A Review on Gut Remediation of Selected Environmental Contaminants: Possible Roles of Probiotics and Gut Microbiota

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Abstract: Various environmental contaminants including heavy metals, pesticides and antibiotics can contaminate food and water, leading to adverse effects on human health, such as inflammation, oxidative stress and intestinal disorder. Therefore, remediation of the toxicity of foodborne contaminants in human has become a primary concern. Some probiotic bacteria, mainly Lactobacilli, have received a great attention due to their ability to reduce the toxicity of several contaminants. For instance, Lactobacilli can reduce the accumulation and toxicity of selective heavy metals and pesticides in animal tissues by inhibiting intestinal absorption of contaminants and enhancing intestinal barrier function. Probiotics have also shown to decrease the risk of antibiotic-associated diarrhea possibly via competing and producing antagonistic compounds against pathogenic bacteria. Furthermore, probiotics can improve immune function by enhancing the gut microbiota mediated anti-inflammation. Thus, these probiotic bacteria are promising candidates for protecting body against foodborne contaminants-induced toxicity. Study on the mechanism of these beneficial bacterial strains during remediation processes and particularly their interaction with host gut microbiota is an active field of research. This review summarizes the current understanding of the remediation mechanisms of some probiotics and the combined effects of probiotics and gut microbiota on remediation of foodborne contaminants in vivo.

Keywords: environmental contaminants; remediation; probiotics; gut microbiota; foodborne

1. Introduction

The anthropogenic activities, rapid industrialization and urbanization have resulted in generation of hazardous toxic pollutants and consequent contamination of soil and water resources. For example, antibiotics (ABs) from medical waste, livestock manure and aquatic breeding have resulted in surface water contamination [1]. In addition, the large area of soil is contaminated by heavy metals (HMs) depositions and pesticides spraying [2]. It is reported that about 2.5 million hectares of soil area in Europe alone is a victim of pollution [3]. In China, mining has resulted in severe HMs contamination of $2.88 \times 10^6$ ha of land, with an additional mean area of 46,700 ha polluted annually [4]. HMs and pesticides can accumulate in agricultural products grown in the contaminated soil [5,6]. Hence, these environmental contaminants are readily transmitted into human body through water and diet, exerting

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negative effects on human health, such as inflammation [7,8], oxidative stress [9–11] and intestinal disorder [12–14]. Remediation of contaminants originated from environment has thus become a primary concern worldwide.

Many strategies have been developed for the remediation of soil and water contamination over the past decades, including physicochemical, microbial and phytoremediation methods. Phyto- and microbial remediation is regarded as useful approach with minimal site disruption [15], and eliminates the requirement for soil excavation and transport [16]. However, the total area that can be repaired in these traditional ways is far smaller than the total area of contamination. Thus, human exposure to contaminants is currently inevitable, and alternative methods are needed to protect not only the environment but also human against environmental contaminants.

Probiotics and live microbes that exert benefit on human health when supplemented in sufficient amounts [17], are considered as a promising tool for protection against foodborne contaminants. Evidences have shown that Lactobacilli can alleviate acute and chronic cadmium (Cd) toxicity [18,19], protect organisms against pesticides toxicity [20,21], reduce the risk of antibiotics associated diarrhea (AAD), and meantime rebalance the gut microbiota (GM) [22]. GM comprises about $3.8 \times 10^{13}$ microorganisms inhabiting in the gastrointestinal tract (GIT), and the majority of these species belong to six bacterial phyla: Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia [23,24]. GM has been known to play significant role in many physiological functions, such as regulating immunity [25] and metabolism [26], and also in the bioavailability and toxicity of various contaminants [27,28]. Mounting evidences have suggested that GM can be modified by probiotics and contribute to detoxication of environmental contaminants [29]. Nevertheless, the possible roles of GM and probiotics in mediating the remediation of foodborne contaminants in mammals have not received much attention, especially how the GM modified by probiotics interacts with contaminants and how these interactions are relevant to host health. The aim of this study was to summarize the impact of environmental contaminants including HMs, pesticides and ABs on GM and host physiology, with focus on the potential mechanisms of probiotics during bioremediation processes. It could help to gain a better comprehension of the remediation mechanism of probiotics and provide new perspectives for future applications with probiotics.

2. Effect of HMs, Pesticides and ABs on the Composition and Function of GM

HMs, pesticides and ABs currently used in diverse industrial and agricultural sectors and in daily life are leading to the spread of contaminants into the environment, therefore increasing health related problems worldwide. During the last few decades, as more roles of GM are revealed, investigators have paid more attention on the impact of contaminants on GM mostly by analyzing stool microbiome in rodents, poultry, and aquatics using high-throughput sequencing techniques. These studies have demonstrated that the GM imbalance is often correlated with the occurrence of disorders of energy metabolism, nutrient absorption, and immune system [30,31].

