Toxicology International, *32(1) : 01-24; 2025. DOI: 10.18311/ti/2025/v32i1/45370*

Online ISSN : 0976-5131; Print ISSN : 0971-6580

Toxicology International

Contents available at: www.informaticsjournals.com/index.php/toxi



Toxic Effects of Xenobiotics on Gut Microbiome and Host Health: A Mini-Review

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Abstract

Each individual has a unique gut microbiota profile that performs many specific functions like nutrient metabolism, conservation of structural integrity of the intestinal mucosal barrier, immunomodulation, as well as protection against opportunistic pathogens. Recent research has confirmed a profound relationship between gut microbiome and our health. Understanding the reason for gut microbiota imbalances and their impact on health can help in maintaining a healthy life as well as in developing modern therapies. In this regard, the impact of external synthetic chemicals on the gut microbial wellness as well as host health is a topic of growing interest. In this article, the potential effects of xenobiotics, such as heavy metals, pharmaceuticals, air pollutants, persistent organic pollutants, pesticides, nanomaterials, microplastics and food adulterants on gut microbiota have been discussed. Overall study revealed that xenobiotics have a direct impact on gut microbial diversity, composition and metabolism. More and more understanding of the relationship between xenobiotics and gut microbes will help in the development of new methodologies of personalised treatments for illnesses caused by xenobiotics.

Major/Key Findings: 1. Relationship between gut microbiome and host health. 2. Gut microbiota imbalances. 3. Potential effects of xenobiotics on gut microbiota.

Keywords: Bacteroidetes, Dysbiosis, Eubiosis, Firmicutes, Gastrointestinal Tract, Gut Microbiome, Probiotic, Xenobiotics

1. Introduction

Any group of microorganisms in a specific environment within the body or a specific part of the body is called a microbiome. The concept of microbiome was first termed by Joshua Lederberg[1]. Microbes carry out various essential biological tasks for the host[2]. This beneficial microbiome resides in multiple tissues, such as the skin, reproductive, respiratory tissues, esophagus, stomach and gut[3]. The human body contains trillions of bacteria which is even more than human cells[4]. Previous research in microbiology was focused on the identification and culture of disease-causing pathogenic bacteria. Very little research work has been done for the characterization of resident bacteria which are beneficial for human beings[5]. There is limited information about how the human microbiome affects both health and diseases in the host. In 2003, the National Institutes of Health launched the Human Microbiome Project to study the human symbiotic microbiome residing in different parts of the body using advanced DNA sequencing technologies[6]. Subsequently, research on the human microbiome and its effect on health is emerging as an important field of work worldwide. From this research, it can be concluded unambiguously that the gut microbiome plays a crucial role in maintaining the wellness of the host. They participate in many physiological functions. The gut microbiota majorly exists in our intestinal mucus layer and they also maintain the shape of the mucus layer[7]. They help us in the digestion of food, synthesizing vitamins and amino acids,

Article Received on: 09.08.2024 Revised on: 29.09.2024 Accepted on: 08.10.2024

nutrient processing and uptake[8] and biotransformation of toxicants[9,10]. They play a very important role in the digestion of carbohydrates, lipids and amino acids as well as alkane degradation and immune defence from pathogenic microbes by immune system modulation[11]. Recent research also shows that there is a clear link between mental health and gut dysbiosis[12]. Together, the mammalian microbiota, gut and brain constitute a complex, dynamic network between the peripheral nervous system, brain and spinal cord through which the gut digestive system regulates the brain's activities. This network is called the Microbiota-Gut-Brain (MGB) axis[13,14]. As a result, considerable research has been done to culture human microbiome. Unfortunately, only 20-30 % of human microbiomes are culturable in the laboratory[15]. With more than 500 million neurons, the gut is also called our second brain. The gut microbiome-drug interaction regulates the efficacy and toxicity of drugs. So, if we want a healthy life, we must take care of our gut microbiome. Since the external environment affects the constitution of the gut microbiome, we must be aware of the factors which can cause dysbiosis i.e. imbalance in the microbiome. Once we understand how external factors alter the gut microbiome, we can develop modern therapeutic methods to restore the gut microbiome and therefore host health. In this context, xenobiotics can have an enormous effect on the gut microbiota balance. The word "xeno" comes from the Greek word "xenos," which means a stranger or foreigner. Thus, xenobiotics are substances that are foreign to an organism. Naturally occurring chemicals may also become xenobiotics when they are present in abnormally higher concentrations. Here, we will try to understand how exposure to xenobiotics can cause changes in gut microbiome composition and therefore host health. Xenobiotics like chemicals used in pesticides, drugs, food, cosmetics and personal care products along with heavy metals, nanoparticles, microplastics and phthalates can cause dysbiosis of the gut microbiota of the host after entering in body.

2. Features of Gut Microbiome

The microbiome is a collection of a basic set of genes found in the entire body to a specific part of the body of all humans[16]. Depending on several factors, a smaller subset of the human population can have a variable human microbiome. This variation may originate from host genotype, physiology, disease condition, lifestyle, host environment, stress and sporadic populations of microbes. Various research works have been undertaken to identify the microbiome composition of different species[17,18]. Enormous improvement in DNA sequencing along with advanced computational techniques has made it possible to analyse the samples collected from different sources[19-23]. A major focus was on 16S ribosomal RNA gene-sequencing of resident microbes in the human body[24-28]. The self-replicating 16S rRNA gene of ribosome encodes the small subunit ribosomal RNA molecules which is essential for the conversion of genetic messages to functional cell components. 16S rRNA can easily be isolated and its gene sequencing is very much beneficial to identify slow-growing bacteria[29]. Most of the available data are regarding gut microbes. The majority of microbes in humans reside in the colon. More than a hundred distinct phylogenetic categories of bacteria reside in the gut of a healthy human adult host. The dominant phylotypes are Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria, Proteobacteria, Verrucomicrobia and Cyanobacteria. Furthermore, two phyla Firmicutes and Bacteroidetes together contribute to 90% of the total microbiota[16,30-33]. The large surface area of the intestinal tract provides enough attachment sites which support the resident bacterial community as well as allow appropriate blood supply to fulfil the nutrient requirement of microbiome development[33]. The microbiome must have self-healing ability after damage. The intestinal microbiome should be considered a separate organ. The composition of the microbiome is an outcome of a natural balance at both microbial and host levels where cooperation is maintained[34]. As a survival strategy, the microbiome should have the ability to grow and overcome the host's defence mechanism but should not affect host health as eventually, that will result in the reduction of the habitat of the microbiome itself. They can improve the host's health while securing their existence. So, they perform structural and metabolic functions in the host as well as stimulate the host immune system. The structure and function of the epithelial barrier of the intestine and organs outside the gastrointestinal tract are preserved by the gut microbiota. This microbiota also acts as a barrier for pathogenic microbes by giving them competition for nutrients and ecological habitat[35]. Our distal intestine acts as an anaerobic bioreactor where intestinal microorganisms digest otherwise indigestible polysaccharides such as pectin, cellulose, hemicellulose and resistant starch. Humans do have not sufficient

enzymes necessary to digest polysaccharides. Microbes in the gut harvest Short-Chain Fatty Acids (SCFAs) during the digestion of polysaccharides. SCFAs can act as substrates for lipid synthesis in the liver and colonocytes can use SCFAs as energy source[36]. In addition, SCFAs can reduce blood cholesterol, inflammation and colonic pH and enhance insulin sensitivity, and nutrient absorption[37]. Some intestinal microbes can produce vitamins and the antidiabetic compound linoleic acid[38]. The presence of microbes is not only confined to guts but the components of the microbiome may be transported to various organs like the brain (cognitive functions), liver (lipid and drug metabolism) and pancreas (glucose metabolism). Thus, intestinal microbial ecosystem balance known as eubiosis is very essential for healthy human beings[39]. As we are born germ-free, the gut microbiome must come from outside. After birth, the intestine of an infant is the first place where microbes start to colonise and eventually produce individualised microbiome fingerprints which may change with age, diet and environment[40]. Although microbial diversity on our planet is vast, the gut microbiota in adults predominantly contains members of just two phylotypes of bacteria, the Bacteroidetes and Firmicutes and one member of Archaea, *Methanobrevibacter smithii*. The selection pressure has made the intestine remarkably exclusive[33]. Gut microbiome ecosystems are the outcome of two strong selective pressures. The first one is the selection pressure of microbes themselves to produce diversified microbial genomics for a reduction in the competition among themselves. On the contrary, the second selection pressure is regulated by the host which tries to homogenise the types of bacteria genomes so that the lack of one does not lead to a collapse of the whole function. The equilibrium between these two selective pressures regulates the microbiome function in a healthy human being. The predominance of any selection pressure

