Review

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

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

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Abstract

Pharmacomicrobiomics is the study of drug-microbiome interactions. In other words, it examines the dynamic relationship between the drug, the host, and the microbiome. This 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 (eg: antibiotics, antidepressants), alternative treatment approaches (eg: CAM treatments- supplements, herbs), non-drug biological therapies, like ECT and TMS. The new term for this approach called Microbiome Based Medication Treatment, which has been seen as an alternative treatment approach and has been studied extensively in the last decade. This review article focuses on current knowledge on drug–microbiome interactions across multiple therapeutic systems, including cardiovascular, central nervous system, gastrointestinal, respiratory, endocrine, oncologic, musculoskeletal, and anti-infective therapies. Furthermore, we highlight the various pathways by which microbes can alter the various mechanisms like drug absorption, bioavailability, efficacy, and incidence of adverse effects, along with the clinical implications of drug-induced dysbiosis.

Keywords: microbiome, pharmacomicrobiomics; gut biotics; fermented foods

1. Introduction

Pharmacomicrobiomics studies the interactions between the gut microbiota, host and medications. It is a new field, and the term was 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 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 variation depends not only on genetics (Pharmacogenetics and Pharmacogenomics) but also from 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. Pharmacomicrobiomics provides a promising framework to help us to better understand the variability of patient responses to drugs.

Emerging evidence suggest that clinical outcomes are strongly affected by individual variability in drug efficacy and safety [3]. Reports highlight that response rate to commonly prescribed drugs fall between 50% to 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 rest of response variability. The gut microbiome, often referred to as the "second genome" plays a vast variety of roles in the human body including immune

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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.

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 remains important to understand the relationship between cardiovascular (CV) medications and the human body. In this section we will 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 [5].

Warfarin dosing can be complicated as it can be affected by several factors and currently, 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) [6]. The result found that the genus *Escherichia-Shigella* was significantly greater in the LRs ($P = 3.189e^{-11}$), while the genus *Enterococcus* was significantly greater in the HRs ($P = 1.249e^{-11}$). 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 ($P = 0.005$) [6].

Administration of aspirin has also shown to have effects on the gut microbiota composition. For instance, Prizment et al. 2020 found that *Prevotella, Veillonella, Clostridium XlVa and Clostridium XVIII clusters* were different in those who received aspirin compared to placebo during a 6-week treatment period. Moreover, the effects of aspirin on the gut microbes suggest that it might decrease the risk of colorectal cancer [7]. Other CV medications like Nifedipine, Amlodipine, Digoxin has been shown to play a role in Gut microbiota-mediated drug interactions [8–10] (See Table 1).

Table 1. Drugs and Their Impact on the Gut Microbiome (Pharmacomicrobiomics).

System	Drug	Key Microbial Changes / Mechanisms	Key References
Cardiovascular	Warfarin	↑ *Escherichia-Shigella* in low responders; ↑ *Enterococcus* in high responders; ↑ microbial vitamin K2 production	Wang et al., 2020 [6]
	Aspirin	Changes in *Prevotella*, *Veillonella*, *Clostridium* clusters	Prizment et al., 2020 [7]
	Statins	*Bacteroides*-dominant → ↑ metabolic disruption; *Firmicutes*-dominant → protective	Wilmanski et al., 2022 [11]
	Amlodipine, Nifedipine	Antibiotics alter absorption via microbiome disruption	Yoo et al., 2016 [8]; Zhang et al., 2018 [9]
	Digoxin	*Eggerthella lenta* metabolizes digoxin	Haiser et al., 2014 [10]
Respiratory	Montelukast, Roflumilast	Drug sequestration and metabolism by gut microbes	Klünemann et al., 2021 [15]
	Inhaled corticosteroids	↑ *Haemophilus influenzae*, *Streptococcus pneumoniae*	Millares & Monso, 2022 [18]
Gastrointestinal	Proton Pump Inhibitors	↑ *Clostridium difficile*; SIBO; ↑ *Enterococcus*, *E. coli*	Janarthanan et al., 2012 [20]; Lombardo et al., 2010 [22]
	Sulfasalazine	Azoreductase-mediated cleavage → 5-ASA	Schröder et al., 1973 [27]
	Laxatives	β-glucosidase, sulfotransferase, anaerobic metabolism	Matsumoto et al., 2012 [30]

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	Parenteral Nutrition	↑ Proteobacteria; ↓ SCFA production	Wang et al., 2023 [32]
Anticancer	Irinotecan	β-glucuronidase → toxic SN38	Ting et al., 2022 [35]
	Cyclophosphamide	Bacterial translocation → Th1 response	Viaud et al., 2013 [38]
	Immune Checkpoint Inhibitors	*Bifidobacterium*, *Bacteroides* enhance response	Sivan et al., 2015 [40]; Vétizou et al., 2015 [42]
Endocrine (Diabetes)	Metformin	↑ *Akkermansia*, SCFA-producing bacteria	Wu et al., 2017 [49]
	GLP-1 agonists	↓ obesity-associated taxa; ↑ leanness taxa	Wang et al., 2016 [45]
	SGLT-2 inhibitors	↑ *Akkermansia*; ↑ SCFAs	Lee et al., 2018 [55]
Miscellaneous	Melatonin	Suppresses deprivation-induced dysbiosis; ↑ *Akkermansia muciniphila* and *Lactobacillus*; ↓ *Bacteroides massiliensis* and *Erysipelotrichaceae*; reduces inflammation via TLR4 signaling; ↑ *E. aerogenes* motility	Park et al. 2020 [66] Chuffa et al. 2015 [67] Paulose et al. 2106 [68]
Antimicrobials	Antiretrovirals (efavirenz, zidovudine)	Antimicrobial activity against *Bacteroides fragilis* and *Prevotella*	Ray et al. 2021 [69]
	Fluconazole	↑ *Firmicutes* and *Proteobacteria*; ↓ *Bacteroidetes*, *Deferribacteres*, *Patescibacteria*, *Tenericutes*	Heng et al. 2021 [70]
Antidepressants	Amitriptyline	Inhibits *Staphylococcus* spp., *Bacillus* spp., *Vibrio cholerae*, *Cryptococcus* spp., *Candida albicans*; protects against *Salmonella typhimurium*; activity against MRSA *Staphylococcus pseudintermedius*	Mandel et al. 2010 [71], Brochmann et al. 2016 [72]
	Clomipramine	Active against methicillin-resistant *Staphylococcus pseudintermedius*	Brochmann et al. 2016 [72]
	Fluoxetine, Escitalopram, Venlafaxine, Duloxetine	Reduction in microbial community richness	Lukic et al. 2019 [73]
	Sertraline	Potent antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*	Bohnert et al. 2011 [74] Ayaz et al. 2015 [75]
	Fluoxetine	↓ *Lactobacillus johnsonii* and *Bacteroidales* S24-7 (taxa associated with body mass regulation)	Lyte et al. 2019 [76]
Antipsychotics	Antipsychotics (general)	↑ *Prevotella*, *Victivallis*, unclassified *Desulfovibrionaceae*	Ticinesi et al. 2017 [77]
	Phenothiazines	Influence bacterial morphology; antimicrobial activity at supraclinical doses	Amaral et al. 2004 [78]
	Chlorpromazine	Inhibits *Staphylococcus aureus* and *E. coli*	Amaral et al. 1991 [79] Ordway et al. 2002 [80]
	Risperidone	↑ *Bifidobacterium* and *E. coli*; ↓ *Clostridium coccoides* and *Lactobacillus*	Yuan et al. 2018 [81]
	Olanzapine	Weight gain absent in germ-free mice; weight gain restored after colonization; prebiotic attenuates weight gain	Morgan et al. 2014 [82] Kao et al. 2018 [83]
	Aripiprazole, Risperidone, Olanzapine	Alterations in *Akkermansia*, *Lachnospiraceae*, and *Sutterella*	Amaral et al. 1991 [79]
Anxiolytics	Propranolol	Inhibits *E. coli*; mixed evidence for *Staphylococcus aureus* inhibition	Hadera et al. 2018 [84] Kruszewska et al. 2004 [85]

