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Article in *Current Pharmaceutical Biotechnology* · June 2023

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To cite this article: Fereshteh Ansari, Chi-Ching Lee, Azadeh Rashidimehr, Soheyl Eskandari, Tolulope Joshua Ashaolu, Esmaeel Mirzakhani, Hadi Pourjafar & Seid Mahdi Jafari (22 Nov 2023): The role of probiotics in improving food safety; detoxification of heavy metals and chemicals, Toxin Reviews, DOI: [10.1080/15569543.2023.2283768](https://doi.org/10.1080/15569543.2023.2283768)

To link to this article: <https://doi.org/10.1080/15569543.2023.2283768>



Published online: 22 Nov 2023.



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The role of probiotics in improving food safety; detoxification of heavy metals and chemicals

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ABSTRACT

Various studies have shown that different types of probiotics as healthy gut microbes, in addition to having beneficial effects on the host's health, have an excellent ability to eliminate and neutralize chemical toxins and unwanted substances in foods, and ultimately, they can increase food safety. The purpose of the present review was to comprehensively discuss the role of probiotics in improving food safety in terms of adsorption/detoxification of heavy metals, pesticides, anti-parasitic drug residues, antibiotic residues, oxidants, and synthetic/authorized food additives (e.g. nitrite and nitrate, acrylamide, heterocyclic amines, and polycyclic aromatic hydrocarbons, acetamide, and oxalate) in the food products. Some recent examples in terms of the role of probiotics in neutralizing chemical agents in the body after consuming contaminated food have also been mentioned. This review shows that probiotics have the potential to inactivate and detoxify various biological and synthetic chemical compounds in foods and the host body after consumption.

ARTICLE HISTORY

Received 3 February 2023
Revised 12 October 2023
Accepted 5 November 2023

KEYWORDS





Probiotics; gut microbes; food safety; detoxification; inactivation; heavy metals

1. Introduction

Providing sufficient and safe food products for the world's growing population is a global concern. Despite all the efforts, thousands of food intoxication occurs every year across the globe, resulting in substantial costs to the individuals, governments, and food industries. The results of a review of global data show that the entire definite food safety occurrences and/or recalls with recognized or suspected reasons over the period 2008–2018 were 2932 (Soon *et al.* 2020). It has to be mentioned that the actual number is multiplied considering the unreported cases and the food safety incidents with unknown causes. Food safety hazards are defined by Codex (1997) as organic, chemical, or physical agents

in, or conditions of, food with the potential to cause an opposing healthiness impact. The contamination may occur during any stage, from production to consumption (Kamboj *et al.* 2020). Therefore, efforts should be made to ensure food safety by the producer by using effective agents so that when the product reaches the consumer, its safe condition is maintained.

It has been shown that probiotics are able to expand the safety of food products through various means, including inactivation of pathogens, detoxification of chemicals, and secretion of chemical substances. Probiotics are a cluster of microorganisms when consumed in suitable amounts, induce health profits to the host ranging from prevention and treatment of diseases in the respiratory, gastrointestinal (GI), and

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urogenital tracts, via immunomodulatory activities (Ashaolu 2020b, Ashaolu and Fernández-Tomé 2021). The origin of probiotics can be traced to fermented foods and age-old fermentation methods that have been employed for centuries across various cultures. Items such as yogurt, kefir, sauerkraut, and kimchi serve as examples of probiotic-rich products that people have traditionally consumed for their potential positive impacts on health (Tamang *et al.* 2016). Moreover, probiotics intended for human consumption can also be derived from the human microflora system. A suitable strain should ensure safety and be harmless to the host (Ayivi *et al.* 2020). Until now, the beneficial and promising role of probiotics in various conditions such as lactose intolerance, obesity and diabetes, acute diarrhea, irritable bowel syndrome and inflammatory bowel diseases, cancer, cardiovascular diseases, urogenital infections, allergy, antiviral activity, gut-brain axis, and oral health are shown (Ayivi *et al.* 2020, Ansari *et al.* 2023, Homayouni Rad *et al.* 2023). The probiotics most frequently utilized belong to the bacterial genera *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, and the yeast *Saccharomyces* (Żólkiewicz *et al.* 2020). Formulations of these probiotics are widely used and marketed with health claims even when vivid practical indications could be found wanting (Ghorbani-Choboghlo *et al.* 2015, Grumet *et al.* 2020). Selected strains must be applicable to and compatible with food processing conditions. Survivability and functionality during harsh production and storage conditions like freezing or drying processes are other important factors. The organisms also must survive in the human GI tract (Pourjafar *et al.* 2016, Abdolhosseinzadeh *et al.* 2018, Moreno *et al.* 2018, Pourjafar *et al.* 2018). Therefore, it is essential to consider such parameters in achieving the health goals of using probiotics.

