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Bi-directional interactions between anti-seizure medications and gut microbial communities mediate host drug response

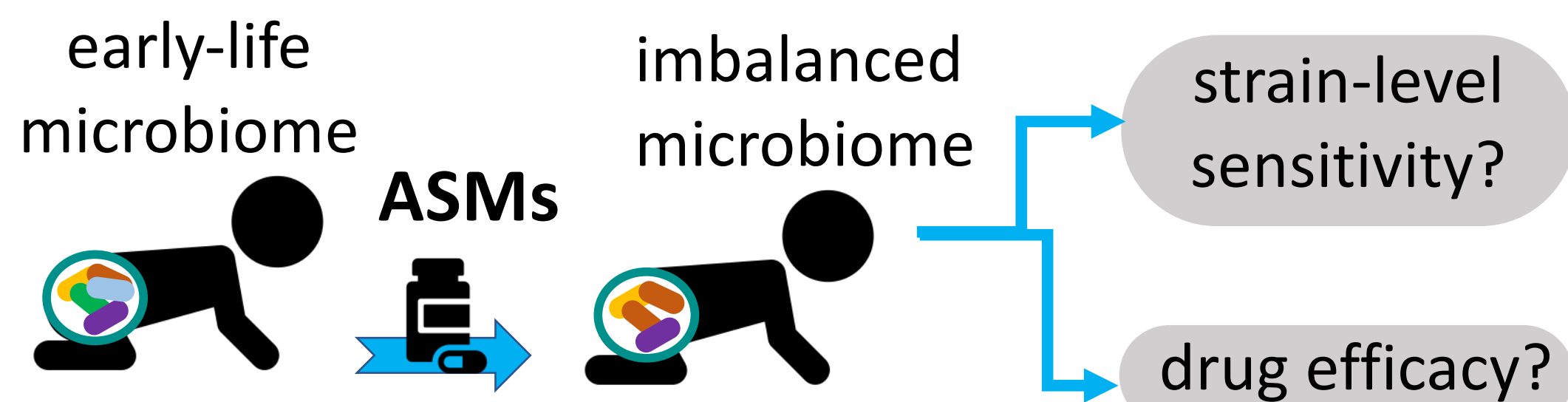
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Background

Antiseizure medications (ASMs) fail to reduce symptoms of epilepsy in 1/3 of the children.
Early life microbiome is vulnerable to xenobiotics.
ASMs disturb early-life gut microbiome dynamics.



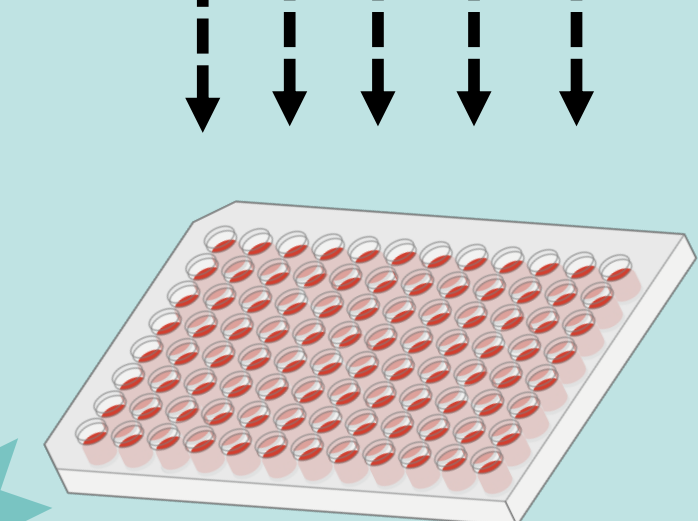
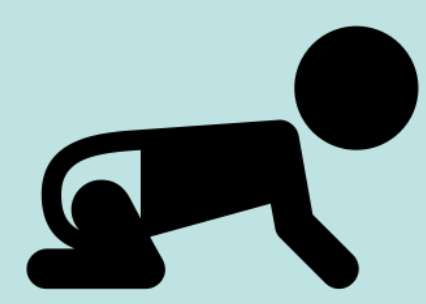
Objective

Dissect reciprocal interactions between the gut microbiome species and ASMs under *in-vitro* conditions.

