Impact of Gut Microbiota Alterations on ADRs in Adult Patients: Clinical Implications, Challenges, Drug Metabolism and Future Directions

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Abstracts

The human gut microbiota is a highly complex and dynamic ecosystem of microorganisms that have been implicated to play an important role in the metabolism of drugs and the causation of ADRs. This review provides an overview of the intricate interactions between gut microbiota and ADRs, focusing on microbial enzymatic activity and biotransformation, their influence on the efficacy and toxicity of drugs. These include altered drug metabolism, systemic toxicity, and susceptibility to increased adverse drug reactions identified as being brought about by dysbiosis; that is, an imbalance of the microbial community. Of course, dieting habits, as well as the incidence of chronic diseases, were significant factors modifying gut microbiota's composition and function, accounting for the drug response differences. The composition of the microbiota profoundly influences pharmacokinetics, defined as absorption, distribution, metabolism, and excretion (ADME), hence its consideration in pharmacotherapy. Pharmacomicrobiomics now provides promising approaches for tailoring drug therapy with the aim of maximizing safety and efficacy in personalized medicine, thus leading to better

outcomes of therapy without burdening healthcare systems by ADRs. This review, therefore, highlights the potential of gut microbiota research in transforming drug development and clinical practice by leveraging advancements in microbiota profiling and multi-omics approaches.

1. Introduction

WHO has described adverse drug reactions as responses to a drug that are noxious and unintended, and occur at doses used in the prophylaxis, diagnosis, or therapy of a disease, or for the modification of physiological function (Chan, 2019). There are cutaneous reactions along with many others that are comprised of adverse drug reactions, making a huge difference for patients in regard to quality of life and outcomes in health. ADRs have a broad clinical spectrum and, more importantly, skin is the main target organ, clearly manifesting how complex and diverse these reactions could be (Chan, 2019). It is, therefore, important to highlight the impact on adult patients with ADRs as it leads to morbidity, mortality, and added healthcare costs. ADR prevalence in adult patients is very high. Research shows that ADRs are a cause of very significant percentages of hospital admissions, with an estimated level of around 6.5% of admission through ADR (Suyagh et al., 2015). This will reflect the call to monitor and report ADR with vigilance as a measure to improve the level of patient safety and therapeutic performance.

Another reason is that the cost burden of ADRs is high, and the cost of drug-related admissions in the UK is estimated to be about £466 million a year (Suyagh et al., 2015). This also explains the economic aspect as well for pharmacovigilance and ADR management in the health care systems. Physiological changes in old age enhance the risk of ADRs. The number of drug interactions is amplified because of several prescriptions that one is given, and thus exposure to potentially inappropriate medications increases one's likelihood of experiencing ADRs. Physiological changes such as altered body composition, decreased renal clearance, and decreased creatinine clearance all add up to cause the accumulation of drug metabolites and increase the likelihood of adverse effects (López-Cruz, 2023). Such adverse drug reactions in the elderly population lead to severe morbidity, including acute hospitalizations and emergency room visits, which further strains healthcare resources (Marengoni et al., 2014).

The types of ADRs that affect the patients are wide-ranging; however, cutaneous adverse drug reactions (CADRs) are a common manifestation. A systematic review of CADRs in the Indian population showed that about 11.39% required hospitalization; serious complications were altered liver functions and septicemia, that occurred in an appreciable proportion of patients (Patel et al., 2014). The mortality rates associated with severe CADRs, such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), are alarmingly high, emphasizing the critical need for early recognition and management of these reactions (Patel et al., 2014). Interaction between drug-drug interactions and ADRs is also another concern, which is very much relevant in cases of polypharmacy among elderly patients. Literature has revealed that ADRs due to drug-drug interaction can lead to serious outcomes such as rehospitalization due to complications like orthostatic hypotension and sedation (Colombo et al., 2018). In managing

multiple drugs, there should be a more profound understanding of pharmacokinetics and pharmacodynamics to reduce risks associated with ADRs (Marengoni et al., 2014).

Incidences in pediatric populations also form a significant challenge. It has been observed through different research studies that the incidence of ADRs may even be the same among pediatric patients as among adults, and the incidence can go up to 36.5% in some treatment settings (Kobayashi et al., 2015). Thus, it also accentuates the monitoring and reporting of ADRs in all age groups because the implications of ADRs for the safety of patients and efficacies of various treatments can run deep. Healthcare professionals, including pharmacists, are responsible for the monitoring and reporting of ADRs. As experts in this field, they can identify the potential ADRs and act accordingly to prevent such events and improve patient safety (Suyagh et al., 2015). They play a very important role in the activities of pharmacovigilance regarding the early identification of ADRs and devising strategies for their prevention.

The gut microbiota is essentially a highly complex and heterogeneous community of microbes. It has been comprehensively described as playing a prominent role in human health and in the metabolism of drugs. A microbial system as such accommodates trillions of bacteria, viruses, fungi, and archaea to serve several crucial metabolic, immunological, and nutritional functions required to maintain the well-being of the host (Petakh et al., 2023). All physiological functions, for instance, the metabolism of the drugs themselves and even digestion and immune response, are influenced by the gut microbiota composition and diversity (Doestzada et al., 2018). One of the major roles that the gut microbiota plays in the metabolism of dietary components and drugs is evident. The gut microbiota is associated with fermentation of indigestible carbohydrates. SCFAs, such as butyrate, have been shown to benefit gut health and systemic inflammation, according to research by Dinakis et al., 2021. The gut microbiota can also influence the bioavailability and efficacy of drugs through its transformation into active or inactive metabolites (Whang et al., 2019). Certain microbial enzymes, for example, activate prodrugs or inactivate drugs and therefore alter the outcome of drug therapy (Whang et al., 2019). This interaction between microbiota and drugs is a new science field known as pharmacomicrobiomics, in which the authors determine the degree to which individual variations in gut microbiota can modify drug response and toxicity (Doestzada et al., 2018).

