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Opinion

Balancing act: counteracting adverse drug effects on the microbiome

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The human gut microbiome, a community of microbes that plays a crucial role in our wellbeing, is highly adaptable but also vulnerable to drug treatments. This vulnerability can have serious consequences for the host, for example, increasing susceptibility to infections, immune, metabolic, and cognitive disorders. However, the microbiome's adaptability also provides opportunities to prevent, protect, or even reverse drug-induced damage. Recently, several innovative approaches have emerged aimed at minimizing the collateral damage of drugs on the microbiome. Here, we outline these approaches, discuss their applicability in different treatment scenarios, highlight current challenges, and suggest avenues that may lead to an effective protection of the microbiome.

Highlights

Medicinal drugs from various therapeutic classes affect the human gut microbiome.

Countermeasures involve strategies to prevent damage, protect, or restore the microbiome.

These approaches include small molecules, adsorbing materials, dietary interventions, probiotics, live biotherapeutic products, and fecal microbiota transplants.

The development of these strategies is at different stages, ranging from early conceptualization to market approval.

The best approach depends on the specific context and the microbiome trait to be protected.

A trade-off between the benefits of drugs and their risk to the microbiome

One of the most notable advancements in microbiology over the past few decades has been the rise of microbiome science. The study of the human microbiome, in particular, has gained substantial attention due to its close link with various health and disease processes. These microbial communities lie at the proverbial crossroads where host genetics [1], immunity [2], diet [3], and the environment [4] meet: they are directly influenced by these factors, and can, in turn, influence several of them. As such, the human microbiome is central to host physiology, and deviations of community composition from a **homeostatic state** (see Glossary) can be both the cause and consequence of various pathologies [5].

This highlights a key characteristic of the microbiome that makes it an enticing subject of study: its malleability, meaning that it can be manipulated to improve host health. But this malleability also makes it susceptible to unintended – often detrimental – changes; such is the case of drug-induced changes in the gut microbiome, the primary focus of this article. As a result, it becomes crucial to develop treatments that maximize the drug's benefits while minimizing its negative impact on gut microbes. Striking the right balance is essential for maintaining a healthy microbiome, avoiding adverse effects, and thus improving the therapeutic outcome. Various strategies have been proposed to either prevent or counteract the effects of drugs on the microbiome, but most are still in the early stages of development, and the most effective approaches have yet to be determined. We argue that drug-, microbe-, and patient-specific strategies targeting different adverse effects used in conjunction are more likely to be successful than a universal solution.

The two sides of microbiome plasticity

Both antibiotics and **human-targeted drugs** can alter the composition and function of the microbiome [6,7]. These alterations can arise from direct drug–microbe interactions or from changes in the microbial environment (i.e., the host) [8], and lead to shifts in the ecological dynamics and functions of the community. In the case of antibiotics, disrupted states can persist for several months. We have shown that over 200 FDA-approved human-targeted drugs inhibit the

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growth of at least one common member of the human gut microbiome *in vitro* [9]; the human-targeted drug categories with the highest proportion of inhibitory compounds included hormones, antineoplastics, and antipsychotics. Overall, drug-induced perturbations can have a wide range of adverse consequences for the host, such as disrupting **colonization resistance** and increasing the risk of obesity [10].

Despite the risk of adverse effects on the microbiome, the benefits of using appropriate pharmaceutical products in clinical practice generally outweigh the potential side effects. There is, however, a potential solution to this conundrum. The same malleability that makes the microbiome vulnerable to antibiotics also allows compensating or preventing these effects. By delivering beneficial microbes, enzymes, adsorbents, nutrients, or other small molecules to the gut, we can positively influence the microbial community and the gut environment [11]. Such strategies can be employed to mitigate the damage to the microbiome during drug therapy (Figure 1, Key figure).

