

Review

Role of Gut Microbiota in the Drug Metabolism: A Review

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Abstract

Drug metabolism and toxicity are significantly influenced by the human gut microbiota. Recent research has brought attention to the possible influence of gut microbiota on drug safety and efficacy, underscoring the need for a deeper comprehension of the relationship between gut microbiota and drug metabolism. This review examines the intricate relationship between medication metabolism and the human gut microbiome. It talks about the many kinds of microbes that live in the human gut and the mutualistic relationship that exists between the gut microbiota and the human host. The paper also outlines the different ways that gut microorganisms might alter drug metabolism, as well as how drugs absorb and are bioavailable. It also talks about how understanding microbiota variances might lead to tailored therapy and gives examples of medications whose efficacy is affected by microbiome interactions. It also lists metabolic pathways that the gut microbiota affects and provides noteworthy instances of how the gut microbiota and drugs interact. In conclusion, it tackles issues like diversity in microbiota composition and clinical translation and potentially beneficial therapeutic techniques that take use of microbiota-drug interactions. The review wraps up by discussing about gut microbiota, concept of gut microbiota, drug metabolism by gut microbiota, stressing the significance of investigating the relationship between drug metabolism and gut microbiota and how it can affect healthcare.

Keywords: gut microbiota, role, drug, metabolism, microbiota

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1 INTRODUCTION

The complex, diversified, and composite ecology of bacteria that live in our gut and happily coexist with the host, supporting human health and wellbeing, is collectively referred to as the gut microbiota. The human gut microbiota performs vital roles in the body and is crucial to human health. The microbiome of the human gut is an ecological system made up of bacteria, yeast, viruses, and parasites, totalling about 100 trillion microorganisms^[1-3]. The gut microbiota is thought to be an important organ that connects to other organs in a variety of ways. This gut microbiota link communicates with the neurological, endocrine, humoral, immunological, and metabolic pathways to facilitate host-microbe communication. Human health now includes the intestinal microbiota as a practical consideration. The gut microbiota is a diverse colony

of bacteria that performs a range of tasks that impact the host's general health. The gut microbiota, which is thought of as an additional organ of the body, is made up of billions of bacteria that typically coexist in a balance that is solely influenced by dietary, genetic, and environmental variables^[1]. Unlike previous ideas which postulate that food was first metabolized by the liver. The gut bacteria interact and metabolize food intake first, according to recent studies. Human health is impacted by gut microbiota, which is also known as the "hidden metabolic organ." Most of the microorganisms found in the gut microbiota are reported to belong to the following classes: *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia*^[2]. The more we learn about the ocean of our gut microbiome, the more we understand the complex but important function that the gut microbiota plays in a variety of illnesses, such as obesity, type 2 diabetes, ulcers, and inflammatory bowel

disease (IBD)^[3]. The microbiome has a major impact on the immune system, metabolism, behaviour, and drug metabolism. With the increasing number of microbiomes identified in the gut, intestinal microbiota can enhance or stimulate the action of a drug or foreign object^[4]. Drug metabolism is influenced directly by the gut microbiota through biotransformation processes such as deamination, demethylation, and hydrolysis. The gut microbiota can even control the effectiveness of certain drugs by altering the host's metabolism, creating a competitive environment for the drug receptor, and affecting the receptor's activity and efficacy^[5]. In addition to their intended therapeutic effect, antibiotics also appear to negatively impact the gut microbiota. *Clostridium difficile* infection, previously known as *Clostridium difficile* infection, is one disease that is directly brought on by drug disruption of the gut microbiota^[6]. Understanding how gut bacteria and drugs interact can change how effective they are as well as perhaps reveal indicators for early illness diagnosis. The influence of the gut microbiota on microbiotics, and their interactions with drugs can change their effectiveness and potentially serve as biomarkers for the preliminary diagnosis of various illnesses^[7]. The interactions among the gut microbiota and medications, along with their toxicity and efficacy, are highlighted in this review.

1.1 The Gut Microbiome

The term "gut microbiota" refers to a community of microorganisms, such as bacteria, fungi, protists, viruses, and archaea, that inhabit a specific environment, which might be anything from a hot spring to the human body. Joshua Lederberg developed the term "microbiome" to "describe the ecological community of commensal, symbiotic, and pathogenic microorganisms that literally take up space in our bodies and have been largely disregarded as factors influencing health and illness^[8]. There are over 100 trillion bacterial cells in the human microbiome^[9,10]. Bacterial cells are 3–10 times more numerous than human cells, even though the human body contains between 10–40 trillion cells^[11]. The microbiome is made up of trillions of viruses, including bacteriophages, fungi, archaea, and other single-celled eukaryotes in addition to this bacterial population. Bacterial cells may be outnumbered by viruses, but fungal cells are found at orders of magnitude lower^[12]. Whether considering horizontal gene transfer possibilities^[13] or simply the more proteins functioning in our gut, the quantity of gene-level variety this introduces is thought-provoking. Since the human genome is thought to contain between 20,000 and 25,000 protein-coding genes^[14], the total number of bacteria, fungi, and viruses in an individual's microbiome would be predicted to be between 2,000 and 20,000 million^[15,16]. Thus, up to 1000 non-human genes exist for every human gene. Additionally impressive is the mass this represents. Microbes are estimated to make up 2–5 pounds of the

human body, or ~1–3% of our total mass^[17,18]. This can have profound consequences on our physiology and well-being, which is not surprising given that a large portion of it resides in our gastrointestinal system, which makes up around 10% of our mass. Microbiomics niches can also be found on the surface of the skin, the linings of the mouth cavity, nasal passages, eyes, lungs, mammary glands, and digestive tract. Figure 1 provides a summary of gut microbiomes.

1.2 Concept

Many of our presumptions have been shaken by the capacity to identify bacteria, at least at the family or genus level, from samples so diluted that detection was previously undetectable. The origin of the microbiome is now being studied. It was believed until that the fetus lived in essentially sterile conditions while inside the mother, however this idea now seems to be inaccurate^[19,20]. Since the baby is coated with maternal microbes that were most likely acquired from the nearby urogenital and digestive tracts, it is intriguing to consider how the microbiota that is present before birth interacts with and influences those that are known to be acquired as the baby passes through the birth canal. Now that we know this, we can wonder what changes take place in the gut microbiota of newborns born by cesarean section. Breastfeeding naturally causes antibodies and microorganisms to be transferred from the milk to the newborn's skin. A young child, however, freely samples its surroundings through its mouth, including toys, pets, other people, and odd objects like rocks, as most parents are aware. Through a constant selection process, different microorganisms from the environment and food are introduced at random, but their establishment is keyed to a final configuration optimized for existence and symbiosis in particular settings. During the first few months of life, the microbiome undergoes significant changes, and by the time the child is around two years old, it appears to have stabilized and is more like what we now know to be a typical adult microbiome^[21]. What the child consumes in their diet has decreased since then.

The development of next-generation sequencing (NGS) has allowed us to better understand the components of the microbiomes represented in the "healthy" general population. The Human Microbiome Project, which is supported by the National Institutes of Health, is the most ambitious initiative of its kind to date. This program's first phase (2008–2013) looked at 300 healthy patients' microbiomes^[22,23]. The fundamental experimental design has adhered to a common overall procedure, even though the specific methods have differed. First, samples are taken from various parts of the body, mainly the skin, gastrointestinal tract (GTI), urogenital tract, oral cavity, and nasal passages. The DNA is then extracted from the microorganisms that are present (the robustness of the sample preparation will

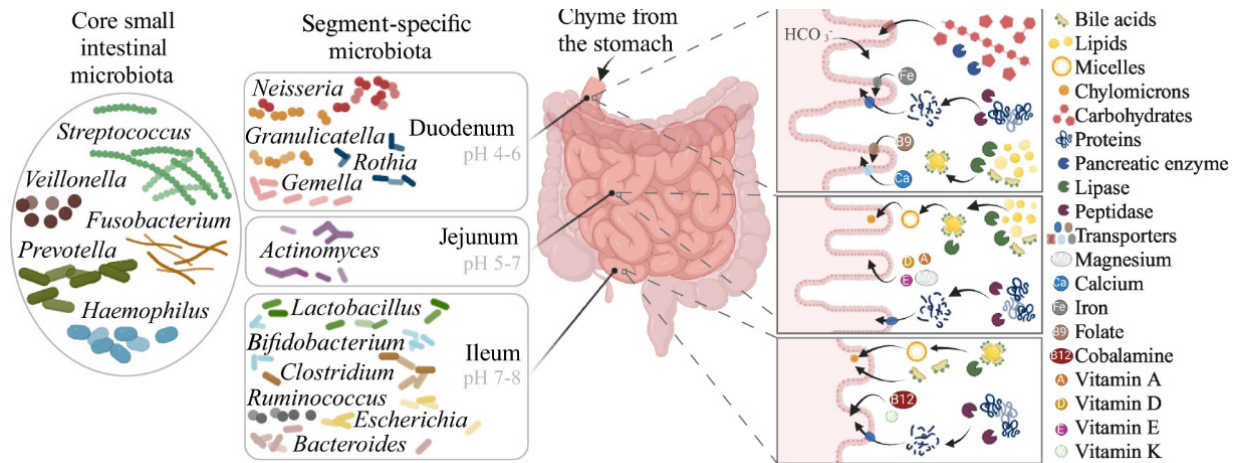


Figure 1. A Summary of Gut Microbiomes. Reproduced from Ref.[DOI: [10.1016/j.tim.2024.02.013](https://doi.org/10.1016/j.tim.2024.02.013)] with permission from CC-BY.

determine if host DNA is present). A library of amplified fragments with sequence tags that enable sequencing on the preferred platform is then produced from these nucleic acid samples after they have been processed for NGS utilizing particular procedures. These tiny amplicons can be semi-selective or completely random (a shotgun method). In parallel, each method offers a vast number of brief reads. Processing and interpreting this incredibly varied collection of brief events is the last step. Small ribosomal subunit RNA (or "16S rRNA") sequences have been used in a large portion of analysis to date to produce identification at the family and genus levels. Sequence data from other, more diagnostic genes is required for further species-level detail. At first glance, the number of distinct genera of microorganisms that are regularly identified in human microbiomes seems to be a small portion of those that have already been described in the master tree of life phylogeny^[23,24]. Each bodily site under test has microbial communities that are "optimized" for their niche, whether it is the skin, mouth cavity, nasal cavity, urogenital tract, GTI, or another site. When microbiomes are categorized according to the species they include, there is significant heterogeneity between individuals. However, they appear more comparable from person to person when categorized by function (e.g., ability to synthesize certain vitamins or digest different types of carbohydrates)^[25]. Until drastic changes occur through ingestion or other introduction of agents that drastically alter the balance, such as chemicals that kill or alter the nutritional balance or inocula of aggressive, potentially pathogenic microorganisms, it seems that each person's microbiome remains stable over time^[26,27].

