Saeed, M.A.A.,et al., Yemeni J Med Sci. 2025; 19(3):1-27
https://doi.org/10.20428/yjms.v19i3.2745
https://journals.ust.edu/index.php/yjms

REVIEW PAPER OPEN ACCESS

The Gut Microbiota's Role in Drug Absorption, Metabolism and Efficacy: Implications for Personalized Medicine

Mohammed Ali Ahmed Saeed [1*], Mahfoudh A.M. Abdulghani [1,2], Fares M.S Muthanna [1], Taha A A Naji [3], Fahmi Shaher [4], Mohammed Muammar Alshameeri [5], Mohammed Ali Al-Wesabi [6], Mahmoud A. Alhafedhi [7], Eidha Ali Bin-Hameed [8]

[1] *Department of Pharmacy, Faculty of Medicine and Health Sciences, University of Science and Technology, Aden, Yemen.*
[2] *Pharmacology Department, International Medical School, MSU, Shah Alam, Selangor, Malaysia.*
[3] *Clinical Nutrition & Dietetics, Department of Health Sciences, Faculty of Medicine and Health Science, University of Science & Technology-Aden – Yemen.*
[4] *Department of Basic Medicine, Faculty of Medicine and Health Sciences, University of Science and Technology, Aden, Yemen.*
[5] *Department of Pathology, Faculty of Medicine and Health Sciences, University of Science and Technology, Aden, Yemen.*
[6] *Department of Dentistry, Faculty of Medicine and Health Sciences, University of Science and Technology, Aden, Yemen.*
[7] *Faculty of Medicine and Health Sciences, University of Science and Technology, Aden, Yemen.*
[8] *Department of Medical Laboratories, Faculty of Medicine and Health Sciences, University of Science and Technology, Aden, Yemen.*

ABSTRACT

Advances in microbiome profiling technologies enable the assessment of individual gut microbiota composition, paving the way for personalized drug therapy. Tailoring medications based on a patient's microbiome could enhance efficacy and minimize side effects. Pharmacogenomics, combined with microbiome analysis, could lead to more accurate predictions of drug responses and optimized treatment plans. In this review, we explore the relationship between drug metabolism and efficacy and the gut microbiome, with a specific focus on enzymatic processes of how gut bacteria metabolize drugs, drugs affected by gut microbiota, and drugs associated with dysbiosis and resulting complications. A comprehensive literature search was performed using PubMed and Google Scholar databases. Articles published between 2013 and 2024 were prioritized to ensure up-to-date findings. The gut microbiota significantly impacts drug absorption by altering drug solubility and permeability through microbial metabolism, modulation of the intestinal barrier, and interactions with transport proteins. Furthermore, medications can significantly impact gut microbiota, leading to dysbiosis and various complications. More studies are needed to elucidate the specific mechanisms through which gut microbiota influences drug action.

Keywords: Gut microbiota, drug absorption, drug metabolism, efficacy, toxicity, dysbiosis, precision medicines.

* *Corresponding author address: mohali141@yahoo.com*

https://doi.org/10.20428/yjms.v19i3.2745
https://journals.ust.edu/index.php/yjms

INTRODUCTION

The gut microbiota or gut microbiome is a complex community of microorganisms residing in the gastrointestinal tract, predominantly in the large intestine. These microorganisms include bacteria, archaea, viruses, fungi, and protozoa, collectively playing a crucial role in human health, influencing metabolism, immune function, and even mental well-being. It is estimated that the human gut contains approximately 100 trillion bacterial cells, with bacteria being the most abundant and diverse group. Over 1,000 bacterial species have been identified predominant phyla including Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria [1, 2, 3].

Firmicutes phylum, which includes genera such as *Lactobacillus*, *Clostridium*, and *Bacillus*. Firmicutes contributes to gut health by fermenting dietary fibers and producing short-chain fatty acids (SCFAs) (are produced when fiber is fermented in the colon. They act as a source of energy for the cells lining the colon). Bacteroidetes represented genera like *Bacteroides* and *Prevotella*, are essential for breaking down complex carbohydrates and maintaining a balanced microbiome [4]. Actinobacteria such as *Bifidobacterium*, support digestion and gut health, while Proteobacteria a diverse group that includes potential pathogenic bacteria, can disrupt gut balance and lead to dysbiosis (microbiome disturbance) when overrepresented. Fungi (e.g., *Candida* species) and archaea (e.g., *Methanobrevibacter*), and viruses, particularly bacteriophages, also contribute to the gut microbiota's diversity and stability, albeit in smaller proportions [5, 6].

The gut microbiota supports digestion and metabolism by breaking down complex carbohydrates and fermenting dietary fibers to producing SCFAs, vital for colon health [7]. Additionally, it plays a critical role in immune system development and regulation, protecting against infections and autoimmune disorders. Certain gut bacteria synthesize essential vitamins, including vitamin K and some B vitamins, further contributing to overall health [8].

Dietary habits strongly influence the composition and function of the gut microbiota. High-fiber diets promote beneficial bacteria, whereas diets high in fat and sugar can lead to microbial imbalances, or dysbiosis [9]. Antibiotic can further disrupt the microbial diversity, often resulting in overgrowth of pathogenic species and conditions such as antibiotic-associated diarrhea. Other factors including physical activity, stress, and sleep can also modulate the gut microbiota, highlighting its dynamic relationship with lifestyle and health [10].

A study found links between growth factors (GFs), microbiota, and body mass index (BMI) in a Saudi cohort. The correlational results showed that GFs and microbiota differed according to sex. Furthermore, fibroblast GF-basic and *Actinobacteria* were significantly correlated in males, while epidermal GF (EGF) and *Proteobacteria* were significantly correlated in females. Interestingly, a combined analysis of the two sexes revealed a strong association between *Firmicutes* and EGF and vascular endothelial GF. Additionally, granulocyte colony-stimulating factor (G-CSF) and hepatocyte GF with *Firmicutes* were found to be correlated in the underweight group. G-CSF and *Actinobacteria* were found to be correlated in the obese group [11].

Precision medicine, sometimes known as "personalized medicine" is an innovative approach to tailoring disease prevention and treatment [12]. Adapting medical decisions to genomic individuality within the framework of a person's particular environment and lifestyle is known as precision medicine. Early instances of precision medicine in action include rare diseases, where sequencing can result in the timely identification of causative mutations and accurate diagnosis in a clinical setting with limited time, and cancer, where sequencing of the patient and tumor genomes can identify specific targets for therapeutic decisions. For the latter, even though the cost of sequencing a person's genome has decreased significantly over the last 1.5 decades, there are still many obstacles to overcome in order to interpret the genome. For example, significant variants may be overlooked due to inadequate coverage or misidentified calls, and the task of interpreting an

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https://journals.ust.edu/index.php/yjms

increasing number of variants with unclear significance in each human genome is becoming more difficult [13].
In this review, we explore the relationship between drug metabolism and efficacy and the gut microbiome, with a specific focus on enzymatic processes of how gut bacteria metabolize drugs, drugs affected by gut microbiota, and drugs associated with dysbiosis and resulting complications.