Methods

Selection of the core children gut microbiome strains
(10 Bacteroidota, 14 Bacillota, 4 Actinomycetota, 1 Verrucomicrobiota, 3 Pseudomonadota)

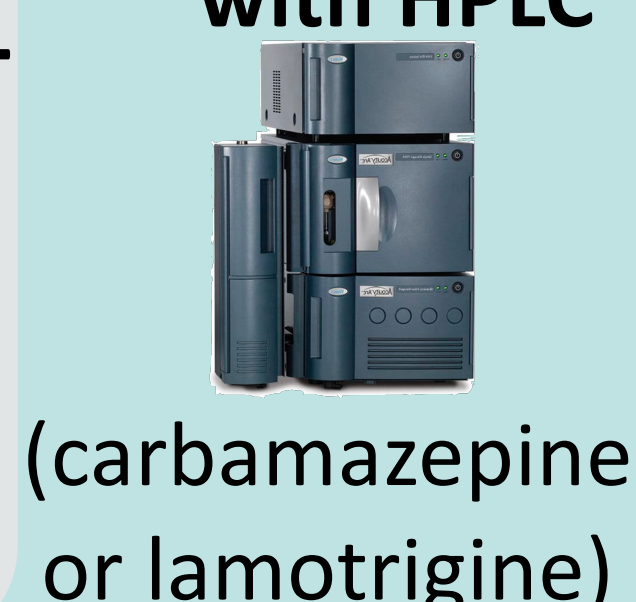
9 ASMs, 6 excipients,



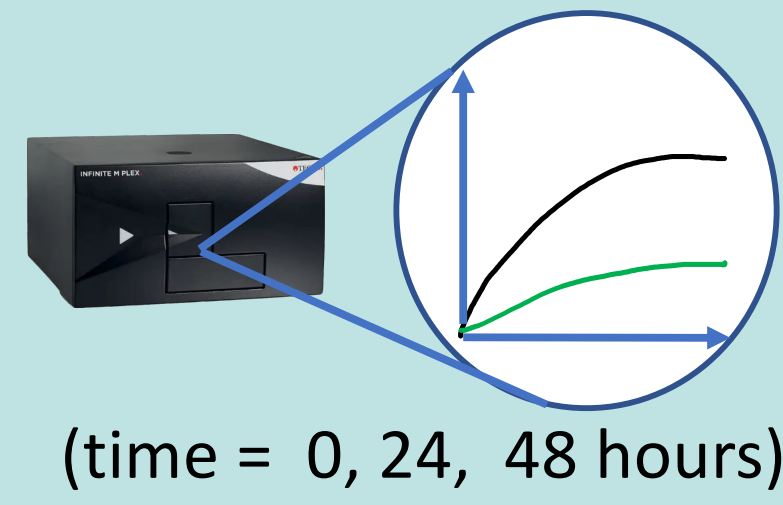
Host response

HT-29 epithelial cells
+ (carbamazepine or lamotrigine)
bacterial supernatants

quantify ASM concentrations with HPLC



growth monitoring



toxicity response
drug response

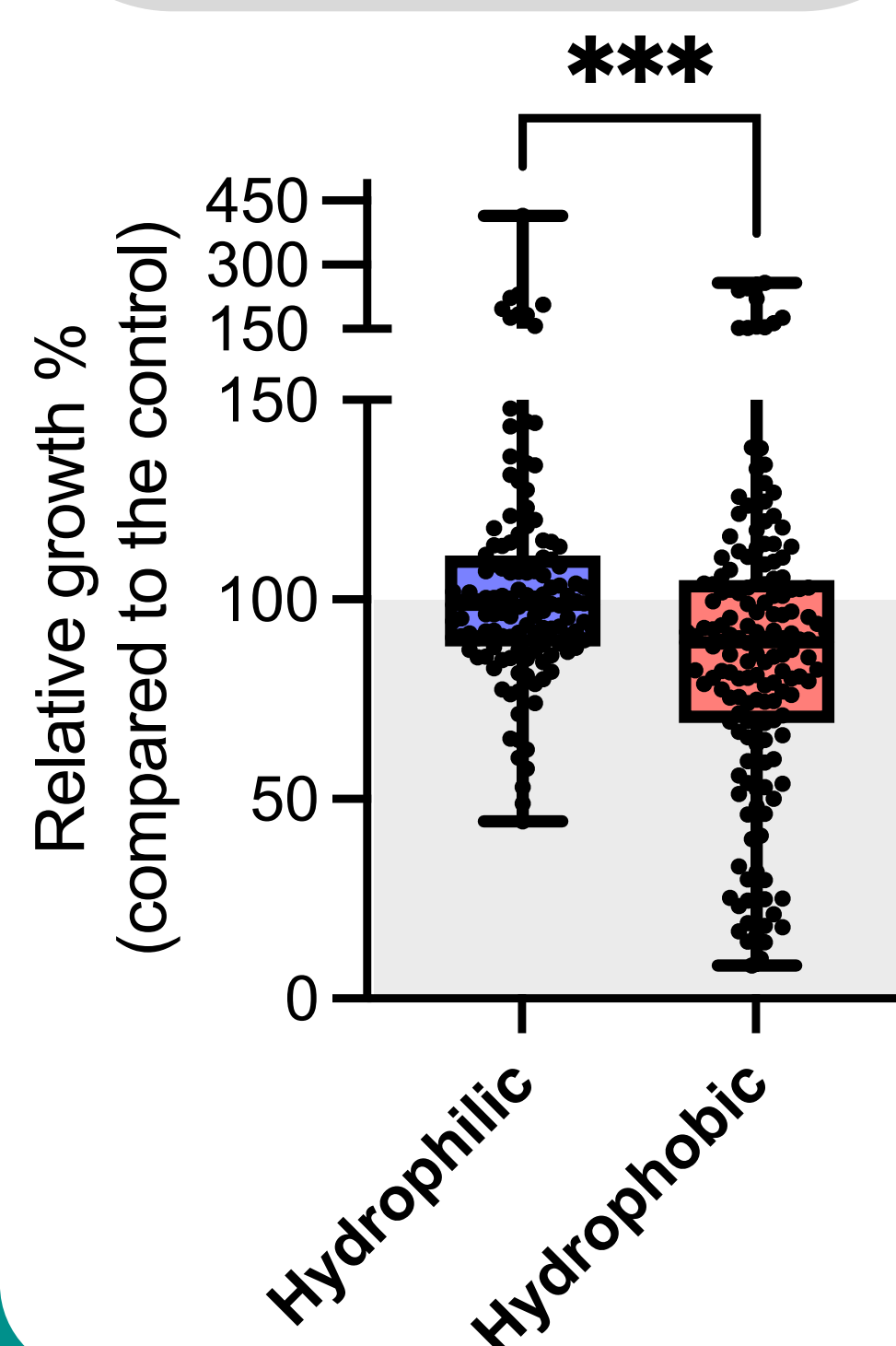
ASMs = Levetiracetam, Gabapentin, Valproate, Ethosuximide, Topiramate, Carbamazepine, Lamotrigine, Lacosamide, Phenytoin
Excipients = Methyl-paraben, Propyl-paraben, Acesulfame K, Maltitol, Sorbitol, Aspartame

Summary

- Hydrophobic ASMs were more inhibitory towards the growth of gut bacterial strains.
- Artificial sweeteners and parabens, positively and negatively impacted the growth of gut strains, respectively.
- Mixed microbial communities reduced the bioavailability of lamotrigine and carbamazepine (mechanisms under investigation).
- Host cells were impacted by ASMs and this effect could be modulated by gut bacterial supernatants (e.g. for drug resistance gene expression).

