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REVIEW

An Evidence-Based Systematic Review of Kratom (*Mitragyna speciosa*) by the Natural Standard Research Collaboration

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ABSTRACT. An evidence-based systematic review of kratom (*Mitragyna speciosa*) by the Natural Standard Research Collaboration consolidates the safety and efficacy data available in the scientific literature using a validated, reproducible grading rationale. This article includes written and statistical analysis of clinical trials, plus a compilation of expert opinion, folkloric precedent, history, pharmacology, kinetics/dynamics, interactions, adverse effects, toxicology, and dosing.

KEYWORDS. adverse effects, dosing, evidence-based, interactions, kratom, Mitragyna speciosa pharmacodynamics, pharmacokinetics, pharmacology, systematic review

SYSTEMATIC AGGREGATION, ANALYSIS, AND REVIEW OF THE LITERATURE

Search Strategy

To prepare this Natural Standard review, electronic searches were conducted in several databases (including AMED, CANCERLIT, CINAHL, CISCOM, the Cochrane Library, EMBASE, HerbMed, International Pharmaceutical Abstracts, Medline, and NAPRALERT) from inception to August 2012. Search terms included the common name(s), scientific name(s), and all listed synonyms. Hand searches were conducted of 20 additional journals (not indexed in common databases), and of bibliographies from 50 selected secondary references. No

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restrictions were placed on language or quality of publications. Researchers in the field of complementary and alternative medicine (CAM) were consulted for access to additional references or ongoing research.

Selection Criteria

All literature were collected pertaining to efficacy in humans (regardless of study design, quality, or language), dosing, precautions, adverse effects, use in pregnancy/lactation, interactions, alteration of laboratory assays, and mechanism of action (in vitro, animal research, human data). Standardized inclusion/exclusion criteria were utilized for selection.

Data Analysis

Data extraction and analysis were performed by healthcare professionals conducting clinical work and/or research at academic centers, using standardized instruments that pertained to each review section (defining inclusion/exclusion criteria and analytic techniques, including validated measures of study quality). Data were verified by a second reviewer.

Review Process

A blinded review was conducted by multidisciplinary research-clinical faculty at major academic centers with expertise in epidemiology and biostatistics, pharmacology, toxicology, CAM research, and clinical practice. In cases of editorial disagreement, a three-member panel of the Editorial Board addressed conflicts, and consulted experts when applicable. Authors of studies were contacted when clarification was required.

Synonyms/Common Names/Related Substances.

- 7-Hydroxymitragynine, 9-O-demethyl paynantheine, 9-O-demethyl-16-carboxy paynantheine, 9-O-demethyl-17-carboxy-16,17-dihydro paynantheine, 9,17-O-bisdemethyl paynantheine, 9,17-O-bisdemethyl-16,17-dihydro paynantheine, 16-carboxy paynantheine, 17-O-demethyl paynantheine, 17-O-demethyl-16,17-dihydro paynantheine, 17-carboxy-16,17-dihydro paynantheine, biak, isopaynantheine, ithang, kakuam, ketum, krathom, kratom, krypton, *Mitragyna speciosa*, *Mitragyna speciosa* Korth., mitraciliatine, mitragynine, mitraphylline, paynantheine, Rubiaceae (family), speciociliatine, speciogynine, thang, thom.
- *Combination product examples*. Krypton (kratom, O-desmethyltramadol).
- *Note*: The cultivation, sale, and possession of *Mitragyna speciosa* are illegal in some countries. Unintentional death has occurred following ingestion

of krypton, a combination preparation containing *Mitragyna speciosa* and O-desmethyltramadol (Backstrom, Classon, Lowenhielm, & Thelander, 2010; Kronstrand, Roman, Thelander, & Eriksson, 2011).

CLINICAL BOTTOM LINE/EFFECTIVENESS

Brief Background

- *Mitragyna speciosa* is a tree found in Southeast Asia and is a member of the *Rubiaceae* family. It exhibits psychoactive properties and opioid-like activity (Chan, Pakiam, & Rahim, 2005; Koch et al., 1992; Roche, Hart, Sangall, Lefberg, & Bayer, 2008; Vicknasingam, Narayanan, Beng, & Mansor, 2010), in addition to analgesic, euphoric, and antitussive effects (McWhirter & Morris, 2010). Mitragynine has been identified as one of the major alkaloids and has been reported in a number of case reports and pharmacological studies (Adkins, Boyer, & McCurdy, 2011).
- Leaves from *Mitragyna speciosa* have been traditionally used for medicinal and stimulant properties to treat chronic pain (Boyer, Babu, Adkins, McCurdy, & Halpern, 2008; Boyer, Babu, & Macalino, 2007; Rosenbaum, Carreiro, & Babu, 2012) and opioid withdrawal (Boyer et al., 2008; Boyer et al., 2007; McWhirter & Morris, 2010; Rosenbaum et al., 2012; Vicknasingam et al., 2010), and they have also been used as an opium substitute (Jansen & Prast, 1988).
- *Mitragyna speciosa* is also commonly referred to as kratom (Lu, Tran, Nelsen, & Aldous, 2009) and has been identified as a herb of abuse for recreational purposes. Individuals using *Mitragyna speciosa* over the long term have shown signs of dependence and symptoms of withdrawal at time of cessation (McWhirter & Morris, 2010). A number of countries and states have passed laws making the tree and leaves of *Mitragyna speciosa* illegal, although it is possible to readily obtain preparations containing *Mitragyna speciosa* over the Internet. Unintentional death has occurred following ingestion of krypton, a combination preparation containing *Mitragyna speciosa* and O-desmethyltramadol (Backstrom et al., 2010; Kronstrand et al., 2011).
- There is lack of available evidence in support of *Mitragyna speciosa* for any clinical indication.

