Mahidol University
Wisdom of the Land

Kratom

Satariya Trakulsrichai
Department of Emergency Medicine
Ramathibodi Poison Center
Faculty of Medicine
Ramathibodi Hospital
Mahidol University

Mahidol University
Wisdom of the Land

Kratom

- *Mitragyna speciosa Korth*
- Rubiaceae (Coffee) family
- Indigenous to Southeast Asia e.g. Indonesia, Malaysia, Thailand
- Kratom, Ketum, Kakuam, Kraton, Biak, Biak – Biak, Maeng Da

- Normal height of 4-16 m, width 5 m
- Different colored veins

Hassan *et al.* Neurosci Biobehav Rev, 2013; Domingo *et al.* Forensic Sci Int, 2017; Corkery *et al*. J Psychopharmacol, 2019

Mahidol University
Wisdom of the Land

- Different colored veins of the leaves: greenish-white or red



Assoc.Prof.Dr.Juraithip Wungsintaweekul. Kratom. ccpe.pharmacycouncil.org › showfile

Flowers

Fruit

Purposes

Asian countries: Southeast Asia

In the past

- **Thailand & Malaysia:** a stimulant to increase work efficiency, endurance, tolerance for manual laborers, a medical remedy
- **Thailand:** In the south: a part of the way of life embedded in local custom and tradition for many years

Veltri C & Grundmann O. Subst Abuse Rehabil. 2019; Hassan *et al.* Neurosci Biobehav Rev, 2013; Singh et al. Hum Psychopharmacol, 2017

In the present

- **Malaysia:** Substitute for illicit opioids
- **Thailand:** One of the most popular illicit substances

: An emerging drug of abuse: **'4 x 100'**, '8 X 100' cocktail

(Kratom, Cola soft drink, cough syrup, tranquilizers or mosquito coils)

The basic 4x100 cocktail includes kratom tea, cough syrup, Coca-Cola, and ice cubes (Photo: Amaralak Khamhong)

Tanguay, 2011 https://www.tni.org/files/download/kratom-briefing-dlr13.pdf

Vicknasingam *et al.* J Drug Policy, 2010; Singh *et al.* J Psychoactive Drugs, 2015; Hassan *et al.* Neurosci Biobehav Rev, 2013; Tungtananuwat &Lawanprasert. Journal of Health Research, 2010

Mahidol University
Wisdom of the Land

Purposes

Western countries

- **“Legal highs”**, popularity in the last two decades
- **Alternative for opioids**
- **Self-treatment**: pain, opioid use disorder, depression, anxiety

- **EMCDDA** (European Monitoring Centre for Drugs and Drug Addiction): **Internet surveys**
  - 2008: one of the most widely offered “legal highs”; **44%** of 27 **online shops**
  - 2011: the most widely offered product; **20%** of **online retailers shipping to EU**
- The 2nd of ‘Top 5 products’ by frequency (marketed by UK-based Internet retailers)

Prozialeck *et al*. Int J Drug Policy, 2019; Grundmann. Drug Alcohol Depend, 2017; EMCDDA; Schmidt *et al.* Forensic Sci Int, 2010; Swogger & Walsh. Drug Alcohol Depend, 2018

Mahidol University
Wisdom of the Land

Consumptions/Availability

Asian countries

- Chewing fresh leaves, smoking dried leaves, brewing as a tea
- In Thailand: restricted area (South)

Hassan *et al.* Neurosci Biobehav Rev, 2013

Western countries

- Raw leaves, capsules, tablets, concentrated extracts, resin, tincture
- 'Head', 'smart', 'vaping', 'smoke', 'herbal' shops
- Internet - A view voiced by peers on psychoactive substance web-sites e.g. Erowid.org, speciosa.org, Reddit.com/r/kratom

Prozialeck *et al*. Int J Drug Policy, 2019; Veltri & Grundmann. Abuse Rehabil, 2019

Mahidol University
Wisdom of the Land

Legal status

Asian countries

- **Illegal** in some countries e.g. Malaysia, Singapore
- **Thailand:** illegal since 1943, Schedule 5 of Thai narcotic Act

Sattaburuth . https://www.bangkokpost.com/news/general/1600566/medical-cannabis-kratom-billpassed-by-nla; Narcotics Act No.7 B.E. The Government Gazette. 2019; Singh *et al*. Hum Psychopharmacol, 2017

- **Indonesia:** legally cultivated, exported on large scale to Asia, North America and Europe

Tanguay, 2011;

https://www.tni.org/files/download/kratom-briefing-dlr13.pdf;

Hassan *et al.* Neurosci Biobehav Rev, 2013;

Indonesia May Ban Kratom Exports

July 05, 2019

By Pat Anson, PNN Editor

A possible ban on the growth and export of kratom in Indonesia is raising alarm among kratom users in the U.S. and around the world. About 95% of the world's supply of kratom comes from Indonesia, where the herbal supplement has become a lucrative cash crop.

https://www.painnewsnetwork.org/stories/2019/7/5/is-indonesia-banning-kratom-exports

พระราชบัญญัติ
ยาเสพติดให้โทษ (ฉบับที่ ๘)
พ.ศ. ๒๕๖๔

พระบาทสมเด็จพระปรเมนทรรามาธิบดีศรีสินทรมหาวชิราลงกรณ
พระวชิรเกล้าเจ้าอยู่หัว

ให้ไว้ ณ วันที่ ๒๕ พฤษภาคม พ.ศ. ๒๕๖๔
เป็นปีที่ ๖ ในรัชกาลปัจจุบัน

พระบาทสมเด็จพระปรเมนทรรามาธิบดีศรีสินทรมหาวชิราลงกรณ พระวชิรเกล้าเจ้าอยู่หัว มีพระบรมราชโองการโปรดเกล้าฯ ให้ประกาศว่า

โดยที่เป็นการสมควรแก้ไขเพิ่มเติมกฎหมายว่าด้วยยาเสพติดให้โทษ

จึงทรงพระกรุณาโปรดเกล้าฯ ให้ตราพระราชบัญญัติขึ้นไว้โดยคำแนะนำและยินยอมของ

หมายเหตุ :- เหตุผลในการประกาศใช้พระราชบัญญัติฉบับนี้ คือ โดยที่ปัจจุบันพืชกระท่อมเป็นยาเสพติดให้โทษในประเภท ๕ ตามพระราชบัญญัติยาเสพติดให้โทษ พ.ศ. ๒๕๒๒ แต่ในหลายประเทศมิได้กำหนดให้พืชกระท่อมเป็นยาเสพติดให้โทษประกอบกับอนุสัญญาเดี่ยวว่าด้วยยาเสพติดให้โทษ ค.ศ. ๑๙๖๑ และพิธีสารแก้ไขอนุสัญญาเดี่ยวว่าด้วยยาเสพติดให้โทษ ค.ศ. ๑๙๗๒ มิได้กำหนดให้พืชกระท่อมเป็นยาเสพติดให้โทษ ดังนั้น เพื่อให้สอดคล้องกับหลักสากลและบริบทของสังคมไทยในบางพื้นที่ที่มีการบริโภคพืชกระท่อมตามวิถีชาวบ้าน สมควรยกเลิกพืชกระท่อมจากการเป็นยาเสพติดให้โทษในประเภท ๕ จึงจำเป็นต้องตราพระราชบัญญัตินี้

https://www.google.com/search?q=%E0%B8%9B%E0%B8%A5%E0%B8%94%E0%B8%A5%E0%B9%87%E0%B8%AD%E0%B8%84+%E0%B8%81%E0%B8%A3%E0%B8%B0%E0%B8%97%E0%B9%88%E0%B8%AD%E0%B8%A1&sxsrf=APq-WBsVoOvV922yYofAyyrwAkuXvzC98g:1650362955908&source=lnms&tbm=isch&sa=X&ved=2ahUKEwiSzvKN8Z_3AhUqR2wGHQnqB3IQ_AUoAXoECAEQAw&biw=1280&bih=601&dpr=1.5#imgrc=0ZB6N4pfJqEGWM

Mahidol University
Wisdom of the Land

ปลดล็อกกระท่อม
ทำความเข้าใจกฎหมายยาเสพติดฉบับล่าสุด
หลังกระท่อมพ้นยาเสพติดประเภท 5

- กฎหมายฉบับนี้มีผลบังคับใช้ 90 วัน นับจากวันประกาศในราชกิจานุเบกษา (26 พ.ค. 64)
- โปรดติดตามข้อกำหนดในกฎหมายต่อไป อาจมีการเปลี่ยนแปลงหลังเข้าสภาฯ

	พ.ร.บ.ยาเสพติดให้โทษ (ฉบับที่ 8) พ.ศ. 2564 **ถูกกฎหมาย**	พ.ร.บ.ยาเสพติดให้โทษ (ฉบับที่ 8) พ.ศ. 2564 **ไม่ถูกกฎหมาย**	มติคณะรัฐมนตรี วันที่ 1 มิ.ย. 64
ปลดล็อกกระท่อมจากยาเสพติดประเภท 5	✓		
เคี้ยวใบกระท่อม	✓		
ต้มน้ำกระท่อม	✓		
ขายใบ/น้ำกระท่อม	—	—	ห้ามขายแก่ผู้มีอายุต่ำกว่า 18 ปี สตรีมีครรภ์และให้นมบุตร ฝ่าฝืนมีโทษปรับไม่เกิน 30,000 บาท
ปลูก/ขาย/นำเข้า/ส่งออกกระท่อมเพื่ออุตสาหกรรม	—	—	ต้องมีใบอนุญาต โดยใบอนุญาตขายมีอายุ 5 ปี นำเข้า/ส่งออก มีอายุ 1 ปี
นำน้ำกระท่อมผสมยาแก้ไอ		✗	ฝ่าฝืนมีโทษปรับไม่เกิน 50,000 บาท
นำน้ำกระท่อมผสมทำสี่คูณร้อย		✗	ฝ่าฝืนมีโทษปรับไม่เกิน 50,000 บาท
นำน้ำกระท่อมผสมน้ำอัดลม/น้ำหวานอื่นๆ	✓		

https://thematter.co/social/politics/quickbite-kratom-law-2-june/144869

Mahidol University
Wisdom of the Land

Legal status

Western countries

- **United Nations Office on Drugs and Crime** (UNODC):
  Kratom-based drugs: currently classified as New Psychoactive Substances (NPS), not appear on the list of emerging drug threats (2019)

Prozialeck *et al*. Int J Drug Policy, 2019; https://wdr.unodc.org/wdr2019/prelaunch/WDR19_Booklet_2_DRUG_DEMAND.pdf

- **Australia, New Zealand:** illegal

- **Europe**: some countries in Europe e.g. Denmark, Finland, Ireland, Lithuania
- **USA**: Legal in **most** states excepts some states e.g. Alabama, Indiana

Veltri & Grundmann. Abuse Rehabil, 2019 ; Prozialeck *et al*. Int J Drug Policy, 2019

Mahidol University
Wisdom of the Land

uspharmacist.com/article/the-dea-changes-its-mind-on-kratom

U.S. Pharmacist
A Jobson Publication

Pharmacy Practice · Diseases · CE · Publications

POWER-PAK C.E.: In Medication Therapy Management

Advertisement

Published March 17, 2017

The DEA Changes Its Mind on Kratom

Gerald Gianutsos, PhD, JD
Associate Professor of Pharmacology
University of Connecticut School of Pharmacy
Storrs, Connecticut

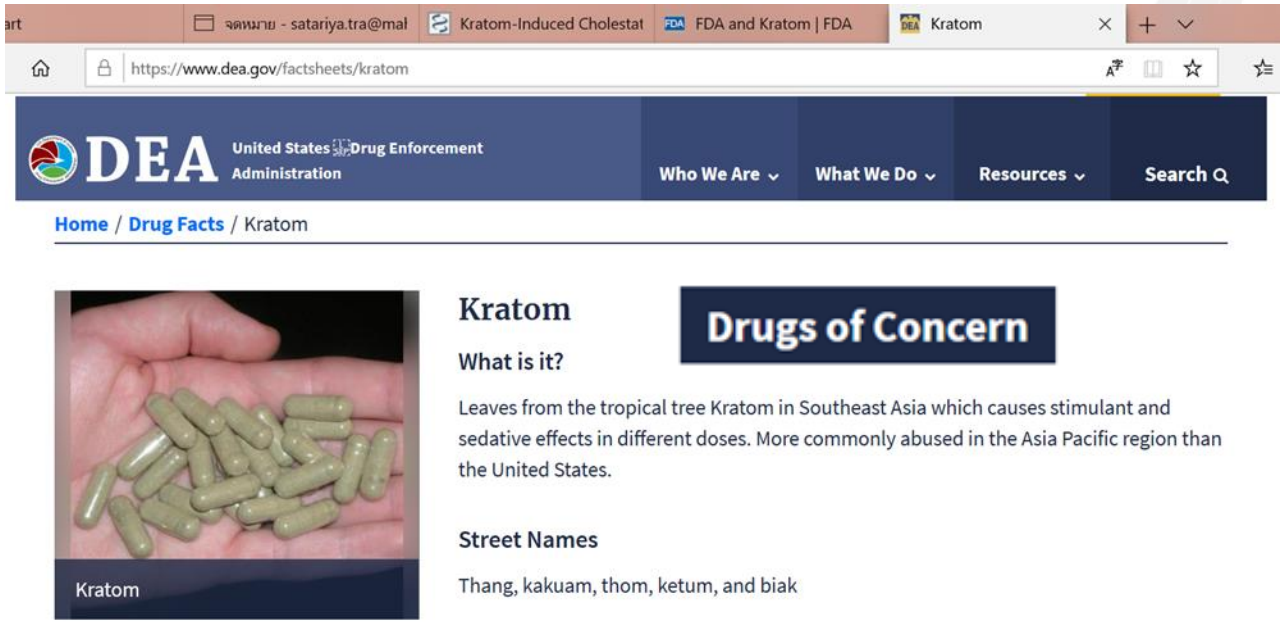
US Pharm. 2017;41(3):7-9.

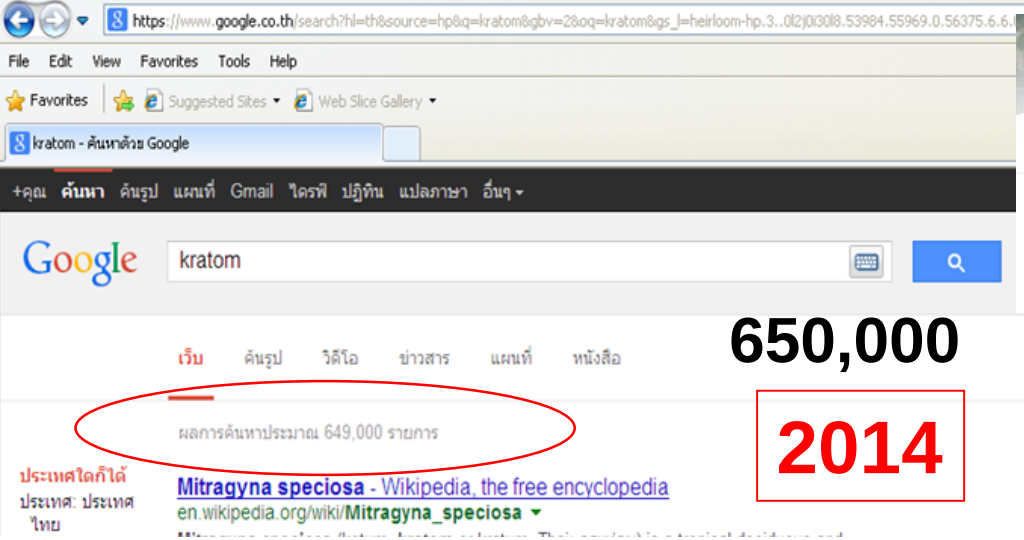
When the Drug Enforcement Administration (DEA) proposes to use its emergency scheduling authority to place a temporary ban on a "legal" drug due to concerns about abuse and safety, it is usually a fairly routine event. However, one recent decision by the DEA to ban a substance was anything but routine, resulting in a widespread public backlash that was sufficient to convince the DEA to reconsider its action.

