Nutrient competition mediates gut microbiome restructuring under drug perturbations

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The continuous emergence of antibiotic-resistant bacteria poses a serious challenge to global public health, threatening decades of medical progress. Meanwhile, the human gut microbiota, a complex ecosystem crucial for host health, is continuously exposed to various drug disturbances, and its complex response mechanisms are difficult to predict. This commentary focuses on a pioneering study, "Nutrient competition predicts gut microbiome restructuring under drug perturbations," which systematically reveals the core role of nutritional competition in determining the response of microbial communities to drugs by high-throughput screening of the effects of 707 clinically relevant small molecule drugs on stool-derived *in vitro* communities (SICs) (Figure 1).[1] This groundbreaking study represents a significant advancement in the intersection of microbial ecology and drug research, providing a new paradigm for understanding and predicting the impact of drugs on complex microbial ecosystems and laying a new direction for future scientific explorations. This work advances beyond traditional ecological models (e.g., Lotka-Volterra) and genome-scale metabolic reconstructions by explicitly integrating nutrient competition as a quantifiable and predictive driver of community restructuring under drug perturbations. Although the SIC model provides a controllable high-throughput platform for studying microbial interactions, it lacks the measurement of various host-related factors, such as immune regulation, intestinal motility, the mucus layer, and the physiological pH gradient, which may regulate drug-microbial interactions *in vivo*. Therefore, the correlation between these findings and the transformation of the human intestinal ecosystem requires further verification in more complex models or clinical cohorts.

Antibiotic resistance, often likened to a silent pandemic, is continuously undermining the effectiveness of critical medical procedures. In parallel, the "collateral damage" of drugs, especially antibiotics,[2] to the microbiota may lead to dysbacteriosis, and even open the door for opportunistic pathogen colonization.[3] Moreover, a broad range of non-antibiotic pharmaceuticals,

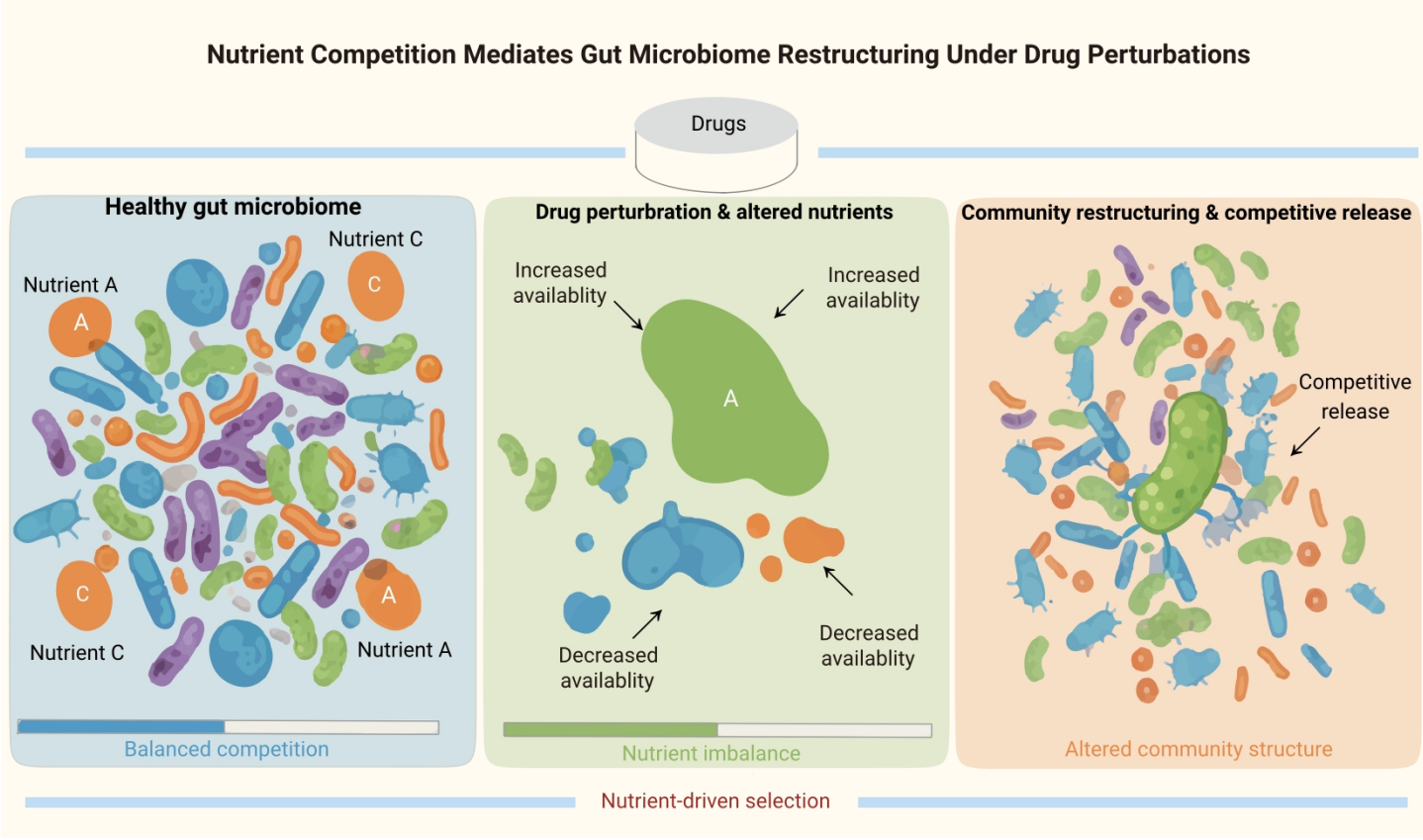

Figure 1. Nutrient competition predicts gut microbiome restructuring under drug perturbations.

