REVIEW

The Potential Use of Kratom (*Mitragyna speciosa*) in Coronavirus Diseases (COVID-19)

Herbal Medicine Research Centre
Institute for Medical Research
National Institutes of Health
Ministry of Health Malaysia

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Report Written By:	**Reviewed By:**
1. Terence Tan Yew Chin 2. Lim Xin Yi 3. Hemahwathy Chanthira Kumar 4. June Chelyn Lee 5. Nur Salsabeela Mohd Rahim 6. Nurmaziah Mohammad Shafie	Dr. Ami Fazlin Syed Mohamed Head of Centre

Herbal Medicine Research Centre (HMRC)
Institute for Medical Research
Level 5, Block C6,
National Institutes of Health Complex
No. 1, Jalan Setia Murni U13/52, Section U13
40170 Setia Alam, Selangor

Disclosure

The authors of this review have no competing interest in this subject.

Disclaimer

This review is essentially a brief report, prepared on an urgent basis, to reflect the highest level of evidence available regarding the subject at this specific time. The conclusion draws on restricted reviews from analysis of pertinent literature, on expert opinion and/or regulatory status where appropriate. All efforts have been made to ensure all relevant published material has been reviewed but this document may still not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of this review.

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Executive Summary

Title

The Potential Use of Kratom (*Mitragyna speciosa*) in Coronavirus Disease (COVID-19)

Objective

The objective is to assess the potential of kratom (*Mitragyna speciosa*) in COVID-19 based on the following:

- Efficacy: Focus on antiviral (viral disease & conditions) or immunomodulatory and possible mechanism(s) of kratom with either effects
- Safety of kratom

Methodology

Electronic databases were searched using pre-determined terminologies such as 'mitragyna speciosa', 'antiviral', immunomodulatory', 'immune response', 'mechanism of action', and 'safety'. Any peer-reviewed journals found were included which are PubMed, Ovid Medline®, EBM Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Cochrane database of systematic reviews. The articles included in the search strategy were limited to those which were published within the year 1966 to March 2020. All clinical and preclinical studies (both in vitro and in vivo) related to safety and efficacy or effectiveness of probiotics in treating viral diseases were included.

Results & Discussion

- Antiviral:
    - Currently, there is no scientific evidence (in vitro, in vivo, and clinical) published on the antiviral activity of kratom or its related compounds.

- Anti-inflammatory:
    - Two in vitro studies studied the anti-inflammatory mechanism of mitragynine and supercritical fluid extract of kratom leaves. The first study showed that mitragynine can significantly reduce cyclooxygenase (COX)-2 expression in lipopolysaccharide (LPS)-treated macrophage cells while another study showed that kratom leaves extracted by supercritical fluid inhibits nitric oxide (NO) activity using Griess assay. Only one animal study showed that the methanol extract of kratom can significantly suppress the development of carrageenan-induced rat paw edema and reduce granulomatous tissue formation in a dose-dependent manner.

- Immunomodulatory:
    - No articles (pre-clinical or clinical) that directly investigated and demonstrated these effects were found while two review papers suggested unclear contributions of immune enhancing effects of kratom towards anti-inflammatory effects.

    - Based on studies conducted in other plants such as cat's claw (*Uncaria tomentosa*), it was inferred that two compounds which can be found in minute quantities in kratom may have the potential to contribute towards immunostimulatory effects.

- Safety:
    - Kratom leaves:
        - Aqueous and ethanol extract of kratom has LD_{50} range from 2,000 to 3,000 mg/kg in Sprague Dawley rats while methanol extract of kratom showed toxicity between 100 to 1,000 mg/kg with toxic effects to liver, kidney and lung in male albino Sprague Dawley rats.

        - Two case reports showing adverse effects (intrahepatic cholestasis) and side effects (withdrawal symptoms of kratom) in humans.

    - Other parts of kratom:
        - Two case reports showing liver toxicity after ingesting kratom in humans.

    - Mitragynine:
        - Animal study showed mitragynine is relatively safe at lower sub-chronic doses (1–10 mg/kg) but exhibited toxicity at a highest dose (sub-chronic 28 days: 100 mg/kg).

        - Four case studies which showed three deaths and one suffering from seizure due to high mitragynine concentration in blood or urine in humans.

