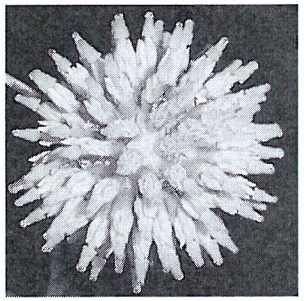
HANDOUT 2

Kratom Science University of Florida Study Results

Christopher R. McCurdy, BSPh, PhD, FAAPS
The Frank A. Duckworth Eminent Scholar Chair
Professor of Medicinal Chemistry & Pharmaceutics
College of Pharmacy, University of Florida
Director, UF CTSI Translational Drug Development Core
AAPS President, 2017-2018

Mitragyna Speciosa

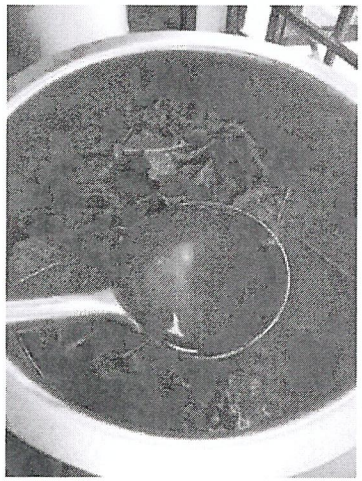


- FAMILY: Rubiaceae
- GENIUS: Mitragyna
- SPECIES: speciosa
- Tree found in tropical Southeast Asia, particularly Thailand and Malaysia.
- Referred to as "Kratom" in Thailand and "Biak Biak or Ketum" in Malaysia.
- Contains over 40 alkaloids that have been isolated to date.[1]

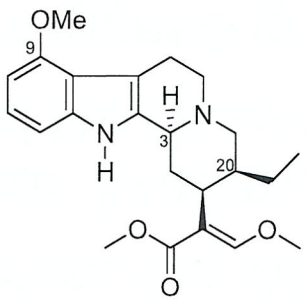
[1] Adkins, J.E.; Boyer, E.W.; McCurdy, C.R. *Curr. Topics Med. Chem.*, **11**, 1165-75 (2011)

UF | College of Pharmacy
UNIVERSITY of FLORIDA

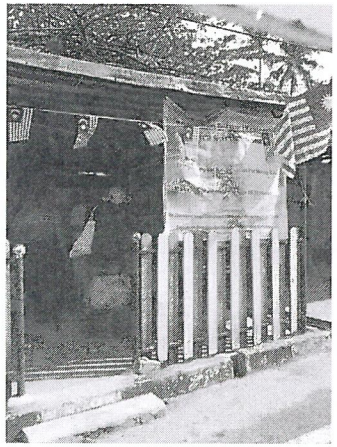
Kratom Use in Southeast Asia



- Kratom tea is used by field workers to relieve pain, as a stimulant to improve work capacity, and to reduce opioid withdrawal[1]
- Recently, polydrug users (METH) are using kratom to reduce use[2]
- The predominant active agent in Kratom is mitragynine (MG)



Mitragynine

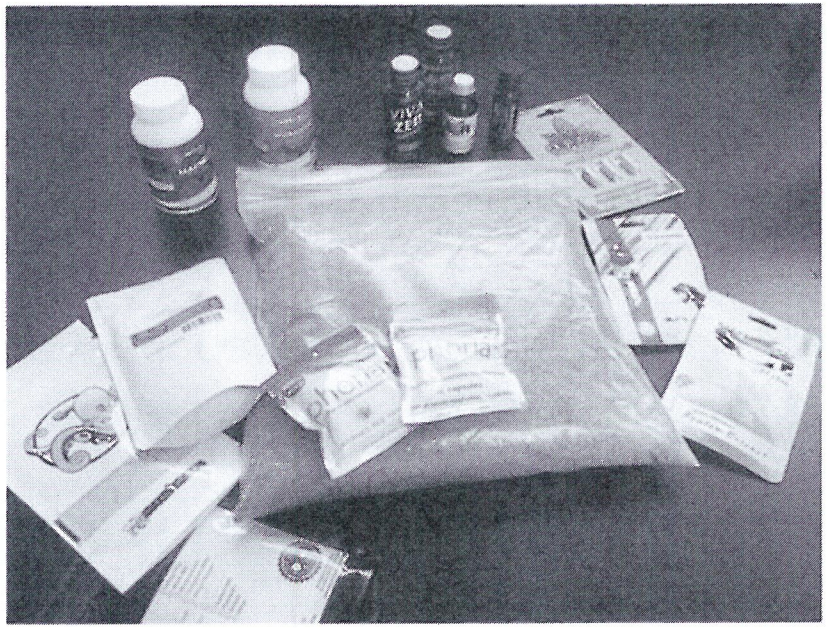


[1] Jansen K.L.R., Prast C.J. *J. Ethnopharmacology*. **23**, 115-119 (1988)
[2] Singh, D. et al. *J. Ethnopharmacology.* **249**, 112462 (2020)