2.1. HMs

HMs, such as Cd, chromium (Cr), arsenic (As), lead (Pb), nickel (Ni) are hard to be remediated and they exert high level of toxicity on animals and humans. About 40–60% of ingested metals are absorbed across the intestinal barrier [32,33], causing oxidative stress, inflammation, tissues damages, and gastrointestinal disorders [34].

HMs cause marked alterations in the composition of the GM (Table 1). First, a decrease in richness as well as the diversity of GM, is often observed after exposure to HMs [35,36]. Second, the ratio of Bacteroidetes to Firmicutes at phylum level is usually increased upon HMs exposure, which was thought to be associated with loss of body weight [37]. Recent studies revealed that exposure to Cd have contributed to profound effects on the microbiome in the intestinal tract of mice [38,39]. The ratio of Firmicutes to Bacteroidetes decreased significantly in mice treated with low (10 or 20 mg/kg) and high concentrations (100 mg/kg) of Cd [14,30]. Similar changes were also observed in mice exposed to
As (10 mg/L) and Cr (VI) (100 mg/L) [29,40]. In Cr (VI)-treated mice, the proportion of Bacteroidetes and Tenericutes increased, and the proportion of Firmicutes declined, significantly. The exception to the tendency of alteration is Pb, where the ratio of Bacteroidetes and Firmicutes decreased [41]. Third, the influence of HMs on GM is usually dose-dependent. Higher concentration of Cd treatment posed a greater impact on intestinal flora than lower concentration [38].

The compositional and functional alterations of the GM are often linked to the intestinal and overall physical health of the host. Generally, the population of beneficial bacteria related to host physiology and biosynthesis was decreased and the number of pathogenic bacterial species correlated with the inflammation and oxidative stress was increased [29,42]. In Cd-treated mice, the abundance of beneficial bacteria such as Bifidobacteri and Lactobacilli was decreased significantly [38], whereas the relative abundance of harmful bacteria, Clostridiales, Prevotella and S24-7 was increased; and Cr (VI) induced the decrease of the relative abundance of Lachnospiraceae in mice [29].

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2.2. Pesticides

Pesticides are widely applied in agriculture to resist insects, weeds, and plant pathogens to promote plant growth. The crops are exposed to pesticides, which can readily get into human GIT through daily diet. Low levels of pesticides exposure can give rise to long-lasting adverse effects on skin, endocrine, and especially nervous system by inducing generation of free radicals that might cause lipid peroxidation, DNA damage, cell death and possible carcinogenic effects [52–54].

Many researchers have demonstrated the essential role of GM in the metabolism of pesticides in host. Some pesticides are known to be metabolized by the enzymes produced by GM. Organophosphate insecticide chlorpyrifos get metabolized into a more toxic molecule 3,5,6-trichloro-2-pyridinol via biotransformation by GM, resulting in biologically relevant and toxic consequences on host health. Whereas certain bacterial species, e.g. Pseudomonas spp. (ATCC700113), L. lactis, E. coli and L. fermentum present in GIT, are capable of utilizing 3,5,6-trichloro-2-pyridinol as their sole carbon and energy source [55–57]. In turn, the composition and function of GM are profoundly affected by long-term exposure to pesticides, correlated with various metabolic and immune diseases [28].

Organophosphorus (OP) pesticide has been extensively applied since 1950s. Chlorpyrifos is a typical OP insecticide that can result in altered host metabolism, increased bacterial translocation, and alterations in GM compositions. For instance, chronic chlorpyrifos exposure in rats increased the abundance of opportunistic pathogens, and unfavorable metabolic-related strains, resulting in obese and diabetic phenotypes [58]. In addition, chlorpyrifos exposure affected the proliferation of subpopulations of some strains (Enterococcus spp., Bacteroides spp.) and increased bacterial translocation in spleen and liver of rats [59,60]. In the simulator of the human intestinal microbial ecosystem (SHIME) model, chlorpyrifos also had a great impact on the population of culturable bacteria, leading to an increase in Enterobacteria, Bacteroides spp., Clostridia count and decrease in Bifidobacterial count [60,61]. Similar experiments conducted in mice showed that the relative abundance of some key microbes was
significantly altered under chlorpyrifos stress, with altered urine metabolites related to the metabolism of amino acids and energy, SCFAs, phenyl derivatives and bile acids [62]. Different bile acids can bind to different receptors and promote the absorption of dietary fats, regulate lipid and glucose metabolism, and shape the GM [63,64]. GM can transform bile acids and altered GM would influence the pool of bile acids and the host’s energy metabolism.

