Pharmacomicrobiomics: Influence of gut microbiota on drug and xenobiotic metabolism

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Abstract
Gut microbiota is the most diverse and complex biological ecosystem, which is estimated to consist of greater than 5 million distinct genes and 100 trillion cells which are in constant communication with the host environment. The interaction between the gut microbiota and drugs and other xenobiotic compounds is bidirectional, quite complicated, and not fully understood yet. The impact of xenobiotics from pollution, manufacturing processes or from the environment is harmful to human health at varying degrees and this needs to be recognized and addressed. The gut microbiota is capable of biotransforming/metabolizing of various drugs and xenobiotic compounds as well as altering the activity and toxicity of these substances, thereby influencing how a host responds to drugs and xenobiotics and this emerging field is known as pharmacomicrobiomics. In this review, we discussed different mechanisms of drug–gut microbiota interaction and highlighted the influence of drug-gut microbiome interactions on the clinical response in humans.

KEYWORDS
drug metabolism, gut microbiota, microbiome, pharmacomicrobiomics, xenobiotics

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1 INTRODUCTION

The gut microbiome is a very diverse and complex biological ecosystem which is estimated to consist of more than 5 million distinct genes and 100 trillion cells. The gut microbiota consists of several dominant phyla, such as Proteobacteria, Bacteroidetes, Actinobacteria, Firmicutes, Verrucomicrobia, and Fusobacteria, although the two phyla Firmicutes and Bacteroidetes make major composition. The gut microbiome has long been neglected by scientists and now become increasingly trending as several studies showed that it plays an important role in different aspects of human health. The human microbiota continuously changes throughout the lifetime of a person and reflects the health status of every individual at different stages of their life. The variations that the gut microbiota goes through can be temporary or permanent and could be caused by diet, stress, hormones, and other environmental factors.

The quest to better understand the gut microbiome, led to the conception of the human genome project and then further to the human microbiome project (HMP), which was funded by the NIH with a defined objective to evaluate specimens of over 250 healthy participants taken from various parts of the body (vagina, gastrointestinal tract, skin, and mouth) using the latest high-throughput technologies. These samples were studied to establish the extent of the microbiome's role in health and disease progression under various circumstances, and to also build a database for the scientific community that makes accessible technical approaches, latest data sources, validated techniques and new discoveries. The current phase of the HMP (Integrative Human Microbiome Project or iHMP) program focuses on understanding the function of the microbiota in selected disorders such as preterm births, inflammatory bowel disorder, type 2 diabetes, and its interaction with the host.

An individual’s gut microbiota is established pretty early in life and develops as the individual matures in age. We humans are exposed to a variety of tiny molecules that are foreign to our bodies (xenobiotics), such as dietary ingredients, environmental pollutants, and medications. The trillions of bacteria that live in our intestines (the human gut microbiota) can change the chemical structures of these chemicals, altering their half-life, bioavailability, and their biological and pharmacological effects. The pharmacokinetic properties of drugs and xenobiotics can be altered by microbial biotransformation, which is sometimes important for prodrug activation and can result in unwanted side effects or loss of efficacy.

In this review, we discuss how the gut microbiota influences drug and xenobiotics metabolism and the impact of drug-gut microbiome interactions on clinical responses.

2 THE GUT MICROBIOME AND PHARMACOMICROBIOMICS

Previously, studies on the microbiome usually carried out by cultivation methods in which various species of bacteria are obtained from different sources and analysed based on their relationship to a disease. However, in the last decade metagenomic sequencing, shotgun sequencing and whole genome sequencing have become insightful methodologies for studying the microbiome. These techniques assist in sequencing other microorganisms including protozoa, fungi and viruses, as well as provide a means to perform detailed and focused analysis of bacterial genes. Other approaches of omics such as metaproteomic and metametabolomics are being used to better understand the gut ecosystem and its role in health and diseases. In addition, another analysis known as culturoomics, a high-throughput culture technique, provides a means to further characterize strains and species individually and it has become an important method to understand the function of unique microbiome taxa in the progression and development of diseases.

This advancement of microbial genomics from culture-based to culture-independent methods has made it possible for the recognition of the molecular fingerprint of the intestinal microbiome as well understanding the association of the gut microbiome with a certain disease or altered drug response.