Our work provides a compelling example of how certain human-targeted drugs can potentially mitigate the side effects of antibiotics on beneficial gut bacteria [12]. Specifically, we have demonstrated that dicumarol can selectively protect *Bacteroides* species, but not pathogens, following erythromycin treatment. We refer to these species-specific antagonistic drug interactions as

Key figure

Strategies for reducing the collateral damage of drugs on the microbiome

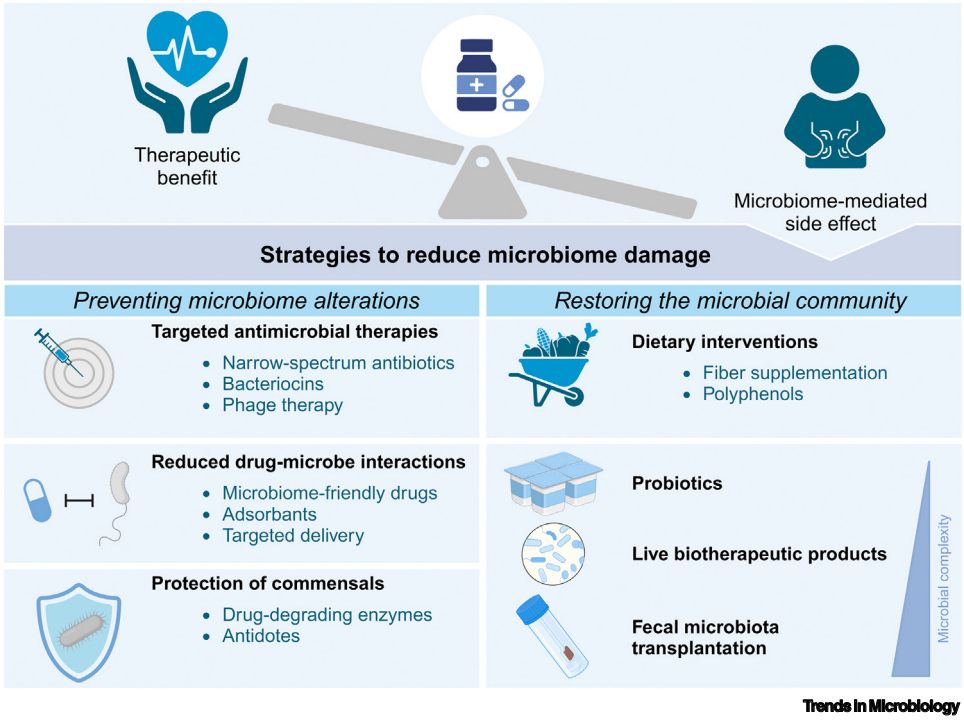

Figure 1. Overall, they can be categorized into two main types: preventive approaches that aim to avoid the drug's impact, and restorative approaches that seek to repair the community's composition after it has been altered. Figure created with BioRender.

Glossary

Adjuvant: additional measures to support or improve a therapy (e.g., to boost the immune system upon vaccination).
Adsorbent: material that collects molecules on its surface (e.g., activated charcoal).
Antidote: a compound that selectively antagonizes the detrimental effect of drugs on gut commensals.
Bacteriocins: a type of antimicrobial peptide produced by bacteria that inhibits the growth of similar or closely related bacterial strains.
Bacteriophage/phage: a type of virus that specifically infects and replicates within bacteria.
Colonization resistance: the ability of indigenous microbiota to prevent colonization by potential pathogens.
Commensal bacteria: beneficial bacteria that are a natural part of a host's microbiome, living in a symbiotic relationship with its host without causing harm.
Fecal microbiota transplantation (FMT): transplantation of stool from healthy donors into the gastrointestinal tract of a patient.
Homeostatic state: condition of stability despite external changes. In the context of the microbiome, this refers to a balanced microbial community that promotes health and prevents disease.
Human-targeted drug: a pharmaceutical compound used because of its therapeutic effect in specific human organs, tissues, or cells.
Live biotherapeutic products (LBPs): a mixture of live microorganisms that are specifically designed and regulated for treating particular diseases, with strict standards for safety and efficacy.
Opportunistic pathogen: a microorganism that typically does not cause disease in healthy individuals but can become pathogenic when the host's immune defenses are compromised.
Polyphenols: a diverse group of naturally occurring compounds, found in plants, which are characterized by the presence of multiple phenolic rings in their chemical structure.
Postbiotic: single molecules or mixtures of bioactive compounds, such as metabolites, derived from bacteria that have a beneficial effect on the host and/or intestinal homeostasis.

antidotes. Administering antidotes simultaneously with antibiotics could help prevent collateral damage to the gut microbiome, even during gastrointestinal infections. By tailoring antidote choice to the specific antibiotic used and the patient's microbiome composition, we could maximize microbiome protection. This approach could prevent the unintended proliferation of antibiotic-resistant and **opportunistic pathogens** such as *Clostridioides difficile*, avoid permanent disruption of the microbiome, such as through the loss of beneficial microbial species, and could even improve the efficacy of other treatments that depend on an intact microbiome, such as anticancer immunotherapies [13].