    - Drug-herb interaction:
        - There is evidence that kratom can inhibit the activities of human recombinant cytochrome P450 (CYP450).

- There are 11 cases of death due to toxic effects of drugs (i.e. propylhexedrine, quetiapine and *O*-desmethyltramadol) complicated by kratom or mitragynine use

Conclusion

Kratom (*Mitragyna speciosa*) has demonstrated some anti-inflammatory properties but only in preclinical studies. Moreover, none of the anti-inflammatory studies were conducted in infectious disease models while data on immunostimulatory effects are scarce. Future studies to expand and extrapolate these findings specifically in the context of viral or respiratory infections is still needed. Therefore, there is currently no good evidence to support kratom as a miracle cure for COVID-19 or any viral respiratory infections. Based on published toxicity studies, safety concerns should be taken seriously as there were reported deaths due to kratom and mitragynine use. It is important to weigh kratom's unclear potential benefits against the safety risks, especially when compared to other medicinal plants with better safety profile.

Full report on kratom (*Mitragyna speciosa*) potential in COVID-19 management

Introduction

Kratom (*Mitragyna speciosa*) is also scientifically known as *Nauclea luzoniensis* Blanco, *Nauclea speciosa* (Korth.) Miq., *Stephegyne speciosa* Korth (1).

It is traditionally used to apply to the wounds in pounded form while poultice of the leaves was used to expel worms for children. It is also useful in relieving fever (2). People in Malaysia traditionally drink *M. speciosa* leaves that have been boiled as an energy booster (3). It also has been reported as one of the herbs in drink preparation for fever with phlegm and 'angin' (4).

Objective

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Methodology

Searching

Electronic databases were searched using pre-determined terminologies such as 'mitragyna speciosa', 'antiviral', immunomodulatory', 'immune response', 'mechanism of action', and 'safety'. Any peer-reviewed journals found were included which are PubMed, Ovid Medline®, EBM Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Cochrane database of systematic reviews. The articles included in the search strategy were limited to those which were published within the year 1966 to March 2020. All clinical and preclinical studies (both in vitro and in vivo) related to safety and efficacy or effectiveness of probiotics in treating viral diseases were included.

Selection

All published articles related to safety and efficacy or effectiveness of kratom in treating viral diseases were included.

Results & Discussion

Efficacy

Antitviral effects:

- Currently, no studies (in vitro, in vivo, and clinical) on the antiviral activity of kratom or its related compounds have been published.

Anti-inflammatory effects:

- An in vitro study in macrophages showed that mitragynine produced a significant inhibition on mRNA expression of cyclooxygenase (COX)-2 induced by lipopolysaccharides (LPS), in a dose dependent manner and this was followed by the reduction of prostaglandin E2 (PGE2) production. On the other hand, the effects of mitragynine on COX-1 mRNA expression were found to be insignificant as compared to the control cells. However, the effect of mitragynine on COX-1 protein expression is dependent on concentration, with higher concentration of mitragynine producing a further reduction of COX-1 expression in LPS-treated cells. (5)

- An in vitro study using Griess assay, which measures the formation of nitrite ion (NO^{2-}) in recombinant mouse interferon gamma/lipopolysaccharide (IFN-γ/LPS) stimulated RAW 264.7 cells, showed that Matrix 5 Step-1 (M5S1) that was extracted from supercritical CO_2 fluid extracts from *M. speciosa* exhibited the highest nitric oxide (NO) inhibitory activity (60.08%) without cytotoxicity

(cell viability, 91.98%) at a concentration of 100 µg/mL. Gas chromatography (GC) and gas chromatography-mass spectrophotometry (GC-MS) analysis revealed palmitic acid as the major constituent (34.90%) of M5S1. This study provides first evidence that M5S1, the non-alkaloidal extract obtained by supercritical fluid extraction of *M. speciosa* leaves possesses potential property in preventing inflammatory diseases mediated by excessive production of NO. (7)

- An in vivo study showed that intraperitoneal administration of the methanol extract of *M. speciosa* (100 and 200 mg/kg) significantly and dose-dependently suppressed the development of carrageenan-induced rat paw edema ($p < 0.05$), representing some anti-inflammatory effect. In the chronic test, however, significant reduction in granulomatous tissue formation in rats was observed only at the highest dose of the methanol extract of *M. speciosa* (200 mg/kg, $p < 0.05$). (6)