Pharmacomicrobiomics refers to the effect of variations in microbiome on the disposition and drug/xenobiotic response. According to Aziz 2018, the coherent study of drug-microbiome interrelationships is the simple principle of pharmacomicrobiomics. More precisely, it is the study of how drug action, temperament, effectiveness, and toxicity are affected by intra- and inter-individual microbiome alterations. The focus here is on the impact of microbiome (i.e., microbial species) differences on clinical outcomes of pharmacokinetics and pharmacodynamics of drugs and xenobiotics, rather than drug-drug interactions with specific microbes.

The composition of the gut microbiota and the presence of some species of bacteria is influenced by the use of antibiotics, internal pH, host’s diet, genetics, the presence and efficiency of digestive enzymes, and other environmental factors. The conditions of the oesophagus, mouth, liver, small intestine, large intestine, and gastrointestinal tract vary as some areas might have low pH which lead to harsh environments that limit species diversity, while other tissues have optimal pH which promotes the growth of microorganisms and maintains species diversity.

The microbiome plays a vital role in the human body’s metabolic mechanisms as well as immunological and
behavioural characteristics, and it may also influence the mechanism of drug metabolism. Since the 20th century, the effect of the intestinal microbiota on drug metabolism and efficacy has been studied and showed that the intestinal microbiota can activate, inactivate or enhance the toxicity of drugs and xenobiotics. The gut microbiota can directly influence the metabolic processes of drugs by biotransformation through various mechanisms such as hydrolytic, demethylation, deamination and reactive reactions. The gut microbiota is also capable of controlling the efficiency of several drugs by modulating the host’s metabolism and creating a competitive environment for the drug receptor (Figure 1).

3 | METABOLISM OF DRUGS BY THE GUT MICROBIOTA

The primary site of drug metabolism is the liver. Drugs are either metabolized by conjugation, reduction, oxidation, isomerization, hydrolysis, or condensation; regardless of the metabolism phases, the aim is to ensure that the drug can be easily excreted. Drug metabolism enzymes are present in several tissues, however more abundant in the liver. Most drugs are metabolized in 2 phases. In the first phase, the reactions are mainly about forming a new or modified functional via non-synthetic reactions (reduction, oxidation, or hydrolysis). The second phase reactions are mainly about conjugating with an endogenous substance in a synthetic reaction such as glucuronic acid, sulfate, or glycine. Synthetic reactions produce water-soluble metabolites that are more easily to be excreted by the kidneys via the urine and the liver via bile than those formed in reactions that are non-synthetic. However, hydrophilic compounds are converted into hydrophobic metabolites by the digestion of drugs delivered orally via the gut microbiota, enabling these substances to be absorbed from the gastrointestinal system into the blood. Majority of hydrophilic drugs which are administered orally travel from the upper intestinal tract to reach the microbiota dense lower intestinal tract to evade pancreatic and gastric juices. The gut microbiota breaks down the drugs to hydrophobic compounds, which are more effective and easily absorbed. Most common drugs which have been identified to be broken down by microbiota in the gut include digoxin, amygdalin, ginsenoside, irinotecan, genistein, lovastatin, glycyrrhizin, prontosil, simvastatin, and baicaline. Antibiotic drugs have the most effect on the gut microbiota. It has been seen that most antibiotics can affect the gut microbiota diversity as well as reduce the gut microbiota enzyme function for up to 3 days or more depending on the duration and dosage of antibiotic drugs taken.

Most available studies on gut microbiota–drug interactions omit the variations in an individual’s microbiome profile. The diversity, however, are the rationale of pharmacomicrobiomics and the data have become more straightforward and accessible after the establishment of the HMP which provides valuable information on the gut microbiota - drug interactions.