Malathion, diazinon and glyphosate are another three representatives of OP pesticide. In malathion-treated mice, gut microbiome development and quorum sensing were perturbed, with an increase in the relative abundance of bacterial genes associated to quorum sensing-related behaviors such as motility and pathogenicity [65]. Sex-specific impact on gut microbiome by diazinon was examined in a mouse model. Specifically, several bacterial genera, including Bacteroidaceae_Bacteroides, Burkholderiales_Other, Clostridiaceae_Other, and Erysipelotrichaceae_Coprobacillus, were only observed in male mice, while Lachnospiraceae_Butyryribrio Lachnospiraceae_Shuttleworthia, and Staphylococcaceae_Staphylococcus were completely inhibited in males after diazinon exposure [66]. The effect of glyphosate on poultry microbiota was evidenced by the elevated resistance of pathogenic bacteria including Salmonella enteritidis, Salmonella gallinarum, Salmonella typhimurium, Clostridium perfringens and Clostridium botulinum, and increased susceptibility of most of the beneficial bacteria such as Enterococcus faecalis, Enterococcus faecium, Bacillus badius, Bifidobacterium adolescentis and Lactobacillus spp. [67].

Organochloric pesticide (OCP), another type of common pesticide, interferes with intestinal flora, lipid metabolism, and tissue and body weight in animals. In mice, OCP induced increased abundance of Firmicutes and Proteobacteria, and decreased abundance of Bacteroidetes, Verrucomicrobia, and Actinobacteria. Meantime, the expression of genes involved in bile acid reabsorption by the terminal ileum was down-regulated, and compensatory expression of genes in synthesis of bile acids was up-regulated in the liver [68]. When permethrin was administered through diet in rat, it caused reduction in abundance of Bacteroides-Prevotella-Porphyromonas species and increase in the abundance of Enterobacteriaceae and Lactobacillus in fecal microbiota; altered SCFAs levels were registered over a 4-month period [69]. Pentachlorophenol exposure in gold fish led to an increased in the Bacteroidetes abundance and a decrease in the ratio of Firmicutes to Bacteroidetes in the gut, which played crucial roles in the reduction of body weight. Bacteroides genus within the Bacteroidetes phylum was significantly correlated with pentachlorophenol exposure dosage and duration [70].

Imidazole is widely used to inhibit fungus in agriculture. Recent studies revealed that GM dysbiosis induced by imidazole exposure is often associated with hepatic metabolism disorder and hepatic toxicity. When imazalil was orally given in zebrafish and mice, the abundance of Bacteroidetes was decreased, and Firmicutes increased in the gut at phylum level. In mice at the genus level, the abundance of Lactobacillus and Bifidobacterium decreased while those of Deltaproteobacteria and Desulfovibrio increased in response to imazalil exposure. In addition, the transcription of genes such as Aco, Cpt1, Acc1, Srebp1a and Fas, related to glycolysis and lipid metabolism was significantly decreased in the mouse liver [71,72]. In the mice that were exposed to carbendazim, the amounts of Bacteroidetes in the feces, and richness and diversity of GM in the cecum decreased significantly after the 5-day exposure. Analysis of operational taxonomic units (OTU) indicated that a total of 361 out of 3271 identified OTUs were significantly changed [31].

2.3. ABs

Abs are widely used in stockbreeding, veterinary and human medicines [73,74]. Part of the ingested ABs by humans and animals can enter the environment through feces or urine [75]. Large quantity of ABs was detected in the ecosystem [76,77]. Hence, humans are readily exposed to antibiotic contamination passively in addition to medical route. The side effects of ABs range from relative mild ones, such as allergy, asthma, and diarrhea to severe ones, e.g., death [78].

ABs administration has been correlated with changes in the population structure of microbiome, which might be linked to a multitude of diseases. In particular, AAD and Clostridium difficile
infections can be common following ABs treatment [79,80]. It has been previously shown that the microbial diversity was significantly reduced after treatment with ampicillin, streptomycin and clindamycin in the cecal and large intestine contents of mice. The Bacteroidetes population was drastically reduced, which never fully recovered following cessation of treatment, and the outgrowth of two dominant genus, Stenotrophomonas and Xanthomonas [81]. The predominant genus Stenotrophomonas is noteworthy since this highly antibiotic resistant bacterium is also a potential emerging opportunistic pathogen [82]. Treatment with clindamycin and ampicillin made the patients susceptible to Clostridium difficile infection and decreased Clostridium scindens count, which is a secondary modulator of bile acid metabolism [83]. A number of recent studies revealed that the abundance of Proteobacteria phylum in microbiota was significantly increased as a consequence of antibiotic administration [84–86]. Proteobacteria encompass a wide variety of pathogens, such as Escherichia, Vibrio, Salmonella, Helicobacter, Yersinia, Legionellales and others. E. coli is responsible for a vast majority of Escherichia-related pathogenesis, and other members of this genus have also been implicated in human diseases [87,88]. Salmonella species are known intracellular pathogens and certain serotypes are responsible for illness [89]. Altogether these findings suggest that altered structure of intestinal microbiota is related to the pathogenesis of diseases.

