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Review

Understanding and role of gut microbiota on drug response and toxicity

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Abstract: The gut microbiota affects human health profoundly, and evidence is mounting that it can cause, worsen, or resolve illnesses. Particularly in drug-induced toxicity, its role in diverse toxicological reactions has garnered attention recently. Drugs may interact directly or indirectly, through the gut flora, whether or not they are taken orally, changing the toxicity. Current research focuses mainly on the one-way effect of xenobiotics on the makeup and activities of gut microbes, which leads to altered homeostasis. However, there are two-way interactions between the gut microbiota and xenobiotics, and it is important to consider how the gut microbiota affects xenobiotics, particularly medications. Therefore, we emphasise the microbiome, microbial metabolites, and microbial enzymes in this review to emphasise how the gut microbiota affects medication toxicity. To aid in the identification of micro-biologic targets and processes linked to drug toxicity, we establish connections between medications, the microbiome, microbial enzymes or metabolites, drug metabolites, and host toxicological reactions. In addition, a summary and discussion of contemporary mainstream approaches to controlling medication toxicity by microbiota targeting are provided.

Keywords: gut microflora; inflammation; drug detoxification; metabolites; immune response

1. Introduction

In recent decades, the role of the microbiome in disease pathogenesis in various vital as well as other organs of the body has attracted attention. Its accumulative weight is equivalent to that of the liver, and its vast numbers surpass those of human cells by magnitudes, suggesting that it has enormous potential for controlling human health and illness. The microbiota, which is considered an essential microorganism system, is found in nearly every bodily niche and is primarily colonised in the gastrointestinal, urogenital, eyes, skin, and airways. The bulk of the microbiota's habitats are found in the gut. They are categorised as viruses, bacteria, fungus, archaea, and several other microorganisms [1].

The majority of intestinal microorganisms are prokaryotes, with Proteobacteria, Firmicutes, Actinobacteria, and Bacteroidetes accounting for more than 90% of the gut microbiota [2]. Diverse taxa have diverse functions for their gut flora. A dysregulated Firmicutes/Bacteroidetes ratio is frequently interpreted as an indication of gut dysbiosis. Several phyla play a crucial role in maintaining host homeostasis. The Firmicutes/Bacteroidetes ratio is linked to metabolic disorders [3].

Certain enzymes, including *β-glucuronidase*, *β-glucosidase*, and *β-galactosidase*, can be secreted by a particular gut microbiota. Additionally, it can produce metabolites, such as lipids, bile acids, vitamins, and amino acids, which are all heavily involved in both the pathogenesis and maintenance of health. Given that the gut microbiota is thought to be a key regulator of human health [4–8].

Research has shown that the intestinal microbiota has a role in the aetiology of diseases in the brain, liver, kidney, gastrointestinal tract [9,10], and other areas of the human body. Treatments such as food modification, FMT, and pre-/pro-/synbiotic supplementation have been used in both human and animal trials [11]. Terms like the gut-liver axis, gut-brain axis, gut-kidney axis, etc. are derived from the interactions between the gut and other organs, and each is made possible via unique routes [12].

However, modifications in one of these axes may trigger modifications in another, leading to a changed microbiome. To put it another way, the gut acts as a link between several human systems. For example, the gut-liver-kidney and gut-liver-brain axis are proposed as important regulators in the pathophysiology of chronic kidney disease [13] and hepatic encephalopathy (HE) [14], respectively.

Throughout the process of developing and using drugs, adverse drug responses might happen. Significant drug toxicity in preclinical and clinical trials results in the discontinuation of the medication's development; nevertheless, significant drug toxicity in marketed pharmaceuticals causes fatalities and eventually leads to the removal of the drug [15]. Therefore, it is possible to decrease compound attrition during medication development and safeguard patient safety by precisely anticipating and preventing headache, delirium, psychosis, and drug toxicity.

Differences in host toxicological reactions to certain medications remain poorly understood, despite the ever-expanding understanding of processes via which pharmaceuticals are metabolised, absorbed, distributed, and removed alongside advances in pharmacogenetics and pharmacogenomics. A new area, i.e., pharmacomicrobiomics, aims to understand how interindividual differences in the microbiome influence the toxicity and effectiveness of drugs [16].

