Bacterial metabolism rescues the inhibition of intestinal drug absorption by food and drug additives

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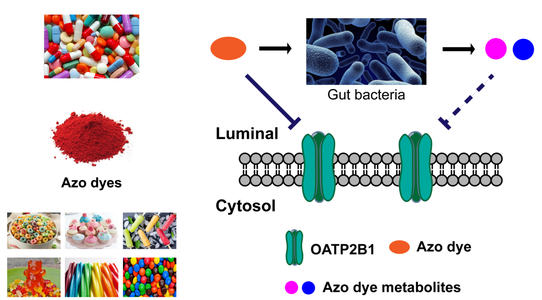
Introduction

1. Azo dyes are commonly added to food and drug products for improved esthetics.
2. The amount of azo dyes certified by the FDA increased 5-fold from 1955 to 2010 and intake may vary dramatically among individuals.
3. Azo dyes are metabolized by human gut bacteria.
4. OATP2B1, the intestinal influx transporter, is abundantly expressed along the GI tract and is important for the absorption of many drugs.
5. OATP2B1 can mediate drug-drug and drug-food interactions.
6. The complex interactions of azo dyes with OATP2B1 and gut bacteria are largely unknown.



Goal

Investigate the effects of azo dyes as inhibitors of the intestinal transporter, OATP2B1 and determine whether gut bacteria modulate these effects.

Methods

- A fluorescent assay using 4',5'-dibromofluorescein (DBF) as substrate was developed to assess inhibition of OATP2B1 transport activity by six orally used azo dyes and their metabolites in stably transfected HEK cells.
- Gut bacteria obtained from human stool samples were screened for azo dye metabolism (negative control: 100 μM dyes without metabolism) and individual bacterial species capable of reducing the dyes were identified by 16S rRNA gene sequencing.

Results

Figure 1. Multiple oral excipients inhibit OATP2B1-mediated transport

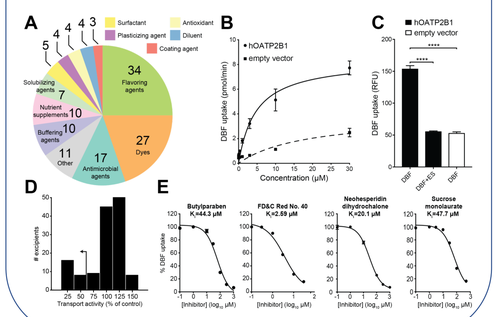


Figure 2. Oral administration of the excipient dye FD&C Red No. 40 reduces fexofenadine bioavailability in mice

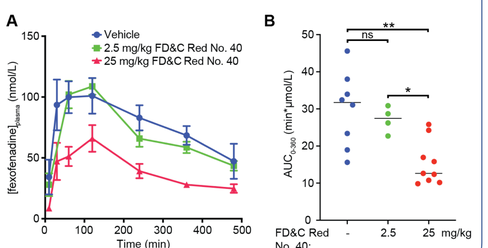


Figure 3. Human gut bacteria metabolize azo dyes

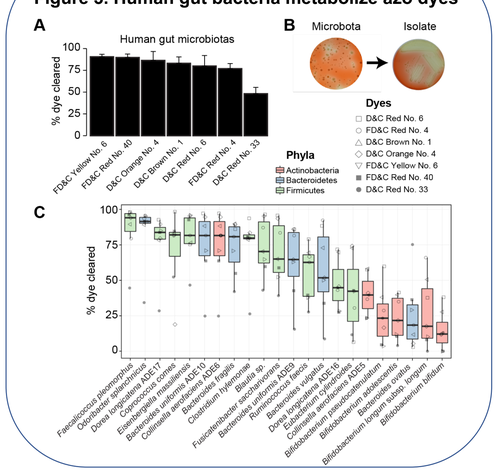
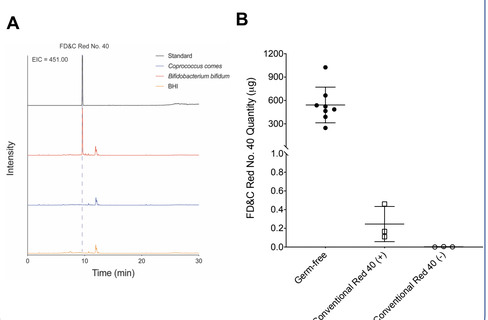
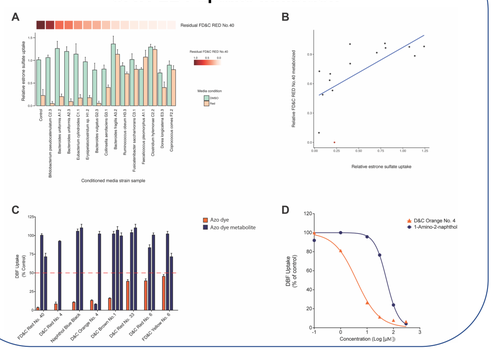


Figure 4. Measurement of FD&C Red No. 40 in azo dye-metabolizing bacteria culture medium and mice stool samples



Results

Figure 5. Microbial metabolism of azo dyes rescues OATP2B1 uptake inhibition



Conclusion

- Excipients may inhibit OATP2B1-mediated drug absorption at clinical relevant concentrations.
- This study is the first to show that azo dyes have inhibitory effect on OATP2B1 *in vitro* and *in vivo*, and that gut bacteria may alleviate the transporter inhibition through azo reduction. These results support a beneficial role for the microbiome in limiting the unintended effects of food and drug additives in the intestine.

Acknowledgement

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