It was suggested to categorize the gut microbiomes into one of three main clusters or enterotypes, which are characterized by the predominance of one of three genera: Bacteroides, Prevotella, or Ruminococcus, to offer a straight forward explanation of an incredibly complex and dynamic community^[28]. According to Wu et al.^[29], the Prevotella group was linked to long-term carbohydrate diets, whereas the Bacteroides group was

more common with long-term protein and animal fat diets. Ten days of food restriction had no discernible effect on either enterotype, indicating that long-term eating patterns had a greater influence on them^[29]. Diversity rose from the stomach to the end of the GTI, with the mouth cavity having the most phylogenetic diversity and the stomach having the lowest. Actinobacteria/Proteobacteria/Firmicutes on the skin, Lactobacillus in the vagina, Streptococcus in the oral cavity, and Bacteroidetes in the GI tract were among the bacterial systematics that were predominant body regions^[30-35]. Additionally, the investigations found several "outliers"—subjects.

1.3 Function

Only a small portion of the apparently numerous roles and beneficial impacts that different microorganisms play within the human body are now understood. Human microbes, for example, are known to: (1) prevent pathogen colonization by competing for attachment sites and essential nutrients^[36,37]; (2) oppose competitors and foreign bacteria by producing substances that range from relatively non-specific fatty acids and peroxides to highly specific bacteriocins^[38]; (3) perform carbohydrate fermentation and absorption, allowing the host to utilize some normally indigestible carbohydrates^[39,40]; and (4) synthesize and excrete vitamins in excess of their own needs, which can be absorbed as nutrients by their host (e.g. human enteric bacteria secrete Vitamin K and Vitamin B12, and lactic acid bacteria produce certain B-vitamins).^[41,42]; (5) have a constant and dynamic impact on the host's immune system and gut^[43]; (6) promote the growth of specific tissues^[44]. The microbiome can affect several diseases, such as IBD^[45-47], malnutrition^[48], celiac disease^[49], obesity^[50,51], asthma^[52], diabetes^[53], cancer^[54], pancreatic disease^[55], allergies^[56], neurological disorders^[57], and heart disease^[58], according to at least preliminary evidence. To impact and interact with their neighbours and their host, all microorganisms continuously release metabolites and secrete significant

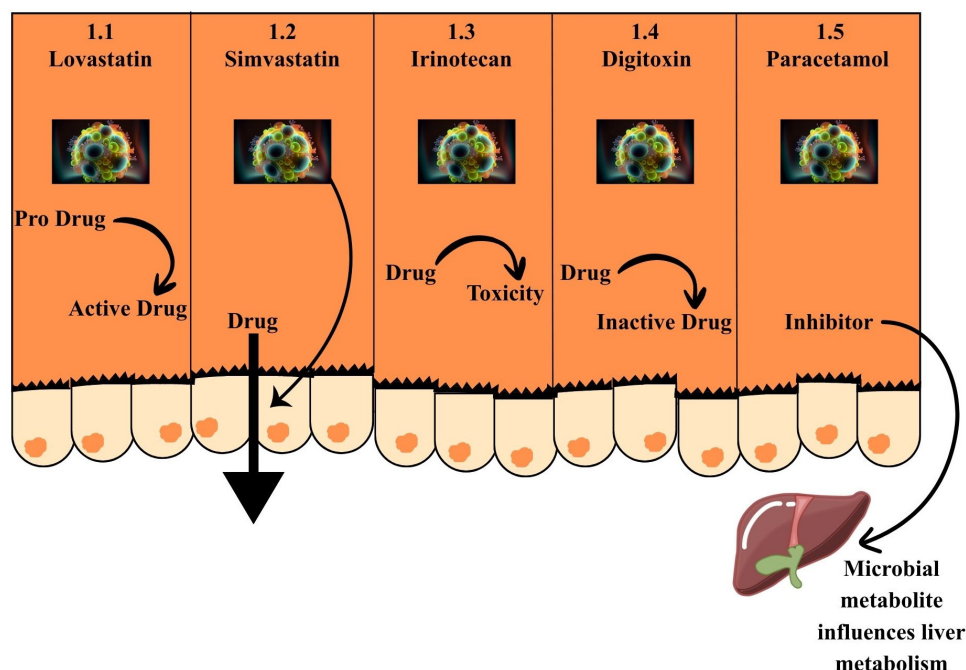


Figure 2. The Ways of Microbiome Affecting Pharmacokinetics of Drugs.

amounts of both tiny and big molecules, along with vesicles carrying RNA, DNA, and protein^[59-61]. Many of these substances can penetrate the intestinal wall and reach the circulation, where they can affect both local and distant organs in the gut microbial community. There are intriguing signs that our mood, eating habits, sleep patterns, and food choices may be influenced by our gut microbiota^[62,63]. As previously mentioned, there are up to 1,000 non-human genes and their products for every human gene in our body. This means that the microbiome gives us access to a vast genetic content reservoir that can produce “niche” metabolisms that are not possible with the human genome alone. Theoretically, the microbiome offers a quick and possibly localized way for metabolic niches to adjust when external environmental conditions change because its metagenome can change far more quickly than the human genome. The recent identification of a gene for seaweed digestion in the Japanese microbiome serves as an illustration of this type of adaptation. This gene is present in environmental microbes that eat seaweed in the water. After passing through someone’s digestive tract on a piece of seaweed, these bacteria eventually transferred a gene to normal bacteria that reside in the human stomach. The gene provided the ability to digest seaweed, a common food in Japan, and is now part of the genetic capacity of the Japanese human microbiome^[64].

Few bacterial species are shared by the GTIs of people and mice, which is a recognized restriction of using mice to investigate the human gut microbiota. Furthermore, a lot of species originating from mice are either unknown or poorly described, which makes it difficult to translate microbiota studies between hosts. Colonizing mice with human microbiotas is one method that has been utilized

to increase the usefulness of mice for human microbiota research^[9]. Mice treated with a human microbiota show impaired immune maturation and performance compared to mice harboring a mouse-derived microbiota, leading to differences in susceptibility to infectious and inflammatory diseases, despite reports that the microbiotas of humans and mice are functionally comparable^[9]. This could be partly caused by certain human bacteria’ poor colonization in the mouse gut. In particular, the quantity and quality of constituent microorganisms, microbial activity, microbe-microbe interactions, and host-microbe interactions all influence the robustness of the gut microbiome. Microbiome resilience is essential for preserving gut microbiome homeostasis, which benefits human health overall by allowing bacteria to operate at their best and hosts to provide efficient immune defense. Numerous illnesses and conditions, including obesity, IBD, diabetes mellitus, hepatic steatosis, metabolic liver disease, and several malignancies, have been connected to long-term disturbances of gut microbiota homeostasis^[27].

1.4 Effect of Microbiome on the Pharmacokinetics of Drugs

One of the many difficulties with oral drug delivery is ensuring that the medication will remain stable in the GTI. The degradative effect of upper gastrointestinal pH has been successfully decreased using formulation techniques including enteric coating. However, it is sometimes overlooked how much the steadily growing population of bacteria contributes to the stability of drugs. According to earlier research, a drug’s presentation in the distal intestine determines how relevant the microbiota is in determining its pharmacokinetic profile^[65]. As a result, it has long been believed that most medications that are absorbed from the small intestine will not interact much with the

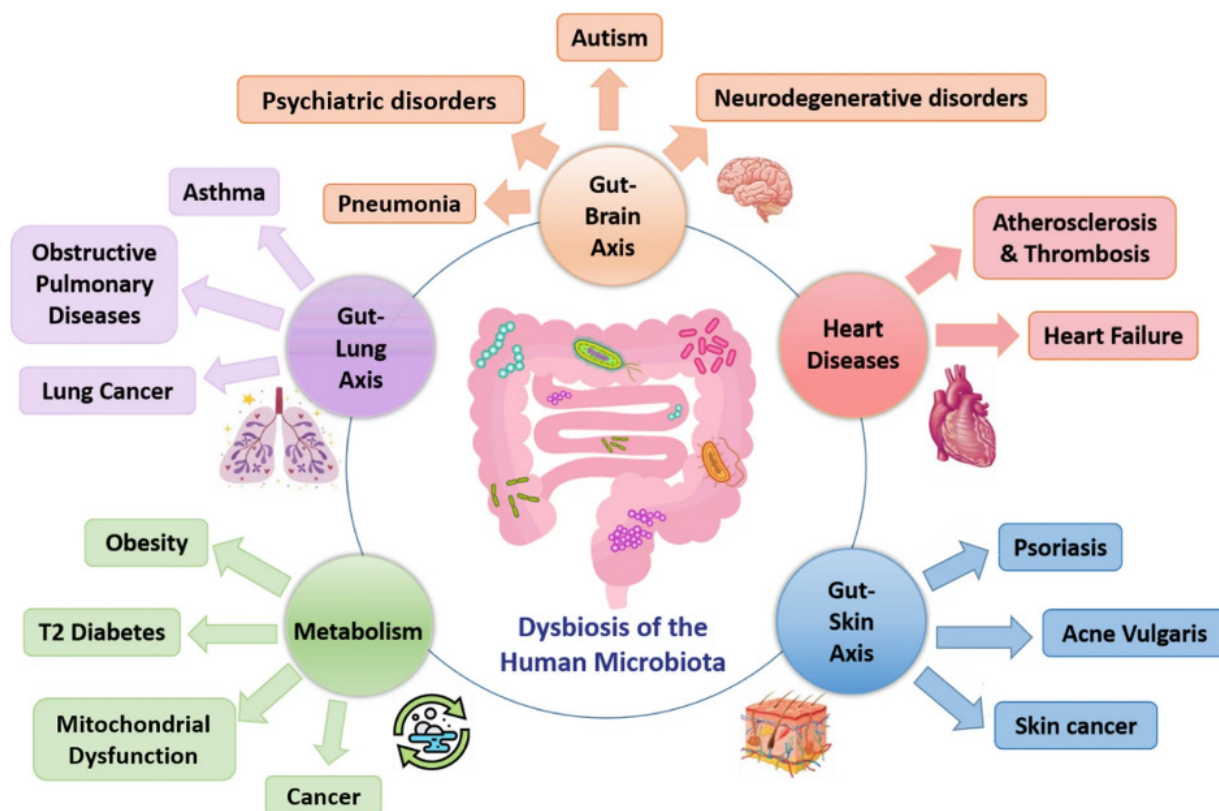


Figure 3. Dysbiosis of Microbiota in Human Diseases. Reproduced from Ref.[DOI: [10.1186/s12967-022-03296-9](https://doi.org/10.1186/s12967-022-03296-9)] with permission from CC-BY.

microbiota unless they are intended for enterohepatic circulation or sustained-release. A paradigm shifts in the gastrointestinal locations of microbial biotransformation that are taken into consideration, however, can result from new discoveries regarding the effects of the small intestinal flora on mammalian hosts^[66]. Low solubility and/or permeability are characteristics of recently developed medication candidates that lead to longer gastrointestinal residence periods and, thus, a higher likelihood of microbial interactions. As a result, it is now more important than ever to consider the many metabolic activities that the microbiome coordinates; some of these are discussed below as well as in Figure 2.