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Mood Stabilisers	Lamotrigine	Antibacterial activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus faecalis*	Qian et al. 2009 [86]
	Lithium; Valproate	Alter caecal microbiome after 4 weeks of treatment	Cussotto et al. 2019 [87]
Microbiome-Based Treatments – Renal	Probiotics, Prebiotics, Synbiotics, FMT	Reduce uremic toxins (indoxyl sulfate, p-cresyl sulfate); ↓ inflammation; slow CKD/AKI progression; prevent stone recurrence	Putri et al. 2019 [88] Liu et al. 2025 [89] Sun et al. 2026 [90]
Microbiome-Based Treatments – Musculoskeletal	Probiotics, Prebiotics, Synbiotics	Modulate gut-bone and gut-muscle axes; ↓ bone resorption; ↑ bone mineral density (especially postmenopausal women)	Li et al. 2021 [91] Sun et al. 2025 [92] Li et al. 2024 [93] Plewa et al. 2026 [94] You et al. 2025 [95]
	Exercise	Positively influences gut microbiota; ↓ inflammation	Papageorgiou et al. [96]

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, those who were *Firmicutes*-dominant were at lower risk [11]. In an animal study with Amiodarone, probiotic administration can change the pharmacokinetics of the medication [12].

Microbiome-based treatments for CVD are an emerging, promising field that aims 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 [13,14].

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 bacteria culture study found that Montelukast, an asthma medication, and Roflumilast, commonly used for COPD, were bioaccumulated as well as biodegraded by different bacteria species [15]. 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 main mechanism of this probiotic was by maintaining the alpha diversity and stability of the gut microbiota of these asthmatic patients [16]. Moreover, the most common used immunomodulatory treatments for asthma include corticosteroids and cytokine mediator antibodies that target mainly type-2 eosinophilic inflammation. These strategies are not effective for all patients especially for 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 [17]. Furthermore, a common treatment for COPD is also 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 only steroid users with low baseline eosinophils showed significant increases in pathogenic bacteria including *Haemophilus influenzae* and *Streptococcus pneumoniae* [18].

Microbiome-based treatments for respiratory diseases, including COPD, asthma, and infections, aim to restore microbial balance via probiotics (e.g., *Lactobacillus*, *Bifidobacterium*), high-fiber diets, and fecal microbiota transplantation (FMT). These approaches target the gut-lung axis to reduce airway inflammation and improve immune response, showing 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 demonstrate high efficacy in

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decreasing inflammation and improving lung function, many approaches require further clinical validation in humans. Future therapies may involve personalized microbiome analysis (using sequencing) and genetically modified probiotics to treat chronic respiratory diseases [19].

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 reduction in the functions of the stomach barrier. This reduction increases the incidence of pathogenic bacteria infiltration, with *Clostridioides difficile* being the most prevalent [4]. A meta-analysis carried out in 2012, which encompassed 300,000 patients, found that there was a 65% increase of *C. difficile* associated diarrhea in patients taking PPIs [20]. Moreover, PPIs have the potential to induce bacterial overgrowth, with the most common strains being *Clostridium*, *Lactobacillus*, and *Streptococcus* species [21]. They can also alter the small bowel composition, and this was demonstrated in a 2010 study which found that 50% of users taking PPIs tested positive for small intestinal bacterial overgrowth (SIBO). Common organisms of this overgrowth included *Escherichia coli* (37%), *Enterococcus* spp. (32%), and *Klebsiella pneumoniae* (24%) [22]. Furthermore, in vitro studies have demonstrated that omeprazole undergoes metabolism into its sulfide metabolite due to microbiome activity, including that of anaerobic bacteria like *Bacteroides* strains [23].

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 [24]. Studies have found that the majority of the drug is reduced by the gut microbiota to release this 5-aminosalicylate (5-ASA) as well as sulfapyridine, which are the pharmacologically active metabolites. This reduction is carried out by the enzyme azoreductase [25]. 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 because of 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 compared to control rats was observed. This might indicate that bacteria do not have an effect on transporters involved in the drug's mechanism of action [26]. Moreover, another study found that germ free mice were not able to split the azo linkage compared to the control group. This demonstrates that the azo cleavage is in fact dependent on the intestinal microbiome [27].

2.3.3. Laxatives

Sodium picosulfate requires sulfotransferase producing bacteria to metabolize it into its active form of 4,4'-dihydroxydiphenyl-(2 pyridyl)-methane (DPM) [28]. 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 [29]. 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 the intestinal peristalsis and ultimately the purgative action [30]. Finally, barbaloin, the laxative component of aloe, is activated into aloe-emodin anthrone (has the purgative action) by intestinal anaerobes such as *Eubacterium* sp. Strain BAR [31].

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2.3.4. Parenteral Nutrition

Total parenteral nutrition (TPN) has been found to cause disruption of the 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 microbiota-derived tryptophan metabolism [32]. Additionally, a mouse model showed that administration of TPN led to a significant expansion of Proteobacteria within the intestinal microbiota [33]. 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 healthy siblings and children on enteral nutrition. The children also showed an increase in *Enterobacteriaceae*, which is a family of gram negative *Proteobacteria* [34].

2.4. Pharmacomicrobiomics of Anticancer Drugs

Microbiome-based treatments for cancer are to manipulate the trillions of microorganisms in the body—primarily the gut microbiota—to enhance the efficacy of conventional therapies (chemotherapy, immunotherapy) and reduce their side effects.

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 [35]. 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. Similar to irinotecan, the metabolism of 5-fluorouracil is also directly affected by the gut microbiome. 5-fluorouracil gets activated from 5-FU into cytotoxic 5-FU triphosphate via vitamin B6 and B9 bacterial ribonucleotide metabolism.

Additionally, anticancer activity can also be modulated by bacteria metabolites, such as short chain fatty acids like butyrate. A human study investigated the fecal metabolomic profile, using nuclear medicine resonance (NMR) spectroscopy, of patients with breast cancer undergoing three cycles of chemotherapy with a combination of three chemotherapeutic agents: 5-fluorouracil, epiribucine, and cyclophosphamide [36]. Results indicated that there was an upregulation of these SCFA after 2-3 cycles of chemotherapy. These SCFA have been found to promote apoptosis, inhibit the invasive phenotypes of breast cancer, and increasing the intracellular concentration of chemotherapies. This suggest that bacteria SCFAs pose a beneficial anti-cancer 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 reactive oxygen species (ROS) production which has been found to be dependent on the microbiota [35].

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.