METHODOLOGY

Search Strategy

A comprehensive literature search was performed using PubMed and Cochrane Library databases. Keywords included "gut microbiota and drug absorption, metabolism and efficacy", "dysbiosis", "precision medicine", "microbiota to enhance or diminish drug absorption", "gut microbiota and adverse effects of drugs". Articles published between 2013 and 2024 were prioritized to ensure up-to-date findings.

Inclusion Criteria

The inclusion criteria for this review were studies involving gut microbiota and drug absorption, metabolism and efficacy, including randomized controlled trials, observational studies, and meta-analyses. Eligible studies focused on outcomes related to drugs affected by gut microbiota.

Exclusion Criteria

Studies were excluded if they involve non-gut microbiota's role in drug absorption, metabolism and efficacy, case reports, or any non-peer-reviewed literature. Case report studies were excluded due to lacked rigorous methodology and had limited generalizability.

FINDINGS

Roles of the Gut Microbiome in Human Health and Disease

The gut microbiome, a diverse and complex ecosystem within the gastrointestinal tract, plays a crucial role in maintaining human health and contributing to disease pathogenesis. It aids in the breaking down of complex carbohydrates and dietary fibers, facilitating nutrient absorption and producing SCFAs, which support colon health and maintain the intestinal barrier integrity. A healthy microbiome prevents the translocation of harmful pathogens and toxins into the bloodstream by preserving the gut's epithelial barrier. Additionally, the gut microbiota is critical for the development and maturation of the immune system, influencing the balance between immunity tolerance and activation [14, 15].

A diverse gut microbiome can suppress pathogenic microorganisms by competing for resources, thereby reducing the risk of infections and inflammatory responses. Alternations in microbiome composition have been linked to metabolic disorders such as obesity and metabolic syndrome. Specific bacterial populations influence energy balance and fat storage, underscoring the microbiome's role in metabolic regulation. Moreover, gut bacteria can metabolize drugs, altering their efficacy and toxicity, which highlights the microbiome's importance in pharmacotherapy [16].

The gut microbiome also impacts mental health via the gut-brain axis-a bidirectional communication system involving biochemical and neurological pathways. Gut microbes produce neurotransmitters such as serotonin and dopamine, which are integral to mood, cognition, and behavior. Additionally, metabolites like SCFAs contribute to the development and function of the central nervous system (CNS). Dysbiosis, an imbalance in the gut microbiota, has been associated with mental health conditions such as depression and anxiety. Microbial metabolic signals to nerve endings beneath the intestinal epithelium may influence stress and anxiety responses, further emphasizing the gut-brain connection [6, 17].

Dysbiosis is also implicated in several diseases, including autoimmune conditions like rheumatoid arthritis and inflammatory bowel disease (IBD), as well as cardiovascular diseases, through mechanisms involving cholesterol metabolism and inflammation. The gut microbiome's influence extends to cancer, particularly colorectal cancer. Certain bacterial species can produce carcinogenic compounds, while others exhibit protective effects. These interactions highlight

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the microbiome's dual role in carcinogenesis and cancer prevention [18]. For example, typhoid fever is caused by *Salmonella enterica* subspecies *enterica* serovar *typhi* (*Salmonella typhi*), which colonizes the gallbladder and causes asymptomatic infection and gallstones. This association is also considered a major risk factor for the improvement of most gallbladder cancers because *Salmonella typhi* produces a typhoid toxin, which is likely carcinogenic and causes DNA damage and changes in the cell cycle that are programmed intoxicated cells. On the other hand, a wild strain of *Clostridium novyi* can eliminate the lethal toxin gene by preventing the phage from transferring the gene present in the spores. The spores will then grow precisely into the tumor, destroying it [19].

Diet is a key modulator of gut microbiota composition and diversity. High-fiber diets promote beneficial bacterial populations, whereas diets rich in fat and sugar can lead to dysbiosis. Additionally, antibiotic use, hygiene practices, and lifestyle factors significantly influence microbiome health and its associated functions [20].

Enzymatic Processes and Gut Bacteria Drug Metabolize

Gut bacteria significantly influence drug metabolism through enzymatic processes such as hydrolysis, oxidation, reduction and conjugation, decarboxylation, and deamination. These microbial reactions can alter the chemical structure of drugs, impacting their efficacy, toxicity, and bioavailability [7, 18].

1. Hydrolysis

Hydrolysis involves the breakdown of a compound by the addition of water, often catalyzed by bacterial enzymes such as esterases and amidases. This process plays a pivotal role in converting prodrugs—chemically inactive compounds—into their active forms. For instance, the hydrolysis of ester bonds in certain drugs releases active therapeutic components. A well-known example is the conversion of aspirin to salicylic acid, the active metabolite responsible for its anti-inflammatory effects [2, 21]. Many prodrugs are specifically designed to be activated by hydrolysis, enabling targeted drug delivery with reduced side effects [9].

2. Oxidation

Oxidation involves the transfer of electrons, resulting in an increase in oxidation state. Gut bacteria utilize enzymes like oxidases and dehydrogenases to metabolize lipophilic drugs into more hydrophilic metabolites, facilitating their excretion. Oxidation typically converts lipophilic compounds into more hydrophilic metabolites, facilitating their elimination [22]. Additionally, bacterial electron transport chains contribute to oxidative reactions. For example, ethanol is oxidized by gut bacteria to acetaldehyde, participating in alcohol metabolism within the gastrointestinal tract [3, 10]. Certain drugs, such as codeine, are also oxidized by bacterial enzymes to form active metabolites like morphine [4, 15].

3. Reduction

Reduction, the reverse of oxidation, involves the gain of electrons or hydrogen. It can convert compounds into more active or less toxic forms. Anaerobic gut bacteria often utilize reductive enzymes, such as nitroreductases, to modify drugs into more active or less toxic forms. An example is the reduction of nitrofurantoin by gut bacteria, resulting in active antibacterial metabolites. Additionally, some bacteria can reduce ketones to alcohols, altering the pharmacological properties of these compounds [22, 23].

4. Conjugation

Conjugation involves the addition of a chemical moiety such as glucuronic acid or sulfate, to drugs or their metabolites, enhancing their water solubility and promoting excretion. While primarily a liver-mediated process, some gut bacteria possess enzymes capable of glucurnnidation, affecting drug reabsorption and enterohepatic circulation [24].

5. Decarboxylation and Deamination

Decarboxylation, the removal of a carboxyl group, often leads to the formation of amines. Gut bacteria, such as *Lactobacillus* species, can decarboxylate amino acids, which can influence neurotransmitter productions, including serotonin and dopamine precursors. Similarly, deamination, the removal of an amine group from a compound, can modify drugs, impacting their

https://doi.org/10.20428/yjms.v19i3.2745
https://journals.ust.edu/index.php/yjms

activity and toxicity. Both processes highlight the diverse enzymatic capabilities of gut microbes and their role in drug metabolism [25].

Influence of Gut Microbiota on Drug Efficacy and Side Effects

Gut microbiota plays a critical role in the metabolism, bioavailability, and therapeutic effects of various drugs, as summarized in Table 1. These interactions can lead to reduced efficacy or increased toxicity, necessitating careful consideration in clinical practice. Digoxin, a cardiac glycoside used to treat heart failure and atrial fibrillation, is significantly influenced its pharmacokinetics and efficacy by gut microbiota [26, 27]. Certain gut bacteria, particularly those in the genus *Eggerthella*, can hydrolyze digoxin, leading to its inactivation. This can result in reduced therapeutic effects in patients with varying gut microbiota profiles. Variations in gut microbiota composition can lead to differences in digoxin bioavailability and efficacy, necessitating individualized dosing [1].