FIGURE 1 Illustration of the influence of gut microbiota on drug and xenobiotic metabolism
Classifying the fingerprints of different microbial populations among patients in terms of their metabolic impact on drugs is responsible for implementing diagnostic indicators that enable treatment regimens to be unique to the available gut microbiota of a patient. These specific treatment regimens, help to update and improve the current treatment strategies that are traditional and which rely on outdated pharmacokinetic and pathologic parameters.25,26

The major concern before administering a drug should be the capability of the drug to alter the host’s gut microbiota status. The effects of antibiotics on the gut microbiota have been studied by various researchers, and it is agreed that gut microbiota dysbiosis caused by antibiotics modulate the immune homeostasis of the host negatively and increase the risk of an individual to catch various bacterial or fungal infections.27 Drugs that are non-antibiotic also affect the gut microbiota as seen in a study which tested several drugs on 1135 participants in a Dutch population cohort. It was discovered that 19 medications influenced the gut microbiota by modifying the microbiome makeup, with strong and significant declines in two Bifidobacterium species (Actinobacteria phylum) and an increased in Escherichia coli.28 In another study done in a cohort of Flemish people, (FGFP cohort) it was reported that almost 10 percent of the observed changes in the gut flora identified as a result of the use of medication.29 The various drugs pointed out by studies were regular medications prescribed for management of common disorders such as type 2 diabetes, heartburn, depression, stomach acid reflux, and heart diseases. The common oral drug identified in these studies is metformin, which helps control blood sugar and used in the treatment of type 2 diabetes. Although the exact mechanism of metformin action is not fully understood, some studies have shown that it inhibits gluconeogenesis in the liver and that its positive influences are promoted by the intestinal microbiota.30,31 The use of metformin in treating diabetes was seen to promote the abundance of bacteria that produce butyrate and degrade mucin such as Akkermansia muciniphila. In a study, faecal samples were obtained from humans treated with metformin and then the faecal materials were transplanted into germ-free mice. This caused the mice to have improved glucose tolerance compared with the mice group that received placebo.32,33 The effect of metformin on the gut microbiota shows how drugs can alter the gut microbiota easily and should be controlled and not administered carelessly.

The earliest records of drug bioactivation by the microbiome was made in the 1930s about the antibiotic drug called prontosil which is a bacterial-specific antibiotic. It was found that although prontosil was inactive in vitro against Streptococci, it actively treated Streptococci infections when administered in mice. This led to the discovery that the active ingredient against bacteria was the azo-reduced metabolite of prontosil known as P-aminobenzenesulfonamide (PABA). Since prontosil was broken down when administered intravenously, it was suggested that the gut microbiota was responsible for the biotransformation of prontosil to PABA in the colon.34,35

Proton pump inhibitors (PPIs) are one of the most commonly used drugs around the world. They are used to treat gastrointestinal reflux problems, ulcers, and other acid-related disorders. PPIs blocks gastric acid secretion, which causes the alteration of the microbiota throughout the gastrointestinal tract and leads to the colonization of the gut by oral microbes due to compromised stomach barrier function which cause changes in taxonomic homeostasis. Different studies have evaluated the impact of PPIs on the gut microbiota and in vitro studies suggest that the use of PPIs directly affect the bacterial growth rates and put the individual at risk of contracting enteric infections such as Clostridium difficile.36–38 In Malaysia, PPIs are the commonly prescribed to both outpatient and inpatient individuals and omeprazole is part of the top-ranking drugs among the 40 most used drugs in the medical settings of Malaysia, followed by esomeprazole.39 Another study conducted in Singapore, which involved 477 inpatients showed that there was overuse of PPIs in the study group and according to the FDA recommendations, less than 50% of patients were prescribed PPIs.40 Although the risk of adverse drug reaction when using PPIs are low, individuals need to check with their healthcare provider if they need PPIs or not before they use it and tighter controls on the sale of PPIs over the counter need to be established worldwide.