Probiotics can be applied for the detoxification of food contaminants, including heavy metals and pesticides. For instance, heavy metals are absorbed and detoxified by Lactic Acid Bacteria (LAB) through several mechanisms (Monachese *et al.* 2012, Mrvčić *et al.* 2012), and pesticides are degraded by the enzymes produced by the probiotics such as organophosphorus hydrolase, organophosphorus acid anhydrase, and methyl parathion hydrolases (Mohammadi *et al.* 2021). The present review provides a broad discussion of the various effects of probiotics on improving food safety. It will be presented in two parts: (i) the role of probiotics in the detoxification of chemicals and heavy metals (current study); (ii) the role of probiotics in the inactivation of food pathogens (forthcoming study).

To the best of our knowledge, it is the first time that these various effects have been comprehensively covered in a review article.

2. Role of probiotics in the adsorption/detoxification of heavy metals

2.1. Sources and distribution of heavy metals and their toxicity on humans

Heavy metals contain a unique group of forty natural elements with a density $>5\text{ g/cm}^3$ (Monachese *et al.* 2012, Huët and Puchooa 2017). Instances of heavy metals are lead (Pb), mercury (Hg), cadmium (Cd), arsenic (As), zinc (Zn), chromium (Cr), and copper (Cu) (Huët and Puchooa 2017). Heavy metals have been detected naturally on the earth's crust since the formation of the earth (Briffa *et al.* 2020). The expansion of recent anthropogenic industrial activities, counting the extraction, smelting, and manufacture of synthetic compounds, has prompted an outstanding increase in heavy metals delivered into the water, soil, and air (McConnell and Edwards 2008).

The three chief causes of pollution by humans are industry, farming, and urbanization. Amongst the polluting industries, the principal is tanneries, materials, galvanizing plants, metallurgic, factories, distilleries, fertilizers, paints, varnishes, pesticides, and pharmaceuticals (Alvarez *et al.* 2017). As a result, many countries face dire consequences.

Heavy metals can exhibit devastating impacts on living organisms and the environment. As stated, they are hazardous even at deep concentrations due to their toxicity (Huët and Puchooa 2017). Heavy metals achieve the highest level after entering the food chain with the phenomena of bioconcentration, bioaccumulation, and biomagnification, and as a consequence, have an adverse effect on human health (Ahmed *et al.*, 2017). Their adverse consequences are perceived in both children and adults and encompass issues disorders of the kidneys, heart, nervous system, reproductive system, and skeleton, and also, in severe cases, may cause death (Goyal *et al.* 2019). Numerous countries retain regulatory rules for heavy metals, and they are frequently screened, modified, and treated in environmental resources; however, significant numbers of these projects and advances are not promptly available in most developing countries, where the weight is most noteworthy (Monachese *et al.* 2012). The net outcome is that individuals all throughout the world are exposed, and new methodologies are needed to diminish the adverse results of the outcomes of the accumulation of those metals.

2.2. Biodegradation of heavy metals using probiotics

Over the most recent twenty years, environmentally friendly methods have been developed to clean contaminated environments utilizing distinctive microbial species (Alvarez *et al.* 2017). They predominantly help in the process of digestion and fortifying the human immune system. These probiotics are, for the most part, viewed as protected and are ordinarily utilized in the dairy industry. Probiotics can likewise be confined to various sources in the environment. These bacterial species display a few alluring attributes that can be misused to profit people just as the environment (Huët and Puchooa 2017). A few genera of LAB, *Bifidobacteria*, and *Saccharomyces boulardii*, are characterized as probiotics; to be specific, “Probiotics are live microorganisms that, when administered in sufficient amounts, confer a health benefit on the host” (FAO/WHO, 2002; (Homayouni *et al.* 2018).

Metals attach onto the bacterial cell walls by three principal mechanisms: (i) binding to peptidoglycans and teichoic acids by ion-exchange reactions; (ii) precipitation by nuclear reactions; (iii) formation of complexes with nitrogen and oxygen ligands. In many studies, the utilization of probiotics such as some LAB, *Bifidobacterium* spp., and some yeasts has been suggested to detoxify or eliminate various heavy metals (Monachese *et al.* 2012, Massoud *et al.* 2019). Because the content of peptidoglycan and teichoic acid in the cell wall of Gram-positive bacteria such as *Bacillus* is high, these microbes have an elevated adsorption capacity for metals. The cell membrane of Gram-negative bacteria is barely in these components, and they are weaker metal absorbers (Monachese *et al.* 2012).

