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Review

Exploring Microbiota-Based Interventions for Different System Diseases: Adjuncts to Targeted Pharmaceutical Therapies

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Abstract

Pharmacomicrobiomics is the study of drug–microbiome interactions. It examines the dynamic relationship between the drug, the host, and the microbiome, and has become a rapidly evolving area in the realm of pharmacology and personalized medicine. Emerging evidence demonstrates that the gut microbiome can influence the pharmacodynamics and pharmacokinetics of drugs through various mechanisms, while drugs can simultaneously alter microbial composition. Treatment approaches include regular targeted pharmaceutical therapies (e.g., antibiotics, antidepressants) and alternative treatment approaches (e.g., CAM treatments such as supplements and herbs). Microbiome-based medication treatment is an alternative treatment approach that has been studied extensively in the last decade. This article reviews the current knowledge on drug–microbiome interactions across multiple therapeutic systems, including cardiovascular, central nervous system, gastrointestinal, respiratory, endocrine, oncologic, musculoskeletal, anti-infective therapies, and supplements (such as melatonin). We also highlight the various pathways by which microbes can alter the mechanisms (such as drug absorption), bioavailability, efficacy, and incidence of adverse effects, along with highlighting the clinical implications of drug-induced dysbiosis.

Keywords: microbiome; Pharmacomicrobiomics; gut biotics; fermented foods

1. Introduction

Pharmacomicrobiomics is the study of the interactions between gut microbiota, the host, and medication. It is a new field, with the name coined by Rizkallah et al. in 2010 [1]. The microbiome plays an important role in human health and disease, influencing processes such as immune regulation and metabolism [2]. Despite the standard dosing of medications, it is well known that individual responses to a specific drug vary greatly in terms of both efficacy and toxicity. Each drug response depends not only on genetics (pharmacogenetics and pharmacogenomics) but also on the composition of the human microbiome. Pharmacomicrobiomics integrates these components by studying how microbial factors, along with traditional pharmacokinetics and pharmacodynamics, can influence drug response, providing a promising framework to help us to better understand the variability of patient responses to drugs.

Emerging evidence suggests that clinical outcomes are strongly affected by individual variability in drug efficacy and safety [3]. For example, response rates to commonly

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prescribed drugs fall between 50% and 75% due to these inter-individual's variabilities [4]. Genetics, although widely studied, only explains a portion of these different responses. Pharmacomicrobiomics has therefore emerged as a promising field to address the remaining unexplained response variability. The gut microbiome, often referred to as the "second genome", plays many roles in the human body, including immune system modulation, metabolism, and drug response regulation [3]. Nevertheless, important gaps remain in translating pharmacomicrobiomic insights into clinical practice. Much of the existing evidence is derived from preclinical models or small observational studies. This review aims to summarize the current knowledge on drug–microbiome interactions across major therapeutic systems, highlighting key mechanisms, clinical implications, and future directions for incorporating pharmacomicrobiomics into personalized medicine.

1.1. "Literature Search and Selection Methods"—Search Strategy

A literature search was performed using the electronic databases MEDLINE (1966–August 2024), EMBASE and SCOPUS (1965–February 2026), and DARE (1966–February 2026). The main search terms were microbiome, pharmacomicrobiomics, drug–microbiome interactions, gut biotics, and fermented foods. Non-English articles were excluded.

This article is a non-systematic, narrative review.

1.2. Mechanistic Framework

Microbiome-based interventions involve live or non-living microorganisms or their derivatives and differ from standard pharmaceuticals in their mechanisms of action. Microbiome-based therapeutics include prebiotics, probiotics, live microorganisms, microbiome mimetics, and others like fermented foods and fecal microbiota transplantation (FMT) [5]. Fecal microbiota transplantation (FMT) is a procedure in which fecal material containing distal gut microbiota is collected from a healthy donor and transferred to a patient with a disease or disordered gut microbiota via a range of delivery routes, including colonoscopy, nasogastric tube, capsules, and enema [6]. They exert a biological effect by modulating microbiome–host interactions and may target any human-associated microbiome, including the gut, skin, oral, respiratory, urogenital, and nasal microbiomes [7]. Importantly, the microbiome plays a central role in regulating host immune responses and therapeutic outcomes, further supporting its relevance as a target for intervention [8,9]. Microbiome-based interventions can be categorized using a schematic mechanistic framework: (a) direct microbial metabolism of drugs (e.g., β-glucuronidase, azoreductase); (b) microbial alteration of host metabolic enzymes or transporters; (c) microbial modulation of immune responses (e.g., in immune checkpoint inhibitors (ICIs)); (d) drug-induced reshaping of the microbiota (e.g., antidepressants, proton pump inhibitors (PPIs)); and (e) microbial metabolites (e.g., short-chain fatty acids (SCFAs), Trimethylamine N-oxide (TMAO)) modulating drug efficacy. A detailed summary of the mechanistic framework is shown in Table 1.

1.3. Mechanisms

Drug–microbiome interactions are bidirectional, influencing drug efficacy, toxicity, and individual treatment responses (pharmacomicrobiomics). Microbes can metabolize, deactivate, or activate drugs, while medications (including non-antibiotics like PPIs, metformin, and antipsychotics) alter microbial composition, sometimes creating adverse effects [23]. Bacteria chemically alter the structure of drugs, with reductive and hydrolytic reactions being the most common (biotransformation) [23]. Microbes can store drugs intracellularly, reducing their availability in the gut (bioaccumulation) [23].

Table 1. Basic mechanisms of drug–microbiome reactions.

Mechanism	Description	Representative Drug Examples (from This Review)	Clinical Consequences	References
Direct Microbial Biotransformation	Bacterial enzymes chemically alter drugs through reduction, hydrolysis, or deconjugation	Sulfasalazine (azoreductase); Irinotecan (β-glucuronidase); Digoxin (*Eggerthella lenta*)	Drug activation or inactivation; altered toxicity (e.g., irinotecan-induced diarrhea); dosing variability	Schröder et al., 1973 [10]; Haiser et al., 2014 [11]; Ting et al., 2022 [12]; Al-Btoosh et al., 2026 [13]
Indirect Microbial Biotransformation	Microbiome modulates host enzymes, transporters, bile acids, and immune pathways	Metformin; immune checkpoint inhibitors; statins; GLP-1 agonists	Altered efficacy; immune responsiveness; metabolic side effects; treatment resistance	Wu et al., 2017 [14]; Viaud et al., 2013 [15]; Sivan et al., 2015 [16]; Al-Btoosh et al., 2026 [13]
Microbial Bioaccumulation	Intracellular sequestration of drugs by bacteria without chemical modification	Montelukast; Roflumilast; antidepressants; cardiovascular drugs	Reduced bioavailability; delayed absorption; variable plasma levels	Klünemann et al., 2021 [17]; Al-Btoosh et al., 2026 [13]
Drug-Induced Microbiome Remodeling (Pharmacoecology)	Drugs reshape microbial composition and function through antimicrobial or metabolic effects	PPIs; antidepressants; antipsychotics; metformin; corticosteroids	Dysbiosis; infection risk; metabolic derangements; altered long-term outcomes	Freedberg et al., 2014 [18]; Lukić et al., 2019 [19]; Morgan et al., 2014 [20]; Al-Btoosh et al., 2026 [13]
Microbial Metabolite-Mediated Modulation	Microbial metabolites influence drug pharmacodynamics and host response	SCFAs (chemotherapy, diabetes); TMAO (CV drugs); bile acids (metformin)	Enhanced or diminished efficacy; modulation of inflammation and immunity	Zidi et al., 2021 [21]; Wilmanski et al., 2022 [22]; Al-Btoosh et al., 2026 [13]

Key potential mechanisms associated with gut microbiota regulation include the modulation of gut microbiota composition, alteration of gut microbiota metabolites, enhancement of intestinal barrier function, and suppression of inflammation [23]. Other mechanisms include the following. (a) Metabolic Interference: Microbes change the environmental conditions of the gut (e.g., pH) or produce metabolites that interfere with host drug metabolism. (b) Pharmacomicrobiomics (microbiome on drugs): Gut bacteria can metabolize drugs, altering their bioavailability, toxicity, and efficacy. For instance, certain gut bacteria metabolize the anti-Parkinson's drug levodopa before it reaches the brain. (c) Pharmacoecology (drugs on microbiome): Beyond antibiotics, many medications affect the microbiome. Over 200 FDA-approved human-targeted drugs inhibit the growth of common gut microbes, including PPIs and anticancer drugs. Proton pump inhibitors (PPIs), metformin, NSAIDs, and laxatives are known to significantly alter gut microbiota, often in a dose-dependent manner [13,24,25].