Scientific Evidence

- No available studies qualify for inclusion in the grading table.

Natural Standard Evidence-Based Validated Grading Rationale™

- Grades reflect the level of available scientific evidence in support of the efficacy of a given therapy for a specific indication.
- Expert opinion and historic/folkloric precedent are not included in this assessment, and are reflected in a separate section of each review ("Expert Opinion and Historic/Folkloric Precedent").
- Evidence of harm is considered separately; the below grades apply only to evidence of benefit.

Level of Evidence Grade	Criteria
A (strong scientific evidence)	Statistically significant evidence of benefit from >2 properly randomized trials (RCTs), OR evidence from one properly conducted RCT AND one properly conducted meta-analysis, OR evidence from multiple RCTs with a clear majority of the properly conducted trials showing statistically significant evidence of benefit AND with supporting evidence in basic science, animal studies, or theory.
B (good scientific evidence)	Statistically significant evidence of benefit from 1–2 properly randomized trials, OR evidence of benefit from >1 properly conducted meta-analysis OR evidence of benefit from >1 cohort/case-control/non-randomized trials AND with supporting evidence in basic science, animal studies, or theory.
C (unclear or conflicting scientific evidence)	Evidence of benefit from >1 small RCT(s) without adequate size, power, statistical significance, or quality of design by objective criteria,* OR conflicting evidence from multiple RCTs without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness, OR evidence of benefit from >1 cohort/case-control/nonrandomized trials AND without supporting evidence in basic science, animal studies, or theory, OR evidence of efficacy only from basic science, animal studies, or theory.
D (fair negative scientific evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from cohort/case-control/nonrandomized trials, AND evidence in basic science, animal studies, or theory suggesting a lack of benefit.
F (strong negative scientific evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from >1 properly randomized adequately powered trial(s) of high-quality design by objective criteria.*
Lack of evidence†	Unable to evaluate efficacy due to lack of adequate available human data.

*Objective criteria are derived from validated instruments for evaluating study quality, including the 5-point scale developed by Jadad et al. (1996), in which a score below 4 is considered to indicate lesser quality methodologically.
† Listed separately in the "Historical or Theoretical Uses That Lack Sufficient Evidence" section.

Historical or Theoretical Uses that Lack Sufficient Evidence

- Analgesic (McWhirter & Morris, 2010), antitussive (McWhirter & Morris, 2010; Nelsen, Lapoint, Hodgman, & Aldous, 2010), anxiety, attention deficit disorder (adult), calming (Chittrakarn, Keawpradub, Sawangjaroen, Kansenalak, & Janchawee, 2010), chronic pain (Boyer et al., 2007; (Boyer et al., 2008; Rosenbaum et al., 2012), depression, detoxification (methadone addiction), diarrhea, drug addiction (opioid), and drug withdrawal (opioid) (Boyer et al., 2007; Boyer et al., 2008; McWhirter & Morris, 2010; Rosenbaum et al., 2012; Vicknasingam et al., 2010), increases energy (Chittrakarn et al., 2010; Vicknasingam et al., 2010), mood, narcotic (euphoric) (McWhirter & Morris, 2010), sexual performance (prolonged or intensified).

Expert Opinion and Historic/Folkloric Precedent

- Reports starting in the mid-1800s give an account of *Mitragyna speciosa* being used as an opium substitute (Jansen & Prast, 1988).
- *Mitragyna speciosa* is an indigenous tree primarily found in Thailand and Malaysia (Chan et al., 2005; Ingsathit et al., 2009; Jansen & Prast, 1988), and

the leaves have been chewed, smoked, or made into a tea (Assanangkornchai, Muekthong, Sam-Angsri, & Pattanasattayawong, 2007; Jansen & Prast, 1988; Roche et al., 2008; Suwanlert, 1975; Ward, Rosenbaum, Hernon, McCurdy, & Boyer, 2011).

- *Mitragyna speciosa* has reportedly been used for centuries for its psychoactive properties, opium-like effects, and ability to treat opioid addiction and opioid withdrawal (Chan et al., 2005; Koch et al., 1992; Roche et al., 2008; Ward et al., 2011). In recent years, it has grown in popularity as a rave drug (Maurer, 2010) and may be readily found on the Internet (Maruyama, Kawamura, Kikura-Hanajiri, Takayama, & Goda, 2009; Schmidt, Sharma, Schifano, & Feinmann, 2011).
- *Mitragyna speciosa* is lacking in the U.S. Food and Drug Administration (FDA) Generally Recognized as Safe (GRAS) list. It is included in the FDA Poisonous Plant Database.