The mechanism of bio-quenching of heavy metals by LAB is believed to represent a multi-layered interaction including biosorption (the mechanism associated with non-metabolic attachment of metal ions with the bacterial cell wall) (Mrvčić *et al.* 2012), (metabolism-related the accumulation of metal ions within bacteria through the cell membrane) (Mrvčić *et al.* 2012) and conversion of more toxic types to less toxic ones (transformation of methylated mercury to mercuric and then to mercury vapor which has low absorption) (Monachese *et al.* 2012). Factors such as exopolysaccharides, organic acids, and other LAB metabolites increase the biosorption of heavy metals (Upreti *et al.* 2011). Thus, human immune cells convert Cr to a less toxic form using *Lactobacilli* and other intestinal-related bacteria (Shrivastava *et al.* 2003). Chronic exposure to Cr can create *Lactobacilli*-resistant strains that are better able to endure metals (Upreti

et al. 2011), and they become less toxic (Shrivastava *et al.* 2003). Although no information is yet available on the ability of the LAB or intestinal microbiota to bind and absorb Hg, fundamental lab studies recommend that specific strains of *Lactobacilli* seem to isolate Hg (Monachese *et al.* 2012). Another study examined the binding capacity of Hg (II) (inorganic Hg) and methylmercury (organic Hg) to various strains of *Lactobacillus*. Both forms bond immediately and occur predominantly at the cell wall. Cell reasonability was unneeded for binding; truth be told, an expansion in binding capacity was noticed for heat-executed cells (Alcántara *et al.* 2017).

2.3. Protective role of probiotics in mitigating heavy metals

There is ample evidence that probiotics are quite possibly the best strategy for protecting food in opposition to toxic pollutants (Feng *et al.*, 2019). Probiotics substantially contribute to human health benefits and are involved in treating various diseases, improving metabolism, and stimulating the immune system (Akhter *et al.* 2015). Likewise, such heavy metal-resistant microorganisms can be utilized as safe agents to treat individuals exposed to heavy metals and a variety of contaminated food sources and dietary supplements (Pérez-Corona *et al.* 2011, Bisanz *et al.* 2014, Lin *et al.* 2019). The defensive impacts of probiotics against heavy metal toxicity have been broadly examined. Single probiotic supplementation or a mix of probiotics in mammals has shown positive outcomes in reducing the toxicity of heavy metals, including Pb, Cd, Cr, As, and Hg (Table 1).

In one investigation on three strains of *Lactobacillus*, three strains of *Bifidobacterium*, and two commercial LAB starter cultures, 99% of Cd and 97% of Pb were eliminated from solutions at concentrations of 0.1 to 1 mg/L. The researchers displayed that the binding of Cd and Pb to the LAB is quick, with the greatest adsorption following 5 min contact, and is pH-dependent, with higher accumulation at near-neutral pH values. They proposed that the pH dependence demonstrates that ion exchange may be incompletely liable for metal binding. The authors likewise state that temperatures of 4 to 37 °C do not influence binding, which indicates the process is not dependent on energy (Halttunen *et al.* 2007). Teemu *et al.* (2008) found that by neutralizing the negative charge of carboxyl and phosphoryl groups, the binding of Pb and Cd by *B. longum* 46 and *L. fermentum* ME3 was decreased by chemical changes, indicating that both

Table 1. Protective impacts of probiotics against toxicity of heavy metals.