1.5 Human Microbiome and Microbiota Dysbiosis in Human Diseases

We now have a better understanding of all the typical microbial communities found in the human body thanks to recent developments in the study of the human microbiome^[67]. According to research on microbiota, interactions between microbes and their hosts occur not only within an organ but also between different kingdoms, forming an inter-kingdom crosstalk that naturally connects them. In fact, the gut microbiota has been well studied and has been demonstrated to have a role in the local regulation of homeostasis in the GTI as well as the lungs and brain in a systematic manner^[68]. Additionally, through the most crucial inter-organ linkages, such as the gut-lung and gut-brain axes, gut dysbiosis contributes to the development of numerous

disorders (Figure 3). Human diseases are caused by microbial dysbiosis. Numerous organs, including the heart, brain, liver, kidneys, and lungs, depend on the gut bacteria to function properly. However, these impacted organs malfunction and numerous linked disorders advance when the microbial equilibrium is disturbed.

1.6 Metabolic Mechanism of Drug Through Microbiota

Researchers that investigate the human microbiome are especially interested in the activities of these bacteria because the colon and small intestine are the main sites of microbial activity. Within our digestive tract reside over a trillion microorganisms, the majority of which are beneficial and play a crucial role in immunological, metabolic, and nutritional processes. Metronidazole or vancomycin, along with the removal of the offending trigger medication, have been the standard treatments for *C. difficile* infection (CDI). However, with recurrence rates as high as 50% and an increasing frequency of fulminant disease, this approach is proving to be increasingly ineffectual. Numerous mechanisms exist for the gut microbiota to impact pharmaceutical metabolism, as seen in (Figure 4). These pathways include interactions that occur directly between the drug and the host as well as indirect effects that are obtained through control of the host's metabolism.

1.6.1 Drug Activation

The activation of pharmaceuticals, particularly prodrugs—inactive compounds that need to be converted

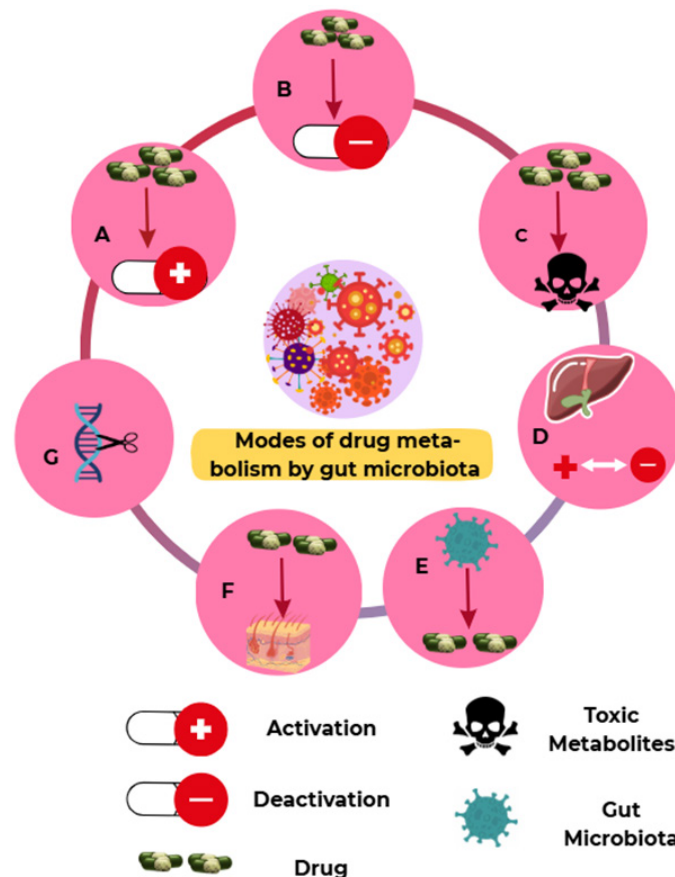


Figure 4. Metabolic Mechanism of Drug Through Microbiota.

into active forms to produce a therapeutic effect—is influenced by the gut microbiota. This conversion can be triggered by enzyme activity arbitrated by the microbiota, increasing the drug's potency and bioavailability.

1.6.2 Drug Deactivation

Contrary to popular belief, the gut microbiota can deactivate medications. This can result in less effective treatment outcomes because the microbiota metabolizes the medication, rendering it inactive or less potent.

1.6.3 Conversion to Toxic Metabolite

When medications are broken down by microbes, toxic metabolites or by products may be formed. These by products can have adverse impacts on the health of the host as well as adverse drug reactions. To avoid negative impacts, close observation of these interactions is necessary.

1.6.4 Drug Reactivation (Enterohepatic Recycling)

The microbiota may have a role in enterohepatic recycling for specific medications. The drug's duration of action is extended through this mechanism, that entails the reabsorption of drug metabolites in the intestine and their subsequent reactivation in the liver.

1.6.5 Direct Binding to Microbial Cells

Because sticky proteins are present on the surfaces

of some bacteria, certain medications may adhere to microbial cells in the gut directly. This binding may change how a medicine is distributed throughout the body and influence how it behaves pharmacologically.

1.6.6 Competitive Binding with Microbial Metabolites

Over binding sites on host enzymes, the drug and microbial metabolites generated during drug metabolism may engage in competition. The rate and degree of drug metabolism may be impacted by this competition, which could result in unanticipated differences for the effects of the medicine.

1.6.7 Alteration of Host Gene Expression

The microbiota in the gut can affect the expression of host genes, as well as those that are essential for drug metabolism. Gene expression modifications caused by the microbiota may affect how the host metabolizes and reacts to medications, which may modify the safety and effectiveness of those medications.

1.6.8 Microbial Translocation and Immunomodulation

The immune system of the host can be significantly impacted by the gut microbiota. Certain components of microorganisms can promote the development of immune cells, and occasionally, immunological

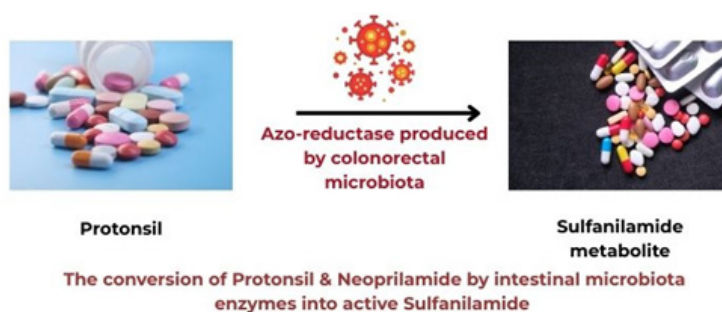


Figure 5. Metabolic Mechanism of Prontosil.

responses can be triggered by microbial translocation *i.e.* the movement of microbes or their products into the bloodstream. The results of treatment may be impacted by these immunomodulatory processes, which may cause autoimmunity or alter the reaction of the body to medications. Optimizing medication therapy requires an understanding and ability to control these interactions^[69]. Thus, human hosts and gut bacteria engage in mutualistic interactions. The human gut microbiota affects several areas of health, such as toxicity and drug metabolism. The makeup and variety of the gut microbiota highlight the significance of microbial diversity in gut function. It outlines the several ways that gut bacteria can impact drug processing and presents the idea of microbiota-mediated drug metabolism^[9].

2 INTERPLAYS BETWEEN GUT MICROBIOTA AND MEDICATION METABOLISM

2.1 Drugs and Their Effects for Drug Metabolism and the Pathways

Drug toxicity and metabolism are significantly influenced by the gut microbiome. We can forecast toxicity and therapeutic efficacy of drugs through a variety of chemical processes by talking about the gut microbiome. Among these mechanisms is the gut microbiome's modification of phase I and II drug metabolism enzymes. Many studies have revealed that there are two key ways that biotransformation happens: direct and indirect. The traditional direct approach uses microbial enzymes to carry out the biotransformation. The indirect mechanism describes how microbial enzymes affect host signalling pathways and receptors, changing how a person reacts to a particular medication (Table 1). By modifying drug transporters and changing gut motility, among other ways, the gut microbiota can affect drug absorption and bioavailability. A reaction of a person to a precise drug can be straight affected by gut microbiota through direct interaction, and the production of enzymes, or significant or minor biochemical changes that cause the drug to become active/inactive or produce hazardous metabolites^[70,71]. A few medications listed below (Table 1) have been deliberated for their effects on drug metabolism and the many pathways that lead to changes in the potency of medication, toxicity, or delivery.

2.2 Metabolic Mechanism of Different Types Drugs

One of the first reported examples of activation for drugs by intestinal microbiota enzymes is the alteration of orally administered prontosil (Prontosil) into a sulfanilamide metabolite (Figure 5). This metabolite is accountable for the antibacterial activity of this prodrug *in vivo* but has minute effect *in vitro*. In mouse models, it was observed that the modification is arbitrated by azo-reductases which are formed by the colon-rectal microbiota^[72]. It involves the formation of a hydrazo compound and then subsequent reduction of a nitrogen bond. Prontosil also undergoes sulphanilamide conversion in the liver and kidneys. Prontosil can be exiled in the GTI through the bile whereas neoprilamide is exiled through the bile without being reduced or absorbed in the intestine owing to high polarity^[73].

An alternative sulphonamide medication called sulfasalazine is triggered biologically by the bacterial enzyme azo-reductase. Although it is physically intact, it undergoes bacterial azo reduction in the colon to release 5-aminosalicylic acid (5-ASA) and sulphapyridine (SP) and is poorly absorbed from the upper intestine^[74]. 5-ASA functions as an active anti-inflammatory agent in the colon and is used to treat IBD. On the other hand, SP possesses antibacterial and immunomodulatory properties that are felt throughout the body. Rheumatoid arthritis is thought to respond well to it^[75]. Some patients may experience sulfasalazine adverse effects, such as headache, skin rash, and appetite loss, when SP is absorbed in the colon^[76]. Balsalazide was made from salicylic acid and 4-aminobenzoyl- β -alanine to avoid side effects. Additionally, the gut bacteria effectively convert it to 5-ASA by secreting azo-reductase^[77]. Olsalazine, an additional sulfasalazine analogue, metabolizes into two 5-ASA by the same process. In faecal samples from rats, guinea pigs, dogs, and humans, the intestinal microbiota further acetylates the active metabolites of these prodrugs, 5-ASA, and SP. For human faecal suspensions, several bacteria convert 5-ASA via acetylation into *N*-acetyl-5-aminosalicylic acid under both aerobic and anaerobic conditions^[78,79].