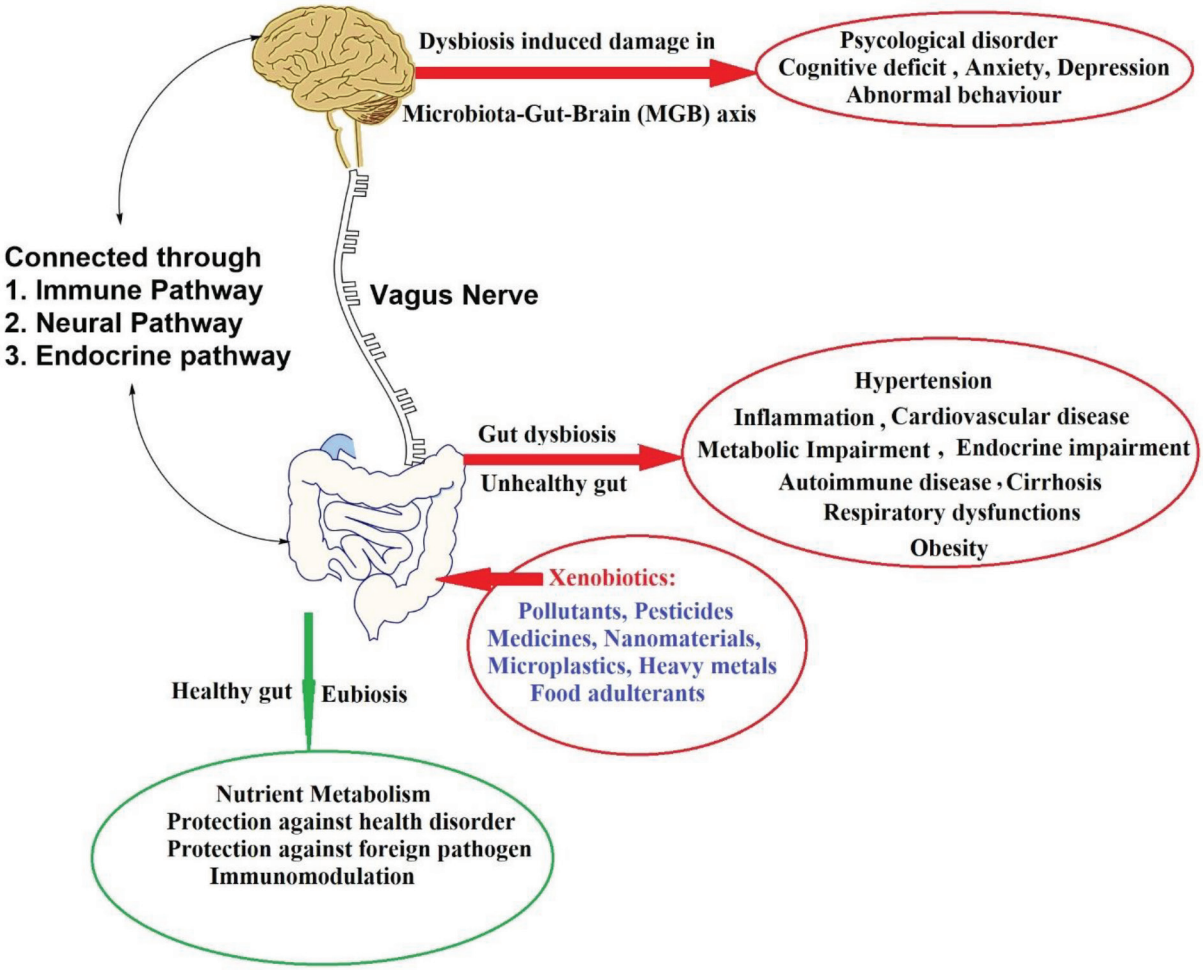


Figure 1. A schematic representation of the effect of xenobiotics on gut microbiome as well as host health.

would result in an imbalance in the gut ecosystem. A gut microbiota is in eubiotic i.e., healthy status if potentially beneficial species are predominant. There could also be pathogenic organisms but in a very low concentration. But when the good bacteria cannot control the bad bacteria, the situation is called dysbiosis. Gut dysbiosis can cause various diseases. There is evidence in the literature that illnesses such as carcinogenic conditions, digestive disorders, liver problems, neurological conditions, type 2 diabetes, cardiovascular diseases, inflammatory bowel conditions, autoimmune disorders, reproductive health and fertility disorders correlate with gut microbiome health[41-44].

3. Xenobiotics and Gut Microbe

Xenobiotic means 'foreign to life'. These are generally the dietary components, environmental chemicals and pharmaceuticals to which an organism is exposed but their metabolism is different than the normal metabolism of that organism. The role of gut microbes in metabolism has been known since 1950. A molecular understanding of gut microbial xenobiotic metabolism may help in the formulation of personalised medicine[45]. Experiments with germ-free animals indicated the involvement of gut microbiome in xenobiotic processing[46]. Orally consumed compounds reach the small intestine through the upper Gastrointestinal (GI) tract, are altered by specific enzymes and reach the liver. The liver has a rich arsenal of enzymes which can metabolise xenobiotics. Subsequently, foreign bodies and their byproducts mix in the bloodstream and impact the tissues present in other organs. On the other hand, intravenously administered compounds directly enter the bloodstream. From there they can be removed from the system with the help of a kidney or large intestine in the form of urine or faeces respectively. There is also a chance to enter the gut through the bile and therefore interact with gut microbes. On the other hand, foreign materials that are not effectively absorbed in the small intestine can reach to large intestine and confront the gut microbes. Thus, xenobiotics can reach gut microbes through different routes. The gut microbial metabolites can be absorbed by the host and circulated systemically or interact locally with the epithelial cells in the gastrointestinal tract. These microbial metabolites are then excreted in faeces or through the urine. The major enzymes required for the metabolism of xenobiotics are extensively found in gut microorganisms. Thus, the gut microbiome and host together generate a complex metabolic mechanism which is not possible for the host alone. This metabolism modifies the functions and lifespans of external materials within the host which ultimately impacts both the microbiome composition and wellness of the host. Some xenobiotics that we encounter every day are heavy metals, pesticides, pharmaceuticals, microplastics, food additives, nanomaterials and several others (Figure 1).

3.1 Heavy Metals

Today, heavy metals are becoming a serious threat. They can cause various health issues in the living systems[47]. The permissible limits for the concentration of toxic heavy metals like lead, arsenic, mercury and cadmium in drinking water are 15 µg/L, 10 µg/L, 6 µg/L and 3 µg/L respectively according to World Health Organization (WHO)[48]. To eliminate the toxic effect of xenobiotic heavy metals, a healthy gut microbiome is required. In the Simulator of the Human Intestinal Microbial Ecosystem (SHIME), R. A. Diaz-Bone *et al.,*[49] demonstrated that metal or metalloids undergo volatilisation or produce metabolites with different mobility. Antibiotic-Treated (AT) and Germ-Free (GF) mice are found to have less amount of heavy metal in their faeces whereas higher concentrations of heavy metals were found in their blood and tissues compared with the control mice, indicating that the gut microbiota plays an important role in decreasing heavy metal absorption and accumulation. During the metabolism of heavy metals, gut microbes help in converting the heavy metal xenobiotic to less toxic metabolites but consequently, the gut microbiome can also suffer from compositional imbalance[50]. Some metals can kill pathogenic, especially multidrug-resistant microbes at very low concentrations. However, this metal toxicity is also expected to harm beneficial microbes such as the gut microbiota. Heavy metals alter intestinal barrier permeability resulting in dysbiosis[51] (Table 1).

3.1.1 Arsenic

Coryell *et al*., have shown that arsenic bioaccumulation was heightened in mice whose microbiomes were altered by antibiotic intake[52]. Transgenic mice without enzymes capable of arsenic detoxification and mice without any germ were found to have a high death rate after high-dose arsenic exposure. On the other hand, Faecal Microbiota Transplantation (FMT) from healthy humans saved the lives of arsenic-exposed

mice. Furthermore, it has been demonstrated that the bacterium *Faecalibacterium prausnitzii* found in healthy human gut[53], can reduce the extent of toxic effect of arsenic to some extent[52]. A greater amount of Proteobacteria was found in the faeces of high-dose arsenic-contaminated children compared to children with low arsenic exposure. Moreover, enhanced expression of two arsenic-resistant genes (ArsB, ArsC) of *Escherichia coli* was observed in extensively arsenic-exposed children in comparison to children without any exposure[54]. Hoen *et al.,*[55] have shown that the effect of arsenic contamination is sex-dependent for human babies. Even low arsenic exposure levels enhanced arsenic levels in urine and increased the amount of *Lactobacillus*, *Bifidobacterium* and *Bacteroides* in the faeces of male babies who were formula-fed (Table 1).

There is a probability of a connection between arsenic exposure and alteration in microbiome composition. However, these deformations were not observed in formula-fed female babies or breastfed babies of either sex. In several studies, it has been shown that in mice exposed to Arsenic, the number of *Bacteroidetes* increases while the number of Firmicutes decreases[55] (Table 1). As observed by Lu *et al.,*[56] when female C57BL/6 mice were exposed to arsenic through water intake, the number of Firmicutes decreased and the bile acid composition along with indole metabolic products of the gut microbiome was also changed. Another research by Chi *et al.,*[57] found that 100ppb arsenic exposure in mice for 13 weeks affected the composition and function of the symbiotic microbiome. There were notable changes in the population of microbes which help in important biological functions like digestion of carbohydrates, lipopolysaccharide biosynthesis, production of SCFAs and stress response. Gokulan *et al.,*[58] have suggested that arsenic exposure even at a young age may have a long-lasting detrimental effect on the restoration of gut microbiota.

