ opioid receptors (38).

Five cross-sectional surveys were conducted to investigate the therapeutic potentials of kratom in the US population, and highlighted the respondents' subjective accounts, describing the effectiveness of kratom as a form of self-prescribed replacement therapy for prescribed opioid or illicit opioid use (18, 27-29, 31). Around 10–66% of American respondents in these surveys agreed that kratom use alleviated opioid withdrawal, reduced prescribed and illicit opioid use, relieved pain related to opioid use, and allowed abstinence from opioid use for more than one year (18, 27, 28). However, kratom use as an acute, self-prescribed treatment for opioid withdrawal is more prevalent than kratom use for long-term replacement therapy for opioid use disorder (29). The participants in the surveys reported milder adverse effects, such as gastrointestinal effects (nausea and constipation) lasting less than 24 hours, and only 2% of the respondents developed moderate or severe kratom-related substance use disorder, especially in those who took a high dose and experienced more frequent dosing (18, 27-29).

Kratom therapeutic potential as an antidepressant and anxiolytic

Two animal studies have suggested that kratom possesses antidepressant properties (39, 40). Three cross-sectional surveys in human subjects further support this theory (18, 27, 28). Intraperitoneal injection of mitragynine in rats demonstrated a reduction in immobility in the forced swim test and tail suspension test without an effect on their locomotion in the open field test, which was associated with a reduced release of corticosterone. This may indicate that the antidepressant effect mitragynine exhibited was mediated by the hypothalamic-pituitary-

Table I: Summary of the 46 selected articles for systematic review

Kratom therapeutic potential for substance withdrawal and dependence

Author(s)/ year/ country	Study design	Participants (N/ gender/ age)	Sampling method	SSE (Yes/No)	Study objective(s)	Outcome measures (Measures/ Intervention)	Findings	Limitations
Kruegel et al., 2016, USA	in vitro study	NA	NA	NA	To examine mitragynine and a number of natural and novel analogs of *Mitragyna speciosa* at the opioid receptors, measuring receptor activation and intracellular signaling.	First receptor-level functional characterization of mitragynine and related natural alkaloids at the mu-, kappa-, and delta-opioid receptors.	(1) MG and 7-HMG are partial agonists of the human mu-opioid receptor and competitive antagonists at the kappa- and delta-opioid receptors. (2) MG and 7-HMG are G-protein-biased agonists of the mu-opioid receptor, which do not recruit β-arrestin following receptor activation.	
Varadi et al., 2016, USA	in vitro study	NA	NA	NA	To evaluate the the pharmacology and SAR studies both in vitro and in vivo of mitragynine pseudoindoxyl, mitragynine and corynantheidine analogs	Receptor-level functional characterization of mitragynine pseudoindoxyl	(1) In vitro, mitragynine pseudoindoxyl and its analogs were potent agonists at the mu opioid receptor but failed to recruit β-arrestin-2. (2) Mitragynine pseudoindoxyl developed analgesic tolerance slower than morphine, showed limited physical dependence, respiratory depression, constipation, and displayed no reward or aversion in CPP/CPA assays.	
Hemby et al., 2018, USA	Animal study	Rats: Experiment 1: MG (n = 9), 7-HMG (n = 8); Experiment 2: MG (n = 8), 7-HMG (n = 8)	NA	NA	To assess the reinforcing effects of MG and 7-HMG	Substitution for morphine self-administration, acquisition of self-administration, and selective opiate receptor antagonism of morphine and 7-HMG self-administration	(1) Prior exposure to 7-HMG increased subsequent morphine intake whereas prior exposure to MG decreased morphine intake.	(1) Food restriction of the rats may enhance acquisition of opiate self-administration and increases intake during the maintenance phase and enhances drug seeking. (2) Kratom is administered orally by humans whereas intravenous administration was used in this study- bioavailability is not the same.
Gutridge et al., 2021, USA	In vitro and animal study	male C57BL/6N WT and δOR knockout mice	NA	NA	(1) To characterize paynantheine, speciociliatine, and four novel kratom-derived analogs (7-Hydroxypaynantheine, Paynantheine Pseudoindoxyl, 7-Hydroxyspeciogynine and Speciogynine Pseudoindoxyl) for their ability to bind and activate δOR, μOR, and κOR. (2) To investigate the compounds' ability to decrease alcohol consumption, while monitoring lead compounds risk for seizure activity, induce reward properties, and affect general locomotion.	Locomotor evaluation, brief and Extended Conditioned Place Preference Paradigms, Seizure Assay, Tail Flick Thermal Nociception Assay, Two-Bottle Choice Alcohol Paradigm and Accelerating Rotarod Test	(1) Paynantheine (lower dose) produced aversion in a limited CPP paradigm but did not produce CPP with additional conditioning sessions. (2) 7-hydroxypaynantheine and 7-hydroxyspeciogynine displayed potency at δOR but limited μOR potency relative to 7-HMG in vitro, and dose-dependently decreased voluntary alcohol consumption in WT but not δOR in KO mice. (3) 7-hydroxyspeciogynine- did not produce significant CPP neither alter general locomotion nor induce noticeable seizures.	(1) Kratom is administered orally by humans whereas intraperitoneal administration was used in this study- bioavailability is not the same.
Grundmann, 2017, USA	Cross-sectional survey	N = 8,049 (human subjects), males and females	NA	No	To investigate the demographics, perceived beneficial and detrimental effects of kratom as well as common doses and purposes of its use among the American kratom users	Self-designed questions	(1) Kratom is primarily used for self-treating pain (68%) and emotional or mental conditions [such as mood disorders, and withdrawal symptoms associated with prescription opioid use (66%)]. (2) Kratom induced dose-dependent negative effects (primarily gastrointestinal related including nausea and constipation, mainly presenting at high (5g or more/dose) and more frequent (22 or more doses/week) dosing.	(1) Cross-sectional design. (2) Bias introduced by online survey and self-reporting format. (3) The sample not representative of the American kratom population.

Table I: Summary of the 46 selected articles for systematic review (continued)

