FEATURES

Frontiers of Microbially-Informed Medicine

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Introduction

Pharmacomicrobiomics is an emerging field at the intersection of pharmaceutical science and the microbiome. In this rapidly developing discipline, research investigates the interactions between current therapeutics and the patient microbiome, often focusing on the gut microbiome. The gut microbiome is a community of trillions of microorganisms that reside in the human gut—namely the stomach, small intestine, and large intestine. These microbes are constantly changing in accordance with patient diet and lifestyle, and recent research has shown that many diseases can be linked to certain microbiome compositions (Blackmer-Raynolds and Sampson, 2023). In the past, most microbiome research has been on metabolic interactions with antibiotics and plant-derived therapies, but pharmaceuticals are the focus in this new frontier of research (Saad et al., 2012).

Current research in pharmacomicrobiomics specifically explores pharmaceutical–microbiome interactions and aims to understand how pharmaceuticals can be most effective for patients. In some cases, this may be attempting to regulate the microbiome composition through the use of probiotics or dietary changes (Arga et al., 2024). In other cases, researchers are now considering the efficacy of personalized pharmaceuticals. These pharmaceuticals are engineered to work better in conjunction with the patient-specific microbiome. This new approach holds great potential in several disease-specific cases including irritable bowel disease, cancer, Parkinson's, and mental illness, yet the field of pharmacomicrobiomics has the potential to revolutionize the treatment of many other diseases with continued research.

In order to illustrate fully the potential of the pharmacomicrobiomics field, it is important to have a comprehensive understanding of the key microbes in the human microbiome and the ways in which they interact with drugs. By studying individual cases where microbes and pharmaceuticals have worked in conjunction as a more efficient treatment or where microbes have attenuated the effects of other pharmaceuticals, exploration and understanding of the frontiers of pharmacomicrobiomics can begin.

Profile of Human Gut Microbiome: Who are the main microbes?

Studies have found that each individual has a microbiome that is completely unique and is influenced both by early development in childhood and day-to-day lifestyle. The more diverse the gut microbiome is, the healthier the individual is, with the most diverse microbiomes even decreasing the individual's chance of developing a number of diseases, both gastrointestinal-related and non-gastrointestinal-related (Rinninella et al., 2019).

The human gut microbiome's vast diversity makes it nearly impossible to detail every unique microorganism that plays a role in our gut. **Figure 1** shows the typical composition of the human microbiome. A broader perspective allows us to gain a deeper understanding of the three most important groups of microbes at the phylum level of order: Firmicutes, Bacteroidetes, and Actinobacteria.

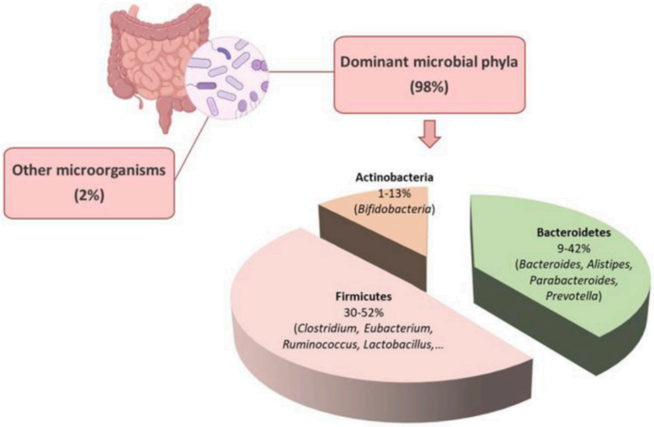

Fig. 1. The typical composition of microbes found in the human gut microbiome (Conz et al., 2023).

Firmicutes

In the Firmicutes phylum, there are five main genera of microorganisms including *Lactobacillus, Bacillus, Clostridium, Enterococcus,* and *Ruminococcus*. Increased presence of Firmicutes is linked to consumption of high-fiber carbohydrates during early childhood development. The primary function of Firmicutes in the microbiome is carbohydrate digestion (Ottman et al., 2012). The different genera of the Firmicutes respond varyingly to high animal protein versus high fiber diets. Firmicutes play a large role in the adult microbiome as they are one of the most dominant phyla next to Bacteroidetes and Actinobacteria (Rinninella et al., 2019).

