Microbiome could be culprit when good drugs do harm

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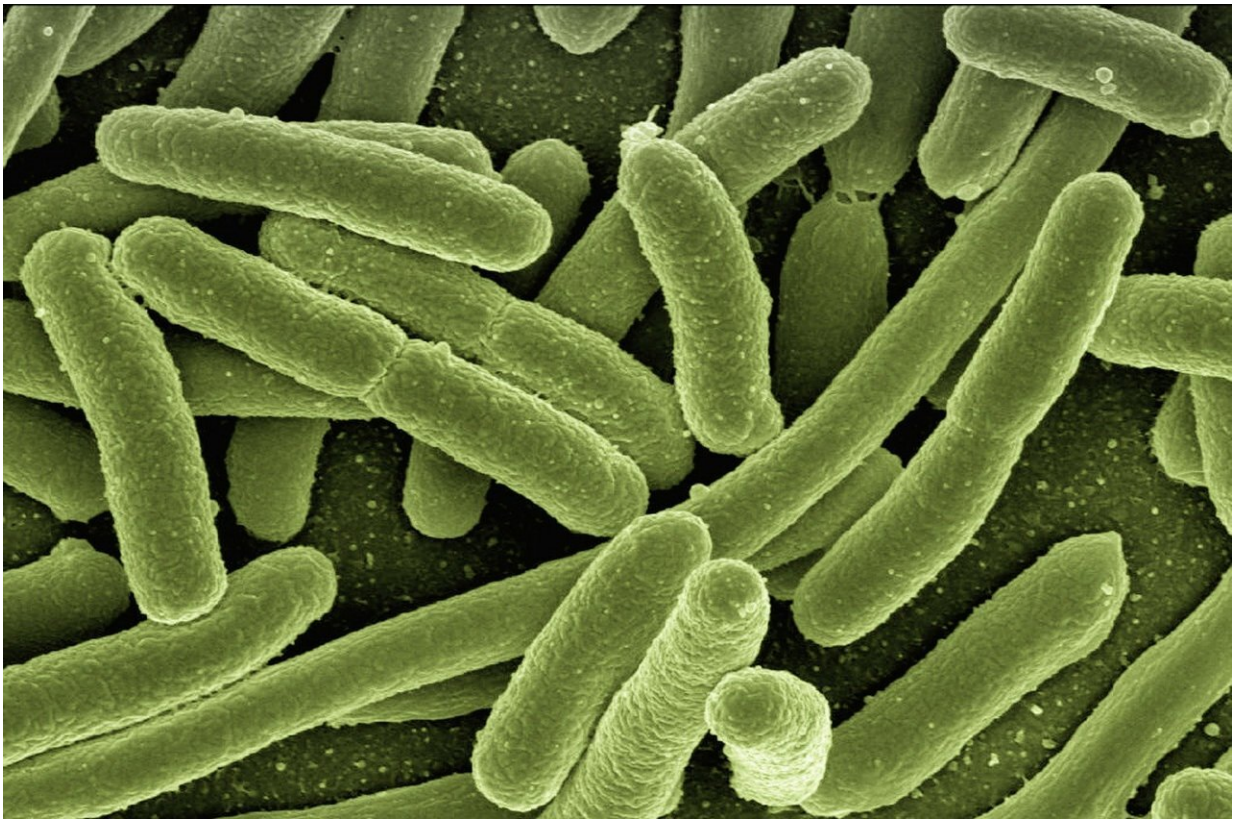

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People sometimes suffer toxic side effects from drugs that help many others. Yale scientists have identified a surprising explanation—the gut microbiome.

The research, published Feb. 8 in the journal *Science*, describes how bacteria in the gut can transform three drugs into harmful compounds.

"If we can understand the microbiome's contributions to drug metabolism, we can decide which drugs to give to patients or even alter the microbiome so patients have a better response," said co-lead author Michael Zimmermann, postdoctoral fellow in the lab of senior author Andrew Goodman in the Department of Microbial Pathogenesis and the Microbial Sciences Institute.

Goodman, Zimmermann, co-lead author Maria Zimmermann-Kogadeeva, and Rebekka Wegmann, now a doctoral student at ETH Zurich, studied an antiviral drug whose breakdown product can cause severe toxicity and identified how gut microbes transform the drug into a harmful compound. They then administered the drug to mice carrying bacteria engineered to lack this drug-transforming ability and measured the levels of this toxic compound. Using this data, they developed a mathematical model that successfully predicted the role of gut bacteria in metabolizing a second antiviral drug and clonazepam, an anti-seizure and anti-anxiety drug.

The study found that the gut microbes were responsible for producing 20 percent to 80 percent of the circulating toxic metabolites derived from the three drugs.

The new model can potentially identify those most at risk of experiencing the side effects of many drugs and help researchers tailor new approaches to minimize this risk to individuals, researchers say.

"Potentially, this approach can be applied to other drugs," said co-lead author Zimmermann-Kogadeeva, who is also a postdoctoral fellow in the Goodman lab.

More information: Michael Zimmermann et al. Separating host and microbiome contributions to drug pharmacokinetics and toxicity, *Science* (2019). DOI: 10.1126/science.aat9931