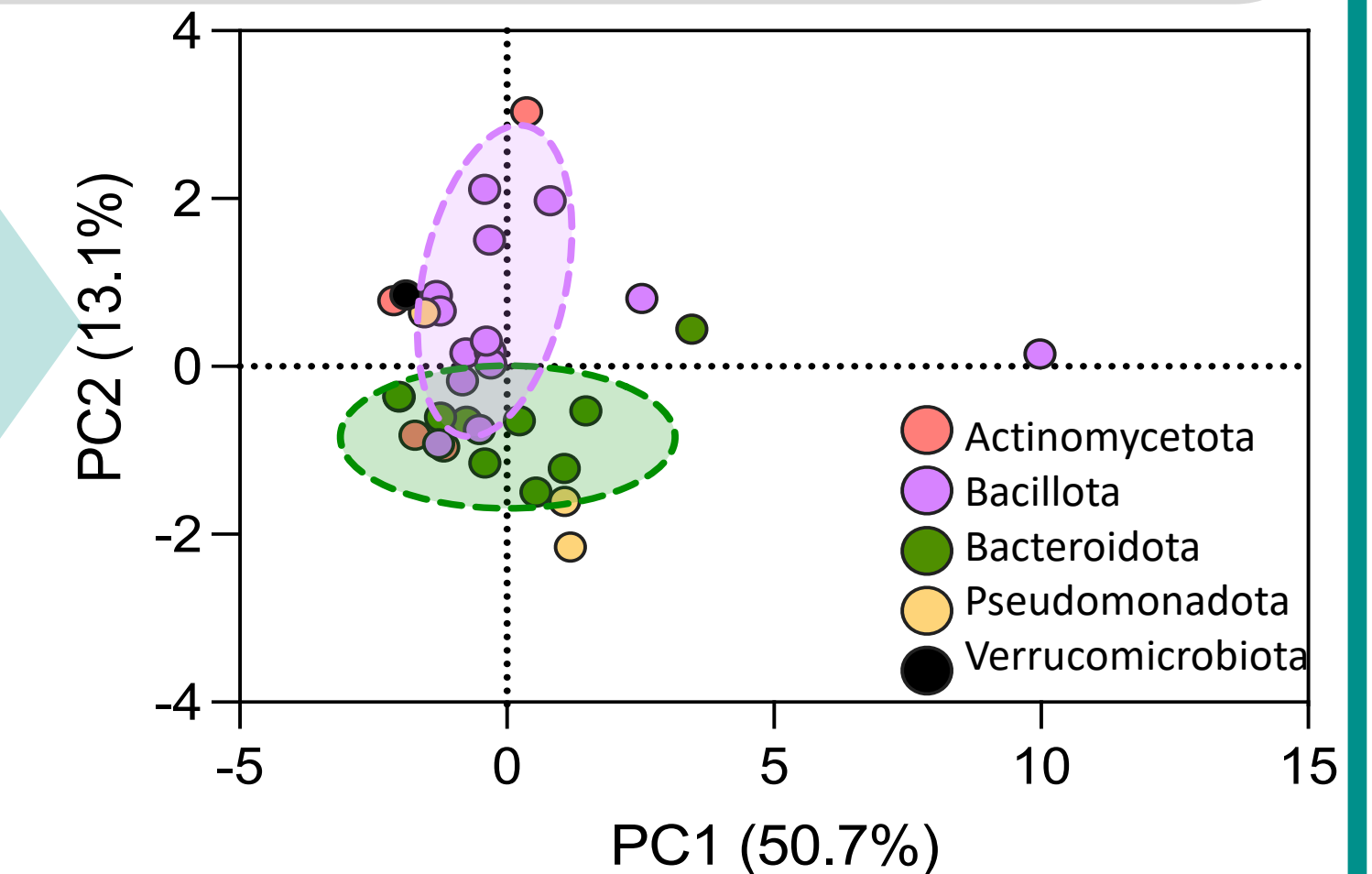