Bacteroidetes

The most important organisms of the Bacteroidetes phylum are *Bacteroides* and *Prevotella*. These microbes are experts at digesting protein and carbohydrates, a mechanism they perform often in the large intestine (Thomas et al., 2011). Bacteroidetes increase when animal proteins are introduced into the childhood diet. High levels of *Bacteroides* are linked to diets that include more animal protein, which is similar to the standard Western diet. A high-fiber diet is linked to a decreased level of *Bacteroides* (Rinninella et al., 2019).

Actinobacteria

Actinobacteria are not as prominent as the other two phyla of microorganisms found in the human gut. Similar to Bacteroidetes, Actinobacteria aid in the digestion of proteins and carbohydrates, mostly in the large intestine (Binda et al., 2018). There is primarily one genus of Actinobacteria of relevance to the gut microbiome, *Bifidobacterium*. Infants who were breastfed tend to have more diverse *Bifidobacterium* microbiota than formula-fed infants. Actinobacteria are also increased by a high animal protein diet (Rinninella et al., 2019).

Within this diverse microbial community, microbes work together to keep us healthy. Different compositions of these key microorganisms have a notable impact on human health. For example, the Bacteroidetes-to-Firmicutes axis is a ratio of the two phyla in the gastrointestinal composition that is being studied as a potential biomarker for obesity among other diseases (Magne et al., 2020). The Bacteroidetes-to-Firmicutes axis is a strong indicator of the level of an individual's microbiome diversity. On average, diversity is maximized when Firmicutes make up ~80% and *bacteroidetes* make up ~15% of the microbial population (Manor et al., 2020).

Naturally, relative microbial diversity is variable, making some individuals more likely to develop certain chronic diseases and conditions. For example, children with obesity have been linked to increased levels of Firmicutes and decreased Bacteroidetes. Furthermore, irritable bowel syndrome patients have been identified with elevated Firmicutes and depleted Bacteroidetes and Actinobacteria (Rinninella et al., 2019). The microbiome has been shown to be indicative of conditions beyond the bowel, including type 2 diabetes, Alzheimer's, Parkinson's, autism, and even stress.

Research Areas at the Forefront

The main focus of the field of pharmacomicrobiomics is the interactions between these microorganisms and pharmaceuticals. There are a plethora of routes that researchers are taking in an attempt to tackle this project that spans multiple disciplines of medicine. These cases range from oncology to psychiatry, and each brings exciting new approaches to their respective fields.

Oncology

The gut microbiome has been linked to interactions with traditional cancer therapeutics. In some cases, the drugs begin to accumulate in the microorganisms, and, in other cases, the microbes directly metabolize the drugs into a less effective alternative. Sometimes, however, the microbes benefit the patient. In most cases, the specifics of the mechanisms of drug-microbe interactions are unknown and are currently under investigation (Conti et al., 2022).

Traditional chemotherapy pharmaceuticals take an untargeted approach in their attacks, simply hoping to have a meaningful efficacy against cancer cells. Research has suggested that *Bifidobacterium* strains may be able to work in conjunction with platinum-based drugs—such as cisplatin and carboplatin—to reduce tumor growth. The bacteria and platinum-based drug work together to boost T cell levels in the body, effectively raising attacks on cancer cells. There are also cases where microbes cause drugs to become reactivated. Drug reactivation can lead to increased microbiome disruption, and even further internal injury (Conti et al., 2022).

In oncology, researchers are currently applying prebiotic, probiotic, antibiotic, and fecal microbiota transplants in an attempt to boost the efficacy and safety of cancer therapies. These approaches are all meant to alter the gut microbiome composition in order to make it more compatible with therapy (Conti et al., 2022). Attempts to personalize oncology using pharmacomicrobiomics represent another exciting frontier. One group was able to develop a method for mapping drug-microbe interactions within an individual (Javdan et al., 2020). This approach, shown in **Figure 2**, illustrates how further mapping would allow for individualized patient predictions of drug efficacy.