From the standpoint of the microbiome, which is now understood to play critical roles in drug metabolism [17,18], pharmacokinetics [19,20], efficacy, and toxicity, it offers a fresh perspective on explaining variability in drug outcomes [21]. These days, evidence-based medicine emphasises the use of pharmacogenetics and pharmacogenomics to interpret patient variances in drug responses [22]. Additionally, as the human gut microbiota expresses many more genes than the host, it should also be highlighted how drugs affect patient outcomes [23].

Drug-metabolizing enzymes regulate the metabolism of both foreign and endogenous drugs. Drugs often lose their pharmacological activity through metabolic change, producing highly water-soluble metabolites that are easily eliminated. Therefore, metabolising enzymes play a very important role. Controlling drug PK is critical. Characterization of enzymes involved in human drug metabolism is crucial for preventing severe adverse effects.

In the present review, we are trying to understand the role of microbiome on drug toxicity and therapeutic alternatives to exploiting them.

1.1. Role of microbial enzymes in drug toxicity

There is growing evidence to show that the metabolic repertoire of microorganisms is greater than that of human cells [24]. Drug transformation is mediated by the microbiota, which also triggers a variety of chemical processes. The majority of drugs are affected by hydrolysis and reduction [25]. Drugs are exposed to

the microbiota either directly or by biliary excretion, regardless of how they are administered [26]. Drugs may undergo microbial changes that change their pharmacokinetic characteristics, activate prodrugs, cause unwanted side effects, or reduce their effectiveness. By means of chemical transformation, the microbial enzymes can either exacerbate or provide relief from the harmful reactions that medications elicit.

1.2. Microbial role in drug activation

The most prevalent metabolic route in the gastrointestinal system is hydrolysis, which is mostly catalysed by microbial proteases, glycosidases, and sulfatases. In addition to producing products like glucose and sulphates to promote microbiological development, these activities often release smaller molecules for further metabolism [24]. However, they can also activate medications and change their toxicity. The gut microbiota is the only source of the hydrolytic enzyme *β-glucosidase*. Aglycones are formed when it releases glucose from glucosides; some of these aglycones are even more hazardous than the glucosides they are associated with. This mechanism is particularly prevalent in the digestion of phytomedicine components by gut microbes.

The main bioactive ingredient in Armeniacae semen, amygdalin, is degraded by the microbial *β-glucosidase* to produce glucose and mandelonitrile, the latter of which is poisonous when amygdalin is present [27]. Similar to this, geniposide, a significant bioactive ingredient found in many phytomedicines such as *Gardenia jasminoides Elli*, *Eucommia ulmoides Oliv.*, and *Rehmannia glutinosa Libosch*. [28], is broken down by microbial *β-glucosidase* into its aglycone genipin [29], and genipin is assumed to be the cause of geniposide-induced hepatotoxicity [30]. By eliminating gut microorganisms, antibiotic therapy may significantly reduce the microbial enzyme and impede the genipin formative process [31].

Numerous enzymes, some of which are exclusively microbial, such as nitroreductases, azoreductases, alkene reductases, and sulfoxide reductases, facilitate the reductive conversions that the gut microbiome mediates [32]. A decrease in gut microbiota chemicals results in changes to their polarity, bioavailability, and action. While the microbiome and the host both express nitroreductases, gut microbial nitroreductases are a class of enzymes that significantly impact medication toxicity. Nitrazepam is a kind of nitrobenzodiazepines that are metabolised into 7-aminonitrazepam, the metabolite that causes nitrazepam-induced teratogenicity, via nitroductases that are generated by the liver and microbiota [33].

Antibiotic therapy, however, significantly reduced malformation and almost eliminated 7-aminonitrazepam synthesis, indicating a direct relationship between nitrazepam-induced teratogenicity and its nitroreduction by gut microorganisms [33]. Another study that used N-nitrosodiethylamine as the substrate verified the metabolic action of nitroreductases to generate toxicity [34]. The gut microbial azoreductase cuts its azide bond reductively to produce sulfapyridine (SP) and 5-aminosalicylic acid (5-ASA), the former of which is in charge of sulfasalazine's adverse effects [35]. Even though azoreductase metabolises ipsalazide and

balsalazide, two analogues of sulfasalazine, their toxicity is eliminated by the altered structure of SP [36].