2. Pharmacomicrobiomics of Different Classes of Drugs/Different System Drugs

2.1. Pharmacomicrobiomics of CV Drugs

Cardiovascular diseases (CVD) continue to be one of the leading causes of death; therefore, it is important to understand the relationship between cardiovascular (CV) medications and the human body. In this section, we discuss some of the most common CV medications, including anti-platelet agents, anticoagulants, antihypertensive medications, lipid-lowering agents, and antiarrhythmic agents, and their interactions with the gut microbiota [26].

Warfarin dosing can be complicated as it is affected by several factors, and few studies consider the role of the gut microbiota. A study collected stool samples from 200 inpatients undergoing heart valve replacement (HVR), which were further classified based on response to warfarin (low responder (LR), high responder (HR), and normal responder (NR) [27]). The results showed that the genus *Escherichia-Shigella* was significantly greater in the LRs ($p = 3.189 \times 10^{-11}$), while the genus *Enterococcus* was significantly greater in the HRs ($p = 1.249 \times 10^{-11}$). Moreover, the amount of vitamin K2 (VK2), which counteracts the effects of warfarin, was much higher in the LR group than in the HR group ($p = 0.005$) [27]. Similarly, a small cross-sectional study examined the relationship between the gut microbiota and TTR (time in therapeutic range) of warfarin. The main findings included an association between H-TTR, better control of anticoagulation, and greater gut microbiota diversity. Beneficial taxa identified included *Bacteroides. stercoris*, *Barnesiella. intestinihominis*, and *Coprococcus.* Overall, this highlights how the gut microbiota influences the therapeutic efficacy of warfarin and might play a role in improving patient outcomes [28].

Administration of aspirin has also been shown to have effects on the gut microbiota composition. For instance, Prizment et al. 2020 found that amounts of *Prevotella*, *Veillonella*, *Clostridium XlVa* and *Clostridium XVIII clusters* were different in those who received aspirin compared to placebo during a 6-week treatment period [29]. Moreover, the effects of aspirin on the gut microbes suggest that it might decrease the risk of colorectal cancer [29,30]. Other CV medications, like nifedipine, amlodipine, and digoxin, have been shown to play a role in gut microbiota-mediated drug interactions [11,31,32] (See Table 2).

Table 2. Drugs and their impact on the gut microbiome (pharmacomicrobiomics).

System	Drug	Key Findings	Type of Evidence	Sample Size	References
Cardiovascular	Warfarin	Increased *Escherichia-Shigella* in patients with impaired responses to warfarin; increased *Enterococcus* in patients with enhanced anticoagulation responses.	Human	*n* = 200	Wang et al., 2020 [27]
	Aspirin	Changes in *Prevotella*, *Veillonella*, and *Clostridium* clusters.	Human	*n* = 50	Prizment et al., 2020 [29]
	Statins	Statin use in individuals with *Bacteroides* dominant gut microbiomes led to lower LDL and higher plasma HMG levels.	Human	*n* = 1848	Wilmanski et al., 2022 [22]
	Amlodipine, Nifedipine	Antibiotics increased the bioavailability of amlodipine by affecting metabolic activities of the gut microbiome; the metabolism of nifedipine might be potentially associated with changes in the gut microbiome.	Human and animal	*n* = 10	Yoo et al., 2016 [31]; Zhang et al., 2018 [32]
	Digoxin	Actinobacterium *Eggerthella lenta* inactivates digoxin.	In vitro	-	Haiser et al., 2014 [11]
Respiratory	Montelukast, Roflumilast	Gut microbes can bioaccumulate these therapies without alteration but can also lead to degradation.	In vitro	-	Klünemann et al., 2021 [17]
	Inhaled corticosteroids	Steroid use significantly increased pathogenic bacteria *Haemophilus influenzae*, *Streptococcus pneumoniae*	Human	*n* = 60	Millares & Monso, 2022 [33]
Gastrointestinal	Proton Pump Inhibitors	Increased incidence of *Clostridium difficile* infection indicating the need for careful risk-to-benefit assessment regarding PPI use. Increased incidence of SIBO after long-term use.	Human	*n* = 309,073	Park et al. 2019 [34]; Lombardo et al., 2010 [35]
	Sulfasalazine	Gut microbes are responsible for azoreductase-mediated cleavage into 5-ASA.	Animal	-	Schröder et al., 1973 [10]
	Laxatives	*Bifidobacterium* bacterial strains hydrolyzed sennosides which promoted intestinal peristalsis. Kanamycin, an aminoglycoside antibiotic, decreased sennoside hydrolyzing bacteria.	Animal and in vitro	-	Matsumoto et al., 2012 [36]
	Parenteral Nutrition	Induce insulin resistance by gut microbiome alterations, decreasing the Lactobacillaceae bacterial family and indole-3-acetic acid (IAA) levels.	Human and animal	*n* = 256	Wang et al., 2023 [37]

Table 2. *Cont.*

System	Drug	Key Findings	Type of Evidence	Sample Size	References
Anticancer	Irinotecan	Bacterial β-glucuronidase reactivate SN-38 (active metabolite of irinotecan) leading to intestinal toxicity.	Animal	-	Ting et al., 2022 [12]
	Cyclophosphamide	Induced Gram-positive bacterial translocation to stimulate T helper 17 (pTh17) cells and memory Th1 immune responses.	Animal	-	Viaud et al., 2013 [15]
	Immune Checkpoint Inhibitors	*Bifidobacterium Bacteroides* enhance response.	Human and animal	-	Sivan et al., 2015 [16]; Vétizou et al., 2015 [38]
Endocrine (Diabetes)	Metformin	Significant increase in *Escherichia* and *A. muciniphila* and decrease in *Intestinibacter* abundance. Altered microbiota associated with improved glucose metabolism.	Human, animal, and in vitro	$n = 40$	Wu et al., 2017 [14]
	GLP-1 agonists	Liraglutide induced a lower weight gain than saxaglitpin. Potentially associated with liraglutide's effect on decreasing obesity-related species (*Roseburia*, *Erysipelotrichaceae Incertae Sedis*, *Marvinbryantia*, and *Parabacteroides*) and enriching lean-related species (genera *Blautia* and *Coprococcus*).	Animal	-	Wang et al., 2016 [39]
	SGLT-2 inhibitors	Lower arterial stiffness, improvements in hyperglycemia and vascular smooth muscle dysfunction. Potentially associated with a reduced Firmicutes: Bacteriodetes ratio and increases in *A. muciniphila.*	Animal	-	Lee et al., 2018 [40]
Miscellaneous	Melatonin	Suppresses stress and sleep deprivation-induced dysbiosis increasing *Akkermansia muciniphila* and *Lactobacillus* and decreasing *Bacteroides massiliensis* and *Erysipelotrichaceae*.	Animal and in vitro	-	Park et al. 2020 [41] Chuffa et al. 2015 [42] Paulose et al. 2016 [43]
Antimicrobials	Antiretrovirals (efavirenz, zidovudine)	Zidovudine has broad antibacterial activity against *Escherichia coli*, *Bacteroides*, and *Prevotella* species. Efavirenz inhibited the growth of *Enterococcus faecalis*, *Prevotella* species, and *Bacteroides* species.	In vitro	-	Ray et al. 2021 [44]
	Fluconazole	Increased *Firmicutes* and *Proteobacteria* and decreased *Bacteroidetes*, *Deferribacteres*, *Patescibacteria*, and *Tenericutes*	Animal	-	Heng et al. 2021 [45]