Prebiotic: a nondigestible food component that selectively stimulates the growth and activity of beneficial microorganisms in the gut.
Probiotic: live microorganism(s) intended to support general health and maintain gut balance, typically subject to less stringent regulation than LBPs.
Synbiotic: a combination of prebiotics and probiotics that work synergistically in a single formulation.

Yet, blindly repurposing drugs as antidotes might lead to unintended consequences due to the effects that these compounds might have on the host. Let us come back to dicumarol, an example that frequently comes up when discussing these results with our peers. Dicumarol should not be directly repurposed as an antidote because it functions as an anticoagulant by antagonizing vitamin K, which is crucial for synthesizing blood-clotting factors in the liver [14]. Even when a human-targeted drug can safely be repurposed as an antidote, alone it is unlikely to be sufficient to mitigate antibiotic damage because each antidote is specific to certain microbial groups, requiring the identification of a large number of antidotes to protect the microbiome as a whole. This may prove challenging to translate into clinical practice. In our view, the value of studying these compounds lies in understanding the molecular workings behind their protective effects on beneficial commensals. Indeed, our ongoing research aims to uncover which cellular processes are altered by antidotes in **commensal bacteria** – not in pathogens – so that these beneficial microbes can evade the action of antibiotics (Figure 2). Ultimately, we hope that this research will set the foundation for the development of **adjuvants** to antibiotics, targeting pathogens without harming commensals or the host [15]. These strategies can be extended to non-antibiotic drugs harmful to the microbiome, so that specific members can be protected, such as those involved in important host-related processes.

Before focusing our attention on strategies to counteract or prevent the adverse effects that drugs can have on the microbiome, it is worth noting that certain drug–microbe interactions