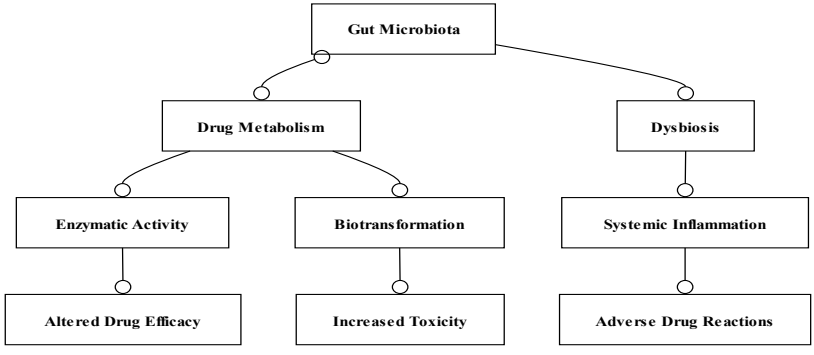

Figure 1. This image depicts the relationship between gut microbiota, drug metabolism, and adverse drug reactions (ADRs).

The gut microbiome is concerned not only with the metabolism of drugs but also with the host's health. Evidence depict that this imbalance in gut microbiota known as dysbiosis is linked to multiple diseases, including obesity, inflammatory bowel disease, and metabolic diseases (Chu & Zhang, 2022). For instance, studies did depict the fact that some form of imbalance in gut microbiota is related to obesity due to the impact various microbial profiles could have on the metabolism of energy and storage of fats. Other key roles are that of gut microbiota, essential for the development and regulation of the immune system, and specifically in certain bacterial populations, for tolerance to immunity and prevention of autoimmunity (Agans et al., 2011).

Maybe the greatest link between gut microbiota and drug metabolism can be seen in the use of antibiotics. Antibiotic therapy is known to alter the gut microbiota, which subsequently decreases the microbial diversity and increases the load of pathogenic bacteria such as Clostridium difficile (Imhann et al., 2015). This may lead to harmful effects like antibiotic-associated diarrhea. It might also affect the metabolism of the drugs being co-administered, causing therapeutic failure or increasing their toxicity (Yoo et al., 2014). For example, the metabolism of a cholesterol-lowering drug, lovastatin, is completely changed by the action of certain gut bacteria and shows how delicate interactions exist between drugs and the microbiome (Yoo et al., 2014). It therefore suggests that gut microbiota influence drug metabolism, thus forming the basis of personalized medicine. Differences in human compositions can lead to differences in efficacy as well as side reactions to drugs amongst patients (Doestzada et al., 2018). This interaction will, therefore, help clinicians tailor drug therapy according to a patient's microbe profile and thereby improve response to treatment while at the same time reducing the side effects of treatment as well (Doestzada et al., 2018).

Furthermore, the recent studies have shown that the gut microbiota is also implicated in the modification of drug efficacy as well as their reduction in toxicity. A balanced gut microbiota can be achieved through different probiotics, prebiotics, and dietetic interventions that may provide a new avenue for the optimization of pharmacotherapy (Petakh et al., 2023). The gut is a complex system of microorganisms that plays an important role in the metabolism of drugs and other xenobiotics. Interference in the microbial community composition of this can bring about changes in the metabolic pathways processing medication, leading to enhanced toxicity or lessened therapeutic effect Meng et al. (2017) Zimmermann-Kogadeeva et al., 2019). Dysbiosis in ADR

The most important role of dysbiosis in ADRs is through its effect on drug metabolism. The gut microbiota can metabolize drugs before their absorption into the blood, which alters their pharmacokinetic properties. For instance, some gut bacteria have enzymes that alter the chemical structure of drugs; these enzymes may activate prodrugs or inactivate active drugs, which leads to unpredictable therapeutic outcomes (Li, 2024; Sharma et al., 2017). This microbial metabolism also yields toxic metabolites that could add up to ADRs occurrence. It is crucial to know the function of the gut microbiome in the metabolism of drugs (Zimmermann-Kogadeeva et al., 2019; Rekdal et al., 2019). Changes in drug absorption and efficacy occur when a set of distinct gut microbiota modifications occur.

Table 1: Summary of gut microbiota's role in drug metabolism and ADR's.

