Developing a Physiologically Based Pharmacokinetic Model Across Various Species Exploring Drug Interaction Potential of Mitragynine

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Mitragynine shows potential to treat opioid use disorder

Figure 1. Kratom tree

Kratom

- Tropical evergreen tree from Southeast Asia
- Opioid- and stimulant-like effects
- People report using kratom to manage opioid withdrawal symptoms, pain, and mood enhancement
- DDI has been observed while co-administered with itraconazole

Mongar, P, et al. *ACS Pharmacology & Translational Science* 7.3 (2024): 823-833.

Mitragynine (MTG)

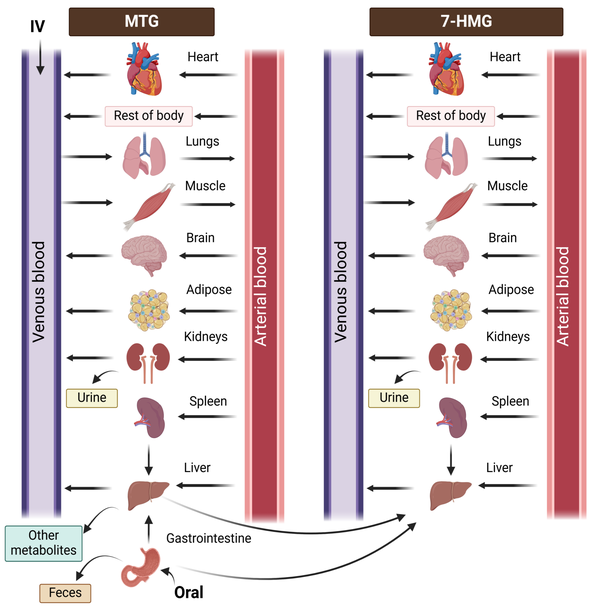
- Major alkaloid in *Mitragyna speciosa*
- Partial μ-opioid agonist
- "Biased agonist" with no β-arrestin recruitment
- The major metabolic enzymes are CYP3A4 and CYP2D6

7-Hydroxymitragynine (7-HMG)

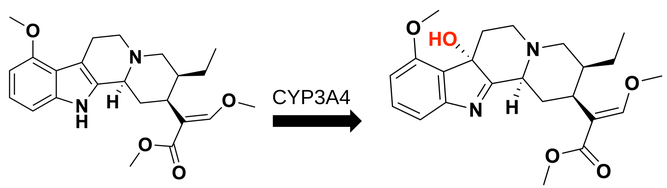
- 7-HMG is an active metabolite of MTG with abuse potential and it is mainly metabolized by CYP3A4

Obeng, S., et al. *J Med Chem*. (2019): *63*(1), 433-439 and Váradi, A., et al. *J Med Chem* (2016): 59(18), 8381-8397

Full PBPK model of MTG and 7-HMG



7-HMG has 22-fold greater binding affinity than MTG at μ opioid receptors

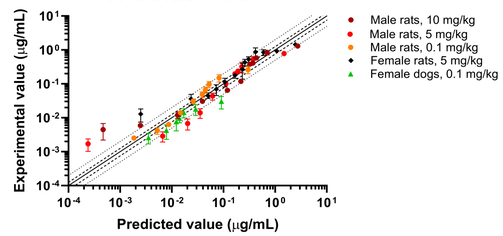


Kamble S. et al. (2019) Xenobiotica 49.11: 1279-1288

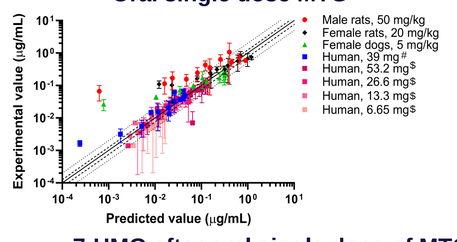
Figure 2. Formation of 7-HMG

Predicted versus observed plasma concentration values of MTG and 7-HMG in different species

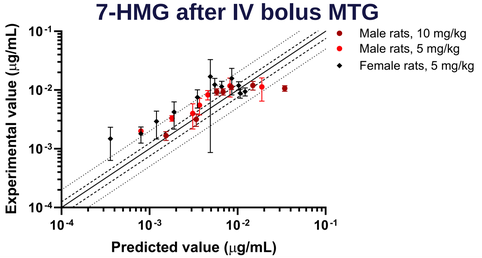
IV bolus MTG



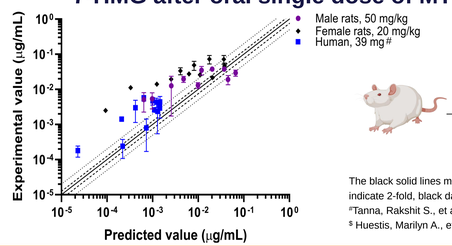
Oral single dose MTG

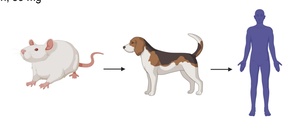


7-HMG after IV bolus MTG



7-HMG after oral single dose of MTG

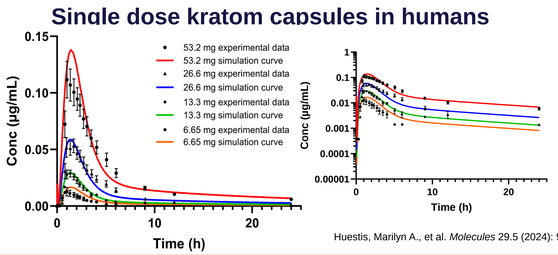




The black solid lines mark the lines of identity. Black dotted lines indicate 2-fold, black dashed lines indicate 1.25-fold deviation.
[#]Tanna, Rakshit S., et al. *Pharmaceutics* 14.3 (2022): 620.
[$] Huestis, Marilyn A., et al. *Molecules* 29.5 (2024): 984.

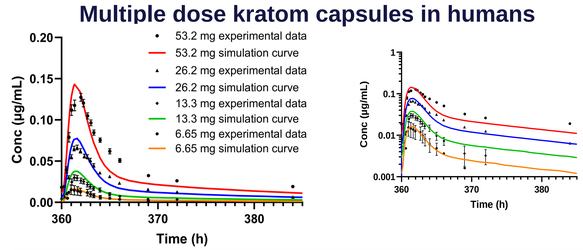
Simulated MTG plasma concentration-time profiles in human

Single dose kratom capsules in humans



Huestis, Marilyn A., et al. *Molecules* 29.5 (2024): 984

Multiple dose kratom capsules in humans



Potential drug-drug interaction

Perpetrator	CYP inhibitors	Victim	Perpetrator AUC ratio	Victim AUC ratio	7-HMG AUC ratio
Itraconazole 200 mg	CYP3A4	MTG 39 mg	1.4	1.0	0.7
ketoconazole 400 mg	CYP3A4	MTG 39 mg	1.0	1.0	0.3
Quinidine 500 mg	CYP2D6	MTG 39 mg	1.0	1.0	1.0
MTG 39 mg	CYP2D6	Atomoxetine 20 mg	1.0	1.1	-
MTG 39 mg	CYP2D6	Fluvoxamine 100 mg	1.0	1.0	-
MTG 39 mg	CYP3A4	Midazolam 15 mg	1.0	2.0	-

Conclusion

- This PBPK model can be applied to predict the systemic exposure of MTG and 7-HMG, aiding in dose selection and evaluating potential DDI involving MTG as both a victim and a perpetrator for CYP450 in humans.

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