ABs can affect the colonization resistance of host. Treatment with cefoperazone [90], tigecycline [79], clindamycin [80], or clindamycin in combination with a five-antibiotic cocktail in C57BL/6 mice had decreased the colonization resistance, as a result of a decrease in Lachnospiraceae and Barnesiella and an increase in Lactobacillaceae and Enterobacteriaceae. These results were largely consistent with human studies [91,92].

Effect of ABs on GM can be persistent. Fouhy et al. (2012) [84] evaluated the short-term recovery of the GM following parenteral ampicillin and gentamicin treatment for infant within 48 hours of birth. It was shown that the abundance of Proteobacteria remained significantly higher and the number of different Bifidobacterium species was reduced in the infants after 8 weeks of treatment with ABs. It is, thus, obvious that the use of certain ABs in early life can significantly affect the evolution of the infant GM. Another study investigated the short and long-term effects of macrolides on 2–7 year old children (N = 142), and found depletion of Actinobacteria, increased abundance of Bacteroidetes and Proteobacteria and increased macrolide resistance, which can persist for over 6 months. Additionally, it was mentioned that the use of macrolides in early life increased the risk of asthma and weight gain [85]. A study in mice reported that Bacteroidetes was drastically reduced following treatment with the antibiotic mixture of ampicillin, streptomycin, and clindamycin and never fully recovered after cessation of ABs treatment [81].

The literature regarding the role of altered GM in the development of ABs-related side effects, however, is scarce. The current understanding is that oral intake of ABs lead to disturbance of composition and more importantly the metabolism of GM, which might correlate with disrupted physiology of the host. Study in mice treated with combinative ABs of penicillin, vancomycin and clortetracycline revealed significant alterations of microbial structure, and altered regulation of hepatic metabolism of lipids and cholesterol, as well as increase of the copies of key genes involved in the metabolism of SCFAs synthesis in fecal and cecal samples [93]. Metagenomic analysis in mice receiving early-life therapeutic-dose pulsed tylosin showed that tylosin intervention decreased the modules involved in glycolysis, gluconeogenesis and tRNA biosynthesis and increased the modules involved in citric acid cycle and nucleoside and amino acid biosynthesis [94]. A study in piglets treated with a mixture of ampicillin, gentamicin and metronidazole also indicated that altered GM was associated with increased metabolism of aromatic amino acids and decreased expression of neurotransmitter in hypothalamus [95].
Table 1. Recent studies on the effects of foodborne contaminants on hosts and GM.