Immunomodulatory effects:

- Kratom has been widely speculated to have immunostimulatory effects based on a general search on non-scientific based websites on google. However, no articles (preclinical or clinical) that directly investigated and demonstrated these effects were found. In two reviews (8,9), the single same study quoted to suggest for immune enhancing effects of kratom was not designed to test for such mechanism and there was no objective assessment of the immune enhancing effects. The article instead suggested that there was unclear contribution of immune enhancing effects of kratom towards anti-inflammatory effects (6).

- Kratom contains mitraphylline and isomitraphyllin in minute amounts (mitraphylline 10.6 g/23 kg dried leaves and isomitraphylline 0.79 g/23 kg dried leaves) (10) which have been reported to contribute towards immunostimulatory effects in other plants such as cat's claw (*Uncaria tomentosa*) (11).

<u>Safety</u>

Kratom leaves:

- Standardised aqueous extract of *M. speciosa* leaves (175, 500 and 2000 mg/kg) was administered orally as a single dose to male and female Sprague Dawley rats (aged between eight and 12 weeks old). The toxicity effect was observed for 14 days and showed no mortality and caused only a slight toxicity effect (signs of fatigue and sleep for male rats while only sign of

fatigue for female rats at highest dose) (lethal dose of 50% (LD_{50}) value > 2,000 mg/kg). (12)

- Ethanol extract of *M. speciosa* leaves was administered orally as a single dose to Sprague Dawley rats. The toxicity effect was observed for 14 days and showed no toxic effect (LD_{50} value > 3,000 mg/kg). Ethanol extract of *M. speciosa* leaves (1,000 and 1,500 mg/kg/day) was administered orally to pregnant Sprague Dawley rats between day 8 and day 13 of gestation day significantly ($p < 0.001$) showed a widening of the vertebral arch in the thoracic, lumber and cervical vertebral regions of spinal cord and significantly ($p < 0.001$) increased the brain diameter of the fetuses. (13)

- Methanol extract of *M. speciosa* leaves administered orally as a single dose to male Swiss mice showed toxic effects (LD_{50} = 4,900 mg/kg) while alkaloidal extract also showed toxic effect with LD_{50} = 173.20 mg/kg (14).

- Standardised methanol extract of *M. speciosa* leaves (100,500 and 1,000 mg/kg) was administered orally as a single dose to adult male albino Sprague Dawley rats. The toxicity effect was observed for 14 days and showed no mortality however it caused toxicity effect at 1,000 mg/kg (significant increase in blood pressure, acute severe hepatotoxicity and mild nephrotoxicity) with LD_{50} > 1,000 mg/kg. (15)

- Standardised methanolic extract of ketum leaves (SMEMS) were orally administered to Sprague Dawley rats with 100, 200, and 500 mg/kg for 28 days. Biochemistry findings showed that liver and kidney were affected with the abnormal values in aspartate aminotransferase (AST), creatinine, globulin, glucose, total protein, and urea. The SMEMS produced toxic effects more to liver, kidney, and lung than other organs as observed histopathologically. The results suggested sub-chronic exposure of ketum is toxic to the physiology of the animals. (16)

- **Adverse effect:** A case report showed a young man aged 25 years old demonstrated intrahepatic cholestasis after ingested two teaspoons (one teaspoon approximately 2.3 to 3.5 g, corresponding five to eight dried *M. speciosa* leaves) twice daily for two weeks (17).

- **Side effect:** A 44-year-old man with a history of alcohol dependence and anxiety disorder admitted to the hospital for the purpose of *M. speciosa* detoxification. He demonstrated dependence on *M. speciosa* with withdrawal symptoms consisting of anxiety, restlessness, tremor, sweating and craving

for *M. speciosa*. The patient described that the detoxification from *M. speciosa* was harder than alcohol in the past. (18)

Other plant parts of kratom:

- A case study of a 70-year-old man with hypertension on amlodipine and osteoarthritis on oxycodone presented with jaundice was reported. The patient reported a history of consumption of the herbal product kratom (*M. speciosa*) for pain twice daily for four days. He reported nausea, fatigue, profound weakness, and 9 kg of weight loss over three weeks and was found to have a total bilirubin of 41 mg/dL. The Roussel Uclaf Causality Assessment Method showed liver injury that was highly probable to be due to kratom. He was diagnosed with herb induced liver injury with cholestasis and clinically improved with supportive care. (19)

- One case of kratom use-associated liver toxicity in a 38-year-old patient was reported. The patient complained of dark colored urine and light-colored stools after using kratom. Laboratory testing at presentation revealed elevated alanine aminotransferase (389 U/L), aspartate aminotransferase (220 U/L), total bilirubin (5.1 mg/dL), and alkaline phosphatase (304 U/L). There was no serology evidence of viral hepatitis A, B, and C. The patient underwent liver biopsy four days after the initial presentation which revealed a pattern of acute cholestatic liver injury, including zone 3 hepatocellular and canalicular cholestasis, focal hepatocyte dropout, mild portal inflammation, and bile duct injury. Kratom was stopped, the patient improved clinically and biochemically and was discharged eight days after the initial presentation. (20)

Mitragynine:

- Mitragynine isolated from *M. speciosa* leaves (5–15 mg/kg/day) was administered intraperitoneally for 28 days to male ICR mice significantly ($p < 0.05$) decreased discrimination ratio time compared to Tween 80 group in object location task and significantly ($p < 0.05$) decreased locomotor activity compared to amphetamine in open-field test (21).

- A case of an accidental death of a 56-year-old woman with a history of chronic obstructive pulmonary disease (COPD) secondary to multidrug toxicity whereby mitragynine toxicity is primarily implicated. Her prescribed medications consisted of Percocet (acetaminophen and oxycodone) and lorazepam. Toxicological analysis of the femoral venous blood using a standardized panel detected oxycodone, lorazepam, and mitragynine. The quantified concentrations of oxycodone (0.19±0.01 mg/L) and lorazepam (63±5 ng/L) were each not toxic in isolation. The referral toxicology laboratory

reported an independently fatal concentration of mitragynine of 2500 ng/mL, based on previously published values from mixed drug toxicity case reports (range of 20-1,060 ng/mL). The measured mitragynine is likely independently fatal and appears to be the highest reported value in the medical literature to date. (22)

- A 33- year-old man with a known history of opioid abuse and mental illnesses was found unresponsive in his basement with no obvious signs of trauma and was pronounced dead after resuscitative efforts. The laboratory toxicology work-up revealed positive findings of caffeine, cotinine, and naloxone with low levels of Δ-9-tetrahydrocannabinol. However, a marked level of mitragynine at 1.9 mg/L was observed. Given the facts and evidence, the medical examiner certified the cause of death as “mitragynine toxicity”. (23)

- A novel case of serious human toxicity following Kratom use was reported on a 64-year-old male and was confirmed via quantitative analysis of urine by high performance liquid chromatography coupled to electrospray tandem mass spectrometry. The case was witnessed to have a seizure at home following kratom consumption. The mitragynine concentration in the urine was reported to be 167±15 ng/mL. (24)

- Male and female Sprague-Dawley rats were administered with three doses of mitragynine (1, 10, 100 mg/kg body weight, p.o.) for 28 days respectively. The groups of rats treated with the lower and intermediate doses showed no toxic effects during the study. However, the relative body weight of the group of female rats treated with the 100 mg/kg dose was decreased significantly. Only relative liver weight increased after treatment with the highest dose of mitragynine in both the male and female treatment groups of rats. Biochemical and hematological parameters were also altered, especially in the highest dose treatment group which corresponds to the histopathological changes. The study demonstrated that mitragynine is relatively safe at lower sub-chronic doses (1 and 10 mg/kg) but exhibited toxicity at a highest dose. (25)

- A 24-year-old man whose medical history was significant for alcohol abuse and depression was found unresponsive in bed. Postmortem peripheral blood initially screened positive for mitragynine/ kratom by routine alkaline drug screen by gas chromatography-mass spectrometry (GC-MS), which was subsequently confirmed by a specific GC-MS selective ion mode analysis following solid-phase extraction. Concentrations were determined in the peripheral blood (0.23 mg/L), central blood (0.19 mg/L), liver (0.43 mg/kg), vitreous (< 0.05 mg/L), urine (0.37 mg/L) and was not detected in the gastric.

