Food and Chemical Toxicology 153 (2021) 112306

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Review

Probiotics as a biological detoxification tool of food chemical contamination: A review

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ARTICLE INFO

Handling Editor: Dr Michael Aschner

Keywords:
Food contaminants
Probiotics
Xenobiotic metabolism
Gut microbiota
Probiotic-xenobiotic-host axis

ABSTRACT

Nowadays, people are exposed to diverse environmental and chemical pollutants produced by industry and agriculture. Food contaminations such as persistent organic pollutants (POPs), heavy metals, and mycotoxins are a serious concern for global food safety with economic and public health implications especially in the newly industrialized countries (NIC). Mounting evidence indicates that chronic exposure to food contaminants referred to as xenobiotics exert a negative effect on human health such as inflammation, oxidative stress, and intestinal disorders linked with perturbation of the composition and metabolic profile of the gut microflora. Although the physicochemical technologies for food decontamination are utilized in many cases but require adequate conditions which are often not feasible to be met in many industrial sectors. At present, one promising approach to reduce the risk related to the presence of xenobiotics in foodstuffs is a biological detoxification done by probiotic strains and their enzymes. Many studies confirmed that probiotics are an effective, feasible, and inexpensive tool for preventing xenobiotic-induced dysbiosis and alleviating their toxicity.

This review aims to summarize the current knowledge of the direct mechanisms by which probiotics can influence the detoxification of xenobiotics. Moreover, probiotic-xenobiotic interactions with the gut microbiota and the host response were also discussed.

1. Introduction

In the last decade, contamination of food by chemicals resulting from industrialization and increasing environmental pollution has been a serious problem in respect to global food safety with serious public health and economic implications (Fung et al., 2018; Rather et al., 2017). Contaminated water and food are the main contributors to human exposure to various toxic substances referred to as xenobiotics. The term "xenobiotics'' refers to chemical substances not normally present in the environment of living organisms (Abdelsalam et al., 2020). These include both synthetic environmental pollutants and naturally produced toxins which are the defense mechanism of other organisms, and also endobiotics when they are present at higher concentrations than their normal levels (Carmody and Turnbaugh, 2014; Soucek, 2011). These chemicals belonging to many groups (i.e. persistent organic pollutants (POPs), polyaromatic hydrocarbons (PAH), polychlorinated biphenyls (PCBs), bisphenols, pesticides, heavy metals, mycotoxins as well as bacterial and herbal toxins) (Mohammadi et al., 2020; Sarlak et al., 2021; Soucek, 2011) exert a negative impact on human health (Thompson and Darwish, 2019). They cause inflammation (Kato et al., 2013), endocrine disruption (Guo et al., 2019; Thompson and Darwish, 2019), oxidative stress (Papadopoulou et al., 2019); (Abolaji et al., 2017), cancer (Ma et al., 2015; Nishida et al., 2018) and intestinal disorders (Feng et al., 2018; Nogacka et al., 2019).

Numerous *in vitro* and *in vivo* studies have shown that long-term exposure to food xenobiotics may disturb the gut microflora of the host, leading to intestinal dysbiosis in both humans and animals (Choi et al., 2013; He et al., 2020; Zhai et al., 2015). For example, mice exposed to a mixture of polychlorinated biphenyls (PCBs), including PCB153, PCB138, and PCB180 significantly reduced gut microflora

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https://doi.org/10.1016/j.fct.2021.112306
Received 26 March 2021; Received in revised form 17 May 2021; Accepted 24 May 2021
Available online 28 May 2021
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composition such as a drop in *Proteobacteria* phylum count (Choi et al., 2013) while arsenic (As) exposure decreased the abundance of the *Firmicutes* community (Lu et al., 2014a). Based on *in vitro* and *in vivo* studies, it has been proven that dysbiosis of the gut microflora is associated with the occurrence of metabolic diseases such as diabetes (Lu et al., 2014b) and obesity (Everard and Cani, 2013), as well as cardiovascular diseases (Ley et al., 2006), allergies (Tang et al., 2013), inflammatory bowel disease (Pascal et al., 2018), and liver cancer (Nishida et al., 2018). Moreover, several studies have reported the effect of xenobiotics on the disturbance of the metabolome of the intestinal microflora (Broom, 2015; Gophna et al., 2017; Petriello et al., 2018). For example, exposure of the rabbits to bisphenol A (BPA) resulted in reduced short-chain fatty acid (SCFA) synthesis and elevated lipopolysaccharide (LPS) level (Yu and Schwabe, 2017).

Recently, there has been an increasing interest in probiotics application with high xenobiotics binding capacity that could be utilized to protect against food contaminants, e.g. to alleviate the acute and chronic heavy metals toxicity by *Lactobacillus* strains (Johnson et al., 2012; Reddivari et al., 2017). *In vitro* and *in vivo* trials have demonstrated that probiotic microorganisms can bind and/or metabolize various chemical pollutants such as organophosphorus pesticides, mycotoxins, and heavy metals (Feng et al., 2018; Majlesi et al., 2017; Zhai et al., 2013). It has been confirmed that oral probiotic supplementation can alleviate the negative health effects of exposure to the food contaminants by modulating the composition of the gut microflora (Abdel-Megeed, 2020; Harishankar et al., 2013; Lénárt et al., 2013; Niderkorn et al., 2007), reduction of the oxidative stress (Chattopadhyay et al., 2019; Giri et al., 2018), enhancement of the intestinal barrier function (Bouhafs et al., 2015; Duan et al., 2020; Feng et al., 2018), modulation of the host gene expression and finally affect on the host's capacity to metabolize xenobiotics (Wang et al., 2018). Probiotics can directly bind certain xenobiotics to the cell wall, and thus reduce their bioavailability and toxicity (Adjei-Fremah et al., 2018; Selwyn et al., 2016). Oral supplementation with xenobiotic-binding probiotic strains can be a simple and effective way to reduce the amount of pollutants absorbed from food in contaminated regions of the world (Daisley et al., 2019). Exposure of humans to xenobiotics will increase with further industrialization, therefore knowledge on mutual interactions between xenobiotics and probiotics and their impact on the gut microbiome and metabolic pathways is crucial in the estimation of the real health risk associated with exposure to these compounds.

This article reviews the available scientific data focused on the utilization of probiotic strains as a promising tool for the reduction of biosorption rate and biotransformation of food contaminants such as bisphenol A, mycotoxins, pesticides, and heavy metals. These chemical contaminants were included in our review because their exposure is frequent in humans and leads to changes in the gut microbiota composition and the host metabolism disruption. In particular, we summarized the current knowledge on the direct mechanisms by which probiotics can influence xenobiotics detoxification. Moreover, probiotic-xenobiotic interactions with the gut microbiota and the host response were also discussed.

2. Probiotic microorganisms

According to the World Health Organization (WHO) definition, probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit on the host" (Hill et al., 2014). Currently, traditional probiotic strains sold on the market include lactic acid bacteria (LAB) such as *Lactobacillus* and *Bifidobacterium* which have a beneficial effect in the treatment of some gastrointestinal disorders (Wosinska et al., 2019). However, other bacteria i.e., *Lactococcus*, *Streptococcus,* and *Enterococcus,* some species of *Bacillus* and *Saccharomyces* yeast are also utilized as probiotic strains (Apás et al., 2014; Shoukat et al., 2019) (Fig. 1). In the last few years, probiotics have been extensively studied for their health-promoting effects (de Melo Pereira et al., 2018; Markowiak and Śliżewska, 2017). Probiotic bacteria and yeast inhibit the pathogen adhesion to the intestinal epithelium, causing the reduction of bacterial toxins, the synthesis of antibacterial substances (bacteriocins, antibiotics) as well as vitamins (Markowiak and Śliżewska, 2017). Moreover, the same probiotic metabolites play an important role in maintaining intestinal homeostasis and promoting gut health (Kerry et al., 2018). For example, studies have indicated that metabolically active SCFAs such as acetic, butyric, and propionic acids produced by *Lactobacillus acidophilus* CRL 1014 are involved in many biological processes that provide metabolic energy sources for human colonic epithelial cells (Markowiak-Kopeć and Śliżewska, 2020; Moens et al., 2019; Wang et al., 2014). It is also known that probiotic strains play an important role in the modulation of the host immune system (Hori et al., 2020). The presence of these microorganisms in the intestines allows to maintain immunological tolerance to environmental antigens and also prevents allergies and autoaggressive reactions (Ho et al., 2019; Pérez-Burillo et al., 2020; Sivieri et al., 2013). Many of these responses result from the probiotic stimulation of specific intracellular signaling pathways in the epithelial cells (Yan and Polk, 2011).

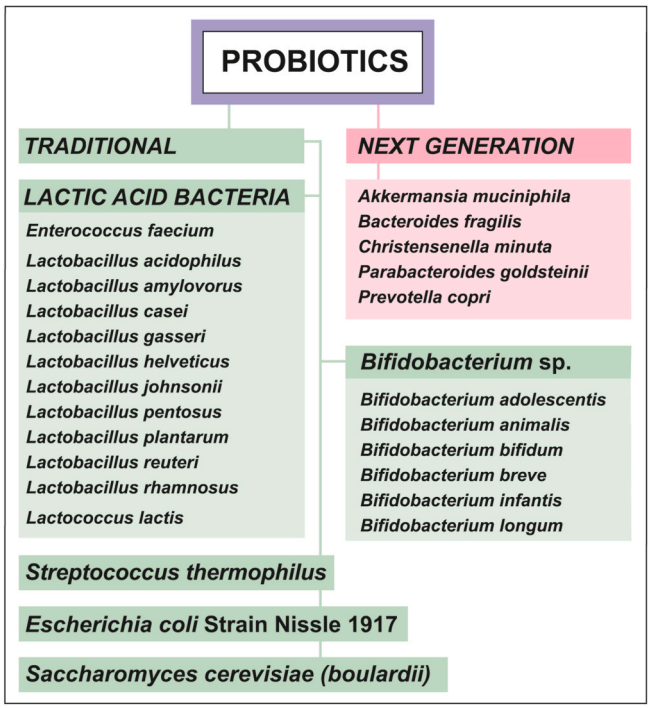


Fig. 1. Probiotic classification.

In recent years, the development of research and increased knowledge about the human intestinal microflora and its importance for human health, apart from traditional probiotics, drives scientists to search for so-called Next-Generation Probiotics (NGPs) (Cani and de Vos, 2017; Langella et al., 2019; Lin et al., 2019). Screening for NGPs from commensal bacteria aims to select efficient strains using "multi-omics" techniques including metagenomics, metaproteomics, and metabolomics (Chang et al., 2019). The goal of this research is the identification and selection of symbiotic microorganisms that can be used as biotherapeutics to alleviate specific diseases such as metabolic disorders associated with obesity, diabetes, and liver diseases (Chang et al., 2019; O'Toole et al., 2017). Recently, the US Food and Drug Administration (FDA) defined a regulatory framework for the use of "live biotherapeutic products" (LBP) in clinical applications, recognizing them as biological products used for the prevention and treatment of diseases (O'Toole et al., 2017).

Currently, potential NGP candidates mainly belong to the genera *Bacteroides*, *Akkermansia*, *Faecalibacterium*, and *Eubacterium* (Wosinska

et al., 2019). One promising candidate is *Akkermansia muciniphila*, which accounts for about 5% of the whole human intestine microbiota and has the potential in alleviating the symptoms of metabolic syndrome (Cani and Van Hul, 2015). Studies in mice have demonstrated that administration of *A. muciniphila* alleviates diet-induced obesity and metabolic disorders (Cani and de Vos, 2017; Everard et al., 2013; Shin et al., 2014). *Prevotella copri* of the phylum *Bacteroidetes* has a beneficial effect in reducing pre-diabetes symptoms, while *Parabacteroides goldsteinii* has anti-obesity and anti-inflammatory properties (Lin et al., 2019). There have also been reports of decreased level of pro-inflammatory IL-6 *in vitro* and increased mucosal integrity correlated with SCFAs production by *Eubacterium limosum* JCM6421 (Kanauchi, 2006). Furthermore, other strains such as *Clostridium butyricum* AQQF01000149 (Zhao et al., 2017), *Enterococcus munditii* (Grau et al., 2017), *Bacillus thuringiensis* as well as *Bacteroides fragilis ZY-312* (Wang et al., 2017a) are considered as a promising candidate of NGPs.