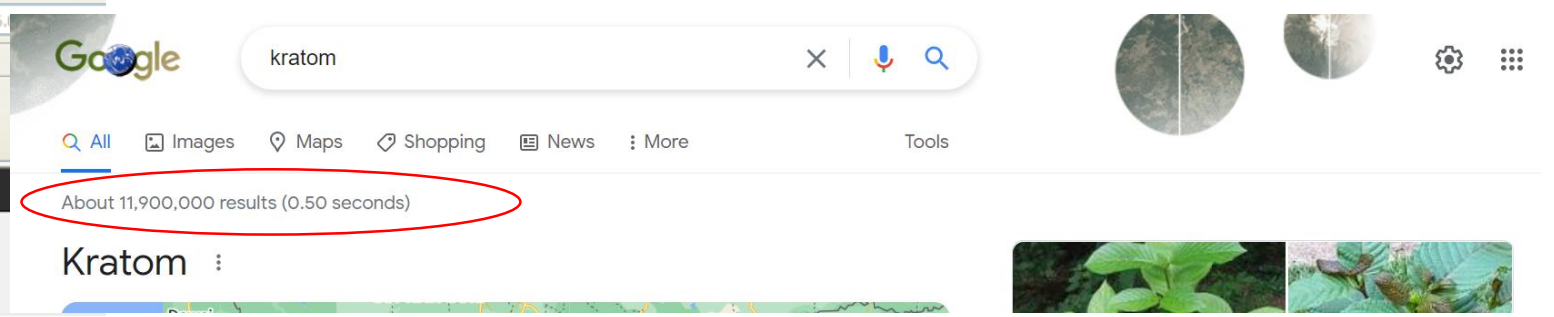
The substance causing the controversy is the herbal opioid-like drug

- The DEA announced its intent to temporarily place mitragynine and 7-HMG into **Schedule I on August 31, 2016**

- The reversal by the DEA



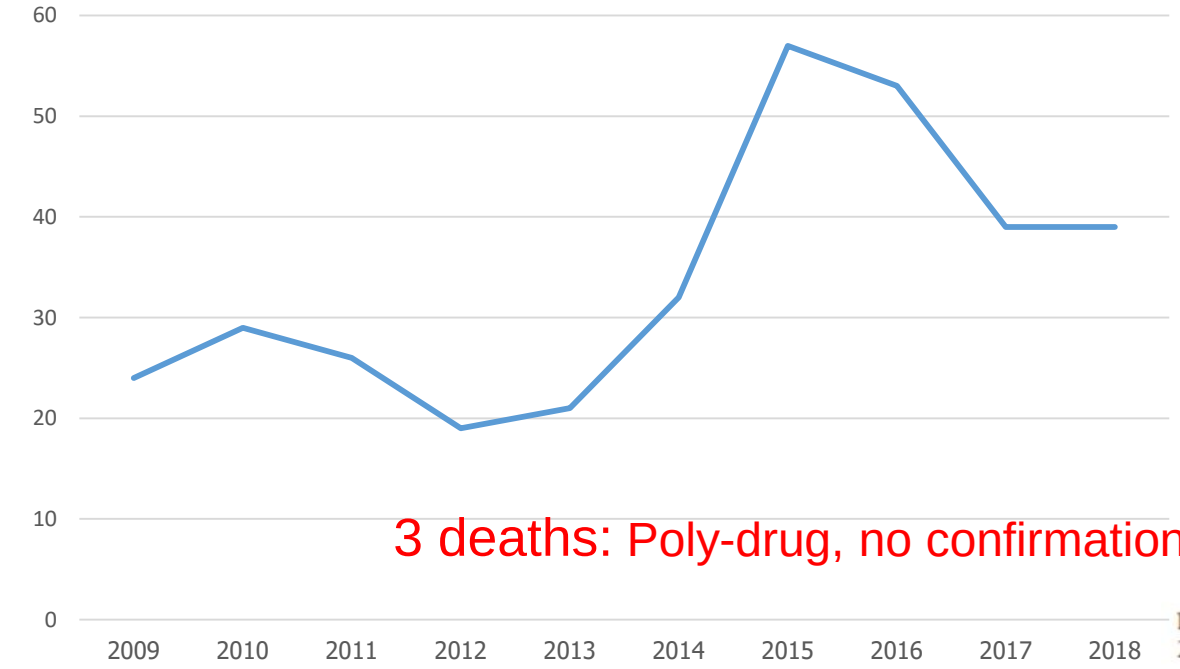




2022 12,000,000

Ramathibodi Poison Center

Number of kratom poisoning cases in 2009-2018



3 deaths: Poly-drug, no confirmation

US National Poison Data System

Eggleston *et al.* Pharmacotherapy., 2019

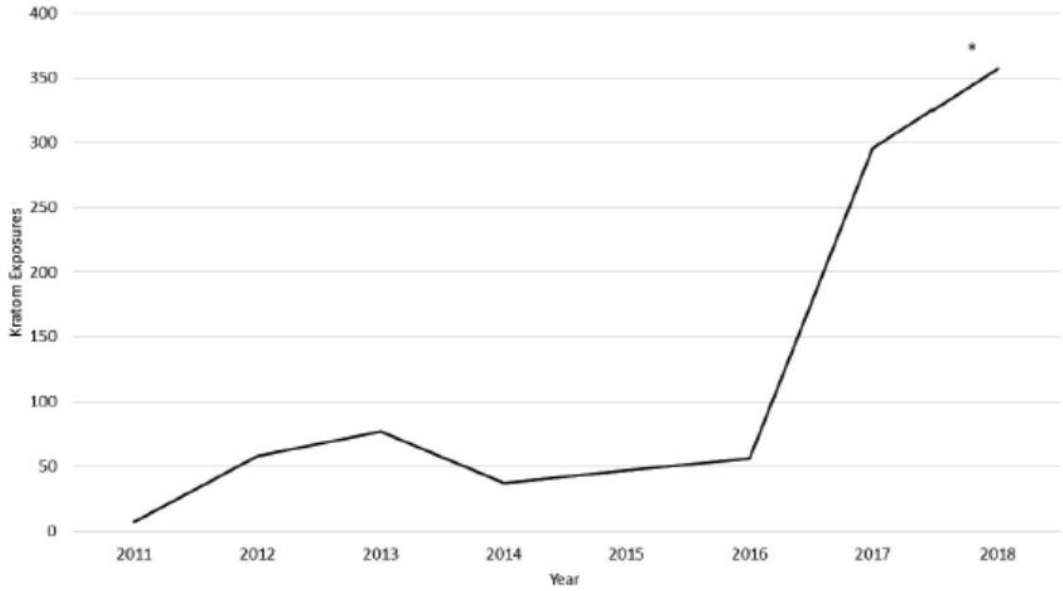
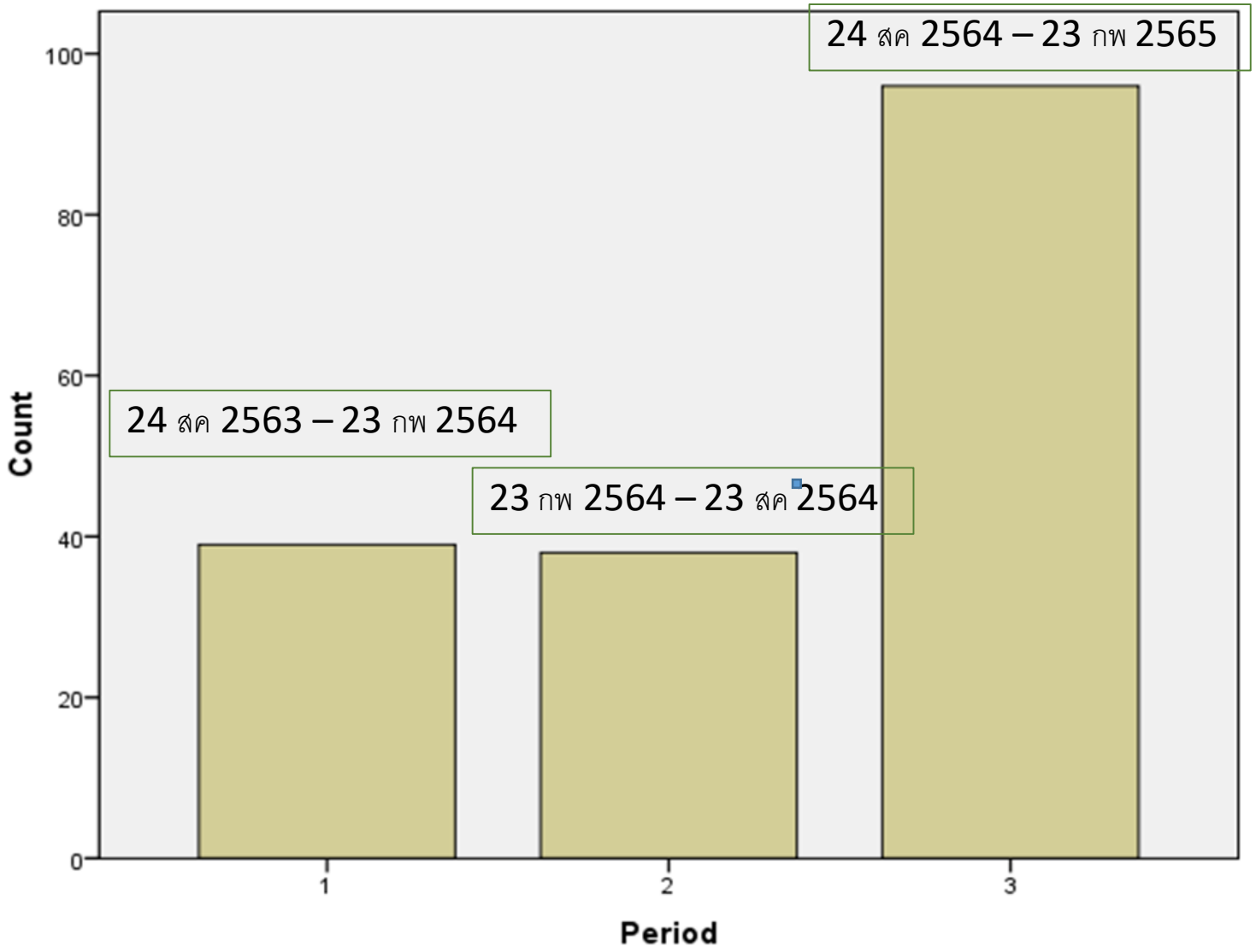


Figure 1. Kratom exposures reported to the National Poison Data System from January 1, 2011, to July 31, 2018. *Data for 2018 is partial and includes exposures from January 1, 2018, to July 31, 2018.

Mahidol University
Wisdom of the Land

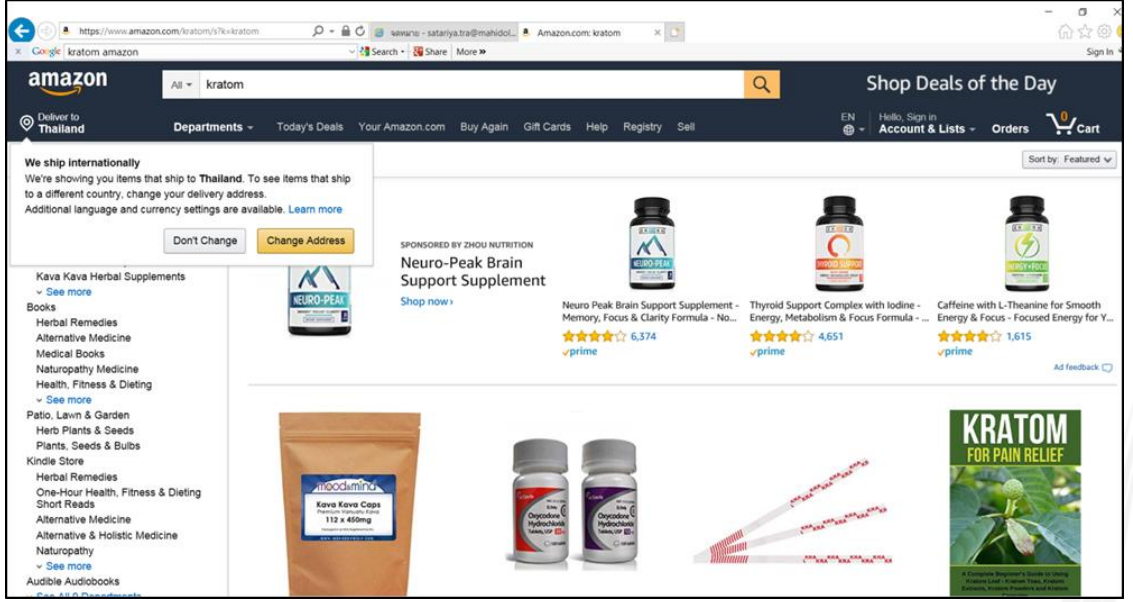
Calls to RPC

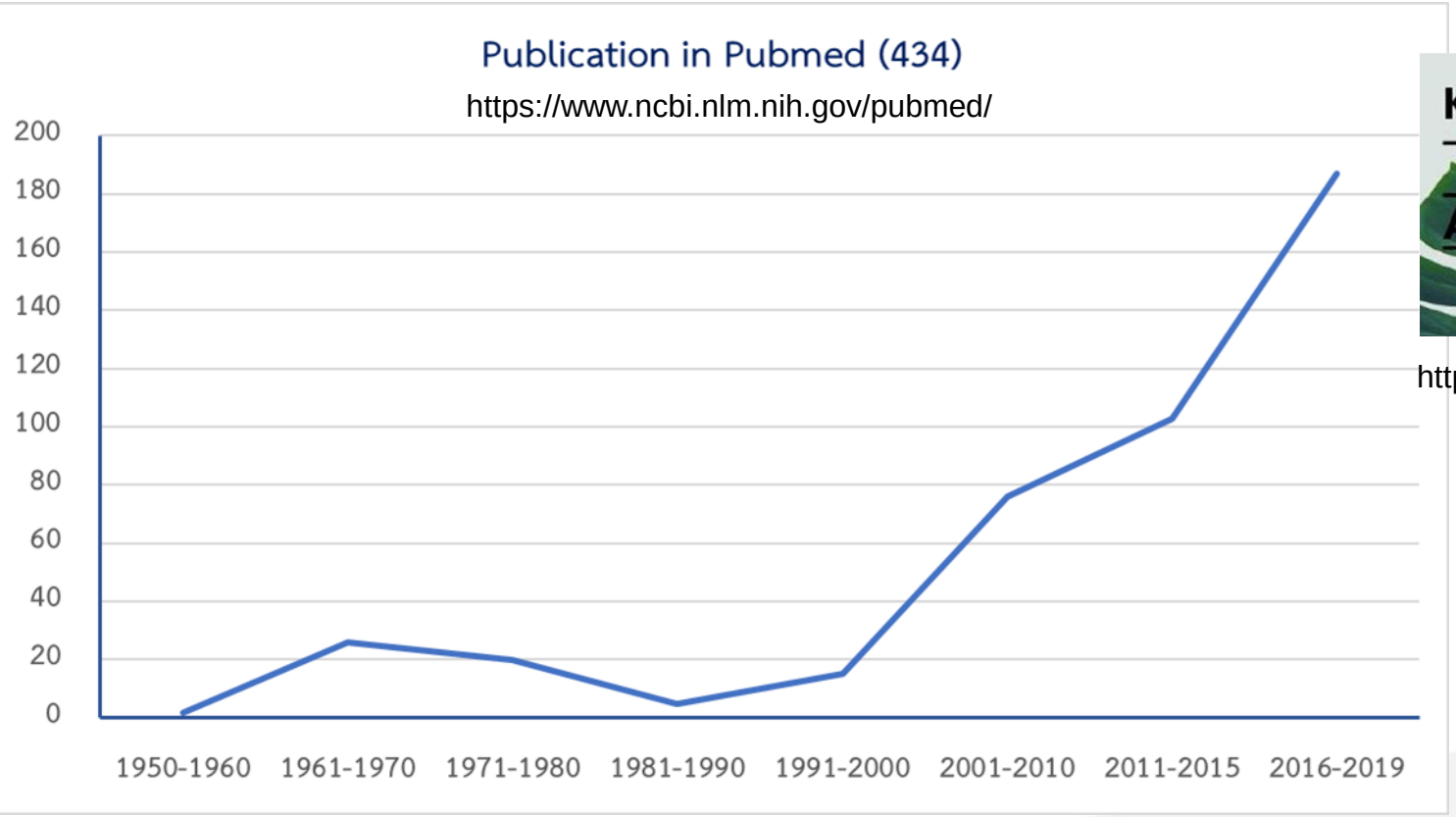


Mahidol University
Wisdom of the Land

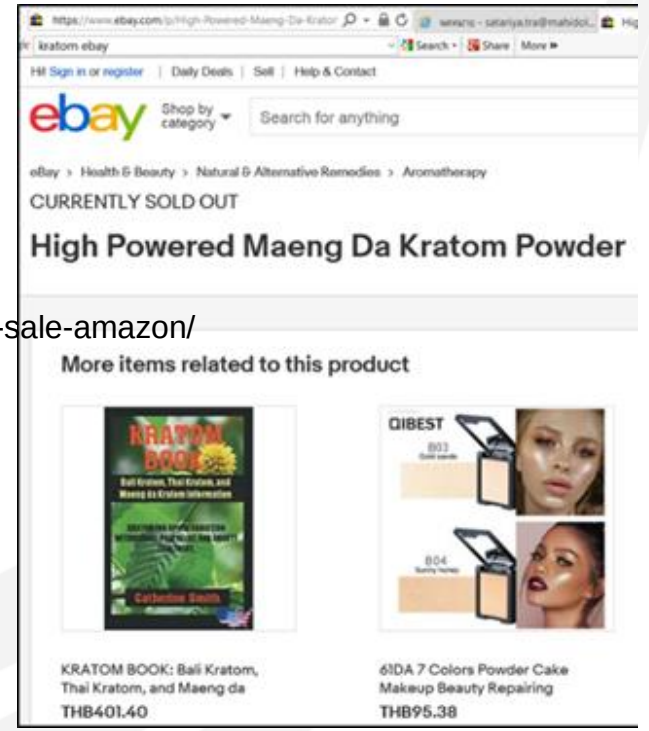
- American Kratom Association: ~ **10–16 million** or more current, regular kratom users in the US

https:// www.americankratom.org/update.html





https://linacre.org/kratom-for-sale-amazon/



Mahidol University
Wisdom of the Land

- 2019 National Survey on Drug Use and Health
- An estimated 0.7% of individuals in the U.S. have used kratom in the past year

Palamar. Am J Prev Med. 2021

- Prevalence and characteristics of self-reported kratom use in a representative US general population sample
- 1,842 respondents, 112 (6.1%): reported use within lifetime

Covvey et al. J Addict Dis. 2020

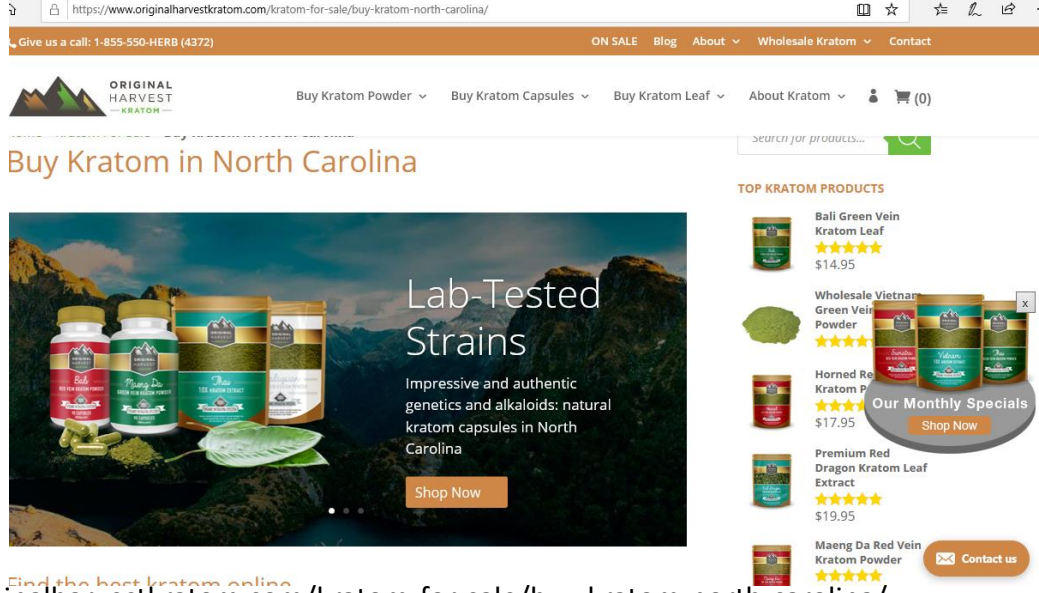
Prevalence and description of kratom (Mitragyna speciosa) use in the United States: a cross-sectional study