Metronidazole is a well-known antibacterial drug that

Table 1. Drugs and Their Effects Listed for Drug Metabolism and the Pathways

Name of Drug/Type of Drugs	Molecular Formula of Drug	Treatment of Diseases	Enzymes Involved	Mechanism
Prontosil or Neoprontosil is an antibiotic	C ₁₂ H ₁₃ N ₅ O ₂ S	Used for the treatment of bacterial infections	Involved enzyme is azo-reductase	This enzyme breaks azo-bond into sulphanilamide
Sulfasalazine, or Olsalazine or Balsalazide is an anti-inflammatory drug	C ₁₈ H ₁₄ N ₄ O ₅ S	Used for the treatment of ulcerative colitis, and rheumatoid arthritis	Used enzyme is azo-reductase	Azo-reductase breaks azo-bond into sulphanilamide 5-amino-salicylic acid
Metronidazole is an anti-bacterial agent	C ₆ H ₉ N ₃ O ₃	Used for the treatment of bacterial infections in different areas of the body and infections due to protozoa	Used bacteria is <i>Clostridium perfringens</i>	<i>Clostridium perfringens</i> break ring into N-(2-hydroxyethyl)-oxamic acid and acetamide
Levamisole is an anti-helminthic drug	C ₁₁ H ₁₂ N ₂ S	Used for the treatment of parasitic worm infections, such as ascariasis and hookworm infections	Bacteroidetes and <i>Clostridium spp.</i> are used for breaking	Bacteroidetes and <i>Clostridium spp.</i> breaks ring into levametabol-I, levametabol-II, and levametabol-III
Omeprazole is an anti-ulcer drug	C ₁₇ H ₁₉ N ₃ O ₃ S	Used for reducing acid in the stomach	Anaerobic bacteria like <i>Bacteroides strains</i> are used	Anaerobic bacteria like <i>Bacteroides strains</i> reduction are utilised to break into sulphide metabolite
Zonisamide is an anticonvulsant	C ₈ H ₈ N ₂ O ₃ S	Used for the treatment of epilepsy	<i>Clostridium sporogenes</i> is used for converting	<i>Clostridium sporogenes</i> is used for reducing Benz-isoxazole ring into 2-sulphamoylacetylphenol
Lactulose is a laxative drug	C ₁₂ H ₂₂ O ₁₁	Used for the treatment of constipation	<i>Bifidobacterium bifidum</i> , <i>Lactobacillus acidophilus</i> , <i>Clostridium perfringens</i> are used for converting	Two enzymes are used for conversions to lactic and acetic acids
Sodium picosulfate is a laxative drug	C ₁₈ H ₁₃ NNa ₂ O ₈ S ₂	Used for the treatment of constipation due to piles, anal fissures, and bowel clearance	Arylsulfate sulfotransferase of <i>Eubacterium rectale</i> is used for conversion	Arylsulfate sulfotransferase of <i>Eubacterium rectale</i> converted into 4,49-(pyridin-2-ylmethanediyl) diphenol
Digoxin is a cardiotonic drug	C ₄₁ H ₆₄ O ₁₄	Used for the treatment of congestive heart failure	<i>Eggerthella lenta</i> having a two gene cytochrome-encoding operon and used for converting	<i>Eggerthella lenta</i> having a two gene cytochrome-encoding operon is used to convert into dihydro digoxin and dihydro digoxigenin
Metformin is an antidiabetic	C ₄ H ₁₁ N ₅	Used for the reduction of high blood sugar levels	<i>Escherichia</i> , <i>Intestinibacter</i> , <i>clostridium</i> , <i>robusta</i> is used	<i>Escherichia</i> , <i>Intestinibacter</i> , <i>clostridium</i> , <i>robusta</i> is utilized for Negative Correlation Hypoglycaemic method
Levodopa is an anti-psychotic	C ₉ H ₁₁ NO ₄	Used for the treatment of postencephalitic parkinsonism and symptomatic parkinsonism	<i>Helicobacter pylori</i> are used as enzyme	<i>Helicobacter pylori</i> is used for dehydroxylation to <i>m</i> -tyramine or <i>m</i> -hydroxy-phenylacetic acid to sequestering it from brain
Acetaminophen is an analgesic	C ₈ H ₉ NO ₂	Used to relieve mild to moderate pain, and to reduce fever	<i>p</i> -cresol-produce bacteria like <i>Clostridium difficile</i> is used for conversion	High baseline microbial metabolite <i>p</i> -cresol compete for clearance by hepatic sulfotransferase and diminish the host's metabolic capacity for Phase II sulfonation of acetaminophen
Sorivudine is an anti-viral drug	C ₁₁ H ₁₃ BrN ₂ O ₆	Used for the treatment of infections due to varicella-zoster virus (VZV)	Bacteroidetes sp. or enterobacteria (<i>Klebsiella pneumoniae</i>) is used for conversion	Bacteroidetes sp. is used to convert into (e)-5-(2-bromovinyl) uracil binding to related enzymes irreversibly to inhibit the metabolism of 5-fluorouracil and incite drug toxicity

Irinotecan is an anticancer drug	$C_{33}H_{38}N_4O_6$	Used for the treatment of colon or rectal cancer	β -glucuronidase is used enzyme	β -glucuronidase hydrolysis of SN-38-G of irinotecan (prodrug) release SN-38 in the intestines which leads to gastrointestinal toxicity
Diclofenac is an anti-inflammatory drug	$C_{14}H_{11}Cl_2NO_2$	Used for the treatment of mild-to-moderate pain, and to relieve symptoms of arthritis	β -glucuronidase is used enzyme	β -glucuronidase reactivate glucuronidases metabolite to cause gastrointestinal toxicity
Indomethacin is an anti-inflammatory drug	$C_{19}H_{16}ClNO_4$	Used for the treatment of moderate acute pain and arthritis or gout,	β -glucuronidase is used enzyme	β -glucuronidase reactivate glucuronidases metabolite to cause gastrointestinal toxicity
Ketoprofen is an anti-inflammatory drug	$C_{16}H_{14}O_3$	Used for the treatment of inflammation, pain, and joint pain	β -glucuronidase is used enzyme	β -glucuronidase reactivate glucuronidases metabolite to cause gastrointestinal toxicity
Statin is a hypolipidemic	$C_{33}H_{35}FN_2O_5$	Used for lowering of high cholesterol levels	Bacteria like <i>Lactobacillus</i> sp. is involved in production of coprostanol	Bacteria like <i>Lactobacillus</i> sp. derived secondary bile acids may compete with simvastatin for hepatic uptake by SLC01B1101 transporters
Nitrazepam is a hypnotic, sedative, anti-convulsant and anxiolytic drug	$C_{15}H_{11}N_3O_3$	Used for the treatment of panic disorders, insomnia, severe anxiety, and seizures	Nitro reductase is used enzyme	Nitro reductase conversion to 7-amino nitrazepam, followed by acetylation to 7-acetyl aminonitrazepam in the liver

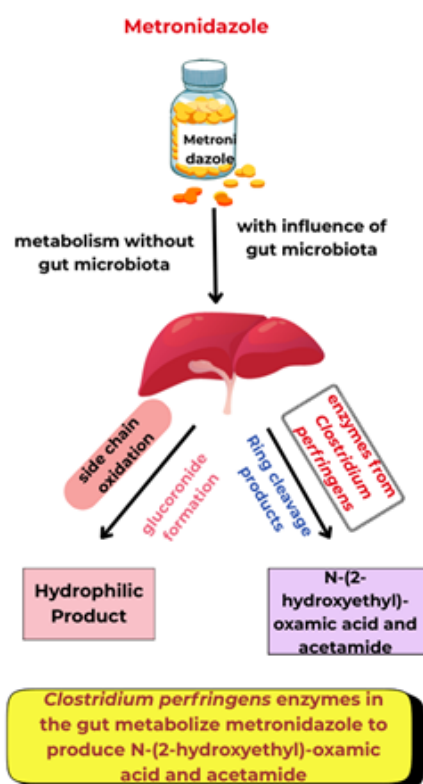
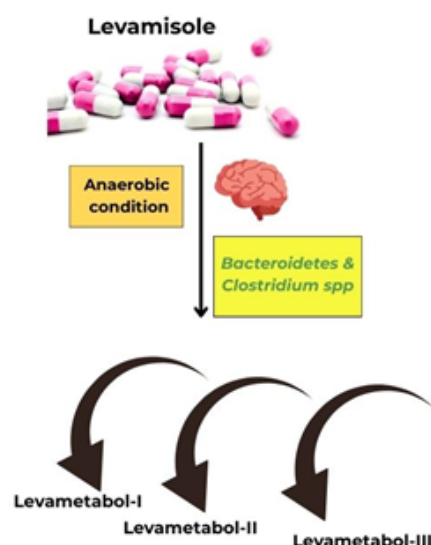


Figure 6. Metabolic Mechanism of Metronidazole.

is mostly used to treat trichomoniasis, amebiasis, and giardiasis. A hydrophilic substance is produced in the liver by side chain oxidation and glucuronide formation of metronidazole^[80]. However, the ring cleavage products are *N*-(2-hydroxyethyl)-acetamide and oxamic acid produced in the intestine by the metabolism of metronidazole by enzymes derived from the anaerobic enterobacterium *Clostridium perfringens* (Figure 6)^[81].

Levamisole is an anti-helminthic drug and has proven to be successful for treating both humans



The conversion of Levamisole by Bacteroidetes & Clostridium species into Levametabol I,II,III

Figure 7. Metabolic Mechanism of Levamisole.

and animals specifically in combating colon cancer. When it is broken down by certain bacteria in the intestine such as *Bacteroidetes* and *Clostridium* spp. In anaerobic surroundings, levamisole produces three metabolites known as levametabol-I, levametabol-II, and levametabol-III (Figure 7)^[82].

Of the connections found between forty-two regularly used medications and the gut microbiota, proton-pump inhibitors (PPIs) account for many of the modifications in the gut microbiome caused by drugs. Some typical examples

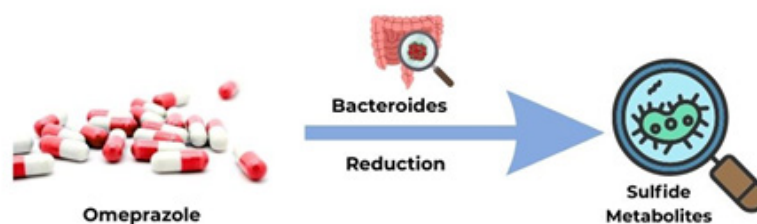


Figure 8. Metabolism of Omeprazole.

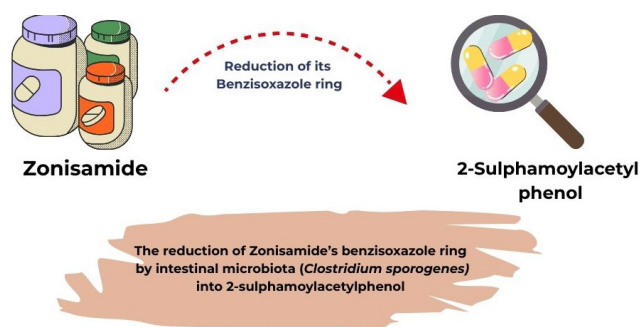


Figure 9. Metabolism of Zonisamide.

include rabeprazole and omeprazole. Furthermore, among all cohorts, PPIs were the only class of drugs associated with alterations in the composition of the gut microbiota. The manufacture of fatty acids, lipids, and L-arginine are among the expected microbial processes that are altered by PPI. The loss of certain bacterial systematics weakens the body's defences against enteric infections, such as those brought on by *Salmonella* and *Clostridium difficile*, which are common in PPI users. It has been shown that using antibiotics causes dysbiosis in the microbial ecology of the gut, which increases the risk of contracting *CDI* later. The use of PPIs reflects this as well^[83]. A common medication recommended for stomach ulcers is omeprazole. Under specific in vitro conditions in the laboratory, it is reduced into sulfide metabolites by anaerobic bacteria, such as strains of *Bacteroides*. However, since oral omeprazole is readily absorbed and does not reach the colon (Figure 8), bacterial contact is unlikely to occur^[84].