Numerous *in vitro* and *in vivo* studies evidence that probiotics maintain healthy homeostasis of the human intestine by influencing the composition and function of the commensal gut microflora (Abenavoli et al., 2019; Azad et al., 2018; Kerry et al., 2018; Wang et al., 2018). The gut microflora consists of about 10^{14} microorganisms, which is ten times more than the total number of human cells (Markowiak and Śliżewska, 2017). The co-evolution of the host and its microbiome has resulted in a symbiotic relationship, where gut microflora plays an important role in the maintenance of host health (Azad et al., 2018; Thursby and Juge, 2017). Many factors can affect the balance of intestinal microbiota such as age, diet, antibiotics, stress, host's genetics, exercise, mode of delivery as well as environmental pollutants (Claus et al., 2016). The gut microflora performs several important functions of the host homeostasis including carbohydrate fermentation, protection against pathogens, protein metabolism, synthesis of vitamins and neurotransmitters (i.e. serotonin, dopamine, and noradrenaline) (Ho et al., 2019; Swanson, 2015). The composition and number of microorganisms differ along the gastrointestinal tract (GI) including about 10^{1}–10^{3} CFU/ml in the stomach and 10^{11}–10^{12} CFU/ml in the colon, respectively (Markowiak and Śliżewska, 2017). In humans, the most abundant phyla in the digestive tract belong to *Proteobacteria*, *Bacteroidetes*, *Firmicutes*, and *Actinobacteria* (Azad et al., 2018; Thursby and Juge, 2017). The properly functioning gut microflora is in the state called eubiosis, and disturbance of this dynamic balance leads to dysbiosis and consequently, adverse health effects on the host (Andrade et al., 2020). Thus, one of the promising tools to prevent gut dysbiosis, is the use of functional probiotic strains to restore gut eubiosis through rebuilding the gut microbiome ecosystem (O'Hara and Shanahan, 2006).

Nonetheless, the selected probiotic strains intended for use must meet the requirements specified in the food law (de Simone, 2019). The general criteria require that microorganisms used for consumption must be safe for humans and animals. For example, they cannot consist of antibiotic-resistant genes in non-stable elements of the genome and have any association with infectious diseases, or cause adverse health effects. Probiotic microorganisms should be isolated from the GI and have the ability to survive the manufacturing process and storage (Zommiti et al., 2020). Besides, competitiveness to the gut microbiota, antagonist activity against pathogens, and the adhesion ability to the intestinal wall as well as the ability to colonize the host organism are required. Other important aspects related to the technological utility of probiotics are the ability to survive and maintain their properties throughout the storage and distribution processes (Andrade et al., 2020; Markowiak and Śliżewska, 2017). In the European Union, health claims for probiotic supplements have to be authorized by EFSA. However, up to now, EFSA has rejected all of the proposed health claims of probiotics because of the unavailability of appropriate evidence. According to the European Union (EU), health claims should only be authorized for use in the EU after a scientific assessment of the highest possible standard has been carried out by the Panel on Dietetic Products, Nutrition, and Allergies (NDA) of the EFSA (Regulation (EC) N 1924/2006) (European Parliament and Council, 2007). In addition, there is no harmonized EU legal framework establishing the conditions for a strain to be considered as probiotic or a positive list of individual strains which have a probiotic status. As mentioned above, in Europe, EFSA introduced the term QPS which involves some additional criteria of the safety assessment of bacterial supplements, including the history of safe usage and absence of the risk of acquired resistance to antibiotics (EFSA, 2020).

In the United States, most probiotics are registered as food or diet supplements and therefore they only need to meet the good manufacturing practices requirements which do not include quality and performance assessments. In the US, the FDA requires probiotics to have GRAS status (Generally Regarded As Safe) (Anadón et al., 2006; de Simone, 2019; Zielińska et al., 2018). Nonetheless, the FDA allows embedding health claims on probiotic supplements if they are supported research evidence and not misleading for the customer. In the United States, probiotics can be also registered as medical food that should be administered under the supervision of a doctor in specific health conditions (Vanderhoof, J.A. & Young R, 2008).

3. Probiotic mechanisms of xenobiotic detoxification

Numerous reports have suggested the possible role of probiotic strains in the binding of xenobiotics and their detoxification in foodstuffs (Muhialdin et al., 2020; Rogowska et al., 2019; Shoukat et al., 2019) and a promising strategy for the alleviation of their toxicity and accumulation in the human body (Chiocchetti et al., 2018; Mohammadi et al., 2020; Zhai et al., 2016). The most commonly used probiotics are lactic acid bacteria (LABs), *Bifidobacterium* sp., and the yeast *Saccharomyces* (*S. cerevisiae* var. *boulardii*) (Armando et al., 2011, 2012, 2012; Bejaoui et al., 2004). These strains have various beneficial properties that can be important in xenobiotic detoxification, such as strong ability to bind, tolerate or detoxify, high tolerance to acid and bile, strong adhesion to the gut mucosa, and strong antioxidant or immunoregulatory capacities enabling them to adapt to xenobiotic-induced changes in the gut environment (Abdel-Megeed, 2020; Feng et al., 2018; Muhialdin et al., 2020). Recent *in vivo* studies have demonstrated that during intestinal transit, probiotics might competitively inhibit the intestinal absorption of food contaminants such as mycotoxins and heavy metals, evidently lowering their availability for the host (Bisanz et al., 2014; Zhai et al., 2013). Moreover, it has been revealed that probiotics can also stimulate intestinal peristalsis, thus facilitate xenobiotics excretion from the body in feces (Monachese et al., 2012; Zhai et al., 2019) as well as limit their entrance into systemic circulation by enhancing intestinal barrier function and regulating the tight junction of the epithelium of the small intestine (Feng et al., 2018, 2020; Zhai et al., 2016).

Multiple studies have shown that changes in the gut microbiota caused by exposure to xenobiotics lead to intestinal dysbiosis which is associated with multiple diseases and adverse health outcomes, including increased toxicity of some xenobiotics (Złoch et al., 2020; Zoghi et al., 2014). The most beneficial effect of probiotic supplementation is the stabilization of the microbial community and restoration of the gut microbiota signature disturbed via xenobiotic exposure (Joannis-Cassan et al., 2011; Złoch et al., 2020). In turn, the gut microbiota modified by probiotics alters the absorption and metabolism of food xenobiotics via acting as a physical barrier and by modifying the intestine pH and oxidative balance (Ju et al., 2019; Shetty et al., 2007) as well as the expression of host detoxification enzymes involved in xenobiotic metabolism (Ju et al., 2019; Złoch et al., 2020; Zoghi et al., 2014) (Fig. 2).

Extensive studies have demonstrated that LABs and some *Saccharomyces* yeast can remove food contaminants due to various mechanisms such as physical adsorption onto the cell surface and/or enzymatic biotransformation via the production of various enzymes and certain metabolites (Chiocchetti et al., 2018; El Khoury et al., 2011; Muhialdin et al., 2020; Wang et al., 2016) (Fig. 3).

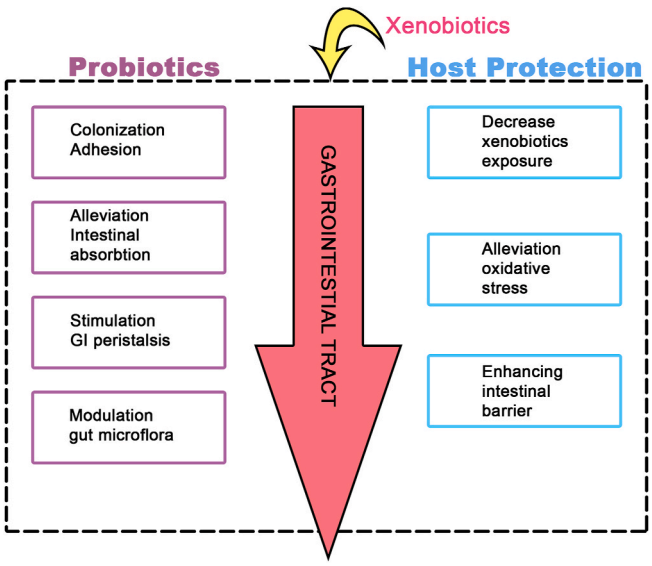


Fig. 2. *In vivo* mechanisms of probiotics protection against food xenobiotics absorption during intestinal transit.

3.1. Physical absorption

Many probiotic strains possess the ability to reduce the level of xenobiotics, particularly via binding (Muhialdin et al., 2020) (Table 1). Physical adsorption is a reversible, metabolically passive physicochemical process, therefore chemicals might interact with both alive or dead microbial cells (Apás et al., 2014; Feng et al., 2018; Shoukat et al., 2019; Xing et al., 2017).

In LABs, the cell wall consists mainly of peptidoglycan and smaller amounts of teichoic and lipoteichoic acids, polysaccharides, and exopolysaccharides (Rogowska et al., 2019; Sangsila et al., 2016; Zoghi et al., 2014). The absorption of xenobiotics into the LAB cell wall is due to the presence of a negative charge on the surface caused by many negatively charged functional groups such as carboxyl and phosphoryl groups (Kanamarlapudi et al., 2018; Zoghi et al., 2014). The main xenobiotic-binding site is peptidoglycan, other minor elements are teichoic acids and lipoteichoic acids (Lili et al., 2018). For example, *Lactobacillus fermentum* ME3 and *Bifidobacterium longum* 46 were proved to bind and remove heavy metals via their surface compounds such as capsular polysaccharides and teichoic acids (Teemu et al., 2008). Moreover, it has been shown that treating the bacteria with acid or heat leads to the partial breakdown of peptidoglycan scaffold, protein denaturation, and the exposure of new xenobiotic binding sites (Lili et al., 2018; Zoghi et al., 2014). The internal layer of the *S. cerevisiae* cell wall consists mainly of the β1,3-glucan–chitin network, while the outer layer contains highly glycosylated mannoproteins covalently bonded to this structure (Klis et al., 2002). The negative charge of the cell wall is due to the numerous phosphodiester bridges in the carbohydrate side chains of the surface proteins (Klis et al., 2002).

It has been shown that the capacity of probiotic strains to xenobiotics biosorption depends on pH value (Lili et al., 2018). Haskard et al. (2000) reported that the detoxification of aflatoxin B_2a (AFB_2a) by *Lactobacillus rhamnosus* GG *in vitro* is highly pH-dependent, while aflatoxin B_1 (AFB_1) did not show such a relationship (Haskard et al., 2000). Patulin (PAT) shows reduced binding under less acidic conditions by *Bifidobacterium bifidum* 6071, *Bifidobacterium animalis* 6165, *L. rhamnosus* 6149, *Lactobacillus delbrueckii* sp. lactis 22170 and *L. delbrueckii* sp. lactis 22165 (Hatab et al., 2012). A similar relationship was observed for *Lactobacillus plantarum* MF042018 that more effectively binds heavy metals (Cd^{2+} and Pb^{2+}) at a more acidic pH (Ameen et al., 2020).

The incubation time is another important factor influencing the effectiveness of probiotic strains in xenobiotics biosorption (Ameen et al., 2020; Król et al., 2018; Lili et al., 2018). It has been shown that 90% of zearalenone (ZEN) was removed by *Lactococcus lactis* during the first 20 min of incubation, while *Bifidobacterium* spp. biosorption increased linearly and reached 88% of ZEN removal during 12 h of incubation (Król et al., 2018). Harishankar et al. (2013) reported that *L. fermentum* and *L. plantarum* have a maximum biosorption rate of Cu^{2+} and Zn^{2+} in the first 5 min of incubation. Similarly, the binding of AFB_1 by *L. rhamnosus* GG and *L. rhamnosus* LC-705 was also a rapid process with neutralization of approximately 80% of the mycotoxin at the beginning of the trial (0 h) (El-Nezami et al., 1998). Moreover, Serrano-Niño et al. (2013) reported that *L. acidophilus* NRRL B-4495, *Lactobacillus reuteri* NRRL B-14171, *L. rhamnosus* NRRL B-442, *Lactobacillus johnsonii* NRRL B-2178, and *B. bifidum* NRRL B-41410 can bind rapidly 19%–25% of aflatoxin M_1 (AFM_1) at the start of the trial (0 h).

The ability of LABs to bind various xenobiotics also depends on their chemical structure (Lili et al., 2018; Vasama et al., 2014). LABs bind heterocyclic amines more effectively depending on their hydrophobicity (Lili et al., 2018). The effectiveness of *L. rhamnosus* GG in removing different aflatoxins (AFB_1, AFB_2, AFG_1, AFG_2) was associated with the polarity of tested compounds. Vasama et al. (2014) reported that the *L. rhamnosus* ability to bind paralytic shellfish toxins (PSTs) decreased in the following order: STX ~ neoSTX > C2 > GTX3 > GTX2 > C1. PSTs with a higher positive charge were removed more efficiently (with C2 exception) which suggests the influence of electrostatic and hydrophobic interactions between probiotic cell walls and tested chemicals (Vasama et al., 2014).

Furthermore, the binding efficiency to the bacterial cell wall is strain-specific (Hernandez-Mendoza et al., 2009; Niderkorn et al., 2006; Oishi et al., 2008). Hernandez-Mendoza et al. (2009) reported that LABs exhibited different degrees of aflatoxin binding; *Lactobacillus casei* L30 had a high ability of the carcinogen AFB_1 binding which was 49.2% compared to the binding rate of *L. casei* ATCC which was 14% under the same test conditions.