The presence and abundance of *E. lenta* can lead to a reduction in the bioavailability of digoxin, meaning that less of the drug is available in the bloodstream to exert its therapeutic effects. Changes in gut microbiota composition, known as dysbiosis, can alter the metabolism of digoxin [28]. For example, antibiotic use can disrupt the gut microbiome, potentially leading to increased levels of digoxin in the bloodstream and an elevated risk of toxicity. The variability in gut microbiota among individuals can lead to differences in digoxin metabolism, resulting in varied therapeutic responses. Some patients may experience enhanced effects or increased side effects based on their gut microbiome composition [29].

Patients on digoxin may require closer monitoring of drug levels, particularly if they have undergone recent antibiotic treatment or have known gut microbiota imbalances [30]. Adjustments in digoxin dosage might be necessary based on microbial influences. Maintaining a healthy gut microbiome through diet, probiotics, or lifestyle changes may help optimize digoxin therapy and mitigate risks associated with dysbiosis [31].

Morphine is an opioid analgesic used for pain management. Gut bacteria can metabolize morphine through oxidation and reduction processes, affecting its analgesic efficacy and side effects. Some bacteria may convert morphine to nor-morphine, which has different pharmacological properties [32]. The presence of specific gut bacteria can influence the pain-relieving effects of morphine, leading to variability in patient responses. The gut microbiota can affect the metabolism of morphine. Certain gut bacteria have been shown to metabolize morphine into various metabolites, which can influence its efficacy and side effects. Some studies suggest that gut bacteria can hydrolyze morphine, potentially altering its pharmacokinetics and leading to variations in therapeutic effects [33].

Dysbiosis, or an imbalance in the gut microbiota, can affect how morphine is metabolized and how the body responds to it. For example, changes in microbial composition may lead to increased sensitivity to morphine's side effects. Opioids, including morphine, are known to cause constipation by slowing gut motility. The gut microbiota plays a role in gastrointestinal function, and dysbiosis might exacerbate opioid-induced constipation [34].

The gut microbiota can influence the central nervous system (CNS) through the gut-brain axis. Changes in microbiota composition may affect pain perception and modulation, potentially altering the effectiveness of morphine in pain management [35]. Gut bacteria are involved in the production of neurotransmitters and signaling molecules that can affect mood and pain sensitivity, further influencing the analgesic effects of morphine. Hence, understanding the role of gut microbiota in morphine metabolism may lead to more personalized pain management strategies. Patients with different microbiota compositions may require different dosages or formulations of morphine [32, 34]. In addition, clinicians should consider the impact of the gut microbiome when monitoring patients for side effects of morphine, particularly gastrointestinal issues like constipation [36].

Codeine is another opioid used for pain relief and as a cough suppressant. The metabolism of codeine to

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https://journals.ust.edu/index.php/yjms

morphine is influenced by gut bacteria through oxidation processes. Variations in gut microbiota can lead to differences in the conversion rate, impacting the drug's effectiveness [37]. Patients with certain microbiota profiles may experience either enhanced effects or increased side effects due to altered metabolism. Codeine is metabolized in the liver to morphine, which is its active form. This conversion is primarily mediated by the enzyme CYP2D6. However, gut microbiota can also play a role in this process. Certain gut bacteria may influence the metabolism of codeine by affecting the bioavailability of the drug or altering its metabolism, although research in this area is still developing [38].

Dysbiosis may affect how codeine is metabolized and how effectively it acts in the body. Changes in the gut microbiome could lead to variations in the conversion rate of codeine to morphine [39]. Patients with different microbiota compositions may experience varying levels of pain relief or side effects from codeine, including constipation, which is a common issue with opioid use. The gut microbiota communicates with the CNS via the gut-brain axis, potentially affecting pain perception and modulation [40]. Changes in the gut microbiota can influence how patients respond to codeine, potentially impacting its analgesic efficacy. Furthermore, gut bacteria are involved in the production of neurotransmitters that can affect mood and pain sensitivity, which may alter how codeine affects pain relief. Understanding the interactions between codeine and gut microbiota may lead to more personalized pain management strategies [40]. For instance, patients with different gut microbiota profiles might require different dosages or formulations of codeine. Clinicians should consider the role of gut microbiota when monitoring patients for side effects of codeine, particularly gastrointestinal issues such as constipation, which can be exacerbated by dysbiosis [37, 41].

Levodopa (L-DOPA) is a standard treatment for Parkinson's disease, primarily used to alleviate motor symptoms by replenishing dopamine levels in the brain. Recent research has uncovered significant interactions between levodopa and gut microbiota, which can influence its efficacy and side effects [42]. Gut bacteria can metabolize levodopa into dopamine and other metabolites before it reaches systemic circulation. This can lead to reduced availability of the drug for its intended action in the brain. The presence of specific gut bacteria can impact the therapeutic outcomes of levodopa treatment, necessitating adjustments in dosing [43].

Levodopa is absorbed in the gastrointestinal tract, and the presence of gut microbiota can affect its bioavailability. Microbial activity can alter the pharmacokinetics of levodopa, potentially impacting how much of the drug is available to the body. Certain gut bacteria may metabolize levodopa into different compounds, which could affect its effectiveness [44]. For example, some bacteria can convert levodopa into inactive forms, reducing its therapeutic potential. Patients with Parkinson's disease often exhibit dysbiosis, characterized by reduced microbial diversity and specific changes in bacterial populations [45]. This dysbiosis may influence the metabolism and absorption of levodopa. Variability in gut microbiota may lead to inconsistent therapeutic responses to levodopa among patients, with some experiencing more pronounced benefits than others [43].

The gut microbiota interacts with the CNS through the gut-brain axis, which may contribute to the motor and non-motor symptoms of Parkinson's disease. Changes in the microbiome can influence inflammation and neurodegeneration, potentially impacting the overall disease progression and treatment response [46]. Gut bacteria are involved in the production of neurotransmitters, such as serotonin and dopamine precursors, which can affect mood and motor function. This relationship may further complicate the treatment of Parkinson's disease with levodopa [47].

Understanding the interactions between levodopa and gut microbiota may lead to more personalized treatment strategies. Microbiome profiling could help predict patient responses to levodopa and optimize dosing regimens. Dietary modifications that promote a healthy gut microbiome may enhance the effectiveness

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of levodopa. For example, a diet rich in fiber could support beneficial bacteria and improve gut health [44]. Several research efforts have shown that the composition and biodiversity of the gut microbiota in vaginally delivered infants during the first few months of life are influenced by both intrapartum antibiotic prophylaxis (IAP) and empirical antibiotic therapy after birth. Whether these changes continue throughout early infancy is unknown, though. Additionally, oral antibiotic courses are commonly administered to newborns and young children for common childhood infections. Early oral antibiotic exposure has been linked in earlier epidemiological research to pediatric celiac disease, inflammatory bowel disease, asthma, allergy disorders, and obesity. Oral macrolide consumption was linked to long-term changes in the gut flora of daycare children in a prior study [48, 49].