Zonisamide is a clinically employed anticonvulsant drug for epilepsy treatment. Reduction of its Benzisoxazole ring occurs due to activity of *Clostridium sporogenes* in vivo, resulting in the construction of 2-sulphamoylacetylphenol (Figure 9)^[85].

Sodium picosulfate and lactulose induce their effects via bacterial metabolism in the gut. Lactulose undergoes conversion by various intestinal bacteria enzymes including *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, and *Clostridium perfringens* which results in the creation of fructose and galactose that are subsequently converted into lactic acid and acetic acid

(Figure 10). The end products facilitate elimination of ammonia and amines into the faeces, alleviating hepatic encephalopathy (HE) by reducing pH in the intestine^[86].

On the other hand, sodium picosulfate is metabolized into 4,4'-[(pyridin-2-yl)methanediyl] diphenol via arylsulfate sulfotransferase of *Eubacterium rectale* in colon (Figure 11)^[87].

Digoxin is an oral cardiac glycoside medication that is used to treat arrhythmias, such as arterial fibrillation, and it also helps control the signs and symptoms of heart failure. Digoxin has a lengthy history of metabolic conversion into dihydrodigoxin and dihydrodigoxigenin via a reductive process that is mediated by the gut microorganism *Eggerthella lentas*. These two metabolites show insufficient binding to the myocardium's Na⁺/K⁺ ATPase in some patients. Nevertheless, because digoxin was significantly converted into the comparatively inactive metabolites dihydrodigoxin and dihydrodigoxigenin (Figure 12)^[88], about 10% of patients did not gain as much from digoxin. The GI tract is one of the main locations of this conversion. Before being absorbed in the stomach, more than 40% of the digoxin that is consumed is changed into inactive metabolites. An additional layer of information on the microbial contribution to host health that is unrelated to human metabolism is revealed by the role of gut bacteria in digoxin efficiency. Certain types of gut bacteria that break down digoxin, including *E. lenta*, have been found to lower the drug's level in specific people^[89].

Among its many therapeutic benefits, metformin

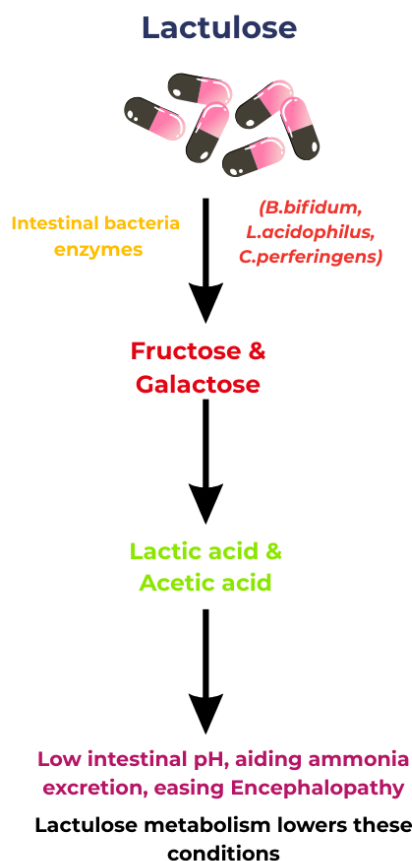


Figure 10. Metabolism of Lactulose.

also modifies the gut microbiota of people with type 2 diabetes. In both people and animals, metformin administration was shown to alter the functioning and composition of the gut microbiota. *B. fragilis* is less common when metformin is used, and it also decreases the action of bile salt hydrolase, which can raise levels of endogenous FXR antagonists (GUDCAs) and suppress FXR signaling (Figure 13). According to intestinal FXR inhibition, this has positive impact on metabolic disorders^[90]. Metformin is a complicated medication that acts through a variety of molecular pathways. Metformin physiologically reduces the synthesis of glucose by acting directly or indirectly on the liver and increases the utilization of glucose, increases GLP-1, and modifies the microbiome in the stomach. Metformin, at the molecular level, suppresses the liver's mitochondrial respiratory chain, which activates AMPK, improves insulin sensitivity (via effects on fat metabolism), and lowers cAMP, which in turn lowers the production of gluconeogenic enzymes. Fructose-1,6-bisphosphatase inhibition by AMP is one of the AMPK-independent actions of metformin on the liver^[91].

The oral progenitor of dopamine was levodopa, often known as L-dopa. In the central nervous system (CNS), it underwent decarboxylation following passage across the blood-brain barrier (BBB). Parkinson's disease (PD) can be treated by increasing dopamine levels in the CNS through this process. Nevertheless, research involving

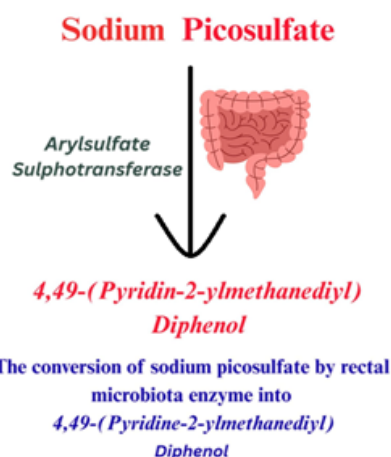


Figure 11. Metabolism of Sodium Picosulfate.

the incubation of levodopa with rat faeces revealed that the primary cause of levodopa's conversion to *m*-tyramine or *m*-hydroxyphenyl acetic acid was the decarboxylation process carried out by gut microbes. This microbial activity causes a decrease in operational L-dopa in the CNS^[92]. Furthermore, *Helicobacter pylori* infections are more common in PD patients than in healthy controls. Subsequent research indicated that *Helicobacter pylori* is the strain most frequently linked to bacterial decarboxylation^[93].

The alteration of acetaminophen by *Clostridium* species involves the breakdown of its metabolites. Our body detoxifies acetaminophen through glucuronidation and sulfation pathways and thus forming harmless metabolites. Certain *Clostridium* strains produce enzymes like β -glucuronidase which have the tendency and ability to reverse this detoxification process and potentially leading to the reactivation of toxic metabolites and hence increasing acetaminophen toxicity^[89]. However, CYP1A cytochrome can convert a tiny portion of excess acetaminophen into *N*-acetyl-*p*-benzoquinone imine^[94]. To aid in detoxification, this metabolite is additionally conjugated with hepatic glutathione (GSH), yet its absence may result in hepatotoxicity. Pre-dose urine levels of the microbial metabolite *p*-cresol are linked with the severity of acetaminophen-induced hepatotoxicity^[95]. High baseline *p*-cresol, which is generated by bacteria like *Clostridium difficile* and competes with acetaminophen for binding to cytosolic sulfotransferases, affects the bioavailability of acetaminophen and its metabolites. Hepatic toxicity or failure is caused by individual differences in acetaminophen metabolism, which are influenced by this interplay. Furthermore, the timing of acetaminophen administration influences its effects on the liver, with nighttime administration resulting in more severe damage than morning treatment^[96]. Research in mice found that the gut microbial metabolite 1-phenyl-1,2-propanedione, which decreases hepatic GSH levels, mediates the diurnal fluctuation of acetaminophen-

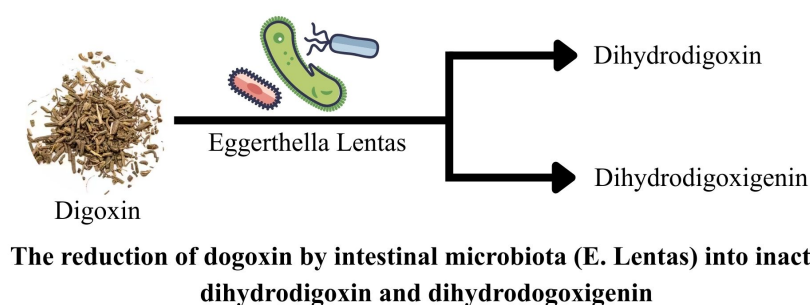


Figure 12. Metabolism of Digoxin.

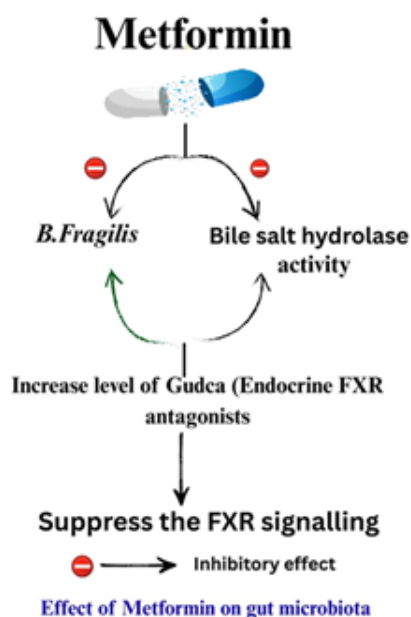


Figure 13. Metabolism of Metformin.

induced hepatotoxicity^[97]. However, due to the complex nature of acetaminophen metabolism and conflicting results in animal experiments, more research is required to fully understand the impact of gut microbial metabolism on acetaminophen-induced hepatotoxicity^[98]. A Japanese antiviral drug called sorivudine works similarly to acetaminophen to cause death^[99]. There have been eighteen acute patient deaths linked to the co-administration of sorivudine with 5-fluorouracil. The sorivudine metabolite (*E*)-5-(2-bromovinyl) uracil, which is produced with *Bacteroidetes* sp.^[100] or enterobacteria like *Klebsiella pneumoniae* ferment, is thought to be the cause of this death. When sorivudine is taken with the oral 5-fluorouracil prodrug at the same time, the metabolite binds to relevant enzymes permanently, preventing 5-fluorouracil from being metabolized and increasing its toxicity^[101].