Table 2. *Cont.*

System	Drug	Key Findings	Type of Evidence	Sample Size	References
Antidepressants	Amitriptyline	Good antimicrobial and antifungal activity. Inhibits *Staphylococcus* spp., *Bacillus* spp., *Vibrio cholerae*, *Cryptococcus* spp., *Candida albicans*; protects against *Salmonella typhimurium*. Activity against MRSP	Animal and in vitro	-	Mandal et al. 2010 [46], Brochmann et al. 2016 [47]
	Clomipramine	Antimicrobial activity against MRSP.	In vitro	-	Brochmann et al. 2016 [47]
	Escitalopram, Venlafaxine, Duloxetine	Reduction in the abundance of *Ruminococcus*, *Adlercreutzia*, and unclassified Alphaproteobacteria. Reduction in *R. flavefaciens* might be associated with their ability to treat depression.	Animal	-	Lukic et al. 2019 [19]
	Sertraline	Increased susceptibility of resistant strains when added to antibiotics. Potent antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa.*	In vitro	-	Bohnert et al. 2011 [48] Ayaz et al. 2015 [49]
	Fluoxetine	Decreased bacterial taxa associated with body mass regulation including *Lactobacillus johnsonii* and *Bacteroidales* S24-7. Microbial changes were associated with mild anxiogenic-like behaviors.	Animal	-	Lyte et al. 2019 [50]
Antipsychotics	Antipsychotics (general)	Increased *Prevotella* and *Enterobacter* species which were significantly associated with dysbiosis. Dysbiosis was strongly associated with mortality at follow-up.	Human	$n = 76$	Ticinesi et al. 2017 [51]
	Phenothiazines	Broad antimicrobial activity against antibiotic-resistant bacteria, including *M. tuberculosis* and *S. aureus.*	In vitro	-	Amaral et al. 2004 [52]
	Chlorpromazine	Inhibits *Staphylococcus aureus* and *E. coli.*	In vitro	-	Amaral et al. 1991 [53] Ordway et al. 2002 [54]
	Risperidone	Increased fecal *Bifidobacterium* and *E. coli*; decreased *Clostridium coccoides* and *Lactobacillus.* Increase in *Bifidobacterium* was associated with weight and BMI changes. Microbial changes might explain the metabolic effects of risperidone.	Human	$n = 41$	Yuan et al. 2018 [55]
	Olanzapine	Accelerates weight gain by inducing gut microbiota changes, including increases in the abundance of class Erysipelotrichi and class Gammaproteobacteria. Concomitant prebiotic might attenuate weight gain.	Animal	-	Morgan et al. 2014 [20] Kao et al. 2018 [56]

Table 2. *Cont.*

System	Drug	Key Findings	Type of Evidence	Sample Size	References
Anxiolytics	Propranolol	Inhibits *E. coli* suggesting potential for antimicrobial agent development. Unknown mechanism; therefore, in vivo studies required.	In vitro	-	Hadera et al. 2018 [57] Kruszewska et al. 2004 [58]
Mood Stabilizers	Lamotrigine	Good antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus faecalis*. No activity against Gram-negative strains.	In vitro	-	Qian et al. 2009 [59]
	Lithium; Valproate	Increased *Clostridium*, *Peptoclostridium*, *Intestinibacter* and *Christenellaceae* species. Did not increase intestinal permeability.	Animal and in vitro	-	Cussotto et al. 2019 [60]
Microbiome-Based Treatments—Renal	Probiotics, Prebiotics, Synbiotics, FMT	Reduce uremic toxins and inflammation in CKD which improves renal function and glycemic control. Can improve eGFR and reduce C-reactive protein levels.	Human	-	Putri et al. 2019 [61] Liu et al. 2025 [62] Sun et al. 2026 [63]
Microbiome-Based Treatments—Musculoskeletal	Probiotics, Prebiotics, Synbiotics	Increased *Alistipes* and *Helicobacter* associated with an increase in post-operative cognitive dysfunction (POCD); Probiotic containing *Bifidobacterium longum*, *Lactobacillus acidophilus*, and *Enterococcus faecalis* decreased POCD.	Human	n = 190	Li et al. 2021 [64] Sun et al. 2025 [65] Li et al. 2024 [66] Plewa et al. 2026 [67] You et al. 2025 [68]
	Exercise	Positively influences gut microbiota by enhancing diversity and increasing fecal SCFAs. Varying responses to exercise interventions might be associated with differences in gut microbiomes.	Human, Animal, and in vitro	-	Papageorgiou et al. 2021 [69]

While aspirin has anti-inflammatory properties, it has a significantly disruptive impact on the gut, making the balance of microbiota crucial for mitigating side effects. Aspirin causes dysbiosis in the gut microbiota by increasing the abundance of Bacteroidetes, decreasing the F/B ratio, and elevating the levels of short-chain fatty acids (SCFAs) and beneficial bile acids (BAs) [70].

Moreover, responses to statins can be explained by variations in the human gut microbiome. Wilmanski et al. 2022 found that while *Bacteroides*-enriched individuals were at higher risk of statin-induced metabolic disruption, individuals in whom *Firmicutes* were dominant were at a lower risk [22]. In an animal study with amiodarone, probiotic administration was found to change the pharmacokinetics of the medication [71].

Microbiome-based treatment is an emerging field with promise for treating CVD. Treatments aim to manage conditions like hypertension, atherosclerosis, and heart failure by manipulating the gut microbiota to restore a healthy balance. These therapies focus on reducing harmful microbial metabolites (such as trimethylamine N-oxide [TMAO]) and increasing beneficial ones (such as short-chain fatty acids [SCFAs]) to improve cardiac function, decrease systemic inflammation, and enhance vascular health [72,73].

Overall, emerging evidence suggests that there is a bidirectional relationship between cardiovascular therapies and the gut microbiota. However, most available data are observational and derived from studies with a small sample size. Therefore, although microbiome-based interventions continue to evolve, more robust longitudinal studies are required to determine clinical applicability and causality before integrating these finding into cardiovascular care, to enhance therapeutic outcomes and reduce adverse effects.

2.2. Pharmacomicrobiomics of Respiratory System Drugs

Multiple studies have demonstrated that microbial dysbiosis can have an effect on the respiratory system, including diseases like asthma and chronic obstructive pulmonary disease (COPD). A bacterial culture study found that Montelukast, an asthma medication, and Roflumilast, commonly used for COPD, were both bioaccumulated and biodegraded by different bacterial species [17]. The results of a human study revealed that co-administering a novel probiotic, Probio-M8 (*Bifidobacterium lactis* M8), with conventional therapy was effective in managing and improving asthma-related symptoms. The probiotic worked by maintaining the alpha diversity and stability of the gut microbiota of these asthmatic patients [74]. Moreover, the most commonly used immunomodulatory treatments for asthma include corticosteroids and cytokine mediator antibodies that mainly target type-2 eosinophilic inflammation. These strategies are not effective for all patients, especially those without a proper activation pathway. Inhaled corticosteroids have been shown to alter the bronchial microbiome which may alter the response of the immune cells to these therapies [75]. Another common treatment for COPD is inhaled corticosteroids. Multiple studies have found that these treatments can have a significant impact on the respiratory microbiome. In fact, a long-term study found that the bronchial microbiome of steroid users with low baseline eosinophils showed a significant increase in pathogenic bacteria, including *Haemophilus influenzae* and *Streptococcus pneumoniae* [33].