Finally, drugs like cyclophosphamide promote the translocation of bacterial strains into lymphoid organs which lead to the accumulation of T-helper cells and the overall development of anti-cancer immunity [35]. A study on chemotherapies for non-hematological malignancy, where 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 [37]. These results are consistent with an animal study which found that cyclophosphamide induces the translocation of Gram-positive bacteria into secondary lymphoid organs promoting T cell immune response activation [38].

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2.4.2. Immunotherapies

By modifying the immune system, known as immunomodulation, microbes can change how a person responds to treatment [35]. Through immunomodulation they mostly modify the pharmacodynamics of these drugs rather than the pharmacokinetics. Microbes can cause direct tumor cell killing via Th1 by the production of polysaccharides that stimulate CD11b+ dendritic cells as well as via the enhancement of suppression of Treg cells through mediation by IL-10 [39]. This leads to decreased colitis and immune related adverse 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 the infiltration into the tumor microenvironment [40]. 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 [41]. Using 16S rRNA sequencing on stool samples, it found that healthy controls showed a greater number of short chain fatty acids as well as more abundance of commensal bacteria. However, this dysbiosis can't be fully attributed to the immunotherapy but could be due to the cancer itself.

An animal and human study demonstrated that the anti-tumor effects of anti CTLA-4, such as Ipilimumab, are dependent on *Bacteroides* species. In the animal study, it was found that mice treated with antibiotics or germ-free mice did not respond to the blockage of CTLA-4. They found that the administration of these *Bacteroides* bacteria overcame this non-responsiveness. They also performed a fecal microbial transplantation from melanoma patients to mice which confirmed that anti CTLA-4 increases *B. fragilis*, *B. thetaiotaomicron,* and *Burkholderia cepacia* [42].

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 were correlated with increase in microbe taxa such as *Enterobacteriales* and *Akkermansia muciniphila* which may play a role in blood sugar control [43]. Consistent with these findings, other studies suggest that *A. muciniphila* is potentially a mediator of the anti-diabetic effects of metformin [44]. 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 gut microbiota changes in mice compared to the corresponding control [45]. Obesity related microbiota phenotypes such as *Erysipelotrichaceae Incertae Sedis* and *Marvinbryantiaw* were decreased, whereas leanness associated phenotypes (*Lactobacillus* and *Turicibacter*) were increased with liraglutide treatment [45].

Moreover, probiotics when used in combination with antidiabetic drugs, increase the beneficial bacteria richness as well as its metabolites like short chain fatty acids [46]. Increase in SCFA-producing bacteria has been associated with improvements in Hb A1C in individuals with type 2 diabetes. Consistent with this, individuals who took a combination of metformin with probiotics demonstrated a decrease in glycemia and insulin resistance.

Metformin ameliorated hyperglycemia and hyperlipidemia in T2DM patients via increasing beneficial bacteria, such as *Blautia* and *Faecalibacterium*. Patient response variability varies to metformin. Good responders showed increased levels of sphingomyelins, acylcholines, and glutathione metabolites [47]. Metformin may act on the gut, as many studies have shown that administration of metformin changes bile acid recirculation [48]. After 4 months of treatment with metformin and placebo, the 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 [49]. In another study, compared to db/db mice, the abundance of Bacteroides improved significantly with increasing levels of SCFAs after being treated with metformin [50]. In conclusion, increasing the level of SCFA-producing

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bacteria might be a mechanism of metformin on gut bacteria, however, the concrete mechanism affecting gut microbiota needs to be further investigated. It may be one of the ways in modulating the response of drugs to improve drug efficacy.

Hippurate (a component found in urine, mainly derive from the disintegration of plant phenolics and aromatic amino acids by the gut microbiota) in patients treated with sulfonylureas increased obviously, which revealed that sulfonylureas might influence the metabolism of gut microbiota [51].

Dipeptidyl peptidase 4 (DPP-4) inhibitors are also commonly used antidiabetic drugs also have an effect on microbiome [52]. SGLT-2 is sodium glucose transporter located in renal tubules and plays an important role in glucose reabsorption [53]. Thus, SGLT-2 inhibitors are used for therapy in Type2 Diabetes Mellitus because they could suppress the reabsorption of glucose to maintain the level of blood sugar [54]. A previous study found that after 8 weeks of dapagliflozin treatment, the proportion of Bacteroidetes and *Akkermansia muciniphila* increased while Firmicutes and Oscillospira decreased [55]. Luseogliflzin was found to increase the number of intestinal bacteria involved in the synthesis of SCFAs and to improve amino acid metabolism [56,57]. Most of the evidence of the antidiabetic's drugs on gut microbiota at this point is from animal studies, with some evolving evidence from human studies. Understanding drug-microbiota interactions allows to optimize treatment responses and minimize side effects in type 2 diabetes therapies.

2.5.2. Thyroid Medications

The microbiome and dysbiosis affects the functioning of the thyroid gland through the gut–thyroid axis [58–62]. Low-certainty evidence from two randomised trials, suggests that routine administration of probiotics, prebiotics or synbiotics may result in little to no benefit in patients with primary hypothyroidism [63–65].

2.6. Miscellaneous Drugs

2.6.1. Melatonin

In an animal study, mice were subjected to water and sleep deprivation and administered melatonin [66]. Melatonin was found to suppress the dysbiosis caused by these deprivations leading to an increase in *Akkermansia muciniphila* and *Lactobacillus* and decreased *Bacteroides massiliensis* and *Erysipelotrichaceae*. Previous studies also found that melatonin reduces inflammatory responses through the signaling pathway mediated by TLR4 which has been found to be associated with the intestinal microbiota implying that melatonin might play a direct effect on gut microbiota modulation [67]. Furthermore, melatonin has been shown to increase the magnitude of *E. aerogenes* motility [68].

2.6.2. 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* [69].

2.6.3. Antifungals

Animal study found that mice treated with 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* [70].

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2.7. Pharmacomicrobiomcs of Psychiatric Drugs

2.7.1. Antidepressants

There have been various studies that 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* [71]. When used in a mouse study, it provided protection from *Salmonella typhimurium* [71]. Other investigations have found that amitriptyline and even clomipramine can be active against methicillin-resistant *Staphylococcus pseudintermedius* [72]. When looking at bacterial richness, certain antidepressants such as fluoxetine, escitalopram, venlafaxime, and duloxetine lead to a reduction in microbial communities [73]. There have been studies looking at sertraline and have found that it has potent antimicrobial effect against *Escherichia coli*, *Staphlyococcus aureus,* and *Pseudomnoas aeruginosa* [74,75]. Fluoxetine was shown to cause a reduction in *Lactobacillus johnsonii* and Bacteroidales S24-7, which belong to bacteria phyla that are associated with body mass regulation [76]. Thus, this may suggest that the associated weight gain seen with antidepressant may be caused by the alterations in the gut microbiome.