Kratom therapeutic potential for substance withdrawal and dependence

Author(s)/ year/ country	Study design	Participants (N/ gender/ age)	Sampling method	SSE (Yes/No)	Study objective(s)	Outcome measures (Measures/ Intervention)	Findings	Limitations
Coe et al., 2019, USA	Cross-sectional survey	N = 2867 (current users) and 157 (former users), males and females	NA	No	To describe reasons of individuals use kratom in place of opioids, specific reasons for use, perceptions of the efficacy of kratom as an opioid substitute, the safety/tolerability of kratom, and anticipated reactions if legal access to kratom were restricted.	Self-design questions	(1) Kratom use for pain relief (48%), anxiety, PTSD, or depression (22%), to increase energy or focus (10%), and to help cut down on opioid use and/or relieve withdrawal (10%). (2) Over 90% of respondents who used it in place of opioids- kratom helpful to relieve pain and withdrawal and reduce opioid use. (3) Only 13% of users experienced bad adverse effects. (4) If kratom was not legally available- 36.4% of respondents will get it where it was legally available, 26.7% try to get it illegally, 24% replace it with something else (the latter will turn to prescription and/or illegal drugs).	(1) Cross-sectional design. (2) Bias as subjects were self-selected and researcher from American Kratom Association. (3) No objective measures.
Garcia-Romeu et al., 2020, USA	Cross-sectional survey	N = 2,798 (human subjects), males and females	NA	No	To characterized American kratom user demographics, use patterns, and perceived drug effects.	PROMIS-GH, BPI, SOWS, DEQ	(1) Kratom- taken orally in doses of 1-3 grams (49%), with daily use (59%) being most common. (2) Kratom was used for pain (91%), anxiety (67%), and depression (65%), with high ratings of effectiveness. (3) 41% used kratom to stop or reduce prescription or illicit opioid use, citing decreased opioid withdrawal and craving related to kratom use, with 411 reporting >1-year continuous abstinence from opioids attributed to kratom use. (4) 1/3 of respondents- experienced mild adverse effects of kratom and lasting ≤24 hours. Only 0.6% sought treatment. 2% had moderate or severe kratom-related substance use disorder (SUD).	(1) Selection bias which involved self-selection. (2) Cross-sectional design. (3) The sample not representative of the kratom using population.
Smith et al., 2021(a), USA	Cross-sectional survey	N = 280 (human subjects), males and females	NA	NA	To provide additional insight into kratom use among adults on social media and add more detailed self-report information	Self-designed questions	(1) Kratom reported as acute self-treatment for opioid withdrawal were more prominent compared to longer-term opioid substitution. (2) Higher kratom doses- greater odds of kratom addiction or withdrawal, with slightly lower odds of desirable effects.	(1) Posts may not be representative of most people's experiences with kratom, or of the broader kratom-using U.S. population. (2) Data were collected solely from Reddit.
Smith et al., 2022, USA	Cross-sectional study	N = 289, males and females	NAD	No	To assess the current state of kratom-use initiation, sourcing, motivations, preference, conceptualizations, and perceived stigma, using survey responses from current and former users.	Self-designed questions	(1) Mean age of use initiation (29.9 years) was older than for other substances, including opioids. Kratom ranked as a preferred substance by 48.5%. (2) Use was less likely among those prescribed buprenorphine in the past year. Past-month cannabis- strongest association with past-month kratom use. (3) Over 40 use motivations were endorsed, many (but not all) supporting the "self-treatment" narrative of kratom use, including use as an opioid, alcohol, or stimulant substitute. Treatment shortfalls were associated with decisions to try kratom.	(1) Cross-sectional design. (2) Self-selection bias.
Idayu et al., 2011, Malaysia	Animal study	48 mice of IRC strain divided into 6 groups (8 per group)	NA	NA	To evaluate the antidepressant effect of mitragynine in the mice	FST, TST	(1) Mitragynine at dose of 10 mg/kg and 30 mg/kg i.p. injected significantly reduced the immobility time of mice in both FST and TST without any significant effect on locomotor activity in open field test. (2) Mitragynine significantly reduced the released of corticosterone in mice exposed to FST and TST at dose of 10 mg/kg and 30 mg/kg.	(1) Kratom is administered orally by humans whereas intraperitoneal administration was used in this study- bioavailability is not the same.

Table I: Summary of the 46 selected articles for systematic review (continued)

Kratom therapeutic potential for substance withdrawal and dependence								
Author(s)/ year/ country	**Study design**	**Participants (N/ gender/ age)**	**Sampling method**	**SSE (Yes/No)**	**Study objective(s)**	**Outcome measures (Measures/ Intervention)**	**Findings**	**Limitations**
Buckhalter et al., 2021, Canada	Animal study	Adult male Wistar rats (Charles River, QC)	NA	NA	(1) To evaluate the dose-dependent effects of a purified alkaloid isolate from kratom on neuronal oscillatory activity in various brain regions in rats following acute and 7 days of administration. (2) Antidepressant effect of purified alkaloid isolate from kratom.	LFP recordings, FST, ΔFosB immunohistochemistry	(1) Acute and 7 days administration of kratom elevated NAc-PFC, VTA-NAc, and VTA-Cg coherence. (3) Low dose kratom had antidepressant-like properties but no kratom-induced changes in ΔFosB expression were evident.	
Yusoff et al., 2016, Malaysia	Animal study	Rats	NA	NA	To assess the addictive profile and cognitive impairments of acute and chronic mitragynine administration	To investigate the addictive profile and cognitive impairments of acute and chronic mitragynine administration	(1) Severe somatic withdrawal signs developed after 12 hours, and increased level of anxiety became evident after 24 hours of withdrawal. (2) Acute mitragynine independently impaired passive avoidance learning, memory consolidation and retrieval, possibly mediated by a disruption of cortical oscillatory activity. (3) Chronic mitragynine administration led to impaired passive avoidance and object recognition learning.	
Hassan et al., 2019, Malaysia	Animal study	Male Sprague Dawley rats	NA	NA	To investigate the effects of mitragynine on spatial learning and synaptic transmission in the CA1 region of the hippocampus in rats.	Morris water maze, field excitatory post-synaptic potentials in the hippocampal CA1 area, baseline synaptic transmission, paired-pulse facilitation, and long-term potentiation	(1) Mice treated with mitragynine- slower rate of acquisition as compared to their control counterparts. (2) Mitragynine significantly reduced the amplitude of baseline (i.e. non-potentiated) field excitatory postsynaptic potentials and minor suppression of long-term potentiation in CA1.	
Hassan et al., 2021, Malaysia	Animal study	30 male Sprague-Dawley rats	NA	NA	(1) To assess whether methadone, buprenorphine and clonidine, could mitigate mitragynine withdrawal effects. (2) To evaluate haematological, biochemical and histopathological effects after mitragynine administration	Withdrawal symptoms were assessed on day 15 (24 hours after abstinence from the drug).	(1) Chronic mitragynine treatment- significant withdrawal behaviour lasting at least 5 days. (2) Methadone, buprenorphine, and clonidine significantly attenuated these withdrawal signs (chewing, head shakes, exploring, digging, yawning, teeth chattering, wet dog shakes, writhing, squeaking on touch, hostility on handling, and diarrhoea). (3) No major effects on blood or organ toxicity were observed.	
Iman et al., 2021, Malaysia	Animal study	100 adult male Swiss albino mice	NA	NA	To investigate the potential role of CB1 receptors in mediating the cognitive deficits induced by a chronic mitragynine sensitization.	Behavioural Design in the IntelliCage System, brain sample collection for immunohistochemistry, QR-PCR and Western blotting	(1) Chronic high-dose mitragynine exposure, but not low-dose exposure, induced hyperlocomotion, potentiated the preference for sucrose reward, increased resistance to punishment, and impaired place learning and its reversal. Comparable deficits were also observed after chronic treatments with Δ-9-THC or morphine. (2) Mitragynine-, morphine-, and THC-induced learning and memory deficits were reversed by co-treatment with the CB1 receptor antagonist, NIDA-41020. (3) Significant upregulation of CB1 receptor expression was found in the hippocampal CA1 region and VTA after chronic high dose mitragynine and morphine, whereas a downregulation was observed after chronic THC.	(1) Kratom is administered orally by humans whereas intraperitoneal administration was used in this study- bioavailability is not the same.