Topic	Key Insights	Citations
Role of Gut Microbiota	Microbiota modulates drug metabolism via enzymatic activity and biotransformation.	Doestzada et al. (2018); Zemanová et al. (2021)
Dysbiosis and ADRs	Dysbiosis leads to altered drug metabolism and increased systemic toxicity.	Zimmermann-Kogadeeva et al. (2019); Yuan et al. (2023)
Antibiotics and Microbiota	Antibiotics disrupt microbial balance, affecting drug efficacy and toxicity.	Imhann et al. (2015); Yoo et al. (2014)
Pharmacokinetics Impact	Gut microbiota influences ADME (absorption, distribution, metabolism, excretion) processes.	Bai et al. (2022); Li (2024)
Personalized Medicine	Individual microbiota profiles enable tailored pharmacotherapy, reducing ADRs.	Kim (2023); Doestzada et al. (2018)

For instance, antibiotics disrupt the balance in the gut flora by reducing its diversity, an effect that would in turn influence drug metabolism that the patient is simultaneously receiving (Yuan et al., 2023; Huang et al., 2020). Disruptions may further increase the chances of ADRs because, in most drugs, the microflora are less efficient to metabolize or degrade them, so the systemic levels of the drug in the body are increased while the risk for toxicity is greater as well (Yuan et al., 2023). This action is further compounded by the formation of toxic metabolites from pathogenic bacteria within a diseased gut environment (Yuan et al., 2023; Huang et al., 2020). Besides, dysbiosis can also affect the necessary immune system responsible for the response of the body to drugs. Systemic inflammation and immune dysregulation, because of imbalanced gut microbiota, can result in hypersensitivity reactions to drugs, making it more susceptible (Chu & Zhang, 2022; Makizaki et al., 2020). For instance, some gut microbial profiles have been found to be associated with enhanced inflammatory responses that further increase the severity of ADRs, especially in immunomodulatory therapies used among patients (Chu & Zhang, 2022; Makizaki et al., 2020). This association between gut health and immune functions is the reason to maintain balanced microbiota so that one may reduce the risk of ADRs.

More specifically, certain drugs have been known to alter the gut microbiota and thus cause side effects. An example is metformin, which is one of the drugs often used to manage type 2 diabetes; this drug is associated with gastrointestinal side effects such as diarrhea and bloating, and it has something to do with its alteration of gut microbial composition (Makizaki et al., 2020). These studies have been shown to cause changes in the gut microbiota induced by metformin, promoting proliferation of specific groups of microbes believed to be responsible for such adverse effects (Makizaki et al., 2020). Such a drug shows how an activity in drug action impacts microbiomes and can create negative responses. It complicates further with the gut-lung axis, where the disturbance of dysbiosis can result in a disorder that may start in the gastrointestinal tract but spreads systemically into the lungs as well, in addition to gastrointestinal health (Han, 2024).

2. Gut Microbiota and Drug Metabolism

The gut microbiota plays crucial roles in the metabolism of drugs through various mechanisms, such as enzymatic activity, biotransformation, and alteration of host metabolic pathways. This complexity in gut microbiota and pharmacokinetic interaction therefore calls for an understanding of changes in the microbiota and their implications on drug efficacy and safety. Among the mechanisms of the gut microbiota is its enzymatic activity. A great number of gut bacteria carry numerous enzymes capable of metabolizing drugs by activating or inactivating pharmacologically active compounds. For example, some enzymes present in the gut bacteria modify the structure of drugs directly; thereby, its bioavailability and its therapeutic effect change (Zemanová et al., 2021). The gut microbiome significantly affects the pharmacokinetics of drugs like metronidazole through the control of the liver's transcription process for cytochrome P450 enzymes, involved in the biotransformation of drugs. As reported by Zemanová et al., 2021, it is clearly demonstrated that there is a microbiota in the gut that also plays a part in modifying the metabolic pathways of how drugs can work.

Besides, gut microbiota indirectly determines drug metabolism in its action because the gut controls the expression of the host's enzymes, which would otherwise participate in the drug's metabolism. For example, it has been proven that gut microbes govern the activity of cytochrome P450, and this class of enzymes has been reported to take a paramount position in metabolizing most drugs (Barretto et al., 2021). For example, the drug nifedipine was found to upregulate the activity of one of the most potent drug-metabolizing enzymes catalyzed by gut microbiota, which is CYP3A1. This, in turn, would significantly affect the pharmacokinetic profile of the drug as depicted by a pharmacokinetic study carried out on nifedipine (Zhou et al., 2023). Such effects elucidate the microbial populations and how they dictate the host's metabolic phenotype leading to differences in the response of the drug. Another way by which gut microbiota impacts the metabolism of drugs is biotransformation. It simply means that drugs are transformed in the gut to become either active or inactive metabolites and, in this manner, alter the actionability of these drugs. The gut microbiota of rats changes the biotransformation of prebiotics so that their bioavailability is enhanced and that of ginsenosides increased as well (Zhang et al., 2021). This means that dietary interventions targeting the optimization of gut microbiota composition may be a promising approach to increasing drug efficacy and safety.

Although this is the case, the role of gut microbiota in drug metabolism extends beyond direct enzymatic activities to include the modulation of systemic metabolic pathways. The PXR, for example is a nuclear receptor modulating gene expression for drug metabolism. It is modulated by the composition of gut microbiota (Barretto et al., 2021). Such a receptor is vital in detoxification of the xenobiotic. Activation through the microbial metabolite may affect the metabolism and distribution of drugs. In this way, relationships between host, microbiota, and drugs are manifested in pharmacotherapy practices. Gut microbiota modulates the kinetics of many drugs, which includes acetaminophen. The study by Kim et al. in 2018 showed that gut microbiota influences the absorption and metabolism of acetaminophen because gut bacteria produce specific enzymes for its biotransformation. Altered pharmacokinetics occurring in antibiotic-treated subjects altered the gut microbiota composition and were associated with differences in drug efficacy and toxicity, as the study by Kim et al. in 2018 demonstrated. Such

findings may indicate that gut microbiota is involved in interindividual variability in response to drugs.