Table 1. Impact of heavy metal xenobiotics on gut microbiome

Name of Xenobiotics	Study Model	Exposure Dose	Impact on the Gut Microbiome	Refer ence
Arsenic	nested study of 50 Children (4–6 years old)	218.8 µg/L (High exposure) and 1.7 µg/L (low exposure) through drinking water	Gammaproteobacteria, Enterobacteriales, Proteobacteria↑ (high exposure group)	Dong *et al.*,[54]
Arsenic	Formula-fed babies (New Hampshire Birth Cohort Study)	A study done in two regions of New Hampshire having arsenic concentrations in well water greater than 10µg/L	*Lactobacillus, Bifidobacterium, Bacteroides*↑ Firmicutes↓ (in male formula-fed babies)	Hoen *et al.*,[55]
Arsenic	Mouse model	10 ppm twice a week for 4 weeks	P_Tenericutes, *F_Erysipelotrichaceae*↑ P-Firmicutes, *F_Clostridiales* ↓	Lu *et al.*,[56]
Arsenic	Mouse model	100ppb for 13 weeks	*Lactococcus*, *Coprococcus*, *Dorea*, *Oscillospira*, *Ruminococcus, Peptostreptococcaceae*, *Lachnospiraceae*, *Clostridiaceae*↓ *Akkermansia*, *Bifidobacterium*, and *Anaerostipes*↑	Chi *et al.*,[57]
Cadmium	Mouse model	20 and 100mg kg^{-1} for 3 weeks	Firmicutes/Bacteroidetes ratio ↓ *Bifidobacteria*, *Lactobacilli* ↓	Liu *et al.*,[59]
Cadmium	Mouse model	10 mg/L Cd supplied in drinking water for 10 weeks	Firmicutes, γ-Proteobacteria↓ *Bacteroidetes*↑	Zhang *et al.*,[61]
Lead	Mouse model	32 ppm for 7-10 weeks	*Bacteroidetes*↓ Firmicutes↑	Wu *et al.*,[62]
Lead	Mouse model	15-week exposure to 0.1 mg/L Pb	*Bacteroidetes*, Proteobacteria↑ Firmicutes↓	Xia *et al.*,[63]
Mercury	Rat Model	Oral administration with MeHg at the dose of 10 µg/kg, 24 hrs before euthanization	*Bacteroidetes*, Proteobacteria↓ Firmicutes↑ *Lactobacillaceae*, *Bacteroidaceae*, *Streptococcaceae*, *Sutterellaceae* ↓ *Desulfovibrionaceae*, *Helicobacteraceae*, *Peptococcaceae* and *Rhodospirillaceae* ↑	Lin *et al.*,[66]

3.1.2 Cadmium

Cadmium (Cd) is a toxic environmental pollutant which inhibits the growth of the organism and is considered a human carcinogen. In their study, Liu *et al.,*[59] have shown after Cd exposure at level 20 and 100mg kg^{-1} for 3 weeks in mice Cd accumulated in some tissues of mice and the gut barrier was impaired. There was a decrease in the population of *Lactobacillus* and *Bifidobacterium* (Table 1). They have also noticed that Cd-treated mice suffer from a reduction in genes taking part in essential functions like digestion of carbohydrates and production of SCFAs[60]. Zhang *et al.,*[61] showed that the population of Firmicutes and γ-proteobacteria decreased significantly in the faeces after 4 weeks of Cd exposure and the amount of Firmicutes reduced in the cecum contents after 10 weeks of Cd exposure.

3.1.3 Lead

Very low concentrations of Lead (Pb) (5µg/dL) can result in gut dysbiosis and adverse effects on mental health[49]. Unlike Arsenic, the toxic effect of Pb exposure is regardless of sex. Pb exposure through drinking water in adult male and female mice has shown altered gut microbiota composition[62]. Xia *et al.,*[63] have shown that the population of Firmicutes significantly decreased, whereas that of Bacteroidetes and Proteobacteria increased compared with the control group after a 15-week exposure to 0.1 mg/L Pb in mice (Table 1).

3.1.4 Mercury

Mercury pollution is becoming a threat to human health. In several cases, it is found that there is a correlation between mental illness and mercury poisoning[64]. If we compare the toxicity levels of different Hg species, their detrimental effect increases with the positive charge on the metal ion and the most toxic in methyl mercury ion. The toxic methyl mercuric chloride can be metabolized to less toxic inorganic mercury by the intestinal flora of the rat and man enabling mercury excretion from the host. But at higher concentrations of mercury pollution, the rate of metabolism by small intestine microbes is reduced, probably because at higher concentrations organomercury compounds overpower intestinal microbes and start to destroy them[64]. This dysbiosis of the gut microbiota in mammals can enhance the methylmercury accumulation causing neurodegenerative disease[65]. Organic methyl mercury exposure can change the structure and function of *Desulfovibrionales, Peptococcaceae* and *Helicobacter* present in gut microbiota in rats. These microbes are associated with neurometabolites such as glutamate and Gamma-Aminobutyric Acid (GABA)[12,66] (Table 1). Nearly 50% of dopamine which is a hormone as well as neurotransmitter is produced by the gut microbiota. This dopamine has a very crucial function in the central nervous system[67]. Zhai *et al.,*[68] found that autistic children have a higher abundance of nine genera *Bacteroides*, *Parabacteroides*, *Sutterella*, *Lachnospira*, *Bacillus*, *Bilophila*, *Lactococcus*, *Lachnobacterium*, and *Oscillospira* in their gut microbiota. Mercury and arsenic exposure are significantly associated with the higher concentration of *Parabacteroides* and *Oscillospira* in the stomachs of children suffering from autism. This study suggested that heavy metal-induced deformation gut microbiome can increase autism spectrum disorders.

3.2 Pharmaceuticals

Orally consumed medicines directly come in contact with the gastrointestinal tract. Hence, the gut microbiome plays an important role in drug metabolism. Individuals' gut microbiomes are different. The metabolism mechanism of drugs by the combination of host enzymes and gut microbiota is also different. This metabolism of drugs regulates therapeutic benefits as well as the side effects. So, it is very important to understand the mechanism of gut microbial metabolism of drugs. In this regard, we can classify drugs into two major categories – antibiotics and non-antibiotics.

3.2.1 Antibiotics

Antibiotics directly attack the microorganisms. So, the microbes present in the gut could also be affected by antibiotic drugs. Gut microbes do not confront antibiotics only by direct administration. Partial absorption of antibiotics is also a major cause of the high abundance of various antibiotics in the environment resulting in passive exposure. Some studies have shown that Subtherapeutic Antibiotic Treatment (STAT) induced in mice did not change the overall microbial census substantially but altered the diversity of the microbiome[69].

Antibiotics may have long-lasting effects on the gut microbiota (Table 2). Fouhy *et al*[70] have shown that the gut microbiota of infants administered with ampicillin and gentamicin (Compound 1 and 2; Figure 1) had an increased abundance of Proteobacteria and a reduced abundance of Actinobacteria even four weeks after the

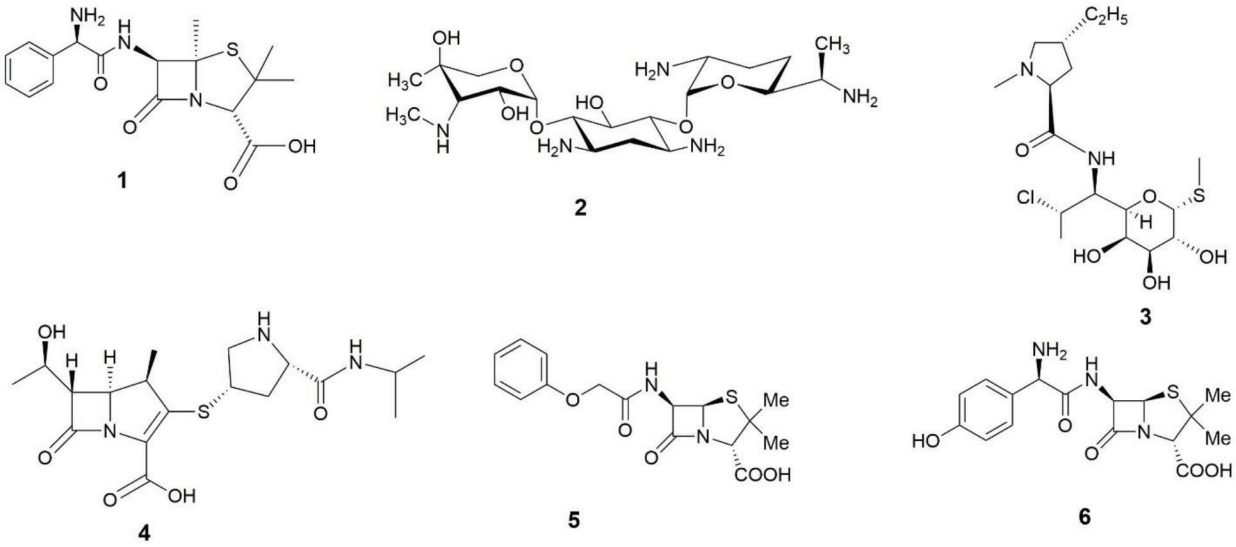


Figure 1. Structure of antibiotics: **1.** Ampicillin **2.** Gentamicin **3.** Clindamycin **4.** Meropenem **5.** Penicillin v, **6.** Amoxicillin.