Digoxin is a drug used in treatment of chronic heart failure. The gut microbiota plays a role in metabolizing digoxin as the gut microbiome can reduce the lactone ring of digoxin hence converting it into its inactive metabolite known as dihydroadigoxin.41 The gut microbiota reduces the effects of digoxin by poorly binding the metabolites to the Na+-K+-ATPase of cardiac cells. Studies have shown that pre-treatment with antibiotics in vitro and in vivo blocks the reduction of digoxin and that the metabolic response in the distal small intestine is catalysed by the gut microbiota.42,43 Other studies have shown that cytochrome-encoding operon (cardiac glycoside reductase 2 [Cgr2]), which is common in gut bacteria known as Egerthella lenta is capable of inactivating digoxin, this relationship between E. lenta and digoxin was observed in a study using samples from healthy patients ex vivo.44,45 Due to the absence of genetic information for E. lenta, there is no in-depth understanding of the mechanism of action of the gut microbiota on digoxin would allow the intestinal microbiota modulation that improves the therapeutic application of digoxin.
Sulfasalazine was developed between 1940 and 1950 with the intention to treat inflammatory conditions because of bacterial infection. However, it was found to be effective in the treatment of ulcerative colitis. Sulfasalazine is a combination of aminosalicylate and sulfapyridine by an azo bond, as sulfasalazine is not absorbed rapidly by the upper gastrointestinal tract, but its azo bond in the colon is decomposed by gut bacteria into sulfapyridine, which is absorbed and mesalazine (5-aminosalicylic acid), which is activated in the colon. In a pharmacokinetic study using healthy volunteers, it was found that intestinal microbiota are essential for the activation of sulfasalazine which helps us understand why the drug is more effective in ulcerative colitis than in Chron’s disease. The rate of metabolism of sulfasalazine by the gut microbiota can be improved by administration of probiotics strains such as Lactobacillus acidophilus L10, Bifidobacterium lactis B94, and Streptococcus salivarius K12 alongside. In an in vitro study, it was observed that after incubation of the contents of rat colon with sulfasalazine plus probiotics or sulfasalazine alone under anaerobic conditions, the probiotics possessed azoreductase activity and a corresponding ability to metabolize sulfasalazine. An increased concentration of 5-acetylsalicylic acid (5-ASA) and sulfapyridine were recovered in the samples which were incubated with sulfasalazine plus probiotics. Because of the gut microbiota metabolism on sulfasalazine, some patients reported side effects such as nausea, skin rash and anorexia when using sulfasalazine which makes it less popular even though sulfasalazine is an effective and low-cost treatment for ulcerative colitis.

The use and abuse of drugs and different kinds of pharmaceuticals is increasing at alarming rates. The global use of medicines reports that the pharmaceutical companies is worth $1.2 trillion in 2018 with an increase of $100 billion compared with 2017. With increasing incidence of chronic illnesses and the need to manage the diseases, there are pharmacies readily available to sell and dispense drugs over the counter this has led to an increase in intake and abuse of drugs. Table 1 shows a list of some over-the-counter drugs that metabolized by gut microbiota.

## 4 | Metabolism of Xenobiotics by the Gut Microbiota

Xenobiotics are defined as chemical substances, synthetic substances, or toxins which are foreign to the living organism’s ecosystem. They are also regarded as chemical substances foreign to the regular metabolism of an organism. Pollutants, dietary compounds and environmental chemicals which humans ingest or inhale are considered xenobiotics. Xenobiotics are metabolized by the liver in three phases to detoxify and remove them from the body. Cytochrome P450 (CYP 450) enzymes metabolize xenobiotics into exogenous and endogenous compounds followed by conjugation and excretion. If xenobiotics are not properly metabolized, they accumulate in the body and this accumulation could cause inflammation leading to severe diseases. Xenobiotics that are not properly absorbed travel from the small intestine to the large intestine where they are influenced by the gut microbiota present in the large intestine. The action of the gut microbiota on xenobiotics is said to be a response-modifying process where the gut microorganisms are capable of metabolizing the xenobiotics by production of enzymes which degrade or activate these xenobiotic substances. The gut microbiota also modulates the levels of host drug metabolitic enzymes to metabolize leftover xenobiotics which are later reabsorbed in the small intestine or excreted via faeces. The microbiota has a powerful metabolizing activity and is capable of biotransformation of xenobiotics including pharmaceutical ingredients, dietary polyphenols, and other compounds. This biotransformation can lead to change in the half-lives of xenobiotics, change in the way xenobiotics affects the human body and change in the rate of xenobiotic blood circulation or speed in reaching their biological receptors.