Antibiotics can disrupt the gut microbiota, leading to reduced efficacy of the antibiotic itself and potential overgrowth of resistant bacteria, such as *C. difficile* [50]. The alteration of the gut microbiome can lead to complications such as antibiotic-associated diarrhea and reduced treatment effectiveness. Antibiotic treatment often leads to dysbiosis, an imbalance in the gut microbiome characterized by a reduction in microbial diversity [51]. Beneficial bacteria may be killed off while resistant pathogens can proliferate. Different antibiotics can have varying effects on specific bacterial populations. For example, broad-spectrum antibiotics can indiscriminately affect many types of bacteria, while narrow-spectrum antibiotics target specific pathogens [52]. Dysbiosis can lead to an overgrowth of opportunistic pathogens, such as *C. difficile*, which can cause severe gastrointestinal distress and colitis. In addition, patients may experience side effects such as diarrhea, bloating, and abdominal pain due to disruptions in normal gut function and microbial balance [49].

Persistent dysbiosis has been linked to various health issues, including obesity, IBD, allergies, and even mental health disorders [52]. To minimize the negative impacts on gut microbiota, antibiotics should be prescribed judiciously. Avoiding unnecessary prescriptions and choosing narrow-spectrum antibiotics when appropriate can help preserve gut health. Educating patients about the potential effects of antibiotics on gut microbiota and the importance of completing prescribed courses can promote better health outcomes [50, 54]. Moreover, supplementing with probiotics (live beneficial bacteria) and prebiotics (substances that promote the growth of beneficial bacteria) can help restore a healthy gut microbiome after antibiotic treatment. In cases of severe dysbiosis, particularly with recurrent *C. difficile* infections, fecal microbiota transplantation (FMT) has shown promise in restoring microbial diversity and function [53].

Aspirin is used for pain relief, anti-inflammatory effects. It is also used in low doses for cardiovascular protection. Recent studies have begun to explore how aspirin affects gut microbiota and the implications of these interactions [55]. Certain gut bacteria can hydrolyze aspirin to salicylic acid, which may affect its therapeutic effects and gastrointestinal side effects. The metabolic activity of gut microbiota can influence the balance between the beneficial effects of aspirin and its potential gastrointestinal toxicity [56]. The variety and composition of the gut microbiota can be impacted by aspirin. Long-term aspirin use may change certain bacterial populations, promoting the growth of some beneficial bacteria while decreasing others, according to some research. Frequent aspirin use has been linked to alterations in microbial diversity, which may have an impact on general and gut health [57]. The anti-inflammatory qualities of aspirin may have an impact on the intestinal environment and the makeup of microorganisms. Aspirin may foster an environment that encourages the growth of good bacteria by lowering inflammation. Aspirin may indirectly change the microbiome by causing gastrointestinal side effects and mucosal damage. Increased gut permeability and dysbiosis may result from damage to the gut lining [58]. While aspirin can benefit gut health through its anti-inflammatory effects, it can also cause gastrointestinal side effects, including ulcers and bleeding. These effects can disrupt the gut microbiota, leading to dysbiosis [59]. Some research suggests that the modulation of gut

https://doi.org/10.20428/yjms.v19i3.2745
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microbiota by aspirin might have protective effects against certain diseases, including colorectal cancer, though more research is needed to confirm these benefits. Aspirin is often used in conjunction with other medications, such as antibiotics or proton pump inhibitors (PPIs), which can also affect gut microbiota. Understanding these interactions is important for managing patient care effectively [60].

The metabolism and toxicology of acetaminophen, one of the most popular over-the-counter analgesics and antipyretics in the world, have been thoroughly studied for many years. The environmental conditions can have a significant impact on how much a substance sulfonates in the human body. Additional research suggests that the aforementioned process is caused by p-Cresol-mediated competitive sulfonation, which slows down the body's metabolism of paracetamol and raises the possibility of hepatotoxicity [61].

It was shown that the inhibition of gastrointestinal tract microbes and metabolic activity may be the cause of the rise in amlodipine in the plasma of rats given antibiotics. Amlodipine's metabolism may be connected to gut flora, as evidenced by the decrease in its metabolites following antibiotic treatment [64].

The gut microbiota produces lipopolysaccharide (LPS), which inhibits intestinal ascorbic acid intake. Patients with certain inflammatory disorders, such as IBD, necrotizing enterocolitis (NEC), and *Salmonella* infection, have higher blood levels of lipopolysaccharide, which is produced by the gut microbiota and pathogens like *Salmonella*. By inhibiting the expression and function of both Hepatocyte nuclear factor 1 alpha (HNF1a) and Specificity protein 1 (Sp1) transcription factors, which were necessary for basal solute carrier family 23 (nucleobase transporters) member 1 (SLC23A1) and Solute carrier family 23 member 2 (SLC23A2) promoter activity, it was discovered that LPS downregulated the expression of SLC23A1 and SLC23A2 transcription. The presence of LPS impeded the carrier-mediated absorption of ascorbic acid because the sodium-dependent vitamin C transporter-1 and -2 sodium-dependent vitamin C transporter type 1 (SVCT-1) and Sodium Vitamin C co-transporter 2 (SVCT-2) carried the reduced ascorbic acid form. These transporters were the result of the SLC23A1 and SLC23A2 genes, respectively [65].

The intestinal flora's enzymes are also crucial for drugs inactivation. Digoxin, a common cardiac glycoside, is significantly metabolically converted to cardiac active metabolites with a reduced lactone ring in many people. It seems that the gastrointestinal tract is where this happens. Digoxin was transformed to reduced derivatives by *Eubacterium lentum*, a common anaerobe of the human colonic flora. Furthermore, the status of digitalization could be significantly changed by changes in the intestinal flora. In addition, digoxin degradation by gut bacteria has now been somewhat inhibited in experiments employing a dietary intervention in mice. The gut *Actinobacterium Eggerthella lenta* may be the cause of the cardiac medication digoxin's inactivation [65].

Table 1: Drugs affected by gut microbiota and their pharmacological / bioavailability outcomes