Table I: Summary of the 46 selected articles for systematic review (continued)

Kratom therapeutic potential for substance withdrawal and dependence

Author(s)/ year/ country	Study design	Participants (N/ gender/ age)	Sampling method	SSE (Yes/No)	Study objective(s)	Outcome measures (Measures/ Intervention)	Findings	Limitations
Suwanlert, 1975, Thailand	Cross-sectional survey	N = 30 (human subjects), 29 males, 1 female	NA	NA	NA	**Self**-designed questionnaire	(1) Kratom dependence was also documented presented with withdrawal symptoms on abstinence such as hostility, aggression, lacrimation, rhinorrhoea, inability to work, aching in the muscles and bones, jerky movement of the limbs. (2) Psychotic symptoms also present in five respondents, such as clouding of consciousness, delusion, and hallucination.	(1) Small sample size. (2) Cross-sectional design. (3) No clear objective of the study. (4) The respondents who reported psychotic symptoms also had history of other illicit drug use and schizophrenia.
Singh et al., 2014, Malaysia	Cross-sectional survey	N = 293 (human subjects), males	Snowball sampling	No	To measure kratom dependence, withdrawal symptoms, and drug craving in regular kratom users in Malaysia	LDQ, MWC, and MCQ-SF	(1) 55% of the regular users had severe kratom dependence, 45% had moderate kratom dependence. (2) Physical withdrawal symptoms included muscle spasms and pain, sleeping difficulty, watery eyes/nose, hot flashes, fever, decreased appetite, and diarrhoea. Psychological withdrawal symptoms were restlessness, tension, anger, sadness, and nervousness. (3) Regular users who consumed ≥3 glasses kratom per day- higher odds of severe kratom dependence, withdrawal symptoms, and kratom craving.	(1) Cross-sectional design. (2) Used of questionnaires not validated for measuring kratom dependence, kratom withdrawal and craving. (3) Sampling method used was snowball sampling (non-probability sampling). (4) Serum mitragynine and 7-HMG not assessed.
Singh et al., 2018a, Malaysia	Cross-sectional study	Kratom users (n= 150), all males, mean age = 34.4 years (SD = 11.2)	Snowball sampling	No	To assess the severity of anxiety and depression during kratom cessation.	BDI-II and BAI	(1) 70% respondents experienced mild anxiety symptoms, while 81% experienced mild depression symptoms during kratom cessation. (2) Higher quantities of kratom tea daily (≥4 glasses) were more likely to experience moderate symptoms of depression during kratom cessation than those who consumed 1-3 glasses of kratom tea per day.	(1) Cross-sectional design of the study. (2) Anxiety and depression symptoms are based on retrospective self-reports. This increased risk of recall bias and social desirability bias. (3) Absence of control group as comparison. (4) The length of abstinence was not measured.
Singh et al., 2018b, Malaysia	Cross-sectional survey	N = 170 (human subjects), males,	Snowball sampling	No	To evaluate the severity of pain and sleep problems following the cessation of kratom tea consumption among regular kratom users	BPI and PSQI	(1) 84% had moderate pain intensity and 70% had moderate pain interference during kratom cessation; 46% experienced insomnia during kratom cessation. (2) Those on ≥4 glasses of kratom tea/juice (about 76-115 mg of mitragynine) daily had higher pain interference and insomnia during kratom cessation as compared to those who consumed 1-3 glasses of kratom tea/juice daily. (3) Cessation from regular kratom tea consumption was not associated with prolonged pain and insomnia.	(1) Cross-sectional design. (2) Sampling method used was snowball sampling (non-probability sampling). (3) Serum mitragynine and 7-HMG not assessed.
Singh et al., 2019b, Malaysia	Cross-sectional survey	N = 63 (human subjects), almost all males (98%)	Convenient sampling	No	To evaluate if kratom use produces dose-dependent effects, with a stimulant effect at low doses and a sedative effect at high doses, in a sample of regular kratom users.	B-BAES	(1) No significant difference in the stimulant and sedative effects between those who consumed >3 glasses a day or less than this amount, regardless of duration of use. (2) No significant differences in the mean scores of B-BAES were found among those who consumed >3 glasses daily or less than this amount among short-term or long-term uses.	(1) Cross-sectional design. (2) Small sample size.
Singh et al., 2019c, Malaysia	Cross-sectional study	Kratom users (n= 150), all males,	Snowball sampling	No	(1) to determine the rate of substance use disorder related to kratom use, and (2) to identify factors that are associated with kratom dependence and withdrawal severity.	MINI, KDS, and COWS	(1) 99% of respondents fulfilled the criteria for substance use disorder related to kratom use, 95% reported withdrawal symptoms on abstinence, 87% reported tolerance, and 93% craving for kratom. (2) Higher quantity (>3 glasses) of daily kratom tea/juice consumption had higher odds of severe kratom dependence and moderate withdrawal.	(1) Cross-sectional design of the study. (2) COWS was not validated for assessing kratom withdrawal symptoms.

Table I: Summary of the 46 selected articles for systematic review (continued)

Kratom therapeutic potential for substance withdrawal and dependence

Author(s)/ year/ country	Study design	Participants (N/ gender/ age)	Sampling method	SSE (Yes/No)	Study objective(s)	Outcome measures (Measures/ Intervention)	Findings	Limitations
Singh et al., 2019d, Malaysia	Cross-sectional comparative study	Kratom (n = 70), controls (n = 29), all males	Convenient sampling	No	(1) To investigate whether regular kratom tea consumption was associated with impaired cognitive function. (2) To determine whether cognitive impairment is dose-dependent.	Cambridge Neuropsychological Test Automated Battery.	(1) Relative to control participants, higher consumption (>3 glasses daily or mitragynine doses between 72.5 mg and 74.9 mg) of kratom tea- associated with deficits in visual episodic memory and new learning. (2) Quality of kratom use on daily basis did not lead to deficit in all neuropsychological domains compared to controls.	(1) Sample not representative of Malaysian kratom using population as solely recruited from one state. (2) Non-equal sample size between kratom and control groups. (3) Low education within the kratom subjects may contribute to lower cognitive scores. (4) Past history of polydrug use among the kratom users was not screened.
Leong Bin Abdullah et al., 2019(a), Malaysia	Cross-sectional study	Kratom users (n = 150), all males, mean age = 34.42 years, SD = 11.28	Snowball sampling	No	To investigate the prevalence of psychosis among kratom users, describe psychotic symptomatology and severity, and examine the associations between kratom use characteristics and the occurrence of psychotic symptoms.	MINI, DSM 5 and BPRS	(1) 4% of subjects presented with any psychotic symptoms. (2) The psychotic symptoms reported were positive symptoms and thought alienation, with a mean BPRS score indicating mild severity of psychotic symptoms. (3) Intake of kratom with diphenhydramine, duration of kratom use, and quantity and frequency of daily kratom use were not associated with occurrence of psychotic symptoms among kratom users.	(1) Cross-sectional design of the study. (2) 4 out of 6 kratom users who exhibited psychotic symptoms in the study had history of using other illicit drugs.
Leong Bin Abdullah et al., 2019(b), Malaysia	Cross-sectional survey	n = 150, all males, mean age = 34.4 years (SD = 11.2)	Snowball sampling	No	To describe the socio-demographic and history of kratom use and determine the quality of life and its associated factors among Malaysian kratom users.	KDS and WHO-QOL-BREF	(1) Severe kratom dependence users had lower physical health related QoL score when compared to that of users with mild to moderately severe kratom dependence. (2) Duration of kratom use and quantity of kratom use were not associated with all the domains of QoL.	(1) Cross-sectional design of the study. (2) No control group as comparison.
Smith et al., 2021(a), USA	Cross-sectional survey	N = 1,510 (human subjects), males and females	NA		To assess important psychosocial factors surrounding kratom use among U.S. adults who reported past 6-month alcohol, opioid, and/or stimulant use	Self-constructed questions	(1) 13.4% reported lifetime kratom use. (2) Higher rates of chronic pain, childhood adversity, anxiety, depression, and lower perceived social rank and socioeconomic status were reported among those with kratom use. (3) 83.2% met diagnostic criteria for any past-year SUD. The strongest predictors of kratom use were use of other drugs: cannabidiol, psychedelics, and non-medical prescription opioids.	(1) Cross-sectional design. (2) May underrepresent people who have used kratom and chosen to stop.
Leong Bin Abdullah et al., 2021, Malaysia	Cross-sectional study	Kratom users (n = 100) vs. control subjects (n = 100), all males,	Snowball sampling	No	To investigate the WHO-QoL-BREF domains of subjects who use kratom and healthy non-drug using controls. Additionally, to determine the associations between the patterns of kratom use and the four QoL domains among those who use kratom.	KDS and WHO-QOL-BREF	(1) The physical health, psychological, and environment QoL scores of the subjects who use kratom were significantly lower than those of the healthy controls. (2) More severe kratom dependence and longer duration of kratom use predicted lower physical health, psychological, and environment QoL.	(1) Sample not representative of Malaysian kratom using population as solely recruited from one state. (2) Cross-sectional design.
Palamar, 2021, USA	Cross-sectional survey	Data from 2019 National Survey on Drug Use and Health (n = 56,136)	NA	NA	To examine the prevalence and correlates of kratom use in the general U.S population	A nationally representative probability sample of non-institutionalized individuals aged ≥12 years in the U.S.	(1) An estimated 0.7% of individuals in the U.S. have used kratom in the past year. (2) Past-year proxy diagnosis of prescription opioid use disorder- increased odds for kratom use with 10.4% of those with use disorder reporting use. (3) Opioid misuse not accompanied with use disorder was not associated with kratom use. (4) Past-year cannabis use both with and without use disorder and past-year cocaine use and prescription stimulant misuse not accompanied with use disorder were at higher odds for kratom use.	(1) Some subgroups of population underrepresented i.e. homeless who do not use shelters and not all kratom users are included as questions did not ask for all preparation of kratom. (2) Risk of overreporting as product used may be wrongly labelled as kratom (not checked).