- The estimated prevalence of past-year kratom use in the adult US population: 0.8% = 2,031,803 adults

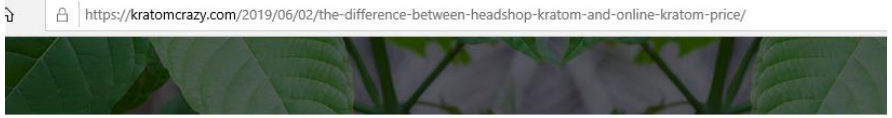
Schimmel *et al*. Addiction. 2020

https://leafoflifekratom.com/shop/kratom/splits-and-samplers/full-kilo-kratom-4-ways/

https://www.wsmv.com/news/confusion-persists-over-kratom-law-in-tennessee/article_5533da4f-2c4a-5c3f-98df-0c498f853eaa.html



https://www.originalharvestkratom.com/kratom-for-sale/buy-kratom-north-carolina/



June 02, 2019 Articles, Kratom Capsules, Kratom Products, Kratom Res

The result can be seen far and wide—price gouging is rampant, both online and in smoke shops and paraphernalia shops across America. Some vendors charge an arm and a leg for bunk while others offer quality kratom at the market price or lower.

too often we come across kratom vendors who mix low-end kratom strains with quality kratom powder in order to

https://kratomcrazy.com/2019/06/02/the-difference-between-headshop-kratom-and-online-kratom-price/

KRATOMCrazy

https://kratomcrazy.com/2015/07/15/buying-kratom-online-choosing-a-supplier-to-order-the-herb-from/

Mahidol University
Wisdom of the Land

Pharmacology

- > 40 indoles alkaloids
- **Mitragynine** (MG): the most prevalence in the extract of leaves
  - 66% from Thailand
  - 12% from Malaysia
- **7-hydroxymitragynine** (7-OH-MG): 2%

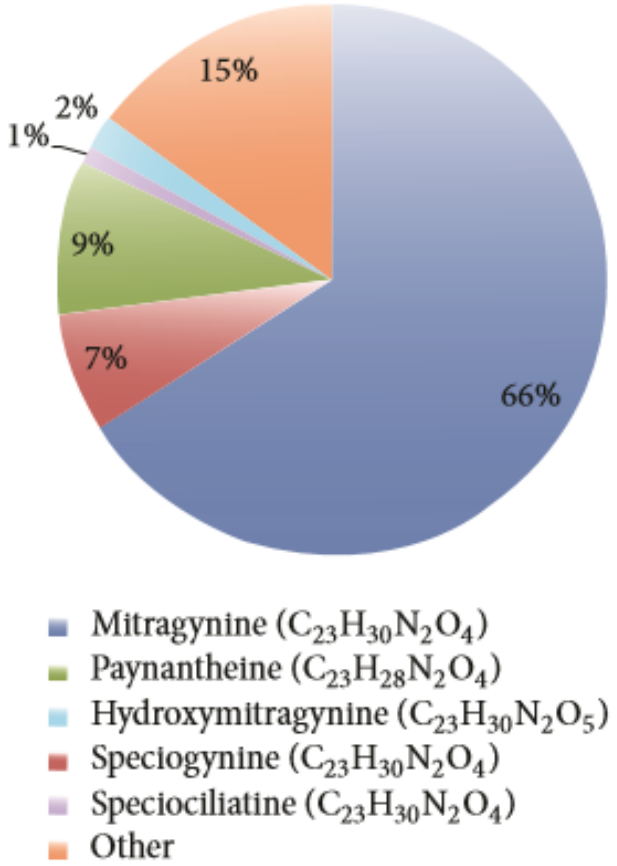


FIGURE 1: An estimate of Thai kratom extract composition. The phytochemicals isolated from various parts of the tree include overall 40 structurally related alkaloids as well as several flavonoids, terpenoid saponins, polyphenols, and various glycosides.

Kruegel & Grundmann. Neuropharmacology., 2018; Cinosi *et al.* Biomed Res Int, 2015

Cinosi *et al.* Biomed Res Int., 2015

Ultrasonics Sonochemistry 19 (2012) 591–595

Contents lists available at SciVerse ScienceDirect

Ultrasonics Sonochemistry

journal homepage: www.elsevier.com/locate/ultsonch

UAE, MAE, SFE-CO_2 and classical methods for the extraction of *Mitragyna speciosa* leaves

Laura Orio [a], Lavinia Alexandru [a,b], Giancarlo Cravotto [a,*], Stefano Mantegna [a], Alessandro Barge [a]

[a] Dipartimento di Scienza e Tecnologia del Farmaco, Università di Torino, Via P. Giuria 9, 10235 Torino, Italy
[b] Dipartimento di Scienze degli Alimenti, Università di Udine, Via Sondrio 2, 33100 Udine, Italy

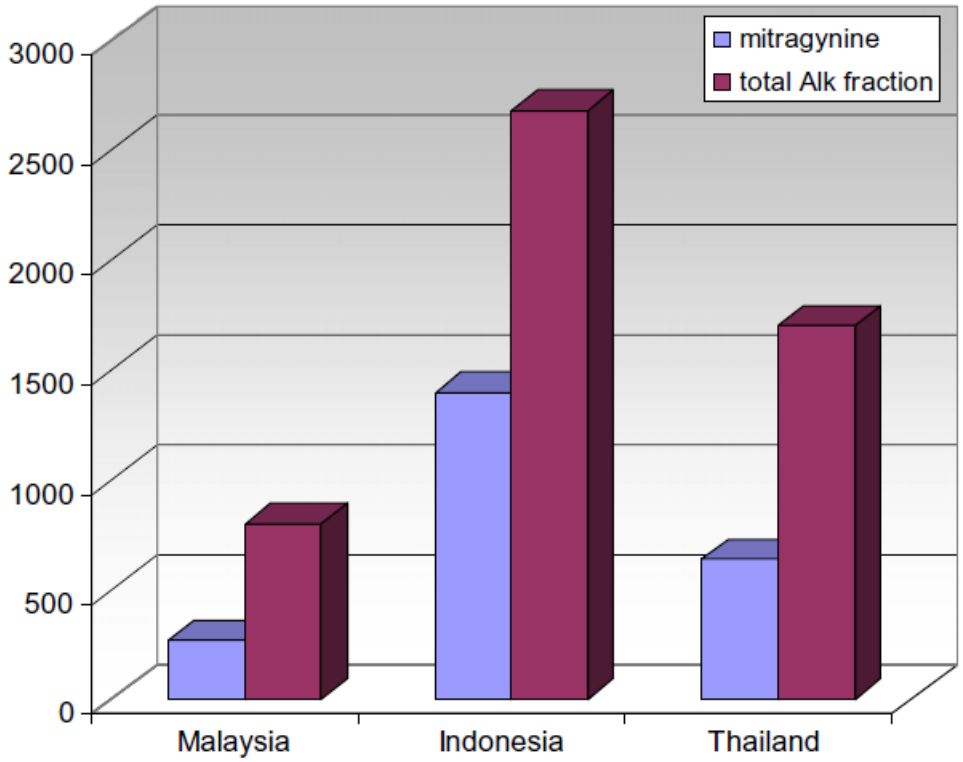


Fig. 7. Total amount of alkaloid fraction related to mitragynine for *M. speciosa* originating in Malaysia, Indonesia and Thailand (USH, met/w 1:1).

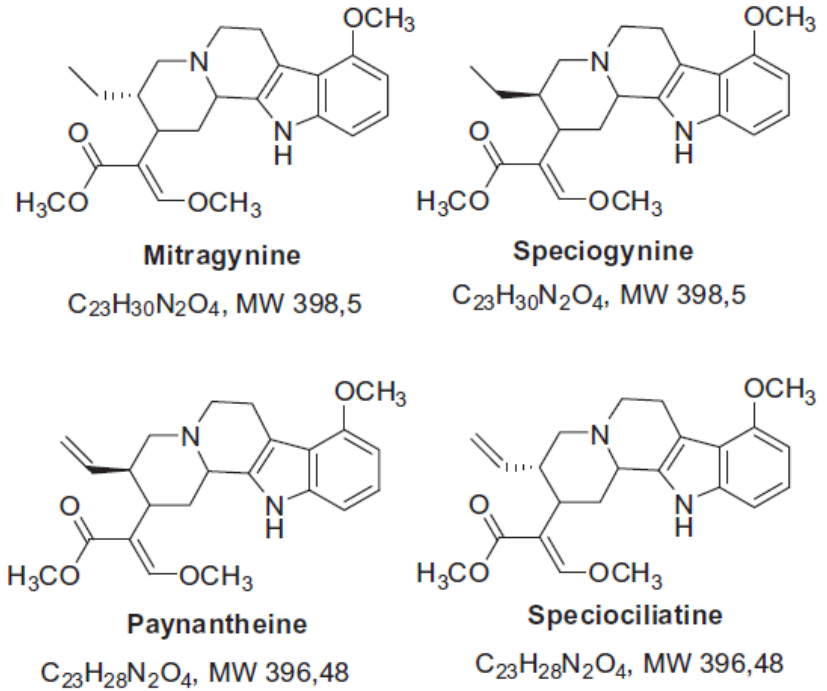


Fig. 1. Chemical structures of most common alkaloids in *M. speciosa*.

Kratom grown in USA

- The predominant alkaloid: “**mitraphylline**”
- **A significant decrease** in the **total amount** of alkaloids
- **MG and 7-OH-MG: lower** than commercial Thai sample

León *et al*. Nat Prod Commun, 2009

Synergistic effects?

Table 1
Alkaloid profile of *Mitragyna speciosa* Korth. The percentage is the estimated content in the alkaloid extracts.

Alkaloid	Percentage	Effect	Reference
Mitragynine	66%	Analgesic, antitussive, antidiarrheal, adrenergic, antimalarial	Hooper (1907); Field (1921); Lee et al. (1967); Ponglux et al. (1994)
Paynantheine	9%	Smooth muscle relaxer	Ponglux et al. (1994)
Speciogynine	7%	Smooth muscle relaxer	Lee et al. (1967); Shellard, 1974; Shellard et al. (1978b); Ponglux et al. (1994)
7-Hydroxymitragynine	2%	Analgesic, antitussive, antidiarrheal	Ponglux et al. (1994)
Speciociliatine	1%	Weak opioid agonist	Lee et al. (1967); Ponglux et al. (1994)
Mitraphylline	<1%	Vasodilator, antihypertensive, muscle relaxer, diuretic, antiamnesic, immunostimulant, anti-leukemic	Seaton et al. (1958); Shellard, 1974; Shellard et al. (1978b); Ponglux et al. (1994)
Isomitraphylline	<1%	Immunostimulant, anti-leukemic	Seaton et al. (1960); Shellard and Philipson (1966); Ponglux et al. (1994)
Speciophylline	<1%	Anti-leukemic	Shellard and Philipson (1966); Beckett et al. (1966)
Rhynchophylline	<1%	Vasodilator, antihypertensive, calcium channel blocker, antiaggregant, anti-inflammatory, antipyretic, anti-arrhythmic, antithelmintic	Seaton et al. (1960); Shellard, 1974; Shellard et al. (1978b)
Isorhynchophylline	<1%	Immunostimulant	Seaton et al. (1958); Seaton et al. (1960); Shellard, 1974; Shellard et al. (1978b)
Ajmalicine	<1%	Cerebrocirculant, antiaggregant, anti-adrenergic, sedative, anticonvulsant, smooth muscle relaxer	Beckett et al. (1966)
Corynantheidine	<1%	Opioid agonist	Takayama et al. (2002)
Corynoxine A	<1%	Calcium channel blocker, anti-locomotive	Shellard et al. (1978a)
Corynoxine B	<1%	Anti-locomotive	Shellard et al. (1978a)
Mitrafoline	<1%		Hemmingway et al. (1975); Shellard et al. (1978a)
Isomitrafoline	<1%		Hemmingway et al. (1975); Shellard et al. (1978a)
Oxindale A	<1%		Shellard et al. (1978a)
Oxindole B	<1%		Shellard et al. (1978a)
Speciofoline	<1%	Analgesic, antitussive	Hemmingway et al. (1975)
Isospeciofoline	<1%		Hemmingway et al. (1975); Shellard et al. (1978a)
Ciliaphylline	<1%	Analgesic, antitussive	Trager et al. (1968)
Mitraciliatine	<1%		Lee et al. (1967)
Mitragynaline	<1%		Houghton et al. (1991)
Mitragynalinic acid	<1%		Houghton et al. (1991)
Corynantheidalinic acid	<1%		Houghton et al. (1991)

Mahidol University
Wisdom of the Land

Pharmacodynamics

- **Complex, Interesting**

Opioid receptors

- Main activity: **mu (μ), kappa (κ), delta (δ)**
- Structurally different from opioids

Non-opioid pathways: receptors

- Alpha-2 adrenergic
- Adenosine A2a
- Dopamine D2
- Serotonin

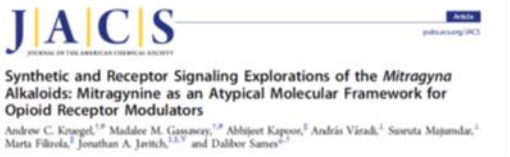
Cinosi *et al.* Biomed Res Int, 2015; Raffa *et al*. J Clin Pharm Ther.,2018

CNS receptor binding for MG

- Adenosine A2A
- Adrenergic (Alpha 2)
- Dopamine D2s
- Opioid, mu
- Opioid, kappa
- Opioid, delta
- Serotonin, 5HT2C
- Serotonin, 5HT7

Boyer *et al*. Addiction, 2008

Multi-Target



In bioluminescence resonance energy transfer (BRE
functional assays at hMOR

Opioid receptors	mu (μ)	kappa (κ)	delt
Mitragynine (66%)	**Agonists (partial)**	**Antagonists** (competitive)	Antagonists (weak competitive)
7-hydroxymitragynine (2%)	**Agonists (partial)**	**Antagonists (competitive)**	Antagonists (weak competitive)
Paynantheine (9%)	Antagonist (competitive)		
Speciogynine (7%)			
Speciociliantine (1%)			

$\mu > \kappa, \delta$

Buprenorphine

Complex interplay of competing “agonist and antagonist” effects at opioid receptors

Mahidol University
Wisdom of the Land

Pharmacodynamics

Opioid pharmacology → Analgesia, euphoria, dependence

- **MG / 7-OH-MG**

  - Partial agonists of μ: expected to attenuate severity of side effects

    "Ceiling effect" on respiratory depression, a similar plateau in analgesic effect

  - 7-OH-MG: hydroxyl group at C-7 increases potency,

    "more potent analgesic than **MG (46-fold), morphine (13-fold)**"

  - **κ-opioid receptor antagonist**: shown antidepressant effects in animals

Kruegel *et al.* J Am Chem Soc, 2016; Bruijnzeel.Brain Res Rev, 2009

- Functional activity vary from agonist to antagonist: to be determined

Horie *et al*. Planta Med, 2005; Prozialeck et al. Int J Drug Policy, 2019; Cinosi *et al.* Biomed Res Int., 2015; Kruegel & Grundmann. Neuropharmacology., 2018; Halpenny. ACS Med Chem Lett. 2017; Prozialeck *et al*. J Am Osteopath Assoc. 2012

Mahidol University
Wisdom of the Land

Pharmacodynamics

Non-opioid pharmacology

- Activation of **descending noradrenergic and serotonergic** pathways in spinal cord /inhibitory systems: antinociceptive activity

  "descending" pain-sensation modulating pathways in brain and spinal cord:

  modify incoming pain signals"

- Stimulate post-synaptic **alpha-2 adrenergic receptors:**

  opioid withdrawal symptoms **"clonidine"**

- Block stimulation of 5-HT2A receptors

Cinosi *et al.* Biomed Res Int, 2015; Pizarro-Osilla. J Emerg Nurs. 2017; Yusoff *et a*l. Behav Brain Res, 2018; Raffa et al. J Clin Pharm Ther.,2018; Meireles *et a*l. Medicines (Basel). 2019; Prozialeck *et al*. J Am Osteopath Assoc. 2012

Mahidol University
Wisdom of the Land

Pharmacodynamics

- Inhibit neurotransmitter release by reversibly blocking neuronal Ca2+ channels: inhibition of pain transduction
- Interacting with neuroendocrine HPA (hypothalamic-pituitary-adrenal) axis systems: antidepressant effect
- Suppressing prostaglandin E2 production in COX-2 pathway:

  anti-inflammatory properties
- $GABA_B$ receptor

Cinosi *et al.* Biomed Res Int, 2015; Pizarro-Osilla. J Emerg Nurs. 2017; Yusoff *et a*l. Behav Brain Res, 2018; Raffa et al. J Clin Pharm Ther.,2018; Meireles *et a*l. Medicines (Basel). 2019; Idayu *et al.* Phytomedicine. 2011

- Use of cells/animal models “might not be easily translatable to humans”

Halpenny. ACS Med Chem Lett. 2017

Mahidol University
Wisdom of the Land

Mitragynine

- Physiological, biochemical, behavioral effects: differ from classical opioids
- Interact with many receptors that classical opioids do not bind
- Described as **"atypical opioids"**, a unique class of drugs

Boyer *et al*. Addiction, 2008; Raffa et al. J Clin Pharm Ther. , 2018; Prozialeck *et al*. Int J Drug Policy, 2019