2.7.2. Antipsychotics

The use of antipsychotics has been found to alter the gut microbiome composition leading to an increase of *Prevotella*, *Victivallis*, as well as an unclassified member of the Desulfovibronaceae family [77]. Phenothiazine antipsychotics have been found to influence bacterial morphology along with exhibit some antimicrobial activity, however, at higher than clinical doses [78]. Studies have found that chlorpromazine can inhibit the growth of *Staphylococcus aureus* and *E. coli* [79,80]. When patients with schizophrenia are treated with risperidone for 24 weeks, this caused a change in the gut microbiome in these patients causing increased Bifidobacterium and *E. coli* with decreased *Clostridium coccoides* and *Lactobacillus* [81]. It has also been found that the interaction between the gut microbiome and atypical antipsychotics may be a factor on the common side effect of weight gain. When germ-free mice were treated with olanzapine, there was not the associated weight gain compared to the control group [82]. Conversely, when the germ-free mice were colonized, this weight gain return [82]. Other evidence that suggests there is an interplay between olanzapine and the gut microbiome was in a study by Kao *et al*. where they found that there was an attenuation of weight gain when rats received a prebiotic along with olanzapine [83]. In a study by Flowers *et al*. it was found that the antipsychotics, aripiprazole, risperidone, and olanzapine caused alterations in the bacterial phyla Akkermansia, Lachnispiraceae, and Sutterella in humans [79].

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 [84,85]. These results suggest that propranolol may exert selective antimicrobial effects depending on bacterial species and experimental conditions.

2.7.4. Mood Stabilisers

Several mood stabilisers 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* [86]. Both lithium and valproate alter the caecal microbiome in rats following four weeks of treatment, indicating that chronic exposure to these agents can modify gut microbial communities in vivo [87].

2.8. Microbiome-Based Treatments for Renal System Diseases

Focuses on modulating the gut-kidney axis, a bidirectional relationship where kidney dysfunction causes gut dysbiosis (imbalance), which in turn produces uremic toxins that accelerate

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renal damage. Interventions such as probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (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 to prevent recurrence of stones [88–90].

2.9. Microbiome-Based Treatments for Musculoskeletal Diseases

In both musculoskeletal system diseases and osteoporosis by focusing on the "gut-bone" and "gut-muscle" axes, one can manage these conditions by modulating gut microbiota [91–94]. Clinical and preclinical studies have shown that probiotic, prebiotic, and synbiotics can reduce bone resorption and improve bone mineral density (BMD), particularly in postmenopausal women [95]. Engaging in regular exercise, which has been shown to positively influence gut microbiota and lower inflammation [96].

2.10. Microbiome Based Therapeutics

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

Microbiome therapies include manipulating the gut microbiome by using various treatments, such as adding, removing, or modifying the bacteria. This can be done using natural or modified microorganisms, antibiotics, bacteriophages, and bacteriocins.

Engineered microbes or microbial consortia 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 to be evaluated. Fermented foods are unique products that have many potential benefits that range from food safety to human health. Increased shelf life and stability of foods 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 [97,98]. However, existing commercial microbiome-directed products often exhibit low efficacy [99].

3. 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. Development of many therapeutic strategies happened such as probiotics, prebiotics, fecal microbiota transplantation, 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.

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 development seen in microbiome research in the past decade, the human microbiome has emerged as a critical determinant of health and disease. In addition to the causal role in health and disease. It has been studied in 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 for its use in clinical practice widely.

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References

1. Rizkallah M, Saad R, Aziz R. The human microbiome project, personalized medicine and the birth of pharmacomicrobiomics. Current pharmacogenomics and personalized medicine. 2010;8(3):182–193. http://www.eurekaselect.com/openurl/content.php?genre=article&issn=18756921&volume=8&issue=3&spage=182. doi: 10.2174/187569210792246326.
2. Mohajeri MH, Brummer RJM, Rastall RA, et al. The role of the microbiome for human health: From basic science to clinical applications. Eur J Nutr. 2018;57(S1):1–14. https://link.springer.com/article/10.1007/s00394-018-1703-4. doi: 10.1007/s00394-018-1703-4.
3. Bolte LA, Björk JR, Gacesa R, Weersma RK. Pharmacomicrobiomics: The role of the gut microbiome in immunomodulation and cancer therapy. Gastroenterology (New York, N.Y. 1943). 2025;169(5):813–827. https://www.clinicalkey.com/#!/content/1-s2.0-S0016508525007553. doi: 10.1053/j.gastro.2025.04.025.
4. Doestzada M, Vich Vila A, Zhernakova A, et al. Pharmacomicrobiomics: A novel route towards personalized medicine? Protein Cell. 2018;9(5):432–445. https://journal.hep.com.cn/pac/EN/10.1007/s13238-018-0547-2. doi: 10.1007/s13238-018-0547-2.
5. Anna Battle &, Ashlan Lane, Hailey Parish, Sean Rushing, Jessica L. Johnson, Abby J. Weldon . Interactions between the gut microbiota and common cardiovascular drugs. US Pharmacist. 2023;48(2):18–21.
6. Wang L, Liu L, Liu X, et al. The gut microbes, enterococcus and escherichia-shigella, affect the responses of heart valve replacement patients to the anticoagulant warfarin. Pharmacological research. 2020;159:104979. https://dx.doi.org/10.1016/j.phrs.2020.104979. doi: 10.1016/j.phrs.2020.104979.
7. Prizment AE, Staley C, Onyeaghala GC, et al. Randomised clinical study: Oral aspirin 325 mg daily vs placebo alters gut microbial composition and bacterial taxa associated with colorectal cancer risk. Alimentary pharmacology & therapeutics. 2020;52(6):976–987. https://onlinelibrary.wiley.com/doi/abs/10.1111%2Fapt.16013. doi: 10.1111/apt.16013.
8. Yoo HH, Kim IS, Yoo D, Kim D. Effects of orally administered antibiotics on the bioavailability of amlodipine: Gut microbiota-mediated drug interaction. Journal of hypertension. 2016;34(1):156–162. https://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=n&CSC=Y&PAGE=fulltext&D=ovft&AN=00004872-201601000-00022. doi: 10.1097/HJH.0000000000000773.
9. Zhang J, Chen Y, Sun Y, Wang R, Zhang J, Jia Z. Plateau hypoxia attenuates the metabolic activity of intestinal flora to enhance the bioavailability of nifedipine. Drug Delivery. 2018;25(1):1175–1181. https://www.tandfonline.com/doi/abs/10.1080/10717544.2018.1469687. doi: 10.1080/10717544.2018.1469687.
10. Haiser HJ, Seim KL, Balskus EP, Turnbaugh PJ. Mechanistic insight into digoxin inactivation by eggerthella lenta augments our understanding of its pharmacokinetics. Gut microbes. 2014;5(2):233–238. https://www.tandfonline.com/doi/abs/10.4161/gmic.27915. doi: 10.4161/gmic.27915.
11. Wilmanski T, Kornilov SA, Diener C, et al. Heterogeneity in statin responses explained by variation in the human gut microbiome. Med (New York, N.Y. : Online). 2022;3(6):388–405.e6. https://dx.doi.org/10.1016/j.medj.2022.04.007. doi: 10.1016/j.medj.2022.04.007.
12. Matuskova Z, Anzenbacherova E, Vecera R, Tlaskalova-Hogenova H, Kolar M, Anzenbacher P. Administration of a probiotic can change drug pharmacokinetics: Effect of E. coli nissle 1917 on amidarone absorption in rats. PloS one. 2014;9(2):e87150. https://www.ncbi.nlm.nih.gov/pubmed/24505278. doi: 10.1371/journal.pone.0087150.
13. Makkieh Y, Shah HH, Imran SB, et al. The gut-heart axis: Exploring the role of the gut microbiome in cardiovascular health – A focused systematic review. American heart journal plus. 2026;61:100687. https://www.clinicalkey.com/#!/content/1-s2.0-S2666602225001909. doi: 10.1016/j.ahjo.2025.100687.
14. Suresh MG, Mohamed S, Yukselen Z, et al. Therapeutic modulation of gut microbiome in cardiovascular disease: A literature review. Heart and Mind. 2025;9(1):68–79. https://doi.org/10.4103/hm.HM-D-24-00044. doi: 10.4103/hm.HM-D-24-00044.
15. Klünemann M, Andrejev S, Blasche S, et al. Bioaccumulation of therapeutic drugs by human gut bacteria. Nature. 2021;597(7877):533–538. https://link.springer.com/article/10.1038/s41586-021-03891-8. doi: 10.1038/s41586-021-03891-8.