1.3. Microbial role in drug reactivation

The metabolism of xenobiotics in the gut microbial community frequently promotes microbial development by providing nutrition and energy generation, even as the host metabolism helps eliminate xenobiotics from the body [24]. Notably, the gut microbiota frequently opposes or reverses host-performed chemical changes, changing the pharmacokinetic and pharmacodynamic characteristics of xenobiotics. The action of microbial *β-glucuronidases* on medicines that are reabsorbed and metabolised in the gut through enterohepatic circulation embodies this well.

A hydrolase often found in bodily fluids, microbiota, and mammalian tissues is *β-glucuronidase*. Numerous harmful drugs are detoxified in the liver by UDP-glucuronosyltransferases (UGTs); however, the metabolites conjugated with glucuronic acid are reabsorbed in the gut, where they are converted back into their poisonous precursors by gut microbial *β-glucuronidases*. The first drug for Alzheimer's disease to be licensed was tacrine, but it was taken off the market because of significant pharmacokinetic variation [37] and the erratic hepatotoxicity that resulted [38]. According to a recent thorough investigation, rats react to tacrine in diverse ways. Strong responders show larger levels of tacrine exposure, increased deglucuronidation capacities, and an abundance of *β-glucuronidase*. The transportation and metabolic routes of drugs within the host are crucial for their reactivation by microbial *β-glucuronidases*.

One of the most widely used anticancer drugs for colon cancer treatment, iminotecan, can be fatally hazardous to at least 36% of patients, the majority of whom have mucositis, diarrhoea, and other gastrointestinal side effects [39]. The liver and the gut microbiota in humans both metabolise iminotecan. Liver carboxylesterases first convert it to bioactive SN-38, and then hepatic UGTs conjugate it with glucuronic acid to form SN-38G. This is subsequently subjected to gut bacterial *β-glucuronidases* to regenerate SN-38, which is also a toxin that causes severe diarrhoea and damage to intestinal epithelial cells [40]. It has been noted that the gut bacterial *β-glucuronidases* play a crucial role in reducing irinotecan-induced gastrointestinal toxicity. The suppression of intestinal bacterial *β-glucuronidases* has been shown to be efficient in reducing irinotecan toxicity and boosting anticancer activity and is thought to be a predictive biomarker of irinotecan-triggered diarrhoea severity [41–44].

Furthermore, inhibiting bacterial *β-glucuronidases* with distinct origins and structures produced quite different results: inhibiting *β-glucuronidases* derived from Firmicutes and Proteobacterium alleviates irinotecan-induced diarrhoea in mice, whereas inhibiting *β-glucuronidases* derived from Bacteroidetes does not, indicating functional diversity in orthologous enzymes of the gut microbiota [45]. Interestingly, the liver and gut microbiota of mice also use the same metabolic route to break down mycophenolate mofetil (MMF) in conjunction with irinotecan. It functions as a prodrug that is hydrolyzed to mycophenolic acid (MPA) to provide effectiveness, and hepatic enzymes then further convert it to glucuronized MPA (MPAG).

The majority of MPAG is eliminated by urine, but 10% of it enters the digestive system and is converted back into MPA by the gut microbial βglucuronidase. This buildup of MPA in the colon is linked to MMF-induced colonic inflammation [46]. Additionally, MMF increases the production of active β-glucuronidase, which aggravates its deleterious effect on the gastrointestinal tract and can be remedied with antibiotics [47].

It has been shown that inhibiting *β-glucuronidase* activity is an effective way to relieve associated drug toxicities, and it is a promising target for the creation of new treatments. Certain natural compounds, like quercetin, have the ability to block *β-glucuronidase* as well as cause the gut microbiota to produce protective metabolites [48]. Unfortunately, the poor pharmacokinetic profile of currently available *β-glucuronidase* inhibitors limits their clinical use [49]. Nevertheless, *β-glucuronidase* might be a useful target for reducing medication toxicity.