- Rats: orally single dose 1000 mg/kg (methanol extract) - No death
- Dogs: 920 mg/kg MG - No toxicity

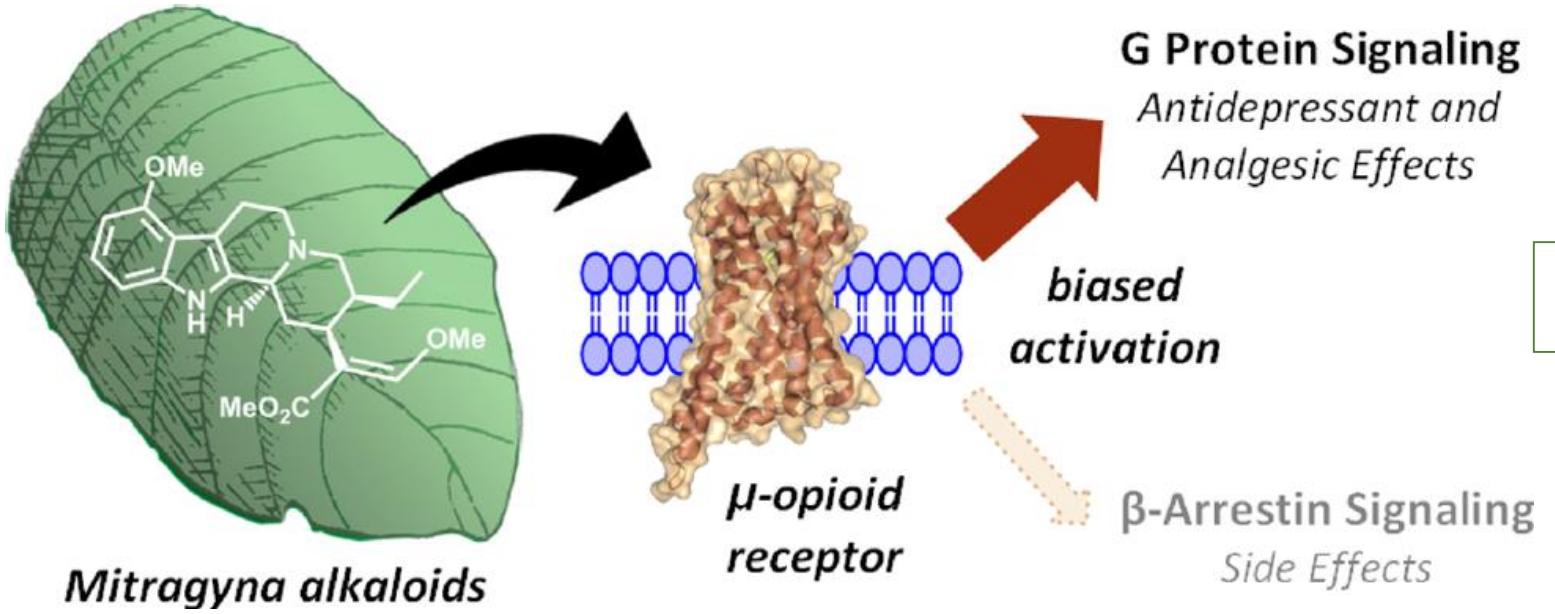
Harizal *et al*. J Ethnopharmacol. 2010; Macko *et al*. Arch. Int. Pharmacodyn. Ther, 1972

Mahidol University
Wisdom of the Land

JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

Synthetic and Receptor Signaling Explorations of the *Mitragyna* Alkaloids: Mitragynine as an Atypical Molecular Framework for Opioid Receptor Modulators

Andrew C. Kruegel,[†,#] Madalee M. Gassaway,[†,#] Abhijeet Kapoor,[∥] András Váradi,[⊥] Susruta Majumdar,[⊥] Marta Filizola,[∥] Jonathan A. Javitch,[‡,§,V] and Dalibor Sames[*,†]



Biased signaling

- MG / **7-OH-MG**: G-protein-biased agonists, not recruit β-arrestin following receptor activation
- Mitragyna alkaloid scaffold: represents a novel framework for development of functionally biased opioid modulators, may exhibit **improved therapeutic profiles**

Kruegel *et al.* J Am Chem Soc, 2016

- Opioids act through opioid receptors: family of G-protein coupled receptors (GPCRs), mediate pain relief through CNS + PNS

Four types of opioid receptors:

- μ-opioid receptor (MOR): tolerance, dependence, addiction, constipation, and respiratory depression
- κ-opioid receptor (KOR): sedation, anxiety, dysphoria, hallucinations
- δ-opioid receptor (DOR): tendency to cause convulsions
- Nociceptin opioid peptide receptor (NOP receptor): useful as spinal analgesics and as entities against substance abuse disorders

- Mixed MOR/NOP receptor agonists: useful as analgesics

Faouzi *et al.* Molecules. *2020*

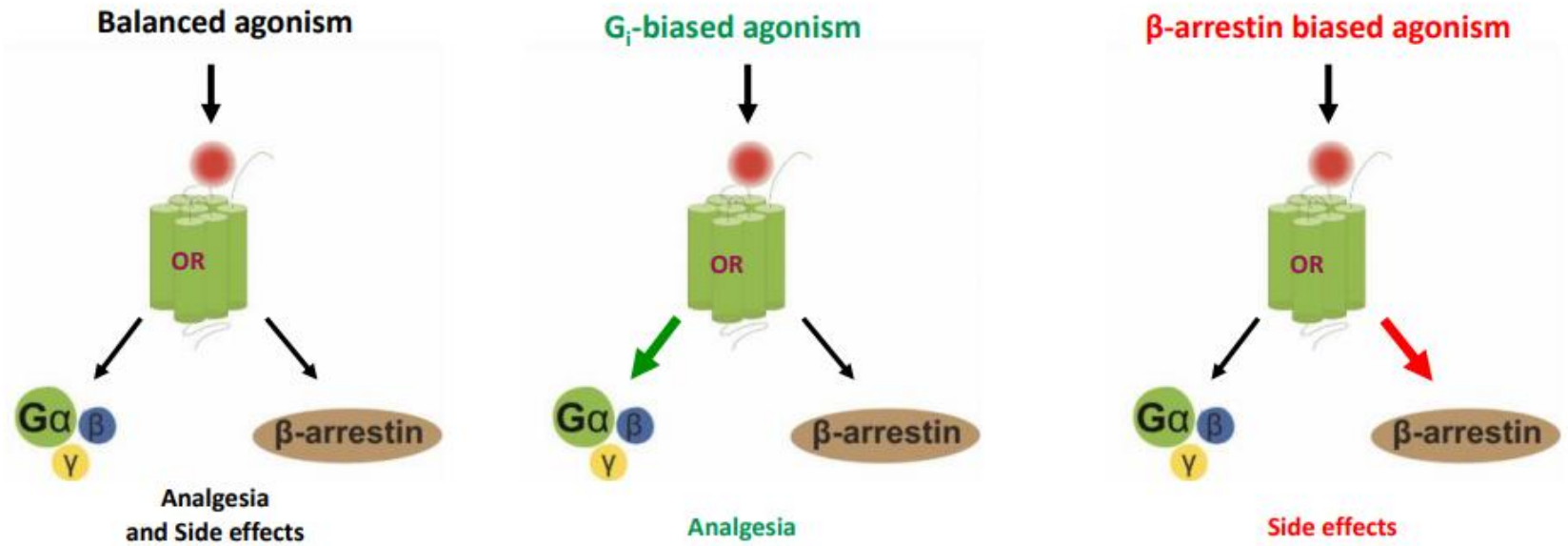


Figure 1. Functional selectivity correlation of opioid agonists. Ligands not recruiting β-arrestin 2 at all opioid subtypes are proposed to dissociate subtype selective adverse effects from its pain-relieving properties. In the case of the μ-opioid receptor (MOR), biased ligands will have less tolerance. For KOR, ligands should have less sedation and anhedonia. Biased DOR agonists should separate convulsions from analgesia while role of biased NOP receptor ligands is less well characterized, although it is possible that memory impairment, sedation, and hypothermia may be dissociated.

Faouzi *et al.* Molecules. *2020*

Mahidol University
Wisdom of the Land

Pharmacokinetics

Mitragynine

- Low Bioavailability (animal: 3%, 21%))
- 85-95% bound to plasma protein
- Passively transported across intestinal wall, blood brain barrier
- Metabolized mainly by liver, predominant through CYP3A4, minor by CYP2D6, CYP2C9, by phase I and II enzymes
- Mostly excreted as metabolites in urine

- Linear, 2-compartment model (human)

Trakulsrichai *et al.* Drug Des Devel Ther, 2015; Cinosi *et al*. Biomed Res Int., 2015; Ya *et al* . Asian J Psychiatr, 2019

Mahidol University
Wisdom of the Land

Neuropharmacology 134 (2018) 108–120

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

The medicinal chemistry and neuropharmacology of kratom: A preliminary discussion of a promising medicinal plant and analysis of its potential for abuse

Andrew C. Kruegel [a], Oliver Grundmann [b, *]

[a] Department of Chemistry, Columbia University, 3000 Broadway, New York, NY 10027, United States
[b] Department of Medicinal Chemistry, University of Florida, 1345 Center Drive, Gainesville, FL 32611, United States

Human: Tmax~1 h, high Vd, T1/2: 23 h

Table 4
Pharmacokinetic parameters of mitragynine and 7-OH.

Compound	Reference	Species/Strain	Dose/Route	Analytical Method	PK parameters in plasma[a]						
					c_{max} (μg/mL)	t_{max} (h)	$t_{1/2}$ (h)	V_d [b] (L/kg)	CL[b] (L/(h*kg))	AUC ((μg*h)/mL)	F
Mitragynine	Janchawee et al., 2007	Wistar Rats	40 mg/kg, p.o.	LC-UV	0.63	1.83	9.43	89.5	~6.3[c]	6.99	~26%[d]
	Valaderes de Moraes et al., 2009	Wistar Rats	20 mg/kg, p.o.	LC-MS/MS	0.424	1.26	3.85	37.9	6.35	3.15	~23%[d]
	Parthasarathy et al., 2010	Sprague-Dawley Rats	50 mg/kg, p.o.	LC-UV	0.70	4.5	6.6	64	7.0	8.2	3.0%
		Sprague-Dawley Rats	1.5 mg/kg, i.v.	LC-UV	2.3	1.2	2.9	0.79	0.29	9.2	
	Vuppala et al., 2011	Sprague-Dawley Rats	5.0 mg/kg, i.v.	LC-MS/MS	3.9	0.017	2.6	8.2	1.2	3.4	–
	Trakulsrichai et al., 2015	Humans	various, oral tea (~0.3 mg/kg[e])	LC-MS	various (~0.105[e])	0.83	23.2	38.0	98.1[f]	various (~0.67[e])	–
7-OH	Vuppala et al., 2013	Sprague-Dawley Rats	4.0 mg/kg, i.v.	LC-MS/MS	3.0	0.033	0.382	1.60	2.65	1.64	–

Asian Journal of Psychiatry 43 (2019) 73–82

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

Pharmacokinetics of mitragynine, a major analgesic alkaloid in kratom (*Mitragyna speciosa*): A systematic review

Kimheang Ya[a,b,c], Wimonchat Tangamornsuksan[d], C. Norman Scholfield[a,c], Janthima Methaneethorn[a,b], Manupat Lohitnavy[a,b,c,*]

[a] Center of Excellence for Environmental Health & Toxicology, Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok, Thailand
[b] Pharmacokinetic Research Unit, Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok, Thailand
[c] Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok, Thailand
[d] Faculty of Medicine and Public Health, HRH Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, Bangkok, Thailand

Table 3
Pharmacokinetics of mitragynine in animals and humans.

Reference	Species	BW (g)	Sample	Dose (mg/kg)	Route (sampling)	Analytical method	LOD	LOQ	C_{max}	T_{max}	k_a	$AUC_{0-\infty}$	V_d, V_d/F	CL, CL/F	k_e	$t_{1/2}$
							μM**	μM**	μM**	hr	1/hr	μM/h**	L/kg	L/hr kg	1/hr	hr
Intravenous administration of mitragynine to rats (1.5-10 mg/kg)																
(Parthasarathy et al., 2010)	male SD rats	280-315	Plasma	1.5	i.v. (tail vein)	HPLC-UV	0.063	0.125	5.77 ± 3.01	1.2 ± 1.1	–	23.09 ± 16.31	0.79 ± 0.42	0.29 ± 0.27	–	2.9 ± 2.1
(Vuppala et al., 2011)	male SD rats	150-250	Plasma	5	i.v. (jugular vein cannula)	UPLC-MS	0.0005	0.0025	9.79 ± 1.76	1 min	–	8.53 ± 2.26	8.2 ± 2.2	1.2 ± 0.2	–	2.6 ± 0.4
(Kong et al., 2017b)	female SD rats	250-300	Dialysed plasma	10	i.v. (jugular vein)	UFLC-MS	–	0.025	[3.81 ± 0.38]	[0.5]	–	11.62 ± 1.10	9.84 ± 0.62	2.26 ± 0.21	0.24 ± 0.03	13.14 ± 1.42
			Brain						[2.31 ± 0.13]	[0.5]	–	6.73 ± 0.35	16.94 ± 1.11	3.78 ± 0.18	0.23 ± 0.01	13.22 ± 2.55
			ECF													
Oral administration of mitragynine to rats (20-50 mg/kg)																
(Janchawee et al., 2007)	male Wistar rats	220-290	Serum	40	p.o. (orbital sinus)	HPLC-UV	0.075	0.251	1.58 ± 0.45	1.83 ± 1.25	1.43 ± 0.90	17.54 ± 7.35	89.50 ± 30.30	7.3[a]	0.07 ± 0.01	9.43 ± 1.74
(de Moraes et al., 2009)	male Wistar rats	200-250	Plasma	20	p.o. (decapitation)	LC-MS/MS	–	0.0005	1.06	1.26	2.4	7.9	37.90	6.35	0.18	3.85
(Parthasarathy et al., 2010)	male SD rats	280-315	Plasma	50	p.o. (tail vein)	HPLC-UV	0.063	0.125	1.76 ± 0.53	4.5 ± 3.6	–	20.58 ± 7.53	64 ± 23	7.0 ± 3.0	0.105[b]	6.6 ± 1.3
Human subjects																
(Trakulsrichai et al., 2015)	Healthy volunteers	–	Plasma and urine	kratom tea***	p.o	LC-MS/MS	–	–	0.26[c]	0.83 ± 0.35	–	1.68[C]	38.04 ± 24.32	98.1 ± 51.34	–	~3 hr

** All values reported values in ug/mL have been converted to μM.

- Female beagle dogs, single dose oral (5 mg/kg) and IV (0.1 mg/kg)
- Large Vd: 6.3 ± 0.6 L/kg, high clearance
- Oral mitragynine dosing: Cmax observed within 0.5 h.
- 7-hydroxymitragynine: Tmax of 1.7 ± 0.6 h
- The absolute oral bioavailability of mitragynine: 69.6%.

Maxwell et al. Planta Med. 2020

- Beagle Dogs: 7-HMG elimination: slow, T1/2 3.6 ± 0.5 h

Maxwell *et al*. Eur J Drug Metab Pharmacokinet . 2021

- Speciociliatine: minor indole alkaloid, male Sprague-Dawley rats
- 2.5 mg/kg intravenous (I.V.) and 20 mg/kg oral (P.O.) dosing
- Vd: 6.2 ± 2.3 L/kg I.V.), absolute oral bioavailability (20.7 %)