Microbiome-based treatments for respiratory diseases, including COPD, asthma, and infections, aim to restore microbial balance using probiotics (e.g., *Lactobacillus*, *Bifidobacterium*), high-fiber diets (prebiotics), and FMT. These approaches target the gut–lung axis to reduce airway inflammation and improve immune response and show promise in mitigating symptoms. Using specific oral commensals like *Rothia mucilaginosa* may counteract pathogen-induced pro-inflammatory responses in the lower airways. While animal models have demonstrated high efficacy in decreasing inflammation and improving lung function, many approaches require further clinical validation in humans. Future ther-

apies may involve personalized microbiome analysis (using sequencing) and genetically modified probiotics to treat chronic respiratory diseases [76].

2.3. Pharmacomicrobiomics of Gastrointestinal (GI) Drugs

2.3.1. Proton Pump Inhibitors

The main action of proton pump inhibitors is to reduce acidity in the stomach; however, this causes a decline in the functions of the stomach barrier. This increases the incidence of pathogenic bacterial infiltration, with *Clostridioides difficile* being the most prevalent [4]. A study found that the use of proton pump inhibitors (PPIs) in admitted patients increased the risk of *C. difficile* infection in a dose-dependent manner (i.e., higher doses led to increased infection risk) [77].

Proton pump inhibitors also have the potential to induce bacterial overgrowth, with the most common strains being *Clostridium*, *Lactobacillus*, and *Streptococcus* species [18]. They can also alter the small bowel composition, as was demonstrated in a 2010 study which found that 50% of users taking PPIs tested positive for small intestinal bacterial overgrowth (SIBO) [35]. Common organisms of this overgrowth included *Escherichia coli* (37%), *Enterococcus* spp. (32%), and *Klebsiella pneumoniae* (24%) [35]. Furthermore, in vitro studies have demonstrated that omeprazole undergoes metabolism into its sulfide metabolite due to microbiome activity, including that of anaerobic bacteria such as *Bacteroides* strains [78].

2.3.2. Sulfasalazine

Sulfasalazine is mainly used for inflammatory bowel disease (IBD), and its anti-inflammatory effects are dependent on the release of amino salicylic acid [79]. Studies have found that the majority of the drug is reduced by the gut microbiota to release 5-aminosalicylate (5-ASA) and sulfapyridine, which are pharmacologically active metabolites. This reduction is carried out by the enzyme azoreductase [80]. An animal study investigated the effects of probiotics containing strains of *Lactobacillus acidophilus* L10, *Bifidobacterium lactis* B94, and *Streptococcus salivarius* on the pharmacokinetics and metabolism of sulfasalazine. The probiotics resulted in a significant increase in the metabolism of the drug due to an increase in azoreductase activity. Consistent with this result, a greater plasma concentration of sulfapyridine was observed. However, no significant changes in the pharmacokinetic profile of the drug were observed compared to control rats. This might indicate that bacteria have no effect on the transporters involved in the drug's mechanism of action [81]. Moreover, another study found that germ-free mice were not able to split the azo linkage, unlike the control group. This demonstrates that the azo cleavage is in fact dependent on the intestinal microbiome [10].

2.3.3. Laxatives

Sodium picosulfate is metabolized into its active form of 4,4′-dihydroxydiphenyl-(2 pyridyl)-methane (DPM) [82] by sulfotransferase-producing bacteria. Lactulose is hydrolyzed into lactic and acetic acids by bacteria found in the colon such as *Lactobacillus* and *Bacteroides* spp. and *Escherichia coli*. These acids can then decrease the pH, allowing for amines in the GI tract to become protonated and excreted in the feces [83]. Sennosides, the main laxative component of senna, are hydrolyzed by the enzyme β-d-glucosidase which is secreted by *Bifidobacterium* (*B. pseudocatenulatum* LKM10070 and *B. animalis* subsp. lactis LKM512) and then converted into rheinanthrone which promotes intestinal peristalsis and ultimately purgative action [36]. Finally, barbaloin, the laxative component of aloe, is activated into aloe-emodin anthrone (the component that produces purgative action) by intestinal anaerobes such as *Eubacterium* sp. Strain BAR [84].

2.3.4. Parenteral Nutrition

Total parenteral nutrition (TPN) has been found to cause disruption in intestinal function, mucosal immunity, and the gut barrier. This leads to infections and metabolic complications, such as hyperglycemia and hypoglycemia. These metabolic changes occur due to parenteral nutrition's disruption of the gut microbiota, leading to reduced metabolism of microbiota-derived tryptophan [37]. Additionally, administration of TPN in a mouse model led to a significant expansion of *Proteobacteria* within the intestinal microbiota [85]. Consistent with these findings, a human study conducted on parenteral nutrition-dependent children with short bowel syndrome revealed that bacterial diversity was reduced compared to their healthy siblings and children on enteral nutrition. The children also showed an increase in *Enterobacteriaceae*, which is a family of Gram-negative *Proteobacteria* [86].

2.4. Pharmacomicrobiomics of Anticancer Drugs

Microbiome-based approaches in oncology seek to manipulate the composition and function of the gut microbiota—comprising trillions of microorganisms—to enhance the efficacy of conventional therapies, such as chemotherapy and immunotherapy, while reducing associated toxicities, largely through modulation of host immunity and metabolic pathways [87].

2.4.1. Chemotherapies

The gut microbiome can directly modify the metabolism of chemotherapeutic drugs. For example, the inactive form of irinotecan, SN-38 glucuronide (SN38G), is activated into SN38 by bacteria expressing the ß-glucuronidase enzyme [12]. This active form can then cause symptoms such as diarrhea, acute weight loss, and mucosal injury. Irinotecan can also have an effect on the microbes by enhancing bacterial growth of these ß-glucuronidase-expressing bacteria, ultimately leading to an increase in cytotoxicity. Similarly to irinotecan, the metabolism of 5-fluorouracil is also directly affected by the gut microbiome. 5-fluorouracil becomes activated from 5-FU into cytotoxic 5-FU triphosphate via vitamin B6 and B9 bacterial ribonucleotide metabolism.

Anticancer activity can also be modulated by bacterial metabolites, such as short-chain fatty acids like butyrate. A human study used nuclear medicine resonance (NMR) spectroscopy to investigate the fecal metabolomic profile of patients with breast cancer undergoing three cycles of chemotherapy with a combination of three chemotherapeutic agents: 5-fluorouracil, epiribucine, and cyclophosphamide [21]. Results indicated that there was an upregulation of these SCFAs after 2–3 cycles of chemotherapy. These SCFAs have been found to promote apoptosis, inhibit the invasive phenotypes of breast cancer, and increase the intracellular concentration of chemotherapies. This suggests that bacterial SCFAs may have a beneficial anticancer effect.

Chemotherapeutic cytotoxicity is also induced in platinum agents by the gut microbiota. The early cytotoxic effects of platinum agents such as oxaliplatin and cisplatin require the production of reactive oxygen species (ROS), which has been found to be dependent on the microbiota [12].

Apart from enhancing chemotherapeutic-related cytotoxicity, microbes can also lead to chemotherapy resistance by activating the Toll-like receptor-4 (TLR) signaling cascade which leads to the switch from cell apoptosis to cell autophagy, thus promoting cell survival. Through metagenomic and transcriptomic analyses, *Fusobacterium nucleatum* was found to be abundant in colorectal cancer tissues inducing chemoresistance by activation of autophagy [88].

Finally, drugs like cyclophosphamide promote the translocation of bacterial strains into lymphoid organs which leads to the accumulation of T-helper cells and the overall development of anticancer immunity [12]. A study on chemotherapies for non-hematological malignancy, in which fecal samples were collected before and after chemotherapy, found that there was an increase in Gram-negative bacteria of the *Bacteroidetes* and *Proteobacteria* phyla, as well as a decrease in Gram-positive bacteria of the phylum *Firmicutes* a week after treatment [89]. These results are consistent with an animal study which found that cyclophosphamide induces the translocation of Gram-positive bacteria into secondary lymphoid organs, promoting the activation of the T-cell immune response [15].