3.2. Xenobiotic metabolism

The influence of probiotics on xenobiotics metabolism has been the subject of many studies (Gao et al., 2018; Ikunaga et al., 2011; Niderkorn et al., 2007; Złoch et al., 2020). Considering the possibility of the formation of derivatives with various properties, the investigation of the impact of the probiotics on changes of biological activity of xenobiotics currently forms an important direction of research. Xenobiotics penetrate the organism primarily via the oral route (Claus et al., 2016), and their distribution, and accumulation in the tissues and organs depend on many factors, such as biological characteristics and forms, route, dose and exposure duration, the capability for binding to ligands in the host cells as well as species sensitivity (Andjelkovic et al., 2019). Readily absorbed xenobiotics pass through the upper GI tract into the small intestine, where they can be absorbed into the bloodstream and through the hepatic portal vein get to the liver (Koppel et al., 2017). In the liver, the metabolism of xenobiotics is mainly aimed at increasing the hydrophilicity and molecular weight of the compounds so that they can be excreted more easily. Liver metabolism is generally considered in three phases (Abdelsalam et al., 2020; Stanley, 2017; Swanson, 2015); phase I involves chemical reactions such as oxidation, reduction, and hydrolysis which are mainly catalyzed by the cytochrome P450 (CYP450), carboxylesterases (CE), and flavin-containing monooxygenases (FMOs); in phase II, transferases catalyze the conjugation reactions of glucuronyl, glutathionyl, acetyl, sulfonyl groups; phase III, transport of compounds without further chemical transformation and remove via kidneys with urine or with bile back into the intestine where they can be metabolized by gut microflora or expelled with feces (Koppel et al., 2017). The above-described II stage of the xenobiotics biotransformation processes conducted by the host typically leads to alleviation and/or reduction in the toxicity of the xenobiotics (Claus et al., 2016). Poorly absorbed xenobiotics pass from the small intestine to the large intestine, where they

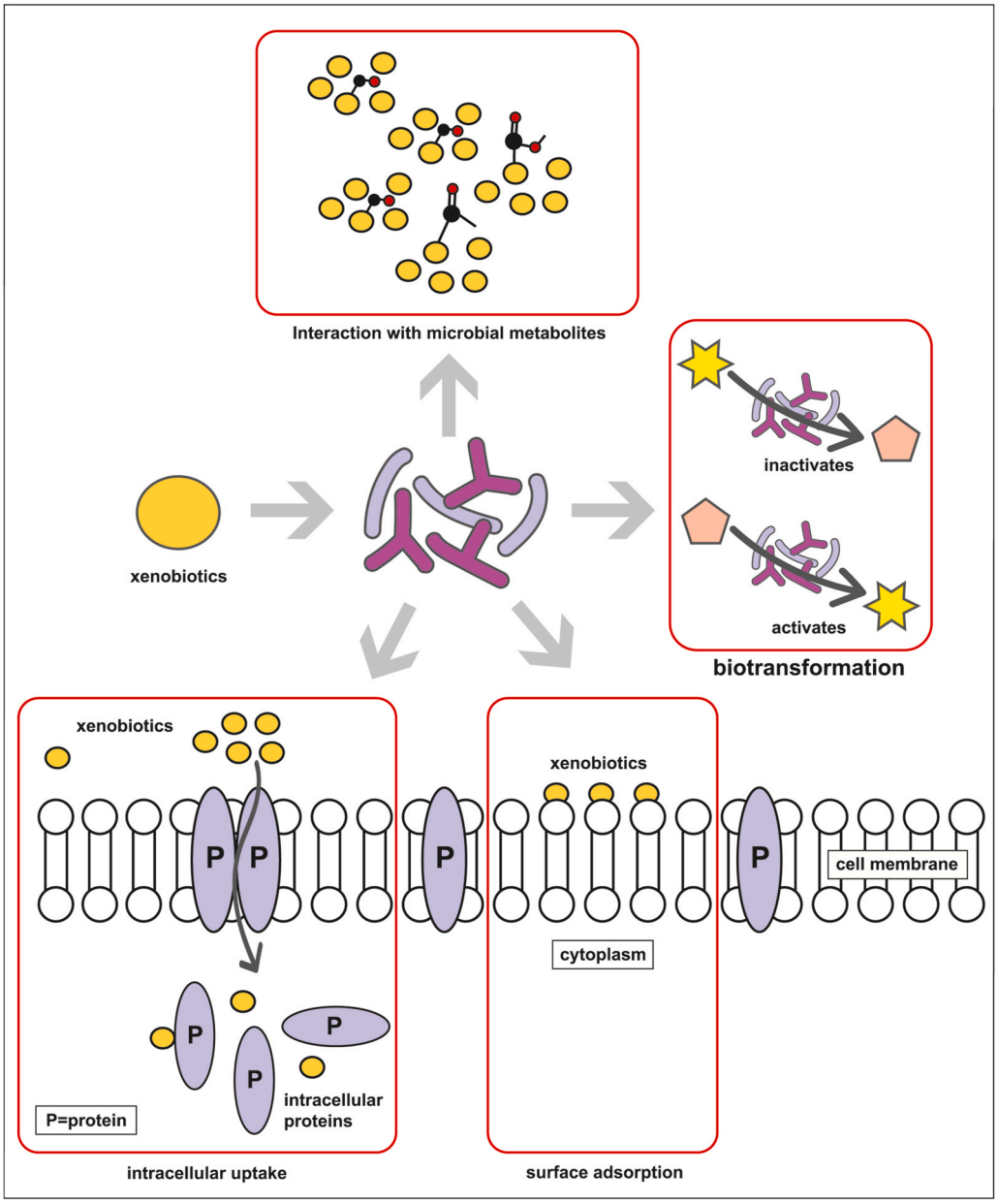


Fig. 3. Mechanisms of food xenobiotics detoxification by probiotic strains. Xenobiotic detoxification pathways by probiotic strains include (1) intracellular uptake (2), surface adsorption, (3) xenobiotics biotransformation (4) interactions with microbial metabolites.

are metabolized by the gut microbiome. Metabolites released in the circulation are either excreted by the kidneys or return through a biliary duct to the gut. Finally, these metabolites are excreted in the feces or reabsorbed in the small intestine (Abdelsalam, 2020; Koppel et al., 2017). It is known, that the majority of human microbiota-xenobiotic interactions occur within the GI tract and direct microbial biotransformation of xenobiotics take place in the colonic region of the gut (Abdelsalam, 2020; Clarke et al., 2019, Collins and Patterson, 2020), but recent studies showed that consumed probiotics can also colonize the environment of the small intestine (Derrien and van Hylckama, 2015; Judkins et al., 2020; Lin et al., 2019; Su et al., 2017).

The biotransformation of xenobiotics via probiotics with gut microflora cooperation can alter xenobiotic half-life, toxicity, and bioavailability as well as the endocrine-disrupting potential (Abdelsalam et al., 2020; Clarke et al., 2019; Złoch et al., 2020). An example of intestinal xenobiotic metabolism is the biotransformation of the mycotoxin ZEN by *Lactobacillus paracasei* to a less toxic form, α- ZOL and β-ZOL (Złoch et al., 2020), and ZEN to α-ZOL by *Lactobacillus* and *Leuconostoc*, respectively (Niderkorn et al., 2007) (Table 1). A range of chemical processes catalyzed by enzymes produced by the gut microflora has been described (Claus et al., 2016; Kolátorová et al., 2018). Many of these enzyme classes have been associated with xenobiotics metabolism e.g., hydrolases, lyases, oxidoreductases, and transferases. The most abundant hydrolases in the GI tract are proteases, glycosidases, and sulfatases, which have a broader range of activity than the host enzymes (Koppel et al., 2017). Concerning xenobiotics and derivatives, they are capable of catalyzing reactions of reduction, hydrolysis, sulfone group removal, dehydroxylation, acetylation, deacetylation proteolysis, denitrification, deconjugation, thiazole ring-opening, deglycosylation, demethylation (Claus et al., 2016). Considering mostly the anaerobic conditions occurring in the intestine, microbes can utilize reducing xenobiotic metabolism to increase the count of possible electron acceptors. However, the hydrolysis reactions enable disconnecting sugar residues from glycolysed food components, providing substrates for the

Table 1
Mechanisms of probiotic removal of food xenobiotics *in vitro*.

Xenobiotic	Probiotic strain	Xenobiotic concentration	Removal ratio [%]	Incubation conditions	Mechanism of removal	Reference
BPA	lyophilized *L. lactis* subsp. *lactis* 712 (10 mg/ml)	2 μg/ml	62	1 h, 30 °C	binding	Endo et al. (2007)
	L. reuteri ATCC55730 (inoculum 0.2%)	1 mg/l	70	48 h, 37 °C	enzymatic degradation	Ju et al. (2019)
	Commercial supplement (*L. casei* 3×10^9 CFU, *L. acidophilus* 3×10^{10} CFU, *L. rhamnosus* 7×10^9 CFU, *L. bulgaricus* 5×10^8 CFU, *B. breve* 2×10^{10} CFU, *B. longum* 1×10^9 CFU, *S. thermophilus* 3×10^8 CFU)	5×10^5 pg/ml	92	24 h, 37 °C	binding	Solouki et al. (2018)
	Heat-treated; *L. plantarum; L. acidophilus* (1×10^{10} CFU/ml)	5 mg/l	72 70	24 h, 30 °C	binding	Zhu et al. (2017)
B(a)P	*B. infantis* BY12 (5×10^8 CFU/ml)	100 μg/m	78	4 h, 37 °C	binding	Shoukat et al. (2019)
	L. plantarum CICC 22135; *L. pentosus* CICC 23163	10 μg/ml	67 64	4 h, 37 °C	binding	Zhao et al. (2013)
	L. reuteri DDL 19; *B. bifidum DDBA* (1×10^{11} CFU/ml)	2,5 mg/ml	98	2 h at 37 °C	binding	Apás et al. (2014)
ZEN	*L. lactis* 56 KY484989 (2 ml of culture at the equivalent of 1.8–2.0 McFarland standard)	800 ng/ml	30	72 h 37 °C	binding and intracellular bioaccumulation	Złoch et al. (2020)
	L. lactis, ($9{,}78 \times 10^8$ CFU/ml)	130 μg/ml	97	24 h, 37 °C	binding	Król et al. (2018)
	Bifidobacterium sp. ($11{,}01 \times 10^8$ CFU/ml)	130 μg/ml	88	24 h, 37 °C	binding	Król et al. (2018)
	L. plantarum ŁOCK 0860	100 μg/ml	73	24 h, 37 °C	binding	Chlebicz and Śliżewska (2020)
	S. cerevisiae ŁOCK 0119	100 μg/ml	58	24 h, 30 °C	binding	Chlebicz and Śliżewska (2020)
	Freeze-dried *L. pentosus* JM0812 (5 mg)	74,60 μg/ml,	83	15 min, 37 °C	binding	Sangsila et al. (2016)
	S. cerevisiae RC009	1 μg/ml	85	1 h at 37 °C	binding	Armando et al. (2012)
DON	*L. delbruekii* ssp. *bulgaricus* R0149 (10^{10} CFU/ml)	10 μg/ml	55	24 h at 30 °C	binding	Niderkorn et al. (2006)
FB1	*L. mesenteroides* R1107 (10^{10} CFU/ml)	10 μg/ml	82	24 h at 30 °C	binding	Niderkorn et al. (2006)
FB2	*L. lactis* CS 43 (13×10^{10} CFU/ml) CS 202, ($11{,}6 \times 10^{10}$ CFU/ml); CS 197 ($12{,}7 \times 10^{10}$ CFU/ml)	10 μg/ml	100	24 h at 30 °C	binding	Niderkorn et al. (2006)
AFB1	*L. pentosus* ŁOCK 1090	100 μg/ml	71	24 h at 37 °C	binding	Chlebicz and Śliżewska (2020)
	S. cerevisiae ŁOCK 0119	100 μg/ml	69	24 h at 30 °C	binding	Chlebicz and Śliżewska (2020)
DON	*L. reuteri* ŁOCK 1096	100 μg/ml	39	24 h at 37 °C	binding	Chlebicz and Śliżewska (2020)
	S. cerevisiae ŁOCK ŁOCK 0119	100 μg/ml	43	24 h at 30 °C	binding	Chlebicz and Śliżewska (2020)
T-2	*L. rhamnosus* ŁOCK 1087	100 μg/ml	73	24 h at 37 °C	binding	Chlebicz and Śliżewska (2020)
	S. cerevisiae ŁOCK 0137	100 μg/ml	72	24 h at 30 °C	binding	Chlebicz and Śliżewska (2020)
OTA	*S. cerevisiae* RC012 (1×10^7 cells/ml)	100 μg/ml	71	1 h at 37 °C	binding	Armando et al. (2012)
Pb	*L. reuteri* Pb71-1, cells pellet 3 mg/ml (wet weight)	6000 μg/l	59	2 h at 37 °C	binding	Bhakta et al. (2012)
Cd	*L. reuteri* Cd70-13, cells pellet 3 mg/ml (wet weight)	1000 μg/l	25	2 h at 37 °C	binding	Bhakta et al. (2012)
	L. plantarum CCFM8610, dry biomass (1 g/l)	5 mg/l	77	1 h at 28 °C	binding	Zhai et al. (2013)
	L. plantarum CCFM8610, heat-killed dry biomass (1 g/l)		73			

BPA-bisphenol A, B(a)P- benzo(a)pyrene, ZEN- zearalenone, DON- deoxynivalenol, FB1- fumonisin B(1), FB2- fumonisin B(2), AFB1 -aflatoxin B1, T-2- T-2 mycotoxin, OTA-ochratoxin A, PAT-patulin, Pb-lead, As- arsenic, Cd-cadmium.

microorganism growth (Spanogiannopoulos et al., 2016).