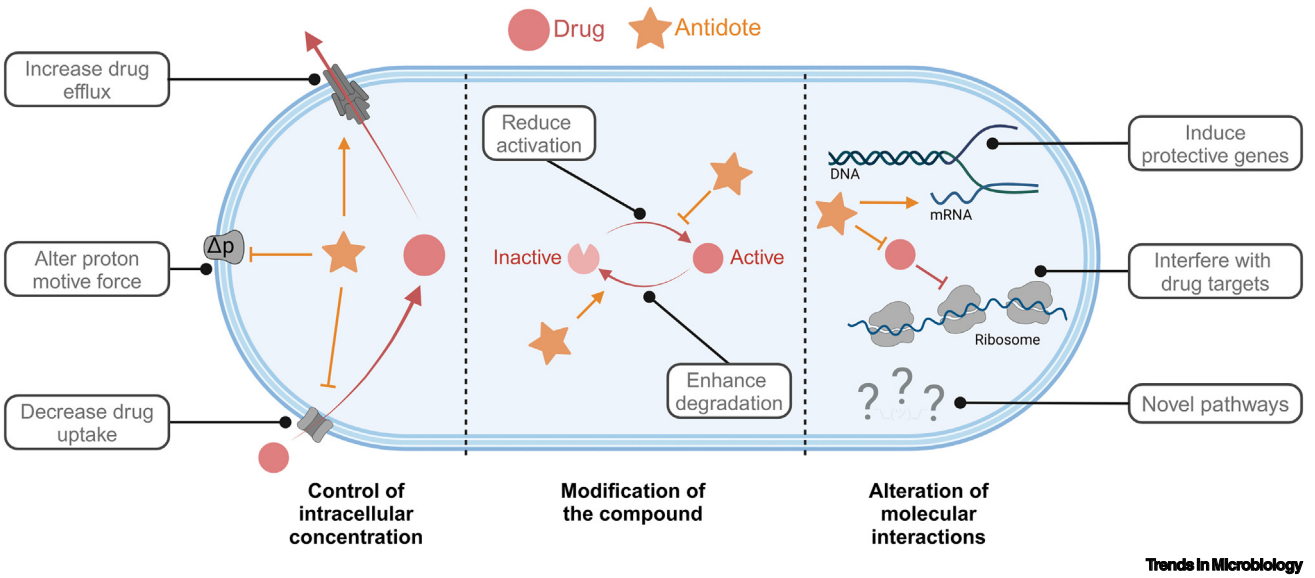

Figure 2. Antidotes can help to counteract the detrimental effect of drugs on commensal microbes via multiple molecular processes. A compound is well suited for microbiome protection when the antagonistic interactions occur on commensal species and not in pathogens. Figure created with BioRender.

may be beneficial to the microbial community or the host. Certain drugs must be biotransformed before they can exert their therapeutic effects, a step that is sometimes performed by the gut microbiome [16]. This is the case with sulfasalazine, a compound used to treat ulcerative colitis and rheumatoid arthritis. Another example is the antidiabetic drug metformin, perhaps one of the best studied interactions between a human-targeted drug and the microbiome. The association between microbiome composition and type 2 diabetes has been shown to be confounded by metformin use [17], a pattern that generalizes to multiple human populations [18]. The antidiabetic effect of metformin is thought to be at least partially mediated by the gut microbiome, as intravenous administration of the drug and oral administration with an antibiotic show limited improvement in glucose tolerance [19]. Metformin users exhibit changes in the abundance of certain taxa, such as increased levels of butyrate producers and the mucin-degrading *Akkermansia muciniphila*. These changes suggest that improved gut epithelial health and altered bile acid metabolism contribute to the antidiabetic effect of the drug [19]. In summary, although most currently described effects of drugs on the microbiome seem detrimental, not all drug–microbiome interactions are harmful and need to be counteracted.

Multiple strategies to prevent or counteract the impact of drugs

Antidotes are just one potential strategy to counteract or circumvent the undesired effects of drugs on the microbial community. Researchers are exploring other approaches, which we can broadly categorize into two groups: preventing microbiome alterations and restoring the microbial community.

Preventing microbiome alterations

Pre-emptive approaches aim to minimize the impact of drugs on the commensals by maintaining the integrity and diversity of the microbiome during drug therapy. This can be achieved by minimizing the use of drugs detrimental to the microbiome, by narrowing the target spectrum of the antibiotics, by reducing the interactions between the drug and the commensals, or by selectively activating protection mechanisms in the commensals (such as the aforementioned antidotes, which are further discussed in subsequent text and in Box 1).

Box 1. The quest for safe antidotes

Compounds that selectively counteract the collateral effects of drugs on gut commensals, so-called antidotes, are valuable tools as long as they can be optimized to avoid impacting the host. However, all the antidotes identified so far also affect the host [12]: dicumarol is an anticoagulant [14], benzbromarone is a uricosuric agent [58,59], and tolfenamic acid is a non-steroidal anti-inflammatory drug [60]. Due to their host activity, these compounds are not easily repurposed for use in combination with antibiotics in clinical settings. As a fellow researcher bluntly put it: 'What's the point of preserving your microbiome if you're going to end up unnecessarily anticoagulated?'.

To find more suitable compounds, a first approach would be to screen large compound libraries for similar antagonistic effects, particularly focusing on compounds that are known or likely to have no effect on the host, such as nutritional compounds. Additionally, modifying the chemical structure of the already identified antidotes could yield derivatives that retain their antagonistic effect without affecting the host.

A complementary approach focuses on identifying the mode of action of antidotes (see Figure 2 in main text). Uncovering the differences between commensals and pathogens that allow antidotes to protect the former but not the latter could provide crucial insights for optimizing antidotes, accelerating their clinical implementation, translating them into medications, and enhancing our general understanding of the gut microbiome and its microbes.

Research using transposon and knockout libraries [61–63] to investigate drug–microbe interactions [27,28,64], alongside large-scale omics analyses of drug-treated microbes [65] is shedding light on potential modes of action. Additionally, modeling methods to predict community dynamics following antibiotic treatment are beginning to be explored [66]. These innovative approaches, combined with comparative genomics across species or strains [67,68], classical molecular biology techniques using gene knockouts in gut microbes [69], and established antibiotic research assays [70,71], will help to elucidate the mode of action of antidotes.