Microbial metabolism of food and endogenous substances has an indirect effect on important host hepatic enzymes that contribute significantly to drug metabolism. For example, Phase I hepatic enzymes, which comprise the cytochrome P450s (CYPs) superfamily and flavin-containing monooxygenases (FMOs), account for 80% of the oxidative metabolism of routinely used drugs. Phase II hepatic enzymes, such as glutathione S-transferases (GST), sulfotransferases (SULTs), and uridine diphosphate-glucuronosyltransferases (UGTs), play critical roles in drug detoxification and removal from the body. The gut microbiota's metabolism of uremic solutes, bile acids, and steroid hormones influences the expression and activity of these enzymes; these microbiome-drug interactions can have negative effects for patients taking medicines that are substrates for these enzymes. Microbiota-produced uremic solute indoxyl sulphate reduces CYP3A4 expression, lowering CYP3A4-mediated metabolic clearance of a wide variety of medications, including erythromycin, nimodipine, and verapamil.

1.4. Role of microbiome on drug inactivation

The inactivation of drugs by microbial metabolism has different effects than the activation and reactivation that often worsen drug toxicity. Through chemical alteration, the microbiome-mediated inactivation lowers medication toxicity while simultaneously increasing adverse effects and decreasing treatment effectiveness. One of the main drugs used to treat Parkinson's disease is levodopa. Reduced effectiveness in the brain and heightened adverse effects in the peripheral tissues and an increased dose schedule of levodopa treatment in Parkinson's disease may be explained by the gut microbiome's inactivation of levodopa [50]. By concurrently giving levodopa and carbidopa, abd AADC inhibitor *(S)-α-Fluoromethyltyrosine*—a substance that suppresses Enterococcus faecali and Eggerthella lenta—blocks the microbial metabolism of levodopa and enhances its bioavailability [51]. This suggests that a useful strategy for managing microbial inactivation-induced reduced effectiveness and increased toxicity might be the targeted suppression of gut microbiota that takes part in drug metabolism. Similarly, Eubacterium lenta inactivates digoxin, a nature-derived cardiac glycoside used to treat arrhythmia and heart failure, in the stomach to generate 20R-dihydrodigoxin [52].

Digoxin needs the unsaturated lactone ring structurally to elicit its therapeutic actions; however, the microbiota reduces it, which results in inactivation. The microbial metabolism of digoxin results in variable toxicity because of its limited therapeutic window and the notable individual variability in gut flora. Despite its identified function in the metabolism of digoxin, Eubacterium lenta is also present in individuals lacking the excretion of 20R-dihydrodigoxin [53]. Digoxin's varying toxic effects and pharmacokinetic characteristics among the population are better understood thanks to the discovery of cardiac glycoside reductase (CGR) in its metabolism. It also provides ways for lowering metabolism and, as a result, regulating digoxin's toxicity [53].

On the other hand, by breaking down harmful drugs into less hazardous metabolites, the microbiome-initiated drug inactivation also serves as detoxification. The anticancer drug doxorubicin has side effects that include vomiting, diarrhoea, hair loss, and even cardiotoxicity. It has been shown that Raoultella planticola functions as an inactivator of doxorubicin by deglycosylating it to produce the less harmful metabolites 7-deoxydoxorubicinol and 7-deoxydoxorubicinolone [54].

This suggests that depending on the toxicity of metabolites following deglycolation, pharmacological activation or inactivation results from microbial metabolism-induced deglycosylation [28,30,54]. Furthermore, mitochondrial inactivation detoxifies arsenic, a hazardous pollutant linked to a number of illnesses such as diabetes, heart disease, and multiorgan malignancies. When assessing arsenic biotransformation and toxicity, the monomethylarsonic acid/dimethylarsinic acid (MMA/DMA) ratio is thought to be a biomarker. In general, pentavalent arsenic species are less dangerous than trivalent arsenic ones. Growing data indicates that the metabolism and toxicity of arsenic are significantly influenced by the microbiota [55].