UF | College of Pharmacy
UNIVERSITY of FLORIDA

Kratom Use in USA

- Widely available across the internet and smoke/vape shops
- June 2019*: American Kratom Association reported 1950 metric tons exported to US every month
- Typical dose 3-5g# suggesting >15 million users



UF | College of Pharmacy
UNIVERSITY of FLORIDA

Kratom = Threat or Therapeutic

- Anecdotally used for chronic pain, mood elevation, opioid use disorder
- Adulterated or contaminated products reported
- Claims that kratom is severely addictive and deadly
- World Health Organization / US Food and Drug Administration
  - Ongoing talks regarding therapeutic vs. harm profiles

Kratom illegal in 6 states (Alabama, Arkansas, Indiana, Rhode Island, Vermont, Wisconsin)

UF College of Pharmacy UNIVERSITY of FLORIDA

Therapeutic Potential of Kratom

- Opioid Detoxification: Kratom has potential to replace several medications used during detoxification (opioid, adrenergic, analgesic and anxiolytic). This would improve medication adherence and chances of completing detoxification.

- Medication Assisted Therapy: Kratom is informally used to reduce opioid use. Kratom withdrawal is mild (<9 on SOWS scale). Polydrug users report Kratom also reduces methamphetamine use.

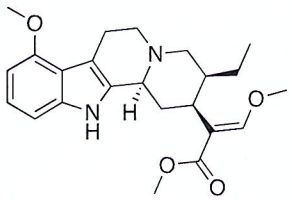
- THE LACK OF A STANDARDIZED PRODUCT HAS PREVENTED RIGOROUS CLINICAL TRIALS TO EVALUATE THESE CLAIMS

UF | College of Pharmacy
UNIVERSITY of FLORIDA

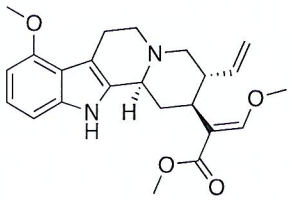
Mitragyna speciosa growing at the University of Florida MREC