Heavy metals	Name of probiotics	Health benefits	Reference
Cd and Pb	Yogurt containing <i>Lactobacillus rhamnosus</i> GR-1	Decreased metal absorption in the intestinal epithelium	(Daisley <i>et al.</i> 2019)
Hg and As	Yogurt containing <i>L. rhamnosus</i> GR-1	Protective impacts against Hg and As in pregnant women	(Bisanz <i>et al.</i> 2014)
Hg	Curd produced from <i>Streptococcus thermophilus</i> <i>L. acidophilus</i> <i>B. bifidum</i>	Reduce the toxic consequences of Hg by feeding high-fiber fermented mare milk	(Abdel-Salam <i>et al.</i> 2010)
Cd	<i>L. plantarum</i> CCFM8610	Shielding effects against Cd cytotoxicity in both human intestinal epithelial cell and mice, alleviate oxidative stress, reverse changes in hepatic and renal damage, the inflammatory response, and reverse tight-junction disruption	(Zhai <i>et al.</i> 2014, Zhai <i>et al.</i> 2016)
Cd	<i>L. acidophilus</i> Rosell-52 <i>L. rhamnosus</i> Rosell-11 <i>B. longum</i> Rosell-175	Mitigation of Cd-induced genotoxicity and toxicity in the gastrointestinal tract of rats	(Jama <i>et al.</i> 2012, Djurasevic <i>et al.</i> 2017)
Cr(VI)	<i>L. acidophilus</i> , <i>Streptococcus faecium</i> <i>B. thermophilum</i> <i>B. longum</i>	Mitigation of toxic effects of Cr (VI) and improved hepatic and renal profiles	(Younan <i>et al.</i> 2016)
Cd and Pb	<i>L. reuteri</i> Cd70-13 <i>L. reuteri</i> Pb71-1	Decent bond to fish intestine milieu for biosorption of heavy metals Pb and Cd	(Bhakta <i>et al.</i> 2012)
Hg	<i>L. plantarum</i> CNR273 <i>Bacillus coagulans</i>	Decreased levels of Hg in the liver and kidneys and significant reduction of Hg in levels of bilirubin, creatinine, urea, alanine transaminase, and aspartate transaminase in rats	(Majlesi <i>et al.</i> 2017)
Pb	<i>L. bulgaricus</i> KLDS1.0207	Enhanced Pb levels in feces, Diminished Pb enrichment in tissues, Enhanced antioxidant index and relieved kidney damage in mice	(Li <i>et al.</i> 2017)
As	<i>L. acidophilus</i> <i>L. rhamnosus</i> <i>B. longum</i> , <i>S. boulardii</i>	Decrease of oxidative stress, inflammation in the uterus, necrosis, protects against mutagenic uterine DNA breakage, and damages to ovarian-uterine tissue in rats	(Chattopadhyay <i>et al.</i> 2019)
Cr (VI)	<i>L. plantarum</i> TW1-1	Improved tissues; reduced damage in liver and oxidative stress; partially reestablished the gut remediation community in mice	(Wu <i>et al.</i> 2017)
Cr (VI) and Pb	<i>B. coagulans</i>	Commercialization of "Sporlac-DS" for the treatment of diarrhea	(Belapurkar <i>et al.</i> 2016)
Cd	<i>Pediococcus pentosaceus</i> GS4	<i>P. pentosaceus</i> GS4 binds to Cd and causes Cd excretion to a significant extent through feces. Therefore, this probiotic strain reduces the toxicity caused by Cd in the vital organs of the intestine and liver in mice,	(Dubey <i>et al.</i> 2019)
Pb and Cd	<i>L. rhamnosus</i> GR-1	Absorption by LGR-1 and thus immobilizing Pb and Cd, and reducing their transport across the intestinal epithelium in vitro	(Daisley <i>et al.</i> 2019)
Cr, Cd, and Cu	<i>Lactococcus lactis</i>	Remarkable removal of heavy metals (Cr, Cd, and Cu) in fish (<i>Cyprinus carpio</i>)	(Kakade <i>et al.</i> 2022)
Cu and Ni	Yogurt containing <i>Pediococcus acidilactici</i> GR-1	More and faster reduction of Cu and Ni in the blood of the people of the probiotic group compared to the control group	(Feng <i>et al.</i> 2022)
Cd, Pb, and Hg	<i>S. cerevisiae</i>	<i>S. cerevisiae</i> can be considered a strong adsorbent of heavy metals in milk as well as a safe tool for providing healthy food	(Masoud <i>et al.</i>)

groups play a vital functional role in binding with Pb and Cu. The association of carboxylate groups of Slayer proteins was also demonstrated through Fourier Transform Infrared Spectroscopy (FTIR) analysis of the cooperation of these proteins got from *L. kefir* with various metal ions (Germino *et al.* 2011).