Brief Safety Summary

- *Possibly unsafe*: When used in all patients, due to a lack of available evidence. When used in patients with thyroid disorders or those using thyroid agents (Sheleg & Collins, 2011); in patients with liver disorders (Kapp, Maurer, Auwarter, Winkelmann, & Hermanns-Clausen, 2011); or in patients with gastrointestinal disorders (secondary sources). When used in combination with cytochrome P450-metabolized agents (Kong et al., 2011).
- *Likely unsafe*: When used in patients with neurologic disorders or in those taking neurologic agents (Arndt et al., 2011; Chan et al., 2005; Koch et al., 1992; McWhirter & Morris, 2010; Roche et al., 2008; Ward et al., 2011). When the product krypton (a combination product containing *Mitragyna speciosa* and O-desmethyltramadol) is used, due to case reports of unintentional death (Backstrom et al., 2010; Kronstrand et al., 2011). When used concomitantly with alcohol, sedatives, benzodiazepines, opioids, or opium-containing agents (secondary sources). When used concomitantly with stimulants, caffeine, caffeine-containing agents, cocaine, yohimbine, or related agents (secondary sources). When used concomitantly with monoamine oxidase inhibitors (MAOIs), including herbs such as Syrian rue (*Peganum harmala*), ayahuasca (*Banisteriopsis caapi*), and passionflower (*Passiflora incarnata*), or certain other antidepressants (secondary sources). When used during pregnancy or lactation, or in children. When used in patients with known allergy or hypersensitivity to Mitragyna species, their constituents, or members of the Rubiaceae family.
- Note: Mitragyna speciosa is illegal in some countries, and there is insufficient evidence in humans to support its use for any indication.

DOSING/TOXICOLOGY

General

- Doses may be based on those most commonly used in available trials, or on historical practice. However, with natural products it is often not clear what the optimal doses are to balance efficacy and safety. Preparation of products may vary

from manufacturer to manufacturer, and from batch to batch within one manufacturer. Because it is often not clear what the active component(s) of a product is, standardization may not be possible, and the clinical effects of different brands may not be comparable.

Standardization

- Well-known standardization for *Mitragyna speciosa* is lacking. According to secondary sources, *Mitragyna speciosa* is available in multiple forms, including dried leaves, powder, and extract. The dried leaves, often referred to as kratom, tend to be the most common form, and the quality may indicate the level of potency in the final product.

Dosing

Adult (Age ≥ 18)

Oral.

- *General*: *Mitragyna speciosa* is utilized as an herbal drug of abuse. According to secondary sources, dosage relies on the potency and form of *Mitragyna speciosa* used. The leaves of *Mitragyna speciosa* have reportedly been chewed, smoked, or made into a tea (Assanangkornchai et al., 2007; Jansen & Prast, 1988; Roche et al., 2008; Suwanlert, 1975).
- *Note*: The cultivation, sale, and possession of *Mitragyna speciosa* are illegal in some countries. Unintentional death has occurred following ingestion of krypton, a combination preparation containing *Mitragyna speciosa* and O-desmethyltramadol (Backstrom et al., 2010; Kronstrand et al., 2011).

Children (Age < 18)

- Insufficient available evidence.

Toxicology

- Reports of severe toxicities following the use of *Mitragyna speciosa* are purportedly rare (Kapp et al., 2011). Serious toxicity due to ingestion of *Mitragyna speciosa* was reported in a 64-year-old male who sustained multiple seizures and a coma, with confirmed elevated mitragynine concentration in the urine of 167 ± 15 ng/ml (Nelsen et al., 2010).
- A report exists of a fatality involving propylhexedrine, an alpha-adrenergic sympathomimetic amine, and mitragynine, a mu-receptor agonist and component of *Mitragyna speciosa* (Holler et al., 2011). Confirmation of the contributing toxic effects of mitragynine was lacking, due to insufficient data regarding drug concentrations.
- Unintentional death occurred in nine individuals (Backstrom et al., 2010) following ingestion of a preparation containing a combination of powdered *Mitragyna speciosa* leaves and O-desmethyltramadol, a mu-receptor agonist, called krypton (Kronstrand et al., 2011). Blood levels of mitragynine (0.02–0.18 mcg/g) and O-desmethyltramadol (0.4–4.3 mcg/g) were taken.

ADVERSE EFFECTS/PRECAUTIONS/CONTRAINDICATIONS

Allergy

Avoid with known allergy or hypersensitivity to *Mitragyna* species, their constituents, or members of the Rubiaceae family.