treatment. Although Actinobacteria *Bifidobacterium* and *Lactobacillus* levels had recovered after eight weeks, the diversity of *Bifidobacterium* species was less than the level before treatment. Some antibiotics destroy intestinal microbial communities and increase the concentration of intestinal pathogens. Treatment with clindamycin and ampicillin (Compound 3 and 1; Figure 1) enhanced the chances of *Clostridium difficile*-induced diarrhoea in hospitalised patients. The use of these two antibiotics decreases *Clostridium scindens*, an intestinal bacterium which provides resistance to *C. difficile* infection in a secondary bile acid-dependent fashion[71]. Palleja *et al.,*[72] observed that 4 days of administration with a combination of antibiotics Meropenem, gentamicin, (Compound 4 and 2; Figure 1) and vancomycin in healthy volunteer men resulted in dysbiosis of the gut microbiome associated with a decline in beneficial *Bifidobacterium* species and increase in disease-causing bacteria like *Enterobacteria*, *Enterococcus faecalis*, and *Fusobacterium nucleatum*. The gut microbiome was returned to eubiotic status after one and a half months. This observation indicated that, unlike infants, adult gut microbiomes may undergo reversible changes after antibiotic treatment. Two-week exposure to vancomycin in humans enhanced the population of disease-causing bacteria of the genus *Klebsiella* and *Escherichia/ Shigella*. After stopping the antibiotic, some patients recovered their microbiome as in previous levels but in some patients, damages were not reversible. This observation again proves that everyone's microbiota reacts differently upon drug intake[73]. In this regard, lincosamides (clindamycin) can produce resistance genes as well as decline the variety of *Bacteroides*[74]. Antibiotics having β-Lactams ring such as penicillin v, amoxicillin, (Compound 5 and 6; Figure 1) ampicillin/ sulbactam and cephalosporins reduce Actinobacteria and Firmicutes and increase Proteobacteria and *Bacteroidetes*[75].

Macrolides like clarithromycin and erythromycin (Compound 1 and 2; Figure 2.) are found to decrease Actinobacteria as well as *Bifidobacterium* and *Lactobacilli* among Firmicutes and increase Proteobacteria and *Bacteroidetes*[76]. Fluoroquinolones class of antibiotics, namely ciprofloxacin and levofloxacin (Compound 3 and 4; Figure 2) reduce anaerobic Gram-negative and anaerobic Gram-positive bacteria but increase aerobic Gram-positive bacteria[74]. Thus, the use of most antibiotics leads to dysbiosis of the gut microbiome by causing an imbalance between beneficial and disease-causing microbes.

In this context, Antimicrobial Resistance (AMR) is emerging as a major public health concern nowadays. AMR was found to be related to nearly 4·95 million deaths in 2019[77]. Researchers have found that there is a relationship between AMR and gut microbiome composition. Understanding the tremendous importance of gut microbes in maintaining host health has made scientists believe that gut microbiota can be utilised to fight against multidrug-resistant infections instead of only synthesising a new arsenal of antibiotics. Bacteria can become resistant through mutations which can be carried over to daughter cells. The gut microbiome contains several antibiotic resistance genes

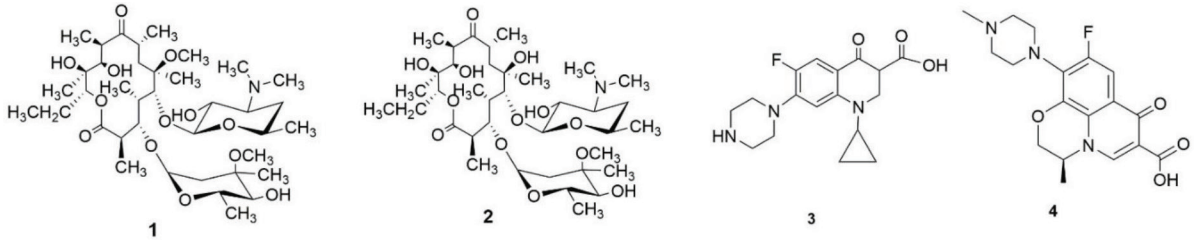


Figure 2. Structure of antibiotics: **1.** Clarithromycin **2.** Erythromycin **3.** Ciprofloxacin **4.** Levofloxacin.

Table 2. Effect of pharmaceuticals on gut microbiome

Name of Xenobiotics	Study Model	Exposure dose	Impact on the Gut Microbiome	Reference
Antibiotics: Penicillin, vancomycin, chlortetracycline	Mouse Model	mid-range of FDA-approved levels in drinking water for 7 weeks	Firmicutes↑ Firmicutes/*Bacteroidetes* ratio ↑	Cho *et al.*,[69]
Antibiotics: ampicillin and gentamicin	Infants	parenteral antibiotic treatment with a combination of within 48 hours of birth	Proteobacteria↑ Actinobacteria ↓ diversity of *Bifidobacterium*↓	Fouhy *et al.*,[70]
Antibiotics: Clindamycin, Ampicillin, Enrofloxacin	Mouse model	clindamycin (200 mg daily), ampicillin (0.1 g / lit), enrofloxacin (0.4g /lit) in drinking water for 21 days	Susceptibility toward *Clostridium difficile infection*↑ *Clostridium cinders*↓	Buffie *et al.*,[71]
Antibiotics: Meropenem, Vancomycin, Gentamicin	12 healthy Caucasian males	a once-daily oral dose of 500 mg meropenem, 500mg vancomycin, 40mg gentamicin for 4 days	*Bifidobacterium*↓ *Enterobacteria*, *Enterococcus faecalis*, and *Fusobacterium nucleatum*↑	Palleja *et al.*,[72]
Antibiotics: Vancomycin	Rheumatoid arthritis (RA) patients	250mg vancomycin four times a day) for 2 weeks	*Megasphaera, Veillonella*↑ *Bacteroidetes*↓ Proteobacteria, Fusobacteria, *Klebsiella, Escherichia/Shigella*↑	Isaac *et al.*,[73]
Antibiotics: Penicillin, Ampicillin, Erythromycin	Preterm Caucasian infants	mothers received intrapartum or infants started antibiotic treatment during the second week.	Actinobacteria, Firmicutes ↓ Proteobacteria and *Bacteroidetes*↑	Arboleya *et al.*,[75]
Non-antibiotic: Metformin	Patients with Type2 Diabetes Mellitus	≥1000 mg/day for more than 3 months.	Firmicutes↑ *Bacteroidetes*↓	Napolitano *et al.*,[82]
Non-antibiotic: Rosuvastatin	Mouse Model	3 mg/kg of body weight	*Bacteroides*, *Butyricimonas*, and *Mucispirillum*↑	Kim[83]
Non-antibiotic: Captopril	Wistar Kyoto rats	Captopril water (100 mg/ kg/ day]) throughout pregnancy and lactation	*Roseburia, Oscillospira*, *Coprococcus*, and *Dehalobacterium*↑	Li *et al.*,[87]

called 'gut resistome' which can act as resistant clones of opportunistic pathogens[78]. So, a new approach to dealing with AMR could be to reduce the population of resistant microbes in the human gut by microbiota modification[79]. In this regard, FMT, the administration of classic probiotics or live microbial consortiums is being used as a successful weapon to reduce colonisation of resistant bacteria[79,80].

3.2.2 *Non-Antibiotics*

Not only antibiotics but non-antibiotic drugs can also cause dysbiosis in gut microbiota (Table 2). On the other hand, gut microbes can affect drug efficacy and side effects. Metformin (Compound 1; Figure 3) is a widely used drug for type 2 diabetes. It inhibits gluconeogenesis in the liver. It shows a lack of effectiveness in regulating blood glucose via intravenous way compared to oral administration indicating the role of the gut and its residing bacteria[81]. In humans, Metformin reduces the bile acids produced by the liver, mostly cholic acid and its derivative in the bloodstream. On the other hand, a connection between gut microbe composition and bile acid concentration has been found. Firmicutes and cholic acid concentration are positively associated whereas *Bacteroidetes* and cholic acid concentration are negatively associated. This observation suggests that gut microbiota may influence the efficiency of metformin[82]. Rosuvastatin (Compound 2; Figure 3) is a drug commonly used for lowering cholesterol. *Bacteroides*, *Butyricimonas* and *Mucispirillum* were abundant in rosuvastatin-treated mice. In addition to that, this bacterial population is strongly associated with the indicators of inflammation in host[83]. The efficiency of Losartan (Compound 3; Figure 3), an antihypertensive drug is closely related to gut microbiome. Robles-Vera *et al.*,[84] have shown that losartan can improve most of the abnormalities in Spontaneously Hypertensive Rats (SHR) used as a cardiovascular disease model. After five weeks of treatment, reports of hypertensive rats were close to control Wistar Kyoto rats (WKY). These improvements are also associated with restoration of Firmicutes/*Bacteroidetes* ratio as well as enhanced diversity of gut microbes. The population of anaerobic bacteria also increased in SHR. Losartan treatment improves intestinal integrity and microbial dysbiosis. Captopril (Compound 4; Figure 3) is a long-lasting antihypertensive drug which shows its benefit even after discontinuation. Mechanistically Captopril inhibits the Renin-Angiotensin system (RAS) which can cause high pressure, heart attack and renal illness. However, its ongoing efficiency may be attributed to its effect on gut microbiome eubiosis. Yang *et al.*,[85] treated SHR and WKY with captopril for four weeks and then studied them sixteen weeks after completion of the treatment. Captopril treatment resulted in declined blood pressure of SHR along with an increase in *Parabacteroides*, *Mucispirillum* and *Allobaculum* abundance. In the 4th week gut microbiome of SHR was found to be enriched with Firmicutes Proteobacteria, *Tenericutes*, and Actinobacteria, along with a reduction in *Bacteroides* in comparison to WKY. These gut microbial changes were found even two months after treatment as captopril continues to affect neuronal activity. Captopril suppresses immuno-inflammatory responses and reduces intestinal overactivation thereby balancing the intestinal flora[86]. Maternal captopril treatment can improve the dysfunctional gut-brain axis and reshape the gut microbiome in spontaneously hypertensive rat male offspring. It was observed that the beneficial *Clostridiales* such as *Roseburia, Oscillospira*, *Coprococcus*, and *Dehalobacterium*, were richer in captopril-treated expecting SHR compared to nontreated pregnant SHR[87]. Thus, from numerous research works, it can be unambiguously said that pharmaceuticals can play an important role in regulating the configuration and development of the gut microbiome which may ultimately enrich or damage host health and drug efficacy. The proper knowledge of the mutual effects of drugs and gut microbiota on each other will open a new tradition of regulating the gut microbiome in personalised treatment and thus can improve the efficacy of drugs.

