The Bitter Taste of Medicines and Their Modifiers in People of Diverse Ancestries

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INTRODUCTION

We used remote sensory testing to investigate differences in bitter perception of medicines and the effectiveness of bitter-reducing excipients in people of diverse ancestry.

- **Bitterness is a barrier to compliance, i.e., taking medicines as prescribed [1]**
  - Many life-saving medicines are bitter
  - Up to one-third of children with chronic conditions refuse medicines [2]
- **There is diversity in bitter taste genotypes and phenotypes**
  - Not everyone perceives the same bitterness from medicines, e.g., propylthiouracil (PROP) [3]
  - Genetic differences in bitter receptors may explain the person-to-person differences in bitterness [3]
  - These genetic differences can be partially explained by ancestry; in the case of PROP, the frequency of variants in the *TAS2R38* bitter receptor gene, the "taster" PAV and "non-taster" AVI haplotypes, differ by global origins (Fig. 1 [4])
- **Bitter blocking improves the palatability of medicines [5] and may vary widely from person to person [6, 7]**
  - Bitter taste can be blocked at the taste cell and receptor levels
  - Bitter perception and blocking are specific for certain ligands that engage specific bitter receptors

PROP Bitterness Determined by *TAS2R38* Genotype

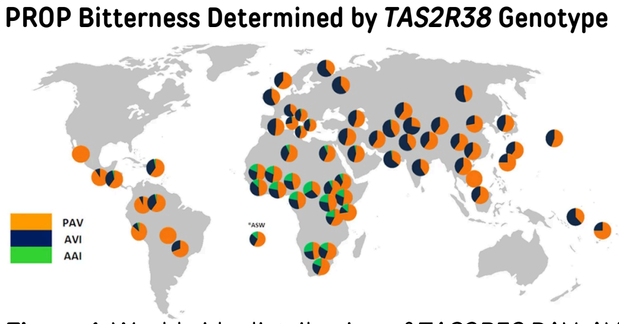
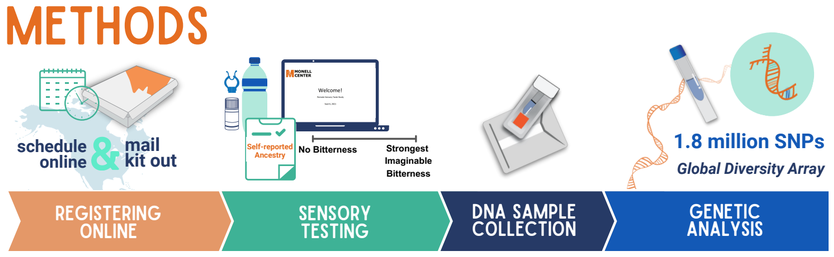


Figure 1. Worldwide distribution of *TAS2R38* PAV, AVI, and AAI haplotypes in the studied populations [4].

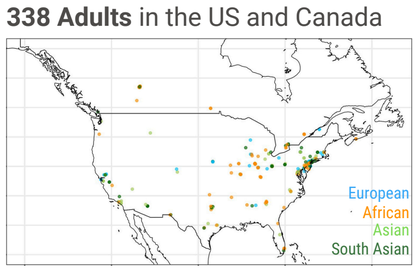
We tested the bitter perception of five medicines and the effectiveness of two bitter-reducing excipients (6-methylflavone and sucralose) on tenofovir alafenamide fumarate (TAF) in participants in the United States and Canada who are of recent African, Asian, and European ancestries. Using a sip and spit procedure, participants rated the bitterness of taste solutions (10 mL each) on the generalized Visual Analog Scale (gVAS). We used a low-cost method of recruiting people of diverse ancestries by supervised remote sensory testing via Zoom™.

METHODS



PARTICIPANTS

338 Adults in the US and Canada



MATERIALS

BITTER MEDICINES

MEDICINE	560 µM Ctrl Propylthiouracil (PROP)	300 µM Moxifloxacin Hydrochloride	500 µM Amodiaquine Hydrochloride	300 µM Praziquantel	200 µM Tenofovir Alafenamide (TAF)
DISEASE	HYPERTHYROID CONDITIONS	TUBERCULOSIS (ANTIBIOTIC)	MALARIA	SCHISTO-SOMIASIS (PARASITE)	HIV-1 & HEPATITIS B

BITTER REDUCERS

USAGE	COMPOUND	
	500 µM 6-methylflavone	2.5 mM Sucralose
	BITTER BLOCKER	SWEETENER (FOOD ADDITIVE)

RESULTS

- There were large person-to-person differences in the bitterness of all medicines tested (Fig. 2)
- The bitterness of medicines differed by ancestry for PROP and Amodiaquine but not others (Fig. 2)
- Sucralose was more effective in African than in Asian participants; 6-methylflavone was less effective than sucralose and worked to reduce bitterness for South Asian, Asian, and African participants (Fig. 3)
- The data showed the expected relationship of the *TAS2R38* genotype to the bitter ratings for PROP, a well-known genotype-phenotype relationship (Fig. 4)