Adverse Effects

- *General*: Adverse effects including dry mouth, changes in urination, nausea, vomiting, small black feces, anorexia, weight loss, and constipation have been reported in the secondary literature. In a case report, serious toxicity, seizures, and coma were reported to have occurred after consumption of *Mitragyna speciosa* (Nelsen et al., 2010). Unintentional death has occurred following ingestion of krypton, a combination preparation containing *Mitragyna speciosa* and O-desmethyltramadol (Backstrom et al., 2010; Kronstrand et al., 2011).
- *Endocrine*: In a reported case, the authors theorized that consumption of large doses of *Mitragyna speciosa* may have resulted in primary hypothyroidism caused by a reduction in the normal response of the thyroid gland to thyroid-stimulating hormone (Sheleg & Collins, 2011).
- *Gastrointestinal*: According to secondary sources, dry mouth, nausea, constipation, small black feces, and vomiting may occur with use of *Mitragyna speciosa*.
- *Genitourinary*: According to anecdote, increase or decrease in urination may occur with use of *Mitragyna speciosa*.
- *Hepatic*: In a case report, intrahepatic cholestasis has been reported as an adverse effect of *Mitragyna speciosa* use (Kapp et al., 2011).
- *Neurologic/CNS*: *Mitragyna speciosa* alone, or in combination with other agents, has been shown to cause dependence and withdrawal symptoms following repeated consumption (Arndt et al., 2011; McWhirter & Morris, 2010). Cases of seizure-like activity have been reported, although often *Mitragyna speciosa* was typically used in combination with another agent (Jansen & Prast, 1988; Roche et al., 2008). Serious toxicity due to ingestion of *Mitragyna speciosa* was reported in a 64-year-old male who sustained multiple seizures and a coma, with confirmed elevated mitragynine concentration in the urine of 167 ± 15 ng/ml (Nelsen et al., 2010).
- *Other*: According to secondary sources, anorexia or weight loss may occur with use of *Mitragyna speciosa*.

Precautions/Warnings/Contraindications

- Use cautiously in all patients due to a lack of available evidence.
- Use cautiously in patients with thyroid disorders or those using thyroid agents, due to a reported case in which authors theorized that consumption of large doses of *Mitragyna speciosa* may have resulted in primary hypothyroidism (Sheleg & Collins, 2011).
- Use cautiously in patients with liver disorders, as intrahepatic cholestasis has been reported as an adverse effect of *Mitragyna speciosa* in a case report (Kapp et al., 2011).
- Use cautiously in combination with cytochrome P450-metabolized agents, as, in laboratory research, *Mitragyna speciosa* has shown the potential to interact with

agents that are substrates for CYP3A4, CYP2D6, and CYP1A2 if used at the same time (Kong et al., 2011).

- Use cautiously in patients with gastrointestinal disorders, as dry mouth, nausea, constipation, small black feces, and vomiting may occur with use of *Mitragyna speciosa*, according to secondary sources.
- Avoid in patients with neurologic disorders or in those taking neurologic agents, as *Mitragyna speciosa* has been suggested to have psychoactive or opium-like effects (Chan et al., 2005; Koch et al., 1992; Roche et al., 2008; Ward et al., 2011). When used alone, or in combination with other agents, it has been shown to cause dependence and withdrawal symptoms (Arndt et al., 2011; McWhirter & Morris, 2010), seizures and coma (Nelsen et al., 2010), or seizure-like activity (Jansen & Prast, 1988; Roche et al., 2008). According to secondary sources, when used concomitantly with neurologic agents, it may cause oversedation or potential respiratory depression.
- Avoid ingestion of the product krypton, a combination preparation containing *Mitragyna speciosa* and O-desmethyltramadol, as unintentional death has been reported in case reports (Backstrom et al., 2010; Kronstrand et al., 2011).
- Avoid with concomitant use of alcohol, sedatives, benzodiazepines, opioids, or opium-containing agents, according to secondary sources suggesting that this may cause oversedation or potential respiratory depression.
- Avoid with concomitant use of stimulants, caffeine, caffeine-containing agents, cocaine, yohimbine, or related agents, according to secondary sources suggesting that this may cause overstimulation or elevated blood pressure.
- Avoid with concomitant use of MAOIs, including herbs such as Syrian rue (*Peganum harmala*), ayahuasca (*Banisteriopsis caapi*), and passionflower (*Passiflora incarnata*), or certain other antidepressants, according to secondary sources suggesting that this may potentially cause serious reactions.
- Avoid use of *Mitragyna speciosa* in large doses, according to secondary sources.
- Avoid during pregnancy or lactation, and in children, due to a lack of available evidence.
- Avoid with known allergy or hypersensitivity to *Mitragyna* species, their constituents, or members of the Rubiaceae family.
- Note: *Mitragyna speciosa* is illegal in some countries, and there is insufficient evidence in humans to support its use for any indication.

Pregnancy and Lactation

- Not suggested due to a lack of sufficient data. Information on Mitragyna speciosa's effects on lactation is lacking in the National Institute of Health's Lactation and Toxicology Database (LactMed).

INTERACTIONS

Mitragyna Speciosa/Drug Interactions

- *Alcohol*: According to secondary sources, there have been reports of concomitant use of alcohol with *Mitragyna speciosa* causing oversedation or potential respiratory depression.