Table I: Summary of the 46 selected articles for systematic review (continued)

Kratom therapeutic potential for substance withdrawal and dependence

Author(s)/ year/ country	Study design	Participants (N/ gender/ age)	Sampling method	SSE (Yes/No)	Study objective(s)	Outcome measures (Measures/ Intervention)	Findings	Limitations
Fauzi et al., 2022, Malaysia	Cross-sectional study	Kratom users (n = 20) vs. non-drug using control subjects (n= 20), all males,	NA	No	(1) To determine the association between expression of the ER stress sensor mRNA in the peripheral leukocytes and the patterns of kratom. (2) To evaluate the correlations between the levels of the ER stress sensor mRNA and the severity of kratom dependence and kratom induced depressive symptoms among kratom users	mRNA expression of BiP, XBP1, ATF4 and CHOP genes; KDS, and BDI-II	(1) Kratom users as compared to controls- higher expression of BiP and CHOP mRNA. (2) Higher expression of BiP, ATF4, and CHOP mRNA-positively correlated with greater severity of kratom dependence and depressive symptoms on abstinence. (3) Hence, activation of ER stress and UPR were associated with regular kratom use, higher severity of kratom dependence and higher severity of depression symptoms on kratom cessation.	(1) Small sample size. (2) As kratom users experienced depressive symptoms when they abstained from kratom use, the severity of depressive symptoms among kratom users was assessed retrospectively, which increase the risk of recall bias.
Choo et al., 2022, Malaysia	Cross-sectional study	N = 215 subjects in MMT, mostly males	Convenient sampling	No	(1) To examine the psychosocial correlates of ketum use in individuals on the MMT programme in Hospital Taiping. (2) To identify the association between methadone dose and the severity of dependence on ketum use in the MMT programme.	SOWS, ASSIST, and KDS	(1) The prevalence of kratom users was 49.3%. (2) Individuals who used other illicit drugs had a higher tendency to use kratom. (1) Higher severity of opioid withdrawal higher odds of using kratom, whereas longer duration of MMT lower odds of kratom use.	(1) Cross-sectional design. (2) Sample not representative of the Malaysian kratom population as recruitment only in one hospital and by non-probability sampling.
Adzrago et al., 2022, USA	Cross-sectional study; data from 2020 National Survey on Drug Use and Health	N = 32,893, males and females	multi-stage stratified probabil-itysam-pling of all 50 states and District of Columbia		(1) To estimate the prevalence of three kratom use categories (i.e., never used kratom, kratom use more than 30 days ago, and kratom use within the past 30 days) (2) To examine the associations between the kratom use categories and past-year MDE and SUDs, adjusting for sociodemographic characteristics.	DSM 5	(1) Major depressive episode was positively associated with kratom use more than 30 days ago. (2) This association was also observed for mild, moderate, or severe alcohol use disorder; and mild, moderate, or severe marijuana use disorder. (3) Illicit drug other than marijuana use disorder was associated positively with kratom use more than 30 days ago and kratom use within the past 30 days	(1) Risk of self-reported bias. (2) Small sample of LGBT group. (3) Cross-sectional design.

Author(s)/ Year/Country	Study design	Findings	Limitations
Boyer et al., 2008, USA	Case report	(1) History: 43 years old man with history of hydromorphone dependence who use kratom to self-treat opioid withdrawal presented with generalized tonic-clonic seizure on co-administering kratom with modafinil. (2) Clinical findings and investigation: lab investigation unremarkable, urine test and toxicological screening indicated only presence of modafinil, CT and MRI scan of brain normal. (3) Outcome: Upon abstinence from kratom use experienced withdrawal symptoms such as rhinorrhea, insomnia, poor concentration, constricted affect and myalgias persisting for 10 days from his last dose of kratom. Kratom withdrawal well managed by buprenorphine/naloxone up to 16mg/day.	(1) Serum mitragynine and 7-HMG not measured.
McWhirter and Morris, 2010, USA	Case report	(1) History: 44 years old man with alcohol dependence and anxiety disorder presented with kratom dependence characterized by withdrawal symptoms on abstinence, such as anxiety, restlessness, tremor, sweating and cravings for the substance. (2) Outcome: Kratom withdrawal was relatively short and benign and successfully treated with a gradually tapering regime of dihydrocodeine and lofexidine.	(1) Serum mitragynine and 7-HMG not measured.