To obtain broadly palatable medicines, formulations need to be tested on people of diverse ancestry

Identify associated receptors with cell-based assays; Test more excipients and mixtures with more drugs and diverse populations

References

1. Mennella *et al.* (2015). BMC Pediatrics, 15(1): 1–6
2. Venables *et al.* (2015). Int J Pharm, 480(1–2):55–62
3. Bufe *et al.* (2005). Curr Biol, 15(4), 322–327
4. Risso *et al.* (2016). Scientific Reports, 6(1)
5. Andrews *et al.* (2021). Eur J Pharm Biopharm, 158:35–51
6. Schwiebert *et al.* (2021). Mol Pharmacol, 99(5):319–327
7. Nguyen *et al.* (2024). Clin Ther, 46(4):345–353

Acknowledgments

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INDIVIDUAL DIFFERECES IN BITTERNESS OF MEDICINES ARE LARGE, BUT THERE ARE ANCESTRAL DIFFERENCES TOO

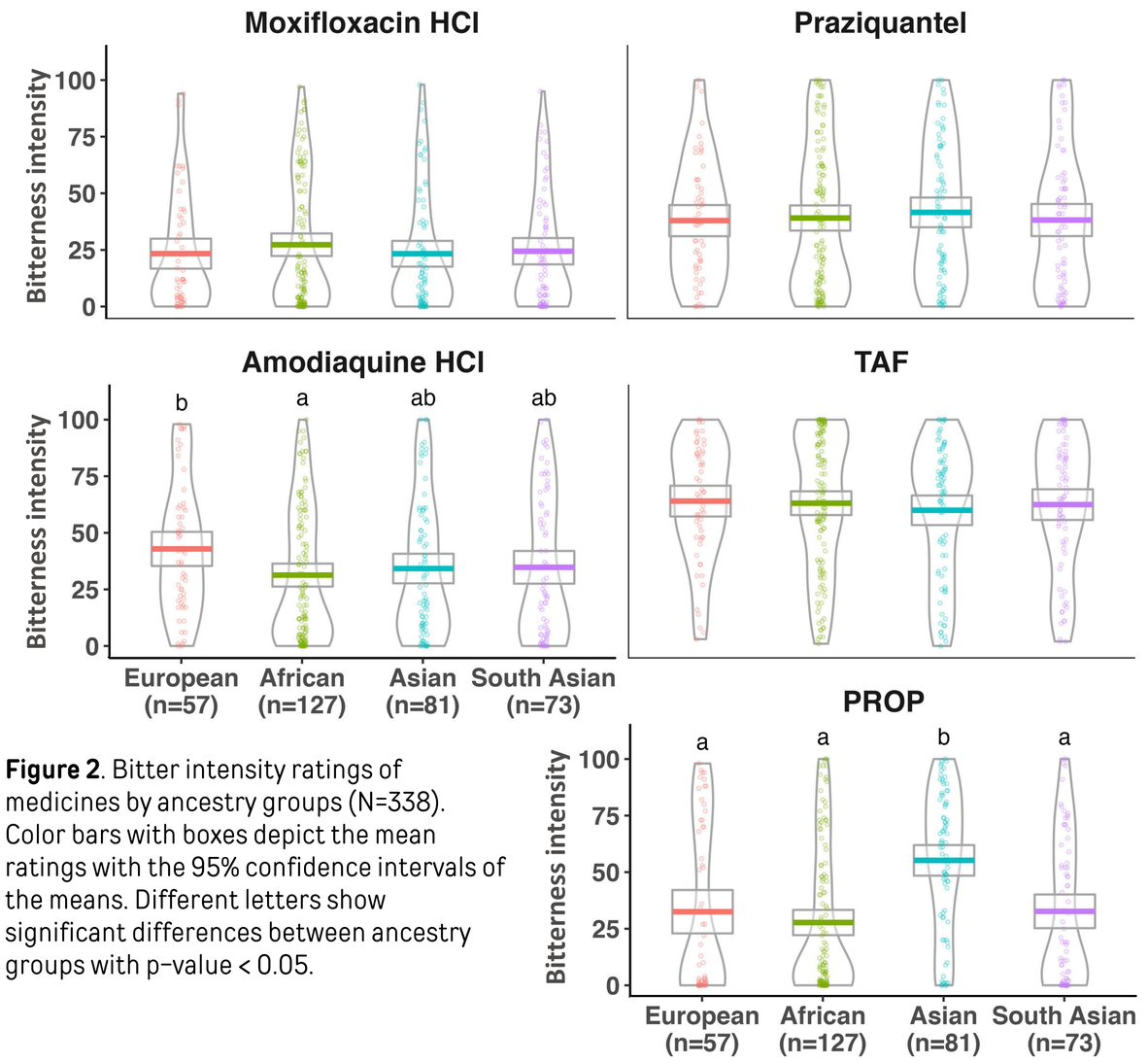

Figure 2. Bitter intensity ratings of medicines by ancestry groups (N=338). Color bars with boxes depict the mean ratings with the 95% confidence intervals of the means. Different letters show significant differences between ancestry groups with p-value < 0.05.