In addition to modifying pharmacokinetics, gut microbiota can also be implicated in modifying the pharmacodynamics of drugs. Metabolic products from gut bacteria can interlude with the drug targets, which may lead to enhance or reduce drug action. As mentioned previously, the products of microbial metabolisms might further influence the activation/deactivation of enzyme or receptors correlated with drug effect, thus determining the outcome (Han et al., 2022). Another newer area of studies that might unearth how drug treatments can be perfected is the interconnectedness of the microbial metabolism of drugs. The implications of gut microbiota in drug metabolism, therefore, take on relevance to the personalized medicine perspective. Individual variability in gut microbiota can result in varying drug metabolism and response, thus requiring consideration for such factors while designing treatment regimens (Zhang et al., 2021; Kim, 2023).

Altered gut microbiota has a significant influence on pharmacokinetics, including the ADME processes of drug absorption, distribution, metabolism, and excretion. Gut microbiota is an integrated community of microorganisms dwelling in the gastrointestinal tract. These microorganisms contribute critically to modifying these pharmacokinetic processes by diverse mechanisms like enzymatic activity, biotransformation, and interactions with host metabolic pathways.

Absorption is the first step of pharmacokinetics and is also one of the actions through which gut microbiota may affect the absorption by modifying the chemical structure and polarity of drugs. Gut bacteria might transform the drug into an absorbed form or adjust its solubility, favoring or impairing the process of its absorption in the intestine (Li, 2024). Some microbial community strains have been known to determine the bioavailability of the drug since the metabolites alter the gut environment either by facilitating or inhibiting the absorption of the drug (Li, 2024). For instance, probiotics have been found to increase the absorption of the drug lovastatin because they alter the colonic environment that results in altering the pharmacokinetic profile of the drug (Li, 2024).

Another area influenced is drug distribution due to gut microbiota. Modulation changes the expression of transport proteins in the intestinal epithelium that takes up and translocate the majority of the drugs across the system (Guo et al., 2021). Since alteration will change availability due to changed modulation of the transport proteins within the gut epithelial lining, alteration at the target tissue will also take place (Guo et al., 2021). Interaction underlines the function of gut microbiota in pharmacokinetic study as microbial composition could significantly change the levels of drug distribution between subjects. Metabolism is another pharmacokinetics, and this pharmacokinetic is largely affected by gut microbiota. The possibility of direct metabolism of drugs by gut microbiota into active or inactive metabolites exists. For example, glycyrrhizic acid is one of the constituents in the traditional Kampo medication; it is bio transformed by the gut microbiota to its active compound (Ishida et al., 2022). Also, the activities of liver cytochrome P450 are highly impacted by gut microbiota, which play a vital role in drug metabolism (Bai et al., 2022). Dysbiosis, an imbalance of gut microbiota, has

resulted in an altered CYP450 activity leading to changed drug metabolism and occurring potential adverse drug reactions (Bai et al., 2022). This interaction requires the consideration of gut microbiota composition in individual responses to pharmacotherapy.

Gut microbiota is involved in the excretion of drugs and their metabolites. It has been suggested that 30% of uric acid is eliminated through the gut, and the gut microbiota can synthesize enzymes that will facilitate excretion (Sun et al., 2022). Dysbiosis may disturb some drugs or metabolites from the gut to exert higher systemic exposure leading to toxicity (Sun et al., 2022). Besides, the gut microbiota also participates in the excretion of heavy metals and other xenobiotics. Modifications of the gut microbial population are proven to influence the detoxification pathway (Fang et al., 2022; Liao et al., 2023). This means that the health of gut microbiota determines the excretion of drugs properly and prevents accumulation and toxicity by drugs. In addition, gut microbiota and pharmacokinetics are the most important areas in personalized medicine. The variations in gut microbiota composition among individuals may result in differences in drug metabolism and response, and it is therefore important to consider such factors in the planning of treatments (Guo et al., 2021).

3. Gut Microbiota Alterations

Alteration of gut microbiota, or dysbiosis, can be caused by various factors: antibiotic utilization, dietary change, chronic disease, and environmental influences. The understanding of these reasons is significant in furthering the explanation of the alterations in gut microbiota implications on human health. Probably the most documented cause for alteration in gut microbiota is the use of antibiotics. For example, antimicrobials diminish the balance of the microbiota. The well microbes dominate when the balance of microbiota decreases. So also, the pathogenic microbes: e.g., Zhang et al. 2013, Chen et al., 2023This may cause reduction of microbial diversity that has long been associated with undesirable health results including increased gut permeability as well as increased inflammation (Chen et al., 2023). For example, an imbalance in the ratio of Akkermansiaceae/Lachnospiraceae has been known to be a microbial indicator of antibiotic-induced dysbiosis and may considerably impact gut health and metabolic disorders (Chen et al., 2023). In addition to that, it is affected by the mode of administration of antibiotics because it dictates the shifts in levels of antibiotic resistance in gut microbiota that is further determined by the impacts of dysbiosis (Zhang et al., 2013).