Human beings rely on intake of food to get nutrients, gain, and replenish energy which is important for our daily activities. As the world population increases and the need for readily available food increases, higher amounts of man-made and synthetic food products are added into processed foods to cut costs and meet increasing demands. The production of food (mainly artificial and processed foods) has been found to release some undesirable xenobiotics (polycyclic aromatic hydrocarbons, nitrosamines and heterocyclic amines) that are usually not present in natural raw foods. The enzymes present in the gut microbiota metabolize natural, processed, and artificial dietary compounds and the metabolized products are used as a source of energy for the host. The gut microbiota also transforms harmful xenobiotics to less toxic and easily excretable compounds. In the bid to reduce the calorie content of carbonated drinks, manufacturers use artificial sweeteners such as aspartame, saccharin, and sucralose which they claim have no calories. A study assessed the effects of these sweeteners on the gut microbiota of mice by adding them to their drinking water and it was found that the gut microbiota composition was altered and the mice also acquired glucose intolerance. MelIQx (2-amino-3,8-dimethylimidazo [4,5-f] quinoxaline) is a heterocyclic aromatic amine released when red meat is being cooked, this amine has been implicated in colorectal cancer development. The gut microbiota has
| **Drug**          | **Pharmacological action**                          | **Effect of gut microbiota on drug metabolism**                                                                                                                                                                                                 | **Effect of drug microbiota on clinical response**                                                                                      | **References** |
|-------------------|----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| Digoxin           | Positive effect on cardiac function (Cardiotonic)  | The bacteria *Eggerthella lenta* affects the concentration of reduced digoxin metabolite. Digoxin and erythromycin or tetracycline concomitant administration resulted in digoxin intoxication. It is also advised that the combined use of both drugs should be avoided. | Potentiates both activity and toxicity                                                                                                   | 23             |
| Metronidazole     | Antiprotozoal and antimicrobial against anaerobic microbes | Metronidazole is commonly used to treat *Bacteroides fragilis* infection. *B. fragilis* strain overexpresses RecA protein causes resistance to metronidazole compared with the wild-type strain. When RecA is inactivated, it leads to an increased sensitivity to metronidazole. | The microbiota causes resistance to the antimicrobial/antiprotozoal effects of metronidazole                                                                                                       | 51             |
| Sorivudine        | Antiviral drug                                      | Use of sorivudine in combination with 5-fluorouracil (5-FU) triggered a toxic interaction in 18 people from Japan. *Bacteroides spp.* present in the gut microbiota causes toxicity due to the production of (E)-5-(2-bromovinyl) uracil (BVU) metabolite which in turn deactivates dihydropyrimidine dehydrogenase (DPD) responsible for the metabolism of 5-FU. When used in Germ-free rats it was observed that they had significantly lower BVU levels in both urine and blood. | Increases the toxicity of sorivudine                                                                                                      | 52,53          |
| Acetaminophen     | Analgesic and antipyretic                           | There is a competitive o-sulfonation between acetaminophen and p-cresol, produced by some gut bacterial communities, which promotes acetaminophen toxicity. The assessment of microbiome activity before acetaminophen administration is mandatory. | The gut microbiota exaggerates the toxicity of acetaminophen                                                                              | 25             |
been seen to be capable of transforming the toxic MelQx to a less toxic MelQx-M1 which helps to reduce the risk of colorectal cancer. This activity of the gut microbiota, however, is different in humans as it is effective in some people but not effective in others. Emulsifiers such as polysorbate-80 and carboxymethylcellulose, which are largely used as ingredients in food, have been found to promote low-grade inflammation and lead to dysbiosis of the gut microbiota in mice, which is one of the causes of metabolic syndrome.

Everyone around the globe today has been exposed to some sort of environmental pollutant as the amount of chemicals used in pesticides, cleaning agents, and beauty and hygiene products are increased dramatically. For instance, azo compounds are commonly used in cosmetics, pharmaceutical, textile, and food production. These azo compounds (azo dyes) have been implicated in risk of developing several allergies, human DNA mutations, and cancer.

Azo-reducing bacteria such as Pseudomonas, Eubacterium, Geobacillus, Clostridium, and Bacillus have been found to express azoreductase enzymes to metabolize the azo dyes with variable azoreduction rates. Most of our daily use beauty and hygiene products such as hand soap, bath gels and toothpaste contain triclocarban (3,4,4,9-trichlorocarbanilide, TCC) as an antibacterial ingredient. This triclocarban bioaccumulates in the environment through bathroom wastewater as a long-lasting organic pollutant which is non degradable. Triclocarban has been shown to influence either indirectly or directly the synthesis of fatty acids by the liver through enhancing bacterial fermentation in which TCC can increase short-chain fatty acids concentrations as well as alters the gut microbial composition. In another study it was shown that TCC decreased Bacteroidetes and increased Lactobacillus and Firmicutes phylum in rats exposed to low-dose of TCC. Another compound triclosan (5-chloro-2-(2,4-dichlorophenoxy) phenol, TCS) is a broad-spectrum antimicrobial substance which commonly present in cosmetics products and toys. According to a study conducted in mice, it was found that TCS affected Bifidobacterium growth and caused colonic inflammation which support the evidence that gut microbiota plays a role in TCS-caused inflammation.