3.3 Air Pollutants

Studies suggest that air pollutants may adversely affect the gastrointestinal tract by altering the relative abundance of the gut microbiome (Table 3). Pollution from vehicles due to fossil fuel combustion is linked to type 2 diabetes and

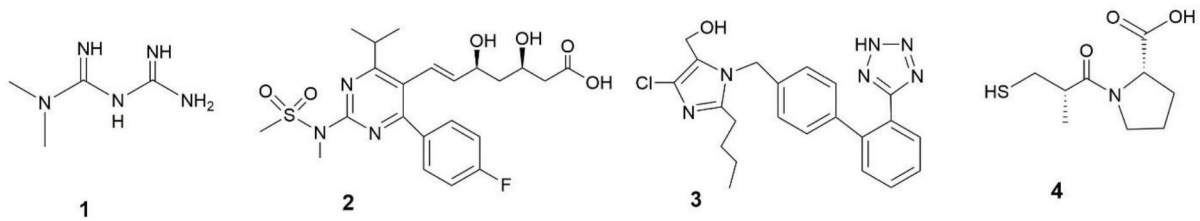


Figure 3. Structure of non-antibiotic drugs: **1.** Metformin **2.** Rosuvastatin **3.** Losartan Captopril.

metabolism dysfunction. Alderete *et al.*,[88] have shown that fasting glucose levels are associated with *Bacteroidaceae* and *Coriobacteriaceae* which are also affected by freeway or highway Traffic-Related Air Pollution (TRAP) exposure. Exposure to freeway TRAP causes a higher abundance of Actinobacteria mainly *Coriobacteriia* and a lower population of Proteobacteria. Phylum Firmicutes, class Clostridia, and order *Clostridiales* are also found to be increased with freeway TRAP exposure. Fouladi *et al.*,[89] have shown that ozone exposure is negatively associated with *Coriobacteriaceae*, *Lactobacillaceae*, *Acidobacteriaceae* and *Bacillaceae* but positively associated with *Bacteroidaceae*. It is also found that increased exposure to NOx was associated with the increase in *the* abundance of *Coriobacteriaceae* and a decrease in the abundance of *Bacteroidaceae* which are related to obesity and altered metabolism[88]. Suspended particulate matter (SPM) can reach the intestine through alveoli into the systemic circulation or through the ingestion of inhaled particles from the airways after mucociliary clearance. There SPM can change the eubiotic balance of gut microbiome. Liu *et al.*,[90] examined 6,627 adults from south China exposed to $PM_{2.5}$ and PM_{10} and found reduced gut microbial alpha diversity. PM exposure decreased Firmicutes, Proteobacteria, and Verrucomicrobia. The relation between *Bacteroidetes* with PM was not consistent. For five cases *Bacteroidetes* abundance increases with PM exposure whereas in seven cases *Bacteroidetes* reduced with exposure. Air pollution causes dysbiosis of gut microbiota as the relative population of Firmicutes, *Bacteroidetes*, and Verrucomicrobia changes resulting in leaky gut and enhancement in the release of proinflammatory cytokine. This makes inflammation even worse in the body along with several mental ailments[55]. Ultrafine particles, the smallest fraction of PM with diameter ≤ 0.1μm have differential effects compared to larger particles. Oral exposure of ultrafine particles in mice for 10 days (3 d a week) showed an increase in the relative abundance of Verrucomicrobia compared to the control group along with a reduced population of Firmicutes, Cyanobacteria, and Actinobacteria[91]. In a murine model, oral exposure to benzo-a-pyrene emitted from combustion led to an increase in *Coriobacteriaceae* and intestinal inflammation[92].

3.4 Persistent Organic Pollutants (POP)

Persistent organic pollutants are toxic chemicals which are slow to break down. So, they stay in the environment for a long time and accumulate in living organisms via the food chain. There are several POPs which are harmful to living systems like Polycyclic Aromatic Hydrocarbons (PAHs), Polychlorinated Biphenyls (PCBs) and Polychlorinated Dibenzo-p-Dioxins (PCDD) and Dibenzofurans (PCDF) (Compound 1 and 2; Figure 4). PCBs are widely used in electrical, heat transfer and hydraulic equipment and as plasticisers in paints, plastics, and rubber products. However recent research has shown that they are potential carcinogens. PCB (Compound 3; Figure 4) induced gut microbiota dysbiosis in mice was observed within two days only (Table 3.). Choi *et al.*,[93] have shown that PCB exposure has significantly changed the abundance of 1,223 bacterial taxa in mice. Phylum Proteobacteria has shown a 4.0- to 5.6-fold decrease in abundance after PCB treatment. On the other hand, phyla, including *Bacteriodetes*, Actinobacteria, Verrucomicrobia, and Firmicutes have shown up to a 2-fold increase after PCB treatment. PCB-induced gut microbiome dysbiosis may result in disruption of the intestinal barrier and translocation of lipopolysaccharides into the bloodstream. It has been observed that PCB-induced reduction in Proteobacteria abundance in sedentary mice can be prevented by exercise. PAHs are another class of POP which shows toxic, carcinogenic, and estrogenic or antiestrogenic properties in the human body. High molecular-weight PAHs are consumed through oral uptake of charcoal-broiled, grilled and

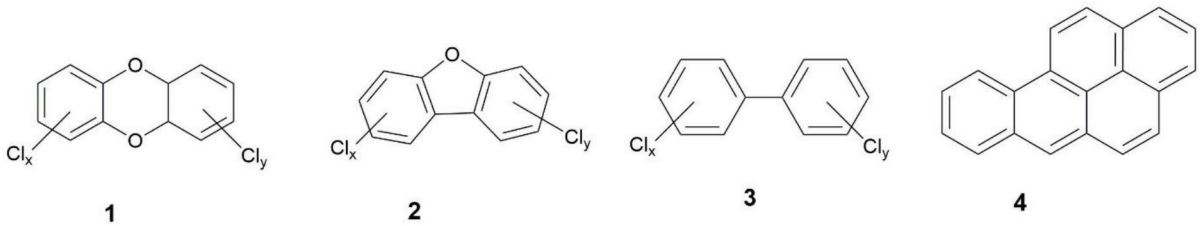


Figure 4. Structure of POP: **1.** Polychlorinated dibenzo-p-dioxins (PCDD) **2.** Dibenzofurans (PCDF), **3.** Polychlorinated biphenyls (PCBs), **4.** Benzo-a-pyrene (BaP).

Table 3. Effect of air pollutants, POPs and bisphenol A (BPA) on gut microbiome

Name of Xenobiotics	Study Model	Exposure dose	Impact on the Gut Microbiome	Reference
Traffic-related air pollution (TRAP): NOx, CO, particulate matter, organic pollutants	Participants from Southern California (2014 – 2016)	mean freeway NOx exposure (0.001–28.6 ppb) NOx as a marker for traffic pollutants	Actinobacteria mainly *Coriobacteriia, Clostridiales* ↑ Proteobacteria ↓	Alderete *et al.*,[88]
PM_1, $PM_{2.5}$, SO_2, NO_2, O_3 and CO	Adult human from Southern China	PM_1, $PM_{2.5}$, SO_2, NO_2, O_3 and CO exposure (October 2015 to February 2016)	Firmicutes, Proteobacteria, and Verrucomicrobia↓	Liu *et al.*,[90]
BaP (benzo[a]pyrene)	Mouse model	50 mg/kg of body weight given orally for 28 days	*Bacteroidales, Lactobacillus*, Verrucomicrobia↓ *Parabacteroides, Paraprevotella* ↑	Ribière *et al.*[92]
PCBs (polychlorinated biphenyls)	Mouse model	Oral dose of (50 µmol/kg) for 2 days	Proteobacteria ↓ Firmicutes↑ Bacteroidetes, Actinobacteria, Verrucomicrobia↑	Choi *et al.*,[93]
PAHs (polycyclic aromatic hydrocarbons)	Children	PAH in umbilical cord blood for prenatal exposure and the urinary hydroxyl PAH concentration for postnatal exposure were measured.	Bacteroidetes↓ *Bacteroidia, Bacteroidales, Clostridium*↓ Firmicutes↑ *Actinobacteria, Proteobacteria, Lactobacillus, Tenericutes, and Lentisphaerae*↑	Gao *et al.*,[94]
2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD)	Mouse model	6 µg TCDD/kg body weight for 26-week	Bacteroidetes↓ Firmicutes↑	Lefever *et al.*,[97]
Di-(2-ethylhexyl) phthalate (DEHP)	Mouse model	500 and 1500 mg/kg body weight per day for 30 days	Firmicutes↑ Actinobacteria↓ Epsilonbacteraeota, Bacteroidetes↓	Fu *et al.*,[99]
Bisphenol A (BPA)	Mouse model	0.5 mg/kg of food for 24 weeks	Proteobacteria↑ Verrucomicrobia, *Akkermansia*↓	Feng *et al.*,[104]
BPA	Rabbit model	orally with 0 or 200 g/kg of body weight/day for 15 days	*Ruminococcaceae, Coprococcus spp., Akkermansia spp.*↓	Reddivari *et al.*,[107]