The diet is the most important factor that describes the gut microbiota. The type and function are very dependent on intake patterns, including dietary fiber, fat, and protein, according to Yao et al., 2023; Morrison et al., 2019. A high-fat diet was found to stimulate the overgrowth of certain Clostridia and Proteobacteria at the expense of beneficial taxa (Morrison et al., 2019). On the other hand, high-fiber diets encourage higher populations of known SCFAs-producing commensal bacteria that are crucial to the balance of the health of the intestine (Yao et al., 2023). This elasticity of the microbiota concerning the shifts in the diets shows how food influences microbial ecologies and how such an alteration is relevant in determining the relevant health impacts, such as reduced risks of many diseases brought about by eating patterns.

Some examples of chronic diseases often having alterations in gut microbiota include IBD, obesity, and diabetes. IBD has dysbiosis, microbial alteration in composition, which is the hallmark of IBD, as microbial profiles were shown to correlate with inflammation and severity (Zákostelská et al., 2016). There was observed an association of chronic pancreatitis pathogenesis with dysbiotic gut microbiota. It implies that the disease itself might deeply affect the microbial composition (Wang et al., 2021). The other one is that early life exposure to antibiotics has been associated with greater risks of later-life metabolic disorders, thereby hinting that chronic health conditions could arise from earlier changes in the gut microbiota (Li et al., 2017). The type of probiotics and prebiotics can seem to interfere in some way in a treatment approach to change the gut microbiota. After each therapy of any antibiotics, the probiotics facilitate maintaining the microbes in a balance as this is viewed as under restraint, and absolute dependence can be detrimental to the process of restorations along with deteriorating the healing status of intestinal microbiota when one is trying to regain normalcy (Chen et al., 2023). It results in a favorable gut environment since it increases the rate of good flora growth. Effects tend to differ through each individual in accordance with how different their microbes may be structured (Yao et al., 2023).

The identification of gut microbiota change is essential for the study of various health conditions and their pathways. Various biomarkers have been suggested to evaluate the type of alteration that occurs, from specific taxa of microbes to the metabolic by-products themselves. The following is an attempt at highlighting common biomarkers used for identification purposes with the help of recent findings. Microbial Taxa The most straightforward approach to indicating changes in gut microbiota is through the existence of microbial taxa. Several bacteria have been isolated and identified as markers for certain diseases. In the case of stroke recovery, it has been determined that some bacteria can be considered as markers between the disease condition and functional recovery Dang et al. (2021).

Metabolomics is another advanced technique that can be employed to determine alteration in gut microbiota. It is validated by establishing the products of gut microorganisms through their metabolic activity to understand the impacts of microbes on the host metabolism. For instance, urinary and fecal metabolomics was used during the study into whether the traditional Chinese herbal medicine protects against antibiotic-induced dysbiosis; it is possible by such a methodology to identify some pivotal metabolic pathways which might end up being related to gut microbiota alterations. In fact, it is theoretically possible through such a methodology that one can possibly identify some such metabolites to act as possible biomarkers for dysbiosis and other associated disorders (Meng et al., 2017). Of all the methods that have been applied to describe the composition of gut microbiota, probably the most widely used one at present is that based on 16S ribosomal RNA (rRNA) gene sequencing. Using this method, it becomes possible to identify bacteria species within the sample and to discover shifts in microbial diversity associated with dysbiosis. For example, an overabundance of particular genera such as Fusobacterium is linked with inflammation in the gut and is considered a biomarker for the early diagnosis of inflammatory bowel disease (Bao et al., 2022). The 16S rRNA sequencing-based profiling of gut microbiome contains high information on the structure of microbial communities and possible health outcomes.

Functional metagenomics Further identification of the microbial taxonomic would reveal the functional capacity of gut microbiota through functional metagenomics. This is concerned with the genetic potential of microbial communities for specific metabolic functions. For example, recently, through metagenomic analysis, gene clusters that are indicative of dietary constituent and drugs' metabolisms have been determined; thus, some insight into the functional state of the gut microbiome and how it is altered in different diseases has been derived (Zhang et al., 2020). Such functional biomarkers are highly likely to prove very important to determine how these perturbations of gut microbiota impact the host health and disease. The inflammation biomarkers also originate from the interference of gut microbiota that triggers systemic inflammation; therefore, an alteration in gut microbiota may cause an increase in pro-inflammatory cytokines. This might be markers for dysbiosis and the general impact it poses (Petakh, 2024). It will give some information regarding gut microbiota disturbances and its associated inflammatory conditions.

The recent development in machine learning has recently proved useful in generating predictive models that depend on gut microbiota composition. An example is the use of a random forest approach for machine learning in a study on colorectal cancer, which stratified pre-treatment and post-treatment microbiota profiles for potential biomarkers for the risk of recurrence (Liu et al., 2018). Such computational approaches will further advance our ability to identify and confirm potential biomarkers related to gut microbiota shifts. Lastly, the clinical setting in which changes in gut microbiota are manifest can itself act as a biomarker. In patients with chronic pancreatitis, certain microbial signatures were demonstrated to correlate with the degree of severity and the effectiveness of therapy; this has indicated that the gut microbiota profile might represent a potential prognostic biomarker (Wang et al., 2021).