It should be emphasized that the microbial metabolism may be contrary to the metabolism of the host e.g. the host enzyme UDP-glucosyltransferase catalyzes the conjugation reactions of xenobiotics with glucuronic acid, which is a beneficial toxicity-lowering process. On the other hand, gut microbial β-glucuronidases enzymes catalyze the deconjugation reaction and reactivate the compounds (Clarke et al., 2019; Ervin et al., 2019). In the case of xenobiotics, this is an unfavorable process but plays an important role in the host body, allowing the bile acids deconjugation (Tralau et al., 2015). Nevertheless, the study of 49 *L. reuteri* strains showed that none of these strains produced harmful substances to the human body (Zhu et al., 2016). It can be seen that *L. reuteri* has great potential in the food industry.

3.3. Microbial metabolites interaction with xenobiotics

Another mechanism of xenobiotic biotransformation is due to interactions with LAB metabolites. e.g. acids, phenolic compounds, fatty acids, low molecular weight bioactive peptides, reuterin, which can bind to xenobiotics and alter their toxicity (Beer et al., 2019; Muhialdin et al., 2020). Reuterin is a multi-component system that has a broad spectrum of antimicrobial activity. It has been reported that reuterin produced from glycerol by *L. reuteri* DSM 20016 can interact with food heterocyclic aromatic amines (HAA) lead to the formation of reuterin-derived metabolites (Beer et al., 2019). HAA are toxicants formed from proteinaceous food during heat processing and are characterized by mutagenic and carcinogenic properties (Barzegar et al., 2019). Bacteria metabolize glycerol to 3-hydroxypropionaldehyde (3-HPA), the key component of reuterin, by cobalamin-dependent glycerol/diol dehydratase. The 3-HPA is then reduced to 1,3-propanediol (PDO) by 1, 3-propanediol dehydrogenase (Engels et al., 2016). 3-HPA is spontaneously dehydrated to acrolein, which is highly reactive and has toxic properties (Zhang et al., 2018). Heterocyclic amine metabolites are formed as a result of covalent attachment to 3-HPA or acrolein (Beer et al, 2017, 2019).

Vanhaecke et al. (2008) studied the metabolism of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) by the human gut microflora *in vivo*. PhIP is a carcinogenic heterocyclic amine that is formed in meat during cooking. The tested subjects consumed 150 g of cooked chicken containing 0.88–4.7 μg PhIP, and afterward urine and feces were collected. Results showed that PhIP was converted to 7-hydroxy-5-methyl-3-phenyl-6,7,8,9-tetrahydropyrido[3′,2':4,5]imidazo[1,2-a] pyrimidin-5-ium chloride (PhIP-M1), which showed no mutagenic activity in the Ames test (Vanhaecke et al., 2008). This conversion occurred by direct reaction with 3-HPA or acrolein derived from glycerol by reuterin-producing bacteria. Beer et al. (2017) assessed the ability of *L. reuteri* 11 DSM 20016 to metabolize seven foodborne HAAs (AαC, Trp-P-1, IQ, MeIQ, MeIQx, norharman, harman). After 72 h of anaerobic incubation HAAs at two different glucose/glycerol ratio (nGlc/nGly = 0.05 and 0.55), AαC and MeIQx were completely metabolized, IQ and MeIQ were converted in 60%–74%. Trp-P-1 and norharman were metabolized to a lesser extent (17%–31%), harman was converted to a minor extent (nGlc/nGly = 0.05) or were not converted (nGlc/nGly = 0.55) (Beer et al., 2017). Moreover, reuterin-derived metabolites can be subsequently transformed, e.g. reduced and hydroxylated by fecal microbiota (Beer et al., 2019).

3.4. Detoxification mechanisms of selected food contaminants by probiotic strains

Chemical contamination is a significant food safety problem and concerns a diverse group of chemical compounds (Ng and von Goetz, 2017). The sources of the contamination can be both natural and anthropogenic (Rather et al., 2017). Natural processes such as volcanic activity, weathering of rocks and soil, earthquakes, erosion, release heavy metals that enter the food chains (Ali et al., 2019; Genchi et al., 2017; Silano and Silano, 2017). Naturally occurring toxins, including e. g. mycotoxins produced by molds (Janik et al., 2020), and paralytic shellfish toxins produced by microscopic algae are the cause of food poisoning in humans (Silano and Silano, 2017; Vasama et al., 2014). On the other hand, anthropogenic sources of food contamination include the use of chemical compounds in agriculture (pesticides, fertilizers) and animal husbandry (antibiotics), migration of contaminants from packaging materials to foodstuff (bisphenol A), contaminants formed during food processing (heterocyclic aromatic amines), as well as contaminated water, air and soil due to human activities e.g., heavy metals, polychlorinated biphenyls (Rather et al., 2017; Silano and Silano, 2017) (Table 2).

Food is an important route of human exposure to various xenobiotics (Ng and von Goetz, 2017). The Annual Food and Feed Rapid Alert System (RASFF) report for 2019 showed 534 mycotoxin notifications, 253 pesticide residue notifications, 136 notifications for metals, and 56 notifications for environmental chemicals (Directorate-General for Health and Food Safety (European Commission), 2020). Most of the mycotoxin notifications concerned aflatoxins found especially in nuts. On the other hand, the second most commonly reported mycotoxin was ochratoxin A (OTA), found mainly in fruits and vegetables (especially raisins and dried figs). The most commonly reported pesticide MRL exceedance in 2019 was chlorpyrifos (CP) (banned in the EU) and most pesticide residues were found in fruit and vegetables (Directorate-General for Health and Food Safety (European Commission), 2020). However, those data relate only to EU food law maximum (residue) levels, not to the total dietary intake values.

3.4.1. Bisphenol A

Bisphenol A (BPA) is an organic synthetic compound used on a mass scale for the production of polycarbonate plastics and epoxy resins (Jalal et al., 2018; Pelch et al., 2019). Several studies have reported that BPA leach into food and beverages from packaging materials (Jalal et al., 2018; Nomiri et al., 2019; Pelch et al., 2019; Wang et al., 2021). BPA has well-documented endocrine properties and is associated with the occurrence of obesity (Hoffmann et al., 2018; K.Y. Kim et al., 2019), diabetes (Chen et al., 2015; Hwang et al., 2018), fertility disorders (Chen et al., 2015; Matuszczak et al., 2019; X.L. Zhang et al., 2015), and various types of cancer (Ma et al., 2015; Song et al., 2015).

Oishi et al. (2008) described the potential of the probiotic *Bifidobacterium breve* and *L. casei* to increase the excretion of orally administered BPA in rats. Both bacterial strains caused a decrease in the concentration of unconjugated BPA in the blood over time and increased excretion of BPA in the feces of tested rats compared to the control group. The percentage of BPA associated with sediment fraction of excrements was two times higher. Besides, analysis of the efficacy of heat-killed non-viable probiotic strains on BPA excretion showed that the nonviable cells promoted the secretion of BPA at similar levels as viable cells. These results suggest that hydrophobic BPA binding by LABs can be the primary pathway of the BPA detoxification rather than enzymatic mechanisms (Oishi et al., 2008). Furthermore, Endo et al. (2007) reported that the BPA-adsorbing ability of *Lactococcus* strains is due to the hydrophobic binding effect. The rate of BPA removal from the medium during the growth of the *L. lactis* subsp. *lactis* 712 (10^9 CFU) was below 9%, but incubation with lyophilized cells of probiotic bacteria led to a decrease in BPA concentration by up to 60%. The effectiveness of probiotics mixtures (*L. acidophilus* and *L.plantarum*) in the binding of BPA was evaluated by Solouki et al. (2018). The synergy of *L. acidophilus* and *L.plantarum* showed the highest binding capacity of 80% in the first 30 min of incubation. In a rodent model, Y. Zhu et al. (2017) indicated that *L. acidophilus* and *L. plantarum* had the highest and most reliable BPA-binding rates of all tested strains; *L. acidophilus and L. plantarum* released 48.11% and 53.24% of bound BPA, in contrast to *L. rhamnosus and Streptococcus thermophilus* for which the ability to release bound BPA was 98.78% and 98.05%, respectively. In rats, Baralić et al. (2020) investigated the possible utilizing of a commercial probiotic supplement

Table 2
Sources and health implications of the food contaminants exposure.

Contaminant	Producer/Source	Food commodity	Health effects	References
FB1 (Mycotoxin)	*Aspergillus flavus*	rice, corn, peanuts wheat, cereals, groundnuts, dried fruits, and spices, maize	• carcinogenic • the causative agent of hepatocellular carcinoma • growth suppression and malnutrition • immune system modulation	Rushing and Selim (2019)
AFM1 (Mycotoxin)	Hydroxylated metabolite of AFB1	milk and other dairy obtained from animals fed with contaminated feedstuff	• DNA damage • gene mutation • chromosomal anomalies	Prandini et al. (2009)
FB1 (Mycotoxin)	*Fusarium verticillioides*, *Fusarium proliferatum*	rice, wheat, barley, maize, rye, oat, asparagus, garlic, beers, dried figs, milk, tea,	• non-genotoxic initiator of cancer • linked to esophagal cancer • defects of the neural tube in humans	Kamle et al. (2019)
DON (Mycotoxin)	*Fusarium graminearum*, *Fusarium culmorum*	wheat, maize, barley, rice, beer, bakery products	• acute effects: nausea, vomiting, gastroenteritis, diarrhea, reduced daily food consumption • chronic effect: • ↓ body weight	Mishra et al. (2020)
T-2 toxin (Mycotoxin)	*Fusarium sporotichioides*, *Fusarium poae*, *Fusarium equiseti*, *Fusarium acuminatum*	wheat, corn, and rice crops	• factor in the etiology of Kashin–Beck disease • damaging to the skin, kidney, liver, brain, hematopoietic, lymphoid, gastrointestinal bone marrow, reproductive system in animal models *in vitro* • neurotoxic • ↑oxidative stress and mitochondrial dysfunction	Dai et al. (2019)
OTA (Mycotoxin)	*Aspergillus ochraceus, Penicillium verrucosum*	wheat, oats, maize, rice, soybeans, peas, beans, broad beans, wine, pumpkin seeds, coffee, wine, dried fruits, nuts, meat,	• nephrotoxic • hepatotoxic • teratogenic • immunotoxic • cause kidney and liver tumors in mice and rats	(Tao et al., 2018; Zhu et al., 2017)
PAT (Mycotoxin)	*Penicillium expansum*	fruits, vegetables. (mostly found in apples)	• acute exposure: nausea, vomiting, ulcers, intestinal hemorrhages, and lesions in the duodenum • neurological, gastrointestinal, and immunological adverse effect inducer • possible genotoxic • damaging to the liver and kidney	Saleh and Goktepe (2019)
Pb (Heavy metal)	anthropogenic (urbanization, agriculture), natural (volcanic activity, weathering of rocks and soils)	sugar beet, orange, pomegranate, grapes lemon, strawberry, buckthorn, peaches fenugreek, rosemary	• neurotoxic (behavior disorders), ↓ cognitive abilities, ↓ intelligence (especially in children) • damaging to the circulatory system and kidneys • ↓ fertility • ↓fetal development during pregnancy	(Kumar et al., 2019; Kumar et al., 2018)
Hg (Heavy metal)	natural (volcanic activity, earthquakes, erosion), anthropogenic sources (industry, coal power plants, chlor-alkali process plant)	fish and other seafood	• risk factor for cardiovascular disease • reproductive and developmental toxicity • neurotoxic, nephrotoxic • adverse effects on the immune system	Genchi et al. (2017)
As (Metalloid)	natural (geological sources), anthropogenic (glass industry, pharmaceuticals industry, pesticides)	drinking water, rice, crops, vegetables	• inorganic As- skin, lung, and bladder cancer • risk factor of skin lesions, cardiovascular diseases, developmental toxicity, type II diabetes • neurotoxic • ↑ glucose metabolism disruption	(Cubadda et al., 2017; Silano and Silano, 2017; Upadhyay et al., 2019)
Cd (Heavy metal)	natural/anthropogenic (phosphate fertilizers, equipment, utensils coating, production of plastics)	grains, cereals, vegetables, starchy roots, tubers, meat, seafood	• factor in etiology of osteoporosis, rheumatoid arthritis, osteoarthritis • endocrine disruptor • carcinogenic to humans	(Kumar et al., 2019; Reyes-Hinojosa et al., 2019; Schaefer et al., 2020)
BPA (Phenol)	anthropogenic (production of polycarbonates, epoxy resins, and other polymeric materials)	transfer from food-contact materials to food (mainly canned food and beverages)	• endocrine disruptor • decrease fertility • adverse effects in neuronal development, • factor in etiology of metabolic, cardiovascular, and immunological diseases	Almeida et al. (2018)
Chlorpyrifos (Pesticide)	anthropogenic (agriculture)	whole-grain food, processed food, livestock, raw milk	• neurotoxic • immunotoxic • endocrine disruptor • risk factor of cardiovascular diseases • ↑ oxidative stress	Ubaid ur Rahman et al. (2021)
Dimethoate (Pesticide)	anthropogenic (agriculture)	fruits, vegetables, crops	• ↑ oxidative stress and lipid peroxidation • adverse effect on the nervous, immune, and reproductive system • toxic for liver, kidney, pancreas	Eken (2021)