The first – and perhaps most obvious – step to prevent the disruption of the microbial community is to avoid the use of drugs known to affect the microbiome whenever possible. This does not imply withholding treatment from the patient, rather, it means selecting medications that would lead to similar therapeutic outcomes without affecting gut microbes, a concept that has been called 'gut neutrality' [20]. This, however, requires the information to be available to healthcare professionals, which underscores the importance of preclinical screening assays that systematically assess drug–microbe interactions and the inclusion of microbial readouts in clinical trials of new drugs. Even when information is available, such as the collateral damage of different antibiotic classes on the microbiome and the associated risk of *C. difficile* infection [21,22], this knowledge is not yet routinely integrated into therapeutic decision-making. Although this may seem like the most straightforward solution, the path to clinical practice is still long.

Alternatively, therapies can be designed to have a narrower mechanism of action. A recent study reported the development of lolamicin, an antibiotic that specifically targets the transport of lipoproteins between membranes of Gram-negative bacteria. Remarkably, lolamicin strongly inhibited pathogens, including *Escherichia coli* and *Klebsiella pneumoniae,* while sparing commensal bacteria as well as Gram-positive pathogens [23]. This principle could also be applied to human-targeted drugs, in particular if the potential off-targets in bacteria are known. Another example of a microbiome-protecting compound is chlorotonil A, which is retained in *C. difficile* spores. This compound prevents the outgrowth of vegetative cells, thereby preventing relapsing infections [24]. Additionally, highly specific approaches are being explored to target pathogens while sparing other species, such as the use of **bacteriophages** [25], **bacteriocins** [26], species-specific antibiotic synergies [27,28] or clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein (Cas) (CRISPR-Cas)-based methods to disrupt specific and essential bacterial genes [29]. However, these methods require precise identification of the causative pathogen before treatment. In addition, the high level of specificity can lead to variability in responses among different bacterial strains due to spatiotemporal adaptations, potentially complicating the effectiveness of these targeted therapies.

The negative effects of drugs on the gut microbiome can be reduced if the drugs do not interact with the gut microbes in the first place. This concept is the basis for using **adsorbent** agents and so-called anti-antibiotics. These substances bind to antibiotics – and to other compounds – allowing the antibiotics to be absorbed by the host while preventing them from reaching gut microbes [30–32]. This approach ensures that the antibiotics maintain their intended concentration in the bloodstream while minimizing disruption to the gut community. However, strategies that locally reduce drug concentrations cannot be used for treating gastrointestinal infections or diseases that require the drug to act in the large intestine, such as inflammatory bowel disease or colorectal cancer. Similarly, co-treatment of intravenous β-lactam antibiotics with oral β-lactamases can destroy β-lactam residues in the colon before they can alter the microbiome [33]. This approach is effective only for β-lactamase-sensitive antibiotics not used with β-lactamase inhibitors. This principle could be applied to other antibiotics and even human-targeted drugs as long as appropriate drug-degrading enzymes are available [34]. Finally, drug concentrations in the gut can be minimized by using targeted drug delivery techniques such as liposomes or nanoparticles [35]. These approaches lower the overall dosage requirements and prevent adverse effects in nontarget organs.

As already mentioned, antidotes can selectively rescue members of the genus *Bacteroides* by antagonizing erythromycin [12] (Box 1). Similar scenarios are conceivable where antidote compounds compete with antibiotics for binding sites, inhibit pathways required for the activation or metabolism of the antibiotic, interfere with drug uptake or efflux, or affect the expression of

genes important for the activity of the antibiotic (Figure 2). Note, however, that a drug's antidote nature is not universal, and a compound that rescues one microbe can inhibit another. Indeed, tolfenamic acid, dicumarol and benzbromarone – compounds that help *Bacteroides* to survive erythromycin exposure [12] – also have adverse effects on other commensals bacteria [9]. We are just beginning to uncover these microbiome-intrinsic protection mechanisms which are largely untapped but could lead to new ways to prevent drug-induced microbiome alterations.