smoked meats and ingestion of soiled or poorly cleaned vegetables, resulting in even higher exposure than by inhalation. PAH may affect the intestinal microbes of hosts, especially of very young babies. This dysbiosis may severely disturb the process of neurodevelopment in children. Gao *et al.*,[94] have shown that PAH exposure increased the population of *Lactobacillus* and reduced the population of *Clostridium* (Table 3). BaP (benzo-a-pyrene) (Compound 4; Figure 4) is a PAH, the major source of which is fuel and biomass burning. Alderete *et al.*,[95] observed that mice exposed to benzo-a-pyrene (BaP) for 28 days orally have shown to affect at least fifteen microbial families. *Bacteroides*, *Paraprevotella* and *Alcaligenaceae* were found to have increased populations whereas *Oscillospira* and *Lactobacillus* had declined populations. Tetrachlorodibenzofuran (TCDF) exposure for 5 days at a dose of 24 mg/kg body weight can reduce the ratio of Firmicutes/*Bacteroidetes* which can alter the bile acid metabolism[96]. TCDF can disturb the Farnesoid X Receptor (FXR) and Aryl Hydrocarbon Receptor (AHR) signalling mechanism, causing substantial inflammation and metabolic disorders in the host. Lefever *et al.*,[97]

reported that 2, 3, 7 and 8-Tetrachlorodibenzo-p-Dioxin (TCDD) exposure for 26 weeks increased the abundance of Firmicutes and decreased the abundance of *Bacteroidetes*. In streptozotocin-induced diabetic mice gut microbiome dysbiosis is associated with damage in the liver and immune systems.

3.5 Phthalates

Phthalates are generally used as plasticisers present in many products like lubricants, flooring materials and daily used items like shampoos and soaps. They can contaminate water sources, air and soil[98]. Many researches have shown that phthalate exposure alters gut microbiota which may cause serious health problems[99-101] (Table 3). Di-(2-Ethylhexyl) Phthalate (DEHP) (Compound 1; Figure 5) is a hormone-damaging chemical that may disturb a woman's ability to reproduce. However, the proper mechanism of this kind of toxic effect on the reproductive system is still unknown. Modern research has proposed that gut microbial dysbiosis may contribute to female reproductive toxicity. Fu *et al*.,[99] have observed that DEHP-exposed mice have a higher population of Firmicutes and a declined population of Actinobacteria, Epsilonbacteraeota and *Bacteroidetes* compared to the control group. This gut dysbiosis changes the functioning ability of microbes and their metabolites like SCFAs, branched-chain amino acids and sugars which are major contributing components of the microbiota–gut-brain axis. Thus, DEHP can also cause neurodevelopmental disorders[101]. Oral administration of DEHP increased the population of *Lachnoclostridium*, whereas decreased *Clostridium sensu stricto*. DEHP altered the metabolite profile in the microbiota. Notably, DEHP can modify the gut microbiome to produce a potentially toxic metabolite p-cresol, which is correlated with neurodevelopmental disorders[102]. It was observed DEHP exposure can expand the abundance of *Lachnoclostridium bolteae* which can produce p-hydroxyphenylacetic acid, the immediate precursor of p-cresol. Thus, DEHP exposure enhanced the accumulation of a known biomarker of ASD (Autism Spectrum Disorder) while inhibiting butyrate synthesis. Butyrate is also a bacterial metabolite which helps in intestinal immune homeostasis and neuroprotective effects[103].

3.6. Bisphenol A

Bisphenol A (BPA) (Compound 2; Figure 5) is a chemical used to manufacture polycarbonate plastics in beverage containers, compact disks, plastic dinnerware, impact-resistant safety equipment, automobile parts and toys. BPA intake occurs from a coating of canned food, especially when the temperature of food/ drink in the container is higher. It is an Endocrine-Disrupting Chemical (EDC) which can cause gut microbiome dysbiosis. Proteobacteria, a dysbiosis marker increases after BPA exposure, but the population of *Akkermansia*, beneficial for the integrity of the gut barrier and reducing inflammation decreases[104] (Table 3). Prenatal BPA exposure in mice decreased *Bifidobacteria* having anti-inflammatory properties and thus resulted in flare-ups in inflammation causing several health as well as mental illness[105,106]. BPA exposure decreased the population of SCFA-producing microbes like *Ruminococcaceae* and *Oscillospira*[107]. BPA can induce chronic inflammatory diseases by increasing serum polysaccharide levels, gut barrier permeability as well as oxidative stress. Recently, Fu *et al*.,[99] have shown that BPA exposure can cause neurotoxicity in mice by damaging microbiota–the gut-brain axis. BPA exposure in male mice showed enhanced neuro-inflammation that affected their mental functions. BPA-induced dysbiosis in the intestinal microbiome decreased mucus production in the colon and serotonin levels in the brain, mucin 2 levels as well as propionic, caproic and butyric acid levels in the gut[108]. BPA affects

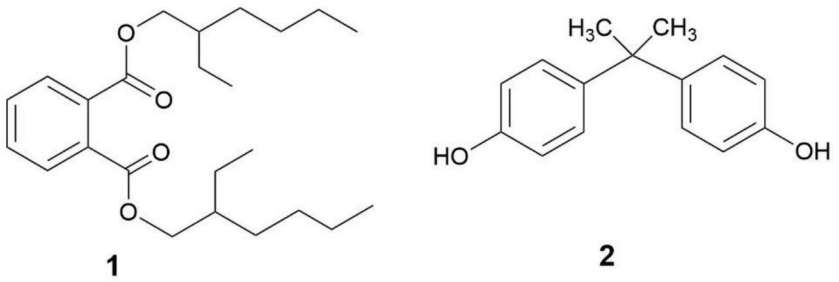


Figure 5. Structure of 1. Di-(2-ethylhexyl) phthalate (DEHP) and 2. Bisphenol A (BPA).

the integrated structure of the barrier between the gut and blood as well as between blood and brain. It causes inflammation in both the brain and gut along with mental ailments. BPA can also attack the gut liver axis causing hepatic inflammation. *Akkermansia* can increase immune response by increasing the thickness of the intestinal mucus and improving gut barrier function[104]. BPA can reduce the population of the beneficial microbe *Akkermansia*. Lack of *Akkermansia* is associated with enhanced levels of inflammatory cytokines such as Interleukin-18, Interleukin-1β, Tumor Necrosis Factor Alpha (TNF-α) and system Lipopolysaccharide (LPS). BPA-induced dysbiosis caused an increase in *E. coli* colony formation resulting in reduced antimicrobial activity and faecal lysozyme[105].

3.7 Nanomaterials

Nanomaterials with dimensions between 1 and 100nm are emerging as contaminants of concern in this era of nanotechnology. Nowadays nanomaterials are extensively used in several products including electronics, paint, textiles, pharmaceuticals, cosmetics, foods, filters and containers[109]. Due to their very

Table 4. Effect of nanomaterials and pesticides on gut microbiome

Name of Xenobiotics	Study Model	Exposure dose	Impact on the Gut Microbiome	Reference
Ag NP exposure	Rat model	9, 18, and 36 mg/kg body weight for 13 weeks	*Lactobacillus, Bifidobacterium*↑	Williams *et al,*[120]
Zinc oxide nanoparticle	Hens	25-100 mg/kg zinc oxide nanoparticle for 15 weeks	*Lactobacillus*↓ *Turicibacter*↑	Feng *et al.,*[121]
Single-walled carbon nanotubes (SWCNTs)	Mouse model	0.05, 0.5, and 2.5 mg/kg in mice for 7days	*Alitipes uncultured_bacterium* and *Lachnospiraceae bacterium A4*↑	Chen *et al.,*[123]
Pesticides: Glyphosate (Gly)	Honey bees	5 mg/L and 10 mg/L glyphosate in sucrose syrup for 5 days	*Guilliamella apicola* ↑ *Snodgrasella alvi* ↓ *Bifidobacterium*↓ *Lactobacillus*↓	Rueda-Ruzafa *et al.,*[124]
	Cow	0, 1, 10, and 100 µg/ml for 48 hrs	*Entodinium* ↓ *Epidinium* ↓ *Ophryoscolex* ↓ Dasytricha↓	Rueda-Ruzafa *et al.,*[124]
Pesticides: Pentachlorophenol (PCP)	Goldfish	0–100 µg/L for 28 days	ratio of Firmicutes/*Bacteroidetes*↓ *Bacteroidetes*↑ *Microbacterium, Chryseobacterium, Legionella, and Arthrobacter*↓	Kan *et al.,*[126]
Pesticides: Imidacloprid	Honeybees	natural field conditions up to 5 weeks of exposure	Alterations in *Frischella spp., Lactobacilli and Bifidobacteria*	Alberoni *et al.,*[127]
Pesticides: Epoxiconazole (EPO)	Rat model	0, 4 and 100 mg/kg/day for 90 days	Firmicutes↓ Proteobacteria, *Bacteroidetes*↑ *Enterobacteriaceae* and *Lachnospiraceae*↑	Xu *et al.,*[129]
Pesticides: Organophosphate Chlorpyrifos (CPF)	Rat model	1 or 5 mg/ kg/day for 21-60 days	*Bacteroides*, *Enterococcus*, and *Clostridium*↑ *Lactobacillus spp*. and *Bifidobacterium spp*. ↓	Condette *et al.,*[130]
Pesticides: Carbendazim (CBZ)	Mouse model	100 and 500mg/kg/body weight through diet for 4 weeks	*Bacteroidetes*↓ Firmicutes, Proteobacteria, *and* Actinobacteria↑	Jin *et al.,*[131]