UF | College of Pharmacy
UNIVERSITY *of* FLORIDA

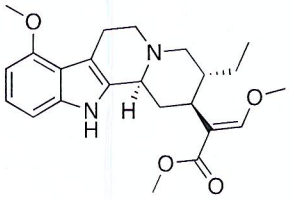
Isolation of kratom alkaloids



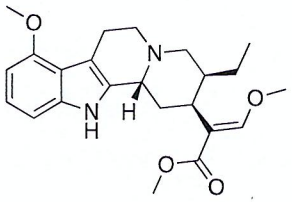
Mitragynine
66%



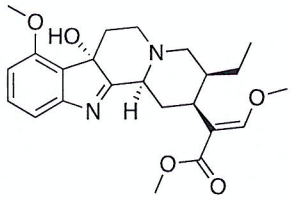
Paynantheine
9%



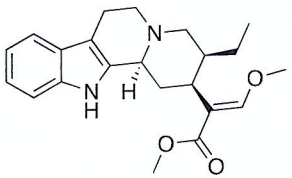
Speciogynine
7%



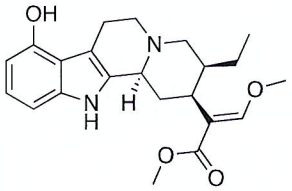
Speciociliatine
~1%



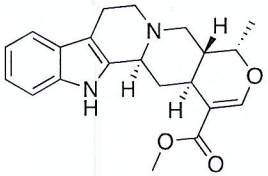
7(-hydroxymitragynine
~2%



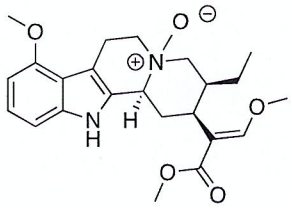
Corynantheidine
<1%



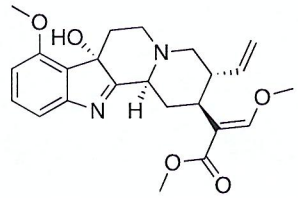
9-Hydroxycorynantheidine
<1%



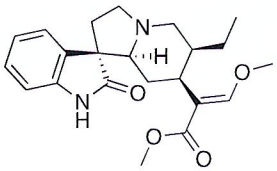
Ajmalicine
<1%



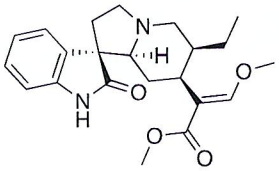
Mitragynine N-oxide
<1%



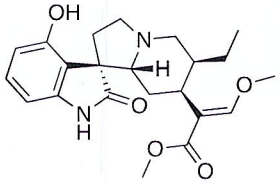
7α-hydroxypaynantheine



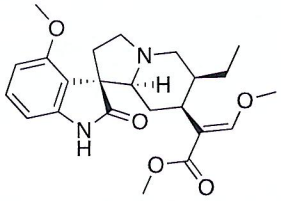
Corynoxine A
<1%



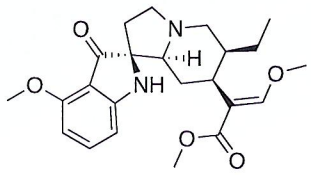
Corynoxine B
<1%



Isospeciofoline
<1%



Mitragynine oxindole B
<1%



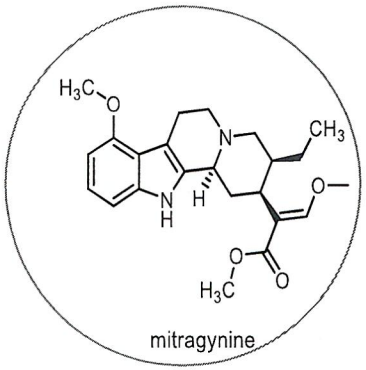
Mitragynine pseudoindoxyl

UF | College of Pharmacy
UNIVERSITY of FLORIDA

Binding and functional effects of mitragynine

- Mitragynine has partial agonist effects at the μ opioid, α_{1A} and α_{1D} adrenergic receptors
- Poison Control Centers: Kratom overdoses resemble stimulants (not opioids)

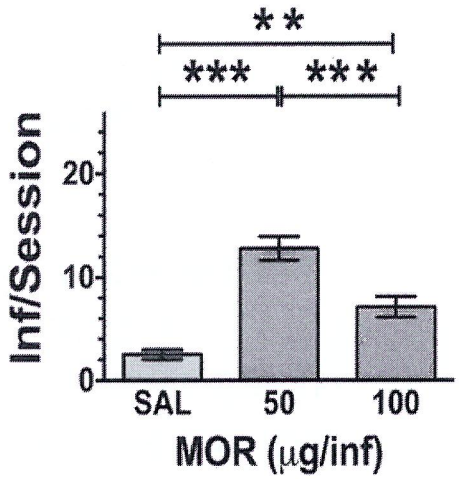
Target	Ki (nM)	Agonist/ Antagonist
μ	136.0	Partial agonist
κ	157	Antagonist
δ		Antagonist
α_{1A}	1,660	Partial agonist
α_{1B}	2,490	Antagonist
α_{1D}	4,610	Partial agonist
α_{2A}	3,590	ND
α_{2B}	9,190	ND
α_{2C}	1,400	ND



Obeng, Samuel, et al. *J Med Chem.* 63 (2019). 433-439.