- *Analgesics*: According to case report data, *Mitragyna speciosa* has been reported to have analgesic effects (McWhirter & Morris, 2010) and to have been used for chronic pain (Boyer et al., 2007; Boyer et al., 2008; Rosenbaum et al., 2012).
- *Antiobesity agents*: According to secondary sources, anorexia or weight loss may occur with use of *Mitragyna speciosa*.
- *Benzodiazepines*: According to secondary sources, there have been reports of concomitant use of benzodiazepines with *Mitragyna speciosa* causing oversedation or potential respiratory depression.
- *Caffeine-containing agents*: According to secondary sources, there have been reports of concomitant use of caffeine with *Mitragyna speciosa* causing overstimulation or elevated blood pressure.
- *Cocaine*: According to secondary sources, there have been reports of concomitant use of cocaine with *Mitragyna speciosa* causing overstimulation or elevated blood pressure.
- *Cytochrome P450 substrates*: In laboratory research, *Mitragyna speciosa* has shown the potential to interact with medications that are substrates for CYP3A4, CYP2D6, and CYP1A2 if used at the same time (Kong et al., 2011).
- *Diuretics*: According to anecdote, increase or decrease in urination may occur with use of *Mitragyna speciosa*.
- *Gastrointestinal agents*: According to secondary sources, dry mouth, nausea, constipation, small black feces, and vomiting may occur with use of *Mitragyna speciosa*.
- *Hepatotoxins*: In a case report, intrahepatic cholestasis has been reported as an adverse effect of *Mitragyna speciosa* (Kapp et al., 2011).
- *Monoamine oxidase inhibitors (MAOIs)*: According to secondary sources, concomitant use of MAO inhibitors or certain other antidepressants with *Mitragyna speciosa* may potentially cause serious reactions.
- *Neurologic agents*: According to secondary sources, there have been reports of concomitant use of neurologic agents with *Mitragyna speciosa* causing oversedation or potential respiratory depression. *Mitragyna speciosa* has reportedly been used for centuries for its psychoactive properties, opium-like effects, and ability to treat opioid addiction and opioid withdrawal (Chan et al., 2005; Koch et al., 1992; Roche et al., 2008; Ward et al., 2011). According to case report data, *Mitragyna speciosa* has been reported to have analgesic and euphoric effects through its agonistic actions on opioid receptors (McWhirter & Morris, 2010).
- *Opioids*: According to secondary sources, there have been reports of concomitant use of opioids with *Mitragyna speciosa* causing oversedation or potential respiratory depression. *Mitragyna speciosa* has reportedly been used for centuries for its psychoactive properties, opium-like effects, and ability to treat opioid addiction and opioid withdrawal (Chan et al., 2005; Koch et al., 1992; Roche et al., 2008; Ward et al., 2011). Reports starting in the mid-1800s give an account of *Mitragyna speciosa* being used as an opium substitute (Jansen & Prast, 1988).
- *Sedatives*: According to secondary sources, there have been reports of concomitant use of sedatives with *Mitragyna speciosa* causing oversedation or potential respiratory depression.

- *Stimulants*: According to secondary sources, there have been reports of concomitant use of amphetamine-like drugs with *Mitragyna speciosa* causing overstimulation or elevated blood pressure.
- *Thyroid hormones*: In a reported case, the authors theorized that consumption of large doses of *Mitragyna speciosa* may have resulted in primary hypothyroidism caused by a reduction in the normal response of the thyroid gland to thyroid-stimulating hormone (Sheleg & Collins, 2011).
- *Yohimbine*: According to secondary sources, there have been reports of concomitant use of yohimbine with *Mitragyna speciosa* causing overstimulation or elevated blood pressure.

Mitragyna Speciosa/Herb/Supplement Interactions

- *Analgesics*: According to case report data, *Mitragyna speciosa* has been reported to have analgesic effects (McWhirter & Morris, 2010) and to have been used for chronic pain (Boyer et al., 2007; Boyer et al., 2008; Rosenbaum et al., 2012).
- *Antiobesity agents*: According to secondary sources, anorexia or weight loss may occur with use of *Mitragyna speciosa*.
- Ayahuasca (*Banisteriopsis caapi*): According to secondary sources, concomitant use of MAO inhibitors, including *Banisteriopsis caapi*, with *Mitragyna speciosa* may potentially cause serious reactions.
- *Caffeine-containing agents*: According to secondary sources, there have been reports of concomitant use of caffeine with *Mitragyna speciosa* causing overstimulation or elevated blood pressure.
- *Coca (Erythroxylum coca)*: According to secondary sources, there have been reports of concomitant use of cocaine with *Mitragyna speciosa* causing overstimulation or elevated blood pressure. "Coca" is not, however, to be confused with cocaine. Coca leaves and cocaine are two different products. Cocaine is an alkaloid derived from the leaves of the coca plant, where it is present in relatively small amounts. Cocaine is a highly addictive stimulant, with the potential for being highly toxic. Although used in some medical settings, the cultivation, sale, and possession of cocaine are illegal in most countries.
- *Cytochrome P450 substrates*: In laboratory research, *Mitragyna speciosa* has shown the potential to interact with medications that are substrates for CYP3A4, CYP2D6, and CYP1A2 if used at the same time (Kong et al., 2011).
- *Diuretics*: According to anecdote, increase or decrease in urination may occur with use of *Mitragyna speciosa*.
- *Gastrointestinal agents*: According to secondary sources, dry mouth, nausea, constipation, small black feces, and vomiting may occur with use of *Mitragyna speciosa*.
- *Hepatotoxins*: In a case report, intrahepatic cholestasis has been reported as an adverse effect of *Mitragyna speciosa* (Kapp et al., 2011).
- *Monoamine oxidase inhibitors (MAOIs)*: According to secondary sources, concomitant use of MAO inhibitors, including Syrian rue (*Peganum harmala*), ayahuasca (*Banisteriopsis caapi*), passionflower (*Passiflora incarnata*), or certain other antidepressants, with *Mitragyna speciosa* may potentially cause serious reactions.