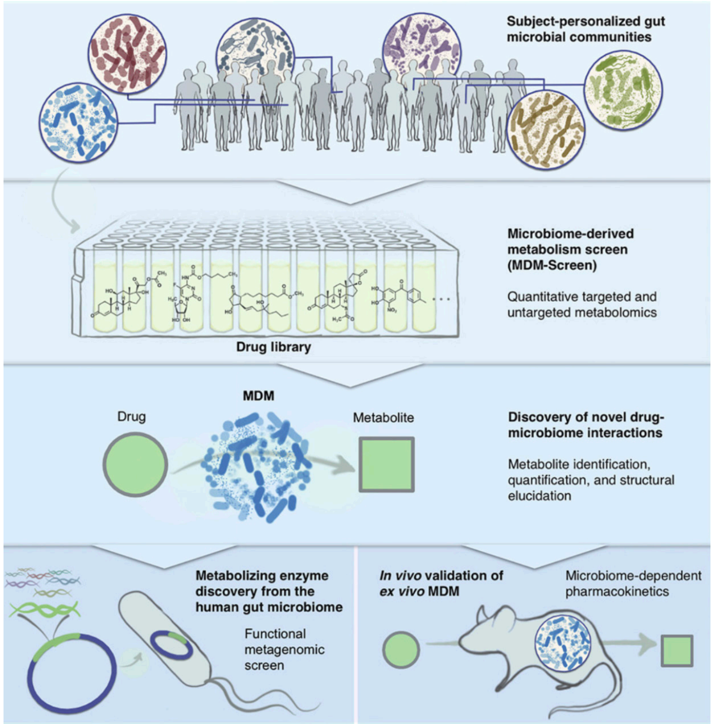

Fig. 2. Possibilities for personalized medicine (Javdan et al., 2020).

Parkinson's

Parkinson's disease is characterized by the loss of dopaminergic neurons, which leads to a deficiency of dopamine in the brain and prevents the brain from executing smooth movements. This loss of fine motor control causes patients to suffer from shaking, stiffness, and instability, significantly impacting their quality of life (National Institute of Neurological Disorders and Stroke, n.d.). The primary drug currently used for Parkinson's patients is levodopa (L-dopa). Levodopa works against Parkinson's disease by crossing the blood-brain barrier and becoming dopamine, serving as a replacement for naturally-produced dopamine in patients with Parkinson's. Often, levodopa is metabolized in the bowel before it can reach the brain, where it is useful. When metabolized outside of the blood–brain barrier, it can no longer cross through to the brain. Even when administered with drugs that are supposed to counteract the metabolism of levodopa, efficacy is still low (Maini Rekdal et al., 2019).

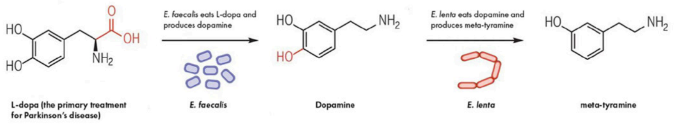

Fig. 3. Levodopa-microbe interaction pathway (Maini Rekdal et al., 2019).

With the rise of pharmacomicrobiomics, a new solution to levodopa metabolism has also become apparent. One study investigated the drug-microbe interactions present during levodopa metabolism. The study found that *Enterococcus faecalis* is likely the primary metabolizer of levodopa, even in the complex microbiome. The levodopa can be even further metabolized by *Enterococcus lenta* (Maini Rekdal et al., 2019). This metabolic process is shown in **Figure 3.** Knowing that these interactions occur will allow researchers to consider more advanced solutions for preventing the metabolism of levodopa.

Irritable Bowel Disease

Irritable bowel disease (IBD) is another medical condition commonly treated by medications that can have their efficacies impacted by drug-microbe interactions. IBD is characterized by increased immune activity within the gastrointestinal tract that leads to extreme inflammation, scar tissue buildup, narrowing, and other complications. IBD treatment can be approached using five different classes of therapeutics: aminosalicylates, corticosteroids, immunomodulators, anti-TNF biologics, and small molecule inhibitors. Sometimes, intestinal microbes can activate therapeutics, but gut microbes can often render these drugs completely useless (Becker et al., 2023).

The immunomodulator class of therapeutics works primarily by repressing the immune system in order to prevent the immune system from attacking the bowel. Thiopurines, a group of immunomodulators, have been connected to microbe interactions that increase the efficacy of the drug and open up a pathway to making thiopurines more localized (Becker et al., 2023). In individuals with IBD, *C. concisus, E. coli*, and *B. fragilis* are more common in the microbiome. These strains together are capable of converting the thiopurines into a more active form of the drug **(Fig. 4).** These microbes could eventually allow the anti-inflammatory effects of thiopurines to be more targeted and their adverse effects to be minimized (Becker et al., 2023)