 doi:10.20944/preprints202602.1498.v1

16. Liu A, Ma T, Xu N, et al. Adjunctive probiotics alleviates asthmatic symptoms via modulating the gut microbiome and serum metabolome. Microbiol Spectr. 2021;9(2):e0085921. https://www.ncbi.nlm.nih.gov/pubmed/34612663. doi: 10.1128/Spectrum.00859-21.
17. Kozik AJ, Huang YJ. The microbiome in asthma: Role in pathogenesis, phenotype, and response to treatment. Annals of allergy, asthma, & immunology. 2019;122(3):270–275. https://www.ncbi.nlm.nih.gov/pubmed/30552986. doi: 10.1016/j.anai.2018.12.005.
18. Millares L, Monso E, Universitat Autònoma de Barcelona. The microbiome in COPD : Emerging potential for microbiome-targeted interventions. 2022. https://ddd.uab.cat/record/292350.
19. Lee JH, Lee SW, Lee SH. Application of microbiome-based therapies in chronic respiratory diseases. J Microbiol. 2024;62(3):201–216. https://agris.fao.org/search/en/records/67f4dcece01f7420ea853303. doi: 10.1007/s12275-024-00124-1.
20. Janarthanan S, Ditah I, Adler DG, Ehrinpreis MN. Clostridium difficile -associated diarrhea and proton pump inhibitor therapy: A meta-analysis. American Journal of Gastroenterology. 2012;107(7):1001–1010. https://www.ncbi.nlm.nih.gov/pubmed/22710578. doi: 10.1038/ajg.2012.179.
21. Freedberg, Daniel E., MD, MS, Lebwohl, Benjamin, MD, MS, Abrams, Julian A., MD, MS. The impact of proton pump inhibitors on the human gastrointestinal microbiome. Clinics in laboratory medicine. 2014;34(4):771–785. https://www.clinicalkey.es/playcontent/1-s2.0-S0272271214000833. doi: 10.1016/j.cll.2014.08.008.
22. Lombardo L, Foti M, Ruggia O, Chiecchio A. Increased incidence of small intestinal bacterial overgrowth during proton pump inhibitor therapy. Clinical Gastroenterology and Hepatology. 2010;8(6):504–508. https://www.clinicalkey.es/playcontent/1-s2.0-S1542356509013317. doi: 10.1016/j.cgh.2009.12.022.
23. Sun C, Chen L, Shen Z. Mechanisms of gastrointestinal microflora on drug metabolism in clinical practice. Saudi Pharmaceutical Journal. 2019;27(8):1146–1156. https://dx.doi.org/10.1016/j.jsps.2019.09.011. doi: 10.1016/j.jsps.2019.09.011.
24. Xie Y, Hu F, Xiang D, et al. The metabolic effect of gut microbiota on drugs. Drug metabolism reviews. 2020;52(1):139–156. https://www.tandfonline.com/doi/abs/10.1080/03602532.2020.1718691. doi: 10.1080/03602532.2020.1718691.
25. Zhang X, Han Y, Huang W, Jin M, Gao Z. The influence of the gut microbiota on the bioavailability of oral drugs. Acta pharmaceutica Sinica. B. 2021;11(7):1789–1812. https://dx.doi.org/10.1016/j.apsb.2020.09.013. doi: 10.1016/j.apsb.2020.09.013.
26. Lee HJ, Zhang H, Orlovich DA, Fawcett JP. The influence of probiotic treatment on sulfasalazine metabolism in rat. Xenobiotica. 2012;42(8):791–797. https://www.tandfonline.com/doi/abs/10.3109/00498254.2012.660508. doi: 10.3109/00498254.2012.660508.
27. Schröder H, Gustafsson BE. Azo reduction of salicyl-azo-sulphapyridine in germ-free and conventional rats. Xenobiotica. 1973;3(4):225–231. https://www.tandfonline.com/doi/abs/10.3109/00498257309151518. doi: 10.3109/00498257309151518.
28. Kim D, Hyun S, Shim S, Kobashi K. The role of intestinal bacteria in the transformation of sodium picosulfate. Japanese Journal of Pharmacology. 1992;59(1):1–5. https://dx.doi.org/10.1254/jjp.59.1. doi: 10.1254/jjp.59.1.
29. Elkington SG, Floch MH, Conn HO. Lactulose in the treatment of chronic portal-systemic encephalopathy. The New England journal of medicine. 1969;281(8):408–412. http://dx.doi.org/10.1056/NEJM196908212810803. doi: 10.1056/NEJM196908212810803.
30. Matsumoto M, Ishige A, Yazawa Y, Kondo M, Muramatsu K, Watanabe K. Promotion of intestinal peristalsis by bifidobacterium spp. capable of hydrolysing sennosides in mice. PLoS ONE. 2012;7(2):e31700–e31700. https://www.ncbi.nlm.nih.gov/pubmed/22384059. doi: 10.1371/journal.pone.0031700.
31. AKAO T, CHE Q, KOBASHI K, HATTORI M, NAMBA T. A purgative action of barbaloin is induced by eubacterium sp. strain BAR, a human intestinal anaerobe, capable of transforming barbaloin to aloe-emodin anthrone. Biological & pharmaceutical bulletin. 1996;19(1):136–138. https://www.jstage.jst.go.jp/article/bpb1993/19/1/19_1_136/_article/-char/en. doi: 10.1248/bpb.19.136.