2.4.2. Immunotherapies

Microbes modify the immune system through a process known as immunomodulation, and in doing so can change how a person responds to treatment [12]. Through immunomodulation, they modify the pharmacodynamics of these drugs rather than the pharmacokinetics. Microbes can cause tumor cells to be directly killed by Th1 through the production of polysaccharides that stimulate CD11b+ dendritic cells, as well as via the increased suppression of Treg cells through mediation by IL-10 [90]. This leads to decreased colitis and adverse immune-related effects.

Bacteria strains such as *B. breve* and *B. longum* can enhance the immunotherapeutic effects of Anti PD1/PDL1 via the activation of DC CD8+ T-cell priming and therefore promote infiltration into the tumor microenvironment [16]. Overall, this leads to a decrease in immune-related adverse events. A study was conducted on patients with non-small cell lung cancer who were administered nivolumab, an anti-PD1 [91]. Using 16S rRNA sequencing on stool samples, the study found that healthy controls showed a greater number of short-chain fatty acids as well as greater abundance of commensal bacteria. However, this dysbiosis cannot be fully attributed to immunotherapy, but could be due to the cancer itself.

An animal and human study demonstrated that the anti-tumor effects of anti-Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), such as Ipilimumab, are dependent on *Bacteroides* species. In the animal study, it was found that neither mice treated with antibiotics nor germ-free mice responded to the blockage of CTLA-4. The administration of these *Bacteroides* bacteria was found to overcome this non-responsiveness. They also performed a fecal microbial transplantation from melanoma patients to mice, which confirmed that anti CTLA-4 increases *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, and *Burkholderia cepacian* [38].

2.5. Pharmacomicrobiomics of the Endocrine System

2.5.1. Antidiabetic Drugs

There is good evidence linking gut microbiota with antidiabetic drugs. For instance, a recent systematic review disclosed that prediabetes and newly diagnosed Type 2 diabetes mellitus (T2DM) patients treated with metformin displayed an increase in microbe taxa such as *Enterobacteriales* and *Akkermansia muciniphila*, which may play a role in blood sugar control [92]. Consistent with these findings, other studies suggest that *A. muciniphila* is a potential mediator of the antidiabetic effects of metformin [93]. Other studies have also demonstrated that GLP-1 receptor agonists can play a role in modulating the gut microbiota. For instance, Wang et al. 2016, demonstrated that liraglutide produced changes in gut microbiota in mice compared to the corresponding control [39]. Obesity-related microbiota phenotypes such as *Erysipelotrichaceae Incertae Sedis* and *Marvinbryantia* were decreased, whereas leanness-associated phenotypes (*Lactobacillus* and *Turicibacter*) increased with liraglutide treatment [39].

Moreover, when used in combination with antidiabetic drugs, probiotics increase the richness of beneficial bacteria and their metabolites, such as short-chain fatty acids [94]. An increase in SCFA-producing bacteria has been associated with improvements in Hb A1C in individuals with T2DMs. Consistent with this, individuals who took a combination of metformin and probiotics demonstrated a decrease in glycemia and insulin resistance [95].

Metformin may be able to ameliorate hyperglycemia and hyperlipidemia in T2DM patients by increasing beneficial bacteria, such as *Blautia* and *Faecalibacterium*. Patient response to metformin varies based on bacterial metabolites. Good responders have shown increased levels of sphingomyelins, acylcholines, and glutathione metabolites [96]. Metformin may act on the gut, as many studies have shown that administration of metformin changes bile acid recirculation [97]. After 4 months of treatment with metformin and placebo, T2DM patients who were treated with metformin were found to have a higher level of bacteria producing SCFAs such as *Blautia*, *Bacteroides*, *Butyricoccus*, *Bifidobacterium*, *Prevotella*, *Megasphaera*, and *Butyrivibrio* compared to placebo [14]. In another study, metformin treatment in a high-fat diet–induced type 2 diabetes mouse model significantly altered gut microbiome composition, with an increase in multiple bacterial species, including members of the genus *Bacteroides*, particularly in metabolically dysregulated mice compared to controls. [98]. In conclusion, increasing the level of SCFA-producing bacteria might be a mechanism of metformin on gut bacteria; however, the exact mechanism affecting gut microbiota needs to be further investigated. This may be a way of modulating the response of drugs to improve drug efficacy. Metformin modifies multiple metabolic pathways through its interaction with the gut microbiota and, in part, confounds the dysbiosis induced by T2DM [96].

Hippurate (a component found in urine, mainly derived from the disintegration of plant phenolics and aromatic amino acids by the gut microbiota) showed a clear increase in patients treated with sulfonylureas, showing that sulfonylureas might influence the metabolism of gut microbiota [99].

Dipeptidyl peptidase 4 (DPP-4) inhibitors are commonly used antidiabetic drugs that have an effect on the microbiome [100]. SGLT-2 is a sodium-glucose transporter located in the renal tubules that plays an important role in glucose reabsorption [101]. SGLT-2 inhibitors are used for therapy in T2DM because they can suppress the reabsorption of glucose to maintain blood sugar levels [102]. A previous study found that after 8 weeks of dapagliflozin treatment, the proportion of Bacteroidetes and *Akkermansia muciniphila* increased, while *Firmicutes* and *Oscillospira* decreased [40]. Luseogliflzin was found to increase the number of intestinal bacteria involved in the synthesis of SCFAs and to improve amino acid metabolism [103,104]. Emerging evidence from both preclinical and clinical studies suggests that SGLT2 inhibitors modulate gut microbiota composition and associated metabolite profiles. In murine models, these changes appear mechanistically distinct from dietary interventions, while in humans they are associated with improved cardiovascular outcomes. Together, these findings support a contributory role of the gut microbiome–metabolite axis in mediating the pleiotropic effects of SGLT2 inhibition [103,104]. A scoping review of animal studies done in 2024 also confirmed SGLTi change gut microbiome diversity and colonic fermentation [105]. Most of the evidence showing the effect of antidiabetic drugs on gut microbiota comes from animal studies, although evidence from human studies is increasing. Vildagliptin, in addition to improving glucose control and insulin resistance, has been shown to modulate the intestinal microbiota, anti-inflammatory cytokine profiles, and metabolomics, and when combined, may explain DPP-4i's neuroprotective effects (Vildagliptin modulates the microbiota and induces an immunometabolic profile compatible with neuroprotection in T2DM [106]).

DPP4 inhibitors and sodium-glucose cotransporter 2 (SGLT2) inhibitors also alter microbiome composition to reduce inflammation. GLP-1 receptor agonists and SGLT-2 inhibitors have shown interactions with gut microbial populations that may alter their therapeutic benefits [107].

Sodium-glucose cotransporter 2 inhibitors and Thiazolidinediones (TZDs) have been suggested to have less pronounced effects on gut microbiota and microbial metabolites than other treatments [108].

The gut microbiome has been shown to predict how well patients with T2DM respond to newer glucose-lowering therapies after treatment initiation, according to new research examining semaglutide and empagliflozin uptake. In a prospective study by Klemets et al., adults with T2DM provided fecal samples at baseline and at 1, 3, and 12 months after initiating semaglutide or empagliflozin [109]. These findings identify the gut microbiome as a potential biomarker for personalized diabetes treatment, aligning with broader efforts to tailor therapy based on biological signatures rather than trial-and-error prescription [109].

2.5.2. Thyroid Medications

Dysbiosis of the microbiome affects the functioning of the thyroid gland through the gut–thyroid axis [110–114]. Low-certainty evidence from two randomized trials suggests that routine administration of probiotics, prebiotics or synbiotics may result in little to no benefit in patients with primary hypothyroidism [115–117].