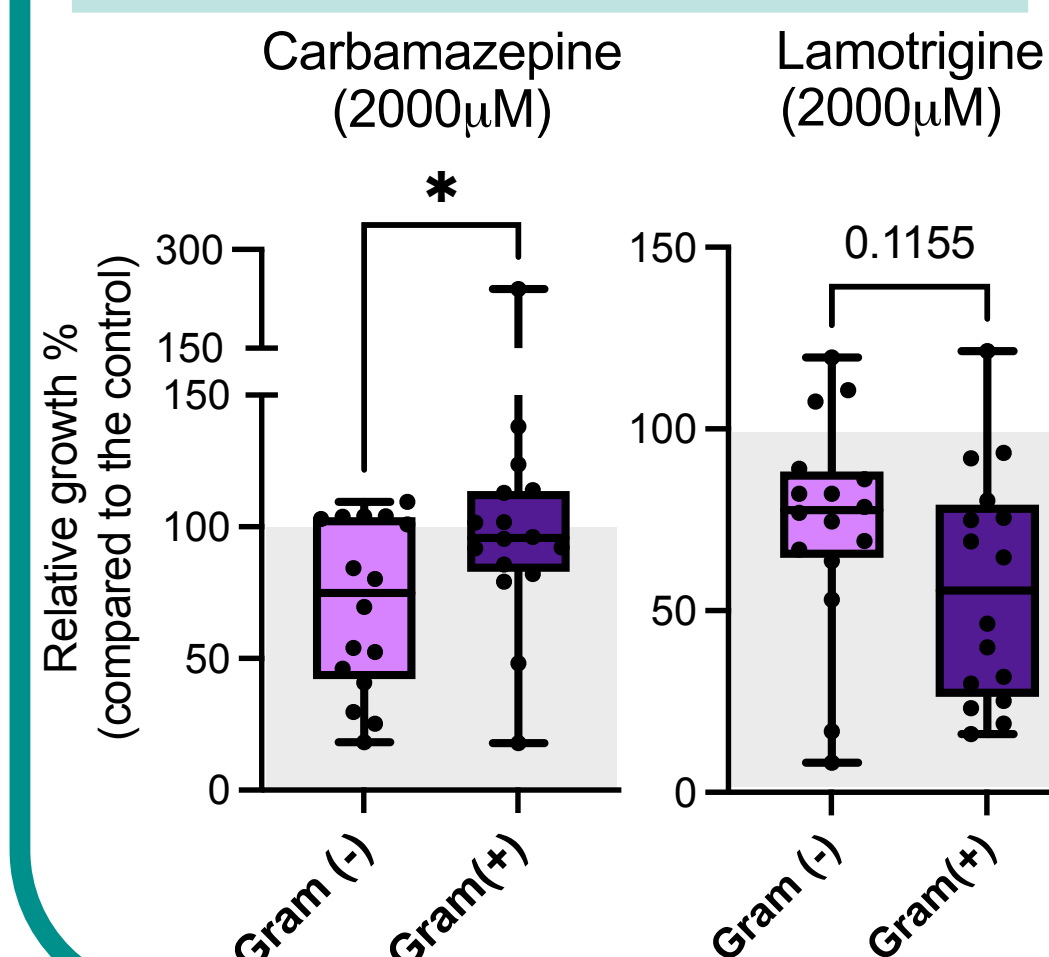
Results