Berthold et al. J Pharm Biomed Anal. 2020

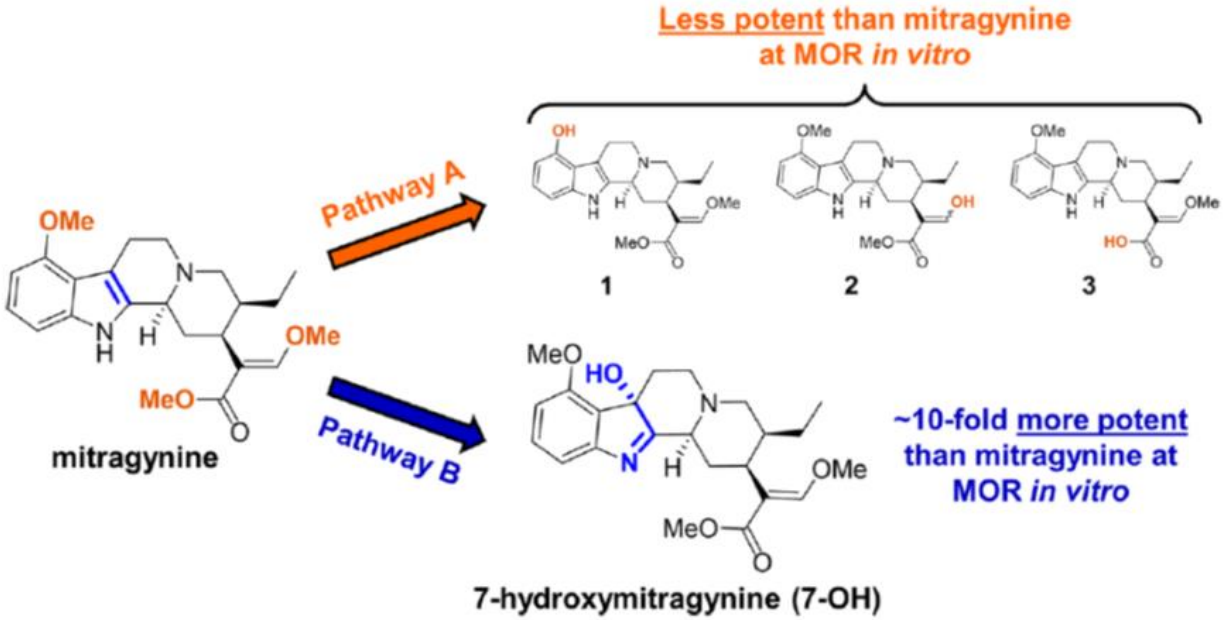
การศึกษา	ผู้เข้าร่วมวิจัย/ ช่องทางที่ได้รับสาร/ ขนาดยา (มก/กก)	วิธีการวิเคราะห์	ระดับความเข้มข้นยาสูงสุด (Cmax) (Mean ± SD)	เวลาที่ระดับยาสูงสุด (Tmax) (hour) (Mean ± SD)	ค่าครึ่งชีวิตส่วนปลาย (terminal t1/2) (hour) (Mean ± SD)	พื้นที่ใต้กราฟความสัมพันธ์ระหว่างระดับยาในเลือดกับเวลา 0-∞ (AUC0-∞) (Mean ± SD)	ปริมาตรกระจายตัวชัดเจน (Apparent volume of distribution, Vd/f) (Mean ± SD)	การขจัดชัดเจน (Apparent clearance, Cl/f) (Mean ± SD)	ชีวปริมาณออกฤทธิ์ทางการกิน (Oral bioavailability,F)
7-OH MG									
Vuppala et al., พ.ศ. 2556 (42)	Sprague-Dawley Rats ทางหลอดเลือดดำ 4 mg/kg	UPLC/ MS/MS	3.0 ± 0.3 µg/mL		22.9 ± 3.6 min	98.3 ± 32.1 (µg min/mL)	1595.8 ± 586.3 mL/kg	44.2 ± 14.8 (mL/min/ kg)	-
Maxwell et al พ.ศ. 2564 (19)	beagle dogs การกิน 5 mg/kg	UPLC/ MS/MS	31.5 ± 3.3 ng/ml	1.7 ± 0.6 h	-	-	-	-	-
Kamble et al พ.ศ. 2564 (41)	Sprague-Dawley rats การกิน 366 mg/kg	UPLC-MS/MS	4.3 ± 0.8 ng/ml	0.9 ± 0.2 h	-	17.4 ± 4.8 h ng/ml	-	-	-
	Feed 0.8 ml/kg		4.0 ± 0.6 ng/ml	3.1 ± 1.7 h	-	41.0 ± 7.6 h ng/ml	-	-	-
Speciociliatine									
Berthold et al พ.ศ. 2564 (43)	Sprague-Dawley rats ทางหลอดเลือดดำ 2.5 mg/kg	UPLC-MS/MS	-	-	6.3 ± 2.0 h	4324.5 ± 670.8 h*µg/l	6.2 ± 2.3 l/kg	0.7 ± 0.2 L/h/ kg	
	การกิน		1581.6 ± 376.1	1.0 ± 0.4 h	3.8 ± 1.2 h	8234.7 ± 1006.6	3.9 ± 1.5	0.7 ± 0.1	20.7
	20 mg/kg		µg/mL			h*µg/l	l/kg	L/h/ kg	
Kamble et al พ.ศ. 2564 (41)	Sprague-Dawley rats การกิน 366 mg/kg	UPLC-MS/MS	21.1 ± 3.3 ng/ml	1.8 ± 0.7 h	-	107.4 ± 25.4 h ng/ml			
	Feed 0.8 ml/kg		23.8 ± 1.4 ng/ml	3.2 ± 1.6 h	-	222.7 ± 22.2 h ng/ml	-		
Corynantheidine									
Kamble et al พ.ศ. 2564 (41)	Sprague-Dawley rats การกิน 366 mg/kg	UPLC-MS/MS	1.8 ± 0.3 Ng/ml	1.0 ± 0.2 h	-	8.2 ± 2.3 h ng/ml	-	-	-
	Feed 0.8 ml/kg		3.1 ± 0.5 ng/ml	3.1 ± 1.7 h	-	30.4 ± 9.1 h ng/ml	-	-	-

Mahidol University
Wisdom of the Land

ACS central science
Research Article
Cite This: ACS Cent. Sci. 2019, 5, 992−1001
http://pubs.acs.org/journal/acscii

7-Hydroxymitragynine Is an Active Metabolite of Mitragynine and a Key Mediator of Its Analgesic Effects

Andrew C. Kruegel, Rajendra Uprety, Steven G. Grinnell, Cory Langreck, Elizabeth A. Pekarskaya, Valerie Le Rouzic, Michael Ansonoff, Madalee M. Gassaway, John E. Pintar, Gavril W. Pasternak, Jonathan A. Javitch, Susruta Majumdar, and Dalibor Sames



Known (Pathway A) and proposed (Pathway B) metabolic transformations of mitragynine.

- MG: converted in vitro in mouse and human liver preparations to 7-OH-MG, mediated by CYP 3A isoforms
- MG is metabolized into 7-OH-MG or another more active compound

Macko *et al . Arch Int Pharmacodyn Ther.,*1972

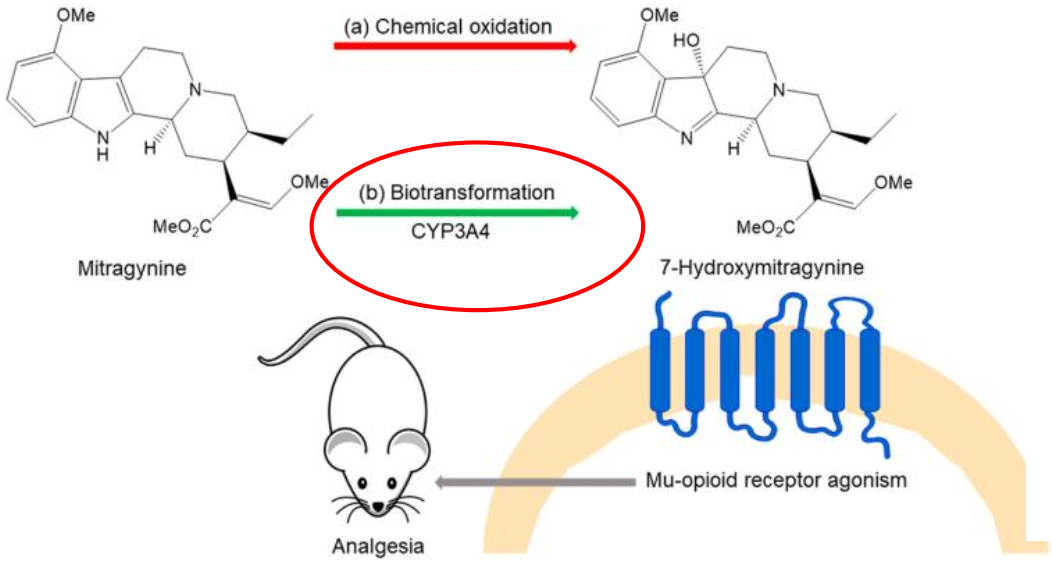


Figure 1. Metabolic transformations of mitragynine to 7-hydroxymitragynine (7-OH), with 7-OH as an active metabolite of mitragynine and a key mediator of its analgesic activity.

Spetea and Helmut Schmidhammer, 2019

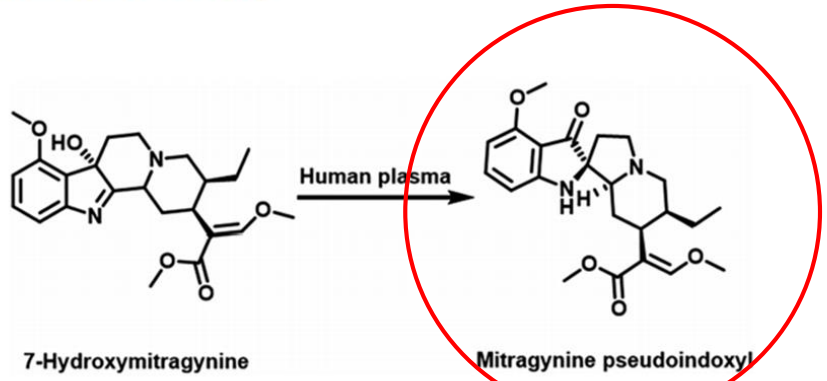


Figure 4. Novel metabolic conversion of 7-HMG to mitragynine pseudoindoxyl in human plasma. The incubation of 7-HMG in human plasma at 37 °C in 5% CO_2 incubator at 100 rpm for 2 h resulted in the metabolic conversion of 7-HMG to mitragynine pseudoindoxyl.

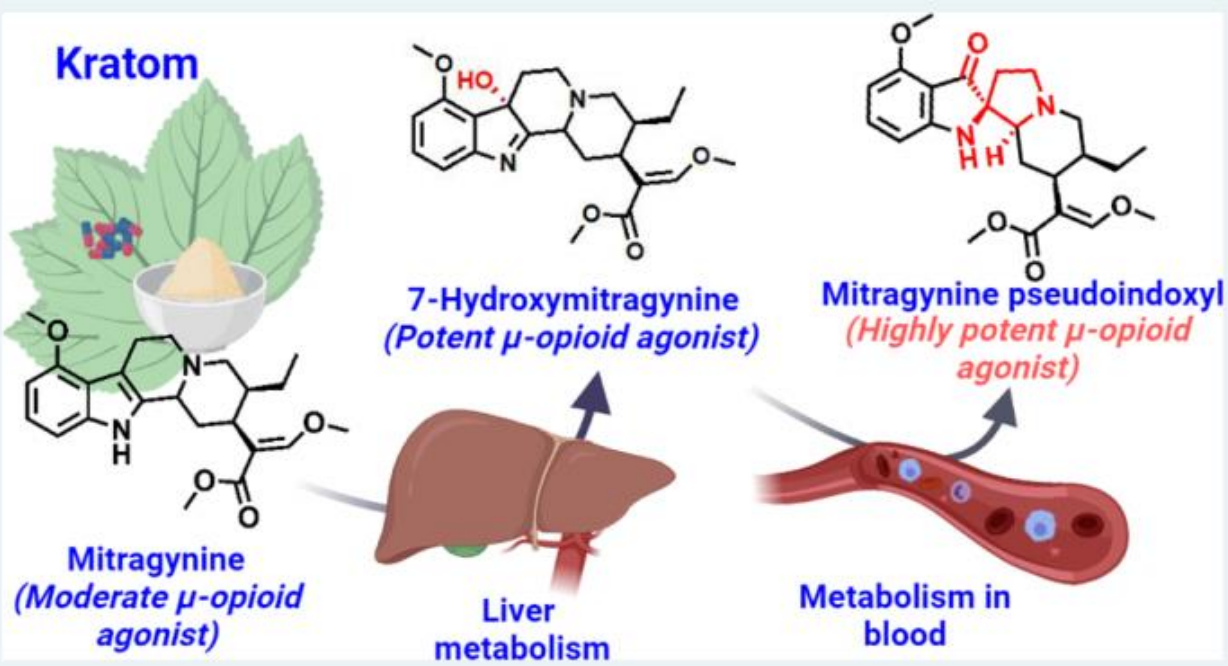
Kamble *et al.* ACS Pharmacol Transl Sci. 2020

- The **limiting rate of conversion of mitragynine into its active metabolite** results in a **built-in ceiling effect of the mitragynine-induced respiratory depression**.
- **'Metabolic saturation'** at high doses

Hill *et al*, 2021

Mahidol University
Wisdom of the Land

Metabolism of a Kratom Alkaloid Metabolite in Human Plasma Increases Its Opioid Potency and Efficacy



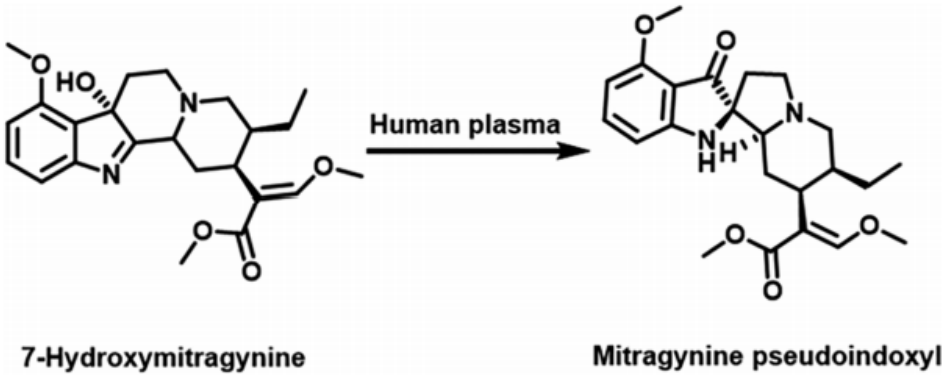


Figure 4. Novel metabolic conversion of 7-HMG to mitragynine pseudoindoxyl in human plasma. The incubation of 7-HMG in human plasma at 37 °C in 5% CO_2 incubator at 100 rpm for 2 h resulted in the metabolic conversion of 7-HMG to mitragynine pseudoindoxyl.

- 7-HMG: stable in rodent, monkey plasma, but unstable in human plasma
- In human plasma: 7-HMG is converted to mitragynine pseudoindoxyl, an opioid that is even more potent than either mitragynine or 7-HMG

Kamble *et al.* ACS Pharmacol Transl Sci. 2020

Mahidol University
Wisdom of the Land

Pharmacokinetics

Effect on human CYPs enzyme activities

MG: Inhibitory effect

- **CYP2D6 (the strongest),** CYP2C9
- CYP3A4, CYP1A2
- P-glycoprotein (P-gp)
- Pregnane X receptor (PXR): transcription factor (regulates the expression of CYPs, P-gp)

9 cases from human PK study:

- CYP 2D6, CYP1A2, P-gp:
- T1/2, Tmax - no difference

Trakulsrichai et al (unpublished)

“Potential herb-drug interactions”

Forensic Science, Medicine and Pathology (2019) 15:110–113
https://doi.org/10.1007/s12024-018-0049-9

CASE REPORT

CrossMark

Fatal combination of mitragynine and quetiapine – a case report with discussion of a potential herb-drug interaction

Hanapi *et al.* Pharmacognosy Res, 2013; Manda *et al*. Phytother Res., 2017; Rusli *et al.* Naunyn Schmiedebergs Arch Pharmacol, 2019; White. Am J Health Syst Pharm, 2018

Mahidol University
Wisdom of the Land

Clinical effects

- **"Dose dependent"**
- Stimulant effects at lower doses **'Coca-like'**
- Opiate effects at higher doses **'Opioid-like'**
- Antipyretic, euphoric, anti-depressant, anxiolytic, immune booster, anti-viral, anti-diabetes, appetite suppressing effects, antinociceptive, anti-inflammatory, antidiarrheal, antitussive, antipyretic, euphoric, lower blood pressure
- Effects: 5-10 minutes after taking
- Long-term, heavy use:

  not alter hematological, chemistry parameters,

  not interfere with abilities to function in society

Table 1. *Dose dependent effects of kratom.*

Kratom use	Dose	Effects
Low to moderate	1-5 grams	Mild stimulant effects that enable workers to stave off fatigue.
Moderate to high	5-15 grams	Opioid-like effects including analgesia, treatment of diarrhea, opioid-withdrawal symptoms, and euphoria.
Very high	Greater than 15 grams	Sedating effects.

Chien *et al.* Pain Physician, 2017

Hassan *et al*, 2013; Singh *et al*. J Ethnopharmacol, 2018; Singh *et al*. J Psychoactive Drugs, 2015; Ulbricht *et al*. J Diet Suppl, 2013

- Regular kratom users in the community setting
- Total cholesterol and LDL of kratom users: significantly lower than those of healthy subjects
- No significant differences in the serum triglyceride and HDL levels
- Higher average daily frequency of kratom use and increasing age: associated with increased serum total cholesterol
- Regular kratom consumption was not linked to elevated serum lipids, except when there is a higher frequency of daily kratom intake

Abdullah *et al*. PLoS One. 2020

- Kratom use and elevated HDL level (≥60 mg/dL) (OR 1.82), and triglyceride level <90 mg/dL (OR 1.75), no associations LDL, cholesterol

La-Up *et al.* Heliyon . 2021

YALE JOURNAL OF BIOLOGY AND MEDICINE 93 (2020), pp.229-238.

ORIGINAL CONTRIBUTION

YALE JOURNAL OF BIOLOGY AND MEDICINE
YJBM
CELEBRATING 90 YEARS 1928–2018

Kratom and Pain Tolerance: A Randomized, Placebo-Controlled, Double-Blind Study

Balasingam Vicknasingam[a], Weng Tink Chooi[b], Azlan Abdul Rahim[a], Dinesh Ramachandram[a], Darshan Singh[a], Surash Ramanathan[a], Nur Sabrina Mohd Yusof[a], Hadzliana Zainal[c], Vikneswaran Murugaiyah[c], Ralitza Gueorguieva[d], Sharif Mahsufi Mansor[a], and Marek C. Chawarski[e,*]

- Pain tolerance was measured objectively in a cold pressor task (CPT) as time (seconds) between the pain onset and the hand withdrawal from the ice bath.
- Pain tolerance increased significantly 1 hour after kratom ingestion
- No discomfort or signs of withdrawal
- Kratom decoction demonstrated a substantial and statistically significant increase in pain tolerance

Mahidol University
Wisdom of the Land

Clinical effects

Short time use effects: nausea, constipation, sleep problems, temporary erectile dysfunction, itching, sweating

Long time use effects:

Anorexia, dry mouth, problems in diuresis, frequent micturition darker skin, hair loss, weight loss, numbness in peripheral areas, twitching, abdominal distention, constipation, **addiction, withdrawal**

Prozialeck *et al*. J Am Osteopath Assoc. 2012; Cinosi *et al.* Biomed Res Int., 2015

Mahidol University
Wisdom of the Land

Clinical effects

Mental health

- Psychotic symptoms

Suwanlert. Bull Narc, 1975

- Kratom use and mental health: **A systematic review**

  - Kratom also enhances mood and relieves anxiety among many users

  - For many, kratom's negative mental health effects - primarily withdrawal symptoms - appear to be mild relative to those of opioids

Swogger & Walsh. Drug Alcohol Depend, 2018

Heliyon 8 (2022) e09468

CellPress

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Heliyon

Research article

Association between kratom (*Mitragyna speciosa*) use and metabolic syndrome

Aroon La-up [a,b], Paleeratana Wongrith [a], Wiraphon Chaichan [c], Apinun Aramrattana [d], Udomsak Saengow [b,e,f,*]

[a] School of Public Health, Walailak University, Thai Buri, Tha Sala, Nakhon Si Thammarat, 80160, Thailand
[b] Center of Excellence in Data Science for Health Study, Walailak University, Thai Buri, Tha Sala, Nakhon Si Thammarat, 80160, Thailand
[c] Narcotics Crop Survey and Monitoring Institute, Office of the Narcotics Control Board, Samsen Nai, Phaya Thai, Bangkok, 10400, Thailand
[d] Northern Substance Abuse Center, Department of Family Medicine, Chiang Mai University, Sri Phum, Muang, Chiang Mai, 50200, Thailand
[e] School of Medicine, Walailak University, Thai Buri, Tha Sala, Nakhon Si Thammarat, 80160, Thailand
[f] Research Institute for Health Sciences, Walailak University, Thai Buri, Tha Sala, Nakhon Si Thammarat, 80160, Thailand

ABSTRACT

Background and aims: There are evidence about effects of kratom (*Mitragyna speciosa*) use on parameters related to metabolic syndrome (MetS). The present study aimed to determine the association between kratom use and MetS.
Methods: This study is a cross-sectional study of 581 subjects (kratom users and non-users) aged 18 and over from the Nam Phu sub-district, Surat Thani province, Thailand. The association was determined using multivariate logistic regression.
Results: MetS prevalence in kratom users and non-users was 11.9% (95% CI, 8.4–16.3%) and 21.6 % (95% CI, 17.1–26.8%), respectively. The use of kratom was associated with the lower odds of MetS (adjusted OR, 0.56; 95% CI, 0.33–0.96). Kratom use were associated with smaller waist circumference, lower triglycerides, and higher high-density lipoprotein.
Conclusions: The current study demonstrated a potential protective effect of kratom use against MetS.