2.6. Miscellaneous Drugs

2.6.1. Melatonin

In an animal study, mice were subjected to water and sleep deprivation and administered melatonin [41]. Melatonin was found to suppress the dysbiosis caused by these deprivations, leading to an increase in *Akkermansia muciniphila* and *Lactobacillus* and decrease in *Bacteroides massiliensis* and *Erysipelotrichaceae*. Previous studies also found that melatonin reduces inflammatory responses through the signaling pathway mediated by Toll-like receptor 4 (TLR4), which has been found to be associated with the intestinal microbiota. This implies that melatonin might have a direct effect on gut microbiota modulation [42]. Melatonin has also been shown to increase the magnitude of *Enterobacter aerogenes* motility [43].

2.6.2. Melatonin and Gut Microbiota

Studies have suggested that melatonin and the gut microbiome exhibit a complex relationship. A systematic review looked at 14 animal studies that investigated the effect of melatonin on the gut microbiota. Although the results differed, the main findings were an increase in richness and diversity of the gut microbiota in mice that received melatonin [118].

In mice infected with *S. aureus* or *E. coli*, melatonin resulted in improved bacterial clearance from blood [119].

Although these findings suggest that melatonin may have a therapeutic effect on dysbiosis-related conditions, more human studies are required to determine clinical applicability. A randomized double-blind placebo-controlled study found that a composite probiotic significantly alleviated abdominal pain duration and severity of discomfort in individuals with irritable bowel syndrome (IBS). However, this study only included 42 individuals who were only followed for 6 weeks. Longer and larger studies are needed for a more complete investigation of melatonin's benefits [120].

2.6.3. Antivirals

In a human study conducted on HIV-1-infected patients treated with antiretroviral therapy (ART) (efavirenz and zidovudine), it was found that these treatments have in vitro antimicrobial activity against the species *Bacteroides fragilis* and *Prevotella* [44].

Microbiome-based antiviral treatments work on ecosystems, including the gut, to strengthen immune defenses and inhibit viral activity. These approaches do not replace conventional antivirals but may serve as adjunct therapies to improve outcomes [121].

This knowledge offers a basis for translating experimental evidence from animal studies into the human context and identifies avenues for leveraging the gut microbiota–IFN–virus axis to improve control of viral infections and performance of viral vaccines [122].

2.6.4. Antifungals

An animal study found that mice treated with the antifungal fluconazole exhibited a significant change in gut microbiota compositions. There was a significant increase in Firmicutes and *Proteobacteria*, but a reduction in *Bacteroidetes*, *Deferribacteres*, *Patescibacteria*, and *Tenericutes* [45]. Microbiome-based antifungal treatments are an emerging area of research where strategies are used for microorganisms or their metabolites to suppress harmful fungi. Instead of killing fungi with traditional antifungal drugs alone, these approaches try to restore a healthy microbial balance so fungi cannot overgrow. They are not yet standard medical therapy, but several approaches are being actively studied, but human trials are limited. Next-generation probiotics, engineered or naturally occurring microbes, are designed to outcompete fungal pathogens [123]. These are being studied for recurrent vulvovaginal candidiasis, gastrointestinal fungal overgrowth, prevention of fungal infections after antibiotics [124]. Some bacteria produce metabolites that serve as natural antifungal compounds, like the SCFA butyrate, that can inhibit fungal growth as well, bacteriocins and biosurfactants from *Lactobacilli* can disrupt fungal cell membranes [125,126].

2.7. Pharmacomicrobiomcs of Psychiatric Drugs

2.7.1. Antidepressants

Several studies have found that antidepressants can have antimicrobial activity. Amitriptyline has been found to inhibit the growth of *Staphylococcus* spp., *Bacillus* spp., *Vibrio cholerae*, *Cryptococcus* spp., and *Candida albicans* [46]. When used in a mouse study, it provided protection from *Salmonella typhimurium* [46]. Other investigations have found that amitriptyline and even clomipramine can be active against methicillin-resistant *Staphylococcus pseudintermedius* [47]. When looking at bacterial richness, certain antidepressants such as fluoxetine, escitalopram, venlafaxime, and duloxetine lead to a reduction in microbial communities [19]. Studies have found that sertraline has a potent antimicrobial effect against *Escherichia coli*, *Staphlyococcus aureus*, and *Pseudomonas aeruginosa* [48,49]. Fluoxetine was shown to cause a reduction in *Lactobacillus johnsonii* and *Bacteroidales* S24-7, which belong to bacterial phyla that are associated with body mass regulation [50]. This may suggest that weight gain associated with antidepressants may be caused by the alterations in the gut microbiome.

Research into the gut–brain axis indicates a strong bidirectional relationship between the gut microbiome and antidepressant treatment. Antidepressants, particularly Selective Serotonin Reuptake Inhibitors (SSRIs), can significantly alter the composition of the gut microbiota, while the baseline microbiome composition can influence how well a patient responds to the drug.

Antidepressants have antimicrobial properties that can alter the diversity and composition of gut microbiome, sometimes leading to long-term changes [127,128]. Treatment has been shown to increase the abundance of beneficial, anti-inflammatory species such as

Bifidobacterium, while reducing pro-inflammatory species like *Escherichia coli*. The specific composition of a patient's microbiome before treatment can help predict whether they will respond to antidepressant therapy. There are few studies demonstrating fecal microbiota as a potential predictor of treatment response in geriatric depression [129,130]. When the gut microbiota is also modulated through probiotics, synbiotics and prebiotics therapy, or in conjunction with specific antidepressants, it may increase efficacy and decrease the adverse events of the drug [131].

2.7.2. Antipsychotics

The use of antipsychotics has been found to alter the gut microbiome composition, leading to an increase in *Prevotella*, *Victivallis*, and an unclassified member of the Desulfovibronaceae family [51]. Phenothiazine antipsychotics have been found to influence bacterial morphology and exhibit some antimicrobial activity at higher-than-clinical doses [52]. Studies have found that chlorpromazine can inhibit the growth of *Staphylococcus aureus* and *E. coli* [53,54]. When patients with schizophrenia were treated with risperidone for 24 weeks, this caused a change in the gut microbiome causing increases in *Bifidobacterium* and *E. coli* and decreases in *Clostridium coccoides* and *Lactobacillus* [55]. The interaction between the gut microbiome and atypical antipsychotics may also be a factor influencing the common side effect of weight gain. When germ-free mice were treated with olanzapine, no weight gain was observed compared to the control group [20]. Conversely, when the germ-free mice were colonized, this weight gain returned [20]. Other evidence that suggests there is an interplay between olanzapine and the gut microbiome was presented by Kao et al. They found an attenuation of weight gain when rats received a prebiotic along with olanzapine [56]. In a study by Flowers et al., it was found that the antipsychotics aripiprazole, risperidone, and olanzapine caused alterations in the *Akkermansia* bacterial genus, Lachnispiraceae family, and *Sutterella* genus [132]. A study by Bretler et al. (2019) examined the link between second-generation antipsychotics and alterations in the gut microbiome in children and adolescent [133]. Notably, it was found that antipsychotics, such as olanzapine and risperidone, can alter the gut microbiome and increase the risk of metabolic side effects and weight gain [133].

Research into microbiome-based treatments for mental health suggests that manipulating the gut microbiota can influence the effectiveness and side effects of antipsychotic medications. While this field is still largely in the experimental stage, it shows potential for enhancing traditional treatments for schizophrenia and bipolar disorder by targeting the gut–brain axis [134]. Second-generation antipsychotics (e.g., olanzapine, risperidone) often cause significant weight gain and metabolic syndrome, which research links to drug-induced alterations in gut microbiota [135,136]. Microbiome-focused interventions aim to reduce these side effects, increasing quality of life and potentially improving medication compliance [135,136].