| Type | References | Models | Pollutants and Dosage | Outcomes | Main Conclusion on GM |
|------|------------|--------|----------------------|----------|-----------------------|
| HMs  | [30]       | Mice   | Cd at 10 mg/L for 10 weeks | Hepatic inflammation, energy metabolism dysregulation | *Firmicutes*, *Bacteroidetes*, *γ- Proteobacteria* |
|      | [41]       | Mice   | Pb at 32 ppm for 2 weeks | Bodyweight ↑ | *Firmicutes/Bacteroidetes*, *Desulfovibrioaceae*, *Barnesiella*, *Clostridium XIVB*, *Lactococcus*, *Enterorhabdus*, *Caulobacteriales* |
|      | [40]       | Mice   | As at 10 ppm for 4 weeks | Perturbed lipid metabolites, indole-containing metabolites, isoflavone metabolites, and bile acid metabolites | *Firmicutes*, *Bacteroidetes* |
|      | [29]       | Mice   | Cr (VI) at 2 mM for 7 weeks | Oxidative stress↑, liver damage, GM disturbance | *Bacteroidetes*, *Tenericutes*, *Firmicutes*, *Paraprevotellaceae*, S24-7, *Lachnospiraceae* |
|      | [58,60]    | Rats   | Chlorpyrifos at 0.3 or 3.0 mg/kg bodyweight/day for 9 days | Obese and diabetic phenotypes↑, bacterial translocation↑ | *Sutterella*, *Candidateis arnhmitius*, *Olsenella*, *Clostridium sensu stricto* 1, *Amphibacillus*, *Enterorhabdus*, *Alloprevotella* |
|      | [65]       | Mice   | Malathion at 2 mg/L in drinking water (~0.6 mg/kg bodyweight/ day) for 13 weeks | Motility and pathogenicity↑ | *Corynebacterium*, S24-7, *Planococcaceae*, *Christensenellaceae*, *Clostridium*, *Lachnospiraceae_Other*, *An aerotipus*, *Blautia*, *Dorea*, *Roseburia*, *Mogibacterium*, *Akkermansia* |
|      | [66]       | Mice   | Diazinon at 4 mg/L for 13 weeks | Taurine level↑, glycine acetyltransferase and threonine dehydrogenase↑ in male mice | *Bacteroidaceae_Bacteroides*, *Burkholderiales_Other*, *Clostridium_Other*, *Erysipelotrichaceae_Coprobacillus*, *Lachnospiraceae_Butyribacillus*, *Lachnospiraceae_Shuttlesworthia*, *Staphylococcaceae_Staphylococcus* ↓ |
|      | [68]       | Mice   | p,p'-dichlorodiphenyldichloroethylene and β-hexachlorocyclohexane at 1 and 10 mg/kg body weight/day, for 4 weeks, respectively | Bile acid reabsorption in the terminal ileum and compensatory↑, bile acid and hydrophobicity↑, the genes expression on synthesis of bile acids in the liver↑ | *Firmicutes*, *Proteobacteria*, *Bacteroidetes*, *Verrucomicrobia*, *Actinobacteria* |
|      | [70]       | Gold Fish | Pentachlorophenol at 0, 10, 50, and 100 μg/L for 28 days | Body weight and liver weight↑, oxidative stress↑, liver damage↑ | *Bacteroidetes*, *Firmicutes*, *Bacteroides*, *Chryseobacterium*, *Microbacterium*, *Arthrobacter*, *Legionella* |
|      | [72]       | Zebrfish | Imazalil at 100 and 1000 μg/L for 1.7 and 21 days | Glucokinase↑, hexokinase 1↑, pyruvate kinase↑, cytosolic Phosphoenol pyruvate carboxykinase (Pepck)↑ in liver↓ | *Bacteroidetes*, *Firmicutes* |
|      | [71]       | Mice   | Imazalil at 25, 50 or 100 mg/kg body weight daily for 4 weeks | Genes related to glycolysis and lipid metabolism↑ | *Lactobacillus*, *Bifidobacterium*, *Deltaproteobacteria*, *Desulfobrio* |
|      | [96]       | Rats   | Epoxiconazole at 4 and 100 mg/kg body weight/day for 90 days | Weight of the liver and kidney↑, total bilirubin and cholinesterase in serum↑, blood glucose↑ | *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Lactobacillaceae*, *Bacteroidacae*, *Enterobacteriaceae*, *Lachnospiraceae* |
|      | [81]       | Mouse  | The mixture of ampicillin, streptomycin, and clindamycin at 1 mg/mL for 2-4 week | The ceca size↑, a deeper shade of brown in ceca | Microbial diversity↑, *Bacteroidetes*, *Stenotrophomonas*↑, *Xanthomonas*↑ |
|      | [95]       | Piglets | The mixture of ampicillin, gentamicin, and metronidazole at 150, 4, and 30 mg/kg/day, respectively, for 25 days | Neurotransmitters in blood and hypothalamus↑, amino acids in feces, blood and hypothalamus↓ | Microbial diversity in feces↑, *Firmicutes*, *Actinobacteria*, *Streptococcus*, *Lactobacillus*, *Bifidobacterium*, *Blautia*, *Klebsiella*, *Eurypathobacillus*, *Spirochaetes*, *Tenericutes*, *Ruminococcus*, *Clostridium*, unclassified *Clostridiales*, *Christensenella*, *Bacteroides*↑, *Prevotella* ↓ |

↑: Increase of relative abundance of the species or the severity of the outcomes; ↓: Decrease of relative abundance of the species or the severity of the outcomes.
3. Probiotics as a Potential Tool in Contaminants Remediation

Increasing evidence demonstrated that oral supplementation of probiotics is one of the effective strategies for protection against foodborne contaminants-induced toxicity. In general, probiotics applied in toxicant remediation are selected based upon their safety and viability during passage through the GIT [97] and importantly their capacity of contaminants adsorption [98]. The probiotic effects on the hosts are usually assessed by monitoring the individual growth, measuring the amount of pollutant and related biomarkers in tissues, and analyzing the compositional and functional changes of stool microbiota using 16S rRNA sequencing in murine and other models. Nonetheless, the interaction between probiotics and the GM is still poorly understood.

3.1. Role of Probiotics in HMs Remediation In Vivo

The protective effects of probiotics against HMs toxicity have been extensively studied. Supplementation of single probiotic or a combination of probiotics in mammalians has shown positive results in alleviating the toxicity of HMs including Cd, Hg, Cr, As and Pb (Table 2).