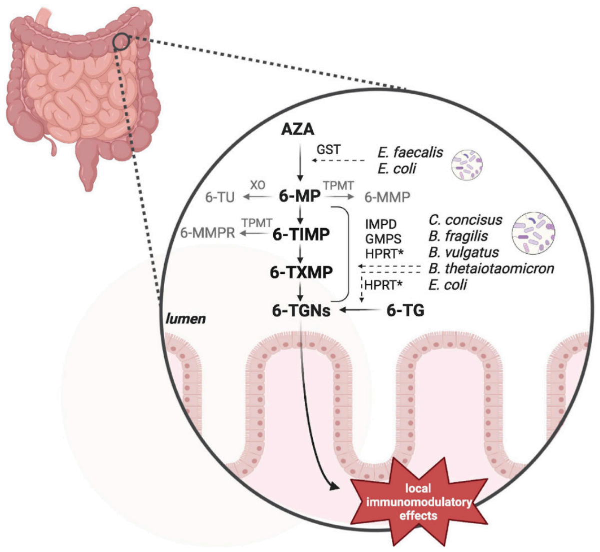

Fig. 4. Thiopurine-microbe interaction pathway (Becker et al., 2023).

Biologics—drugs produced by biological mechanisms—are very popular in the IBD treatment space. These therapeutics work to prevent inflammation in IBD patients. In order to do this, they primarily block messages from the immune system. TNF-α inhibitors are a group of therapeutics that both promote healing and block an essential protein in the inflammatory cycle (Biologics and Inflammatory Bowel Disease (IBD), n.d.). Patients often gain antibodies against the medications and must switch. Notably, some microbes may be able to degrade these antibodies naturally (Becker et al., 2023). Furthermore, if doctors had a clear understanding of the microbiome-biologic interactions, it may be easier to predict the most effective treatment.

Psychiatry

Studies have shown that the gut microbiome even has an impact on mental health and mood. For example, the microbiome has been shown as relevant in patients with psychotic disorders. Increased gut microbiome diversity has been linked to healthy patients, while decreased diversity is generally linked to patients with mental health disorders. Patients who take antipsychotic and antidepressant medications experience an increase in *Bifidobacteria* and *Lactobacillus* strains and an overall improved gut microbiome diversity in comparison to before treatment (Minichino et al., 2024).

There is a strong correlation between postpartum depression and gut microbiome disruptions. After birth, it is common for patients to experience fluctuations in microbiome composition, mainly related to Firmicutes and Bacteroides. This can cause changes to the processing of molecules such as estrogen, progesterone, and serotonin. One enzyme, β-glucuronidase, is known for its role in metabolizing estrogen to an overactive form. Research suggests that the microbiome disruption that occurs postpartum may also interfere with this enzyme—and potentially others—causing a decrease in hormones like estrogen and progesterone. This lack of hormone balance may be one contributor to the development of postpartum depression (Zhang et al., 2023).

Further research must be conducted at the intersection of psychiatry and medicine. At this point, correlations between prescriptions and microbiome diversity have been made, but there is little known about the mechanisms involved. An emphasis on the mechanisms in further studies may illuminate better solutions for patients.

Discussion

The field of pharmacomicrobiomics promises to provide a novel approach to the treatment of a large variety of medical problems. As this new field emerges, there are some limitations to current solutions. With such a new field, there is a necessity for more specific research on mechanistic interactions, and, unfortunately, there are many drugs and microbes to be documented. It will take a large amount of time to completely understand every interaction. There is a necessity for more clinical *in vivo* and *in vitro* experimentation.

The cases presented here are at the forefront of innovation. As researchers continue to realize the importance of these microbe–medicine interactions, research may be able to illuminate further interactions. The efficacy of old drugs and new drugs alike may be optimized by these studies. It seems as though the field is quickly moving towards precision medicine, which would allow practitioners to present solutions that take patient biology and lifestyle into account in order to best treat ailments (Zhao et al., 2023). By gaining a better understanding of the molecular mechanisms involved in complex interactions, researchers become closer to identifying improved solutions for patients across many disciplines. Studying pharmacomicrobiomics allows for more informed engineering and application of pharmaceuticals.

Pharmacomicrobiomics studies create exciting possibilities for medicine in the future. Focusing on drug–microbe interactions in the gut has the potential to greatly improve clinical outcomes of therapeutics. In all fields of medicine, if doctors could compare a patient's individual microbiota profile with potential drug interactions, patients would be able to avoid wasting time finding the proper treatment. Prescriptions could be optimized for patients, avoiding unnecessary side effects. If there was a greater understanding of drug–microbe interactions, doctors and researchers would also have a better understanding of how pharmaceuticals behave within our bodies. This expansion of understanding would altogether improve healthcare efficiency and societal health.

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