Studies indicate that specific prebiotics and probiotics may help restore the microbial balance altered by antipsychotics. These "psychobiotics" could improve metabolic outcomes, reducing the metabolic syndrome commonly seen with antipsychotic use [5]. It has also been found that there are differences in gut bacteria composition between treatment-responsive and treatment-resistant individuals, particularly with medications like clozapine, indicating that gut bacteria may play a role in treatment resistance [137].

2.7.3. Anxiolytics

Propranolol, a commonly used anxiolytic, exhibits antimicrobial properties in vitro. It consistently inhibits the growth of *E. coli*, although findings regarding its activity against *Staphylococcus aureus* are mixed across studies [57,58]. These results suggest that pro-

pranolol may exert selective antimicrobial effects depending on bacterial species and experimental conditions.

Gut dysbiosis appears to be closely linked to anxiety disorders; disruptions in the gut microbiota may trigger or exacerbate symptoms of anxiety [138]. Probiotic interventions could represent a promising therapeutic avenue, with animal study results appearing promising, but there is a relative scarcity of high-quality, large-scale randomized controlled trials (RCTs) in humans [139].

2.7.4. Mood Stabilizers

Several mood stabilizers have been shown to influence microbial growth and gut microbiota composition. Lamotrigine demonstrates in vitro antibacterial activity against Gram-positive organisms including *Bacillus subtilis*, *Staphylococcus aureus*, and *Streptococcus faecalis* [59]. Both lithium and valproate alter the cecal microbiome in rats following four weeks of treatment, indicating that chronic exposure to these agents can modify gut microbial communities in vivo [60].

2.8. Microbiome-Based Treatments for Renal System Diseases

The gut–kidney axis is a bidirectional relationship by which kidney dysfunction causes gut dysbiosis (imbalance), which in turn produces uremic toxins that accelerate renal damage. Interventions such as probiotics, prebiotics, synbiotics, and FMT aim to reduce these toxins (e.g., indoxyl sulfate, p-cresyl sulfate), decrease inflammation, and slow the progression of chronic kidney disease (CKD) and acute kidney injury (AKI), and also play a role in preventing recurrence of stones [61,62].

2.9. Microbiome-Based Treatments for Musculoskeletal Diseases

Evidence suggests that the gut microbiota has different modulatory effects depending on the type of musculoskeletal disease. A systematic review focusing on the role of the gut microbiota in orthopedic surgery included 18 research articles, indicating a significant correlation between the microbiome composition and surgical outcomes. Bacterial genera such as *Alistipes* and *Helicobacter* were associated with an increased risk of post-operative cognitive dysfunction (POCD) [140].

Similarly, a randomized controlled trial found that administration of a probiotic pre-operation significantly reduced the incidence of POCD in elderly patients who underwent elective lower extremity orthopedic surgery. Long-term follow up was not performed, so the effects of probiotics on POCD remain unknown. Moreover, although there is a potential link between surgical outcomes and the gut microbiome, more studies investigating the specific microbes and metabolites involved are required [141].

A double-blind placebo-controlled clinical trial assessed the effects of a probiotic, *Lactobacillus casei* Shirota, on distal radius fracture in 264 elderly patients. While the Michigan Hand Questionnaire (MHQ) score increased for all participants during recovery, those who received the probiotic exhibited a faster increase. These results suggest a potential role of probiotics in promoting initial healing of hand fractures; however, more studies utilizing different probiotic strains are required [142].

2.10. Microbiome-Based Therapeutics

Microbiome-based therapeutics include prebiotics, probiotics, live microorganisms, microbiome mimetics, and others like fermented foods and FMT [5]. Interventional studies involving probiotics, prebiotics, and synbiotics offer promise, but have produced inconsistent results. Emerging research also explores FMT and personalized nutrition as potential strategies to modify the gut microbiota. These approaches require rigorous safety evaluation in the immunocompromised patients [5,143].

Microbiome therapies manipulate the gut microbiome using various methods, such as adding, removing, or modifying the bacteria. This can be done using natural or modified microorganisms, antibiotics, bacteriophages, and bacteriocins [5].

Engineered microbes and microbial consortia are designed to produce therapeutic compounds or modulate host responses. Although targeted therapeutics, such as modified bacteria, postbiotics, and phages, have been tested in several preclinical settings, their full effectiveness and safety remain unevaluated. Fermented foods are unique products that have many potential benefits, ranging from food safety to human health. Increased shelf life and stability is a long-standing safety benefit of the fermentation process. Most current studies focus on short-term outcomes; there are limited clinical data on the safety and effectiveness of long-term use of microbiome-based therapies [143,144]. However, existing commercial microbiome-directed products often exhibit low efficacy [145].

2.11. Other Drug–Microbiome Interactions

The bidirectional interaction between drugs and the gut microbiome can lead to changes in drug bioavailability, bioactivity, or toxicity, potentially affecting treatment efficacy. Understanding these interactions is crucial for personalized medicine, as it allows for the modulation of the gut microbiome to improve treatment outcomes. This includes potential therapeutic interventions such as diet, pre-/probiotics, FMT, and modulation of PXR/FXR/AhR pathways [13,24,25,146]. The study by Yang M et al. supports the role of the microbiome in maintaining host homeostasis under physiological challenges [147]. It explores how host physiological states (e.g., hypoxia) modulate lipid metabolism via the bile acid pathway. The sections on "cardiovascular and endocrine drugs," are highly relevant to the current review, as they explain the crosstalk between host metabolism and microbial metabolites [148]. A multi-omics study by Liu et al. reveals how the gut microbiota facilitates host adaptation in severe environments.

The bidirectional relationship between pharmacological agents and the human gut microbiome represents an emergent and significant area of research, carrying profound implications for the field of personalized medicine and the optimization of therapeutic interventions. This may be particularly pertinent for variable response to drugs (Table 3), as individual gut microbiome profiles may play an important role in their differential metabolism and effectiveness.

2.12. The Regulatory Framework for Microbiome-Based Therapies

Regulatory frameworks for microbiome-based therapies are currently evolving, as an increasing number of promising microbiome-based medicinal products continue to emerge [149,150]. In the United States, the Food and Drug Administration (FDA) oversees the safety and efficacy of these products; in Canada, this role is carried out by Health Canada. However, due to multiple challenges, including a lack of clinical studies and analytical methods to fully characterize the function of the microbiome, the integration of microbiome-based therapies into clinical practice remains limited. Therefore, the continued development and refinement of these regulatory frameworks are still necessary to fully elucidate the clinical impact of these therapies [149,150].

Table 3. Conceptual framework for drug–microbiome interactions (pharmacomicrobiomics).