(*continued on next page*)

Table 2 (*continued*)

Contaminant	Producer/Source	Food commodity	Health effects	References
B(a)P (PAH)	industrial processes, food preparation, incomplete combustion	grilled meat, smoked fish, seafood, vegetables, fruits, oil, grain, cereals	• human carcinogen • hepatotoxic • immunotoxic • neurotoxic • ↑ oxidative stress	Verma et al. (2012)

FB1- fumonisin B(1), AFM1 -aflatoxin M1, FB1- fumonisin B(1), DON- deoxynivalenol, OTA-ochratoxin A, PAT-patulin, Pb-lead, Hg-mercury, As- arsenic, Cd-cadmium, BPA-bisphenol A, B(a)P- benzo(a)pyrene, PAH- polycyclic aromatic hydrocarbon.

containing *S. boulardii*, *L. rhamnosus*, *L. planarum* LP 6595, and *L. planarum* HEAL9 to alleviate toxicity induced by phthalates (DEHP, DBP) and BPA mixture. The oral treatment with probiotic formulation significantly reduced systemic inflammation in rats and had protective effects on the liver, kidneys, spleen, lipid status, and serum glucose level. Moreover, significant changes in biochemical, hematological, and hormonal parameters were noticed (Baralić et al., 2020).

In the *in vitro* assays, the degradation potential of BPA by six probiotic strains (*L. reuteri*, *Lactobacillus brevis*, *L. casei*, *Bacillus subtills*, *L. delbrueckii*, *Lactobacillus helveticus*) has been evaluated by Ju et al. (2019). Results showed that the *L. reuteri* has the highest ability to the BPA degradation, which was 69.83%. In addition, the ability of the intracellular extract to degrade BPA was around 55%, in contrast to the 3% degradation of the BPA observed in the extracellular extracts. Moreover, intracellular extracts were prepared as enzyme microsphere sustained-release preparation (EMSP) and utilized to remove BPA from canned beverages (black tea, orange juice, cold mung bean tea). The removal rate was approximately 92% after one day and 100% after 27 days indicating that EMSP may possess the potential to remove BPA from food products (Ju et al., 2019).

3.4.2. Benzo(a)pyrene

A significant food safety issue is the presence of the cancerogenic polycyclic aromatic hydrocarbon benzo(a)pyrene (B(a)P). B(a)P is found in grilled meat, smoked fish, seafood, vegetables, fruits, oil, grain, and cereals (Das and Bhutia, 2018). After ingestion, B(a)P is distributed to the kidneys, bladder, liver, and because of lipophilic nature to the mammary fat and bone marrow (Verma et al., 2012). The pathway of B(a)P biotransformation involves enzymes of both phase I and phase II and leads to the generation of numerous metabolites (Verma et al., 2012). The cancerogenic metabolite of B(a)P is BaP-7,8-dihydrodiol-9, 10-epoxide (BPDE) converted by the phase I cytochromes P450 1A1 and 1B1, can form DNA adducts by covalent binding with the guanine, which can lead to DNA damage (Tung et al., 2014; Verma et al., 2012). Other adverse effects caused by B(a)P include oxidative stress and disturbance of cell signaling pathways (Verma et al., 2012).

Several studies have evaluated the ability of probiotic strains to detoxify the B(a)P (Apás et al., 2014; Shoukat et al., 2019; Zhao et al., 2013). Zhao et al. (2013) reported that *L. plantarum* CICC 22135 and *Lactobacillus pentosus* CICC 23163 possessed the highest efficacy of B(a)P detoxification with removal rates of 66.76% and 64.31%, respectively. Apás et al. (2014) reported the ability of *L. reuteri* DDL 19, *Lactobacillus alimentarius* DDL 48, *Enterococcus faecium* DDE 39, and *B. bifidum* DDBA to bind of the B(a)P and its removal. Finally, the highest binding ability of *L. reuteri* and *B. bifidum* at the level of 97% and 96% were recorded. Moreover, for these strains, the high stability of the bacterial-mutagen complex during DMSO washing resulted in only a small release of B(a)P (Apás et al., 2014). It has recently been reported that the peptidoglycan structural integrity of *Bifidobacterium* is important in the mechanism of B(a)P binding (Shoukat et al., 2019). Peptidoglycan from *Bifidobacterium infantis* BY12 showed the highest binding rate with B(a)P out of nine tested strains (Shoukat et al., 2019).

3.4.3. Mycotoxins

Currently, worldwide contamination of food crops with mycotoxins reaches 50–80% (Eskola et al., 2020), leading to huge agricultural and industrial losses (Marin et al., 2013). The main source of mycotoxins contamination is maturing corn, cereals, soybeans, peanuts, and other food and feed crops (Alshannaq and Yu, 2017; Marin et al., 2013). Moreover, mycotoxins were found in food products such as eggs, milk, cheese, and meat as the result of livestock feed contamination (Adegbeye et al., 2020). Mycotoxins are secondary fungal metabolites produced by members of fungal genera *Aspergillus*, *Fusarium*, *Penicillium*, and *Alternaria* (Agriopoulou et al., 2020), among which the most important in terms of occurrence and toxicity are ZEN, AFs, deoxynivalenol (DON), PAT, T2-toxin, and fumonisins (Greeff-Laubscher et al., 2020; Mishra et al., 2020). They have been shown to have varied toxic potency such as mutagenicity, teratogenicity, neurotoxicity as well as carcinogenicity (Greeff-Laubscher et al., 2020).

The presence of various mycotoxins in food products and their toxicological properties are major threats to human and animal health (Alshannaq and Yu, 2017; Janik et al., 2020). ZEN is one of the *Fusarium* metabolites considered as an endocrine-disrupting compound due to the possibility of binding to the estrogen receptor (ERα and ERβ) (Rai et al., 2020; Sangsila et al., 2016; Zinedine et al., 2007). *In vitro* and *in vivo* trials have shown that exposure to ZEN can lead to female reproductive system disorders, such as infertility, ovarian atrophy, and hyperestrogenism (Alshannaq and Yu, 2017). Exposure to aflatoxins, like AFB_1 is associated with an increased risk of hepatocellular carcinoma in humans and animals (Rushing and Selim, 2019). DON is known to cause symptoms such as nausea, vomiting, diarrhea, abdominal pain, headache, and fever in humans, whereas fumonisins can cause severe toxicity in animals (Alshannaq and Yu, 2017). T-2 toxin has disadvantageous effects on the reproductive system such as reduction of fertility, inhibition the reproductive hormone production, and disturbance of the structure and function of the reproductive organs (Yang et al., 2020).

In numerous studies, the mechanisms of mycotoxins detoxification by probiotics were broadly discussed (Armando et al., 2012; Fuchs et al., 2008; Niderkorn et al., 2007; Złoch et al., 2020). Niderkorn et al. (2006) screened 22 LAB strains and propionic acid bacteria (PAB) with high *Fusarium* mycotoxin binding capacity. The results showed that the ability of *Lactobacillus* to remove DON was up to 55%, 82% for fumonisins B1 (FB1), and 100% for fumonisins B2 (FB2), respectively. These strains were also effective at binding more than 88% of ZEN. Rogowska et al. (2019) compared the ability to the ZEN detoxification by *L. lactis* 56 and mouse L929 cell-line. Results showed that *L. lactis* neutralized ZEN in the medium by almost 30%, while the efficiency of eukaryotic cells in ZEN metabolism was nearly 54%. Besides, the L929 cell-line could degrade ZEN into α- ZOL and β-ZOL, which are endocrine disruptors. On the other hand, ZEN detoxification by *L. lactis* 56 took place by biosorption and consisted of three stages. The proposed mechanism of the first and second stage was associated with xenobiotics bioaccumulation in the bacterial cell wall, followed by intracellular bioaccumulation (Rogowska et al., 2019). Furthermore, Król et al. (2018) determined the biosorption of ZEN by *L. lactis and Bifidobacterium*. The results showed that the binding mechanism of ZEN by *L. lactis* was expressed in two kinetic steps with an initial biosorption of about 90% during the first 20 min of incubation and with the slower second step of approximately 7% of ZEN biosorption. Furthermore, a viability assay showed that ZEN in concentration 130 μg/ml increased mortality of the

bacteria. These adverse effects on microorganisms might be due to the cytogenetic effect and apoptosis caused by ZEN, but the process is not fully understood (Król et al., 2018). Nonetheless, Lioi et al. (2004) reported that the bacterial cells by the ZEN can initiate chromosome aberrations in *vitro* in a bovine lymphocyte. The increased DNA fragmentation in three cell lines, Vero, Caco-2, and DOK, after 24 h ZEN exposure was also reported (Abid-Essefi et al., 2004).

Recently, Złoch et al. (2020) showed that *L. paracasei* effectively binds the ZEN and metabolizes to less toxic forms, i.e. α- ZOL and β-ZOL with a dominance of β-ZOL. Moreover, the significant effect of ZEN exposure on probiotic metabolism and viability of *L. paracasei* was also observed. In another study, the ability of *L. pentosus* JM0812 to bind to ZEN *in vitro* was increased with mycotoxin concentration and the maximum adsorption rate was 83.17% (Sangsila et al., 2016). Yang et al. (2019) described the ability to bind 89% ZEN (4 μg/ml) by *Pediococcus pentosaceus* xy46 after 48 h of incubation.

Among the mycotoxins, aflatoxin M_1 (AFM_1) is considered possibly carcinogenic to humans as it belongs to group 2B on the IARC list (Alshannaq and Yu, 2017). AFM_1 is a highly toxic compound found in milk that is dangerous to the health of consumers, especially young children (Pierides et al., 2000). In many studies (El Khoury et al., 2011; Elsanhoty et al., 2014; Gonçalves et al., 2015, 2020, 2020; Mohammadi et al., 2020; Shetty et al., 2007), it has been demonstrated that many bacteria and yeasts that possess AFs binding ability could be used for detoxification of food products. Pierides et al. (2000) reported that the higher AFM_1 removal ability from food was mainly associated with the rapid fermentation capability of the *L. rhamnosus* LC-705 strain compared to *L. rhamnosus* GG (Pierides et al., 2000). *In vivo* study by Elsanhoty et al. (2014) showed the effect of native LABs to remove AFM_1 using contaminated yogurt. The highest reduction of AFM_1 was achieved after 7 days of fermentation with LAB starter cultures composed of 50% *S. thermophilus* and *Lactobacillus bulgaricus* and 50% *L. plantarum*. Mohammadi et al. (2020) showed a high ability of *Bifidobacterium bifidum* at an inoculation level of 10^7 CFU/ml to degrade AFM_1 in contaminated Feta cheese. On the other hand, Sarlak et al. (2017) reported that treatment of doogh (Iranian fermented milk drink) with heat-killed *L. acidophilus* LA-5 had a higher AFM_1 removal capability compared to live bacteria on the first day of storage. Furthermore, *L. acidophilus* and *B. animalis* were highly effective in the detoxification of PAT and OTA. *L. acidophilus* caused a decrease of about 95% of OTA and *Bifidobacterium* reduced the level of PAT by about 80% (Fuchs et al., 2008).