Hydrophobic ASMs were more inhibitory towards gut strains.



Bacterial growth in presence of ASMs depended on bacterial physiology.

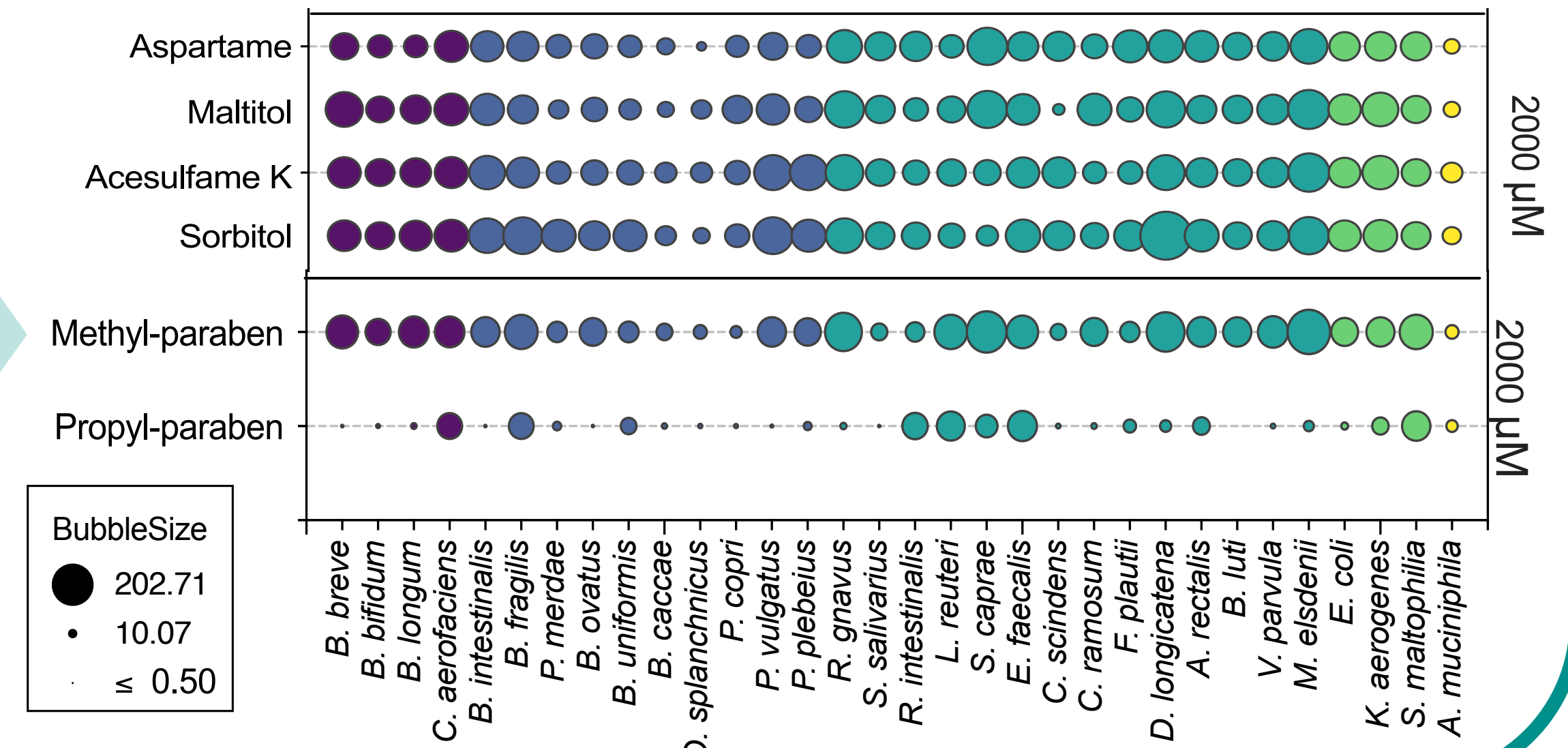
Bacillota and Bacteroidota species were differently impacted by the ASMs based on PCA analysis.