THE BITTER SUPPRESSION DIFFERED DEPENDING ON THE BITTER-REDUCING EXCIPIENT AND ANCESTRY

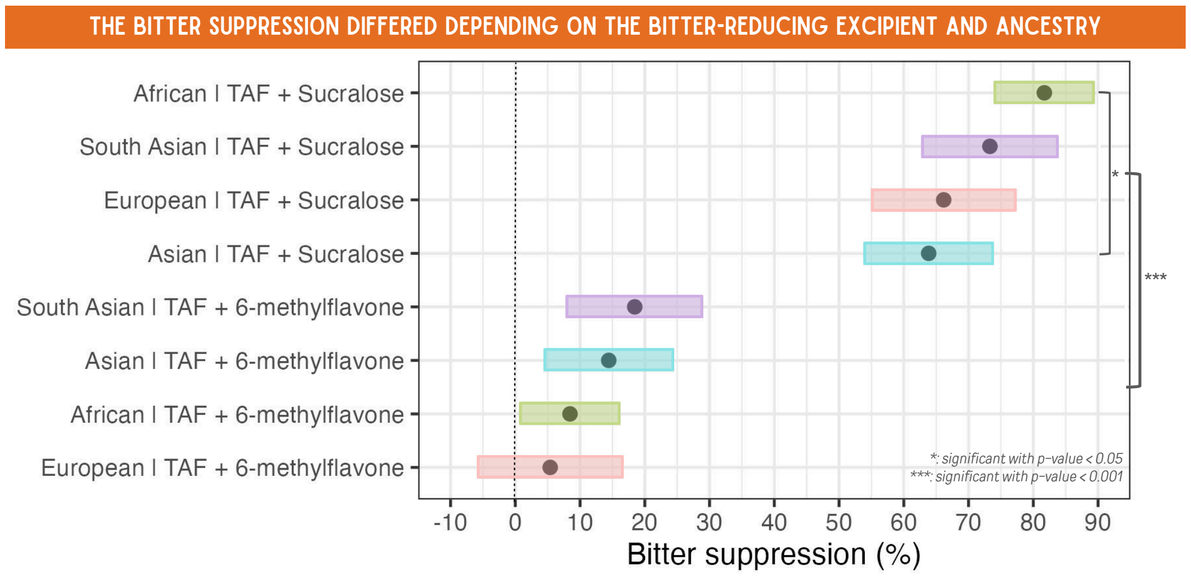

Figure 3. Mean bitter suppression of TAF with the excipient for participants who perceived TAF as bitter (greater than 25 on the 100-pt scale) (N = 284). Color bars depict the 95% confidence intervals of the means. Bitter suppression score (%) was calculated by subtracting the bitterness intensity rating of the mixture from that of TAF alone, expressed as a percentage.

GENETIC VARIATION IN PROP BITTERNESS

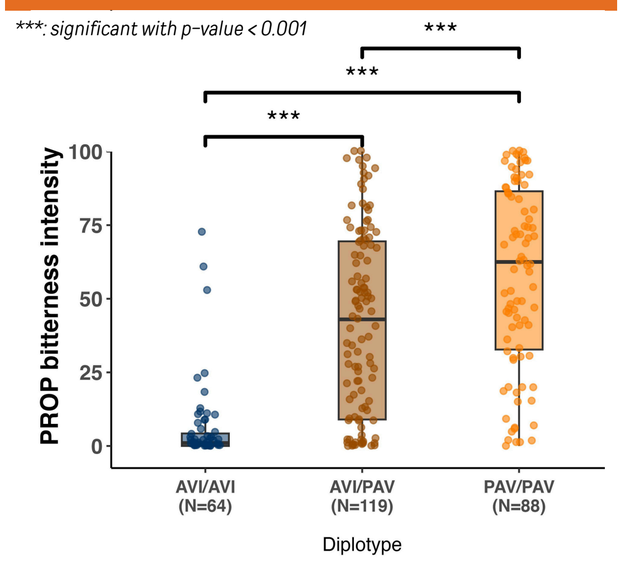

Figure 4. The expected relationship of the *TAS2R38* genotype to PROP sensitivity.

CONCLUSIONS

- Person-to-person differences in bitterness of medicines were striking. Bitter-reducing excipients work better for some people than others.
- The contribution of ancestral differences to bitterness was common but not universal. The bitter-reducing efficacy differed by ancestry.
- Bitter receptor gene variants partially explain person-to-person bitterness rating differences in PROP, but not other medicines.