- *Neurologic agents*: According to secondary sources, there have been reports of concomitant use of neurologic agents with *Mitragyna speciosa* causing oversedation or potential respiratory depression. *Mitragyna speciosa* has reportedly been used for centuries for its psychoactive properties, opium-like effects, and ability to treat opioid addiction and opioid withdrawal (Chan et al., 2005; Koch et al., 1992; Roche et al., 2008; Ward et al., 2011). According to case report data, *Mitragyna speciosa* has been reported to have analgesic and euphoric effects through its agonistic actions on opioid receptors (McWhirter & Morris, 2010).
- Opium poppy (*Papaver somniferum*): According to secondary sources, there have been reports of concomitant use of opioids with *Mitragyna speciosa* causing oversedation or potential respiratory depression. *Mitragyna speciosa* has reportedly been used for centuries for its psychoactive properties, opium-like effects, and ability to treat opioid addiction and opioid withdrawal (Chan et al., 2005; Koch et al., 1992; Roche et al., 2008; Ward et al., 2011). Reports starting in the mid-1800s give an account of *Mitragyna speciosa* being used as an opium substitute (Jansen & Prast, 1988). In the United States, the Drug Enforcement Administration (DEA) lists opium as a Schedule II controlled substance. Opium poppy cultivation and poppy straw are prohibited in the United States. Codeine, hydrocodone, morphine, and thebaine are opium derivatives and are also listed as Schedule II controlled substances.
- *Passionflower (Passiflora incarnata)*: According to secondary sources, concomitant use of MAO inhibitors, including passionflower (*Passiflora incarnata*), with *Mitragyna speciosa* may potentially cause serious reactions.
- *Sedatives*: According to secondary sources, there have been reports of concomitant use of sedatives with *Mitragyna speciosa* causing oversedation or potential respiratory depression.
- *Stimulants*: According to secondary sources, there have been reports of concomitant use of amphetamine-like agents with *Mitragyna speciosa* causing overstimulation or elevated blood pressure.
- Syrian rue (*Peganum harmala*): According to secondary sources, concomitant use of MAO inhibitors, including Syrian rue (*Peganum harmala*), with *Mitragyna speciosa* may potentially cause serious reactions.
- Thyroid agents: In a reported case, the authors theorized that consumption of large doses of *Mitragyna speciosa* may have resulted in primary hypothyroidism caused by a reduction in the normal response of the thyroid gland to thyroid-stimulating hormone (Sheleg & Collins, 2011).
- Yohimbe (*Pausinystalia yohimbe*): According to secondary sources, there have been reports of concomitant use of yohimbine with *Mitragyna speciosa* causing overstimulation or elevated blood pressure.

Mitragyna Speciosa/Food Interactions

- Caffeine-containing foods: According to secondary sources, there have been reports of concomitant use of caffeine with *Mitragyna speciosa* causing overstimulation or elevated blood pressure.

Mitragyna Speciosa/Lab Interactions

- Insufficient available evidence.

Mitragyna speciosa/Nutrient Depletion:

- Insufficient available evidence.

MECHANISM OF ACTION

Pharmacology

- Constituents: *Mitragyna speciosa consists* mainly of the alkaloid mitragynine, an opioid mu-receptor agonist (Kapp et al., 2011; Kronstrand et al., 2011; Sheleg & Collins, 2011; Takayama et al., 2002). Other alkaloids found in *Mitragyna speciosa* include isopaynantheine, mitraciliatine, mitraphylline, paynantheine, speciociliatine, speciogynine, and 7-hydroxymitragynine (Arndt et al., 2011; Babu, McCurdy, & Boyer, 2008; Chittrakarn et al., 2010; Philipp, Meyer, Wissenbach, Weber, Zoerntlein, Zweipfenning, & Maurer, 2011; Philipp, Wissenbach, Weber, Zapp, & Maurer, 2010; Philipp, Wissenbach, Weber, Zapp, & Maurer, 2011; Philipp, Wissenbach, Weber, Zapp, Zoerntlein, Kanogsunthornrat, & Maurer, 2010).
- Analgesic effects: According to case report data, *Mitragyna speciosa* has been reported to have analgesic effects through its agonistic actions on opioid receptors (McWhirter & Morris, 2010). According to review and case report data, *Mitragyna speciosa* has been used for chronic pain (Boyer et al., 2007; Boyer et al., 2008; Rosenbaum et al., 2012).
- CYP 450 effects: A laboratory study reported inhibition of CYP3A4, CYP2D6, CYP1A2, and potentially CYP2C19 by *Mitragyna speciosa* (Kong et al., 2011).
- Neurologic effects: *Mitragyna speciosa* has reportedly been used for centuries for its psychoactive properties, opium-like effects, and ability to treat opioid addiction and opioid withdrawal (Chan et al., 2005; Koch et al., 1992; Roche et al., 2008; Vicknasingam et al., 2010). According to case report data, *Mitragyna speciosa* has been reported to have analgesic and euphoric effects through its agonistic actions on opioid receptors (McWhirter & Morris, 2010). According to secondary sources, *Mitragyna speciosa* displays a yohimbine-like binding to alpha-adrenergic and delta-opioid receptors at low doses, although binding crosses over to mu-opioid receptors as doses increase. According to secondary sources, *Mitragyna speciosa* has been reported to prevent or delay symptoms of withdrawal through its interaction with adrenergic and opioid receptors.