One well-known example of how intestinal microbiota might reactivate a medication after it has been inactivated in the liver is the metabolism of irinotecan (CPT-11). To generate the active metabolite SN-38, CPT-11, an injectable prodrug for colorectal cancer, must be digested by a carboxylesterase in serum and

tissues^[102]. After conjugating SN-38, hepatic UDP-glucuronosyltransferase 1A1 creates the inactive SN-38-G^[103]. But bile secreted into the intestines turns SN-38-G into SN-38 when β -glucuronidase, which is made by bacteria like *Clostridium ramosum*, *Bacteroides vulgatus*, and *Escherichia coli* deconjugates it back to SN-38. Reactivation causes undesirable side effects that are dose-limiting, including immune system suppression, delayed diarrhoea, and weight loss^[104]. Like SN-38, long-term use of non-steroidal anti-inflammatory medicines (NSAIDs) containing carboxylic acid, such as diclofenac, indomethacin, and ketoprofen, might result in severe events related to enteropathy. The reactivation of active metabolites by microbial β -glucuronidase is the cause of these processes, which are linked to the enterohepatic circulation of glucuronides^[105]. The severe adverse effects caused by CPT-11 and related NSAIDs, especially indomethacin, are said to be lessened by antibiotic treatment or the use of inhibitors targeting microbial β -glucuronidase. The lack of bacterial de-glucuronidation causes less indomethacin to be absorbed back into the bloodstream, which increases clearance and shortens its half-life, according to later research^[106].

Because of their strong inhibition of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, which lowers plasma levels of low-density lipoprotein cholesterol, statins are commonly used as prodrugs to treat hypercholesterolemia^[107]. Initially, individual differences in the therapeutic efficacy of statins were partially attributed to genetic variations^[108-109]. However, later studies have demonstrated that gut microbiota also influences statin bioavailability^[110]. Statins and the gut bacteria both create bile acids, which are transported via liver and gut enzymes like the organic anion transporter SLCO1B1^[111]. The SLCO1B1 gene possesses a single nucleotide polymorphism, rs4149056, which has been connected to plasma concentrations of seven bile acids (taurocholic acid, tauro lithocholic acid, lithocholic acid, glycocholic acid, and 7 α -hydroxycholesterol). Simvastatin and bile acids may compete with one another for hepatic absorption through the SLCO1B1 transporter due to genetic variation^[112]. Additionally, studies have revealed that when lovastatin was incubated with rat or human fecalase samples, it created four metabolites,

Table 2. Conversion of Phytoconstituents by Gut Microbiota

Compound	Microbial Source	Product
Glycyrrhizin	<i>Eubacterium sp.</i> strain GLH	18 β -Glycyrrhetic acid (highly absorbable)
Buddleoside	<i>Escherichia sp.</i> , <i>Escherichia sp.</i> , <i>Bacillus sp.</i> , <i>Enterococcus sp.</i>	Acacetin (anticancer compound) via acacetin-7-glucoside
Ginsenoside Rb1	<i>Ruminococcus spp.</i> , <i>Oscillibacter spp.</i> , <i>Sutterella spp.</i> , <i>Holdemania spp.</i>	20-O- β -D-Glucopyranosyl-20-(S)-protopanaxadiol (compound K)
Sennosides	Reductases & 3- β -D-glucosidase enzymes	8-Glucosyl-rheinanthrone or sennidin monoglucosides

one of which was an active β -hydroxy acid metabolite that inhibits HMG-CoA reductase. Consequently, the gut microbiota may affect the pharmacokinetics of simvastatin by co-metabolizing or competing for statin absorption^[104,113].

The hypnotic, sedative, anticonvulsant, and anxiolytic actions of nitrazepam cause teratogenic consequences^[114]. Nitro reductase from the intestinal microbiota converts nitrazepam to 7-aminonitrazepam in this process, and the liver then acetylates it to 7-acetyl amino nitrazepam^[115]. Both metabolites show teratogenicity, although the rat liver's reductive metabolism is not as strong as the GTIs.

The roots of *Glycyrrhiza uralensis* and *Glycyrrhiza glabra* are the source of glycyrrhizin. In Japan, this sweet-tasting substance is utilized to cure hepatitis C. *Eubacterium sp.* strain GLH which is responsible for the full conversion of glycyrrhizin into the highly absorbable form of 18 β -glycyrrhetic acid (Table 2)^[116]. Certain bacteria (*Enterococcus spp.*, *Escherichia spp.*, and *Bacillus spp.*) have α -L-rhamnosidase and β -D-glucosidase that can convert buddleoside into the anticancer compound acacetin-7-glucoside (Table 2)^[117]. *Oscillibacter*, *Ruminococcus*, *Holdemania*, and *Sutterella* bacteria help ginsenoside Rb1 undergo metabolic conversion into the bioactive molecule 20-O- β -D-glucopyranosyl-20 (S)-protopanaxadiol, (compound K) (Table 2)^[118]. Reductases and 3- β -D-glucosidase enzymes found in the gut microbiota reduce sennosides to generate 8-glucosyl-rheinanthrone or sennidin monoglucosides. The latter is then converted in the gut into rheinanthrone, which has purgative effects (Table 2)^[116].

3 GUT DISEASE CONNECTION

An individual's general well-being is greatly influenced by their gut health. The health of our gut directly influences our physical, mental, and emotional states. A healthy gut contributes to a strong immune system as approximately 70% of our immune cells are developed in the gut. Additionally, the gut produces neurotransmitters like serotonin which is also known as the "feel-good" hormone. This indicates the important connection between gut health and mental well-being. Numerous medical issues, including obesity, autoimmune

illnesses, allergies, and even mood disorders such as depression, and anxiety have been connected to poor gut health^[119,120]. Comprehending gastrointestinal disorders is essential for determining their origins, manifestations, and remedies. These encompass a spectrum of conditions, from minor to severe, including gastrointestinal infections, gut-brain axis problems, IBD, and irritable bowel syndrome. These diseases can cause symptoms like abdominal pain, bloating, diarrhoea, constipation, and changes in bowel habits. To comprehend gut diseases, medical professionals examine factors such as genetics, immune system dysfunction, gut microbiota imbalance, environmental triggers, and lifestyle factors. Diagnostic tests like endoscopy, blood tests, stool analysis, and imaging studies aid in identifying the specific disease. Through appropriate diet, stress reduction, physical activity, and other methods, we can sustain a healthy gut and improve our general state of health and happiness^[121].

3.1 Gut Microbiota Dysbiosis

IBD is caused by gut microbiota dysbiosis, which is caused by a complex interaction between host genetics and the gut microbiota that upsets the normal balance of bacteria in the gut and results in an overgrowth of pathogenic bacteria and a decrease in beneficial bacteria. It is believed that this dysbiosis sets off an aberrant immune response that damages the intestinal mucosa and causes persistent inflammation. Changes in the gut microbiota's composition are one mechanism of dysbiosis; another is the breakdown of the intestinal barrier, which permits bacteria to get through the mucosal lining and incite an immunological response. Furthermore, microbial metabolites such short-chain fatty acids, which can have both pro- and anti-inflammatory properties in the gut, can be produced because of dysbiosis^[122].

The metabolic condition known as type 2 diabetes is quite common and is typified by elevated blood sugar and insulin resistance. Research has become increasingly clear over time on the role gut microbiota plays in the onset and course of this illness. Patients with type 2 diabetes have been shown to have altered gut bacterial diversity and composition. Poor glucose metabolism has been linked to decreased abundance

of some bacteria, such as butyrate-producing species, and increased abundance of dangerous bacteria, such as *Clostridium difficile*. Furthermore, insulin signaling, inflammation, and gut permeability are all impacted by gut microbiota and are critical components of type 2 diabetes pathophysiology^[123]. Additionally, research has suggested a possible connection between the development of insulin resistance and intestinal dysbiosis. A better understanding of the complex interactions between type 2 diabetes and gut microbiota may lead to the development of novel therapeutic approaches, such as dietary modifications, probiotics, and prebiotics, that target the restoration of a healthy gut microbiota to enhance metabolic health in those who suffer from the condition^[124].

3.2 Effect of Short-Chain Fatty Acids on Gut Microbiota

The synthesis of short-chain fatty acids (SCFAs) is one way that the gut microbiota affects non-alcoholic fatty liver disease (NAFLD). When dietary fibres ferment, gut bacteria produce chemicals called SCFAs. These SCFAs have been shown to have several beneficial effects on liver health. For example, they can promote the synthesis of liver glycogen, which helps regulate blood sugar levels. Additionally, SCFAs can stimulate the production of intestinal hormones that regulate appetite and energy metabolism. Another mechanism involves the gut microbiota's influence on the gut barrier function^[125]. Dysbiosis, or an unbalanced population of gut microbes, has been linked to increased gut permeability, which can allow pathogenic bacteria to enter the bloodstream and cause inflammation in the liver. It is possible that this ongoing inflammation plays a role in the onset and development of NAFLD. Furthermore, by producing endotoxins like lipopolysaccharide (LPS), the gut microbiota can also have an impact on NAFLD. Increased LPS has been linked to insulin resistance and liver inflammation in people with NAFLD. All things considered, these processes demonstrate the critical role that the gut microbiota plays in affecting NAFLD and offer prospective targets for medical therapies^[126].

3.3 Role of Depression on Gut Microbiota

Depression has been associated to changes in the diversity and makeup of gut bacteria, or gut microbiota dysbiosis, and its onset and course. Many studies have shown that the gut microbial community is often out of balance in depression sufferers, with a drop in helpful bacteria and an increase in potentially dangerous ones^[127]. Increased intestinal permeability brought on by this dysbiosis may permit the transport of microbial components into the bloodstream, inciting inflammation, and immunological reactions. Moreover, the creation of neuroactive substances like short-chain fatty acids, which have a direct impact on mood regulation and brain function, can also be a consequence of gut dysbiosis.

The link between depression and dysbiosis of the gut microbiota creates new opportunities for therapeutic interventions, such as the use of prebiotics, probiotics, and dietary changes to promote mental health and restore a healthy gut microbial balance^[128].

3.4 Relation Between Autism Spectrum Disorders (ASD) and Gut Microbiome

There is a complex relation between ASD and gut microbiome. Numerous studies have shown that the gut microbiota makeup of people on the autism spectrum differs significantly from that of neurotypical people. Changes in the variety, abundance, and ratio of different bacterial species are among these variations. Furthermore, there is evidence linking certain chemicals produced by gut microbiota to symptoms of ASD. It's crucial to remember that research is still ongoing to determine the precise pathways by which the gut bacteria affect ASD. More research is required to clarify the intricate relationship between gut microbiota and ASD and maybe identify new therapeutic targets for autistic people^[129,130].

Research on the connection between gut microbiota and disorders like depression or ASD is ongoing and developing^[129,130]. Research has shown that people with ASD have different gut bacterial diversity and composition than neurotypical people^[129,130]. Research examines how gut bacteria produce neuroactive substances that affect brain development and function through the gut-brain axis, while the precise mechanisms are still being studied^[130]. Whether the changes in the microbiome are a cause or an effect of ASD is still unclear^[129]. Research suggests a strong correlation between gut microbiome composition and depressive symptoms. The gut produces a majority of the body's serotonin, a neurotransmitter critical for mood regulation, and gut bacteria can influence its production. Inflammation driven by gut dysbiosis is also being studied as a potential contributing factor to depression. In both cases, while compelling correlations exist and preclinical studies show promise, the research is still nascent, and more rigorous clinical trials are needed before specific microbiome-based treatments become standard practice^[129,130].