Table I: Summary of the 46 selected articles for systematic review (continued)

Kratom therapeutic potential for substance withdrawal and dependence			
Author(s)/ year/ country	**Study design**	**Findings**	**Limitations**
Galbis-Reig, 2016, USA	Case report	(1) History: 37 years old lady with history of postpartum depression treated partially had history of taking kratom with increasing dosage for 1.5 years with failed attempts to detoxified from kratom and presented with weight loss, insomnia, cravings, and decreased overall energy level. She presented to a treatment facility for detoxification after being coerced by family. (2) Clinical findings and investigation: All blood investigations and urine drug screening were unremarkable, but urine lab test for mitragynine was positive at a cutoff value of 10 ng/ml. (3) Outcome: She was started on clonidine detoxification with COWS monitoring and she developed severe kratom withdrawal with myalgias, bone pain, abdominal cramping pain, nausea, and blurred vision due to rapid pupillary dilatation. After dose adjustment, she responded and stabilized after 3 days of admission. She was discharged with oral naltrexone to be started 7 days after discharge.	(1) Serum mitragynine and 7-HMG not measured.
Buresh, 2018, USA	Case report	(a) History: 60-year-old woman who presented with history of chronic pain which was managed with tramadol, oxycodone–acetaminophen, pregabalin and kratom presented with inability to stop kratom use (at a dose of 0.25 ounces every 4 h) due to rebound pain and withdrawal symptoms. Outcome: She was started on buprenorphine/naloxone which eventually titrated to dose of 16 mg (4 mg, 4 times/day) which keep her kratom withdrawal and pain under remission. (b) History: 57-year old man with history of opioid dependence due to prescribed oxycodone switched to kratom for 1 year prior to clinic visit. Outcome: He was started on buprenorphine/naloxone which eventually titrated to dose of 24 mg (6 mg, 4 times/day) and he was on remission fully at 7 months after treatment.	(1) Serum mitragynine and 7-HMG not measured.
Davidson et al., 2018, USA	Case report	(1) New-born was born to 29 years old single mother who was on oral gabapentine, clonazepam, prenatal vitamins and kratom (5g, 1-3 times/ day) and a chronic smoker by spontaneous vaginal delivery. Developed reduced oral intake, jitteriness, hypertonia, sneezing, excessive crying, excessive suck, and poor feeding associated with spit up after 24 hours of delivery. (2) Clinical findings and investigation: complete blood count and urine toxicology were unremarkable. (3) Outcome: Neonatal withdrawal syndrome was diagnosed and treatment with oral morphine 0.1 mg/kg/day divided every 4 hours and after 3 days of treatment, response was observed and medication gradually weaned off.	
Nellhaus et al., 2018, USA	Case report	(1) History: New-born to 33 years mother with history of kratom use during pregnancy to substitute for prescribed opioid dependence for chronic pain as well as cigarette smoking and caffeine use during pregnancy. The new-born developed high-pitched crying, facial grimacing, irregular respiratory pattern, mottling, and mild undisturbed tremors on first day of life. (2) Clinical findings and investigation: umbilical cord toxicology revealed unremarkable findings indicating no opioid use at later pregnancy. (3) Outcome: New-born was diagnosed with neonatal withdrawal syndrome and treated with clonidine at DOL2 and weaned off at DOL6 before discharged at DOL8. Growth was normal thereafter.	
Mackay and Abraha- ms, 2018, Canada	Case report	(1) History: New-born to 29 years mother with history of opioid use disorder due to chronic back pain which she self-treated with kratom 2 years back with dosage up to 18 to 20 g 3 times/day until late pregnancy. The new-born developed feeding intolerance, jitteriness, irritability, and emesis on postpartum day 2. (2) Outcome: New-born was diagnosed with neonatal withdrawal syndrome and treated with IV morphine to a maximum dose of 10 µg/kg/h and switch to oral morphine and transferred to mother at day 7 of life.	
Khazaeli et al., 2018, USA	Case report	(1) History: 52 years old lady with depression and chronic pain treated with prescribed opioid and self-treated with kratom for 9 months prior complaint of unable to abstain from kratom use due to withdrawal characterized by anxiety, rhinorrhoea, diarrhoea, stomach discomfort, increased pain, and restlessness. (2) Outcome: He was started on buprenorphine/naloxone which was titrated to 8-2 mg twice daily and he achieved remission from kratom use. Urine lab analysis for mitragynine and 7-HMG were negative.	
Murthy and Clark, 2019, Canada	Case report	(1) History: New-born to mother with history of kratom use (consumed 3 to 4 times/day) to self-treat anxiety and restless leg syndrome and was also on low dose of citalopram. The new-born developed excessive sucking, irritability, jitteriness, sleeplessness and increase tone at day 1 of life. (2) Outcome: New-born was diagnosed with neonatal withdrawal syndrome and treated with oral morphine. The new-born was unable to wean off morphine with 2 failed attempts at day 2 and day 12. Morphine was finally weaned off at 2 months of life and this prolonged with- drawal was belief to be due to sustain in-utero exposure.	
Schmuhl et al., 2019, USA	Case report	(1) History: 20-year old college student with attention deficit hyperactive disorder on dextroamphetamine started on kratom to self-treat adverse effects of dextroamphetamine such as insomnia and anxiety. He complaint of unable to stop kratom use due to withdrawal symptoms (nausea, palpitation, and irritability) on abstinence. (2) Outcome: He was started on buprenorphine/naloxone titrated to a dose of alternating days of 4-1 mg and 2-0.5 mg where he achieve remis- sion from kratom use and able to continue dextroamphetamine on when needed basis.	

Table I: Summary of the 46 selected articles for systematic review (continued)