small size and high surface area-to-volume ratios, Nanoplastics (NPs) can enter the living body very easily. NPs can induce very much toxic oxidative stress. Various types of nanomaterials such as silver composites, nano-TiO_2, carbon nanomaterials, and nano-ZnO are cytotoxic to bacteria, viruses and fungal organisms[110-117]. To get the advantages of their antimicrobial properties nanomaterials are added to paints, fabrics, antimicrobial surfaces, filters etc[118]. Due to NPs' ability for biodistribution and potential antimicrobial activity, NPs can also affect our gut microbiome. Although it was found that short-term exposure to silver nanoparticles for twenty-eight days in mice did not affect the gut microbiome[119], Williams *et al.*,[120] have shown that Ag NP exposure (9, 18 and 36 mg/kg body weight) in rats for 13 weeks reduced the abundance of Firmicutes and disturbed the expression of immunomodulatory genes in the ileum (Table 4). More than 25 mg/kg zinc oxide nanoparticle exposure to hens altered their microbiome diversity. The population of Firmicutes was decreased with increasing amounts of ZnO NPs and when ZnO NP exposure was 100 mg/kg, microbiome diversity was significantly reduced. Majorly, Bacilli, *Fusobacteria* and Proteobacteria were altered and *Lactobacillus* was reduced by ZnO NPs[121]. In piglets, low-level exposure to nano-ZnO through their diet altered the gut microbiome composition differently in specific locations. An increase of *Lactobacillus* in the colon *Streptococcus* in the ileum was found. On the other hand, reduction of *Oscillospira* and *Prevotella* in the colon along with *Lactobacillus* in ileum were recorded[122]. Oral administration of Single-Walled Carbon Nanotubes (SWCNTs) with doses 0.05, 0.5 and 2.5 mg/kg in mice for 7 days induced a metabolic inflammation response along with an increase in the abundance of proinflammatory bacteria *Alitipes,* uncultured_*bacterium* and *Lachnospiraceae bacterium A4*[123] (Table 4).

3.8 Pesticides

Due to the antimicrobial efficacy of some pesticides, they can affect the residential microbiome in living bodies and the overall health of animals. The metabolites after digestion of pesticides by gut microbes can affect the eubiosis of intestinal microbes themselves as well as host health[38] (Table 4). Glyphosate (Gly) (Compound 1; Figure 6) is one of the most popular herbicides used in agriculture. Gly acts as an inhibitor of 5-Enolpyruvylshikimate-3-Phospate Synthase (EPSP synthase in plants. It has the same effect also in bacteria[124]. It majorly affects the beneficial bacteria but harmful *Clostridium spp.* and *Salmonella* strains are resistant to Gly. Leino *et al.*,[125] have shown that Glyphosate can affect at least half of core human gut microbiota constituents. Another widely used pesticide Pentachlorophenol (PCP) (Compound 2; Figure 6) hinders the development of fish by causing oxidative stress and cellular damage in the liver and colon. Kan *et al.*,[126] have shown that PCP exposure in goldfish reduced the ratio of Firmicutes/*Bacteroidetes* and also increased the population of *Bacteroides* but the population of *Microbacterium*, *Chryseobacterium*, *Legionella* and *Arthrobacter* reduced. Neonicotinoid (Compound 3; Figure 6) insecticides such as Imidacloprid have a long-term effect on the gut microbial community of honeybees leading to intestinal dysbiosis. Various microbial genera and species such as *Frischella spp.*, *Lactobacilli* and *Bifidobacterial* were affected and the microbial diversity was significantly decreased[127]. Epoxiconazole (EPO) (Compound 4; Figure 6) is extensively used in agriculture as a popular fungicide[128]. Xu *et al.*,[129] have shown that a high dose exposure of EPO in drugs through diet for 90 days reduced the relative abundance of Firmicutes whereas numbers of Proteobacteria and *Bacteroidetes* were increased. The relative abundance of *Enterobacteria*ceae and *Lachnospiraceae* was also enhanced. It was observed that these microbiota dysbiosis due to EPO exposure can also

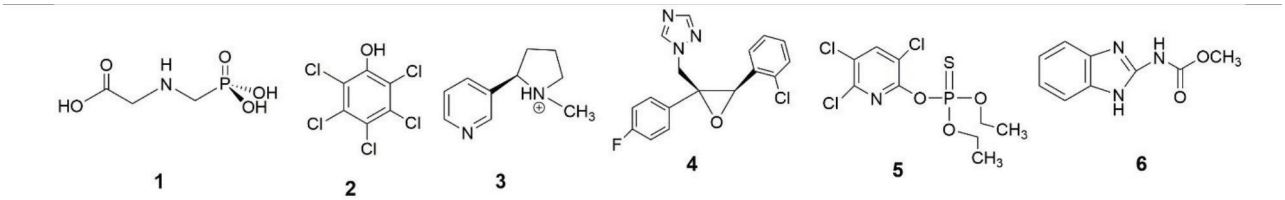


Figure 6. Structures of pesticides: **1.** Glyphosate **2.** Pentachlorophenol **3.** Neonicotinoid **4.** Epoxiconazole **5.** Chlorpyrifos **6.** Carbendazim.

be linked to impaired liver function. Organophosphate Chlorpyrifos (CPF) (Compound 5; Figure 6) is used to control insects in a variety of crops. Perinatal exposure to CPF can decrease rat pups' body weight, length, and intestinal development. These defects can be correlated with a CPF-induced increase in the relative abundance of *Bacteroides*, *Enterococcus*, and *Clostridium* and a decrease in the relative abundance of *Lactobacillus spp*. and *Bifidobacterium spp*. in rat intestines. Microbiota dysbiosis by CPF exposure has affected the mucosal barrier, increased bacterial translocation and stimulated the innate immune system[130]. Carbendazim (CBZ; methyl 2-benzimidazolecarbamate) (Compound 6; Figure 6) is a fungicide, high dose exposure of which in mice caused obesity, fatty liver development and enhanced level of system proinflammatory cytokines like interleukin-1β and interleukin-6. Jin *et al*.,[131] have shown that these adverse effects were related to gut microbiome dysbiosis caused by CBZ. CBZ decreased the relative abundance of *Bacteroidetes* and enhanced the relative abundance of Firmicutes, Proteobacteria and Actinobacteria at the phylum level.

3.9 Food Additives

Food additives are frequently used to increase food storage time, texture, colour, flavour, aroma and nutritional content. It has been proven that sustained intake of several food additives in high doses can cause diseases like colitis, colorectal cancer and metabolic syndrome[132]. It is very important to understand the effect of food additives on gut microbes so that we become aware of the toxic substances we are taking to satisfy our taste buds. There are several categories of food additives which are being used today.