Probiotics utilized to reduce the toxicity of HMs are generally Lactobacilli, as they have excellent binding capacity for HMs, evidently lowering the availability of HMs for the host [99]. It has also been speculated that living probiotic strain L. plantarum CCFM8610 might competitively inhibit the intestinal absorption of Cd by increasing the dissolution and uptake of divalent essential elements like Ca, Mg, and Fe [18]. Probiotic strains can also promote gastrointestinal peristalsis, hence the excretion of HMs in feces is facilitated [18]. Furthermore, probiotic strains can limit the entrance of HMs by enhancing intestinal barrier function and regulating tight junction of epithelium of small intestine. Administration of L. plantarum CCFM8610 reversed all of the reductions of mRNA expression of tight-junction proteins (ZO-1, ZO-2, occludin, and claudin-1) caused by Cd exposure, decreased intestinal permeability and reduced Cd leakage into systemic circulation [50]. Preventing systemic absorption of HMs by probiotics thus leads to alleviation of oxidative stress in various tissues and consequent mitigation of tissue damages as reported [100–102]. For example, co-treatment of L. plantarum CCFM8610 and Cd cause a decreased production of metallothionein and downregulation expression of genes in the mitogen-activated protein kinases (MAPK) pathways in the liver [19]. Metallothionein has a high affinity for divalent cations [103] and the MAPK pathway is associated with reactive oxygen species production [19]. More recently, evidences have suggested that probiotics play a role in restoring the altered composition and function of GM induced by HMs. L. reuteri DSM17938 intervention contributed to restoring intestinal homeostasis in patient with low-Ni diets and the increase of lactic acid bacteria (LAB) biodiversity [104].

To date, almost all studies on the efficacy of probiotics were carried out in animals, the only case reported in human was that of L. rhamnosus GR-1 (LGR-1)-supplemented yogurt which protected against the absorption of As and Hg in pregnant women and children [105]. Moreover, the effect of HM bioremediation by probiotics is strain-dependent and specific. Although the strain LGR-1 was effective in reducing Hg and As absorption, it could not significantly reduce the blood levels of Pb and Cd in populations, indicating the need for specific probiotics or cocktails of probiotics for protection against different types of HMs.
3.2. Probiotics’ Role in Pesticides Remediation In Vivo

Expensive drugs have been developed and long-time therapies have been employed to fight against damages caused by pesticides [106]. More economic alternatives are hence needed to reduce the adverse effects of pesticides. Mounting evidences have highlighted probiotics in mitigating the adverse effects of pesticides (Table 2), and their protective mechanisms are summarized as below. First, *Lactobacilli* protect against pesticides-induced oxidative stress and downstream cellular damage. A few researches have shown that supplementation with *Lactobacillus plantarum* ATCC334 could decrease DNA damage in rats exposed to a carcinogen 1,2-dimethylhydrazine [54]. Second, probiotics maintain the integrity of intestinal barrier and reduce the absorption of pesticides [108]. It was found that *L. plantarum* MB452 enhanced the expression of tight junction proteins occludin, ZO-1, ZO-2, and cingulin in the Caco-2 intestinal cell-line [109]. Probiotics *L. rhamnosus* strain GG (LGG) and LGR-1 reduced the absorption of parathion or CP in a Caco-2 Transwell model [21]. Third, recent studies found that a few probiotics, mainly *Lactobacillus* from dairy products and wheat, were capable of degrading OCP enzymatically with phosphohydrolase [98,110]. Fourth, *Lactobacilli* stimulate host’s own immunity and detoxification mechanisms to resist pesticides and pathogen invasion. In the study using pattern insects, *L. casei* was found stimulating phase-II detoxification system and rescued malathion-induced physiological impairments in *Caenorhabditis elegans* [20]. Probiotic *L. plantarum* ATCC14917 has shown to stimulate immunity, and lower the pathogenic microorganism (*Serratia marcescens*) infections in fruit flies exposed to imidacloprid [111].

3.3. Probiotic Intervention in AAD Patients and Animal Models

There are a significant number of studies demonstrating the benefits of probiotics in reducing the occurrence of AAD, allergy, lactose intolerance, reduction of cholesterol etc. [112,113]. Patients receiving ABs for treatments are prone to suffer from gastrointestinal disturbances result from damage...
of the GI mucosal cells and disruption of the gut ecological balance. Probiotics replenish the natural GIT with nonpathogenic bacteria, and are considered as living drugs that help with ABs-associated diseases, without affecting the efficacy of ABs.