Kratom therapeutic potential for substance withdrawal and dependence			
Author(s)/ year/ country	**Study design**	**Findings**	**Limitations**
Agapoff and Kilaru, 2019, USA	Case report	(1) History: 35-year old man with depression self-treated his depression with kratom which eventually titrated to a dose of 30g per day and complaint that he could not abstain from kratom use due to withdrawal symptoms (irritability and restlessness, headache, abdominal upsets, joint pain, rhinorrhoea, lacrimation, sweating, and muscle spasm). (2) Outcome: he was started on buprenorphine/naloxone which was titrated to a dose of 8-2 mg (4-1 mg, 2 times/day) to reach remission from kratom use.	
Eldridge et al., 2019, USA	Case report	(1) History: New-born to a mother with history of oxycodone use and abstain from use for 2 years by self-treatment with kratom presented with sneezing, jitteriness, excessive suck, facial excoriations, irritability, resting tremors, high-pitched cry, and hypertonia at 33 hours of life. (2) Clinical findings and investigation: urine drug screening was negative. (3) Outcome: New-born was diagnosed with neonatal withdrawal syndrome and treated with morphine (0.03 mg/kg every 3 hours per unit NAS protocol) until signs resolved. Then, recurrent withdrawal recurred and treatment with clonidine ensued (1 µg/kg every 3 hours). Subsequently, symptoms reside and clonidine discontinued at 5th day of life and patient discharged at 8th day of life.	
Kucharik et al., 2019, USA	Case report	(1) History: 55 years old lady with history of chronic back pain, depression and anxiety who was in post-surgery state (after elective subtotal colectomy and ileorectal anastomosis for colonic inertia) developed nausea, vomiting, confusion, agitation, visual and auditory hallucination on post-op day 2 suspected of unusual kratom withdrawal (consumed 5–10 g, oral kratom daily for years to self-treat chronic pain). (2) Clinical findings and investigation: Post-op day 4 developed aspiration pneumonia and septic shock but stabilized in ICU. (3) Outcome: Discharged on post-op day 12 and well. No treatment was given for suspected kratom withdrawal symptoms.	(1) Serum mitragynine and 7-HMG not measured. (2) The symptoms she developed in post-op day 2 could be delirium secondary to aspiration pneumonia or post-operative.
Sablaban and Gautam, 2020, USA	Case report	(1) History: 27 years old man with history of oxycodone dependence self-treated with kratom for two weeks with overdose (15g 3 times/day) presented with a surge of anxiety and obsessive thoughts of sexual assault and homicidal ideation when attempted to wean off kratom. (2) Clinical findings and investigation: All blood investigations and urine drug screening unremarkable but COWS score indicated mild opioid withdrawal with rhinorrhoea and lacrimation. (3) Outcome: Treated with IV lorazepam 2mg and symptoms completely resolved.	(1) Serum mitragynine and 7-HMG not measured.
Muller et al., 2021, Germany	Case report	(1) History: 63 years old man with history of major depressive disorder, generalized anxiety disorder and Meniere's disease complicated by alcohol use disorder succumb to sleep disorder after successful treatment of his alcohol use disorder. He self-medicate with kratom for its anti-depressant, anxiolytic effects and symptomatic relief of Meniere's disease for 7 years before tolerance to kratom developed. (2) Clinical findings and investigation: All blood investigations and urine drug screening unremarkable except presence of mitragynine and lorazepam (to treat sleep problem and anxiety). (3) Outcome: Stabilize on antidepressant (need to switch from mirtazapine to venlafaxine), augmentation with quetiapine and lorazepam before discharged. But relapse to kratom use 2-3 weeks after discharge.	(1) Serum mitragynine and 7-HMG not measured.
Settle and Yang, 2022, USA	Case report	(1) History: 38 years old lady with history of major depressive disorder and past history of opioid use disorder presented with suicidal attempt (overdose with her prescribed medications). She also gave a history of kratom use disorder when she attempted to substitute buprenorphine/ naloxone treatment for her opioid use disorder with kratom. She would present with kratom withdrawal (agitation, anxiety, shakes, and spasms of her extremities) if attempted to abstain from kratom. Eventually, her kratom use disorder had worsened her major depressive disorder. (2) Clinical findings and investigation: indicated she had moderate hypotension and mild lactic acidosis, otherwise unremarkable. (3) Outcome: After restarted on her medications (duloxetine and quetiapine) and later buprenorphine/naloxone, she became more stable and kratom withdrawal remitted. She decided to continue with buprenorphine/naloxone maintenance.	(1) Serum mitragynine and 7-HMG not measured. (2) Later urine drug test on follow up not mentioned.

SSE = sample size estimation, 7-HMG = 7-hydroxymitragynine, MG = mitragynine, NA = not applicable, CPP = conditioned place preference, SD = standard deviation, FST = force swim test, TST = tail suspension test, LFP = local field potential, VTA = ventral tegmental area, NAC = nucleaus accumbens, PFC = prefrontal cortex, Cg = cingulate cortex, BDNF = brain-derived neurotrophic factor, Δ-9-THC = Delta 9-tetrahydrocannabinol, LDQ = Leeds Dependence Questionnaire, MWC = Marijuana Withdrawal Checklist, MCQ-SF = Marijuana Craving Questionnaire-Short Form, BPI = Brief Pain Inventory, PSQI = Pittsburgh Sleep Quality Index, QoL = quality of life, KDS = kratom dependence scale, WHOQOL-BREF = World Health Organization Quality of Life Questionnaire-BREF, ER stress = endoplasmic reticulum stress, BiP = binding immunoglobulin protein, XBP1 = X-box binding protein 1, ATF-4 = activating transcription factor 4, CHOP = C/-EBP homologous protein, BDI-II = Beck Depression Inventory version II, MINI = Mini International Neuropsychiatric Interview, DSM 5 = Diagnostic and Statistical Manual for Mental Disorder 5th Edition, BPRS = Brief Psychiatric Rating Scale, COWS = Clinical Opioid Withdrawal Scale, BAI = Beck Anxiety Inventory, PROMIS-GH = 10-item Patient-Reported Outcomes Measurement Information System Global Health, BPI = 15-item Brief Pain Inventory, SOWS = 16-item Subjective Opiate Withdrawal Scale, DEQ = 13 items from the Drug Effects Questionnaire, B-BAES = Brief-Biphasic Alcohol Effects Scale, DSM-V = Diagnostic and Statistical Manual of Mental Disorders 5th Edition, ASSIST = Alcohol, Smoking and Substance Involvement Screening Test, COWS = Clinical opioid withdrawal scale, HPA = hypothalamic-pituitary-adrenal axis, MDE = major depressive episode, SUD = substance use disorder

Table II. Critical appraisal of the cross-sectional studies selected in this systematic review

	Grundmann, 2017	Coe et al., 2019	Garcia-Romeu et al., 2020	Smith et al., 2021(a)	Smith et al., 2022	Suwanlert, 1975	Singh et al., 2014	Singh et al., 2018a	Singh et al., 2018b	Singh et al., 2019b	Singh et al., 2019c	Singh et al., 2019d	Leong Bin Abdullah et al., 2019(a)	Leong Bin Abdullah et al., 2019(b)	Smith et al., 2021(a)	Leong Bin Abdullah et al., 2021	Palamar, 2021	Fauzi et al., 2022	Choo et al., 2022	Adzrago et al., 2022
Introduction																				
1. Were the aims/objectives of the study clear?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Methods																				
2. Was the study design appropriate for the stated aim(s)?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the sample size justified?	Yes	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	No	No	Yes
4. Was the target/reference population clearly defined? (Is it clear who the research was about?)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
7. Were measures undertaken to address and categorize non-responders?	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
8. Were the risk factor and outcome variables measured appropriate to the aims of the study?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialled, piloted or published previously?	No	No	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
10. Is it clear what was used to determined statistical significance and/or precision estimates? (e.g., p values, CIs)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were the methods (including statistical methods) sufficiently described to enable them to be repeated?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Results																				
12. Were the basic data adequately described?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13. Does the response rate raise concerns about non-response bias?	NS	NS	NS	NS	NS	NS	NS	No	No	No	No	No	No	NS	No	No	No	No	No	No
14. If appropriate, was information about non-responders described?	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
15. Were the results internally consistent?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
16. Were the results for the analyses described in the methods, presented?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Discussion																				
17. Were the authors' discussions and conclusions justified by the results?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
18. Were the limitations of the study discussed?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Others																				
19. Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
20. Was ethical approval or consent of participants attained?	Yes	Yes	Yes	Yes	Yes	NS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

NS = not stated

adrenal axis (39). In addition, repeatedly administering kratom in rats also resulted in an increase in coherence in the nucleus accumbens-prefrontal cortex, ventral tegmental area-nucleus accumbens, and ventral tegmental area-cingulate cortex. These are the areas of the brain involved in depression's pathophysiology. Administering kratom in rats creates an antidepressant effect without affecting changes in the DeltaFosB, indicating that kratom was not associated with a risk of drug dependence (40).

In the context of human subjects, cross-sectional surveys of the US population (total respondents = 13,714) indicated that 22–66% of the respondents use kratom to self-treat depression, anxiety, and posttraumatic stress disorder with good ratings on effectiveness (18, 27, 28). The adverse effects profile of kratom was also well-tolerated, with only 13% of the respondents had severe adverse effects (27).