Furthermore, it has been shown that LABs can potentially be utilized to detoxify corn silage contaminated with *Fusarium* toxins. Niderkon et al. (2007) tested 202 fermentative bacterial strains for their capability to bind and metabolize DON, ZEN, and fumonisins B(1), B(2), FB(1), and FB(2). The results showed that *Streptococcus* and *Enterococcus* were effective in the binding of *Fusarium* toxins, i.e. DON (33%), ZEN (49%), FB(1) (24%), and FB(2) (62%) in simulating corn silage conditions. Furthermore, 8 *Lactobacillus* strains and 3 *Leuconostoc* strains were able to metabolize ZEN to α-ZOL, which has more estrogenic properties than the native compound (Niderkorn et al., 2007). Recently, several new bacterial species considered as NGP candidates have been identified to have DON detoxification abilities (Jia et al., 2021; Silano and Silano, 2017). *Nocardioides* WSN05-2, isolated from rhizosphere soil of wheat, showed the high capability to completely degrade DON (1000 μg/ml), under aerobic conditions after 10 days of incubation (Ikunaga et al., 2011). Similarly, *B. sutilis* ASAG216, isolated from the intestine of a donkey was shown to be capable of efficiently detoxifying DON in bacterial culture (82.8%) and culture supernatant (80.0%) after 8 h of incubation over a wide range of temperature and pH conditions (Jia et al., 2021). The results of this study showed that the ability of *B. sutilis* ASAG216 to degrade DON depends on the bacterial biotransformation associated with extracellular proteins and the activity of enzymes such as dehydrogenases (DHs). Moreover, the ability to biotransform 100% of DON (100 μg/ml) by *Eggerthella* sp. DII-9, isolated from chicken intestines to a less toxic form of the deepoxy-4-deoxynivalenol (DOM1) within 48 h has also been reported by Gao et al. (2018).

Furthermore, several studies have reported the possibility of mycotoxins elimination by yeast (Armando et al., 2011, 2012, 2012; Bejaoui et al., 2004). Chlebicz and Śliżewska (2020) described the detoxification of AFB_1, DON, Fumonisins, T-2 Toxin and ZEN (100 μg/ml) by *S. cerevisiae*. All tested mycotoxins were neutralized by yeast but at a different rate; the highest reduction was noticed for fumonisin B1 and B2 mixture (67–74%) and the lowest for DON (22–43%). Moreover, a positive correlation was also reported between the amount of the cell wall of *S. cerevisiae* strains and OTA and ZEN removal ability (Armando et al., 2012). Goncalves et al. (2020) compared the capacity of neutralization of AFM_1 by heat-killed *S. cerevisiae* and *L. rhamnosus* and *L. lactis* in Frescal cheese. Complete mycotoxin removal was observed after 20 days of incubation in the yeast variant, while incubation of the LAB/yeast mix reduced the AFM_1 binding time to 10 days. Nonetheless, Čvek et al. (2012) reported that the biosorption of mycotoxins by probiotic strains might be a reversible process. The extension of incubation resulted in the release of the part of ZEN bounded by *L. rhamnosus* GG (ATCC 53103) and *L. plantarum* A1 back into the medium.

3.4.4. Heavy metals and metalloids

Heavy metals are non-degradable, environmental contaminants that are a significant hazard to human and animal health (Rai et al., 2019; Rehman et al., 2018; Zoghi et al., 2014). The main heavy metals occurring in food are lead (Pb), mercury (Hg), copper (Cu), As, cadmium (Cd), which are highly toxic at low exposure levels, and bioaccumulative (El-Kady and Abdel-Wahhab, 2018). The sources of these heavy metals in the food chains are both natural, such as water, grains, vegetables, starchy roots, tubers, organ meats, seafood, or anthropogenic resulting from their use in the phosphate fertilizers, equipment and utensils coating, and the production of plastics (Rai et al., 2019). Physical methods of removing heavy metals are ineffective, cost-consuming, and can produce toxic waste (Zoghi et al., 2014). Consumption of heavy metal-contaminated plants/food leads to their accumulation in the liver, kidneys, muscles, intestine, and other organs of the living organisms (Kumar et al., 2019). It was reported that approximately 40–60% of ingested metals absorbed via the intestinal barrier lead to oxidative stress, tissue damages, inflammation, and gastrointestinal disorders (Nagata et al., 2013; Reyes-Hinojosa et al., 2019). Some heavy metals including Pb, Hg, As are classified as endocrine disruptors because of their capability to bind to hormone receptors including steroid (estrogen and androgen receptor), glucocorticoid, and mineralocorticoid receptors. Glucocorticoid and mineralocorticoid receptors and corticosteroid homeostasis are potential targets for endocrine-disrupting chemicals (Zhang et al., 2019). For example, Cd affects the biosynthesis and secretion of progesterone and binds to estrogen and androgen receptors (Kumar et al., 2019).

The intestinal microflora is one of the targets of heavy metal toxicity, which is related to the disturbance of its composition and metabolite synthesis (Duan et al., 2020; Jin et al., 2017; Richardson et al., 2018; Xia et al., 2018a). Xia et al. (2018b) showed that Pb exposure alters the ratio of *Bacteroidetes* to *Firmicutes* and disrupts hepatic metabolism in adult zebrafish. In mice, the effect of perinatal Pb exposure on the decrease of *Lactococcus*, *Enterorhabdus*, and *Caulobacterales* and increase of *Desulfovibrionaceae*, *Barnesiella*, and *Clostridium* in the abundance has been reported (Wu et al., 2016). A similar effect of disruption in the composition of the gut microbiome was also observed in mice exposed to Cd (S. Zhang et al., 2015), As (Lu et al., 2014a), and chromium (Cr) (Wu et al., 2017). Moreover, Pb and Cd exposure affected the concentrations of SCFAs by reducing the abundance and metabolic activity of *Ruminococcus*, *Bacteroides*, and *Oscillospira* genera (Gophna et al., 2017).

Increasing evidence has indicated that LABs, as well as *Saccharomyces* yeast, possess the ability to heavy metals detoxification and bioremediation (Alcántara et al., 2017; Bhakta et al., 2012; Duan et al., 2020). The main probiotic detoxification mechanism is the biosorption

of metal ions into the cell wall followed by bioaccumulation inside the bacteria by cell membrane transition (Abdel-Megeed, 2020). The alleviation of heavy metal toxicity is correlated with the structure of the probiotic cell wall consisting of peptidoglycan with carboxyl and phosphoryl functional groups responsible for metal chelation (Kumar et al., 2018). Xing et al. (2017) showed that *in vitro* ability of four strains of LABs such as *B. longum* BB79, *L. paracasei* Kgl6, *L. pentosus* ITA23, and *Lactobacillus acidipiscis* ITA44 to Pb reduction in the gut content of laying hens was associated with the increase of Pb binding sites on the bacterial surface and cell wall biosorption. Similarly, several *L. plantarum* strains were found to be effective in alleviating the toxic effects of administrated Pb and Cd in mice via intestinal sequestration and gut barrier protection (Kirillova et al., 2017). Zhai et al. (2013) demonstrated that oral supplementation of the *L. plantarum* CCFM8610 strain could significantly protect against chronic Cd toxicity in mice. Both living and dead cells of *L. plantarum* CCFM8610 possess good Cd binding capability and can remove >70% of Cd from 5 mg/l solution during 1-h incubation. *L. plantarum* CCFM8610 increased fecal Cd excretion and decreased its accumulation in tissues by limiting Cd absorption in the intestine and increasing fecal Cd excretion. Moreover, a significant protective effect of *L. plantarum* CCFM8610 against Cd-induced oxidative stress and mice hepatic and renal damage was also observed (Zhai et al., 2015). On the other hand, *L. plantarum* CCFM8610 reversed heavy metal-induced changes in the relative abundance of *Flavobacterium* and *Pseudomonas* in Cd-intoxicated fish (Zhai et al., 2017).

Other strains, *L. reuteri* Cd70-13 and *L. reuteri* Pb71-1 showed a strong adhesion to the fish intestinal mucosa and protection against Cd and Pb toxicity (Bhakta et al., 2012); the Cd and Pb removal rates were 25% and 59%, respectively. Moreover, different previous studies have indicated that species of *L. plantarum* TW1-1 (Wu et al., 2017), *L. plantarum* CCFM8661 (Zhai et al., 2019), *L. reuteri* P16 (Giri et al., 2018), as well as *L. brevis* 23017 (Jiang et al., 2018), possess the ability to detoxify metals such as Cr, Pb, Cd, and Hg, respectively. These strains promote fecal excretion via the enhancement of intestinal heavy metals sequestration and through stimulating gut peristalsis causing a reduction of their absorption in the intestine. Besides, in mice *L. plantarum* CCFM8661 influenced excretion of Pb by promoting hepatic bile synthesis and increasing excretion of bile acids in feces (Zhai et al., 2019), whereas *L. plantarum* TW1-1 inhabited absorption of Cr via making it less soluble and less prone to cross cell membranes in the digestive tract (Wu et al., 2017).

In mice, Majlesi et al. (2017) reported that *L. plantarum* and *Bacillus coagulans* had protective effects after Hg intoxication via alleviation of the absorption and accumulation of Hg in the liver. *In vitro*, Alcántara et al. (2017) demonstrated the capacity of *L. casei* BL23 strain to biosorption of the Hg^{2+} as well as methylmercury (CH_3Hg^+), which is the main Hg form in food. The mechanism of Hg transformation to less toxic forms depended on the cell wall anionic polymer lipoteichoic acid associated with increased Hg biosorption. It is known that Hg is a toxic, widespread heavy metal with adverse effects on the kidneys and central nervous system (Bernhoft, 2012) as well as induction of oxidative stress through the formation of reactive oxygen species (ROS) (Teixeira et al., 2018). A few research have shown that supplementation with *L. rhamnosus* GR-1 can alleviate human exposure by binding or sequestering heavy metals and finally increasing their excretion in feces (Daisley et al., 2019; B. Kim et al., 2019). A study of the human population in Tanzania showed the potential of yogurt supplemented with *L. rhamnosus* GR-1 in lowering the level of toxic metals in the blood such as Hg and As in both pregnant women and children (Bisanz et al., 2014). Recently, Daisley et al. (2019) have shown that *L. rhamnosus* GR-1 possesses the ability to reduce the apical-to-basolateral translocation of Pb and Cd in a Caco-2 model of the intestinal epithelium. The high ability of *L. rhamnosus GR-1* to bind Pb and sequester Cd in Caco-2 line-cells has been linked to the chemical structure of the bacterial cell wall, in particular with hydrophobic and electron-donating groups (B. Kim et al., 2019).

Several *in vivo* studies have investigated the use of NGPs as heavy metals detoxification candidates (S. Feng et al., 2019; Ninkov et al., 2015; Zhai et al., 2020). In mice, oral supplementation with *Faecalibacterium prausnitzii* A2-165, *Oscilibacter ruminantium* GH1 significantly promoted the fecal Pb excretion and reduced Pb accumulation in blood and kidney as well as increased the expression of the intestinal tight junction-related proteins (Zhai et al., 2020). The beneficial effect of oral supplementation with *A. muciniphila* ATTC BAA-835 on the gut microbiome composition of acute and chronic Cd-exposed mice was also reported (S. Feng et al., 2019; Ninkov et al., 2015). Moreover, the protective role of *F. prausnitzii* A2-165 against the acute As toxicity in exposed mice has been associated with arsenite (As[III]) S-adenosylmethionine methyltransferase (ArsM) activity involved in As detoxification (Coryell et al., 2018).

3.4.5. Pesticides

Organophosphorus pesticides (OPPs) are massively used worldwide insecticides as inhibitors of acetylcholinesterase enzyme activity which leads to excessive cholinergic stimulation (Jokanović, 2018; Sarlak et al., 2021; Trinder et al., 2015). In humans, exposure to OPPs is associated with endocrine and metabolic disruption, neurodegeneration, cancer, heart disease, and allergic disease (Jokanović, 2018; Li et al., 2018; Pace et al., 2015; Trinder et al., 2016). The ability of probiotics to reduce the exposure of OPPs has been reported in several studies (Li et al., 2018; Mohammadi et al., 2020; Trinder et al., 2015; Zhang et al., 2016). Trinder et al. (2016) reported that *L. rhamnosus* GG (LGG) and *L. rhamnosus* GR-1 (LGR-1) could significantly reduce the intestinal absorption of CP and parathion by passive binding in a Caco-2 Transwell model. The reduction in the OPPs absorption was more visible with LGG than with LGR-1, and the OPP-binding efficiency was more evident with CP than with parathion. Further study (Trinder et al., 2016) in the *Drosophila melanogaster* model showed that *L. rhamnosus* GG (LGG) supplementation mitigated the toxicity of CP and mortality of *D. melanogaster* after exposure to lethal amounts of CP. The median survival of *D. melanogaster* after administration of 10 μM CP was 3 days whereas 9% of *D. melanogaster* supplemented with probiotic strain survived to 12 days post-exposure.