Mahidol University
Wisdom of the Land

Toxicities

Poisoning signs and symptoms

- Nystagmus, stupor, vertigo, motor excitement, rombergism, giddiness
- Tremors of face, extremities, tongue

- **Little to no respiratory depression**
- Significant opioid toxic syndrome: not commonly reported

Vicknasingam *et al*. Int J Drug Policy,2010; Trakulsrichai *et al.* J Psychoactive Drugs, 2013; Ward *et al.* CNS Drugs, 2011; Macko *et al*. Arch Int Pharmacodyn Ther, 1972

Mahidol University
Wisdom of the Land

Toxicity Reports

- **Seizures:** alone or combined with other drugs

Nelsen *et al*. J Med Toxicol, 2010; Boyer *et al*. Addiction, 2008; Trakulsrichai et al. J Psychoactive Drugs, 2013; Tatum et al. Epilepsy Behav Case Rep, 2018

- **Liver injury:** Cholestatic, mixed, hepatocellular

: onset usually within 2 to 8 weeks

Botejue *et a*l. Cyreus, 2021; Aldyab *et al*. Gastroenterology Res, 2019; Osborne *et al.* J Investig Med High Impact Case Rep, 2018, fernandes *et al*. J Investig Med High Impact Case Rep, 2019; Griffiths *et al*. J Am Pharm Assoc (2003), 2018; Riverso *et al.* Gastroenterology Res, 2018; Drago *et al.* Oncologist, 2017; Dorman *et al*. Hepatology, 2015; Antony & Lee. Am J Ther, 2019; Tayabali et al. J Community Hosp Intern Med Perspect, 2018; LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet].

: symptomatic, developed jaundice with a median latency of 14 days,pattern was variable (the U.S. drug induced liver injury network and a review of the literature)

Jawad Ahmad *et al.* Drug Alcohol Depend. 2021

: Liver biopsy: mimicking primary biliary cholangitis

Gandhi *et al.* World J Hepatol. 2020

Mahidol University
Wisdom of the Land

- Mean age: 36 years
- Higher prevalence in men
- Onset: usually within 1-8 wk after regular use of powder or tablets
- Ingested doses varied from 3 g to 15 g daily
- The most common pattern: **hepatocellular**, cholestatic and mixed
- Usually recovered after it was discontinued; normalization of parameters occurred in 40 d

WJCC World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com
World J Clin Cases 2021 July 16; 9(20): 5490-5513
DOI: 10.12998/wjcc.v9.i20.5490
ISSN 2307-8960 (online)

SYSTEMATIC REVIEWS

Herb-induced liver injury: Systematic review and meta-analysis

Vinícius Remus Ballotin, Lucas Goldmann Bigarella, Ajacio Bandeira de Mello Brandão, Raul Angelo Balbinot, Silvana Sartori Balbinot, Jonathan Soldera

Kratom	*Mitragyna speciosa*	33	36	20 (62)	United States (75), Canada (6.2), Sweden (6.2)	Jaundice (70), choluria (53.3), abdominal pain (43.5), nausea (23.3), fatigue (23.3)	1125	957	304	258	11.7	11.3	11 (39.2)	Hepatocellular (45.4), cholestatic (27.2), mixed (21.2)	11	Acetylcysteine (12.7), udca (7.6), corticoid (5.1), liver transplantation (5.1), supportive care (48.7)	Recovery (90.6), died (9.3)

Mahidol University
Wisdom of the Land

Toxicity Reports

- **Neonatal abstinence syndrome** (NAS)

Trakulsrichai *et al.* J Psychoactive Drugs, 2013; Murthy & Clark. Paediatrics & Child Health, 2019; Mackay & Abrahams. Can Fam Physician, 2018; Eldridge *et al*. Pediatrics, 2018

- **Hypothyroidism**

Sheleg & Collins. J Addict Med, 2011

- **Intractable nausea and vomiting**: in naïve ingestion of kratom for analgesia

Singh *et al.* Int J Emerg Med. 2020

- **Phytochemical**

Saingam et al. Int J Drug Policy. 2013

Mahidol University
Wisdom of the Land

Toxicity Reports

Others

- Posterior reversible encephalopathy syndrome (amphetamine, benzodiazepine, cannabinoids, opiates), Intracerebral hemorrhage

Regan & Papadakos. JAAPA . 2021; Castillo. Proc (Bayl Univ Med Cent), 2017

- Secondary hypogonadism: raising prolactin levels

LaBryer et al. J Investig Med High Impact Case Rep, 2018

- ARDS/ Pulmonary injury
- Torsade de Pointes: inhibition rapid delayed rectifier potassium current in human cardiomyocytes, ventricular fibrillation

Sheikh et al. BMJ Case Rep . 2021; Fluyau & Revadigar. Front Psychiatry. 2017; Lu *et al*. PLoS One, 2014

- Severe rhabdomyolysis, pressure necrosis, compartment syndrome

Tobarran *et al*. J Addict Med . 2021

“Most from the western countries”

Mahidol University
Wisdom of the Land

In vitro studies

Prolonged QTc interval

Increased risk of torsades de pointes

Clinical study

Induce increased QTc interval: dose dependent

Few case reports

ventricular arrhythmia and cardiopulmonary arrest

National poison data

Tachycardia

Hypertension

Coroner and autopsy reports

Coronary atherosclerosis, myocardial infarction, hypertensive cardiovascular disease, left ventricular hypertrophy, cardiac arrhythmia, cardiomegaly, cardiomyopathy, focal band necrosis in the myocardium, and myocarditis

frontiers in Pharmacology

REVIEW
published: 27 September 2021
doi: 10.3389/fphar.2021.726003

The Adverse Cardiovascular Effects and Cardiotoxicity of Kratom (*Mitragyna speciosa* Korth.): A Comprehensive Review

Mohammad Farris Iman Leong Bin Abdullah[1]* *and Darshan Singh*[2]

[1]Lifestyle Science Cluster, Advanced Medical and Dental Institute, Universiti Sains Malaysia, Kepala Batas, Malaysia, [2]Centre for Drug Research, Universiti Sains Malaysia, Gelugor, Malaysia

Background: Kratom or *Mitragyna speciosa* (Korth.) has received overwhelming attention recently due to its alleged pain-relieving effects. Despite its potential therapeutic value, kratom use has been linked to many occurrences of multiorgan toxicity and cardiotoxicity. Accordingly, the current narrative review aimed to provide a detailed account of kratom's adverse cardiovascular effects and cardiotoxicity risk, based on *in vitro* studies, poison center reports, coroner and autopsy reports, clinical case reports, and clinical studies.

Methods: An electronic search was conducted to identify all research articles published in English from 1950 to 2021 using the major research databases, such as Google Scholar, Web of Science, PubMed, Scopus, Mendeley, EMBASE, Cochrane Library, and Medline. We then analyzed the literature's discussion of adverse cardiovascular effects, toxicity, and mortality related to kratom use.

Results: Our findings revealed that, although *in vitro* studies have found kratom preparations' most abundant alkaloid—*mitragynine*—to cause a prolonged QTc interval and an increased risk of torsades de pointes, a clinical study examining humans' regular consumption of kratom did not report such a risk. However, this latter study did show that regular kratom use could induce an increased QTc interval in a dose-dependent manner. A few case reports also highlighted that kratom consumption is associated with ventricular arrhythmia and cardiopulmonary arrest, but this association could have ensued when kratom was co-administered with another substance. Similarly, analyses of national poison data showed that kratom's most common adverse acute cardiovascular effects include tachycardia and hypertension. Meanwhile, coroner and autopsy reports indicated that kratom's cardiovascular sequelae encompass coronary atherosclerosis, myocardial infarction, hypertensive cardiovascular disease, left ventricular hypertrophy, cardiac arrhythmia, cardiomegaly, cardiomyopathy, focal band necrosis in the myocardium, and myocarditis. Given the available data, we deduced that all cardiac eventualities reported in the literature could have been compounded by polysubstance use and unresolved underlying medical illnesses.

Conclusion: Although kratom use has been associated with death and cardiotoxicity, especially at higher doses and when associated with other psychoactive drugs, the dearth

OPEN ACCESS

Edited by:
Dâmaris Silveira,
University of Brasília, Brazil

Reviewed by:
You Yun,
China Academy of Chinese Medical Sciences, China
Francisco Assis Rocha Neves,
University of Brasília, Brazil

*Correspondence:
Mohammad Farris Iman Leong Bin Abdullah
farris@usm.my

Specialty section:
This article was submitted to Ethnopharmacology, a section of the journal Frontiers in Pharmacology

Received: 18 June 2021
Accepted: 02 August 2021
Published: 27 September 2021

Citation:
Leong Bin Abdullah MFI and Singh D (2021) The Adverse Cardiovascular Effects and Cardiotoxicity of Kratom (Mitragyna speciosa Korth.): A Comprehensive Review. Front. Pharmacol. 12:726003. doi: 10.3389/fphar.2021.726003

CLINICAL TOXICOLOGY
https://doi.org/10.1080/15563650.2020.1812627

Taylor & Francis
Taylor & Francis Group

CLINICAL RESEARCH

Is kratom (*Mitragyna speciosa* Korth.) use associated with ECG abnormalities? Electrocardiogram comparisons between regular kratom users and controls

Mohammad Farris Iman Leong Abdullah[a], Kok Leng Tan[b], Suresh Narayanan[c], Novline Yuvashnee[c], Nelson Jeng Yeou Chear[c], Darshan Singh[c], Oliver Grundmann[d] and Jack E. Henningfield[e,f]

[a]Lifestyle Science Cluster, Advance Medical and Dental Institute, Universiti Sains Malaysia, Kepala Batas, Malaysia; [b]Regenerative Medicine Cluster, Advance Medical and Dental Institute, Universiti Sains Malaysia, Kepala Batas, Malaysia; [c]Centre for Drug Research, Universiti Sains Malaysia, Minden, Malaysia; [d]Department of Medicinal Chemistry, College of Pharmacy, University of Florida, Gainesville, FL, USA; [e]Pinney Associates Inc., Bethesda, MD, USA; [f]School of Medicine, Johns Hopkins University, Baltimore, MD, USA

ABSTRACT

Objectives: Little is known about the cardiotoxic effects of kratom (*Mitragyna speciosa* Korth.), a medicinal plant. This analytical cross-sectional study investigated the prevalence of electrocardiogram (ECG) abnormalities and QTc intervals in regular kratom users compared with non-kratom-using control subjects.

Methods: We enrolled regular kratom users and non-kratom-using control subjects from three communities. Demographic data, clinical data, kratom use characteristics, and ECG findings were recorded. The mitragynine content of kratom juice was quantified using a validated gas chromatography–mass spectrometry (GC–MS) method.

Results: A total of 200 participants (100 kratom users and 100 control subjects) participated in this study. The prevalence of ECG abnormalities in kratom users (28%) did not differ from that of control subjects (32%). Kratom use was not associated with ECG abnormalities, except for significantly higher odds of sinus tachycardia (OR = 8.61, 95% CI = 1.06–70.17, $p = 0.035$) among kratom users compared with control subjects. The odds of observing borderline QTc intervals were significantly higher for kratom users compared with control subjects, regardless of the age of first use, the duration of use, the daily quantity consumed, and the length of time that had elapsed between last kratom use and ECG assessment. Nevertheless, there were no differences in the odds of having prolonged QTc intervals between kratom users and controls. The estimated average daily intake of mitragynine consumed by kratom users was 434.28 mg.

Conclusion: We found no link between regular kratom use and electrocardiographic abnormalities with an estimated average daily intake of 434.28 mg of mitragynine.

- No link between regular kratom use and ECG abnormalities

Table 3. Resting ECG report for the participants.

Variables	Kratom users ($n = 100$) *n* (%)	Control subjects ($n = 100$) *n* (%)	OR (95% CI)	*p*-Value
Any ECG abnormalities				
Yes	28 (28)	32 (32)	0.83 (0.45–1.51)	0.538[a]
No	72 (72)	68 (68)		
ECG abnormalities reported				
1st Degree heart block				
Yes	4 (4)	7 (7)	0.55 (0.16–1.95)	0.351[b]
No	96 (96)	93 (93)		
Sinus tachycardia				
Yes	8 (8)	1 (1)	8.61 (1.06–70.17)	0.035[b*]
No	92 (92)	99 (99)		
Sinus bradycardia				
Yes	1 (1)	5 (5)	0.19 (0.02–1.67)	0.212[b]
No	99 (99)	95 (95)		
T inversion				
Yes	4 (4)	3 (3)	1.35 (0.29–6.18)	0.999[b]
No	96 (96)	97 (97)		
Inferior leads (II, III and aVF)	1 (1)	3 (3)		
Anterior leads (VI–V4)	2 (2)	0 (0)		
Lateral leads (I, aVL, V5–V6)	1 (1)	0 (0)		
Left axis deviation				
Yes	7 (7)	8 (8)	0.87 (0.30–2.48)	0.791[a]
No	93 (93)	92 (92)		
Right axis deviation				
Yes	2 (2)	1 (1)	2.02 (0.18–22.65)	1.000[b]
No	98 (98)	99 (99)		
Incomplete right bundle branch block				
Yes	3 (3)	1 (1)	3.06 (0.31–29.95)	0.621[b]
No	97 (97)	99 (99)		
Left ventricular hypertrophy				
Yes	4 (4)	2 (2)		0.683[b]
No	96 (96)	98 (98)	2.04 (0.37–11.41)	
Prolonged QTc interval				
Yes	5 (5)	5 (5)	1.00 (0.28–3.57)	1.000[a]
No	95 (95)	95 (95)		

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Deaths in Colorado Attributed to Kratom

TO THE EDITOR: Kratom (*Mitragyna speciosa*) is an herbal drug identified by the Food and Drug Administration (FDA) as an opioid for which there is "no evidence of safety or effectiveness for any medical use."[1] The drug is derived from

available with the full text of this letter at NEJM .org). Autopsy reports were reviewed for all 15 deaths, which included 13 men and 2 with a median age of 28 years (range, 2 On the basis of toxicology testing, 11 c

Gershman *et al*. N Engl J

jwatch.org/fw113826/2018/02/08/kratom-contains-opioids-fda-says?query=pfwTOC&jwd=000012

NEJM Journal Watch

HOME SPECIALTIES & TOPICS NEWS BLOGS CME

MEDICAL NEWS | PHYSICIAN'S FIRST WATCH

February 8, 2018

Kratom Contains Opioids, FDA Says

By Kelly Young

Edited by Susan Sadoughi, MD, and Richard Saitz, MD, MPH, FACP, DFASAM

Compounds in the botanical kratom (*Mitragyna speciosa*) are opioids, the FDA said in a statement. People use kratom recreationally or to self-treat opioid withdrawal symptoms.

Using computational models, the agency found that 22 of kratom's 25 most prevalent compounds bind strongly to mu-opioid receptors in a way that's similar to scheduled opioid drugs.

Forty-four deaths associated with kratom have been reported, including eight since November 2017. The agency reported one kratom-related fatality in a person with no evidence of other opioid use. Other fatality reports suggest that people are mixing kratom with other drugs, including prescription opioids, benzodiazepines, loperamide, and illicit drugs.

The agency cautions: "Kratom should not be used to treat medical conditions, nor should it be used as an alternative to prescription opioids. There is no evidence to indicate that kratom is safe or effective for any medical use. And claiming that kratom is benign because it's 'just a plant' is shortsighted and dangerous."

NEJM CareerC

PHYSICIAN JOE

News & Analysis

News From the Centers for Disease Control and Prevention

En español

Research | Medical & Health Professionals | Patients & Families | Parents & Educators | Children & Teens

NIH National Institute on Drug Abuse
Advancing Addiction Science

Enter your keywords Search

Connect with NIDA:

Drugs of Abuse | Related Topics | Publications | Research | Funding | News | About NIDA

Home » Publications » DrugFacts » Kratom

Kratom

Print Share

DrugFacts

Revised April 2019

Español PDF (299KB)

Cite this article

What is kratom?

I tree (*Mitragyna speciosa*) native to h leaves that contain compounds that can (mind-altering) effects.

Additional Drug Facts

NIH NIDA

NIDA FOR TEENS

THE SCIENCE BEHIND DRUG ABUSE

Can a person overdose on kratom?