By promoting arsenic methylation and lowering the MMA/DMA ratio, the gut microbiota lessens the toxicity of arsenic [56]. Due to its capacity to encode methyltransferase, supplementary Faecalibacterium prausnitzii offers protection against arsenic poisoning, even if antibiotic therapy and a germ-free state enhance it [57]. Given that the microbiome plays a role in the metabolism of arsenic and the toxicity that results, it is possible to reduce drug toxicity by using microbial inactivation of xenobiotics to aid in detoxification.

Even though fecal microflora or accessible separated species were used by many researchers to study the impact of microbial metabolism on drug toxicity prior to the 1980s, this field is still largely unknown despite the development of high-throughput techniques in recent years.

Microbial incubation can reveal the effects of *β-glucosidase* and other enzymes that are only produced by the gut microbiota. However, the host and gut microbiota overlap many metabolic pathways, making it difficult to distinguish the role of the microbes in drug metabolism from that of the host. In addition, systematic studies on microbial metabolism are limited by the individual differences in gut microbial diversity and function. The only current mainstream approaches are germ-free animal models and nonspecific antibiotics.

Periodically, the metabolic profiles of medicines in conventional, gnotobiotic, and germ-free animal models are compared in an effort to disentangle the role of gut

microbes on drug pharmacokinetics and toxicity from the host [23]. Disentangling the roles of the host and microbiome in drug metabolism and hazardous effects is more challenging though, as the germ-free condition may cause changes in the host's metabolic characteristics. However, a deeper comprehension of the particular species and enzymes involved in drug metabolism may help with dosage and medication selection.

1.5. Regulating the drug toxicity via nuclear receptors

Nuclear transcriptional factors are important regulators of the production of phase II enzymes and transporters, as well as CYP450s. To improve the clearance, they serve as sensors of xenobiotics and harmful metabolites of endogenous metabolism. Microbiota-nucleus transcription factor connections are studied using germ-free animal models, which provide valuable insights. The expression levels of PXR and CAR in germ-free mice are considerably less than in the particular pathogen-free mice, which causes CYP450 expression to be reduced as a result [58]. Contradictory findings have been noted in another study, indicating that germ-free mice exhibit greater levels of PXR and CAR in conjunction with CYPs such as CYP2A4, CYP2B13, CYP2C38, and CYP4A14 [59]. Different studies may yield different results due to variations in the expression of nuclear regulators during different growth stages [60]. However, it has been determined that the gut microbiota is involved in controlling nuclear regulator expression, which in turn controls the expression of metabolic enzymes and transporters. The finding that compounds originating from the gut microbiota, particularly microbial products of aromatic metabolism, function as either agonists or antagonists of PXR and AHR, confirms this [61].

AHR and PXR ligands have been found to be associated with a number of microbial tryptophan catabolites, including skatole, indole, tryptamine, and a series of indolyl-3-(lactate, pyruvate, acrylate, propionate, acetate, aldehyde, acetamide, ethanol) [62]. It is commonly known that these microbial tryptophan catabolites stimulate the intestinal mucosa's innate immunity and cause quick inflammatory reactions by stimulating or opposing epithelial nuclear receptors [63].

A fresh approach to drug development has been suggested in the form of microbial metabolite imitation. Strong PXR agonists, such as indole and indole 3 propionate, are designed to lessen colitis by enhancing the expression of CYP3A4 and multidrug resistance 1 (MDR1) and preventing NF-κB activation [64].

While a large body of research has shown how the gut microbiota may influence how host metabolic enzymes are expressed, very few have examined the impact of certain xenobiotics on metabolic alterations and the ensuing harmful effects. It has been discovered recently that AHR activation reduces intestinal toxicity caused by chemotherapy by progressively blocking the tryptophan-kynurenine-kynurenic acid axis metabolism [65]. In addition, it has been discovered that indole 3-propionic acid, via PXR activation, protects against gastrointestinal tract injuries and radiation-induced hematopoietic system damage [66]. These investigations suggest that by activating nuclear factors, it is possible to use gut

microbial metabolites and their analogues to reduce drug-induced gastrointestinal toxicity.

Nuclear regulators are thought to be implicated in xenobiotic toxicity by controlling endogenous metabolism, as these nuclear factors also take part in endogenous metabolism, and xenobiotics might cause harm by altering the host metabolome. Myopathy is a side effect of statins, a family of medications intended to control blood cholesterol and lower the risk of heart disease. They also raise the risk of type 2 diabetes mellitus. It is thought that changes in cholesterol and glucose metabolism as well as PXR-dependent gut dysbiosis are responsible for the adverse effects of statins [67,68].