According to the literature (Li et al., 2018; Mohammadi et al., 2020; Sarlak et al., 2021), pesticide degradation can be potentially carried out by enzymes such as carboxylesterases, phosphatases, phosphotriesterases, and organophosphorus hydrolases. For example, Zhou and Zhao (2015) observed a correlation between phosphatase production of *L. bulgaricus* and OPPs dissipation. Furthermore, several studies have shown that some *Lactobacillus* strains possess the natural capability to degrade the various classes of pesticides *in vitro* and mitigate pesticide poisoning *in vivo* (Bouhafs et al., 2015; Trinder et al., 2016; Villarini et al., 2008). The effectiveness of LABs such as *L. delbrueckii* subsp. *bulgaricus*, *L. acidophilus*, *L. casei*, *L. rhamnosus,* and *S. thermophilus* to eliminate the pesticides like CP, CP-methyl, diazinon, dichlorvos, fenthion, malathion, phorate, pirimiphos-methyl, and trichlorfon from skimmed milk was reported by Zhou and Zhao (2015). The highest ratio of dichlorvos degradation estimated for *L. bulargaricus* after 24 h of incubation was associated with the production of phosphatase enzyme. Similar results have been reported by Zhao and Wang (2012). *L. bulgaricus*, *L. paracasei*, and *L. plantarum* exhibited strong acceleration of the degradation of the OPPs in skimmed milk. Among seven tested pesticides, dimethoate and methyl parathion had the lowest degradation rate in comparison with malathion that was the most labile (Zhao and Wang, 2012). The pesticides-degrading ability of 121 *l. plantarum* strains was also reported by Li et al. (2018); six of the strains (P9, IMAU10585, IMAU10209, IMAU40100, IMAU80070, IMAU80110) showed a strong capacity of degrading alike dimethoate, phorate, and omethoate. Moreover, among the six selected strains, *L. plantarum* P9 was the most resistant to simulated gastrointestinal juices and bile. However, the correlation between phosphatase activity and OPPs degradation was not found, which indicates that another group of bacterial enzymes was

associated with OPPs degradation.

In vivo, the role of LABs in the degradation of organophosphorus (OP) insecticide CP was examined during Kimchi fermentation (Cho et al., 2009; Islsm et al., 2010). The results showed that during fermentation, CP was rapidly degraded until day 3 (83.3%) and completely degraded by day 9. Four CP-degrading LABs, namely *Leuconostoc mesenteroides* WCP907, *L. brevis* WCP902, *L. plantarum* WCP931, and *Lactobacillus sakei* WCP904 isolated from CP-impregnated kimchi utilized CP as a source of carbon and phosphorus (Cho et al., 2009). Similarly, inoculation of rice straw with viable *L. casei* WYS3 cells led to 33.3–42% removal of CP whereas heat-killed cells removed 77.2% of CP. Moreover, the ability of *L. brevis* WCP902 and *L. mesenteroides* WCP907 to CP degradation was determined by the increase of *opdB* and *opdE* expression encoding organophosphorus hydrolase (Oph) involved in the detoxification of CP (Islam et al., 2010). The results of this study showed that both biosorption and biotransformation mechanisms were responsible for CP degradation.

4. Probiotic influences on host responses to xenobiotics exposure

4.1. Host gene expression

Studies have shown that the gut microbiota affects the host gene expression through epigenetic modifications induced by bacterial metabolites (Krautkramer et al., 2017; Lukovac et al., 2014; Trinder et al., 2015; Wellen et al., 2009). It has been shown that microbial metabolites such as butyrate, one of SCFA's can enhance histone acetylation *in vitro* (Hinnebusch et al., 2002) inhibit histone deacetylases (Waldecker et al., 2008), or increase the expression of histone deacetylases (Lukovac et al., 2014; Wellen et al., 2009) whereas vitamin B3 is an inhibitor of Class III histone deacetylases (Houtkooper et al., 2010). Dalmasso et al. (2011) reported dysregulation of miRNA expression profiles in the ileum and the colon of germ-free (GF) mice colonized with microbiota from pathogen-free mice. Among eight miRNAs differentially expressed in the colon, miR-665 was directly involved in microbiota-regulated host genes expression. Upregulation of miR-665 in GF mice significantly downregulated the Abcc3 expression gene involved in mediating the metabolism of xenobiotics and endogenous toxins (Dalmasso et al., 2011).

Recent studies have revealed that probiotics possess the ability to modulate miRNA expression, and the potential mechanism of probiotics acting on the host can be correlated with the regulation of miRNA levels (Behrouzi et al., 2020; Teng et al., 2018; Zhao et al., 2021). For example, *L. plantarum* Z01 (LPZ01) was found to induce the miRNA expression involved in the alleviation of cecal inflammation in chickens (Chen et al., 2017). In mice, miRNAs that involved in the inflammatory response in colitic mice were induced via EcN 1917 supplementation (Secher et al., 2018). Similarly, *Bacillus coagulans* R11 altered the composition of the bacterial community by influencing the host fecal miRNAs (Zhao et al., 2021).

Several studies have been reported that gut microflora regulates the expression of the host genes involved in xenobiotic metabolism (Giri et al., 2018; Li et al., 2017; Selwyn et al., 2015, 2016, 2016; Trinder et al., 2015). An *in vitro* study on the human colonic epithelial cell line (HCoEpiC) incubated with live human gut microbiota showed the changes in the expression of 5000 host genes, including 588 genes associated with specific bacterial taxa in comparison with HCoEpiC incubated without microflora (Richards et al., 2019). The relative abundance of the *Collinsella* was associated positively with *Gltp* expression involved in glycolipid transfer and associated with metabolic syndrome *in vitro*. Transcriptome sequencing of the liver of GF and conventional (CV) mice showed that lack of gut microbiota altered the gene expression of phase I and phase II drug-metabolizing enzymes (Fu et al., 2017). The relatively lower expression level of the cytochrome P450 family was observed in the intestine of GF than in CV mice. Moreover, several phase II enzymes such as Ugt1a1, 2a3, Sultc2, 2b1, and Gasto 1 were upregulated in the intestine of GF mice. Li et al. (2017) reported that gut microflora can affect the expression of genes involved in drug processing. GF mice had upregulated *Cyp2c* and downregulated *Cyp3a* expression, encoding cytochrome P450 enzymes. Moreover, the administration of bioaccumulative xenobiotic, polybrominated diphenyl ethers (PBDEs) resulted in differential gene expression depending on the presence of the gut microbiome (Li et al., 2017). The lack of gut microbiota enhanced Cyp3a enzyme activity in the liver of gnotobiotic mice (Toda et al., 2009). In mice, supplementation with a mixture of probiotic strains, such as *B. breve*, *B. longum*, *B. infantis*, *L. acidophilus*, *L. plantarum*, *L. paracasei*, *L. bulgaricus*, *and S. thermophilus* upregulated several xenobiotic-metabolizing enzymes in the liver such as Cyp4v3, alcohol dehydrogenase 1, and carboxyesterase 2a, and downregulation of multiple phase II glutathione-S-transferases (Selwyn et al., 2016). The downregulation of Cyp2E1 in cecal, Cyp3A9 duodenal, and Cyp1A1 in the proximal part of jejunum, ileum, and caecum after the administration of *L. casei* was also reported in rats (Matuskova et al., 2011). Additionally, drug processing genes were regulated differently depending on gender which indicates that the maturation of female hormones impacts the gut microbiome and the expression of genes involved in xenobiotics metabolism (Selwyn et al., 2015).

In dairy cattle, Adjei-Fremah et al. (2018) reported that treatment with a probiotic mixture of *L. acidophilus*, *S. cerevisiae*, *E. faecium*, *Aspergillus oryza,* and *Bacillus subtilis* affected the global transcriptome profile in blood and upregulated the expression of 1168 genes and downregulated the expression of 9691 genes involved in homeostasis and immunity pathways such as the Toll-like receptor (TLR), inflammation response and Wingless signaling pathways. In pigs, supplemented with *L. plantarum* JDFM LP11, RNA-seq analysis of the ileum showed upregulation of three genes and downregulation of 22 genes among which eight genes were related to the innate defense response and cytokine production (Sofu et al., 2015). A study in the fish model showed that *L. reuteri* P16 supplementation upregulated the gene expression of pro-inflammatory cytokines (TNF-α, IL-1β) involved in the NF-*k*B signaling pathway as well as downregulated of heat-shock proteins, HSP70 and HSP90 in the kidney of *Cyprihus carpio* upon Pb-exposure (Giri et al., 2018). Similarly, the potential impact of *L.brevis 23017* on the modulation of P38 and NF-*k*B signaling pathways in the gut, colon, and duodenum and alleviated inflammatory response in Hg-exposed mice has also been reported (Jiang et al., 2018). The impact of oral probiotic supplementation on alleviating the adverse effect of xenobiotic exposures on the host health is summarized in Table 3.

4.2. Intestinal permeability

The intestinal barrier separates the intestinal lumen from the internal environment of the organism and is composed mainly of intestinal epithelial cells, intercellular junction complexes, immune cells, and mucus layer (L. Feng et al., 2019). The mucus layer protects the underlying cells against unfavorable biological, chemical, and physical factors and it is also a habitat for commensal microorganisms (Paone and Cani, 2020). Epithelial cells are selectively permeable, which means that they take up nutrients under physiological conditions and constitute a barrier to unfavorable compounds (Peterson and Artis, 2014). The proper functioning of the intestinal barrier is necessary to maintain the host's health. Disruption of homeostasis and increased permeability are associated with diseases like inflammatory bowel disease, celiac disease, and gluten sensitivity, irritable bowel syndrome, Crohn's disease, and others (Camilleri, 2019).

A considerable number of *in vitro* studies with different intestinal cell lines have revealed that probiotics can play a protective role against xenobiotic-induced increased gut permeability (Clarke et al., 2019; Orlando et al., 2018; Wang et al., 2018). An *in vitro* study on porcine intestinal epithelial cell line (IPEC-J2) showed the beneficial action of *L. plantarum* ZLP001 towards the decrease of IL-6, IL-8, TNFα, and the expression of tight junction-associated proteins such as claudin-1,

Table 3
Application of probiotic strains in detoxification of food contaminants *in vivo*.

Xenobiotic	Dose	Animal model	Probiotic strain	Effect (host's response)	Reference
Cd	60 mg Cd/kg b. w.	Adult male Kunming mice	*Lactobacillus plantarum* CCFM8610	• ↓ intestinal Cd absorption • ↓ Cd accumulation in tissue • ↓ renal and hepatic oxidative stress • ↓ histopathological changes of liver	Zhai et al. (2013)
BPA	0,8 ± 0,1; 2,1 ± 0,1; 4,0 ± 0,3 mg/kg,	Nine-week-old female Fischer 344 rat	*Bifidobacterium breve* Yakult (BbY); *Lactobacillus casei* strain Shirota (LcS)	• ↓ the area under the blood concentration-time curve of BPA • ↑ BPA excretion in feces (2.4 times higher) • ↑ the percentage of BPA bound to the sediment fraction of the feces	Oishi et al. (2008)
BPA + DEHP + DBP	50 mg/kg b.w./day DEHP þ 50 mg/kg b.w/day DBP þ 25 mg/kg b.w./day BPA	Male outbred Wistar rats	commercial multi-stain preparation capsules contain ≥8.5×10^9 lyophilized cells (2.5×10^9 *Saccharomyces boulardii*, 2×10^9 *Lactobacillus rhamnosus*, 2×10^9 *Lactobacillus planarum* LP 6595 and 2×10^9 *Lactobacillus planarum* HEAL9)	• ↓ systemic inflammation • protective effects on liver, kidneys, spleen, lipid status • ↓ serum glucose level • reversed the changes in biochemical, hematological and hormonal parameters • ↓ relative liver size, food consumption • mitigated changes in organ histology	Baralić et al. (2020)
DDT	100 mg/kg	Wistar albino rats	Commercial muli-strain preparation (*B. infantis)*, *L. acidophilus*, *B. thermophilum*, *L. casei*, *B. longum*, *L. helveticus*, *L. plantarum*, *Lactococcus lactis*, *Leuconostoc mesenteroides*, *L. paracasei*, *L. brevis*	• ↓ pro-inflammatory cytokine levels, • ↑ improved the antioxidant activity by: • ↓ NF-κB and ↑ the IL-10 level	Karamese (2020)
AFB1	1.5 mg or 4.8 mol/kg of bw	Five-week-old Han-Wistar rats	*L. rhamnosus* GG	• ↑ excretion of AFB1 with feces due to the binding with probiotic strain • ↓ AFB1-associated weight loss • ↓ the AFB1- induced hepatotoxic effects • ↑ fecal AFB1 excretion	Abid-Essefi et al. (2004)

Cd-cadmium, BPA-bisphenol A, DBP- dibutyl phthalate, DEHP- Bis(2-ethylhexyl) phthalate, DTT-dichlorodiphenyltrichloroethane, AFB1 -aflatoxin(B1).

occludin, and ZO-1 (Wang et al., 2018). *Lactobacillus* can enhance the expression of genes involved in tight junction signalings such as E-cadherin and β-catenin, to strengthen the intestinal barrier integrity (Orlando et al., 2018). Furthermore, *Lactobacillus* proteins can promote mucous adhesion by displaying surface adhesins and integrate with glycoprotein mixture (mucin) secreted by the intestinal epithelial cell to ensure competitive foreclosure of pathogens from the mucus (Clarke et al., 2019).