3.5 Role of Gut Microbiota in the Treatment of Cancer

The gut microbiota can affect the effectiveness of cancer treatments in numerous ways. The immune response being modulated is one such way. The immune system is largely controlled by the gut microbiota, and some bacteria have been shown to recover the effectiveness of immunotherapy in cancer patients. Chemotherapeutic medications can also be metabolized by gut microbiota, which alters their bioavailability and efficacy. Prodrugs have been demonstrated to be activated by some bacteria, turning them into active versions that more effectively

target cancer cells^[131]. In addition, the gut microbiota can modulate the function of the gut barrier and lower inflammation, that can facilitate the treatment of cancer. Additionally, the microbiota has the capacity to generate compounds that either directly combat cancer or improve the outcomes of radiation and chemotherapy. These include secondary bile acids, which have been demonstrated to cause apoptosis in cancer cells, and short-chain fatty acids, that can overpower the growth of tumours. To create targeted medicines that can leverage the power of the microbiota to improve treatment outcomes, it is imperative to comprehend these potential mechanisms of gut microbiota-mediated impacts on cancer treatment^[132].

Several processes of how drugs affect the gut flora were examined. At least two action modalities have been identified for how the use of drug may affect gut microbial assemblages. The first way is that medications may cause the microbiome to move from other parts of the body to the gut. It is generally recognized that PPIs^[83] can lower the stomach's acidity barrier, allowing oral bacteria to enter the gut and cause microbial dysbiosis. Drugs can alter intestinal microenvironments and directly impact bacterial development in the second action mode, which may be the predominant one. For example, it has been discovered that metformin encourages the growth of bacteria in the gut that create short-chain fatty acids. These bacteria eventually contribute to the therapeutic impact of metformin in relieving glucose homeostasis and insulin resistance. It is possible for this second action mode to be bidirectional. Drugs that exhibit antimicrobial properties, such as antibiotics, can also prevent the growth of bacteria rather than encouraging it. In a seminal high-throughput study^[7], the authors methodically evaluated the antimicrobial properties of more than 1000 medications, including 835 human-targeted medications that work by targeting human cells. Interestingly, 24% of these medications had antibacterial activity, slowing the growth of at least one of the 40 bacterial strains that were examined. Eight of these appeared to be hazardous to bacteria, impacting at least half of the strains' growth rates. These medications included two anti-inflammatory and anti-rheumatic medications (auranofin and diacerein), one medication for gout (benzbromarone), one medication for peptic ulcer illness (oxethazaine), and four antineoplastic medications (daunorubicin, 5-fluorouracil, streptozotocin, and floxuridine). Given that these medications are frequently cytotoxic, this finding clearly illustrates the negative consequences of cancer therapy on the gut flora^[7].

Further, to comprehend the gut microbiota's significant influence on health and disease as well as its relationship with medications, modern microbiome research makes use of sophisticated instruments and a variety of evidence streams, from controlled animal models to extensive human data. A few modern research instruments were covered. Shotgun metagenomics and 16S rRNA gene

sequencing are two common high-throughput sequencing techniques used to determine the composition and functional potential of microorganisms^[30]. To provide a comprehensive picture of microbial activity, these are increasingly combined with metatranscriptomics (gene expression), metaproteomics (proteins), and metabolomics (metabolites). Furthermore, certain microbial communities (specified consortia) or complex human microbiota (humanized models) infect germ-free (GF) mice that are bred in sterile conditions. This enables scientists to investigate the mechanisms and causal effects of certain bacteria in a regulated genetic and environmental context. Next, there is a "renaissance" in cultivation that aims to extract bacteria that were previously unculturable. Finally, systems like the Simulator of the Human Intestinal Microbial Ecosystem and human stem cell-derived organoids (mini-guts) are used to simulate the gut environment and study host-microbe interactions and drug responses in a more accessible setting^[132]. These techniques include the iChip (isolation chip) and high-throughput anaerobic culturing, which help obtain pure strains for mechanistic studies that surpass the precision of metagenomic data alone.

Research using humanized GF mice has shown a causal relationship between different host characteristics and the microbiota. An important discovery revealed that when the gut microbiota of obese human twins was transferred into GF mice, the receivers of the fat twin's microbiota gained more weight than the recipients of the lean twin's microbiota^[133]. The immune system affects the colonization patterns of human gut microorganisms, with some harmful bacteria exhibiting higher colonization stability, according to other studies employing humanized mice with a functional human immune system (double humanized models). Certain microbial mutualisms have been revealed via gnotobiotic models. When mice are cocolonized with *Bacteroides thetaiotaomicron* and the archaeon *Methanobrevibacter smithii*, for instance, the bacterium's metabolism is redirected, increasing host adiposity and improving dietary energy harvest.

Clinical investigations have shown that fecal microbiota transplantation (FMT) is a very successful treatment, especially for recurrent *Clostridium difficile* infections^[6]. Additionally, FMT is being investigated in pilot studies for diseases including alcohol use disorder and HE, with encouraging outcomes like decreased alcohol cravings and enhanced cognitive performance. Prebiotics are most likely to change the composition of the gut microbiome, according to a recent meta-analysis of more than 70 clinical intervention studies. Probiotics and synbiotics, as well as diet alone, also significantly improve cardiometabolic characteristics. Genetically modified bacteria are being tested in early clinical trials. Patients with enteric hyperoxaluria had lower urine oxalate levels in a trial utilizing the modified bacteria *Fosia vulgatus*, which was engineered to break down oxalate. This is

a step toward using gene editing on the microbiome to treat illnesses. Personalized strategies to modify the microbiome are being used in emerging studies for diseases including IBD, which have shown notable improvements in clinical symptoms and may work in concert with current biologic treatments.

4 GUT MICROBIOTA AND PERSONALIZED MEDICINE

Precision medicine finds the gut microbiome to be a compelling target because of its adaptability. There are presently numerous classifications and intensities of microbiome-based treatments, varying in their specificity when it comes to addressing the microbiome. They include probiotics, prebiotics, symbiotics, and FMT. Numerous other strategies are being investigated because of the growing body of knowledge about the unique microbiota-driven mechanisms underlying disease pathogenesis, prognosis, and treatment outcomes. These include engineering bacteria to carry out tasks, using biologic agents and small-molecule medications to change the function of microorganisms or their interactions with hosts, and using native or engineered phases to modify the composition and function of microorganisms. Six general disease groups have been researched in relation to the gut microbiome: autoimmune or inflammatory illnesses, cancer, metabolic diseases, cardiovascular diseases, allergies, and atopic disorders^[133,134]. Healthy people have a varied microbiome with many helpful bacteria that are resistant to alterations brought on by physiological stress. On the other hand, the microbiome of people who suffer from illnesses is less varied, contains fewer good bacteria, and is more likely to cause inflammation. Numerous illnesses, including cirrhosis, IBD, diabetes, and colorectal cancer, are associated to dysregulation of the microbiome-host interaction. Through genotoxicity, inflammation, and metabolism, the microbiome can influence carcinogenesis and, as a result, be used to create anticancer treatments^[135]. Through the generation of different metabolites, which the diet is an excellent source of, the gut microbiome may have a role for the development of cancer. Drug response may also be influenced by the microbiome, and tailored medicines may be very important in healthcare initiatives, particularly when it comes to cancer. The prognosis, treatment response, and disease phenotype can all be predicted using the gut microbiome as a biomarker. To cure a variety of illnesses, including IBD and *Clostridium difficile* infection, efforts are being undertaken to develop synthetic microbial communities. The precision medicine strategy, which includes gut microbiota, can have therapeutic potential. When it comes to targeting non-invasive biomarkers for specific illnesses or malignancies, the microbiome can be a useful tool. To prevent or lessen metabolic diseases like prediabetes and type 2 diabetes, microbial metabolites can act as microbial biomarkers. In IBD, the gut microbiota has verified to be a key indicator

of the disease's phenotype and response to therapy. Healthy individuals have a very diversified microbiome that includes a large variety of helpful bacteria that are resilient to the alterations brought on by physiological stress^[136]. Though there has not been much information available in this area via traditional methods like culturing, modern techniques like NGS have been able to identify the bacteria, viruses, and archaea in the body and provide a reasonable understanding of this population and their combinations. Every human body organ has a different microbiome, and each organ has different impacts on inflammation and cancer due to this. The occurrence of cancer in a certain organ may be caused by these distinctions. For example, the higher microbial density in the colon increases the risk of colorectal cancer relative to the small intestine^[137]. Different clinical outcomes are caused by the microbiome, and these variations may account for an individual's treatment response. Therefore, customized therapies can be very important in healthcare programs, particularly when it comes to cancer, since they consider each person's unique genetic information and enhance treatment reactions. Because the gut microbiota controls the host's inflammatory reactions, it can be useful in the treatment of cancer. The possibility that microbial metabolites contribute to the onset of cancer has been recognized. These metabolites are abundant in the diet. The high-fat, high-protein meals that are typical of the current Western diet are one of risk factors for development of cancer. By influencing inflammation, metabolism, and genotoxicity, the microbiome can affect the growth of cancer and subsequently be leveraged to create anticancer treatments. Three main ways that microbiota can influence carcinogenesis are through metabolism, genotoxicity, and inflammation. The generation of different metabolites by the gut microbiota may performance a role for the growth of cancer. To cure a variety of illnesses, including *Clostridium difficile* infection, IBD, and efforts are being undertaken to build synthetic microbial communities as part of the precision medicine strategy, which includes gut microbiota, which may have therapeutic potential^[138]. In IBD, the gut microbiota has proven to be a critical indicator of the disease's phenotype and response to therapy.

5 RELATIONSHIPS BETWEEN THE GUT MICROBIOME AND IMMUNE SYSTEM

Both the general and local immune systems are significantly impacted by the gut microbiota. By producing mucus and antimicrobial peptides, the local gut microbiota sustains barrier function and promotes the growth of gut-associated lymphoid tissue (GALT)^[139]. Furthermore, GALT affects inflammatory cell morphologies differently from non-inflammatory cell phenotypes. T lymphocytes comprise one-sixth of the gut epithelium's cells. Furthermore, lymphoid tissue contains B lymphocytes, dendritic cells, and plasma cells, primarily in Peyer's

patches or the colon mucosa^[140,141]. Through the generation of microbiota metabolites, native microbiota or pathobionts can differentiate T helper (Th) cells into Th1, Th2, Th17, and regulatory T (Treg) cells. Th17 and Th1 are stimulated by filamentous bacteria, while *Clostridium* activates Tregs and the anti-inflammatory cytokine interleukin 10 (IL-10). Tregs and IL-10 are stimulated by *B. fragilis*. On the other hand, dysbiosis-induced overstimulation of Th1 and Th2 cells may result in an overabundance of proinflammatory cytokines^[142]. Tolerance development is significantly influenced by intestinal colonization^[143]. This information is important for preventing immune-mediated illnesses. Indeed, autoimmune, or allergic disorders may arise because of a decline in immunological tolerance. *E. coli* or *C. difficile*-induced dysbiosis is linked to atopic dermatitis or eczema. There are two effects of SCFA generation. They are the primary source of energy for enterocytes and promote Treg maturation and proper activity^[144]. Numerous connections between the gut microbiota and several organs have been identified. When there is dysbiosis, they might cause illnesses. Stress, anxiety, sadness, schizophrenia, cognitive decline, and autism can all be caused by the gut-brain axis. Hormonal, metabolic, behavioral, and regulatory abnormalities are produced via the gut-brain endocrine axis. Hypertension, athero-sclerosis, thrombotic events, and cardiovascular illnesses are all caused by the gut-heart axis. The cause of chronic obstructive pulmonary disease is the gut-lung axis. Hepatocellular cancer, non-alcoholic fatty liver, and liver inflammation are all caused by the gut-liver axis. Diabetes and inflammation of the pancreatic cells are caused by the gut-pancreas axis. Bone demineralization and osteoporosis are caused by the gut-bone axis. Sarcopenia, fragility, and muscle impairment are caused by the gut-muscle axis. Aging, wrinkles, atopic dermatitis, psoriasis, and acne are all caused by the gut-skin axis. Infertility, ovarian malfunction, ovarian cancer, and postmenopausal osteoporosis are all caused by the gut-reproductive axis. Chronic kidney disease, acute kidney damage, inflammation, nephrolithiasis, and nephropathy are all caused by the gut-kidney axis.