4. Link Between Gut Microbiota and ADRs

There is growing evidence in the literature that links alterations in gut microbiota to adverse drug reactions (ADRs) in adult patients. Several studies have shown how changes in gut microbiota composition and function can influence drug metabolism, efficacy, and toxicity, which has significant clinical implications. One of the major ways through which alterations in gut microbiota contribute to ADRs is through their effects on drug metabolism. Vila et al. pointed that widely prescribed medications, such as proton pump inhibitors and metformin, disrupt the gut microbiota composition as well as its metabolic functions. Thereafter, these altered microbiotas also impact health conditions and drug activity, thus having a direct causative relationship of ADRs with microbiota changes Vila et al. (2020). The study puts more emphasis on the understanding of how drug-induced changes in gut microbiota may lead to adverse effects, especially in patients with pre-existing gastrointestinal conditions.

Specifically, certain gut bacteria have been reported to modulate the therapeutic effects of drugs. Zhou et al. demonstrated that Bacteroides fragilis is involved in the efficacy of methotrexate (MTX) for treating arthritis by regulating metabolites that can alleviate drug toxicity. This research identified the possibility that mucositis resulting from MTX administration could trigger bacterial translocation, thereby making it even more complex and may cause ADRs as

well (Zhou et al., 2022). Thus, it reveals the impact of the gut microbiota on drug pharmacodynamics as well as the induction of side effects. Aside from the direct effects of the microbiota-bacterial interaction, the overall profile of the gut microbiota influences drug absorption and bioavailability. Research by Li indicated that gut microbiota could alter the chemical structure and polarity of drugs, impacting their absorption and efficacy. This modification can result in enhanced toxicity or diminished therapeutic efficacy, thus clearly linking microbiota composition with ADRs (Li, 2024). These results highlight the importance of taking gut microbiota into account in pharmacotherapy.

Zhou et al. further investigated the interaction between gut microbiota and drug-induced gastrointestinal toxicity. They found that homeostasis of gut microbiota is essential for the maintenance of health in the intestines and the regulation of drug metabolism. Dysfunction in gut microbiota led to changed drug responses like ineffectiveness of the treatment and ADRs. Their study explored MTX-induced intestinal toxicity and provided an example by illustrating the immune response as well as disruption of gut microbiota (Zhou et al., 2018). This therefore indicates that it is necessary to monitor gut microbiota for forecasting and management of ADRs among patients undergoing treatments with drugs like MTX. Other studies to support the involvement of gut microbiota in the metabolism of drugs include Bai et al. whose research proved that gut microbiota can control the expression of cytochrome P450 enzymes, an element critical for the metabolism of drugs. Their study proved that the alterations of gut microbiota would impact drug efficacy and toxicity, thus firmly linking the changes in microbiota to ADRs, as explained by Bai et al. (2022). This has possible implications of using microbiota-targeted interventions to reduce ADRs occasioned by individual drugs.

Weersma et al. highlighted the drug-gut microbiome interactions by discussing how most non-antibiotic drugs are known to alter the composition and function of the microbiome, which, in turn, impacts health outcomes and drug efficacy, thus establishing a role for pharmacomicrobiomics in explaining ADRs (Weersma et al., 2020). It is also discussed in the review that the gut microbiome enzymatically transforms drugs to change their bioavailability and toxicity, and that is very essential for clinicians when prescribing medications. Additionally, Sun et al. researched gut microbiota involvement in the mechanisms of liver injury caused by antithyroid drugs. In this regard, they identified a correlation between gut microbiota changes and higher risks of liver injury. Their conclusions support the concept that gut microbiota could mediate adverse drug reactions through pathways associated with lipopolysaccharide-related signaling (Sun et al., 2020). This research adds to the overall body of evidence linking ADRs with gut microbiota changes, particularly those related to drug-induced liver toxicity. Lastly, Zimmermann et al. noted that it is essential to know how gut microbiota can influence drug metabolism and systemic exposure to drugs and their metabolites. Their study showed that microbiome drug metabolism may significantly influence the efficacy and toxicity of drugs, which calls for further research in this area (Zimmermann et al., 2019). This means that interventions aimed at modulating gut microbiota could improve drug safety and efficacy.

5. Clinical Implications

One of the key areas of research is gut microbiota in drug metabolism and its implication in personalized medicine. Yip and Chan presented a discussion on how gut microbiota manipulation via probiotics, prebiotics, and fecal transplantation could be used to alleviate drug-induced gastrointestinal toxicity, especially in chemotherapeutic agents such as irinotecan Yip & Chan (2015). This may suggest that personalized interventions targeting the gut microbiome can strengthen the therapeutic impact while reducing the ADRs. In addition, the pharmacomicrobiomics science has been acknowledged. It is focused on the relationship between gut microbiota and the drug response. Ting et al. argued that gut microbiota can indeed influence pharmacokinetics, the way drugs are absorbed, distributed, metabolized, and eliminated; and pharmacodynamics, which refers to the sensitivities of differing pharmacological effects (Ting et al., 2022). Such understanding will thus enable clinicians to individualize drug therapy based on each patient's profile of microbiomes, potentially increasing drug efficacy and safety.