 doi:10.20944/preprints202602.1498.v1

32. Wang P, Sun H, Maitiabula G, et al. Total parenteral nutrition impairs glucose metabolism by modifying the gut microbiome. Nat Metab. 2023;5(2):331–348. https://link.springer.com/article/10.1038/s42255-023-00744-8. doi: 10.1038/s42255-023-00744-8.
33. Miyasaka EA, Feng Y, Poroyko V, et al. Total parenteral Nutrition–Associated lamina propria inflammation in mice is mediated by a MyD88-dependent mechanism. The Journal of Immunology. 2013;190(12):6607–6615. https://www.ncbi.nlm.nih.gov/pubmed/23667106. doi: 10.4049/jimmunol.1201746.
34. Engstrand Lilja H, Wefer H, Nyström N, Finkel Y, Engstrand L. Intestinal dysbiosis in children with short bowel syndrome is associated with impaired outcome. Microbiome. 2015;3(1):18. https://www.ncbi.nlm.nih.gov/pubmed/25941569. doi: 10.1186/s40168-015-0084-7.
35. Ting NL, Lau HC, Yu J. Cancer pharmacomicrobiomics: Targeting microbiota to optimise cancer therapy outcomes. Gut. 2022;71(7):1412–1425. https://gut.bmj.com/content/71/7/1412.full. doi: 10.1136/gutjnl-2021-326264.
36. Zidi O, Souai N, Raies H, et al. Fecal metabolic profiling of breast cancer patients during neoadjuvant chemotherapy reveals potential biomarkers. Molecules (Basel, Switzerland). 2021;26(8):2266. https://www.ncbi.nlm.nih.gov/pubmed/33919750. doi: 10.3390/molecules26082266.
37. Papanicolas LE, Sims SK, Taylor SL, et al. Conventional myelosuppressive chemotherapy for non-haematological malignancy disrupts the intestinal microbiome. BMC cancer. 2021;21(1):1–591. https://www.proquest.com/docview/2543469642. doi: 10.1186/s12885-021-08296-4.
38. Viaud S, Saccheri F, Mignot G, et al. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. Science. 2013;342(6161):971–976. https://www.jstor.org/stable/42620142. doi: 10.1126/science.1240537.
39. Mager LF, Burkhard R, Pett N, et al. Microbiome-derived inosine modulates response to checkpoint inhibitor immunotherapy. Science. 2020;369(6510):1481–1489. https://www.ncbi.nlm.nih.gov/pubmed/32792462. doi: 10.1126/science.abc3421.
40. Sivan A, Corrales L, Hubert N, et al. Commensal bifidobacterium promotes antitumor immunity and facilitates anti–PD-L1 efficacy. Science (American Association for the Advancement of Science). 2015;350(6264):1084–1089. https://www.jstor.org/stable/24740937. doi: 10.1126/science.aac4255.
41. Vernocchi P, Gili T, Conte F, et al. Network analysis of gut microbiome and metabolome to discover microbiota-linked biomarkers in patients affected by non-small cell lung cancer. International Journal of Molecular Sciences. 2020;21(22):8730. https://www.ncbi.nlm.nih.gov/pubmed/33227982. doi: 10.3390/ijms21228730.
42. Vétizou M, Pitt JM, Daillère R, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science. 2015;350(6264):1079–1084. https://www.jstor.org/stable/24740936. doi: 10.1126/science.aad1329.
43. Cao TTB, Wu K, Hsu J, et al. Effects of non-insulin anti-hyperglycemic agents on gut microbiota: A systematic review on human and animal studies. Frontiers in endocrinology (Lausanne). 2020;11:573891. https://www.ncbi.nlm.nih.gov/pubmed/33071980. doi: 10.3389/fendo.2020.573891.
44. Whang A, Nagpal R, Yadav H. Bi-directional drug-microbiome interactions of anti-diabetics. EBioMedicine. 2019;39:591–602. https://www.clinicalkey.com/#!/content/1-s2.0-S2352396418305504. doi: 10.1016/j.ebiom.2018.11.046.
45. Wang L, Li P, Tang Z, Yan X, Feng B. Structural modulation of the gut microbiota and the relationship with body weight: Compared evaluation of liraglutide and saxagliptin treatment. Sci Rep. 2016;6(1):33251. https://link.springer.com/article/10.1038/srep33251. doi: 10.1038/srep33251.
46. Palacios T, Vitetta L, Coulson S, et al. Targeting the intestinal microbiota to prevent type 2 diabetes and enhance the effect of metformin on glycaemia: A randomised controlled pilot study. Nutrients. 2020;12(7):2041. https://www.ncbi.nlm.nih.gov/pubmed/32660025. doi: 10.3390/nu12072041.
47. Naja K, Anwardeen N, Al-Hariri M, Al Thani AA, Elrayess MA. Pharmacometabolomic approach to investigate the response to metformin in patients with type 2 diabetes: A cross-sectional study. Biomedicines. 2023;11(8):2164. https://www.proquest.com/docview/2856868113. doi: 10.3390/biomedicines11082164.

 doi:10.20944/preprints202602.1498.v1

48. Napolitano A, Miller S, Nicholls AW, et al. Novel gut-based pharmacology of metformin in patients with type 2 diabetes mellitus. PloS one. 2014;9(7):e100778. https://www.ncbi.nlm.nih.gov/pubmed/24988476. doi: 10.1371/journal.pone.0100778.
49. Hao Wu, Eduardo Esteve, Valentina Tremaroli, et al. Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug. Nature Medicine. 2017;23(7):850–858. doi: 10.1038/nm.4345.
50. Zhang W, Xu J, Yu T, Chen Q. Effects of berberine and metformin on intestinal inflammation and gut microbiome composition in db/db mice. Biomedicine & pharmacotherapy. 2019;118:109131. https://dx.doi.org/10.1016/j.biopha.2019.109131. doi: 10.1016/j.biopha.2019.109131.
51. Huo T, Xiong Z, Lu X, Cai S. Metabonomic study of biochemical changes in urinary of type 2 diabetes mellitus patients after the treatment of sulfonylurea antidiabetic drugs based on ultra-performance liquid chromatography/mass spectrometry. Biomedical chromatography. 2015;29(1):115–122. https://api.istex.fr/ark:/67375/WNG-V6T96PZX-X/fulltext.pdf. doi: 10.1002/bmc.3247.
52. Zhang Q, Xiao X, Li M, et al. Vildagliptin increases butyrate-producing bacteria in the gut of diabetic rats. PLOS ONE. 2017;12(10):e0. https://www.ncbi.nlm.nih.gov/pubmed/29036231. doi: 10.1371/journal.pone.0184735.
53. Rahmoune H, Thompson PW, Ward JM, Smith CD, Hong G, Brown J. Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with Non–Insulin-dependent diabetes. Diabetes (New York, N.Y.). 2005;54(12):3427–3434. http://diabetes.diabetesjournals.org/content/54/12/3427.abstract. doi: 10.2337/diabetes.54.12.3427.
54. Rizzo M, Al-Busaidi N, Rizvi AA. Dapagliflozin therapy in type-2 diabetes: Current knowledge and future perspectives. Expert opinion on pharmacotherapy. 2015;16(3):281–284. https://www.tandfonline.com/doi/abs/10.1517/14656566.2015.981528. doi: 10.1517/14656566.2015.981528.
55. Lee DM, Battson ML, Jarrell DK, et al. SGLT2 inhibition via dapagliflozin improves generalized vascular dysfunction and alters the gut microbiota in type 2 diabetic mice. Cardiovascular Diabetology. 2018;17(1):62. https://www.ncbi.nlm.nih.gov/pubmed/29703207. doi: 10.1186/s12933-018-0708-x.
56. Shinnosuke Hata, Takuro Okamura, Ayaka Kobayashi, et al. Gut microbiota changes by an SGLT2 inhibitor, luseogliflozin, alters metabolites compared with those in a low carbohydrate diet in db/db mice. Nutrients. 2022;14:3531. doi: 10.3390/nu14173531.
57. Deng X, Zhang C, Wang P, et al. Cardiovascular benefits of empagliflozin are associated with gut microbiota and plasma metabolites in type 2 diabetes. Journal of clinical endocrinology and metabolism. 2022;107(7):1888–1896. https://www.ncbi.nlm.nih.gov/pubmed/35397165. doi: 10.1210/clinem/dgac210.
58. Bargiel P, Szczuko M, Stachowska L, et al. Microbiome metabolites and thyroid dysfunction. Journal of clinical medicine. 2021;10(16):3609. https://www.proquest.com/docview/2565282233. doi: 10.3390/jcm10163609.
59. Su X, Zhao Y, Li Y, Ma S, Wang Z. Gut dysbiosis is associated with primary hypothyroidism with interaction on gut-thyroid axis. Clinical science (1979). 2020;134(12):1521–1535. https://search.proquest.com/docview/2411531234. doi: 10.1042/CS20200475.
60. Stramazzo I, Capriello S, Filardo S, Centanni M, Virili C. Microbiota and thyroid disease: An updated systematic review. In: Advances in microbiology, infectious diseases and public health. Vol 1434. Switzerland: Springer International Publishing; 2023:125–144. https://library.biblioboard.com/viewer/d95833a1-29c5-11ee-ba25-0a9b31268bf5. 10.1007/5584_2023_770.
61. Zhang J, Zhang F, Zhao C, et al. Dysbiosis of the gut microbiome is associated with thyroid cancer and thyroid nodules and correlated with clinical index of thyroid function. Endocrine. 2019;64(3):564–574. https://link.springer.com/article/10.1007/s12020-018-1831-x. doi: 10.1007/s12020-018-1831-x.
62. Zheng D, Liao H, Chen S, et al. Elevated levels of circulating biomarkers related to leaky gut syndrome and bacterial translocation are associated with graves' disease. Frontiers in endocrinology (Lausanne). 2021;12:796212. https://www.ncbi.nlm.nih.gov/pubmed/34975767. doi: 10.3389/fendo.2021.796212.
63. Zawadzka K, Kałuzińska K, Świerz MJ, et al. Are probiotics, prebiotics, and synbiotics beneficial in primary thyroid diseases? a systematic review with meta-analysis. Annals of Agricultural and Environmental