Mental health drawbacks on kratom use as therapeutic agent

The major mental health drawback of kratom use as a therapeutic agent is its addictive potential, characterized by its association with development of withdrawal symptoms and craving on abstinence, tolerance and cross-tolerance, and the risk of developing kratom-related substance use disorder (16, 17, 19, 20, 22, 29, 32-35, 41-58).

An animal study in rats documented that chronic administration of mitragynine induced withdrawal behaviors such as chewing, head shakes, exploring, digging, yawning, teeth chattering, wet dog shakes, writhing, squeaking on touch, hostility on handling, and diarrhea, which lasted for at least 5 days. These withdrawal signs were attenuated by administering opioid agonists (such as buprenorphine and methadone) and α-adrenergic antagonist (such as clonidine) (57).

In the context of studies on human subjects, cross-sectional surveys in regular Malaysian kratom users reported that all of the respondents developed kratom dependence that was characterized by physical withdrawal symptoms, such as muscle spasms and pain, sleeping difficulty, watery eyes/nose, hot flashes, fever, decreased appetite, and diarrhea. In addition, psychological withdrawal symptoms included restlessness, feeling tension, irritability, sadness, and nervousness. When assessment was performed using a validated structural psychiatric interview (such as the MINI International Neuropsychiatric Interview), 99% of regular kratom users developed a kratom-related substance use disorder, while 95% had withdrawal symptoms, 87% had tolerance, and 93% had craving upon abstinence from kratom use (17, 22). Regular kratom users who consumed an average of at least three glasses of kratom juice on a daily basis had higher odds of developing severe kratom withdrawal and craving upon abstinence, and kratom dependence (17). Moreover, 70% of regular kratom users also experienced moderate pain interference and 46% had insomnia upon cessation. The risk of pain interference and insomnia increased in those who consumed an average of more than four glasses of kratom juice per day (containing 76-115 mg of mitragynine) (20). Interestingly, regular kratom users who consumed an average of more than four glasses of kratom juice per day (contained 76-115 mg of mitragynine) also had higher odds of experiencing moderately severe depression symptoms during kratom cessation (19). A cross-sectional survey in Malaysia on opioid dependent respondents who were on methadone maintenance treatment showed that 49.3% of the participants had a history of kratom use, and those who were still experiencing opioid withdrawal and used other illicit drugs were at higher odds of using kratom (34). Another interesting finding is that a higher average quantity of kratom use on a daily basis (more than three glasses of kratom juice), regardless of the duration of kratom use, did not contribute to increasing stimulant and sedative effects (21). Contrastingly, activation of the endoplasmic reticulum stress response and unfolded protein response were associated with regular kratom use, higher severity of kratom dependence, and higher severity of depression symptoms during kratom cessation, which were similar to findings among regular cocaine users, thereby indicating kratom's stimulant effect (33). Kratom dependence has a significant impact on the quality of life (QoL) of regular kratom users in Malaysia. Quality of life related to the physical, psychological, and environmental health among regular kratom users were significantly lower than that of healthy controls who did not use drugs. In fact, significantly lower levels of physical health-related QoL were reported among those with severe kratom dependence as compared to those with mild to moderately severe kratom dependence (25, 26).

Cross-sectional surveys among the US population denoted that those with substance use disorder were at higher odds of regular kratom use (29, 32, 35). Meanwhile, 13.4% of the US population reported a lifetime history of kratom use and those who had a diagnosis of any substance use disorder in the past year were at higher odds of using kratom, especially those on cannabidiol, psychedelics, and nonmedical prescription opioids (29). Surveys with a higher sample size of the US population (total sample size of 89,029 respondents) indicated that the prevalence of kratom use was at 0.7%, whereby those with prescription opioid use disorder, those who used cannabis with or without cannabis use disorder, cocaine and prescription stimulant misuse, and alcohol use disorder were at a higher odds of using kratom (32, 35).

Additionally, case reports from Western countries (US and Germany) documented that kratom use as a self-prescribed replacement therapy for prescription or

illicit opioid dependence was associated with severe withdrawal symptoms (rhinorrhea, insomnia, poor concentration, constricted affect, myalgia, anxiety, restlessness, tremors, sweating, bone pain, abdominal cramping pain, nausea, blurred vision due to rapid pupillary dilatation, palpitation, irritability, headache, joint pain, lacrimation, confusion, visual and auditory hallucinations, and obsessive thoughts of sexual assault and homicidal ideation), craving, and tolerance, which often required treatment with buprenorphine/naloxone, dihydrocodeine and lofexidine, clonidine, or intravenous lorazepam (41-43, 45, 49, 51, 52-56, 58). In addition, neonatal withdrawal syndrome related to maternal kratom use (characterized by reduced oral intake, jitteriness, hypertonia, sneezing, excessive crying, excessive suck, poor feeding associated with spit up, high-pitched crying, facial grimacing, irregular respiratory pattern, mottling, mild undisturbed tremors, irritability, emesis, facial excoriations, and resting tremors), which usually developed at day 1 of life and required treatment with intravenous or oral morphine or clonidine, was also reported in several case reports from the US and Canada (46-48, 50, 53).

Nevertheless, despite the possible addictive potential of kratom, regular kratom use may not contribute to other adverse mental health effects, such as cognitive impairment and psychosis (23, 24). Animal studies reported that acute administration of mitragynine in mice impaired their memory consolidation and retrieval and disrupted passive avoidance learning (due to disruption of cortical oscillatory activity), while chronic administration of mitragynine contributed to object recognition learning and passive avoidance (44). Treating with mitragynine in mice also led to a slower rate of acquisition in spatial learning, potentiated the preference for sucrose reward, increased resistance to punishment, impaired place learning and its reversal, and induced hyperlocomotion which was similar to the findings upon administration of Δ-9-tetrahydrocannabinol (59, 60). However, cognitive assessment in regular kratom users only denoted impaired performance in visual episodic memory and new learning among those who consumed an average of more than three glasses of kratom juice on a daily basis. Other domains of cognitive assessment using the Cambridge Neuropsychological Test Automated Battery exhibited no difference in scores when regular kratom users were compared with healthy controls (23).

Despite this, Suwanlert (1975) explained that five out of 30 kratom respondents exhibited psychotic symptoms (altered consciousness, delusion, and hallucination). These psychotic respondents were also complicated by comorbid use of other illicit substances (amphetamine, alcohol, and heroin) and a history of schizophrenia (16). In a cross-sectional study with a larger sample size of regular kratom users (n = 150), only 4% of the participants experienced psychotic symptoms, such as positive symptoms and thought alienation. Quantity and frequency of kratom use on a daily basis, as well as the duration of kratom use, did not increase the occurrence of psychotic symptoms. The rate of occurrence of psychotic symptoms was also no significantly higher than that in the global general population (24).