NAS (Non-caloric Artificial Sweeteners) are widely used food adulterants which add sweetness to drinks and snacks without any high caloric consumption. However, scientists have become concerned about the hazards of NAS. Suez *et al*.,[133] have shown that consumption of commonly used NAS formulations including saccharin, sucralose and aspartame (Compound 1, 2 and 3; Figure 7) resulted in intolerance to glucose in mice due to changes in gut microbial structure and function. The gut microbes of saccharin-consuming mice were found to have dysbiosis with more than 40 Operational Taxonomic Units (OTUs). The relative abundance of *Bacteroides* genus order *Clostridiales* was increased (Table 5). Interestingly, NAS did not induce any glucose intolerance in any antibiotic-treated or microbe-free mice. These NAS-induced metabolic defects were fully transferred to mice free of germs when faeces of NAS-consuming mice were transplanted in germ-free mice. These observations proved the relation between NAS-created intolerance to glucose and gut microbial health. Oliver-Van Stichelen *et al*.,[134] have shown that prenatal exposure to other artificial sweeteners like acesulfame-K and sucralose in mouse pups damaged the detoxification capability of the liver due to

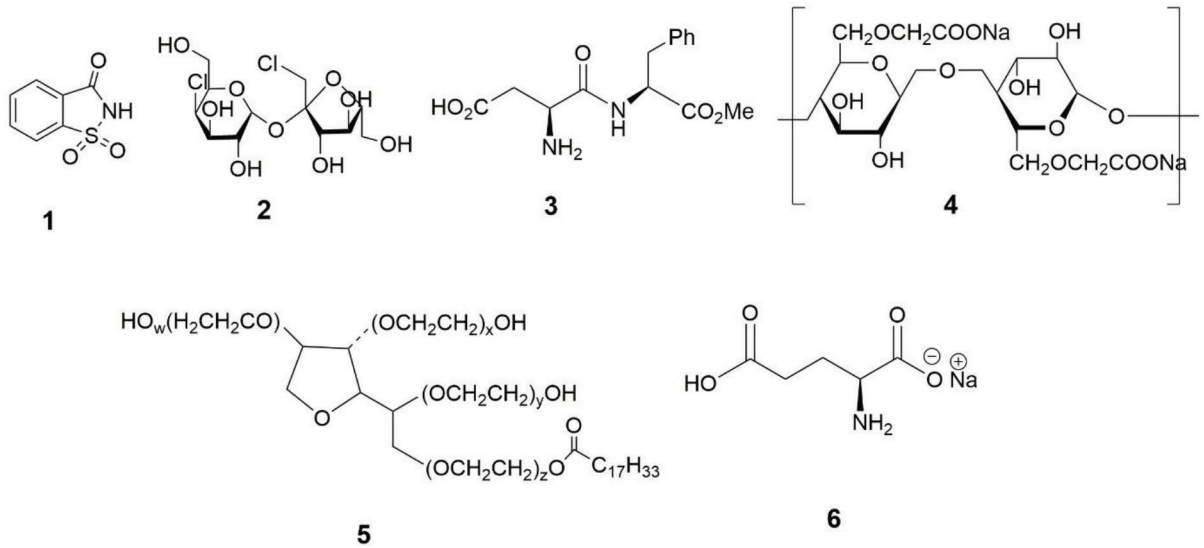


Figure 7. Structures of food additives: **1.** Saccharin, **2.** Sucralose, **3.** Aspartame **4.** Carboxymethyl cellulose (CMC) **5.** Polysorbate 80 (P80) **6.** Monosodium glutamate (MSG).

altered microbiome and their metabolites. Another FDA-approved NAS, neotame when consumed by mice can reduce the α-diversity of the gut microbiome. Neotame taken orally can reduce the release of malic and glyceric acids while enhancing the release of lipids and cholesterol in the host stool[135]. Emulsifiers like Carboxymethyl Cellulose (CMC) and Polysorbate 80 (P80) (Compound 4 and 5; Figure 7) are generally used in processed foods like bread, cakes etc to give them tempting texture, artificial freshness and storage time. The detergent-like properties of emulsifiers can damage the barrier integrity of gut tissue by causing alteration in microbiome composition and their metabolites. Oral administration of carboxymethylcellulose or polysorbate-80 to mice for twelve weeks enhanced the population of *Ruminococcus gnavus* which is mucus-degrading bacteria but the level of beneficial *Bacteroidales* is reduced in the feces (Table 5.). Gut microbial dysbiosis causes diminishing of the stomach mucus layer, inflammation, obesity and glucose dysregulation. This type of emulsifier-induced symptoms could not be observed in germ-free mice. In addition to that, these damages could be relocated to germ-free mice by FMT from diseased mice[136]. Sustained intake of P80 and CMC-enriched diet by mice induced inflammation in the colon, which ultimately developed neoplastic lesions[137].

Food preservatives are used to inhibit enzymatic reaction, aerial oxidation and growth of microbes in food. Commonly used synthetic preservatives are salt, vinegar, nitrites, benzoates, sulfites and sorbates. Although they have been believed to be benign till now, modern researchers have suggested that food preservatives can trigger gut microbiota dysbiosis in vitro and animal models[138]. Sodium bisulfite and sodium sulfite inhibited the growth of four beneficial gut bacteria named *Lactobacillus* species *casei*, *plantarum* and *rhamnosus*, and *Streptococcus thermophilus in vitro*[139]. Peng *et al.*,[140] have shown that Potassium sorbate can weaken the immune system of zebrafish by altering the composition and function of the gut microbiome. Nitrate exposure can cause metabolism disorder arising from gut dysbiosis in *Bufo gargarizans* tadpoles (Table 5). The aerobic Proteobacteria occupied the niche of anaerobic

Table 5. Effect of food additives and microplastics on gut microbiome

Name of Xenobiotics	Study Model	Exposure Dose	Impact on the Gut Microbiome	Reference
Non-caloric artificial sweeteners (NAS)	Mouse model	Saccharin 0.1 mg/ml for 5 weeks	*Bacteroides* genus, *Clostridiales*↑	Suez *et al.*,[133]
Non-nutritive sweeteners (NNS)	Mouse model	mixed solution of sucralose and acesulfame-K for 21 days	Costridiales, *Lactobacilli, Enterobacteria*↑ Verrucomicrobia, *Akkermansia muciniphila*↓	Oliver-Van Stichelen *et al.*,[134]
Emulsifier: carboxymethylcellulose or polysorbate-80	Mouse model	1.0% w/v in drinking water for 12 weeks	Verrucomicrobia, *Ruminococcus gnavus*↑ *Bacteroidales*↓	Chassaing *et al.*,[136]
Food preservatives: Sulfites	In-vitro study	10–50 and 1000-2000ppm $NaHSO_3$	*Lactobacillus* species *casei*, *plantarum rhamnosus*, and *Streptococcus thermophilus*↓	Irwin *et al.*,[139]
Food preservatives: Potassium sorbate (PS)	Zebrafish	0.1 g L^{-1} and 1 g L^{-1} aqueous solutions of PS for 2 weeks	*Reyranella and Sphingomonas, Ochrobactrum and Plesiomonas*↑ *Rhizobacter*↑	Peng *et al.*,[140]
Food preservatives: Nitrate	Rat model	1.84–2.45 mg/day nitrate intake	*Lachnospiraceae and Erysipelotrichales*↑	Khambadkone *et al.*,[141]
Monosodium glutamate (MSG)	Piglets	3% MSG with diet for 30 days	*Faecalibacterium prausnitzii and Roseburia*↑	Feng *et al.*,[142]
Microplastics	Mouse model	0.2 to 2 mg/Kg microplastics for 28 days	Proteobacteria↑ *Ruminiclostridium, Lachnoclostridium, Anaerotruncus and Ruminiclostridium*↓	Qiao *et al.*,[144]

Bacteroidetes and Fusobacteria due to nitrate exposure. This preservative also hindered the fatty acid metabolism pathway and amino acid metabolism pathway. Nitrated meat products are found to be associated with mania in humans as well as altered behaviour and brain gene expression in rats[141].

Monosodium Glutamate (MSG) (Compound 6; Figure 7) is a well-known flavour enhancer. Feng *et al.*,[142] have shown that MSG and fat intake by growing pigs developed diversified gut microbiota. MSG along with fat increased the population of microbes associated with energy extraction. MSG enhanced the abundance of *Roseburia* and *Faecalibacterium prausnitzii* whereas fat increased the amount of *Prevotella* in the gut.

3.10 Microplastic

Plastics are indispensable materials nowadays starting from packaging to everyday products such as pharmaceuticals, cosmetics, textiles, facemasks and surgical instruments. Microplastics (MPLs) and Nanoplastics (NPLs) are harmful forms of plastics considered to be an environmental threat worldwide. They are environmentally, chemically, or mechanically degraded plastic particles which can be incorporated by living systems through inhalation of contaminated air, ingestion of contaminated water and food, and other routes[143]. Prolonged exposure of carboxylated polystyrene M/NPLs (PS-COOH) and polystyrene amine M/NPLs (PS-NH_2) in mice damaged GI tract resulting in a reduction of tight junction barrier integrity. Oral exposure to these M/NPLs was found to have sufficient gut microbiota dysbiosis. The M/NPLs exposure enhanced the population of opportunistic pathogens which are associated with weakening of intestinal barrier function but decreased beneficial microbes with tight junction-promoting functions[144] (Table 5).

4. Conclusion

In conclusion, we can say that there is a profound relationship between xenobiotic exposure and the health of the gut microbiome which is our second brain. The evidence from this review reveals that xenobiotics can alter the gut microbial balance and their metabolic functions. A clear understanding of the relationship between xenobiotics and gut microbiome as well as host health can open a new era of microbiome-based therapy. A lack of knowledge about the metabolic activities of the human gut microbiome is preventing us from using the gut microbial community to get good health or treat diseases. In future, more and more research should be done to enrich our knowledge about the relationship among xenobiotic exposures, gut microbiota, and host health. This knowledge will help us in developing novel therapeutic techniques to reverse gut microbe changes and restore gut homeostasis as well as host health. The understanding of mechanisms involved in xenobiotic-induced alteration in gut microbiome will guide us to achieve the detoxification of these chemicals.

5. Data Availability Statement

The data used, analysed, and reviewed were collected from the corresponding research articles and online research databases included in the Reference section. All the figures have been created using ChemDraw Ultra 18.0 software. The Scheme has been created using ChemDraw Ultra 18.0 and Microsoft Paint software. The Graphical Abstract has been created using Microsoft Paint and Microsoft Powerpoint software.

6. References

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