There have been multiple reports of deaths in people who had ingested kratom, but most have involved other substances. A 2019 paper analyzing data from the National Poison Data System found that between 2011-2017 there were 11 deaths associated with kratom exposure. Nine of the 11 deaths reported in this study involved kratom plus other drugs and medicines, such as diphenhydramine (an antihistamine), alcohol, caffeine, benzodiazepines, fentanyl, and cocaine. Two deaths were reported following exposure from kratom alone with no other reported substances.* In 2017, the FDA identified at least 44 deaths related to kratom, with at least one case investigated as possible use of pure kratom. The FDA reports note that many of the kratom-associated deaths appeared to have resulted from adulterated products or taking kratom with other potent substances, including illicit drugs, opioids, benzodiazepines, alcohol, gabapentin, and over-the-counter medications, such as cough syrup. Also, there have been some reports of kratom packaged as dietary supplements or dietary ingredients that were laced with other compounds that caused deaths. People should check with their health care providers about the safety of mixing kratom with other medicines.

*(Post et al, 2019. *Clinical Toxicology*).

those reporting poor overall health (6.7%) had higher rates of occupational COPD among never smokers.

There also were differences between men and women never smokers with respect to job-related COPD risks. Among women, those in the information and transportation and moving materials industries had the highest prevalence of COPD, at 5.1% and 4.5%, respectively. In contrast, among men, those working in agriculture, fishing, hunting, administrative and support, waste management, remediation services, arts entertainment, and recreation had the highest COPD rates (2.3% for each category).

"Efforts to reduce adverse workplace exposures (including exposure to dust, vapors, fumes, chemicals, and indoor and outdoor air pollutants) and promote research to characterize the many contributing risk factors in COPD are needed to reduce the prevalence of COPD," the authors wrote.

Kratom-Related Deaths

More than 90 deaths in the United States have been caused by kratom between July 2016 and December 2017, according to a CDC report.

Kratom (*Mitragyna speciosa*), a plant native to Southeast Asia, has been growing in popularity as an herbal supplement. Consuming low doses of it may have stimulant-like effects, while higher doses may produce opioid-like effects, the report's authors note. Because of its potential for abuse, the

US Drug Enforcement Administration (DEA) has called it "a drug of concern." The US Department of Health and Human Services has recommended that the DEA reclassify kratom as a schedule I substance, according to documents obtained by STAT news. And the US Food Administration has issued warnings about high levels of heavy metals and salmonella in kratom products. The agency has also issued warning letters to companies making unproven claims that kratom products may be used to treat opioid withdrawal and pain.

Now, the recent CDC report has found that 152 unintentional overdose deaths involved kratom between July 2016 and December 2017, accounting for 0.56% of the 27 338 US overdose deaths during that period. Multiple drugs were detected in nearly every kratom-related death. Fentanyl and its analogues were the most common sub- ed in individuals with kratom- ses and were ruled the cause % of these overdoses, fol- in (32.9%), benzodiazepines cription opioids (19.7%), and %). Coroners determined kra- use of death in 91 of 152 cases. of kratom-related deaths oc- ndividuals with a history of sub- and 90% had no evidence of ally supervised pain care. The st the majority of these deaths o substance misuse involving and could help public health of- prevention strategies, the au- **Bridget Kuehn, MSJ**

erences are available through links in the article text online.

This Issue Views 10,127 | Citations 0 | Altmetric 46

News From the Centers for Disease Control and Prevention

May 28, 2019

Kratom-Related Deaths

Bridget Kuehn, MSJ

JAMA. 2019;321(20):1966. doi:10.1001/jama.2019.6339

Original Paper

Characteristics of deaths associated with kratom use

John M Corkery[1], Peter Streete[2], Hugh Claridge[3], Christine Goodair[3], Duccio Papanti[1], Laura Orsolini[1], Fabrizio Schifano[1], Kanav Sikka[1], Sophie Körber[4] and Amy Hendricks[5]

Psychopharm

Journal of Psychopharmacology
2019, Vol. 33(9) 1102–1123

DOI: 10.1177/0269881119862530
journals.sagepub.com/home/jop

Fatalities

UK/ non-UK

Poly-drug users

Only mitragynine/7-hydroxymitragynine	6	26
'Legal high'/NPS	25	13
of which, synthetic opioid (5 U-47700; 12 novel fentanyls)	18	12
Synthetic cathinone (4 bupropion)	5	1
Benzodiazepine	8	2
PCP-like	1	0

Table 1. Summary of main characteristics of case reports of deaths associated with kratom/Krypton use.

Variable	Characteristic	Frequency
Country of death	Canada	1
	Germany	2
	Ireland	1
	Norway	1
	Sweden	9
	Thailand	1
	USA	131
	United Kingdom	10

- Some claim that no deaths have occurred in South East Asia

Singh *et al.* Brain Res Bull, 2016

Tungtananuwat W and Lawanprasert S (2010) Fatal 4x100; Home-made kratom juice cocktail. *J Health Res* 24: 43–47.

Table 3. Main classes of other substances noted in post-mortem toxicology and cause of death for human fatalities associated with kratom/Krypton use.

Class of substance	Frequency	
	Toxicology	Cause of death
Only mitragynine/7-hydroxymitragynine	6	26
'Legal high'/NPS	25	13
of which, synthetic opioid (5 U-47700; 12 novel fentanyls)	18	12
Synthetic cathinone (4 bupropion)	5	1
Benzodiazepine	8	2
PCP-like	1	0
Stimulant (e.g. cocaine, MDMA, etc.)	25	11
of which, amphetamine/methamphetamine	9	3
Cocaine	10	5
MDMA, MDA, ephedrine, pseudoephedrine	7	4
DMAA	1	0
2,4,5 TMA	1	0
THC/cannabis/cannabinoid	11	0
GHB	1	1
Anxiolytic	18	4
Anti-depressant (excluding benzodiazepine)	15	3
Anti-epileptic (excluding gabapentin, pregabalin)	9	1
Gabapentinoid	13	6
Anti-histamine	21	10
Anti-psychotic	16	2
Benzodiazepine	50	18
Any opiate/opioid	77	44
O-desmethyltramadol (9 Krypton cases)	10	1
Heroin	21	12
Fentanyl	22	16
Morphine	13	8
Codeine	8	7
Tramadol	6	1
Methadone	3	2
Other opiates/opioids	24	11
Non-opioid pain-killer	8	1
Loperamide	5	0
Dextromethorphan	4	1
Muscle relaxant	3	1
Alcohol	22	8
Caffeine	12	0
Helium	0	2
Inhalant	2	0
	2	0
	15	1
	1	8
Not stated/unascertained	19	53
No kratom/mitragynine	1	1

Original Paper

Characteristics of deaths associated with kratom use

John M Corkery[1], Peter Streete[2], Hugh Claridge[3], Christine Goodair[3], Duccio Papanti[1], Laura Orsolini[1], Fabrizio Schifano[1], Kanav Sikka[1], Sophie Körber[4] and Amy Hendricks[5]

Journal of Psychopharmacology
2019, Vol. 33(9) 1102–1123

DOI: 10.1177/0269881119862530
journals.sagepub.com/home/jop

Table 5. Cases involving mitragynine/7-hydroxymitragynine/kratom alone in cause of death.

Deaths	
Mitragynine blood level	Mean 2.128 (range 0.016–16.000 mg/L) (*n* = 15)
Main autopsy findings/cause of death	Cerebral oedema = 2; Hypoxic encephalopathy = 2; Seizures = 2; Anoxic brain injury = 1; Underlying heart condition = 1; Atherosclerosis = 1; Severe atherosclerosis = 1; Cardiomegaly = 1; Left ventricular hypertrophy = 3; Hypertensive cardiovascular disease = 1; Cardio-respiratory arrest = 2; Pulmonary oedema/congestion = 9; Pulmonary emboli = 1; Congested larynx, trachea and bronchi = 1; Aspiration of gastric contents = 2; Haemophilus influenzae and haemophilus parainfluenzae pneumonia = 1; Enlarged liver = 1; Fatty change of liver = 2; Congested liver = 1; Renal calculi = 1; Distended bladder = 1; Thyroid disease = 1; Ulcerative colitis = 1; Chronic alcoholism = 1; Mitragynine/kratom toxicity/toxic effects = 18; Mitragynine/kratom intoxication = 6; Kratom overdose = 2; Combined effects of mitragynine and 7-hydroxymitragynine = 1

Risk

- Poly-drug users
- Underlying diseases

PK study: dose 23 mg - the highest Cmax: 0.105 mg/L

Trakulsrichai *et al*. Drug Des Devel Ther, 2015

MG: 8.7 to 1800 ng/mL in cases with drug toxicity as the cause of death Schmitt *et al*, 2021

Case Reports > Am J Forensic Med Pathol. 2021 Dec 1;42(4):335-340.
doi: 10.1097/PAF.0000000000000691.

The Causes of Death and Pathological Findings of Kratom Users: A 5-Year Retrospective Analysis

Worrapat Jittasopa [1], Smith Srisont

Abstract

Kratom is a psychoactive substance in Thailand. The major psychoactive chemical component of Kratom is mitragynine. This study aims to elucidate the characteristics and pathologies of autopsied cases where mitragynine was present and quantify the amounts of mitragynine. The autopsy reports in which the blood samples were positive for mitragynine were selected in Ramathibodi Hospital between January 2015 and December 2019. Data from autopsy reports comprised sex, age, circumstances of death, pathological findings, other substances, causes of death, and mitragynine concentrations. Mitragynine was quantitatively analyzed using liquid chromatography-mass spectrometry/mass spectrometry. Twenty-four cases from 2160 autopsy cases were found to be positive for mitragynine. The most commonly observed pathological findings were pulmonary edema (7 cases) and coronary atherosclerosis (6 cases). Antihistamine (8 cases), ethanol (4 cases), and amphetamine (4 cases) were commonly found. The mitragynine concentrations were 0.0035 to 3.6 mg/L (median 0.069). One interesting case involved a 43-year-old man whose pathological findings showed chronic asthma with a high concentration of mitragynine in the blood (3.6 mg/L), although no other substances were detected. In conclusion, the use of mitragynine may be a direct or indirect cause of death, whereas the lethal concentration has yet to be clearly determined.

Mahidol University
Wisdom of the Land

Contents lists available at ScienceDirect

Preventive Medicine

journal homepage: www.elsevier.com/locate/ypmed

Risk of death associated with kratom use compared to opioids

Jack E. Henningfield[a,b,*], Oliver Grundmann[c], Jane K. Babin[d], Reginald V. Fant[a], Daniel W. Wang[a], Edward J. Cone[a,b]

[a] PinneyAssociates, Bethesda, MD, United States of America
[b] The Johns Hopkins University School of Medicine, United States of America
[c] College of Pharmacy, Department of Medicinal Chemistry, University of Florida, Gainesville, FL, United States of America
[d] The Law Office of Jane K. Babin, PC, San Diego, CA, J.D. University of San Diego School of Law, J.D. Law, Purdue University, United States of America

Table 2
Death rate and relative risks per estimated number of kratom users and nonmedical opioid users.

Drug class	Number of deaths "associated with kratom by the in FDA in 2017"	Use in past year	Death rate for past year use	Risk relative to kratom use
Kratom (estimate avg. 4 g/day/user)	6[a] (2017)	16,250,254[b]	0.000000369	1
Kratom (estimate avg. 6 g/day/user)	6[c] (2017)	10,833,502[d]	0.000000554	1
Any opioid	47,600[e] (2017)	11,401,000[f]	0.0042	11,382.1:1
Heroin	15,482[g] (2017)	324,000[h]	0.048	130,081.3:1

- The risk of overdose death: > 1000 times greater for opioids than for kratom

THE AMERICAN JOURNAL OF DRUG AND ALCOHOL ABUSE
https://doi.org/10.1080/00952990.2020.1836185

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

A comparative analysis of kratom exposure cases in Thailand and the United States from 2010-2017

Christian Davidson[a], Dazhe Cao[a,b], Taylore King[a], Stephanie T. Weiss[a,b], Sunun Wongvisavakorn[c], Natthasiri Ratprasert[c], Satariya Trakulsrichai[c], and Sahaphume Srisuma[c]

[a]Department of Emergency Medicine, Division of Medical Toxicology, University of Texas Southwestern Medical Center, Dallas, TX, USA; [b]North Texas Poison Center, Parkland Health and Hospital System, Dallas, TX, USA; [c]Ramathibodi Poison Center, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

ABSTRACT

Background: Interest in the Southeast Asian natural remedy kratom has increased in Western countries recently, along with increasing concern over its potential toxic effects.

Objective: To describe and compare demographics, common co-exposure substances, clinical effects, treatments, and medical outcomes of kratom "abuse" exposures in the United States (US) and Thailand.

Methods: This is a retrospective analysis of kratom "abuse" exposures, defined as use when attempting to gain a psychotropic effect, reported to the National Poison Data System (NPDS) in the US and the Ramathibodi Poison Center (RPC) in Thailand from 2010 to 2017. Multivariate analysis identified risk factors for severe medical outcomes, defined as both ICU admissions and death.

Results: Nine-hundred-twenty-eight cases were included (760 from NPDS and 168 from RPC). A greater proportion of cases involved co-exposures in Thailand (64.8% versus 37.4%; odds ratio [OR] = 3.10, 95% confidence interval [CI] = 2.15–4.47, $p < .01$). Both countries had a similar prevalence of opioid and benzodiazepine co-ingestions, but the US had more co-ingestions with other sedatives (4.6% versus 0%, OR = 0, 95% CI = 0–0.47, $p < .01$). Common clinical effects included tachycardia (30.4%), agitation/irritability (26.2%), and drowsiness/lethargy (21.1%). Six deaths occurred, including one single-substance exposure in the US, three multiple-substance exposures in the US, and two multiple-substance exposures in Thailand. IV fluid administration was provided more frequently in the US (OR = 18.82, 95% CI = 5.85–60.56, $p < .01$).

Conclusions: Despite lower frequencies of co-ingestants overall, US kratom abuse exposures yielded greater clinical severity. This disparity may be attributable to differences in the products labeled "kratom," greater sedative co-exposures in the US, and/or differences in population genetics or use patterns.

ARTICLE HISTORY
Received 23 February 2020
Revised 4 July 2020
Accepted 9 July 2020

KEYWORDS
Kratom; Mitragyna speciosa; mitragynine; 7-hydroxymitragynine; use; co-ingestion

Table 1. Characteristics of kratom abuse exposures reported to National Poison Data System and Ramathibodi Poison Center during 2010 to 2017.

Characteristics	Number of cases; n (%) NPDS exposure (760 cases)	RPC exposure (168 cases)	Total exposure (928 cases)	*P* value
Age (years) (Median [interquartile range])	28 (22–35)	23 (19–35)	27 (22–35)	NS
Age group (years)				<0.01
0 < 20	84 (11.1)	50 (29.8)	134 (14.4)	
20 < 30	335 (44.1)	64 (38.1)	399 (36.5)	
30 < 40	211 (27.8)	22 (13.1)	233 (25.1)	
40 < 50	66 (8.7)	11 (6.6)	77 (8.3)	
50+	43 (5.7)	21 (12.5)	64 (6.9)	
Unknown	21 (2.8)	0 (0)	21 (2.3)	
Gender				<0.01
Male	592 (77.9)	160 (95.2)	752 (81.0)	
Female	166 (21.8)	8 (4.8)	174 (18.8)	
Unknown	2 (0.3)	0 (0)	2 (0.2)	
Route of exposure				
Aspiration	1 (0.1)	0 (0)	1 (0.1)	NS
Dermal	1 (0.1)	0 (0)	1 (0.1)	NS
Ingestion	640 (84.2)	166 (98.8)	806 (86.9)	NS
Inhalation/nasal	78 (10.3)	14 (8.3)	92 (9.9)	<0.01
Other	3 (0.4)	0 (0)	3 (0.3)	NS
Parenteral	15 (2.0)	0 (0)	15 (1.6)	NS
Unknown	83 (10.9)	0 (0)	83 (8.9)	NS
Chronicity				<0.01
Acute	477 (62.8)	100 (59.5)	577 (62.2)	
Acute on chronic	85 (11.2)	24 (14.3)	109 (11.7)	
Chronic	106 (13.9)	44 (26.2)	150 (16.2)	
Unknown	92 (12.1)	0 (0)	92 (9.9)	
Number of substances				<0.01
Single-substance	476 (62.6)	59 (35.2)	535 (57.7)	
Multi-substance	284 (37.4)	109 (64.8)	393 (42.3)	

NPDS: National Poison Data System. RPC: Ramathibodi Poison Center. NS: non-significant p value ≥ 0.05.