No.	Drugs affected by gut microbiota	Pharmacological / Bioavailability outcomes	References
1	Acetaminophen	Decrease bioavailability and activity	[61]
2	Aconitine	Decreased toxicity	[62]
3	5-Aminosalicylic acid	decrease bioavailability	[61]
4	Amiodarone	Increase bioavailability	[63]
5	Amlodipine	Increase bioavailability and activity	[64]
6	Amygdalin	New toxicity	[62]
7	Ascorbic acid	The absorption of ascorbic acid is decreased by LPS generated from the gut microbiota	[65]

https://doi.org/10.20428/yjms.v19i3.2745
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8	Aspirin	The bioavailability of aspirin is increased when antibiotics are used or after the quick ascent to the plateau	[65]
9	Atorvastatin	Variability in farnesoid X receptor (FXR) receptor signaling	[66]
10	Baicalin	Increased activity	[62]
11	Balsalazide	Increase activity and toxicity	[61]
12	Barbaloin	New activity	[62]
13	Berberine	The absorption of berberine is facilitated	[65]
14	Calcitonin	Decrease bioavailability and activity	[61]
15	Captopril	Decreased intestinal permeability and improved villi length	[66]
16	Chloramphenicol	Decrease bioavailability and increase toxicity	[61]
17	Clonazepam	Decrease bioavailability and increase toxicity	[61]
18	Daidzein	Increased activity	[62]
19	Deleobuvir	Decrease bioavailability and activity	[67]
20	Diclofenac	Released of diclofenac from glucuronides and increase toxicity	[68]
21	Digoxin	Inactivate digoxin	[65]
22	Epacadostat	Decrease bioavailability and activity	[69]
23	Ginsenoside	New activity	[62]
24	Glycyrrhizic acid	The bioavailability of glycyrrhizic acid is increased by the supplements of *Lactobacillus murinus*	[65]
25	Glycyrrhizin	Increased activity	[62]
26	Hesperidin	Increased activity	[62]
27	Indomethacin	The half-time is shortened and drug's systemic exposure is reduced when pretreated with antibiotics	[65]
28	Insulin	Decrease bioavailability and activity	[61]
29	Irinotecan	Release of SN-38 from glucuronides and increase toxicity	[70]
30	Kakkalide	Increased activity	[62]
31	Ketoprofen	Release of ketoprofen from glucuronides and increase toxicity	[61]
32	Lactulose	Decrease bioavailability and activity	[61]
33	Levamisole	Increase bioavailability and activity	[61]
34	Levodopa	Decrease bioavailability and activity	[61]
35	Loperamide oxide	Decrease bioavailability and activity	[61]
36	Lovastatin	The bioavailability and pharmacological effects are decreased when antibiotics are used	[65]
37	Metronidazole	Decrease bioavailability and activity	[61]
38	Morphine	Increases drug action and toxicity	[61]
39	Mycophenolic acid	AUC0____12 h of the mycophenolic acid is decreased while CL is increased when pretreated with antibiotics	[65]
40	Naringin	Increased activity	[62]
41	Nifedipine	The bioavailability of nifedipine is increased when antibiotics are used or in the hypoxic condition	[65]
42	Nitrazepam	Increase toxicity	[61]
43	Nizatidine	Decrease activity	[61]
44	Olsalazine	Increase activity and toxicity	[61]

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45	Prontosil	Activate the drug and the bioavailability is decreased when pretreated with antibiotics	[65]
46	Puerarin	Increased activity	[62]
47	Ranitidine	Decrease bioavailability and activity	[61]
48	Risperidone	Decrease bioavailability and activity	[61]
49	Rosuvastatin	Variability in farnesoid X receptor (FXR) receptor signaling	[66]
50	Rutin	Increased activity	[62]
51	Simvastatin	Enhanced plasma concentration of simvastatin is positively correlated with increased levels of several secondary bile acids	[65]
52	Sorivudine	Decrease bioavailability and activity	[61]
53	Succinylsulfathiazole	Increase bioavailability and activity	[61]
54	Sulfasalazine	Activate the drug and the bioavailability is decreased when pretreated with antibiotics	[65]
55	Syringin	Increased activity	[62]
56	Tectoridin	Increased activity	[62]
57	Warfarin	alteration in coagulation status	[66]
58	Zonisamide	Increase bioavailability and activity	[61]

Impact of Gut Microbiota on Drug Absorption: Changes in Solubility and Permeability

The gut microbiota plays a crucial role in influencing drug absorption through various mechanisms that affect drug solubility and permeability [72]. Gut bacteria can metabolize drugs, leading to the formation of metabolites that may have different solubility properties compared to the parent compound. For example, hydrolysis of prodrugs by gut bacteria can convert them into their active forms, potentially increasing their solubility and enhancing absorption [73]. Furthermore, gut microbiota ferment dietary fibers to produce SCFAs (such as acetate, propionate, and butyrate). These compounds can lower the pH of the intestinal environment, which may enhance the solubility of certain drugs, particularly weakly acidic compounds, thus facilitating their absorption [74].

The gut microbiome contributes to maintaining the integrity of the intestinal barrier. A healthy microbiota promotes the expression of tight junction proteins that help prevent the leakage of toxins and pathogens while allowing for the proper absorption of nutrients and drugs [75]. Dysbiosis, or an imbalance in the microbiota, can disrupt these tight junctions, affecting drug permeability [75]. The presence of specific bacteria can influence the composition of the gut mucus layer, which acts as a barrier and can affect drug permeability. Some bacteria may produce mucus-degrading enzymes that alter the thickness and composition of this layer, potentially enhancing or reducing drug absorption [76]. Gut microbiota can influence the expression and activity of various drug transporters (e.g., efflux and influx transporters) located in the intestinal epithelium [78]. Changes in transporter activity can significantly affect the absorption of drugs. In addition, efflux Transporters (e.g., P-glycoprotein) can pump drugs back into the intestinal lumen, reducing their bioavailability. Gut bacteria may modulate the expression of these transporters, impacting the extent of drug absorption. Similarly, the expression of transporters that facilitate drug uptake can be influenced by the microbiome, affecting how well drugs are absorbed [17, 27].

The gut microbiota interacts with dietary components, which can also influence drug solubility and absorption. For example, high-fiber diets can promote the growth of beneficial bacteria that enhance solubility and absorption of certain drugs through SCFA production [10, 36]. In addition, the gut microbiota competes for nutrients and substrates, which can affect the availability of these substances for drug absorption. For instance, a high abundance of certain bacteria may

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consume nutrients that would otherwise enhance drug solubility [79].

Examples of How Microbiota Can Enhance or Diminish Drug Absorption

The gut microbiota can significantly influence drug absorption through various mechanisms that either enhance or diminish the bioavailability of medications [80].

1. Enhancing Drug Absorption

Enalapril is a prodrug that is converted to its active form, enalaprilat, by gut bacteria through hydrolysis. This conversion enhances its therapeutic effects by making it bioavailable. Gut bacteria ferment dietary fibers to produce SCFAs such as acetate and butyrate [22, 81]. These SCFAs can lower intestinal pH, which may enhance the solubility of certain weakly acidic drugs, leading to improved absorption. Some beneficial gut bacteria can enhance the integrity of the intestinal barrier, promoting a favorable environment for drug absorption. For instance, probiotics like *Lactobacillus* species can improve mucosal health, potentially facilitating drug uptake [82].

2. Diminishing Drug Absorption

Digoxin can be hydrolyzed by gut bacteria as mentioned previously, leading to the formation of inactive metabolites. This reduces the drug's efficacy by lowering its bioavailability in the bloodstream [28, 83]. Gut bacteria may compete for substrates that are also necessary for drug absorption. For instance, a high abundance of certain bacteria can consume nutrients and substrates, decreasing the availability of these substances for drug uptake [84]. Certain gut microbiota can modulate the expression of efflux transporters, such as P-glycoprotein, which pumps drugs back into the intestinal lumen, reducing their absorption. For instance, the presence of specific bacteria can enhance P-glycoprotein activity, diminishing the absorption of drugs like fexofenadine [84, 85]. Furthermore, the gut microbiota may also have an impact on the bioavailability of lovastatin, a type of lipid-lowering medication. According to research, rats given antibiotics before to treatment had a much lower systemic exposure to one of lovastatin's metabolites as compared to controls [65].