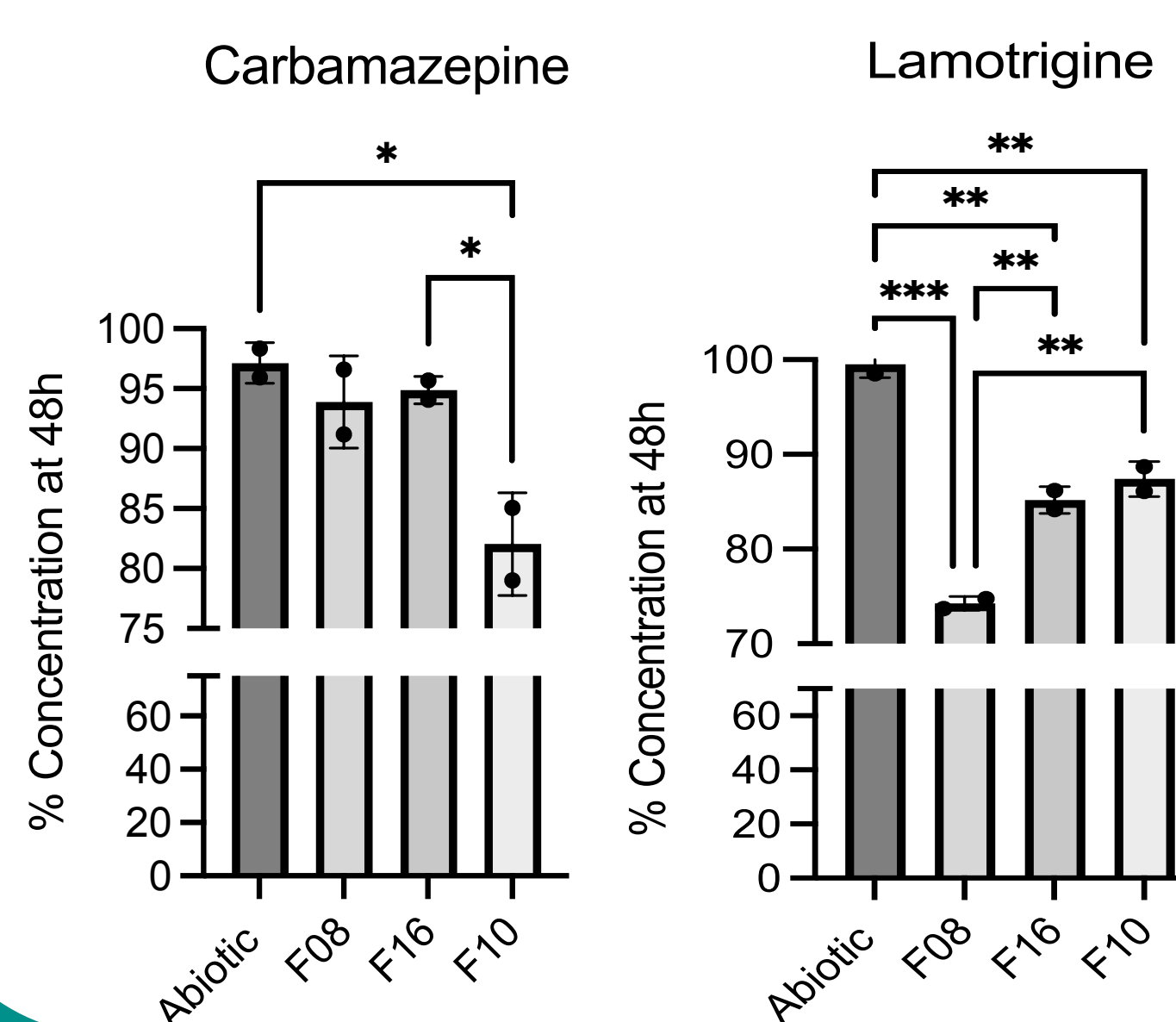
Carbamazepine and lamotrigine impaired the growth of Gr (-) and Gr (+) bacteria, respectively.

Drug excipients greatly influenced gut bacterial growth.

Propyl-paraben inhibited growth of 26 strains out of 32.
Sweeteners stimulated the growth of majority of the strains.