Recent evidence has demonstrated that exposure to xenobiotics including environmental pollutants can disrupt gut permeability (Braniste et al., 2010; Duan et al., 2020; L. Feng et al., 2019; Grenier and Applegate, 2013; Condette et al., 2014; Liang et al., 2019; Liew and Mohd-Redzwan, 2018; Liu et al., 2020). In mice, exposure to BPA to the intestinal barrier caused abnormalities in epithelial morphology, increased the level of endotoxins in plasma and colonic mucosa, decreased the number of goblet cells (responsible for mucosa production), and a decreased of thigh junction proteins (Collins and Patterson, 2020; Zhai et al., 2013). Furthermore, Braniste et al. (2010) reported decreased colonic paracellular permeability in adult female rats after perinatal exposure to BPA. Disturbances in intestinal permeability have also been described after exposure to mycotoxins (Grenier and Applegate, 2013; Liew and Mohd-Redzwan, 2018), pesticides (Condette et al., 2014; Liang et al., 2019) as well as heavy metals (Duan et al., 2020; Liu et al., 2020). Alteration in permeability may be due to xenobiotic-induced gut dysbiosis (Duan et al., 2020) and changes in the protein expression, e.g. tight junction proteins (Liew and Mohd-Redzwan, 2018). In mice, *L. plantarum* CCFM8610 and CCFM8661 affected the excretion of heavy metals including Pb by enhancing hepatic bile acid synthesis and increasing the excretion of bile acids in feces (Abdel-Megeed, 2020; BretonÔ. et al., 2013; Clarke et al., 2019). The protective role of *L. plantarum* TW1-1 in the reduction of Cd-induced cytotoxicity and reversing tight junctions damage in the human colon adenocarcinoma (HT) cell line was also reported (Zhai et al., 2016). Furthermore, *L. plantarum* TW1-1 inhibits Cr absorption, causing it less soluble and thus less susceptible to penetration via the cell membranes of the GI tract (Wu et al., 2017).

4.3. Oxidative stress

Many common food contaminants, like mycotoxins, pesticides, and heavy metals can cause oxidative stress, which is characterized by an increase in lipid peroxidation and a decrease in antioxidant enzyme activity (da Silva et al., 2018; Feng et al., 2018). Enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), and glutathione peroxidase (GPx) are crucial for host protection and enable the maintenance of host homeostasis (da Silva et al., 2018). Oxidative stress induces DNA and protein damage that comprise normal physiological functions, leading to a variety of human diseases and aging (Zhao et al., 2020). LABs with probiotic potentials have been reported to have antioxidative properties, which are effective against heavy metals, induced oxidative stress in mice (Zhai et al., 2013), rats (Nardone et al., 2010), and fishes (L. Wang et al., 2018). Numerous investigations indicate that probiotics can protect against oxidative stress (Bouhafs et al., 2015; Chattopadhyay et al., 2019; Feng et al., 2018; Ojekunle et al., 2017; Zhao et al., 2020) via the production of microbial antioxidant metabolites such as butyrate, folate, and vitamins B_1, B_{12} (Feng and Wang, 2020; Yang Wang et al., 2017). LABs can induce the activity of host antioxidative enzymes, thus regulating the antioxidant system and alleviating oxidative stress (Feng and Wang, 2020). Moreover, the antioxidant effect of probiotic strains is associated with inhibition of lipid peroxidation activity, scavenging free radicals, and decrease DNA lesions in host tissues (Feng et al., 2020; Ojekunle et al., 2017; Zhao et al., 2020). A meta-analysis of 23 reports, including various animal models and human trials, showed that the administration

of probiotics increases SOD and GPx activity in serum and liver (Zhao et al., 2020). On the other hand, LAB supplementation can regulate the gut microbiota, and it has been speculated that LABs may exert their antioxidative effects partially by the reconstruction of the host gut microbiota composition (Feng and Wang, 2020).

The antioxidant capacity of Cd and Pb-resistant LAB strains has been reported by Ojekunle et al. (2017). *Lactobacillus* sp. CaD1 had the highest 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging ability of 72.48% and the highest reducing ability of 73.72% as compared with *Lactobacillus* sp. CaD2 and *Leuconostoc* sp. WD2. Additionally, *L. plantarum* CaD1 showed a protective effect against Cd and Pb-induced hepatotoxicity; significantly alleviated the hepatic injury and the tissue damage (Ojekunle et al., 2017). In contrast, *L. plantarum* BJ0021 did not reverse the decline in SOD and CAT enzyme activity due to exposure to endosulfan, an organochlorine pesticide. However, the tested strain successfully reduced lipid peroxidation and apoptosis of liver and kidney cells in the rodent model (Bouhafs et al., 2015). Moreover, the impact of the intracellular content of *L. casei* CRL 431 (IC431) on AFB_1-induced oxidative stress in rats was evaluated by Aguilar-Toalá et al. (2019). The CAT and GPx activities, as well as total antioxidant capacity (TAC) capacity, were significantly higher in plasma of rats given both AFB_1 and *L. casei* CRL 431 than rats exposed to the mycotoxin only. Furthermore, lower hepatic lipid peroxidation and oxidative stress index in the liver and plasma of rats co-administered with probiotics and AFB_1 were noticed.

In another study, Chattopadhyay et al. (2019) evaluated the possible role of the probiotic supplement containing *L. acidophilus, L. rhamnosus, B. longum, B. bifidum*, and *S. boulardi* to mitigate the adverse health effects of As exposition in a rodent model. In rats exposed to sodium arsenite (1.0 mg/100 g body weight), a significant decrease in the activity of SOD, CAT, and peroxidase in the uterine tissue was observed. Friques et al. (2020) showed that probiotic kefir may restore a disturbed balance between ROS and nitric oxide (NO) after BPA treatment. The administration of kefir decreased $O_2^{\bullet-}$ formation and increased NO bioavailability. Wu et al. (2017) described the protective properties of *L. plantarum* TW1-1 against Cr toxicity in the liver and kidney of tested mice. Cr exposure resulted in the increase of malonaldehyde (MDA) and reduction in total superoxide dismutase (T-SOD), glutathione (GSH), CAT, glutathione disulfide (GSSG). *L. plantarum* TW1-1 supplementation reduced liver histopathological changes, oxidative stress, inflammation, and Cr accumulation in both the liver and kidneys. In *Cyprinus carpio fish*, co-treatment with Pb and L. *reuteri* P16 showed a protective role of this probiotic strain against Pb-induced oxidative stress (J. Wang et al., 2018). The antioxidant ability of *L. reuteri* P16 was associated with the reduction of MDA content and an increase in the activity of the serum GPx and SOD enzymes. Similar results were obtained by Mohapatra et al. (2012). In fish (*Labeo rohita*), dietary supplementation with *B. subtilis*, *L. lactis*, and *S. cerevisiae* significantly decreased the heat shock protein (HSP70) expression, reduced Pb-induced stress, and led to better fish growth and immunity (Mohapatra et al., 2012). Moreover, *Pedidococuss acidilactici* BT36 isolated from Tibetan plateau yogurt was found to possess strong antioxidant activity (Isolauri et al., 2017). In Cr-exposed mice, BT36 administration modulated the gut microflora and altered the expression of 788 genes involved in antioxidant stress and anti-inflammatory mechanisms (P. Feng et al., 2020). The elevated levels of the SOD, CAT, rubredoxin (RXN), rubrerythrin (RBR), thiol peroxidase (TPX), and peroxiredoxin (PRX) expression in presence of the BT36, which may directly or indirectly scavenge ROS have been found (T. Feng et al., 2020).

5. Summary

Humans are exposed to a multitude of chemicals including environmental pollutants through contaminated food. Long-term exposure to these contaminants, especially food xenobiotics is associated with a variety of intestinal disorders via disruption of the gut microbiome balance, referred to as dysbiosis. Methods of alleviating the negative effects of food xenobiotics and removing them from the host body are currently an important area of research. Extensive *in vitro* studies have evaluated the effectiveness of utilizing probiotic strains to detoxify several xenobiotics and pollutants such as pesticides, toxins, and heavy metals. Moreover, *in vivo* studies performed in animal models, especially combined with experiments in GF mice, have indicated that oral supplementation of probiotics can alleviate the toxicity of xenobiotics. Nevertheless, it must be remembered that food is a complex matrix consisting of many different xenobiotics that can show synergistic or addictive properties, which is not taken into account by model studies on single strains and isolated pure substances. Exposure to a xenobiotic mixture called “cocktail effects” can have a more pronounced toxicity effect compared to individual chemicals. Additionally, the probiotic ability to remove xenobiotics highly depends on various factors like pH, cell concentration, temperature, the chemical structure of contaminants and is closely related to specific bacterial strains.

To summarize, more *in vivo* research should be performed to evaluate the action of food xenobiotics and the possible role of probiotics in their detoxification. A better understanding of the mutual probiotic-xenobiotic-host axis may lead to the alleviation and/or reduction of xenobiotic-induced gut dysbiosis and chronic toxicity. Nevertheless, the use of dietary interventions by consumption of dairy fermented products supplemented with xenobiotic-binding probiotic strains may offer a simple and effective way to counteract the negative effect of exposure to xenobiotics absorbed by food, especially if highly polluted regions of the world are concerned.

Funding

This work was supposed by Prof. Wacław Dąbrowski Institute of Agricultural and Food Biotechnology – State Research Institute, project no. ZM-142-01.

Credit author statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

Acknowledgments

The results presented in this review constitute part of Ś.P. doctoral thesis, performed in the “AgroBioTechPhD” Doctoral Program of the Prof. Wacław Dąbrowski Institute of Agricultural and Food Biotechnology – State Research Institute.

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Glossary

3-HPA: 3-hydroxypropionaldehyde
AFB1: aflatoxin B1
AFB2a: aflatoxin B2a
AFM1: aflatoxin M1
As: arsenic
ArsM: arsenite (As[III]) s-adenosylmethionine methyltransferase
B(a)P: benzo(a)pyrene
BPA: bisphenol A
BPDE: BaP-7,8-dihydrodiol-9,10-epoxide
CAT: catalase
Cd: cadmium
CE: carboxylesterases
CP: chlorpyrifos
Cu: copper
CV: conventional
DOM1: deepoxy-4-deoxynivalenol
DON: deoxynivalenol
EMSP: enzyme microsphere sustained-release preparation
FMOs: flavin-containing monooxygenases
FB1: fumonisins B1
FB2: fumonisins B2
FDA: Food and Drug Administration
GF: germ-free
GI: gastrointestinal tract
GPx: glutathione peroxidase
GR: glutathione reductase
GRAS: Generally Regarded As Safe
GSH: glutathione
GSSG: glutathione disulfide
HAA: heterocyclic aromatic amines
Hg: mercury
LAB: lactic acid bacteria
LBP: live biotherapeutic products
LPS: lipopolysaccharide
MDA: malonaldehyde
NGPs: Next-Generation Probiotics

NIC: newly industrialized countries
NO: nitric oxide
OPPso: rganophosphorus pesticides
OTA: ochratoxin A
PAB: propionic acid bacteria
PAH: polyaromatic hydrocarbons
PAT: patulin
Pb: lead
PBDEs: polybrominated diphenyl ethers
PCBs: polychlorinated biphenyls
PDO: 1,3-propanediol
PhIP: 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine
PhIP-M1: 7-hydroxy-5-methyl-3-phenyl-6,7,8,9-tetrahydropyrido[3′,2’: 4,5]imidazo[1,2-a]pyrimidin-5-ium chloride
POPs: Persistent Organic Pollutants
PRX: peroxiredoxin
PSTs: paralytic shellfish toxins
QPS: Qualified Presumption of Safety
RASFF: Food and Feed Rapid Alert System
RBR: rubrerythrin
ROS: reactive oxygen species
RXN: rubredoxin
SOD: superoxide dismutase
T-SOD: total superoxide dismutase
TAC: total antioxidant capacity
TPX: thiol peroxidase
ZEN: zearalenone