UF College of Pharmacy UNIVERSITY of FLORIDA

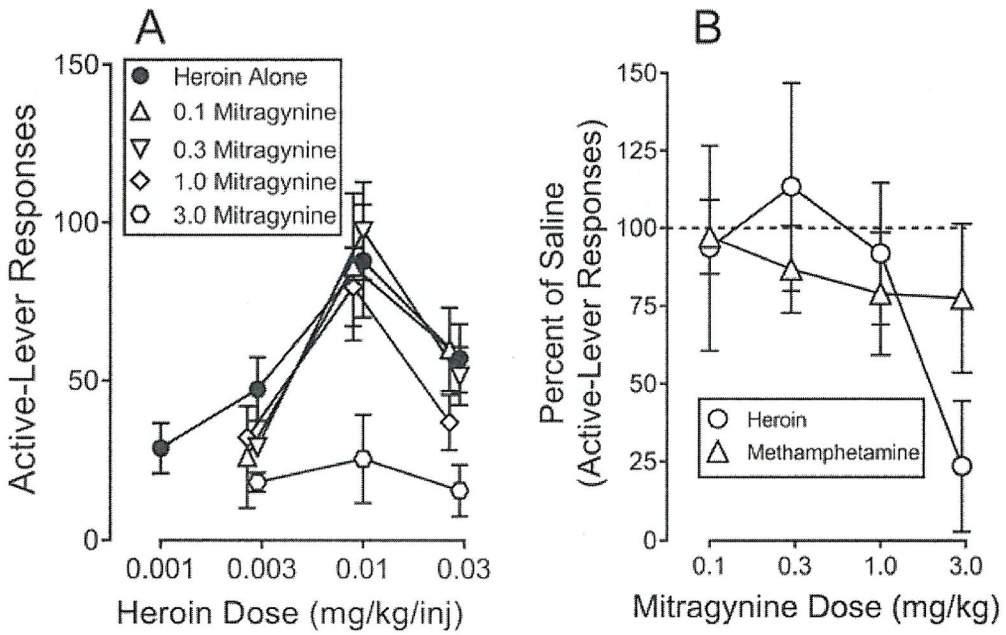
Substitution of MG and 7-HMG for morphine



Hemby SE, et al. *Addict Biol*. 2018 June 27.

UF | College of Pharmacy
UNIVERSITY of FLORIDA

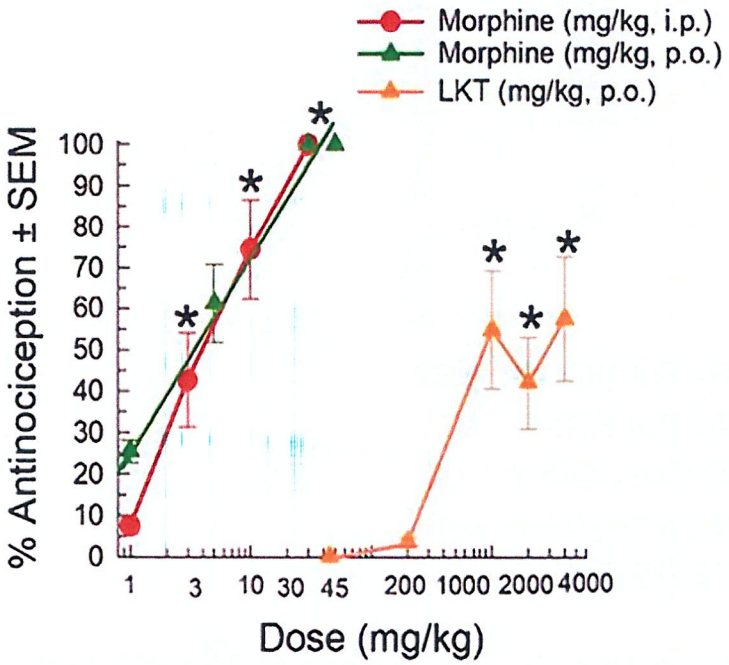
MG administration *reduced* heroin self-administration



Yue K, Kopajtic TA, Katz JL. *Psychopharmacology* (Berl) 2018 Oct; 235(10):2823-2829