Significant research has recently confirmed the presence of the so-called "gut-brain axis." The gut and brain communicate with each other in both directions. On the one hand, the brain might regulate the gut immune system, mucus formation, and peristalsis, among other gastrointestinal processes^[145]. However, several neurotransmitters are engaged in the two-way communication between the host and the microbiota, while the gut microbiome releases SCFAs and other metabolites that affect brain activity^[146]. Through the production of intestinal hormones or the conversion of dietary components into substances like SCFAs, neurotransmitters like serotonin, gamma amino butyric acid, tryptophan, and vitamins that affect the BBB and cerebral functions, the gut microbiome may have an

indirect impact on the brain through the gut nervous system, which sends signals to the brain^[147].

Bacteria like *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, and *Streptococcus* are among the main makers of neurotransmitters under normal circumstances^[148,149]. Furthermore, the BBB is impacted by SCFAs, and several additional immunological pathways have an impact on memory, behaviour, and movement^[150,151]. It should be noted that the Mediterranean diet, which is heavy in vegetables and fiber, promotes the growth and activity of good bacteria in the brain^[152]. Depression and sleep disturbances impact over 20% of patients with intestinal dysbiosis^[153,154].

According to current research, people with neuro-vegetative diseases as multiple sclerosis (MS), Alzheimer's disease (AD), and PD have very different microbiota compositions from healthy controls^[155]. A greater number of Firmicutes and a lack of Fusobacteria are commonly observed in MS^[156]. There are fewer Firmicutes and Actinobacteria in the stool microbial composition of AD patients. Firmicutes, including *Turicibacteriaceae* and *Ruminococcaceae* are less prevalent in these patients^[157]. In patients with PD, fewer gut bacteria, including *Lechnospiraceae* and *Faecalibacterium prausnitzii*, produce SCFAs^[158].

6 CURRENT LIMITATIONS AND TECHNICAL CHALLENGES

Despite technological advancements like culturomics, gut microbiota research is limited by the ecosystem's enormous complexity (1,000+ species, many of which are unculturable), the difficulty of connecting snapshots to function, technical biases in sequencing, a lack of standardized methods, a limited understanding of non-bacterial microbes (fungi, viruses), and difficulties converting correlations into clinical causality.

A rapidly developing field of study with significant ramifications for the field of personalized medicine^[159,160] is the dynamic interplay between gut flora and pharmacological drugs. However, this emerging field faces several obstacles: Standardization is the biggest obstacle. To ensure comparable study outputs, it is crucial to establish carefully established techniques for examining drug interactions with the gut flora. This calls for the thorough implementation of consistent methods for data analysis and interpretation, as well as the standardization of approaches covering sample collection, storage, and processing^[161]. The ethical aspect is a second crucial concern. A complicated web of ethical issues arises when the gut microbiota is purposefully altered for medicinal objectives. These worries include concerns about informed consent, privacy, and the possibility of personal health information being misused. To guarantee the security and effectiveness of interventions based on the microbiome,

the field of regulatory issues also deserves consideration. Moreover, a broad research agenda and stringent validation processes are necessary for the integration of microbiome-based therapies into clinical practice. This project includes the crucial work of proving the effectiveness of such therapies in extensive clinical trials, deciphering their complex mechanisms of action, and closely examining any possible adverse consequences. Although there are many obstacles to overcome when researching the relationship between gut flora and medications, there are also several interesting directions for future study in this area. Future research must focus on understanding the complex mechanisms governing interactions between drugs and gut bacteria, developing new methods to modify the gut microbiota, and investigating potential therapeutic applications resulting from these interactions. Overcoming these challenges could improve our understanding of MDI and make it easier to incorporate targeted and microbiome-based therapies into clinical practice^[161].

Furthermore, the sequencing of brief segments of the 16s rRNA gene hypervariable region, which has a total of 1,542 base pairs, may overlook pertinent genetic variations outside of the sequenced area, making it impossible to differentiate between closely related bacterial species because of sequence homology^[162]. Regarding the second problem, it has been noted that selecting different data processing software and sequencing platforms may also add additional variability, resulting in variations in sample characterization based on their accuracy, sensitivity, and error rate. Like this, the use of various analytical pipelines for data processing may result in variations in the composition of microbiota because different pipelines have different steps, and there is currently little research on the benefits and drawbacks of software packages^[162].

The collection and handling of samples (contamination, storage), DNA extraction (lysis efficiency, inhibitors), sequencing (primer bias, shotgun cost), complex bioinformatics (large data, artifacts), and functional analysis (culturing the unculturable, linking function to host health, understanding metabolite flux, building trustworthy models) are all technical challenges in gut microbiota research. Transforming discoveries into treatments requires standardizing procedures, creating better instruments, and going beyond simple correlation to prove causation^[162].

7 FUTURE DIRECTION

The impact of gut microbiota on drug metabolism is a rapidly developing topic that has great promise for further research and development. Personalized medication regimens could result from developing strong methodology for defining an individual's gut microbiota makeup and function, which is one of the many attractive paths for research and applications. This could involve creating

databases linking microbiota profiles to drug responses, allowing clinicians to make more precise treatment decisions. Research on interventions to manipulate the gut microbiota like probiotics, prebiotics, and transplantation of faecal microbiota should be intensified. These approaches can be used to boost drug efficacy and lessen adverse effects by altering the microbial communities. The gut microbiota can be a source of novel drug metabolites or bioactive compounds, potentially leading to the discovery of new drugs or drug combinations that exploit microbial metabolic pathways. The integration of microbiome data into clinical practice can be facilitated by using artificial intelligence and machine learning algorithms to examine large-scale drug-response and microbiome information. These algorithms can help identify complicated correlations and predictive biomarkers. Integrating microbiome data with other "omics" data like genomics, metabolomics, and transcriptomics, will afford a more wide-ranging understanding of drug-microbiota interactions. Long-term investigations into how the gut microbiota evolves over time and its impact on drug responses are needed. This will help shed light on the stability and resilience of microbiota-mediated drug effects. Further, new techniques like HuMiX, nontargeted functional metagenomic screening, microbially derived metabolic screening, and bacterial gene editing, can be used which will be providing comprehensive drug-gut microbiota interaction. Researchers are requested to use novel technologies for understanding of the gut microbiota-drug interaction^[163].

The identification of novel interactions and reactions between gut bacteria and xenobiotics, as well as other advancements in feature generation, machine learning, and deep learning algorithms, will present previously unheard-of chances to create reliable prediction models. The gold standard for verifying the computational predictions is still experimental validation of the anticipated gut bacterial-metabolite interactions and gut bacterial biotransformation of xenobiotics. Thus, it can be said that AI-based computational methods show promise in anticipating the gut bacterial biotransformation of xenobiotics and offer leads for experimental validations, all while minimizing the enormous effort required to experimentally identify every such biotransformation and validating only the predicted metabolic cases^[164]. Further, the gut microbiota linked to multi-omics data can be investigated using AI and ML, which can also be used to find microbial biomarkers for the noninvasive assessment of illness risk or the development of treatments that target gut microbes. Personalized nutrition or therapies can be applied after stratifying patients according to their gut flora using AI and ML.

8 CONCLUSIONS

In conclusion, a fascinating and developing area of biomedical research is the investigation of the influence of gut microbiota on drug metabolism. Trillions of

microbes that live in the human gut are becoming increasingly obvious as they shape drug reactions, impacting everything from safety to efficacy. The ramifications in this field are enormous, as we learn more about it. The therapeutic potential of drugs can be aided or hindered by the gut microbiota; this information can be used to create more individualized and successful treatment plans. Research on gut microbiota has a bright future ahead of it. By customizing care to unique microbiome profile of each patient, it has the potential to completely transform the way that medicine is practiced. Furthermore, it might result in the identification of novel medications, therapeutic targets, and creative interventions that take advantage of the intricate interactions that exist between pharmacological chemicals and the microbiota. Researchers can also discuss how the human gut microbiota functions as a real organ and how important it is to both human health and sickness. While the functional properties of the complex gut microbiota are still largely unknown in this field of study, some encouraging studies have been published that point to a huge potential for changing the pathophysiology of ailments and therapeutic methods. According to recent research, healthy immune system operation and the prevention of autoimmune diseases depend heavily on the early growth of the gut microbiota. The impact of gut microbiota on medication metabolism has remained the subject of an unparalleled surge of understanding. We are getting closer to a time when healthcare is both customized and integrated with the complex ecosystems that exist inside of us as we work through these obstacles and broaden our knowledge of function of gut microbiota in medication metabolism. Global patient quality of life and better healthcare outcomes are anticipated because of this confluence of science and medicine.

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Conflicts of Interest

The authors declared no conflict of interest.

Data Availability

No additional data are available.

Author Contribution

Shrey K wrote the original draft. Ashis KS reviewed and edited the manuscript. Ashok KY reviewed and edited the manuscript, and supervised the study.

Abbreviation List

5-ASA, 5-aminosalicylic acid
AD, Alzheimer's disease
ASD, Autism spectrum disorder
BBB, Blood-brain barrier

CDI, C. difficile infection
CNS, Central nervous system
CPT-11, Metabolism of irinotecan
FMT, Faecal microbiota transplantation
GALT, Gut-associated lymphoid tissue
GF, Germ-free
GTI, Gastrointestinal tract
HE, Hepatic encephalopathy
HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA
IBD, Inflammatory bowel disease
LPS, Lipopolysaccharide
MS, Multiple sclerosis
NAFLD, Non-alcoholic fatty liver disease
NGS, Next-generation sequencing
NSAIDs, Non-steroidal anti-inflammatory medicines
PD, Parkinson's disease
PPIs, Proton-pump inhibitors
SCFAs, Short chain fatty acids
SP, Sulphapyridine

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