The most often used non-nucleoside reverse transcriptase inhibitor, efavirenz, has been linked to hepatic steatosis and dyslipidemia side effects. The fundamental mechanism is that efavirenz effectively activates PXR, which in turn controls important hepatic lipogenic genes. This leads to enhanced hepatic cell lipid absorption and cholesterol production [69]. One of the main defense mechanisms against oxidative stress brought on by xenobiotic toxicity is the activation of nuclear factor erythroid-derived 2-like 2 (Nrf2). Under normal circumstances, Nrf2 is attached to Kelch-like ECH associating protein 1 (Keap1) in the cytoplasm. However, in times of high oxidative stress, Nrf2 is released, translocates to the nucleus, and binds to the antioxidant response element (ARE), inducing the activation of defense genes [70].

Lactobacilli activates hepatic Nrf2, which reduces APAP-induced hepatotoxicity [71]. The in vitro activation of Nrf2 by Lactobacilli-derived 5-methoxyindoleacetic acid (5-IAA) is comparable to the impact of oral Lactobacilli administration, suggesting that Lactobacilli activate Nrf2 by 5-IAA secretion [71]. Additionally, the gut microbiota controls the circadian liver transcriptome and detoxification pattern, resulting in APAP-induced hepatotoxicity that varies during the day and is more severe at night [72].

The gut microbiota modulates drug toxicity through metabolic intervention and host defense activation. It does this by exerting significant impacts on nuclear factors. But the majority of what we now know about the microbiome's impact on nuclear factors is very limited, and it hardly touches on the effects it may have on xenobiotic metabolism and toxicity. Further understanding of how the microbiota affects nuclear factors to modify medication toxicity is needed.

1.6. Regulation of drug toxicity via host metabolism

Numerous metabolites that the microbiome produces contribute to the physiology of the host; these metabolites' production, roles, and mechanisms of action have all been thoroughly studied in other places [5,6]. The microbial metabolites, exemplified by bile acids and SCFAs, play a significant role in the host's metabolism of endogenous chemicals and have been linked to a number of metabolic disorders, such as obesity, hyperglycemia, and nonalcoholic fatty liver disease (NAFLD) [73,74]. Apart from their typical roles in influencing health and illnesses, microbiological metabolites take part in xenobiotics' host metabolism, which controls their harmful and metabolic effects.

The interaction between 5-fluorouracil (5-FU) and sorivudine is a classic example of how adverse drug-drug interactions can result from microbial metabolites interfering with the host drug metabolism. 5-FU is used to treat colon cancer, yet adverse effects to the mucosa, such as mucositis and diarrhoea, are commonly reported. Hepatic dihydropyrimidine dehydrogenase (DPD) is primarily responsible for detoxifying the human body; its suppression leads to the buildup of 5 FU and subsequently exacerbates negative consequences.

By vieing for the host's metabolic enzymes, the microbiome produces both endogenous and external metabolites and indirectly contributes to the metabolism of the host. While the activation of nuclear receptors caused by changes in the microbiota can result in a variety of alterations related to drug metabolism and toxicity, the competition of microbial metabolites with host enzymes often increases drug toxicity by impeding host detoxification. Despite the increasing interest in comprehending the interaction between the microbiome and host metabolism, more research is needed to clearly connect medication metabolism with microbial changes to host metabolic enzymes.

1.7. Modulation of drug toxicity via regulating the immune response

The effects of the microbiome on drug metabolism and immunity form a major basis for the postulated involvement of the microbiome in modifying drug toxicity [75]. In contrast to the impact of direct microbial metabolism on medication toxicity, a diverse array of chemicals and receptors modulate the immune-regulated drug toxicity associated with the microbiome. Drugs can directly harm the host and trigger immunological responses, but some can produce toxicity that is mediated via the interplay between the immune system and the microbiota.