including but not limited to antidiabetics (e.g., metformin), non-steroidal anti-inflammatory drugs (NSAIDs), and antipsychotics, has been demonstrated to suppress the growth of human gut commensals directly.[4] They reveal that many non-antibiotic drugs similarly alter microbiome composition, likely by creating new nutritional landscapes through the selective inhibition of specific community members. However, due to the complex network of interactions within the microbiota, the drug sensitivity of a single species makes it difficult to predict its fate in the community context. Nutrient competition among community members has been shown to cause competitive release, in which rare opportunistic pathogens expand due to antibiotic inhibition of the

commensal bacteria that normally outcompete them. A less susceptible species can be indirectly affected when its competitors or cross-feeding partners are inhibited. Although nutrient competition emerges as a central predictive mechanism, other ecological interactions—such as quorum sensing, bacteriocin production, phage dynamics, and metabolic cross-feeding—also shape community responses to drugs and warrant integration in future models.

Through systematic screening and modeling, this study identifies nutrient competition as the core mechanism predicting gut microbiome restructuring under drug disturbance. Key findings include: (1) Both antibiotics and many non-antibiotic drugs alter composition via nutrient competition; (2) Composition shifts correlate with metabolite use; (3) Species' fates depend on both direct sensitivity and competitive interactions; (4) Species extinction occurs but can be reversed via reintroduction; (5) Strain replacement may arise through higher-order interactions; (6) Communities resist antibiotic resistance evolution; (7) Drug responses vary quantitatively across communities due to distinct competition networks; (8) Non-monotonic dose responses emerge from competition-inhibition interplay. The work establishes a nutrient-centric quantitative framework to understand, predict, and intervene in drug-microbiome interactions.

The innovative study presents a dynamic culture model and consumer-resource (CR) simulations as crucial tools for investigating and predicting community responses to drug perturbations. The consumer-resource (CR) model, a mathematical framework describing how species compete for limited resources, was used here to simulate how drug-induced changes in species growth rates reshape community composition through nutrient competition. This sophisticated approach facilitates the observation of how nutrient competition quantitatively adjusts species' abundances under drug stress. Notably, the susceptibility of a species in isolation was a poor predictor of its behavior in a community; however, when rescaled relative to the susceptibilities of other community members—a proxy for nutrient competition—the correlation with its abundance changes in the community became strong. This rescaling strategy underscores that a species' fate is tuned by both its direct drug susceptibility and its relative fitness within the competitive landscape. Furthermore, the study found that the dose-response of species to drugs may exhibit non-monotonic behavior in the community context, which can be reasonably explained by the interaction of nutrient competition and drug inhibition. For instance, a sensitive species might be suppressed at low drug concentrations; still, as its competitors are more strongly inhibited at higher concentrations, it may paradoxically expand due to increased resource availability. These experimental observations are further supported by the computational CR model, which shows that many counterintuitive dose-response patterns can be reproduced even when only nutrient competition is considered, highlighting the emergent properties of complex ecosystems.

The data generated in this work have important clinical and pharmaceutical application potential.[5] By mapping the nutrient competition networks within microbial communities, we can better predict which species may expand opportunistically during drug treatment—a phenomenon directly related to opportunistic infections and the efficacy of microbiome-mediated drugs. This predictive capability could inform the selection of drugs with lower collateral damage or guide the co-administration of prebiotics or probiotics to stabilize susceptible keystone species. It should be noted that inter-individual variations in baseline microbiome composition, diet, host genetics, and health status may influence nutrient competition networks and thereby modulate drug responses. Future models should incorporate such variability to enhance their generalizability in clinical settings. Furthermore, the suppressed resistance evolution in communities suggests that the multi-species environment may naturally inhibit the emergence of resistance, providing a new perspective for designing combination therapies that leverage the ecological dynamics of microbial communities to suppress resistance. Translating these predictions to clinical practice will require several key steps: validating the CR model in animal or human interventional studies, developing standardized protocols for mapping individual nutrient competition networks, and addressing practical challenges such as sample stability, data integration, and real-time monitoring in patients. The consumer-resource modeling framework developed in this study could be integrated with AI methodologies, as exemplified by recent advances in antibiotic discovery, which can simulate and optimize therapeutic interventions for desired microbiome outcomes.

In conclusion, just as the discovery of zosurabalpin marks a remarkable milestone in antibiotic research by targeting a novel pathway, the study by Shi et al. highlights the central role of nutrient competition in mediating the response of microbial communities to drugs, providing a quantitative framework for predicting and mitigating the side effects of drug treatment on the microbiota. This innovative approach, elucidating the ecological rules governing microbiome stability, represents a significant shift in our strategy to manage the microbiome in the face of chemical perturbations. The potential of this framework, particularly in predicting and preventing dysbiosis, not only confronts a critical healthcare challenge but also underscores the significance of continued innovation at the intersection of microbiology and pharmacology. Looking forward, several research avenues appear promising: (1) developing more physiologically relevant in vitro models (e.g., gut-on-a-chip, organoid co-cultures) that incorporate host elements; (2) integrating multi-mechanism interactions (e.g., phage dynamics, metabolic cross-feeding) into predictive frameworks; (3) initiating longitudinal clinical studies to validate and calibrate model predictions; and (4) exploring ecology-based combination therapies that leverage microbial community dynamics to suppress resistance and promote resilience.

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AUTHOR CONTRIBUTIONS

All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.