Restoring the microbial community

Contrary to pre-emptive methods, restorative interventions aim to return the community to a healthy state, effectively reversing the changes caused by the drugs. We still lack a deep understanding of the principles that govern microbiome recovery after perturbations, which hinders our ability to rationally develop effective intervention strategies to correct a disrupted microbiota. Nonetheless, diverse methods are available that are mainly grounded in empirical observations. These include dietary interventions, the intake of **probiotics** or **live biotherapeutic products (LBPs)**, and **fecal microbiota transplantation (FMT)**. Importantly, since restoration approaches typically do not depend on the specific drugs causing the perturbation, they are broadly suited to counteract a wide spectrum of microbiome disturbances.

Dietary interventions can strongly influence the microbiome and thus be used for restoration [11]. Food components that support the growth of beneficial microbes are known as **prebiotics**. Fiber and other plant-derived substances are particularly well-studied for their positive effects on host health through microbiome modulation [36]. Dietary fibers promote the growth of bacteria that produce short-chain fatty acids (SCFAs), which are crucial for immune regulation [37] and the maturation of the gut epithelium, helping to maintain the gut's anaerobic environment [38]. Research in mice has shown that fiber supplementation can counteract antibiotic-induced disruptions to the microbiome by preserving gut anaerobic conditions [39,40]. Additionally, prebiotics can help to prevent enteric infections following drug treatment, as SCFAs can inhibit the growth of harmful gut pathogens such as *Salmonella* Typhimurium [41]. Besides fiber, other plant-derived compounds, such as **polyphenols**, have been shown to reduce the loss of microbial species after antibiotic treatment in mice [42]. The use of **postbiotics** is also being explored; these are single molecules or mixtures of bioactive compounds, such as metabolites, derived from beneficial microbes [43].

Probiotics are preparations containing one or a few live bacteria or yeast strains that provide health benefits to the host [44]. These microorganisms are expected to help restore the homeostasis of a drug-disturbed microbiome [45], although not necessarily to its pre-treatment state. They are commonly used during and after antibiotic treatment, with or without a medical prescription [46], to restore the microbiome or avoid gastric side effects. However, the benefits of using probiotics after a course of antibiotics are debated due to the small sample sizes of trials conducted so far, which has prevented researchers from reaching a definitive conclusion about their effectiveness. A clinical trial of multi-strain probiotic supplementation following antibiotic treatment found that probiotics slowed the return to baseline microbiome composition and impaired the recovery of the host's transcriptional profile compared to spontaneous recovery [47]. Similarly, a recent meta-analysis concluded that probiotics may not significantly improve microbiome diversity after treatment [45].

Unlike probiotics, LBPs are specifically engineered or selected microbial strains designed to treat particular diseases or conditions, offering more precise therapeutic benefits [48]. Their effectiveness in restoring drug-perturbed microbiomes has been primarily studied in the context of *C. difficile* infection [49]. Recently, innovative methods have emerged to make even strictly

anaerobic species usable as LBPs. For example, techniques such as co-isolation and adaptive evolution have enabled *Faecalibacterium prausnitzii* to tolerate oxygen exposure [50].

On the other end of the complexity spectrum is FMT. This procedure involves administering feces from healthy donors into the recipient's gastrointestinal tract using capsules, colonoscopy, or enema. The aim is to restore the microbiome by transferring a complex community of microorganisms directly into the gut. FMT has been successfully used to treat *C. difficile* infections and has been shown to reduce the abundance and expression of antimicrobial resistance genes in recipients [51,52]. Studies in mice have demonstrated that disruptions in the microbiome caused by antibiotics and chemotherapy can be immediately reversed with FMT [53]. However, FMT is a complex procedure that requires thorough screening of the donor's feces to prevent infections, specialized administration methods, and can lead to unintended gastrointestinal and immune side effects [54]. Consequently, several alternatives are under development [55], including spore preparations from human feces (FDA-approved, Seres Therapeutics), filtered stool products (FDA-approved, Rebiotix/Ferring), pills with freeze-dried stool (Finch Therapeutics), and cocktails of a few individually selected and cultivated bacteria (Vedanta Biosciences), which bring us back to LBPs with defined compositions.