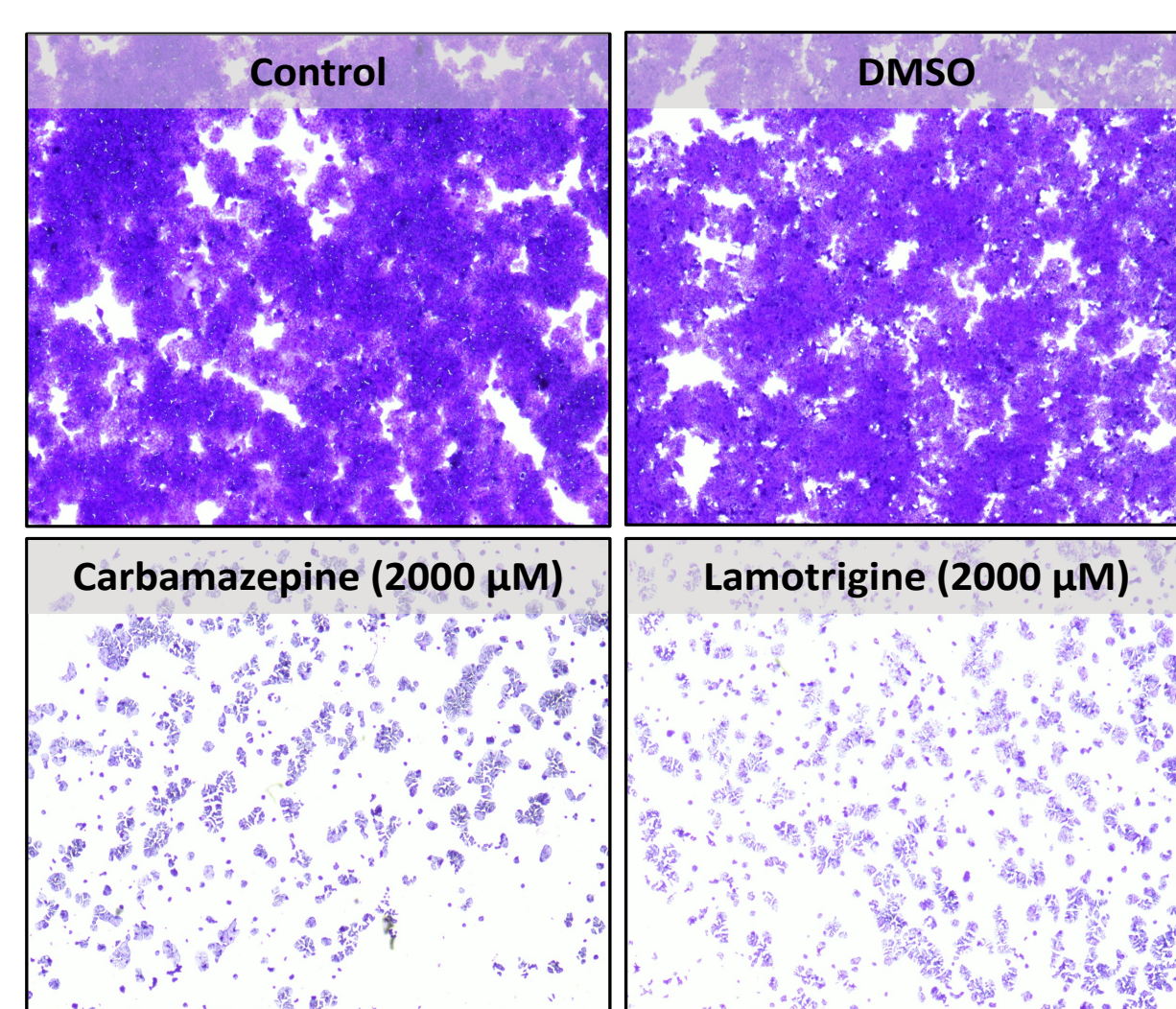
Gut microbiota reduces bioavailability of ASMs.



Feces-derived microbial communities reduced carbamazepine and lamotrigine concentration up to 26% (≈ 100 mM).

Inoculum composition had significant impact on the rate of carbamazepine and lamotrigine dissipation.

Carbamazepine and lamotrigine were toxic towards HT29 cells.



Supernatants of *B. longum* and mixed communities reduced carbamazepine-induced toxicity and drug resistance in host epithelial cells.