Other studies that have been supportive of the use of gut microbiota data in precision medicine are those by Feng et al. They indicated that the manipulation of gut microbiota could be tailored to enhance drug responses and reduce side effects, thereby improving the outcome of treatment (Feng et al., 2020). This is based on the identification of specific biomarkers associated with changes in gut microbiota, which may guide the decision-making process. In the domain of chronic diseases, according to Nunes, integration of multi-omics approaches, like metagenomics and metabolomics, can give an all-encompassing understanding of the gut microbiota-disease axis in T2DM (NUNES, 2024). This may further open avenues for individualized therapy based on interventions in the gut microbiota, thereby promoting the safety and efficacy of drugs in the treatment of chronic diseases.

Furthermore, Cheemala's review also pointed out that gut microbiota data could be used in the design of personalized nutrition and therapeutic interventions and, therefore, stressed the importance of gut microbiota in gastrointestinal and cardiovascular health (Cheemala, 2024). This would mean that personalized dietary advice based on the gut microbiota composition can supplement pharmacotherapy, thus improving treatment outcomes. Yu et al. further progressed this discussion by demonstrating that alterations in the gut microbiome can impact drug response to therapeutic interventions for the treatment of hyperuricemia (Yu et al., 2018). Such correlations can be turned toward the identification of disease remission biomarkers along with the detailed mechanisms of these drugs, therefore promoting the integration of gut microbiome data into personalized medicines. The emerging role of gut microbiota in drug safety studies was discussed by Wilson and Nicholson, who introduced that understanding the interactions between gut microbiota and drug metabolism can lead to more personalized health care approaches (Wilson & Nicholson, 2017).

6. Challenges and Limitations

The gut microbiota is a large and diverse population of microorganisms, including bacteria, archaea, viruses, and fungi. It is challenging to draw definite conclusions about the role of specific microbial species or communities in health and disease due to the complexity of the gut microbiota. Overlap of the potential biomarkers makes it difficult to interpret the data on gut microbiota, so it is believed that the effect of their combination should be considered, rather than that of a singular species, on health conditions such as autism spectrum disorder Wang & Fu (2023). The complexity demands advanced analytical approaches to characterise and better understand microbiota data. The gut microbiota composition might greatly vary from region to region, dietary factors, and environmental factors. As reported by Hu et al., it is challenging to study intrinsic factors of gut microbiota in wild animals due to interference from a number of extrinsic factors (Hu et al., 2022). The data would thus not easily allow direct comparisons between studies since regional differences may confound results and lower their generalizability.

The methodology used in the study of gut microbiota has its biases and limitations. The most applied method is 16S rRNA gene sequencing, which does not capture all the microbial diversity and function. Wang et al. noted that the uneven alteration patterns in gut microbiota may be a problem when therapeutic effects in animal models are evaluated, thus requiring caution when interpreting the results obtained from these studies (Wang et al., 2019). Besides, the choice of sequencing platform, bioinformatics tools, and statistical methods can all affect the results and their interpretation. The gut microbiota interacts with many host factors, including genetics, diet, and immune status, which makes interpretation of microbiota data even more complicated. Xu et al. discussed how interactions between gut microbiota and the mammalian nervous system sometimes result in both adaptive and dysfunctional neurological processes. In essence, changes in microbiota might not explain fully observed health effects (Xu et al., 2022). This interaction requires that research on gut microbiota be approached holistically and encompass both the microbial and the host factors. The composition of the gut microbiota is dynamic, and it keeps changing with variations in diet, medication, or exposure to the environment. Wang and Liu explain that the stochasticity of the dynamics of the gut microbiota leads to the further implication that temporal fluctuations in microbiota may even complicate time-series data analysis (Wang & Liu, 2021). The proper interpretation of microbiota data and its implications for health requires understanding the temporal dynamics.

According to Nelson et al., failure to replicate or standardize species-specific gut microbiota limits validation since such observations were observed in other studies (Nelson et al., 2012). Standardizing methodologies would thus forward advancement of the field and making such research in microbiota reliable. Ethical and practical difficulties are quite substantial when humans are taken as subjects of study concerning interventions with effects on gut microbiota. As in the example above, many questions regarding the donor selection process and screening procedure for fecal microbiota transplantation raise concerns. Thus, research to observe gut microbiota functions in both disease and healthy states may become relatively cumbersome. Such composition informs the data, although the functional implications from that are much more complicated. Health impact diversity does not seem unidirectional or predictable; diverse compositions could be potentially useful for attaining similar outcomes; and in so doing, it

reflects a situation whereby functional redundancy might have to be envisaged in those microbial communities Moeller et al., 2017.

7. Future Directions

Table 2: Key finding tool, technology and description.

Tool/Technology	Description	Key Study/Findings	Citation
Multi-Omics Approaches	Integrates genomics, transcriptomics, proteomics, and metabolomics to provide a comprehensive view of gut microbiome and host interactions.	Revealed microbial determinants impacting antidepressant treatment outcomes using plasma metabolomics.	Wang et al. (2023)
Metagenomics and 16S rRNA Sequencing	Characterizes diversity and composition of gut microbiota to explore roles in drug metabolism and ADRs.	Identified core microbiota in colorectal disease patients through 16S rRNA sequencing.	Liu et al. (2021)
Glycomic Profiling	Analyzes glycan structures produced by gut microbiota and their effects on drug metabolism and immune responses.	Highlighted changes in glycan production linked to altered gut microbiota.	Oinam et al. (2021)
AI and Machine Learning	Uses advanced models to analyze microbiome data and predict outcomes related to drug therapy.	Introduced MIST for microbial species identification and source tracking using sequencing data.	Song (2023)
Transcriptomic Analysis	Studies gene expression changes influenced by gut microbiota to identify pathways involved in ADRs.	Explored Parkinson's-associated microbiota impacts on transcriptome in Drosophila.	Liu (2023)
Environmental and Host Factor Integration	Examines environmental and host influences on gut microbiota for a holistic understanding of microbiota dynamics.	Demonstrated gut bacterial adaptations reflecting environmental influences.	Park et al. (2024)
Advanced Statistical and Bioinformatics Tools	Utilizes computational methods to analyze microbiome complexity and variability, enhancing data interpretation.	Highlighted the need for improved tools to capture microbial diversity and functional insights.	Vojinović et al. (2019)
Fecal Microbiota Transplantation (FMT)	Transfers gut microbiota from a healthy donor to restore microbiome balance and potentially optimize drug responses.	Demonstrated FMT's efficacy in restoring gut health and improving drug response in mice.	Wang (2024)