Dysbiosis, or an imbalance of gut microbiota, can disrupt the tight junctions between intestinal epithelial cells, leading to increased permeability. This can affect the absorption of both beneficial nutrients and drugs, potentially leading to reduced drug efficacy [5]. Understanding the interaction between microbiota and drugs is crucial for optimizing drug therapy. For instance, variations in gut microbiota among individuals can lead to differences in drug absorption and therapeutic outcomes. This highlights the importance of considering the microbiome when prescribing medications and the potential need for personalized approaches to treatment [86].

Inter-Individual Differences in Microbiota Composition Leading to Variability in Drug Response

The gut microbiota is highly diverse and varies significantly among individuals, influenced by factors such as genetics, diet, environment, and lifestyle. These inter-individual differences can lead to significant variability in drug response, including differences in efficacy and the occurrence of adverse effects [87]. Each individual has a unique microbiome profile, which can be influenced by factors such as, high-fiber diets which may promote the beneficial bacteria, while high-fat, high-sugar diets can lead to dysbiosis. Furthermore, geography and ethnicity differences exhibit distinct microbial compositions due to environmental and dietary differences. In addition, conditions like obesity, diabetes, and gastrointestinal diseases can alter microbiota composition [88]. Some gut bacteria are involved in the metabolism of antidepressants, which can affect their efficacy and side effects. Furthermore, the microbiota can influence the effectiveness of antibiotics and the risk of developing resistance or adverse effects, such as *Clostridium difficile* infection following antibiotic treatment [48, 50].

Understanding the interplay between microbiota and pharmacogenetics (how genes affect drug response) can lead to more personalized medicine approaches [89]. By considering both genetic and microbiome profiles,

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healthcare providers can tailor drug therapies to improve efficacy and minimize adverse effects. Hence, personalized dosing strategies based on microbiome composition may enhance treatment outcomes for various conditions, particularly in fields like oncology, psychiatry, and chronic disease management [90].

Case Drugs Illustrating the Effects of Microbiota on Therapeutic Outcomes

Understanding how gut microbiota influence therapeutic outcomes is crucial in pharmacotherapy. Here are several case studies that highlight these effects.

1. Digoxin

Digoxin is commonly used for heart failure and atrial fibrillation. Its efficacy can be affected by gut microbiota. A study found that patients with higher levels of *Eggerthella lenta*, a gut bacterium, had significantly lower serum levels of digoxin after administration [30, 31]. *E. lenta* can hydrolyze digoxin, rendering it inactive. Patients with a microbiome profile rich in *E. lenta* required higher doses of digoxin to achieve therapeutic levels, illustrating how microbiota composition can directly influence drug efficacy [25, 27].

2. Codeine

Codeine is a prodrug that is metabolized to morphine to exert its analgesic effects. In a group of patients receiving codeine for pain management, those with a specific composition of gut bacteria (including *Clostridium* species) showed increased conversion rates of codeine to morphine [37-41]. Patients with a microbiome that favored this metabolic pathway experienced better pain relief and fewer side effects compared to those whose gut microbiota did not support effective metabolism, highlighting variability in analgesic response based on microbiota [37-41].

3. Levodopa

Levodopa is a standard treatment for Parkinson's disease, aimed at increasing dopamine levels in the brain. A cohort study showed that patients with specific gut microbiota profiles had lower levodopa absorption rates, affecting their clinical outcomes [43, 45]. Those with a more favorable microbiome experienced better symptom control and fewer fluctuations in their condition. This demonstrates the importance of gut health in managing Parkinson's disease and optimizing levodopa therapy [42, 44].

4. Antibiotics

Antibiotics are used to treat bacterial infections, but their effectiveness can be influenced by the gut microbiota. In a group of patients treated with clindamycin, some developed *Clostridium difficile* infections post-treatment [49]. Patients with a less diverse gut microbiota were more susceptible to *C. difficile* overgrowth following antibiotic treatment, leading to severe gastrointestinal complications. This case emphasizes the role of a healthy microbiota in preventing antibiotic-associated adverse effects [51].

5. Cancer Immunotherapy

Immunotherapy, particularly checkpoint inhibitors, has variable success rates in cancer treatment. Research has shown that patients with certain gut microbiota compositions responded better to treatments like pembrolizumab (a PD-1 inhibitor) [91, 92]. Specifically, those with higher levels of *Faecalibacterium prausnitzii* and *Bacteroides fragilis* exhibited improved responses. These patients had better overall survival rates and disease progression outcomes, suggesting that manipulating the microbiome could enhance the efficacy of immunotherapy [93].

An anticancer medication that causes PD-L1 inhibition was the subject of a published study. In this instance, animals with a greater relative abundance of *Bifidobacterium* species showed improved PD-L1 blocking efficacy. Via maturing dendritic cells and increasing T-cell reactivity, this effect can be brought about via fecal microbiome transplantation, cohousing mice with beneficial species, or administering probiotics containing *Bifidobacterium* [94].

How Changes in Gut Microbiota Can Lead to Adverse Effects of drugs and systems dysfunction

The gut microbiota plays a vital role in maintaining health, and alterations in its composition—known as dysbiosis—can lead to a range of adverse effects, particularly in relation to drug metabolism and overall health [95].

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1. Drug Metabolism and Efficacy

Dysbiosis can affect the metabolism of prodrugs, leading to inadequate activation. For example, the prodrug codeine is metabolized to morphine by certain gut bacteria [38]. If these bacteria are diminished, patients may experience reduced analgesic effects. Furthermore, some bacteria can metabolize and inactivate drugs. For instance, *Eggerthella lenta* can hydrolyze digoxin, reducing its therapeutic efficacy and requiring higher doses for effectiveness [31].

2. Increased Risk of Adverse Drug Reactions (ADRs)

Dysbiosis can lead to an increase in the absorption of toxic metabolites. For example, the use of antibiotics can disrupt gut microbiota, allowing for the overgrowth of pathogenic bacteria like *Clostridium difficile*, which can cause severe intestinal infections [51]. In addition, changes in microbiota can exacerbate side effects associated with medications. For example, patients with certain gut bacteria may experience gastrointestinal toxicity from drugs that are otherwise well-tolerated by individuals with a more balanced microbiome [96].

3. Immune System Dysfunction

The gut microbiota plays a crucial role in shaping the immune response. Dysbiosis can disrupt this balance, leading to increased inflammation and autoimmune responses. This can exacerbate conditions like IBD or even influence responses to immunotherapies [93]. Hence, an imbalanced microbiome can compromise the intestinal barrier, leading to increased permeability (often referred to as "leaky gut"). This can allow pathogens to enter the bloodstream, resulting in systemic infections and further complications [97].

4. Metabolic Disorders

Changes in gut microbiota composition can influence metabolic pathways, leading to conditions such as obesity and type 2 diabetes. Certain bacterial profiles are associated with increased energy harvest from food, contributing to weight gain and metabolic dysregulation [22]. In addition, dysbiosis can affect lipid metabolism and contribute to atherosclerosis. For example, gut bacteria can convert dietary choline into trimethylamine N-oxide (TMAO), a compound linked to cardiovascular disease [10].