Halogenated compounds are commonly used ingredients in making pharmaceuticals, disinfecting agents and pesticides. These compounds affect the gut microbiota negatively, they have been found to cause gut microbiota dysbiosis by altering the ratio of Firmicutes to Bacteroidetes therefore leading to disturbances in the immune system and increasing an individual's risk for obesity. For instance, 2,4-dichlorophenoxyacetic acid (2,4-D), is commonly used as a herbicide by disrupting hormonal pathways in plants which lead to plant death.
Evidence from a study to assess its effect in mice showed that 2,4-D caused a state of dysbiosis in the gut microbiota of mice exposed to an occupational dose of 2,4-D (15 mg/kg of body weight per day) with increase in Streptomyces coelicolor, Dehalococcoides ethanogenes, and Methylophilum extorquens strains in the treatment group compared with the control group. The microbial metabolites and metabolism of carbohydrates, urea and amino acids were also affected by 2,4-D exposure in mice causing the pathway abundances of these compounds to be significantly increased in 2,4-D treated mice gut microbiome. Another xenobiotic compound naturally available in the environment is arsenic, which is very toxic to humans especially in its inorganic form. It has been identified that high exposure to arsenic could cause skin, liver, and kidney cancer. In a study conducted to investigate the role of gut microbiota in arsenic metabolism, it was found that when the gut microbiome is in a state of dysbiosis, the toxic effects of arsenic was highlighted via promote one-carbon metabolism. However, when the gut microbiota is in a balanced state, the arsenic is absorbed and the methylation of arsenic is enhanced. Although the exposure of the gut microbiota to arsenic might disturb the gut microbiota, some microorganisms such as Bilophila, Clostridium, Bacteroides, Alistipes, and other genera of bacteria are capable of methylation of arsenic because they have more than one gene encoded in their genome that is resistant to arsenic. Some enzyme families encoded in the gut microbiota include beta-glucuronidases, which hydrolyse the glucuronic acid component from polysaccharides and drugs, azoreductases which reduce azo dyes, transferases which transfer methyl or acyl groups, proteases that hydrolyse polypeptide chains, glycosidases which render molecules less polar, and nitro reductases with less polar metabolites leading to more inactive or toxic metabolites.

5 | IMPACT OF DRUG–GUT MICROBIOTA INTERACTION ON CLINICAL RESPONSES

The metabolism of drugs by the gut microbiota was first discovered in 1930 when the biotransformation of prontosil was recorded. This relationship or interaction between drugs and the gut microbiota can either lead to positive or negative effects, positive such as in the case of conversion of prontosil to the antibiotic PABA, reactivation of sulfasalazine which is a pro drug into active ingredient 5-aminosalicylic acid (5-ASA) or negative such as inducing the toxicity of the drugs or xenobiotic compounds. Toxicity as a result of the gut microbiota biotransformation of certain drugs to a toxic metabolite is harmful and may cause several adverse effects to the host. This can be seen in the metabolism of some anti-cancer chemotherapeutic drugs by gut microbiota such as the action of bacterial β-glucuronidase enzyme which converts the non-toxic metabolite of irinotecan SN-38G to express the cytotoxic SN-38 metabolite. This toxicity to the intestinal cells is the main reason why 80% of patients treated with irinotecan experience severe diarrhea.

The bacterial β-glucuronidase enzyme produced by gut microbiota is also responsible for the toxicity experienced with the use of non-steroidal anti-inflammatory drugs (NSAIDs), which could result in gastroduodenal mucosal lesions in about 50% of people who use NSAIDs regularly. Most bacteria in the gut microbiota are capable of producing β-glucuronidase and this has proven to be one of the major challenges in designing a bacterium-specific target drugs which would lead to reduced drug toxicity. A study in 2010 reported that some β-glucuronidase inhibitors can inhibit bacterial enzyme activities but did not cause any harm to the host epithelial cells. This has been seen in a study using mice where the drug toxicity after irinotecan administration in combination with E. coli GUS, (EcGUS) was reduced significantly.