UF | College of Pharmacy
UNIVERSITY of FLORIDA

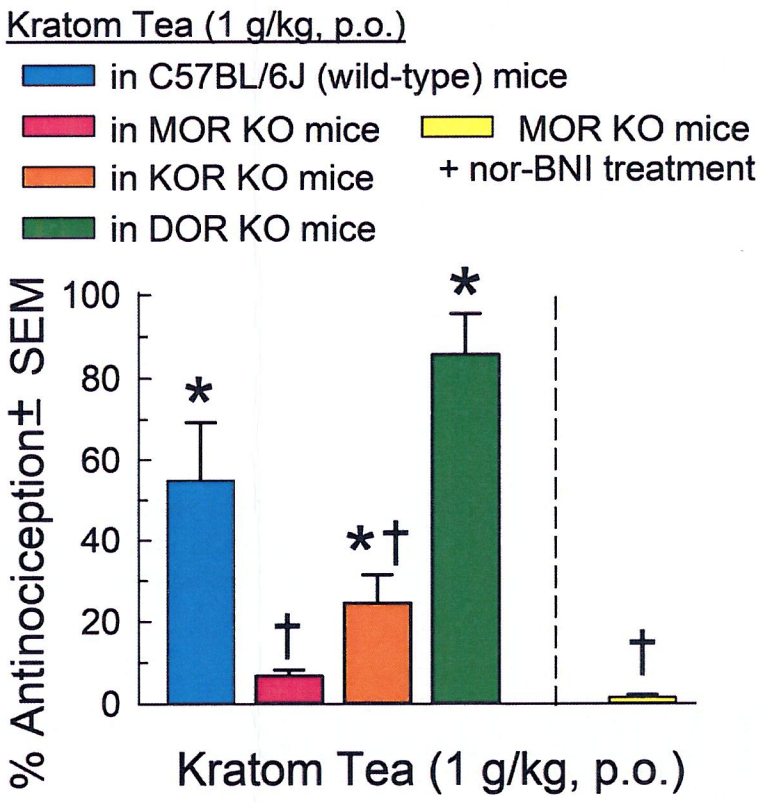
Antinociception with LKT



Wilson, L.L. et al, Drug and Alcohol Dependence, 2020 Nov 1;216:108310

UF College of Pharmacy
UNIVERSITY of FLORIDA

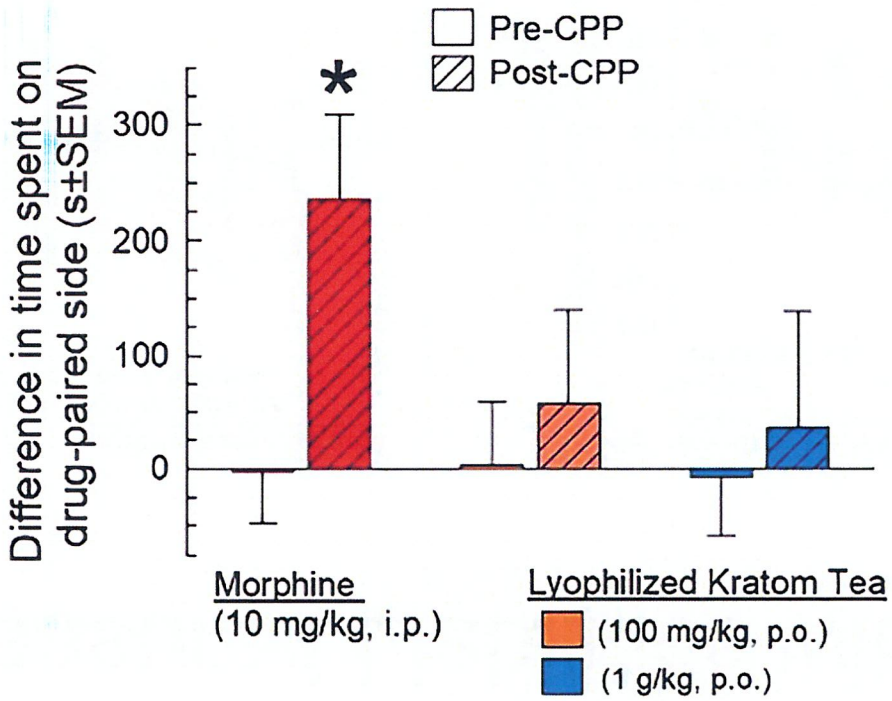
LKT analgesia is mediated through MOR & KOR



Wilson, L.L. et al, Drug and Alcohol Dependence, 2020 Nov 1;216:108310

UF College of Pharmacy
UNIVERSITY of FLORIDA

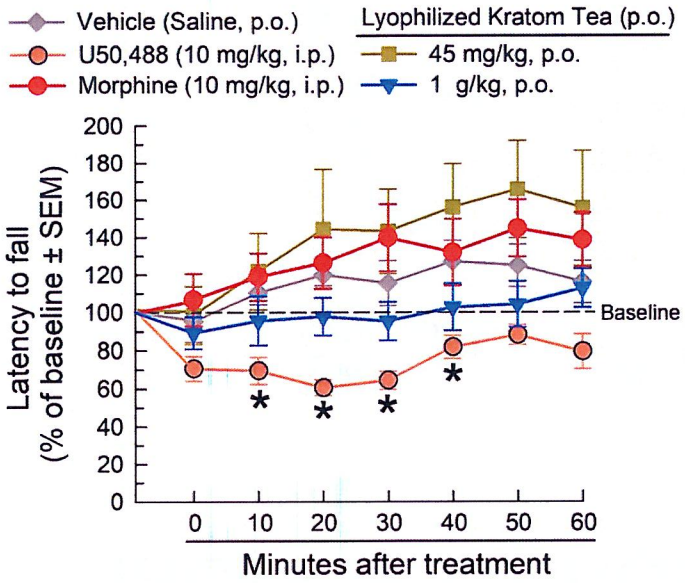
LKT lacks a Conditioned Place Preference