 doi:10.20944/preprints202602.1498.v1

Medicine. 2023;30(2):217–223. https://www.ncbi.nlm.nih.gov/pubmed/37387369. doi: 10.26444/aaem/162732.

64. Spaggiari G, Brigante G, De Vincentis S, et al. Probiotics ingestion does not directly affect thyroid hormonal parameters in hypothyroid patients on levothyroxine treatment. Frontiers in endocrinology. 2017;8(NOV):316. https://www.ncbi.nlm.nih.gov/pubmed/29184537. doi: 10.3389/fendo.2017.00316.
65. Ejtahed H, Angoorani P, Soroush A, et al. Our little friends with big roles: Alterations of the gut microbiota in thyroid disorders. Endocrine, metabolic & immune disorders drug targets. 2020;20(3):344–350. http://www.eurekaselect.com/openurl/content.php?genre=article&issn=1871-5303&volume=20&issue=3&spage=344. doi: 10.2174/1871530319666190930110605.
66. Park YS, Kim SH, Park JW, et al. Melatonin in the colon modulates intestinal microbiota in response to stress and sleep deprivation. Intestinal Research. 2020;18(3):325–336. https://search.proquest.com/docview/2415834714. doi: 10.5217/ir.2019.00093.
67. Chuffa LGA, Fioruci-Fontanelli BA, Mendes LO, et al. Melatonin attenuates the TLR4-mediated inflammatory response through MyD88- and TRIF-dependent signaling pathways in an in vivo model of ovarian cancer. BMC cancer. 2015;15(1):34. https://www.ncbi.nlm.nih.gov/pubmed/25655081. doi: 10.1186/s12885-015-1032-4.
68. Paulose JK, Wright JM, Patel AG, Cassone VM. Human gut bacteria are sensitive to melatonin and express endogenous circadian rhythmicity. PloS one. 2016;11(1):e0146643. https://www.ncbi.nlm.nih.gov/pubmed/26751389. doi: 10.1371/journal.pone.0146643.
69. Ray S, Narayanan A, Giske CG, Neogi U, Sönnerborg A, Nowak P. Altered gut microbiome under antiretroviral therapy: Impact of efavirenz and zidovudine. ACS infectious diseases. 2021;7(5):1104–1115. http://dx.doi.org/10.1021/acsinfecdis.0c00536. doi: 10.1021/acsinfecdis.0c00536.
70. Heng X, Jiang Y, Chu W. Influence of fluconazole administration on gut microbiome, intestinal barrier, and immune response in mice. Antimicrob Agents Chemother. 2021;65(6). https://www.ncbi.nlm.nih.gov/pubmed/33722893. doi: 10.1128/AAC.02552-20.
71. Mandal, Anurup(Jadavpur University Department of Pharmaceutical Technology Division of Microbiology), Sinha, Chandrima(Jadavpur University Department of Pharmaceutical Technology Division of Microbiology), Jena, Aditya Kumar(Jadavpur University Department of Pharmaceutical Technology Division of Microbiology), Ghosh, Soma(Jadavpur University Department of Pharmaceutical Technology Division of Microbiology), Samanta, Amalesh(Jadavpur University Department of Pharmaceutical Technology Division of Microbiology). An investigation on in vitro and in vivo antimicrobial properties of the antidepressant: Amitriptyline hydrochloride. Brazilian journal of microbiology. 2010;41(3):635–642. https://www.ncbi.nlm.nih.gov/pubmed/24031539. doi: 10.1590/S1517-83822010000300014.
72. Brochmann RP, Helmfrid A, Jana B, Magnowska Z, Guardabassi L. Antimicrobial synergy between carprofen and doxycycline against methicillin-resistant staphylococcus pseudintermedius ST71. BMC veterinary research. 2016;12(1):126. https://www.ncbi.nlm.nih.gov/pubmed/27342694. doi: 10.1186/s12917-016-0751-3.
73. Lukić I, Getselter D, Ziv O, et al. Antidepressants affect gut microbiota and ruminococcus flavefaciens is able to abolish their effects on depressive-like behavior. Transl Psychiatry. 2019;9(1):133. https://link.springer.com/article/10.1038/s41398-019-0466-x. doi: 10.1038/s41398-019-0466-x.
74. Bohnert JA, Szymaniak-Vits M, Schuster S, Kern WV. Efflux inhibition by selective serotonin reuptake inhibitors in escherichia coli. Journal of Antimicrobial Chemotherapy. 2011;66(9):2057–2060. https://www.ncbi.nlm.nih.gov/pubmed/21700628. doi: 10.1093/jac/dkr258.
75. Ayaz M, Subhan F, Ahmed J, et al. Sertraline enhances the activity of antimicrobial agents against pathogens of clinical relevance. Journal of biological research (Thessalonike, Greece). 2015;22(1):4. https://www.ncbi.nlm.nih.gov/pubmed/26029671. doi: 10.1186/s40709-015-0028-1.
76. Lyte M, Daniels KM, Schmitz-Esser S. Fluoxetine-induced alteration of murine gut microbial community structure: Evidence for a microbial endocrinology-based mechanism of action responsible for fluoxetine-induced side effects. PeerJ (San Francisco, CA). 2019;7:e6199. https://www.ncbi.nlm.nih.gov/pubmed/30643701. doi: 10.7717/peerj.6199.