All restoration methods that depend on living organisms face a common challenge: they may be affected by residual antibiotics or other human-targeted drugs. To reduce this interference, these methods should be applied only after drug concentrations in the intestine have sufficiently decreased.

Choosing the right approach

From our brief overview of available methods, it is clear that each aims to address different problems and has its own advantages and drawbacks. Instead of relying on a single approach, we recommend pursuing multiple methods simultaneously, so that their strengths can complement each other. Combinatorial strategies are beginning to emerge, such as in **synbiotics,** which couple living microorganisms and bacterial growth-promoting substrates to provide health benefits to the host [56].

To select the appropriate countermeasures, the drug's target and location, its intestinal concentration, its effect on the host and the commensals affected should be clearly identified. For instance, using an adsorbent such as activated charcoal, along with an antidote, might be effective during macrolide treatment. However, this approach would be less suitable for treating a gastrointestinal infection or if the primary therapy involves a proton pump inhibitor, which affects the microbiome by altering host physiology rather than directly interacting with microbes [57]. Additionally, strategies such as antidotes must be tailored to the microbiome of the patient, as their effectiveness relies on using the right compounds on the right microbes; given that the effect of certain compounds can be strain-specific, a high taxonomic resolution is required for healthcare professionals to make an informed decision. Therefore, it is crucial to understand the general problem, the intended outcome, and the specific characteristics of the microbial community being intervened.

The successful implementation of these therapeutic strategies depends on a thorough understanding of the ecological, evolutionary, and biochemical foundations of drug–microbe interactions. This means that, as a field, we must continue to study the functions of individual bacterial genes, strains, and species, their ecological relationships, their responses to various chemical compounds, and the interactions between microbes, drugs, and the host. By doing so, we will be able to develop tools to prevent harm or help the microbial community to recover.

Concluding remarks

Approaches to mitigate the collateral damage of drug treatment on the gut microbiome are still in their early stages, and their efficacy, safety, and clinical usefulness are yet to be proven. For more selective and specific measures, such as antidotes to protect the gut microbiome, we lack a fundamental understanding of the underlying cellular processes. This knowledge is essential for optimizing these methods and expanding their clinical applications.

Key challenges include understanding what constitutes a healthy and functional microbiome and determining whether overall microbial diversity and biomass are important or if specific species or microbial functions play a more crucial role (see Outstanding questions). A deeper functional understanding will pave the way for more targeted and personalized strategies, potentially rekindling interest in microbiome-based therapies among pharmaceutical companies.

Outstanding questions

When protecting the microbiome from drug-induced damage, which aspect should be prioritized: total biomass, specific microbial functions, the presence of key individual species, or a combination thereof?

How can the engraftment of LBPs into a microbiome be optimized?

Do LBPs interfere with other therapies by degrading or bioaccumulating drugs, or by disrupting immunotherapies that rely on a healthy microbiome?

Given that the adverse effects of drugs on the microbiome take a long time to become clinically apparent, or appear only under certain conditions, which microbiome metrics should be evaluated by regulatory agencies for approval of microbiome-preserving therapeutics?

Does the use of microbiome-protecting compounds such as antidotes lead to the emergence and transmission of antimicrobial resistance?

What strategies can be implemented to protect commensal species from indirect drug effects, such as drug-induced alterations in host physiology?

Since the gut microbiome can indirectly affect therapeutic outcomes – for example, by altering the expression of the drug target in the host through bacterial metabolites – how can these adverse effects be mitigated?

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Declaration of interests

L.M. is listed as a co-inventor on the following patents (or patent applications): EP3838269A (published 23 June 2021) Compounds & Pharmaceutical Compositions for Prevention-Treatment of Dysbiosis, Antidotes for Microbiome Prevention; WO/2019/158559 (published 22 August 2019) Repurposing compounds for the treatment of infections and for modulating the composition of the gut microbiome; and WO/2019/154823 (published in 15 August 2019) *In vitro* model of the human gut microbiome and uses thereof in the analysis of the impact of xenobiotics.

Declaration of generative AI and AI-assisted technologies in the writing process

ChatGPT-4, a language model developed by OpenAI in San Francisco, CA, USA, helped in language editing and proofreading.

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