5. Neurological Effects

The gut microbiota communicates with the central nervous system via the gut-brain axis. Dysbiosis has been linked to neurological conditions, including anxiety and depression [98]. Changes in microbiota can affect neurotransmitter levels, leading to mood disturbances and cognitive issues. Furthermore, medications for mental health conditions may have altered efficacy or side effect profiles in individuals with dysbiosis, complicating treatment strategies [99, 100].

Drugs Associated with Dysbiosis and Resulting Complications

Certain medications can disrupt the gut microbiota, leading to dysbiosis and a range of complications [28]. This section focused on drugs associated with dysbiosis and resulting complications and summarized in Table 2. Antibiotics are commonly used to treat bacterial infections but can indiscriminately affect both pathogenic and beneficial gut bacteria. Antibiotic use can disrupt the normal gut flora, allowing *Clostridium difficile* to proliferate, leading to severe diarrhea, colitis, and potentially life-threatening complications [48, 49]. Disruption of the microbiome can lead to decreased immune function, increasing susceptibility to opportunistic infections. Proton Pump Inhibitors (PPIs) are used to treat conditions like gastroesophageal reflux disease (GERD) by reducing stomach acid production. Reduced stomach acidity can disrupt the balance of gut bacteria, leading to Small Intestinal Bacterial Overgrowth SIBO, which can cause bloating, diarrhea, and abdominal pain. Furthermore, the alteration in gut flora can increase susceptibility to infections such as enteric infections [50, 52].

It is vital to understand that PPI-induced alterations in the microbiota may be a contributing factor to disorders of clinical significance. For instance, earlier research identified alterations in the gut microbiota that result in a reduced ability to colonize and resist enteric infections, such as *Salmonella*, *Campylobacter*, and *Clostridium difficile*. These alterations are comparable to those currently seen in PPI users. Given that *C. difficile* infections are known to arise in the changed gut microbial environment after antibiotic use, this may

https://doi.org/10.20428/yjms.v19i3.2745
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also be the case when PPIs are used. Furthermore, PPI introduction and discontinuation affect the clinical trajectory of decompensated liver cirrhosis, possibly via altering the gut microbiota [1].

Non-steroidal anti-inflammatory drugs (NSAIDs) are used for pain relief and inflammation reduction. NSAIDs can disrupt the gut barrier function and alter the microbiome, leading to gastrointestinal bleeding, ulcers, and dysbiosis. Changes in the microbiota can exacerbate inflammatory responses, potentially worsening underlying conditions [78, 100]. Metformin is an oral anti-hyperglycemic agent commonly prescribed for the management of type 2 diabetes. In addition to its effects on glucose metabolism, recent research has highlighted the significant interactions between metformin and gut microbiota. Metformin has been shown to alter gut microbiota composition, potentially leading to gastrointestinal side effects such as diarrhea and discomfort. Changes in microbiota may affect the metabolism of other medications, leading to variable therapeutic responses [102, 103].

Notably, metformin treatment dramatically reduces the abundance of *Intestinibacter* and increases that of *Escherichia coli* (*E. coli*). These results are consistent with cross-sectional cohorts that compared Type 2 diabetes (T2D) patients who were not treated to those who were treated with metformin. The authors then transplanted fecal samples from either placebo-treated or metformin-treated donors into germ-free mice. They found that the mice that received fecal samples from metformin-treated volunteers had lower blood glucose levels, suggesting that the gut microbiota directly affects blood glucose levels. Common biological pathways and genes encoded in various metformin-affected bacteria, such as metalloproteins or metal transporters, are thought to mediate this effect, as the impact of metformin on bacteria that produce short-chain fatty acids (butyrate) and the prevalence of *Akkermansia muciniphila*. Furthermore, it is clinically known that up to one-third of metformin users experience gastrointestinal side effects, such as bloating, nausea, and diarrhea. These side effects can be attributed to changes in the body caused by metformin, such as an increase in virulence factors and genes related to gas metabolism, which are primarily caused by an increase in *E. coli* species [1].

Chemotherapy drugs are used to treat cancer but can have significant effects on gut microbiota. Chemotherapy can lead to a decrease in microbial diversity, resulting in dysbiosis which can impair immune function and increase the risk of infections. Many chemotherapy agents cause nausea, vomiting, and diarrhea, compounded by dysbiosis, leading to further complications in gut health [104].

Certain antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), can influence gut microbiota. SSRIs may cause gastrointestinal disturbances, including nausea and diarrhea, which can be exacerbated by alterations in gut microbiome composition. Dysbiosis may influence the gut-brain axis, potentially affecting mood and cognition further [105].

Table 2: Drugs associated with dysbiosis and their complications

No.	Drugs associated with dysbiosis	Resulting complications	References
1	Antibiotics	decreased immune function, increasing susceptibility to opportunistic infections	[48, 49]
2	Proton Pump Inhibitors	Small Intestinal Bacterial Overgrowth (SIBO), which can cause bloating, diarrhea, and abdominal pain	[50, 52]
3	NSAIDs	gastrointestinal bleeding, ulcers	[77, 101]
4	Metformin	gastrointestinal side effects such as diarrhea and discomfort	[102, 103]

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5	Chemotherapy	Impair immune function, increase the risk of infections, nausea, vomiting, and diarrhea	[104]
6	Selective serotonin reuptake inhibitors	gastrointestinal disturbances, including nausea and diarrhea, affecting mood and cognition	[105]

Precision Medical Treatment Focused on Gut Microbiota

Nowadays, one effective method for treating illnesses is to modify the gut microbiota, particularly by precise editing. Probiotic and prebiotic supplements, for instance, have been used to treat conditions like ulcerative colitis and diarrhea that are linked to the gut flora. In animal models of colitis, tungstate's precise editing of the gut microbiota has demonstrated adequate efficacy in preventing the dysbiotic expansion of the Enterobacteriaceae family during intestinal inflammation. Research on altering gut microbiota to enhance drug results is still in its infancy, despite the large number of studies that describe treating diseases by altering gut microbiota alone [18].

The therapeutic effects of programmed cell death protein-1 (PD-1) blocking vary depending on the quantity of *A. muciniphila* present, according to a metagenomic analysis of stool samples from patients with epithelial malignancies. According to a dynamic examination of hepatocellular cancer patients undergoing anti-PD-1 immunotherapy, *Proteobacteria* took over in non-responders by the 12th week. When the oral and intestinal bacteria of melanoma patients receiving PD-1 inhibition were examined, it was shown that responding patients had a comparatively higher abundance of *Ruminococcaceae*. Additionally, research on statins, histamine-2 blockers, NSAIDs, and berberine has shown that the gut microbiota exhibits significant interindividual variability, which in turn influences the heterogeneity of medication response. Understanding the diversity of gut microbiota is therefore essential to achieving the aim of precision medicine [18].

Role of Probiotics in Enhancing Drug Metabolism and Efficacy

Probiotics, defined as live microorganisms that confer health benefits when administered in adequate amounts, have gained attention for their potential to influence drug metabolism and enhance therapeutic efficacy [106]. Probiotics can help restore a healthy gut microbiota composition, especially after dysbiosis caused by antibiotics or illness. A balanced microbiota is crucial for optimal drug metabolism. In addition, by promoting the growth of beneficial bacteria, probiotics can improve the overall health of the gut environment, which can enhance the absorption and metabolism of certain drugs [50].