1.8. Interplay between the microbiome and immune system

The immune system regulates the preservation of gut homeostasis, but the microbiome is essential to the growth and development of key elements of the host's innate and adaptive immune systems. On the other hand, a compromised immune system can also result in gut dysbiosis, which can increase pathogenic and/or Gram-negative bacteria and metabolites, disturb the epithelial barrier, and make the system more susceptible to infections. Gut dysbiosis can also promote inflammation and oxidative stress. The intestinal mucosa serves as an interface for two-way communication between the microbiome and the host immune system, as well as a natural barrier against pathogenic infection and commensal infiltration from the gut [76].

There are several chemicals and receptors that facilitate the reciprocal exchange of information between the host immune system and the microbiome. Intestinal paneth cells, which constitute one of the phylogenetically ancient components of the innate immune system, generate antimicrobial peptides, or AMPs. Multiple interactions between intestinal AMPs and the microbiota alter its structure [77]. In addition, pattern recognition receptors (PRRs) like TLRs and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) play a major role in mediating the crosstalk between the microbiome and the host innate immune system. These

PRRs identify pathogen-associated molecular patterns (PAMPs) and trigger the innate immune system in response [78,79].

Bacteroides fragilis produces a microbial compound called polysaccharide A (PSA), which is recognised by TLR2/1 and C-type lectin-like receptor. This recognition activates the anti-inflammatory arm of the phosphoinositide 3 kinase (PI3K) pathway, which in turn trains CD4+ Tregs to produce the immunomodulatory cytokine IL-10. Primary response protein 88 (MyD88) of myeloid differentiation functions as an adapter for inflammatory signalling pathways that are downstream of TLR and interleukin-1 (IL-1) receptor family members [80]. Its absence is linked to changed microbiota configuration and a lack of sensitivity to microbial ligands for TLR4 [81].

After identifying pathogenic bacteria or metabolites, certain PRRs combine to form inflammasomes. These inflammasomes then trigger inflammatory caspases, which release cytokines and cause pyroptotic cell death, as was previously discussed [82]. It is well known that inflammatory proteins, such as NLRP3 and NOD-pyrin domain-containing 6 (NLRP6), reversely control the makeup of microbes and preserve intestinal homeostasis [83,84]. The microbiome has the ability to modify innate immune responses, which are governed by immune cells like macrophages and natural killer (NK) T cells. This can impact the functionality of immunological organs like the liver [85,86]. The microbiome affects the innate immune system, but it also plays a role in the control of the host's adaptive immune system.

It is shown that the IgA antibody response, which mediates the preservation of gut homeostasis, may be activated by commensal bacteria [87]. Furthermore, microbial metabolites represented by SCFAs have a significant role in host adaptive immunity via suppressing the growth of proinflammatory Th17 cells and promoting the development of Treg cells [88] and anti-inflammatory forkhead box protein P3 (Foxp3) [89,90]. Strong evidence of the connection between the microbiota and human immune system has been found in a recent human study that compared the effects of immunomodulatory drugs with those of the microbiota. The study found that the microbiota affects systemic immune cell dynamics over time [91].

2. Challenges and limitations

Pharmacomicrobiomics is a rapidly evolving field that studies the complex relationship between gut bacteria and medication responses. While there have been considerable improvements in these areas, however, there are still various issues in this area: (1) Standardised procedures are lacking for sample collection, sequencing, and data processing in pharmacognostic investigations.

This makes it difficult to compare study data and produce clinical practice guidelines. (2) The gut microbiota is a dynamic ecosystem influenced by factors such as nutrition, lifestyle, and genetics. Distinguishing between the impact of these variables and drug-induced microbiome alterations can be challenging. (3) Individual Variability in Drug Response (IVDR): The gut microbiota varies significantly between individuals, which might have an influence on drug-microbiota interactions. (4) Limited knowledge of mechanisms: Although there is evidence of drug-microbiota interactions, the mechanisms remain unclear. It is unknown how