Section	Conceptual Focus	Key Mechanisms	Representative Drug/System Examples (from This Review)	Clinical Impact	References
I. Drug and Effects on the Microbiome	Pharmaceuticals alter microbial composition, diversity, and metabolic function ("pharmacoecology")	• Antimicrobial activity of non-antibiotic drugs • Altered gut pH and bile acid pools • Changes in microbial diversity and resilience	**PPIs:** ↑ *Enterococcus*, *Streptococcus*, *C. difficile*, SIBO **Antidepressants:** reduced microbial richness (fluoxetine, sertraline) **Antipsychotics:** microbiome-dependent weight gain (olanzapine) **Metformin:** ↑ *Akkermansia muciniphila*, SCFA producers **Inhaled corticosteroids:** ↑ airway pathogens	Dysbiosis, infection risk, metabolic side effects, long-term shifts in drug response, contribution to obesity and insulin resistance	Freedberg et al., 2014 [18]; Lukić et al., 2019 [19]; Morgan et al., 2014 [20]; Wu et al., 2017 [14]; Al-Btoosh et al., 2026 [13]
II. Microbiome and Modulation of Drug Response	Gut microbes directly and indirectly modify drug pharmacokinetics and pharmacodynamics	**Direct biotransformation:** enzymatic activation, inactivation, toxification **Indirect biotransformation:** modulation of CYP enzymes, bile acids, microbial metabolites (SCFAs, p-cresol) **Bioaccumulation:** microbial drug sequestration **Immune modulation**	**Sulfasalazine:** azoreductase → 5-ASA **Digoxin:** *Eggerthella lenta* inactivation **Irinotecan:** β-glucuronidase-mediated toxification **Statins:** bile acid-dependent metabolic effects **Metformin:** SCFA-mediated variability in glycemic response **Immune checkpoint inhibitors:** response linked to *Bifidobacterium*, *Akkermansia*	Explains inter-individual variability in efficacy and toxicity; altered bioavailability; dosing unpredictability; immune-related adverse events	Schröder et al., 1973 [10]; Haiser et al., 2014 [11]; Ting et al., 2022 [12]; Wilmanski et al., 2022 [22]; Wu et al., 2017 [14]; Al-Btoosh et al., 2026 [13]
III. Microbiome-Based Therapies	Intentional manipulation of the microbiome to improve drug response or treat disease	• Probiotics, prebiotics, synbiotics • Fecal microbiota transplantation (FMT) • Diet, fermented foods • Engineered microbes, postbiotics, phage therapy (emerging)	**Adjunct probiotics:** improved asthma control; enhanced metformin response **FMT:** recurrent *C. difficile*, emerging oncology applications **Renal disease:** reduction in uremic toxins (indoxyl sulfate, p-cresyl sulfate) **Musculoskeletal disease:** gut–bone and gut–muscle axis modulation	Potential to restore drug responsiveness, reduce adverse effects, and enable precision medicine beyond pharmacogenomics	Liu et al., 2021 [74]; Lee et al., 2024 [76]; Putri et al., 2019 [61]; Sun et al., 2026 [63]; Pitashny et al., 2025 [145]

↑: Increased, →: Next step/process.

2.13. Advantages and Limitations of Microbiome-Based Treatment

The human microbiome has emerged as a critical determinant of health and disease, and microbiome-based treatment has its own challenges and opportunities.

Advantages: Microbiome-targeted therapies (MTTs), including probiotics, prebiotics, synbiotics, and FMT, have attracted wide attention. Probiotics can be defined as live microorganisms similar to the beneficial bacteria that are naturally present in the human GIT, conferring a health benefit on the host when administered in adequate amounts. Commonly used probiotics include *Lactobacillus*, *Bifidobacterium*, *Bacillus*, *Enterococcus*, and *Saccharomyces boulardii*. Prebiotic agents can be categorized as polyols, oligosaccharides, and soluble fiber, and can stimulate growth and survival of probiotics. Synbiotics describe the synergistic combination of probiotics and prebiotics found in products such as foods, drugs, and supplements [151]. Microbiome mimetics: Microbiome mimetics describes any intervention that replicates the interaction between the microbiome and the host that yields a therapeutically beneficial outcome. This can include bacterial-derived products, small molecules, conventional therapeutics, or host-derived products. The majority of research has focused on postbiotics and paraprobiotics, which are molecules or components of bacteria that confer a health benefit. Paraprobiotics (inactivated, non-viable microbial cells) and postbiotics (soluble metabolic byproducts) are functional components derived from probiotics that provide health benefits without requiring live bacteria [152].

Limitations of previous studies include (i) limiting the analysis to a single type of MTT (e.g., only FMT) and lacking a comprehensive discussion on probiotics, prebiotics, synbiotics, and FMT simultaneously; (ii) inclusion of non-randomized controlled trials (case reports, cohort studies, etc.); (iii) inclusion of studies on MTTs as adjuvant therapy and monotherapy simultaneously; (iv) combining data from trials of probiotics and synbiotics; and (v) few studies providing data on the efficacy of preventing endoscopic recurrence or inducing endoscopic remission [153]. One of the biggest challenges in microbiome-based treatments is the large differences in gut microbiome composition and function among individuals.

3. Future Research

Researchers are exploring how altering the microbiome can enhance the efficacy of traditional pharmaceutical drugs [154,155]. Future research on microbiome-driven therapeutics is shifting from general probiotics to precision, engineered, and synthetic microbial consortia designed to treat diseases by restoring specific ecological functions in the gut, skin, and vagina. Key advancements focus on personalized "next-generation" probiotics, phage therapy, and metabiotics to combat metabolic, inflammatory, and cancer-related illnesses [145].

Key Research Directions and Future Strategies:

- **Synthetic Bacterial Communities:** Development of rationally designed cultured consortia of bacteria that can be customized to fix individual dysbiosis.
- **Precision Medicine Approach:** Using multi-omics and big data to analyze a patient's unique microbiome to deliver targeted treatments that improve engraftment and clinical outcomes.
- **Engineered Phage Therapy:** Utilizing lytic phages for precise, targeted removal of pathogenic bacteria without destroying beneficial, commensal flora.
- **Beyond the Gut:** Moving beyond gastrointestinal diseases to explore therapeutics for skin, vaginal, and respiratory microbiomes, along with influencing the microbiome–gut–brain axis.
- **Postbiotics and Metabolites:** Using metabolites or heat-killed bacteria (postbiotics) to modulate the immune system and manage metabolic inflammation.

- **Addressing Challenges:** Future studies aim to overcome regulatory hurdles, improve manufacturing scalability, and ensure the safety and longevity of microbial engraftment in the host.

Key therapeutic targets include metabolic syndrome, inflammatory bowel diseases, and enhancing cancer immunotherapy effectiveness.

4. Conclusions

The human microbiome, often referred to as the "second genome," plays a crucial role in regulating immune responses, metabolic activities, and maintaining gut homeostasis. Disruption of the microbiome, known as dysbiosis, is associated with various health disorders. Many therapeutic strategies have been developed, such as probiotics, prebiotics, FMT, and microbial-based drugs. However, the clinical application of these therapies is often hindered by factors such as inter-individual variability of microbiomes, the complexity of microbial interactions, and gaps in mechanistic understanding.

Emerging technologies with microbiome-based therapies are increasingly capable of establishing causality. As a metric, this approach offers diagnostic or prognostic value, predicting who is at risk or who might benefit from specific therapies. As a modifier, it becomes a tool, manipulated through diet, probiotics, or microbial transplants to restore health with targeted treatments.

Microbiota-based interventions, including FMT, probiotics, and prebiotics, show promise as adjuvants to targeted pharmaceutical therapies for various systemic diseases. They act by reducing dysbiosis, restoring microbial diversity, and modulating immune responses to boost treatment efficacy. There is a trend toward a shift toward personalized medicine, targeting specific metabolic pathways, and validating safety for clinical application. Combining microbiota-based interventions with conventional treatments (e.g., combining probiotics with immunosuppressants) has demonstrated superior efficacy compared to conventional treatments alone, especially for autoimmune and metabolic disorders.

Establishing rigorous regulatory standardization for FMT and microbiome-derived products is crucial for safety, reproducibility, and successful integration into clinical practice. New pharmacological models and methodologies should be considered in microbiota-based intervention research, as standard animal disease models may lack species-specific microbiome effects and have limited translatability.

Despite promising clinical and experimental data, most human studies are observational. Therapeutic effects exhibit significant heterogeneity, depending on the strain or combination of strains used, the dose, duration of intervention, and the initial composition of the host microbiome. With the developments made in microbiome research in the past decade, the human microbiome has emerged as a critical determinant of health and disease, in addition to playing a causal role in health and disease. It has been studied through targeted treatment using diet, gut biotics, or microbiota transplantation. Overall, microbiome-based medication treatment is moving slowly from concept to clinical application. More research is needed before it can be widely used in clinical practice. Regulatory pathways for live biotherapeutics are still evolving.

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