Therapeutic concentrations of venlafaxine, diphenhydramine and mirtazapine were also detected together with a negligible ethanol of 0.02% (w/v). The present case describes the distribution of postmortem mitragynine concentrations where it was determined to contribute to death, together with therapeutic concentrations of venlafaxine, diphenhydramine, mirtazapine and alcohol. (26)

- In a brine shrimp lethality test, the toxicity level of mitragynine showed the high toxicity with lethal concentration of 50% (LC_{50}) of 44 µL/mL, followed alkaloid extract (62 µL/mL) and aqueous extracts (98 µL/mL) (27).

Drug-herb interaction:

- Alkaloid extract of *M. speciosa* leaves inhibited the activities of human recombinant cytochrome P450 (CYP450) with the IC_{50} values of 0.636 µg/mL (CYP2D6) and 0.78 µg/mL (CYP3A4) and 39 µg/mL (CYP1A2). Competitive inhibition was demonstrated for CYP2D6 while non-competitive inhibition for CYP3A4, CYP1A2 and CYP2C19. (28)

- Methanol extract of *M. speciosa* leaves inhibited the activities CYP450 enzymes with the IC_{50} values of 3.6±0.1 µg/mL (CYP2D6) and 142.8±13.8 µg/mL (CYP3A4) (29,30).

- Animal studies on mitragynine have indicated a risk for drug-drug interactions, namely through modulating hepatic cytochrome P450 activity and drug metabolism. Mitragynine also appears to inhibit hepatic demethylases and transferases, as well as glucuronidation by UDP-glucuronosyltransferases (UGT) such as UGT2B7 and UGT1A1. This bears important implications for a possible interaction when kratom is co-administered with other drugs known to be UGT substrates (e.g. buprenorphine and ketamine, metabolised by UGT2B7). (31)

- A death involving abuse of propylhexedrine and mitragynine is reported. Toxicology results revealed the presence of 1.7 mg/L propylhexedrine and 0.39 mg/L mitragynine in his blood. Both drugs, as well as acetaminophen, morphine, and promethazine, were detected in the urine. The cause of death was ruled propylhexedrine toxicity, and the manner of death was ruled accidental. Mitragynine may have contributed as well, but as there are no published data for drug concentrations, the medical examiner did not include mitragynine toxicity in the cause of death. (32)
- The case of a 27-year-old man who was found deceased with a toxic blood concentration of quetiapine in conjunction with the qualitative presence of

mitragynine is reported. Investigative and autopsy findings suggested perimortem hyperthermia and seizure-like activity. Postmortem forensic toxicology performed on subclavian blood demonstrated valproic acid was quantitatively positive at 8.8 µg/mL, quetiapine was quantitatively positive at 12,000 ng/mL and mitragynine was qualitatively positive. The cause of death was ruled as acute toxic effects of quetiapine complicated by mitragynine use. (33)

- Nine cases of intoxication were reported where both mitragynine and *O*-desmethyltramadol were detected in the postmortem blood samples. Neither tramadol nor *N*-desmethyltramadol was present in these samples, which implies that the ingested drug was *O*-desmethyltramadol. The blood concentrations of mitragynine ranged from 0.02 to 0.18 µg/g, and *O*-desmethyltramadol concentrations ranged from 0.4 to 4.3 µg/g. The addition of the potent mu-receptor agonist *O*-desmethyltramadol to powdered leaves from kratom was postulated to contribute to the unintentional death of the nine cases presented. (34)

Conclusion

Kratom has demonstrated some anti-inflammatory properties but only in preclinical studies. Moreover, none of the anti-inflammatory studies were conducted in infectious disease models while data on immunostimulatory effects are scarce. Future studies to expand and extrapolate these findings specifically in the context of viral or respiratory infections is still needed. Therefore, there is currently no good evidence to support kratom as a miracle cure for COVID-19 or any viral respiratory infections. Based on published toxicity studies, safety concerns should be taken seriously as there were reported deaths due to kratom and mitragynine use. It is important to weigh kratom's unclear potential benefits against the safety risks, especially when compared to other medicinal plants with better safety profile.

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