interactions change across medications and people. (5) Therapeutic translation: While pharmacomicrobiomics has intriguing therapeutic applications, several challenges must be addressed before it can be implemented in practice. Developing microbiota-based biomarkers for treatment response requires extensive validation research and regulatory approval. (6) Ethical issues: Personalised medicine, including the use of microbiome data, requires ethical considerations. Concerns include privacy, data sharing, and potential discrimination based on microbial traits. (7) Small sample numbers in pharmacomicrobiomics investigations might impair statistical power and generalizability of findings. More extensive research is needed to validate and build on preliminary findings. (8) Population diversity: Pharmacomicrobiomics research has mostly focused on Western populations, resulting in a lack of variation in ethnicity, location, and lifestyle characteristics. This reduces our understanding of how drug-microbiota interactions may differ between communities. (9) Confounding variables: Diet, age, gender, and environmental exposures might affect gut flora, making it difficult to discriminate between medication effects and other factors. To address these challenges, researchers, clinicians, and industry partners should collaborate to develop standardised methodologies, improve understanding of drug-microbiota interactions, and translate findings into safe and effective clinical practice.

3. Conclusion

The complex relationship between drugs and the microbiota has a significant impact on the toxicity. Drugs have the potential to change the makeup and function of microbes, which could lead to toxicity because of increased risk factors brought on by dysbiosis in the gut; however, the microbiome also produces enzymes and metabolites that are involved in drug metabolism and host detoxification patterns, which could change the toxic effects of drugs. In addition, the microbiota influences immunological responses that can be used to mitigate drug toxicity.

To understand the relationship between the microbiome and drug toxicity systemically, the microbial components that affect drug toxicity may be linked as follows: drug, microbiome, microbial enzymes/metabolites, drug metabolites, host toxicant responses. The ultimate objective is to identify the microbial species that cause the interaction between medication toxicity and the microbiome and to use strategies to target them in order to minimise drug toxicity. Currently, pro-, pre-, and synbiotic supplementation, FMT, and dietary manipulation are the methods for reducing medication toxicity by focusing on the microbiome; none of these methods is drug-specific.

Targeting specific microbial species, enzymes, or metabolites can improve drug toxicity, as seen in the successful manipulation of levodopa's peripheral toxicity by targeting a microbial enzyme. To do this, though, we must completely understand the microbial drug metabolism pathways and the processes behind drug toxicity. We can only take advantage of the microbiome's amazing potential to lessen toxicity and increase the effectiveness of medications by developing a thorough grasp of these mechanisms (**Figure 1**).

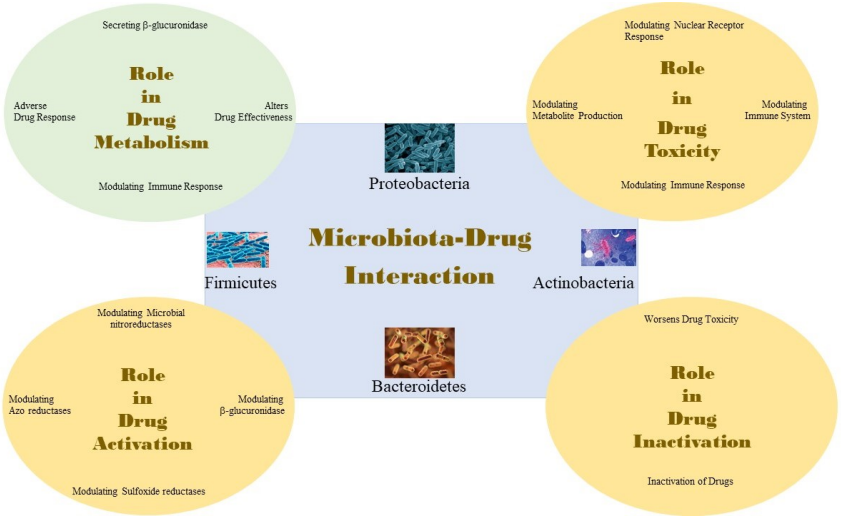

Figure 1. Drug-Microbiota interaction and role of microbiota on drug metabolism.

Precision medicine is hindered by the heterogeneity of the human microbiota, the rise of multi-drug-resistant bacteria, and the impact of various medications on microbial pathways. Nonetheless, precision medicine remains the perfect possibility for future theranostics, with a complete understanding of the role of the microbiota on IVDR permitting stratification of patients based on recognised biomarkers, microbiota types, and metabotypes.

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