Metformin drives concerns about the transmission of antibiotic resistance genes: A case study in anaerobic digestion system

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Abstract:

More than 10% of the adult population suffers from diabetes worldwide, making the anti-diabetic drug metformin (MET) one of the most produced and consumed drugs globally. Of particular concern is its potential contribution to the transmission of antibiotic resistance genes (ARGs), yet its impact on engineered ecosystems remains unknown. Herein, we show that the presence of MET intensifies the transmission of ARGs during anaerobic digestion (AD) in antibiotic-rich conditions. Specifically, in contrast to individual exposure to MET or sulfamethoxazole (SMZ), the coexistence of MET and SMZ increased the abundance of three typical ARGs (*tetA*, *sul1*, *macB*) by 9.84–333.36%. Co-occurrence network analysis reveals that combined exposure to MET and SMZ significantly increased network complexity in the AD system, with the average degree rising from 1.556 to 5.836 compared to single exposure. The combined exposure enhanced interactions between microorganisms, ARGs, and mobile genetic elements (MGEs), thereby increasing the diversity of ARG hosts and facilitating the diffusion of ARGs. Metagenomic binning analysis identified 43 out of 58 ARG hosts as being associated with fermentation, acetogenesis, and methanogenesis, indicating their involvement in the core metabolic processes of AD. Additionally, the co-exposure of MET and SMZ promoted their proliferation within the AD system, enhanced the conversion of substrates to methane. Further analysis indicated that this combined exposure may exacerbate oxidative stress in microbial cells, increase cell membrane permeability, enhance transmembrane transport, and promote conjugative plasmid transfer, all of which contribute to the horizontal gene transfer (HGT) of ARGs. Structural equation modeling analysis confirmed that MGEs are the most significant driving factor for the transfer of ARGs during AD under combined exposure to MET and SMZ. Overall, our findings highlight the role of MET in promoting the transmission of ARGs in a typical man-made anaerobic digestion ecosystem. In the context of the "One Health" concept, reassessing the environmental impact of MET could inspire new approaches to understanding the health of both human society and the environment.