Pharmacodynamics/Kinetics

- Absorption: In laboratory research, absolute oral bioavailability of mitragynine has been calculated to be 3.03% (Parthasarathy et al., 2010).
- Distribution: According to case report data, mitragynine has been shown to bind selectively to mu- and kappa-opioid receptors (Boyer et al., 2008).
- Metabolism: Tests in humans and rats have identified mitragynine as the main alkaloid in *Mitragyna speciosa*, and paynantheine as the second most prevalent alkaloid (Kapp et al., 2011; Kronstrand et al., 2011; Philipp et al., 2010; Sheleg & Collins, 2011; Takayama et al., 2002). Tests with paynantheine in rat urine identified 9-O-demethyl paynantheine, 16-carboxy paynantheine, 9-O-demethyl-16-carboxy paynantheine, 17-O-demethyl paynantheine, 17-O-demethyl-16,

17-dihydro paynantheine, 9,17-O-bisdemethyl paynantheine, 9,17-O-bisdemethyl-16,17-dihydro paynantheine, 17-carboxy-16,17-dihydro paynantheine, and 9-O-demethyl-17-carboxy-16,17-dihydro paynantheine as phase I metabolites (Philipp et al., 2009; Philipp et al., 2010a; Philipp et al., 2010b; Philipp et al., 2011).

- Elimination/half-life: In rats, mitragynine revealed a biphasic elimination from plasma after intravenous administration (Parthasarathy et al., 2010).
- Onset of action: According to secondary sources, onset of action of *Mitragyna speciosa* has been noted to occur within 5–10 min following use.
- Duration: According to secondary sources, duration of action of *Mitragyna speciosa* has been noted to last for several hours after use, depending on the physiology of the individual.
- Half-maximal inhibitory concentration (IC_{50}): Through assays, *Mitragyna speciosa* was detected to have inhibitory effects on CYP3A4, CYP2D6, and CYP1A2, with half-maximal inhibitory concentration (IC_{50}) values of 0.78, 0.636, and 39 mcg/ml, respectively, and weak inhibition for CYP2C19 (Kong et al., 2011).

HISTORY

- Research and reports on the use of *Mitragyna speciosa* and its effects have purportedly been taking place since the mid-1800s (Jansen & Prast, 1988).
- According to secondary sources, a law called the Kratom Act 2486 was passed by the Thai government and went into effect on August 3, 1943, which made planting *Mitragyna speciosa* trees illegal and forced all existing trees to be cut down. As *Mitragyna speciosa* is indigenous to Thailand, the law was reportedly not very effective. According to the Narcotics Acts of 1979, *Mitragyna speciosa* is scheduled a category of five agents. A method often taken to bypass regulations is to use *Mitragyna javanica,* a related species of *Mitragyna speciosa*, as a substitute, although this has been found to be not as effective.
- Unsubstantiated reports have noted that *Mitragyna speciosa* is an integral piece of Thai culture and that the banning of the plant occurred primarily due to economic reasons, rather than health or social concerns. Allegedly, the Thai government was losing money after implementing taxes involved with the opium trade, which in turn caused individuals to switch to a related species of *Mitragyna speciosa* to control symptoms of withdrawal. With World War II and reduced revenues from the opium trade, the belief is that the Thai government initiated the ban on *Mitragyna speciosa* in order to eliminate competition in the opium market.
- In the United States, secondary sources have reported numerous states prohibiting the use of krypton, a combination preparation containing *Mitragyna speciosa,* some restricting the sale to minors and others banning *Mitragyna speciosa* entirely.

EVIDENCE TABLE

- No available studies qualify for inclusion in the Evidence Table.

Explanation of columns in Natural Standard Evidence Table

1	2	3	4	5	6	7	8	9	10
Condition	Study design	Author, year	N	Statistically significant?	Quality of study 0–2 = poor 3–4 = good 5 = excellent	Magnitude of benefit	Absolute risk reduction	Number needed to treat	Comments

Condition

- Refers to the medical condition or disease targeted by a therapy.