In order the drug–gut microbiota interactions to be truly effective in clinical responses, we need to fully understand the mechanisms by which the host gut microbiota interacts with other molecules within the host, the diet, genetics of the host, and how these factors contribute to the metabolism of drugs and other xenobiotic compounds. We also need to get a better comprehension of how to manipulate these factors and interactions in ways that allow for better clinical response and preferable treatment of a disease. These manipulations can be done by several means, such as administering antibiotics targeting a particular microorganism that metabolize certain drugs to produce toxic metabolites. Another strategy of manipulating the gut microbiota is to destabilize an entire class of enzymes by disrupting activities of essential cofactors. In one instance, oral tungsten treatment in mice used to deactivate molybdenum-cofactor-dependent enzymes was seen to prevent the proliferation of E. coli, and other Enterobacteriaceae, which led to reduced inflammation. The gut microbiota can also be modified by selectively depleting microbial strains that have no desirable benefits from the gut microbiota. This can be done by using bacteriophages (bacterial viruses).

Ultimately, the interactions between the intestinal microbiota and medication or xenobiotics which are found within the host’s system are bidirectional. At one end of the spectrum, drugs and other xenobiotic compounds can influence the gut environment, change homeostasis, disrupt microbial diversity, and can influence intestinal function. While at the other end of the spectrum, the gut microbiota influences the way host responds to a drug or
xenobiotic by metabolizing the drug through releasing enzymes which biologically transform the drug structure and either activates or deactivates the drug thereby modifying its bioactivity or toxicity. This ability of the gut microbiota to be modified makes it an ideal target influence therapy.

6 | INFLUENCE OF GUT MICROBIOTA ON CHEMOTHERAPEUTIC DRUGS

Chemotherapy is a method of cancer care that involves administration of one or more anti-cancer chemotherapeutic agents as a part of defined protocol. Chemotherapy can be given with the goal of curing cancer (which usually involves a combination of several chemotherapeutic agents), or it can be given with the goal of extending life or reducing symptoms (palliative chemotherapy). Chemotherapeutic drugs are mainly regarded as non-specific intracellular poisons used to impede tumour cell mitosis or cause DNA damage of tumour cells.

The use of chemotherapeutic drugs is currently one of the most effective ways for cancer management. Chemotherapy medications can be administered orally and many are administered intravenously with the aim to inhibit tumour growth and proliferation. However, due to the lack of defined targets for chemotherapeutic agents, cytotoxic effects continue to produce unavoidable consequences.

The influence of the gut microbiota on chemotherapeutic agents is bi-directional. Meaning that the gut microbiota plays a role in the clinical responses of the patient to chemotherapeutic drugs and the chemotherapeutic agent also plays a role in influencing the gut microbiota composition and diversity. Despite the fact that different chemotherapeutic medications have various effects, the overall impact was determined to be a decrease in Lactobacillus and Bifidobacterium, as well as an increase in E. coli and Staphylococcus based on clinical research. This change in microbiota composition and bacteria translocation is linked to an activated inflammatory response and weakened barrier function making the host more susceptible to severe side effects. Intake of probiotics which are beneficial microorganisms during chemotherapy has been proven to help to lessen the negative effects of chemotherapeutic agents on the gut microbiota. Although probiotic formulations specific for cancer patients are not yet popular, several studies have shown that administering probiotics either as a mixture or singly to cancer patients is beneficial for the management of microbiota-mediated drug activity modulation.

The gut microbiota plays a major role in influencing the efficacy of the chemotherapeutic drugs because most of the drugs depend on the gut microbiota to convert them into their active forms before they can exhibit their anticancer prowess. Table 2 summarizes some chemotherapeutic drugs and how the gut microbiota influences their efficacy.

7 | CONCLUSION

The variation of the ways in which humans respond to the same therapeutic agent in a clinical practice is a common occurrence in patients. This was previously attributed to the genetic variation across population, however with the advancement in the HMP, it is reported that gut microbiota diversity also may influence the clinical response among different patients receiving the same therapy. Recently, some advancement has been achieved in understanding the interactions between the gut microbiota and drug metabolism. The gut microbiota now being researched deeply to be used as a promising strategy for drug design and personalized therapy. Although there is better understanding of the key microbial species involved in the metabolism of drug and xenobiotics, precise tools and studies need to be developed to quantify gut microbiota abundance and metabolic activities in situ.