 doi:10.20944/preprints202602.1498.v1

77. Ticinesi A, Milani C, Lauretani F, et al. Gut microbiota composition is associated with polypharmacy in elderly hospitalized patients. Sci Rep. 2017;7(1):11102–11. https://link.springer.com/article/10.1038/s41598-017-10734-y. doi: 10.1038/s41598-017-10734-y.
78. Amaral L, Viveiros M, Molnar J. Antimicrobial activity of phenothiazines. In vivo (Athens). 2004;18(6):725–731. http://iv.iiarjournals.org/content/18/6/725.abstract.
79. Amaral L, Lorian V. Effects of chlorpromazine on the cell envelope proteins of escherichia coli. Antimicrobial Agents and Chemotherapy. 1991;35(9):1923–1924. http://aac.asm.org/content/35/9/1923.abstract. doi: 10.1128/AAC.35.9.1923.
80. Ordway D, Viveiros M, Leandro C, et al. Chlorpromazine has intracellular killing activity against phagocytosed staphylococcus aureus at clinical concentrations. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy. 2002;8(3):227–231. https://dx.doi.org/10.1007/s10156-002-0188-4. doi: 10.1007/s10156-002-0188-4.
81. Yuan X, Zhang P, Wang Y, et al. Changes in metabolism and microbiota after 24-week risperidone treatment in drug naïve, normal weight patients with first episode schizophrenia. Schizophrenia research. 2018;201:299–306. https://www.clinicalkey.es/playcontent/1-s2.0-S0920996418302743. doi: 10.1016/j.schres.2018.05.017.
82. Morgan AP, Crowley JJ, Nonneman RJ, et al. The antipsychotic olanzapine interacts with the gut microbiome to cause weight gain in mouse. PloS one. 2014;9(12):e115225. https://www.ncbi.nlm.nih.gov/pubmed/25506936. doi: 10.1371/journal.pone.0115225.
83. Kao AC, Spitzer S, Anthony DC, Lennox B, Burnet PWJ. Prebiotic attenuation of olanzapine-induced weight gain in rats: Analysis of central and peripheral biomarkers and gut microbiota. Transl Psychiatry. 2018;8(1):66–12. https://link.springer.com/article/10.1038/s41398-018-0116-8. doi: 10.1038/s41398-018-0116-8.
84. Michael Hadera, Selam Mehari, N. Saleem Basha, Nebyu D. Amha, Yacob Berhane. Study on antimicrobial potential of selected non-antibiotics and its interaction with conventional antibiotics. Pharmaceutical and Biosciences Journal. 2018:1–7. https://doi.org/10.20510/ukjpb/6/i1/173522. doi: 10.20510/ukjpb/6/i1/173522.
85. Kruszewska H, Zareba T, Tyski S. Examination of antimicrobial activity of selected non-antibiotic drugs. Acta Poloniae pharmaceutica. 2004;61 Suppl:18. https://www.ncbi.nlm.nih.gov/pubmed/15909927.
86. Qian Y, Lv P, Shi L, Fang R, Song Z, Zhu H. Synthesis, antimicrobial activity of lamotrigine and its ammonium derivatives. J Chem Sci. 2009;121(4):463–470. https://link.springer.com/article/10.1007/s12039-009-0055-2. doi: 10.1007/s12039-009-0055-2.
87. Cussotto S, Strain CR, Fouhy F, et al. Differential effects of psychotropic drugs on microbiome composition and gastrointestinal function. Psychopharmacology. 2019;236(5):1671–1685. https://link.springer.com/article/10.1007/s00213-018-5006-5. doi: 10.1007/s00213-018-5006-5.
88. Putri DNA, Moreen Nababan CC. Microbiota-based therapies for chronic kidney disease. Intisari Sains Medis (ISM) (Manado). 2019;10(1). https://doi.org/10.15562/ism.v10i1.239. doi: 10.15562/ism.v10i1.239.
89. Liu C, Wang J, Lei L, Li L, Yuan X. Gut microbiota therapy for chronic kidney disease. Frontiers in immunology. 2025;16:1660226. https://www.ncbi.nlm.nih.gov/pubmed/41000396. doi: 10.3389/fimmu.2025.1660226.
90. Sun Z, Gong Q, Wang Z, et al. Microbiota-gut-kidney axis and targeted therapeutic strategies in kidney diseases. International journal of biological sciences. 2026;22(3):1142–1161. https://www.ncbi.nlm.nih.gov/pubmed/41608641. doi: 10.7150/ijbs.124499.
91. Li R, Boer CG, Oei L, Medina-Gomez C. The gut microbiome: A new frontier in musculoskeletal research. Curr Osteoporos Rep. 2021;19(3):347–357. https://link.springer.com/article/10.1007/s11914-021-00675-x. doi: 10.1007/s11914-021-00675-x.
92. Sun N, Zhao Y, Zhang A, He Y. Gut microbiota and osteoarthritis: Epidemiology, mechanistic analysis, and new horizons for pharmacological interventions. Frontiers in cellular and infection microbiology. 2025;15:1605860. https://www.ncbi.nlm.nih.gov/pubmed/40740348. doi: 10.3389/fcimb.2025.1605860.
93. Li Z, Wang Q, Huang X, Wu Y, Shan D. Microbiome's role in musculoskeletal health through the gut-bone axis insights. Gut microbes. 2024;16(1):2410478. https://www.tandfonline.com/doi/abs/10.1080/19490976.2024.2410478. doi: 10.1080/19490976.2024.2410478.

 doi:10.20944/preprints202602.1498.v1

94. Plewa P, Graczyk P, Figiel K, Dach A, Pawlik A. Gut and joint microbiome and dysbiosis: A new perspective on the pathogenesis and treatment of osteoarthritis. Pathogens (Basel). 2026;15(1):62. https://www.ncbi.nlm.nih.gov/pubmed/41599046. doi: 10.3390/pathogens15010062.
95. You Y, Xiang T, Yang C, et al. Interactions between the gut microbiota and immune cell dynamics: Novel insights into the gut-bone axis. Gut microbes. 2025;17(1):2545417. https://www.tandfonline.com/doi/abs/10.1080/19490976.2025.2545417. doi: 10.1080/19490976.2025.2545417.
96. Papageorgiou M, Biver E. Interactions of the microbiome with pharmacological and non-pharmacological approaches for the management of ageing-related musculoskeletal diseases. Therapeutic advances in musculoskeletal disease. 2021;13:1759720X211009018. https://journals.sagepub.com/doi/full/10.1177/1759720X211009018. doi: 10.1177/1759720X211009018.
97. Ullah I, Yasmin M. Microbiome-based therapeutics: Emerging trends in health biotechnology. Premier Journal of Science. 2024. https://premierscience.com/wp-content/uploads/2025/05/pjs-24-314.pdf. doi: 10.70389/PJS.100022.
98. Alagiakrishnan K, Morgadinho J, Halverson T. Approach to the diagnosis and management of dysbiosis. Frontiers in nutrition. 2024;11:1330903. https://www.ncbi.nlm.nih.gov/pubmed/38706561. doi: 10.3389/fnut.2024.1330903.
99. Pitashny M, Kesten I, Shlon D, Hur DB, Bar-Yoseph H. The future of microbiome therapeutics. Drugs. 2025;85(2):117–125. https://link.springer.com/article/10.1007/s40265-024-02107-3. doi: 10.1007/s40265-024-02107-3.