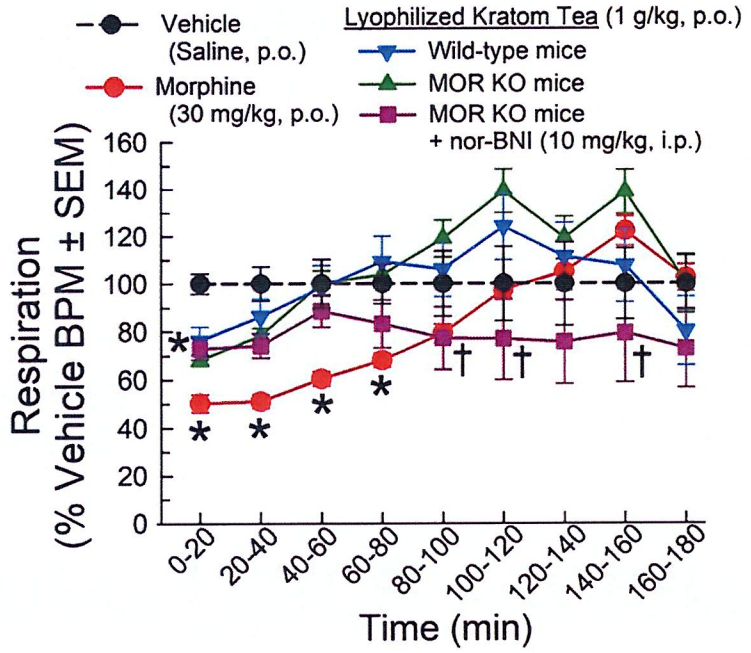


Wilson, L.L. et al, Drug and Alcohol Dependence, 2020 Nov 1;216:108310

UF College of Pharmacy
UNIVERSITY of FLORIDA

Measured Liabilities with LKT

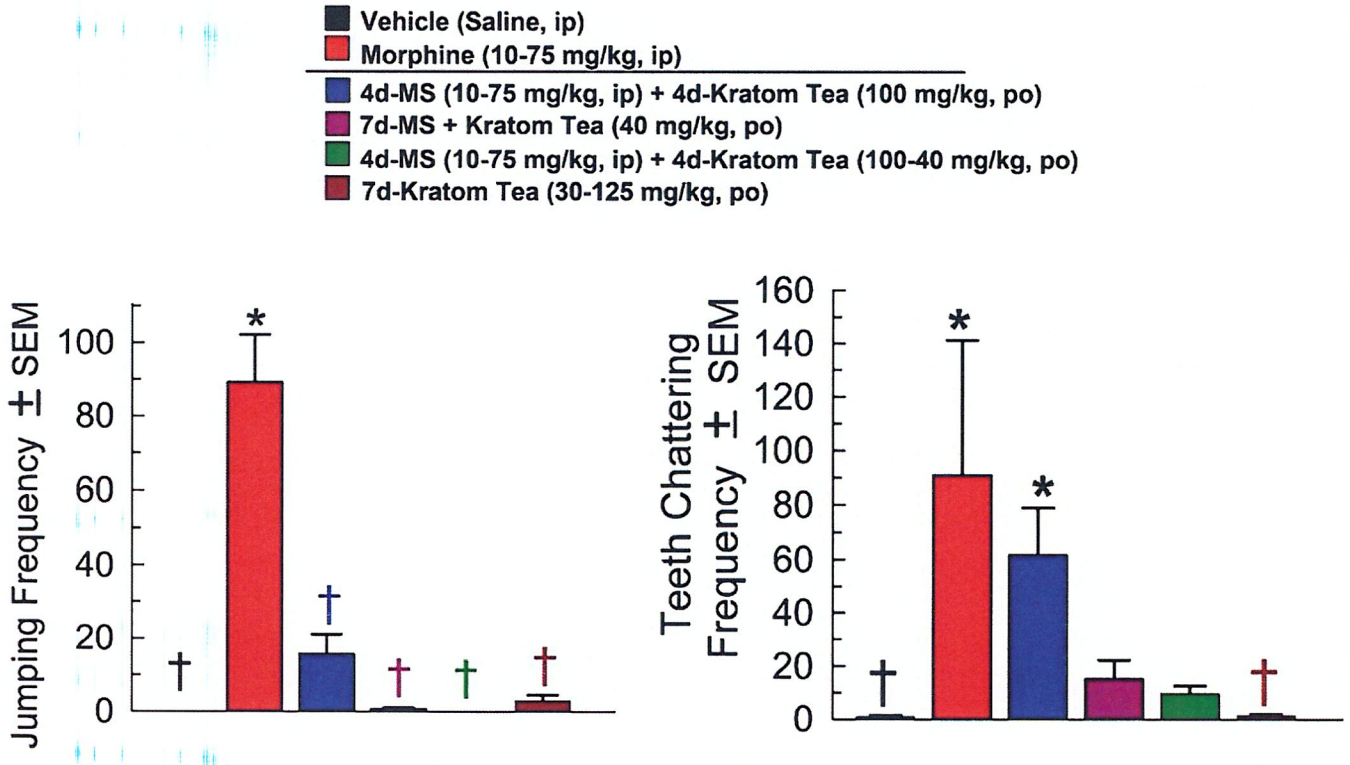




Wilson, L.L. et al, Drug and Alcohol Dependence, 2020 Nov 1;216:108310

UF College of Pharmacy
UNIVERSITY of FLORIDA

Reduction of Naloxone PPT Withdrawal



Wilson, L.L. et al, Drug and Alcohol Dependence, 2020 Nov 1;216:108310

UF College of Pharmacy UNIVERSITY of FLORIDA

Assessing opioid physical dependence with naloxone precipitation: Less withdrawal after repeated mitragynine treatment (5 days)

Measure:	Saline	Treatment (twice/d for 4 d +1) Morphine	Mitragynine	Statistical analysis: (One-way ANOVA)
Forepaw Tremor	20.2 ± 8.0	9.8 ± 3.7	29.2 ± 10.1	$F_{(2,27)}$ =1.56, p=0.23
Wet dog shakes	0.8 ± 0.51	1.0 ± 0.45	0.6 ± 0.22	$F_{(2,27)}$ =0.24, p=0.79
Straightening	5.7 ± 2.33	3.7 ± 1.22	2.7 ± 1.65	$F_{(2,27)}$ =0.72, p=0.49
Stool consistency	1.1 ± 0.41	3.8 ± 1.02	2.4 ± 0.78	$F_{(2,27)}$ =3.02, p=0.07
Jumping Frequency	0.0 ± 0.0	89 ± 13.3	2.4 ± 2.29	$F_{(2,27)}$ =42.6, p<0.0001