Probiotics can produce enzymes (such as β-glucuronidases) that may alter the metabolism of drugs. Certain probiotics can enhance the bioavailability of digoxin by influencing its metabolism, improving therapeutic outcomes. Furthermore, probiotics may convert inactive prodrugs into their active forms, facilitating quicker therapeutic action. For instance, they can help in the hydrolysis of certain medications, making them more bioavailable [107].

Probiotics can strengthen the intestinal barrier, enhancing nutrient and drug absorption. A healthier gut lining can facilitate the effective uptake of medications. In addition, probiotics ferment dietary fibers to produce SCFAs, which can lower intestinal pH and improve the solubility of certain drugs, thus enhancing their absorption [21].

Probiotics can alleviate gastrointestinal side effects associated with certain medications, such as antibiotics and NSAIDs. By maintaining gut health, they can reduce symptoms like diarrhea and discomfort. Furthermore, probiotics can modulate the immune response, potentially reducing the inflammatory side effects of some medications and enhancing their overall safety profile [48].

Probiotics may enhance the efficacy of cancer treatments by modulating the immune response. Certain strains have been shown to improve the response to immunotherapy, potentially leading to better patient outcomes. In addition, emerging research

https://doi.org/10.20428/yjms.v19i3.2745
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suggests that probiotics may influence the gut-brain axis, potentially enhancing the efficacy of antidepressants and anti-anxiety medications by improving gut health and neurotransmitter levels [108]. The integration of probiotics into pharmacotherapy could lead to more personalized treatment approaches, considering individual microbiome profiles to optimize drug efficacy [109]. Further research is needed to identify specific probiotic strains that can enhance the metabolism and efficacy of particular drugs, paving the way for the development of targeted probiotic therapies.

Potential of Prebiotics in Supporting Beneficial Microbiota

Prebiotics are non-digestible food ingredients that promote the growth and activity of beneficial microorganisms in the gut. They play a crucial role in maintaining a healthy microbiota and enhancing overall gut health [110].

1. Promotion of Beneficial Bacteria

Prebiotics are selectively fermented by beneficial gut bacteria, such as *Bifidobacteria* and *Lactobacilli*. This selective growth helps to increase the abundance of these beneficial strains, which can outcompete harmful bacteria and support a balanced microbiome. Furthermore, by fostering the growth of beneficial bacteria, prebiotics contribute to greater microbial diversity in the gut, which is associated with better health outcomes [111].

2. Production of Short-Chain Fatty Acids (SCFAs)

When prebiotics are fermented by gut bacteria, they produce SCFAs such as acetate, propionate, and butyrate. These SCFAs have several health benefits. SCFAs serve as an important energy source for colon cells, supporting gut health and function [112]. In addition, SCFAs have anti-inflammatory properties and can help regulate immune responses, potentially reducing the risk of IBD and other gastrointestinal disorders [113].

3. Improvement of Gut Barrier Function

Prebiotics can enhance the integrity of the intestinal barrier, reducing intestinal permeability (often referred to as "leaky gut"). A robust gut barrier helps prevent the translocation of pathogens and toxins into the bloodstream [114]. In addition, by promoting the growth of beneficial bacteria, prebiotics help maintain a healthy mucosal layer, which is vital for optimal gut function and protection against infections [115].

4. Modulation of Metabolism

Some studies suggest that prebiotics can influence body weight and fat metabolism by altering gut microbiota composition and SCFA production, which may enhance satiety and reduce fat storage [116]. Prebiotics may help improve insulin sensitivity and glucose metabolism, potentially reducing the risk of type 2 diabetes [117].

5. Support for Immune Function

Prebiotics can enhance the immune response by promoting the growth of beneficial bacteria that stimulate the production of immune cells and cytokines. This can lead to improved overall immunity and lower susceptibility to infections [118]. There is emerging evidence that prebiotics may help reduce the risk of allergies and asthma, particularly when introduced during infancy, by promoting a healthy gut microbiome [119].

6. Potential in Disease Prevention

In gastrointestinal tract (GIT) disorders, supporting beneficial microbiota, prebiotics may help prevent and manage GIT disorders such as irritable bowel syndrome (IBS), IBD, and constipation [120]. Furthermore, the gut-brain axis suggests that a healthy gut microbiome can influence mental health. Prebiotics may contribute to improved mood and cognitive function by supporting beneficial gut bacteria that produce neurotransmitters [121-123].

Current Research Gaps in Gut Microbiota and Drug Interactions

The gut microbiota plays a crucial role in drug metabolism, efficacy, and toxicity, but several research gaps remain in understanding these interactions fully. There is a need to elucidate the specific metabolic pathways through which gut microbiota influence drug metabolism. Understanding how different microbial populations contribute to the activation or inactivation of drugs can help predict responses. Furthermore, research is needed to identify and characterize the

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enzymes produced by gut microbiota that modify drugs, including phase I and phase II metabolic processes.

In addition, individual differences in gut microbiota composition can lead to varying drug responses. More studies are required to understand how genetic, environmental, and dietary factors influence these variations. Integrating pharmacogenomic data with microbiome profiles could provide insights into personalized medicine approaches, but this area is still underexplored. Finally, exploring how to manipulate gut microbiota to enhance drug efficacy or reduce toxicity is an emerging field. More studies are needed to identify effective strategies for microbiota modulation, such as dietary interventions or microbiome-targeted therapies.

CONCLUSION

Understanding the gut microbiota and the factors that influence its composition is critical for advancing health care, particularly in pharmacology, where its role in drug metabolism and efficacy is increasingly evident. Gut bacteria modulate drug pharmacokinetics and pharmacodynamics through enzymatic processes such as hydrolysis, oxidation, reduction, conjugation, decarboxylation, and deamination. These metabolic interactions impact drug absorption, solubility, permeability, and transport, highlighting the microbiome's pivotal role in shaping drug bioavailability and therapeutic outcomes.

Inter-individual differences in gut microbiota composition contribute significantly to variability in drug responses, including efficacy and safety. This underscores the need for a personalized approach to pharmacotherapy that accounts for microbiome-related variability. As research progresses, integrating microbiome profiling into clinical trials could enhance our understanding of drug efficacy and safety, enabling more precise participant stratification and treatment strategies.

Moreover, the impact of medications on gut microbiota should not be overlooked. Many drugs can disrupt the microbial ecosystem, leading to dysbiosis, immune dysfunction, and metabolic disturbances. Clinicians should consider the potential for microbiota disruption when prescribing medications and monitor patients for related complications. Identifying specific probiotic strains that enhance drug metabolism and efficacy represents a promising avenue for future research, paving the way for targeted probiotic therapies that optimize treatment outcomes.

Incorporating the gut microbiome into the broader framework of precision medicine will be essential for addressing the complexities of drug-microbiota interactions. This holistic approach has the potential to transform pharmacological practices and improve patient care by aligning treatment strategies with individual microbiome profiles.

CONFLICT OF INTEREST

The authors declare that no conflict of interest associated with this work.

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