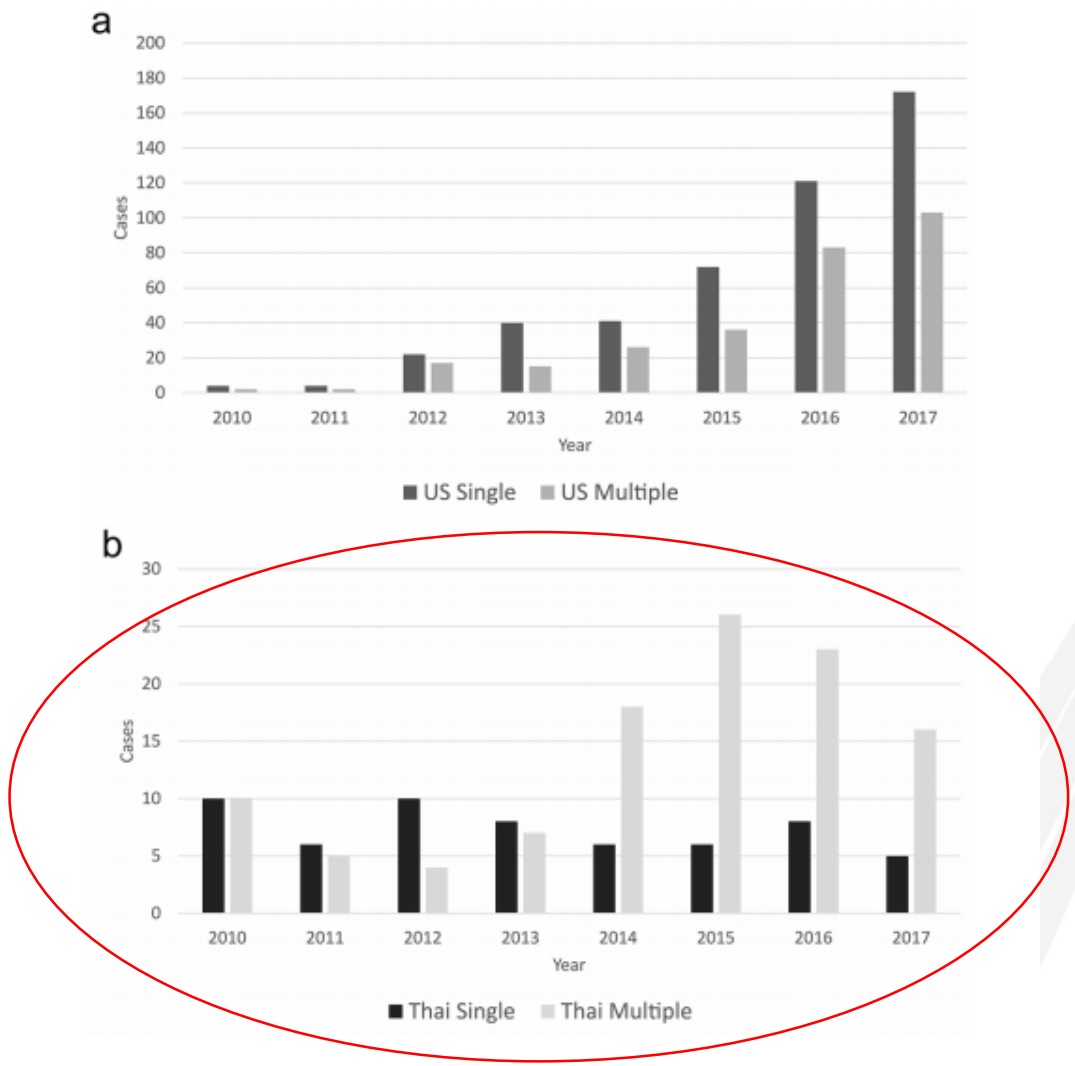


Figure 1. (a) Kratom abuse exposure cases reported to the National Poison Data System (US) by Year, 2010–2017 (single and multiple substance exposures). (b) Kratom abuse exposure cases reported to Ramathibodi Poison Center (Thailand) by Year, 2010–2017 (single and multiple substance exposures).

Table 2. Common co-ingested substances in kratom abuse exposures reported to National Poison Data System and Ramathibodi Poison Center during 2010 to 2017.

	Number of cases; n (%)					
Substance	NPDS exposure (760 cases)	RPC exposure (168 cases)	Total exposure (928 cases)	Odds ratio*	95% CI	*P* value
Ethanol	65 (8.6)	15 (8.9)	80 (8.6)	1.04	0.54–1.91	NS
Opioids	56 (7.4)	13 (7.7)	69 (7.4)	1.05	0.52–2.01	NS
Stimulants	22 (2.9)	36 (21.4)	58 (6.3)	9.15	5.04–16.82	<0.01
Other	34 (4.5)	13 (7.7)	47 (5.1)	1.79	0.85–3.58	NS
Marijuana	33 (4.3)	18 (10.7)	51 (5.5)	2.64	1.36–4.98	<0.01
Benzodiazepine	35 (4.6)	7 (4.2)	42 (4.5)	0.90	0.33–2.11	NS
Sedatives	35 (4.6)	0 (0)	35(3.8)	0	0–0.47	<0.01
Amphetamines	14 (1.8)	15 (8.9)	29 (3.1)	5.2	2.3–11.9	<0.01
Hallucinogens	19 (2.5)	0 (0)	19 (2.0)	0	0–0.90	0.03
Cough and cold	2 (0.3)	18 (10.7)	20 (2.2)	45.48	10.65–405.89	<0.01
Dextromethorphan	15 (2.0)	4 (2.4)	19 (2.0)	1.21	0.28–3.87	NS

NPDS: National Poison Data System. RPC: Ramathibodi Poison Center. *Odds ratio more than 1 indicates a greater proportion of occurrences in RPC group. 95% CI: 95% confident interval. NS: non-significant p value ≥ 0.05.

- Both countries had a similar prevalence of opioid and benzodiazepine co-ingestions, but the US had more co-ingestions with other sedatives

Table 7. Multivariate analysis of common clinical effects of kratom abuse exposure.

Clinical effects and factors	Odds Ratio	*P* value	95% Confident interval
Agitation/irritability			
Country*	0.49	<0.01	0.31–0.77
Age	1.02	0.01	1.00–1.03
Cocaine	8.00	0.01	1.59–40.21
Hallucinogens	3.69	<0.01	1.42–9.56
Coma			
Country*	0.25	0.02	0.08–0.80
Opioids	3.40	<0.01	1.65–7.00
Sedatives	3.64	<0.01	1.50–8.86
Confusion			
Country*	0.40	<0.01	0.22–0.71
Dextromethorphan	2.97	0.03	1.10–8.00
Hallucinogens	3.07	0.02	1.18–7.96
Other Substances	3.15	<0.01	1.63–6.11
Drowsiness/lethargy			
Country*	0.47	<0.01	0.29–0.78
Benzodiazepines	3.90	<0.01	2.04–7.44
Opioids	2.56	<0.01	1.51–4.35
Other Substances	2.22	0.02	1.16–4.28
Sedatives	2.73	0.01	1.35–5.53
Hallucinations/delusions			
Country*	0.35	0.03	0.14–0.89
Hallucinogens	3.26	0.05	1.03–10.38
Herbal Remedies	4.39	0.01	1.44–13.41
Other Substances	3.51	<0.01	1.55–7.93

NS: non-significant p value ≥ 0.05. *OR<1 indicates a greater proportion of occurrences in the US

- Six deaths: 1 single-substance exposure, 3 multiple-substance exposures in the US, 2 multiple-substance exposures in Thailand
- Despite lower frequencies of co-ingestants overall, US kratom abuse exposures yielded greater clinical severity
- This disparity may be attributable to differences in the products labeled "kratom," greater sedative co-exposures in the US, and/or differences in population genetics or use patterns

Table 5. Deaths and critical care unit admission associated with kratom abuse exposures reported to National Poison Data System and Ramathibodi Poison Center during 2010 to 2017.

	NPDS exposure (760 cases)			RPC exposure (168 cases)			
Medical outcome	Single substance exposure (476 cases)	Multiple substance exposure (284 cases)	Total (760 cases)	Single substance exposure (59 cases)	Multiple substance exposure (109 cases)	Total (168 cases)	Total (928 cases)
Death	1 (0.2)	3 (1.1)	4 (0.5)	0	2 (1.8)	2 (1.2)	6 (0.7)
Survival after Intensive care unit admission	64 (13.4)	81 (28.5)	145 (19.1)	0	1 (0.9)	1 (0.6)	146 (15.7)

NPDS: National Poison Data System and RPC: Ramathibodi Poison Center

Table 6. Multivariate analysis of factors associated with deaths or intensive care admission in kratom abuse exposures reported to National Poison Data System and Ramathibodi Poison Center.

Factors	Odds ratio	*P* value	95% Confident interval
Cases reported by NPDS (United States)	18.82	<0.01	5.85–60.56
Multiple-substance exposure	2.79	<0.01	1.92–4.04

Multivariate analysis included age, gender, countries, and number of substances ingested.

Mahidol University
Wisdom of the Land

Withdrawal signs and symptoms

- Aggression, tearfulness, rhinorrhea, jerky movements, irritability, yawning, myalgias, diarrhea, arthralgias, myalgia, insomnia, fatigue, chest discomfort, hostility, aggression

Trakulsrichai *et al.* J Psychoactive Drugs, 2013

- Milder than opiates

McWhirter & Morris. Eur Addict Res, 2010

- Symptoms begin 12 hours after last use in most

Stanciu *et al.* J Psychoactive Drugs, 2019; Boyer *et al*. Addiction, 2008; Galbis-Reig 2016; Mackay and Abrahams 2018; Manda *et al*. Planta Med, 2014; McWhirter & Morris. Eur Addict Res, 2010

- Withdrawal intensity: predicted by duration, frequency, daily amount of use

Saingam *et al*. J Psychoactive Drugs, 2016

Mahidol University
Wisdom of the Land

Kratom products

- Kratom products: ~ 2% MG, none or 0.01%- 0.02% 7-OH-MG

Kruegel & Grundmann. Neuropharmacology., 2018

- Mixing with others: "Krypton" powdered Kratom leaves, O-desmethyltramadol

Kronstrand *et al*. J Anal Toxicol, 2011

- Adulteration: 7-OH-MG higher than in leaves

Lydecker *et al. J Med Toxicol* , 2016

- Contamination: Salmonella

: Toxic metals - nickel and lead

Dixon *et al*. Ann Clin Lab Sci. 2019; https://www.fda.gov/news-events/public-health-focus/laboratory-analysis-kratom-products-heavy-metals;
https://www.fda.gov/food/outbreaks-foodborne-illness/fda-investigated-multistate-outbreak-salmonella-infections-linked-products-reported-contain-kratom;
https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-risk-heavy-metals-including-nickel-and-lead-found-some

: Bacteria and fungi, Ni, Pb, Cr

Walter C Prozialeck *et al.* Int J Environ Res Public Health . 2020

Mahidol University
Wisdom of the Land

Diagnosis/Laboratories

Human/animals

- HPLC, GC-MS, LC-MS
  - LC/MS: detect in serum and urine following "kratom" use for 2 weeks

Kapp et al. J Med Toxicol. 2011; Micromedex

Labmedica.com

- Mitragynine (Kratom)* - ELISA - Randox Toxicology
- Development of an immunochromatographic strip
- Monoclonal antibody against MG as a recognition probe

Limsuwanchote *et al.* Drug Test Ana , 2017

MG in Kratom plant material

- LC/MS, IMS, HPLC, GC/MS
- Direct analysis in real time-high-resolution mass spectrometry (DART-HRMS)

Fowble & Musah. Forensic Sci Int. 2019

Mahidol University
Wisdom of the Land

Poisoning

- **Supportive & symptomatic treatments**
- Animal literatures: conflicting results regarding the efficacy of opioid receptor antagonists in reversing Kratom effects
- Successful naloxone reversal

Overbeek *et al*. Clin Pract Cases Emerg Med. 2019

- Report: Intravenous Lipid emulsion

AggarwalJ Intensive Care Soc. 2018

Mahidol University
Wisdom of the Land

Withdrawal symptoms

- **Supportive & symptomatic treatments**

Reports: treatments as opioid withdrawal

- Dihydrocodeine and lofexidine

McWhirter & Morris. Eur Addict Res , 2010

- Symptom-triggered clonidine therapy and scheduled hydroxyzine

Galbis-Reig. WMJ., 2016

- Buprenorphine-Naloxone Maintenance

Buresh M. J Addict Med. 2018; Diep *et al*. A A Pract. 2018; Schmuhl *et al*. Subst Abus. 2019; Kalin et al. J Opioid Manag 2020; Abdullah *et al*. Curr Drug Targets. 2020

Patients using <20 g of kratom/d: 4/1 mg-8/2 mg , >40 g/d: 12/3 mg-16/4 mg of buprenorphine-naloxone/day

Weiss & Douglas. J Addict Med. 2020

- Mostly buprenorphine but also a few cases of naltrexone and methadone

Stanciu *et al*. WMJ. 2021

Mahidol University
Wisdom of the Land

Pharmacotherapy for Management of 'Kratom Use Disorder': A Systematic Literature Review With Survey of Experts

Cornel Stanciu, MD, MRO; Saeed Ahmed, MD; Bryan Hybki, MD; Thomas Penders, MS, MD; David Galbis-Reig, MD

ABSTRACT

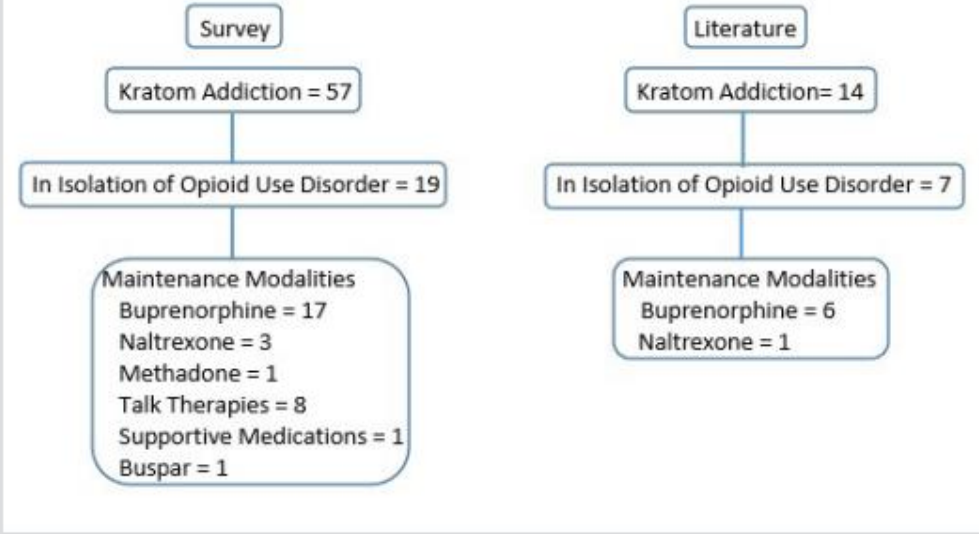
Objectives: An increasing number of Americans are turning to kratom for self-management of various pain, anxiety, and mood states and as an opioid substitute. Addiction to this unique botanical develops and carries a high relapse risk and, to date, there are no guidelines on how to maintain long-term abstinence. The aim of this article is to compile all available information on management of "kratom use disorder" (KUD)—as coined here—from the literature, with evidence from the clinical practice of expert addictionologists in an attempt to develop a standard of care consensus.

Methods: A systematic literature search was conducted to capture all relevant cases pertaining to maintenance treatment for KUD. Results were supplemented with case reports and scientific posters gleaned from reliable online sources and conference proceedings. Additionally, a survey of members of the American Society of Addiction Medicine (ASAM) was administered to assess the practice patterns of experts who treat patients with KUD in isolation of a comorbid opioid use disorder (OUD).

Results: Based on a literature review, 14 reports exist of long-term management of KUD, half of which do not involve a comorbid OUD. Pharmacological modalities utilized include mostly buprenorphine but also a few cases of naltrexone and methadone, all with favorable outcomes. This is supported by the results of the expert survey, which demonstrated that those who have managed KUD in isolation of a comorbid OUD reported having utilized buprenorphine (89.5%), as well as the other medications for opioid use disorder (MOUD).

Conclusions: This is the first comprehensive review to examine the existing literature referring to management of KUD in combination with a survey of current experts' clinical consensus regarding pharmacological management. Based on this information, it seems reasonable that the indication for MOUD should be extended to cases of moderate to severe KUD.

Figure 3. Pharmacological Modalities for Managing Kratom Use Disorder When Found in Isolation of Opioid Use Disorder



Mahidol University
Wisdom of the Land

Possibilities of medical use

- Controversies
- Potential therapeutic use **OR** dangerous & addictive substance of abuse
- The unique pharmacologic profile, but high abuse liability, potential for drug interactions and toxicities including deaths

Mahidol University
Wisdom of the Land

Possibilities of medical use

Kratom

"Multi-Target"

"Atypical opioids"

- **Opioid receptor** (μ) → **Opioid substitute**, **Addiction/withdrawal**, **Pain killer**
- α2 adrenergic receptor → **Opioid substitute**, **Addiction/withdrawal**, **Pain killer**
- Descending noradrenergic/ serotonergic pathway → **Pain killer**
- Neuroendocrine HPA axis systems → Antidepressant
- Dopamine/κ-opioid receptor → Antidepressant
- COX-2 pathway → Anti-inflammation

Mahidol University
Wisdom of the Land

Kratom extract/Mitragynine

Opioid substitute or Analgesics:

- Agonists: opioid, alpha-2 adrenergic receptors **"Buprenorphine + clonidine"**
- PK: long T1/2, linear ➡ dose adjustment
- Tolerance slower than morphine, lower potential for addiction

Váradi *et al.* J Med Chem, 2016; Fakurazi *et al.* Molecules, 2013; Hemby *et al*. Addict Biol. 2019; Meepong & Sooksawate. TJPS, 2019

- Fewer lethal side effects and toxicities

  attenuated respiratory depression/constipation compared to morphine in several animal species

Macko *et al*. Arch Int Pharmacodyn Ther, 1972

- Easy to manage withdrawal symptoms
- Dose of MG: ~ 68–75 mg, ~ 214.29 mg

Vicknasingam *et al*. Int J Drug Policy,2010; Saref *et al.* J Ethnopharmacol. 2019

- **"Harm reduction agent"**

Mahidol University
Wisdom of the Land

Kratom extract/Mitragynine

- **Alcohol substitute**

Kumarnsit *et al*. Fitoterapia, 2007; Cheaha *et al*. Phytomedicine, ; Gutridge *et al,* 2021

- **Amphetamine substitute**

In Thailand, M. speciosa preparations are consumed by the three wheeled motorized ‘taxis’ as an amphetamine substitute

The Encyclopedia of Psychoactive Plants: Ethnopharmacology and Its Applications (Schuldes, 1995); Hassan *et al.* Neurosci Biobehav Rev, 2013

- **Antidepressant**

Kumarnsit et al. Neurosci Lett, 2007

- **Antidepressant and Antipsychotic**

Johnson *et al.* Yale J Biol Med. 2020

- Structurally modified derivatives: e.g. 9-hydroxycorynantheidine (MG), MGM-9, MGM- 15, MGM-16 (7-OH-MG): higher potency, lesser side-effects

Matsumoto *et al*. Life Sci, 2006; Chin & Mark-Lee. Curr Drug Targets, 2018

Mahidol University
Wisdom of the Land

Conclusions

- Emerging Drugs of Abuse: local to worldwide
- Interesting pharmacology, dose-dependent: stimulant, opiate effects
- Toxicities, addiction and withdrawal
- Clinical differences between Asian and western countries:
  Purposes, pattern of use, products
- Mainly a substance of abuse, however; possibility of drug development
  - More effective opioid substitute or pain killer
  - Fewer lethal side effects and toxicities, easy to manage withdrawal
- More well-controlled clinical trials and scientific research works

Mahidol University
Wisdom of the Land

Thank you for your attention

Sawasdee