This encompasses the very vital aspect of tailoring treatment protocols in personalized medicine to the unique needs of an individual through their personal microbiome. When the clinician knows the specific gut bacteria involved in metabolizing a drug, then they can probably administer a better dose of the medication. As proposed by Cheemala, the use of the information obtained from gut microbiota might give way to targeted interventions in controlling diseases, particularly gut health Cheemala (2024). In that sense, this could decrease the likelihood of ADRs as it would be a sure correlation of the given therapies with a patient's characteristic microbiome.

Routine profiling of the microbiota in clinical practice might be meaningful for insights into a patient's health. Techniques like 16S rRNA sequencing or metagenomic analysis can thus be used in assessing the diversity and composition of gut microbiota. For example, Massara et al. proposed a study protocol for investigating gut microbiota in children by integrating growth data with diet and microbiota information (Massara et al., 2022). Such profiling may help identify dysbiosis that may be related to several diseases, and this can be diagnosed early and treatments targeted. Tracking the changes occurring in the gut microbiota due to drugs may avoid potential ADRs. Bruno et al. cited the impact of PPIs on the gut microbiota composition, causing dysbiosis and GI disorders (Bruno et al., 2019). The treatment will be improved in terms of safety by the routine change of the type of medication based on changes in the microbiota.

According to Xue et al., appropriate probiotics will be able to prevent lung infections through regulation of gut microbiota as outlined in their review on the role of gut microbiota in respiratory diseases (Xue et al., 2023). Clinicians could suggest prescribing certain probiotics or other dietary changes that benefit the gut for those on antibiotic or other categories of drugs interfering with the microbiota. The integration of gut microbiota studies in the clinical practice setting would involve education of the healthcare providers regarding the role of the microbiome in health and disease. It could center on the role of gut microbiota in drug metabolism, ADRs, and patient management generally. This should enable clinicians to take into consideration microbiota information when making their treatment decisions for patients and hopefully improve patient outcome. If researchers cooperate with clinicians, then it will become easier to apply gut microbiota research to clinic environments. Clinical trials assessing the impact of microbiota-targeted interventions on drug safety and efficacy can be used to provide strong evidence for the integration of microbiota data into routine care. For instance, studies that assess the effect of FMT on drug metabolism and ADRs will be significant in generating relevant insights to be translated into clinical applications (Zou et al., 2022).

With the help of clinical guidelines established considering considerations about gut microbiota, such practices can be standardized among various health care settings. Recommendations from guidelines based on existing evidence may probably cover profiling, monitoring, and interventions concerning microbiota. Such recommendations may contribute to establishing a basis for incorporating data related to microbiota into clinical practice and improving providers' capacity for patient care. AI and machine learning models can be applied to the analysis of microbiota data and its implications for drug safety. The technologies may be able to identify patterns or predict the outcome with the aid of microbiome profiles, thereby supporting the clinical decision-making process. For example, AI applications can screen very large datasets or look for correlations in gut microbiota composition and the ADR, thus leading a physician to take suitable action (Song, 2023).

8. Conclusion

The gut microbiota plays an important role in drug metabolism and the occurrence of ADRs; its impact on personalized medicine can potentially be great. Dysbiosis, because of antibiotic use or diet, appears to interfere with pharmacokinetics and dynamics, thereby creating an increased

tendency for ADRs. Gut microbiota can significantly modulate efficacy and toxicity of drugs through modulation of enzymatic activity and through impacts on systemic inflammatory pathways. Thus, the integration of gut microbiota profiling into clinical practice is an innovative approach towards optimizing pharmacotherapy, and so treatments are tailor-made according to the specific composition of the microbiota of the individual. With advancements in multi-omics technologies and targeted interventions in the microbiome, including probiotics and dietary modifications, drugs may be safer and more effective. Further research efforts will be made at deconstructing the interactions among gut microbiota and drugs and further advancement to the creation of more effective, predictive models about ADRs. A science bridge across current research with micro-biological content to applied healthcare practice can actually allow health care professionals in society to adopt precision medicine towards effective patient-focused intervention that helps overcome ADR and therapeutic issues associated with adverse therapy outcomes.

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Author contributions

When the first author was drafting the original manuscript, the corresponding author helped him to complete the work. Before the work is sent to a journal for publication, each author approval the final permission. Each co-author contributed to the manuscript's editing, literature collection, and table and figure creation.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

Ethical Approval

Not Applicable

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