DISCUSSION

This systematic review provides a comprehensive overview of the therapeutic potential of kratom in the context of mental health and the drawbacks associated with psychological adverse effects, which provide valuable data for the assessment of risk versus benefit of using kratom as a therapeutic agent in psychiatry. Nine studies (which included four in vitro and/or animal studies and five online cross-sectional surveys in human subjects) reported the potential of kratom as a therapeutic agent for replacement therapy for opioid and alcohol dependence. In addition, five studies highlighted the potential of kratom as an antidepressant and/or anxiolytic, whereby two were animal studies and three were online cross-sectional surveys on human subjects. However, the main safety concern is the addictive potential it displays, especially with a higher quantity of kratom use on a daily basis, such as risk of developing kratom dependence, craving, tolerance, and kratom-related substance use disorder. Twenty-nine studies elaborated on this, including two animal studies, 11 studies in human subjects (mostly cross-sectional surveys), and 16 case reports. It is of great concern that the addictive potential of kratom use may also deplete QoL. Despite the link between kratom use and cognitive impairment evidenced in animal studies, regular kratom use did not appear to lead to cognitive impairment in human subjects except for visual episodic memory and new learning impairment. Regular kratom use also did not contribute to a higher prevalence of occurrence of psychotic symptoms compared to the general population.

As comparison, a systematic review by Swogger and Walsh (2018) also reported similar findings, wherein kratom exhibited therapeutic potential for opioid replacement therapy and may induce antidepressant and anxiolytic effects, but the main concern is kratom withdrawal symptoms which make it difficult to maintain abstinence in some regular users [9]. In another systematic review aimed to investigate pre-clinical evidence of the efficacy of kratom as a therapeutic agent and its safety concern also revealed similar findings, whereby kratom has therapeutic value in treatment of opioid and alcohol withdrawal and dependence, but its potential to induce kratom withdrawal and dependence on regular use is one of the major concern for safety. In addition, other main adverse effects of kratom use are learning impairment and hypercholesterolaemia (61).

Historically, kratom use as a traditional herbal therapeutic agent for replacement therapy among people

with opioid dependence was documented in Malaysia and Thailand. However, the mechanism behind the effectiveness of kratom to relieve opioid withdrawal symptoms was not investigated until recently (12, 62). There are several points that supported kratom use as a therapeutic agent for replacement therapy for opioid dependence: [a] mitragynine, the most abundant psychoactive alkaloid of kratom extract, was reported to act as a partial agonist at the μ opioid receptors, allowing it to relieve opioid withdrawal symptoms, and yet does not contribute to severe opioid-related adverse effects and significant euphoria (36); [b] mitragynine does not recruit β-arrestin, explaining the lower risk of developing respiratory depression, constipation, and severe withdrawal symptoms upon abstinence among regular kratom users (37); [c] regular kratom use is not associated with social functional impairment, does not lead to risky drug use behavior (such as intravenous injection and random sexual intercourse), and does not contribute to criminal behavior (9, 63, 64). When treating alcohol dependence, it may be mediated by the potent binding affinity of δ opioid receptors but has low affinity to bind to μ opioid receptors as depicted by the mechanism of action of the kratom-derived analogs [7-hydroxypaynantheine and 7-hydroxyspeciogynine] (38).

In the context of the therapeutic potential of kratom as an antidepressant and anxiolytic agent, the effects could be explained by the affinity of mitragynine to bind to adrenergic and serotonergic receptors, such as adrenergic 2A, 2B, and 2C, as well as serotonergic 2A receptors (65-67). Two kratom-derived analogs, such as paynantheine and speciogynine, have been reported to exhibit 5-HT1A receptor agonism and stand out as potential antidepressant agents (67). In addition, kratom's antidepressant effect may be mediated by activating the c-Fos pathway and the higher FOS protein level in the dorsal raphe nuclei, the region of the brain rich in serotonergic nuclei (68).

As the psychoactive alkaloids of kratom are agonist at the μ opioid receptors, it is expected that regular kratom use will increase the risk of kratom-related substance use disorder. The risk of kratom-related substance use disorder characterized by kratom withdrawal symptoms and craving upon abstinence and development of tolerance were well documented in the 29 articles (including 16 case reports) selected for our review. Nevertheless, cross-sectional surveys of kratom users in the US with large sample sizes (total sample size = 13,994) reported that only 2% of the respondents develop moderate or severe kratom-related substance use disorder, especially in those who had high dose and more frequent dosing of kratom (18, 27-29). Hence, the 16 case reports selected for our review may represent those outliers who experienced severe kratom withdrawal upon abstinence and presented to the hospital for treatment (41-43, 45-56, 58).

Moreover, the degree of kratom withdrawal and kratom dependence among regular kratom users reported in Southeast Asia and the West may exhibit noticeable difference. The regular kratom users in Southeast Asian presented with more profound severity of kratom withdrawal symptoms and kratom dependence compared with those in the West. This may be contributed by the difference in preparation of kratom available between the two regions, whereby fresh kratom leaves are chewed in Thailand and kratom tea make by boiling fresh kratom leaves in water are consumed in Malaysia, wheareas kratom leave powder are available in the West. Hence, kratom consumed in Southeast Asia may be in its natural form compared to those available in the West which may be adulterated with other substances [62].

Limitations of the selected literatures and the systematic review

The findings in this review should be interpreted with caution as there are a few limitations. First, although we found that kratom may be a potential therapeutic agent for replacement therapy for opioid dependence, acting as an antidepressant or anxiolytic, data were gathered from in vitro and/or animal studies and cross-sectional surveys. There is no data from more intensive research, such as clinical trials. Hence, future studies with more vigorous research methodology (such as a randomized, controlled trial) is recommended to confirm our review findings. Second, the sample in the cross-sectional surveys were also not representative of the general population or the country's kratom using population as respondents are self-selected to participate in these surveys. Hence, probability sampling is recommended for a future study in order to recruit a sample this is representative of the kratom using population of the country. Third, the data gathered in the selected cross-sectional surveys were a subjective account of the respondents regarding their experience of using kratom, whereby there was no objective measuring instruments used in these surveys except in the survey conducted by Garcia-Romeu et al. (2020) (28). Fourth, the findings in in vitro or animal studies should not be extrapolated to represent human subjects as the conditions in each are different. For example, mitragynine or other kratom derivatives in animal studies is administered by intraperitoneal injective which bypassed the first pass metabolism in the liver, unlike oral administration as performed in human subjects. Fifth, among the care reports selected for review, none were screened for the serum level of mitragynine and 7-HMG. Hence, we do not know the cut-off range of serum level of mitragynine and 7-HMG which led to severe kratom withdrawal symptoms requiring treatment and hospitalization. Moreover, some of the case reports were complicated by history of other illicit or prescription drug use and mental illnesses such as depression, anxiety, and attention deficit hyperactive disorder. Sixth, though kratom is reported to have therapeutic effects, the alkaloid contents of

kratom products used in western studies have not been characterized. Finally, while kratom is reported to cause dependence, this domain has not been scientifically and intensively studied in humans, as previous studies could have trumped up this narration.

With regards to limitations of the systematic review, first, it did not include research articles and case reports or case series published in languages other than English. Hence, we may miss out on a rich amount of data by only looking at studies reported in English. Second, this review did not include articles in the preprint version as these were not peer reviewed and their contents may change after completing the peer-review process. Hence, we may not have gathered the latest data on mental health benefits and drawbacks of kratom use.

CONCLUSION

In the absence of human clinical trial, coupled with various considerable adverse events of kratom (not limited to psychological side effects), evidence to support kratom as potential therapeutic use remains inconclusive. Based on our findings, mitragynine, 7-hydroxypaynantheine, and 7-hydroxyspeciogynine may be worthy of further exploration in view of their therapeutic potentials for replacement therapy, while paynantheine and speciogynine may be potential candidates to explore for treating depression and anxiety disorders.

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