There are many favorable outcomes of probiotics in reducing the risk of AAD in adults and children based on extensive meta-analyses, and only a few studies using probiotics in patients undergoing antibiotic failed to acquire significant effect [114,115]. In a trial study with 246 children, co-treatment of Saccharomyces boulardii and ABs has been reported to lower the risk of diarrhea from 20.9% to 8.8% [116]. The updated results of meta-analysis, based on 10 RCTs, also showed that S. boulardii effectively prevented AAD in patients, with decrease of risk from 17.4% to 8.2% in adults [117]. The efficacy of LGG for preventing AAD in children and adults has also been evaluated. Treatment with LGG reduced the risk of AAD in patients receiving ABs from 22.4% to 12.3% [118].

The efficacy of probiotic strains in reducing the risks of AAD in humans have been evidenced, however, the underlying mechanism of these probiotic strains is less well understood. By reviewing recent literatures (Table 2), probiotics have been proposed to be effective in alleviating ABs-associated diseases through multiple routes (Figure 2): (1) mediating the structure of gut microbial community [81,121,122] by promoting beneficial bacteria and suppressing opportunistic pathogens. A cocktail of L. rhamnosus A 191, L. acidophilus, B. breve and B. longum significantly caused suppression of gut opportunistic pathogens Enterobacteriaceae and promotion of Firmicutes following ABs treatment in mice [81]. In another study, it was confirmed that probiotic cocktail of four Lactobacillus species JUP-Y4 treatment decreased the levels of Desulfovibrionales, and promoted the levels of Akkermansia [122]. High abundance of Desulfovibrionales were related with Crohn’s disease [123] and human infections [124,125], and Akkermansia are biomarkers of intestinal health [126] and inversely linked with the severity of Crohn’s disease and ulcerative colitis [127]. Two probiotics Phaeobacter inhibens S4Sm and Bacillus pumilus RI06-95Sm in black molly, have been shown to colonize in intestine and reverse mortality caused by streptomyein by inhibiting Vibrio anguillarum [121], which are known opportunistic pathogens in fish [128] and are thought to be “r-strategists” capable of rapid growth and virulence in disturbed microbial communities [129,130]. (2) Improving immune function of host by enhancing anti-inflammation [131–134]. Shi et al. (2017) used two Lactobacillus cocktails (LacA and LacB, each contains four strains) to restore the cefixime-induced GM disturbance in mice, and alleviate intestinal inflammation possibly due to beneficial SCFAs production [134]. A probiotic compound of Streptococcus thermophiles, B. breve, B. longum, etc., also reportedly restored the expression of anti-inflammatory cytokine IL-10 completely without affecting pro-inflammatory mediators in mice following broad-spectrum antibiotic treatment. At the meantime, adaptive immunity was also restored, with increase of CD4+, CD8+, and B220+ cell numbers in the intestinal lamina propria [132]. Separate studies demonstrated that S. boulardii can up-regulate antitoxin A secretory IgA expression in animal models of AAD [135,136]. (3) Enhancing intestinal barrier function. A probiotic cocktail JUP-Y4 modulated ampicillin induced gut barrier dysfunction and GM disturbance in mice. Increased expression of intestinal epithelial tight-junction proteins, and reduced inflammatory cytokines in the ileum and the colon following JUP-Y4 use contributed to cæcum tumefaction attenuation and a decrease in gut permeability [122]. Probiotics have also been shown to increase epithelium mucus production, which is a critical element of the epithelium barrier [137,138]. Probiotics also assist in producing antagonistic activity like bacteriocins against pathogenic bacteria, and inhibiting bacterial translocation by competing for receptors or adhesion to endothelial cells [139–141].
Table 2. Recent studies on the protective effects of probiotics against foodborne contaminants toxicity.