The gut microbiota does not just directly or indirectly metabolize drugs and xenobiotics, but it also plays a role in the activity of gut bacterial enzymes and expression of metabolizing genes. Ultimately, most drugs and xenobiotics disturb the gut microbiota composition and diversity leading to dysbiosis which can cause the development of several diseases and health concerns. The current limitations with pharmacomicrobiomics research include lack of diversity of populations studied and the bureaucracy involved in the translation of pharmacomicrobiomics findings to personalized medicine.

The field of pharmacomicrobiomics is still trending and further understanding of how the gut microbiota metabolizes drugs, activates, deactivates, or induces the toxicity of anti-cancer agents, antibiotics or hypertension drugs will create more possibilities for the gut microbiota to be explored. In addition, more clinical trials should be conducted to improve our understanding on the interactions between gut microbiota and commonly prescribed drugs, especially for chronic diseases.

AUTHOR CONTRIBUTIONS
Ifomega Julieth Dikeocha and Mohammed Abdullah Alshawsh developed the review idea; Ifomega Julieth Dikeocha carried out the literature search and drafted the manuscript: Abdelkodose Mohammed Al-kabsi,
| Chemotherapeutic drug     | Pharmacological action                                                                 | Effect of gut microbiota on anti-cancer drug metabolism                                                                 | Effect of gut microbiota on clinical response                                                                 | Reference |
|---------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|-----------|
| Irinotecan (CPT-11)       | Prodrug administrated intravenously in CRC treatment, active when converted to SN-38 by carboxylesterase | Deconjugation of the detoxicated SN-38-glucuronone back to its active form SN-38 by intestinal microbiota-produced—glucuronidase enzyme could cause diarrhoea and intestinal injury and the increased concentration of SN-38 in the colon causes diarrhoea and intestinal injury | The gut microbiota exaggerates the toxicity of the drug                                                         | 103,104   |
| 5-Fluorouracil (5-FU) + Sorivudine | 5-FU is an inhibitor of thymidylate synthase, critical in DNA replication of tumour cells | Sorivudine is metabolized to Bromo vinyl uracil by intestinal bacteria, particularly the Bacteroides species which then inhibits the enzyme dihydropyrimidine dehydrogenase, which is responsible for 5-FU detoxification causing major systemic side effects such as diarrhoea and decrease in leukocyte and platelet counts | The gut microbiota produces metabolites that promote the toxicity of the 5-FU                                      | 53,105   |
| Oxaliplatin               | Causes tumour cells to produce reactive oxygen species (ROS) to cause cell death by destroying DNA | The gut microbiota increases the expression of enzymes that produce reactive oxygen species (ROS), which can cause DNA damage in tumour cells and lead to cell apoptosis. For example, NADPH oxidase 2 (Nox2) can transfer electrons to make superoxide, which can then be converted to H₂O₂ by an enzyme termed compartment-specific superoxide dismutase | Gut microbiota improves the efficacy of oxaliplatin                                                                  | 106      |
| Gemcitabine               | A nucleoside analog, Inhibits DNA synthesis, used to treat pancreatic, lung, breast or bladder cancer | Gamma proteobacteria, a microbiota species found primarily in the duodenum can convert gemcitabine to inactive metabolites by expressing a long isoform of the enzyme cytidine deaminase, hence contributing to drug resistance | The gut microbiota inactivates the drug and promoting drug resistance                                               | 95       |
| Cyclophosphamide (CTX)    | Induces naïve CD4+ T cells to become Th1 and Th17, which has a systemic anticancer effect | In the presence of bone marrow-derived dendritic cells, symbiotic bacteria (such as Lactobacillus johnsonii and Enterococcus hirae) reach the mesenteric lymph nodes and stimulate the generation of a specific subset of “pathogenic” T helper 17 (pTh17) cells and memory Th1 immune responses against tumor cells in the spleen | Gut microbiota enhances the anti-cancer immune response and improves the efficacy of cyclophosphamide            | 104      |
Muhammad Miftahussurur and Mohammed Abdullah Alshawsh reviewed the manuscript and made amendments where needed.

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The authors declare that they have no conflict of interest.

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