Rearing Frequency	55.4 ± 6.59	4.2 ± 0.94	57.8 ± 14.5	$F_{(2,27)}$ =10.8, p=0.0004
Forepaw Licking Frequency	15.1 ± 3.27	0.2 ± 0.2	14.7 ± 3.12	$F_{(2,27)}$ =10.6, p=0.0004
Teeth Chattering Frequency	0.4 ± 0.27	37.1 ± 11.0	10.9 ± 5.31	$F_{(2,27)}$ =7.22, p=0.003

*Wilson LL et al., Cellular and Molecular Neurobiology. 2021 July; **41(5):**1131-1143*

UF College of Pharmacy UNIVERSITY of FLORIDA

Conclusions of opioid dependence testing in mice

- Kratom Tea and mitragynine alone displayed little-to-no physical dependence
- Substitution of Kratom Tea or mitragynine for morphine in physically-dependent mice ameliorated some effects of opioid withdrawal

ADDICTION

SSA SOCIETY FOR THE STUDY OF ADDICTION

LETTER TO THE EDITOR | Free Access

Not all kratom is equal: The important distinction between native leaf and extract products

Oliver Grundmann ✉ Albert Garcia-Romeu
Christopher R. McCurdy Abhisheak Sharma Kirsten E. Smith
Marc T. Swogger Stephanie T. Weiss

First published: 09 October 2023 |
https://doi.org/10.1111/add.16366

UF College of Pharmacy
UNIVERSITY of FLORIDA