| Type   | References | Models | Contaminants | Dosage | Supplementation Dosage | Main Conclusion                                                                 |
|--------|------------|--------|--------------|--------|-------------------------|----------------------------------------------------------------------------------|
| HMs    | [142,143]  | Rats   | Cd           | CdCl₂ at 70 ppm, the mixture of L. acidophilus Rosell-52, L. rhamnosus Rosell-11 and B. longum Rosell-175 (5 x 10⁸ CFU/g food) for 5 weeks | Marked decrease genotoxicity and the toxicity to lactobacilli, promoted Cd excretion in feces; decreased Cd in body; relieved liver and kidney damage, increased the number of L. acidophilus in feces |
|        | [144]      | Rats   | Hg           | A total of 0.5 mL HgCl₂ at 20 µg/mL and 1 mL B. coagulans and L. plantarum CNR273 (10⁹ CFU/mL) daily for 48 days | Marked increase Hg excretion in feces; reduce Hg levels in liver and kidney; prevent oxidative stress; reduce liver and kidney damage; increase the number of fecal LAB and the total bacteria counts |
|        | [145]      | Mice   | Pb           | A total of 2 mg (CH₃COO)₂Pb·3H₂O in 0.4 mL plain water, L. bulgaricus KLDS1.0207 1 x 10¹⁰ (high dose), 1 x 10⁹ (medial dose) and 1 x 10⁸ (low dose) CFU/mL in 0.4 mL skim milk | Lower mortality rates, increased Pb excretion in feces, decreased tissue Pb enrichment, improved the antioxidant in the liver and kidney, and relieved renal pathological damage |
| Pesticides | [101]    | Rats   | As           | NaAsO₂ at 1.0 mg/100 g body weight, the mixture of L. acidophilus, L. rhamnosus, B. longum, and S. bouardi at 0.25 mg/100 g body weight for 16 days | Reduction of oxidative stress, inflammation in uterine, protection against mutagenic uterine DNA-breakage, necrosis, ovarian-uterine tissue damages |
|        | [29]       | Mice   | Cr (VI)      | A total of 1mM K₂Cr₂O₇ in drinking water, L. plantarum TW1-1 (1 x 10⁹ CFU/once every other day) for 7 weeks | Promoted Cr excretion in feces, reduced Cr accumulation in tissues; decreased oxidative stress and damage in liver; partially restored the GM community |
|        | [107]      | Rats   | Endosulfan   | Endosulfan at 4 mg/kg bodyweight from the 6th to 20th day of gestation, L. plantarum Bf0021 0.1 mL per os and one hour before the administration endosulfan | Significantly reduced the cholesterol level and marked depletion of hepatic enzymes, decreased the number of apoptotic nuclei in kidney |
|        | [20]       | Caenorhabditis elegans | Malathion    | Exposure to malathion at 300 nM for 4 h at 20 °C after administration L. casei liquid cultures of 0.1 OD at 600 nm for 4 h | Reproduction protection with increase of rate of egg laying and brood size, and rescued locomotion of C. elegans |
|        | [21]       | Drosophila melanogaster | Chloropyrifos parathon | Co-exposure 10 µM chloropyrifos parathon and 100 µL L. rhamnosus GG (10⁹ CFU) for 12 days | Prolonged overall survival and decreased early deaths |
|        | [81]       | Mice   | Different ABs | Ampicillin, Streptomycin, and Clindamycin at 1 mg/mL, A cocktails of L. rhamnosus A191, L. acidophilus, B. breve, B. longum (4 x 10⁷/mL) at 0.1 mL/mouse for 2 weeks | Lead a rise in microbial diversity; small increase in Firmicutes, increase in Enterobacteriaceae, and a bloom of Anaerotruncus, decrease in Xanthomonas |
|        | [121]      | Fish   | Streptomycin sulfate | A total of 200 g/mL of streptomycin sulfate daily for 13 days, 1 x 10⁷ CFU/mL P. inhibens S4Sm and B. pumilus RI06-95Sm daily for 5 days following ABs treatment | Probiotics can colonize fish microbiome, decrease mortality in fish with subtle GM changes |
|        | [122]      | Mice   | Ampicillin    | Ampicillin (500 mg/kg) twice-daily for 14 days, a cocktail of L. plantarum, L. casei, L. rhamnosus and L. helveticus (2 x 10⁷ CFU/0.2 mL/dose) for 4 weeks | Restore diversity of GM, decrease Firmicutes, reduce Desulfovibrionales, Dorea, Ruminococcaceae, Clostridiia and Helcocibacter, enrich Akkermansia, Alistipes and Porphyromonadaceae |
Figure 2. Schematic representation of proposed mechanisms of probiotic action on antibiotics associated diarrhea (AAD).

4. Conclusions and Future Perspectives

The foodborne contaminants, such as HMs, pesticides and ABs, cause harmful effects on animal and human health. GM is a major player in the remediation of these contaminants. Both contaminants-induced toxicity and impaired structure and metabolic activity of GM have significant impacts on target organs, causing tissue damage and other disease. Dietary supplementation with probiotics appears to be a promising adjunct intervention for effectively reducing the damage caused by foodborne contaminants and re-balancing the GM of humans and animals under a constant threat of pollutants.

The understanding of host-GM interactions must be further developed using a series of techniques such as metagenomics, metatranscriptomics and metabolomics, to provide meaningful insights into the mechanisms of GM, and to clarify the causal relationship between GM and GM-associated symptoms. Additionally, this work needs to be extended to human studies, as majority of research on contaminants remediation using probiotics comes from animal models, rather than humans. Meanwhile, almost all of current studies on the GM and contaminants solely rely on stool microbiota, which is part of the GM and may yield limited conclusions [146]. Hence gut mucosal sampling should also be considered in future studies. Furthermore, the colonization of probiotics in human may vary from person to person, depending on factors such as the composition of individual community, the composition of the colonizers, and intrinsic host factor [147]. Thus, in future applications with probiotics in human, personalized probiotic regimen based on the consumer at different contexts must be considered.

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