Study Design

Common types include:

- Randomized controlled trial (RCT): An experimental trial in which participants are assigned randomly to receive either an intervention being tested or placebo. Note that Natural Standard defines RCTs as being placebo-controlled, while studies using active controls are classified as equivalence trials (see below). In RCTs, participants and researchers are often blinded (i.e., unaware of group assignments), although unblinded and quasi-blinded RCTs are also often performed. True random allocation to trial arms, proper blinding, and sufficient sample size are the basis for an adequate RCT.
- Equivalence trial: An RCT which compares two active agents. Equivalence trials often compare new treatments to usual (standard) care, and may not include a placebo arm.
- Before and after comparison: A study that reports only the change in outcome in each group of a study, and does not report between-group comparisons. This is a common error in studies that claim to be RCTs.
- Case series: A description of a group of patients with a condition, treatment, or outcome (e.g., 20 patients with migraine headache underwent acupuncture and 17 reported feeling better afterwards). Case series are considered weak evidence of efficacy.
- Case-control study: A study in which patients with a certain outcome are selected and compared to similar patients (without the outcome) to see if certain risk factors/predictors are more common in patients with that outcome. This study design is not common in the complementary and alternative medicine literature.
- Cohort study: A study which assembles a group of patients with certain baseline characteristics (for example, use of a drug), and follows them forward in time for outcomes. This study design is not common in the complementary and alternative medicine literature.
- Meta-analysis: A pooling of multiple trials to increase statistical power (often used to pool data from a number of RCTs with small sample sizes, none which demonstrates significance alone but in aggregate can achieve significance). Multiple difficulties are encountered when designing/reviewing these analyses; in particular, outcomes measures or therapies may differ from study to study, hindering direct comparison.

- Review: An author's description of his or her opinion based on personal, non-systematic review of the evidence.
- Systematic review: A review conducted according to pre-specified criteria in an attempt to limit bias from the investigators. Systematic reviews often include a meta-analysis of data from the included studies.

Author, Year

- Identifies the study being described in a row of the table.

N

- The total number of subjects included in a study (treatment group plus placebo group). Some studies recruit a larger number of subjects initially, but do not use them all because they do not meet the study's entry criteria. In this case, it is the second, smaller number that qualifies as *N*. Here, *N* includes all subjects that are part of a study at the start date, even if they drop out, are lost to follow-up, or are deemed unsuitable for analysis by the authors. Trials with a large number of drop-outs that are not included in the analysis are considered to be weaker evidence for efficacy. For systematic reviews, the number of studies included is reported. For meta-analyses, the number of total subjects included in the analysis or the number of studies may be reported.

Statistically Significant?

- Results are noted as being statistically significant if a study's authors report statistical significance, or if quantitative evidence of significance is present (such as p values). *P* = pending verification.

Quality of Study

- A numerical score between 0–5 is assigned as a rough measure of study design/reporting quality (0 being weakest and 5 being strongest). This number is based on a well-established, validated scale developed by Jadad et al. (1996). This calculation does not account for all study elements that may be used to assess quality (other aspects of study design/reporting are addressed in the "Evidence Discussion" sections of reviews).
- A Jadad score is calculated using the seven items in the table below. The first five items are indications of good quality, and each counts as one point towards an overall quality score. The final two items indicate poor quality, and a point is subtracted for each if its criteria are met. The range of possible scores is 0 to 5.

Jadad score calculation

Item	Score
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?	0/1

Was the study described as double blind?	0/1
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc.)?	0/1
Was there a description of withdrawals and dropouts?	0/1
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.).	0/–1
Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0/–1

Magnitude of Benefit

- This summarizes how strong a benefit is: small, medium, large, or none. If results are not statistically significant "NA" for "not applicable" is entered. In order to be consistent in defining small, medium, and large benefits across different studies and reviews, Natural Standard defines the magnitude of benefit in terms of the standard deviation (SD) of the outcome measure. Specifically, the benefit is considered:

- Large: if >1 SD
- Medium: if 0.5 to 0.9 SD
- Small: if 0.2 to 0.4 SD

- In many cases, studies do not report the standard deviation of change of the outcome measure. However, the change in the standard deviation of the outcome measure (also known as effect size) can be calculated, and is derived by subtracting the mean (or mean difference) in the placebo/control group from the mean (or mean difference) in the treatment group, and dividing that quantity by the pooled standard deviation (Effect size = [Mean Treatment – Mean Placebo]/SDp).

Absolute Risk Reduction

- This describes the difference between the percent of people in the control/placebo group experiencing a specific outcome (control event rate), and the percent of people in the experimental/therapy group experiencing that same outcome (experimental event rate). Mathematically, Absolute risk reduction (ARR) equals experimental event rate minus control event rate. ARR is better able to discriminate between large and small treatment effects than relative risk reduction (RRR), a calculation that is often cited in studies ([control event rate – experimental event rate]/control event rate). Many studies do not include adequate data to calculate the ARR, in which cases "NA" is entered into this column. *P* = pending verification.

Number Needed to Treat

- This is the number of patients who would need to use the therapy under investigation, for the period of time described in the study, in order for one person

to experience the specified benefit. It is calculated by dividing the ARR into 1 (1/ARR). P = pending verification.

Comments

- When appropriate, this brief section may comment on design flaws (inadequately described subjects, lack of blinding, brief follow-up, not intention-to treat, etc.), notable study design elements (crossover, etc.), dosing, and/or specifics of study group/subgroups (age, gender, etc.). More detailed description of studies is found in the "Evidence Discussion" section that follows the "Evidence Table" in Natural Standard reviews.

EVIDENCE DISCUSSION

- No available studies qualify for inclusion in the Evidence Discussion.

BRANDS USED IN CLINICAL TRIALS/THIRD-PARTY TESTING

- Not applicable.

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