More commercial probiotic yogurts contain *L. rhamnosus*, just as the *S. boulardii*, which have *in vitro*

partiality for toxic metals, for example, Pb, Hg, As, and Cd (Ibrahim *et al.* 2010, Bisanz *et al.* 2014). Latterly, probiotic foods have supplied a nutritious and cost-effective means of combating the side impacts of exposure to toxic metals in developing countries. Other studies using *L. rhamnosus* GR-1 as a heavy metal-resistant probiotic have reported mitigation of Cd and Pb through the human intestinal epithelium

(Bisanz *et al.* 2014, Daisley *et al.* 2019), and yogurt containing *L. rhamnosus* supplement, which was distributed among children and pregnant women, appears to cause broad shielding effects against Hg and As poisoning in susceptible populaces, especially pregnant women (Bisanz *et al.* 2014). Evaluations in rats additionally displayed mitigation of the toxic impacts of Hg and As after taking various probiotic supplements (Abdel-Salam *et al.* 2010, Majlesi *et al.* 2017, Chattopadhyay *et al.* 2019).

Aluminum, a recognized neurotoxic metal, is involved in learning and memory weakening by the accumulation of beta-amyloid peptides and, at the same time inducing reactive oxygen species (Zatta *et al.* 2002, Li *et al.* 2017). There is an indication that the consumption of probiotics, counting *Lactobacillus* and *Bifidobacterium*, expands memory work and improves discernment through the intestinal axis of the brain (Bravo *et al.* 2011, Messaoudi *et al.* 2011, Ohland *et al.* 2013). *L. plantarum* CCFM639 can mitigate brain oxidative stress in mice (Tian *et al.* 2017), which in adaptation to probiotic supplements, may affect physiology and behavior in both healthy and infected states (Gareau 2014). Improvement of Cd and Hg- prompted liver and kidney damage in albuminous rats was reported by genetically modified probiotic *E. coli* Nissle 1917 creation of pyrroloquinoline-quinone with citric acid oral supplementation (Raghuvanshi *et al.* 2016).

Elimination or reduction of heavy metals using probiotics in animals and humans is mainly achieved through the process of adsorption on the microbial superficial, which prevents intestinal absorption of heavy metals and raises fecal excretion (Wu *et al.* 2017). It has also been described that some probiotics use biotransformation processes to treat some heavy metals. For example, the oxidative stress of inorganic selenium (Se) and Cr (VI), using different probiotics, was decreased to bioactive organo-Se and Cr (III) compounds, respectively (Shakibaie *et al.* 2017, Wu *et al.* 2017). According to a study by Majlesi *et al.* (2017), around 53 different strains of LAB have the property of detecting various heavy metals for detoxification. Also, a few strains of *S. cerevisiae* have also been recorded in terms of probiotic properties along with the chelating activity of heavy metals (Chiocchetti *et al.* 2019). However, most past research examines have depended on various species of *Lactobacillus* for detoxification of heavy metals with food benefits (Chiocchetti *et al.* 2019).

Food sources contaminated by heavy metals can likewise be exposed to microorganisms resistant to

heavy metals for their expulsion. For this interaction, likewise, the above-mentioned probiotics can be utilized for processed food. The use of LAB to diminish metal levels in food in two investigations shows that the impact varies relying on the food matrix. According to Schut *et al.* (2011), the high Cu binding capacity of *L. buchneri* DSM 20057 was diminished in wine, must, and grape juice samples. The reduced effect was ascribed not exclusively to the low pH values of the food samples yet in addition to the presence of intrinsic metal cations, phenolic compounds, and organic acids. On the other hand, in the study of Zhai *et al.* (2016), they achieved a significant reduction (46–62%) of Cd in vegetable and fruit juices with *L. plantarum* CCFM8610, with the rate of the decrease being reliant upon the juice. The authors likewise tried the LAB strain as a starter culture, fermenting fruit juices for 36 h, a treatment that significantly reduced Cd concentrations (56–81%). In another examination, LAB and yeast were used in the preparation of dairy products, for example, yogurt fortified with Se, kefir, and spar (Alzate *et al.* 2008, Shakibaie *et al.* 2017).

Lactobacillus spp. possess a lengthy history of safe application in foods and have currently been used as a probiotic (Younan *et al.* 2016). In addition, as part of the normal gut flora, this genus has been employed in food requests and can be a helper in vindicating the poisonousness of metals. These microorganisms have resistant instruments that prevent cell injury and can attach or separate heavy metals and eliminate them over the feces (Younan *et al.* 2016). They will likewise diminish oxidative stress brought about by heavy metal toxicity based on *in vitro* studies (Bhakta *et al.* 2012) and the ability to detoxify other food toxins (Stidl *et al.* 2008). It was reported that *L. casei* could reduce oxidative stress by diminishing lipid peroxidation as well as refining lipid metabolism in the liver and blood (Zhang *et al.* 2010). In another study, *L. plantarum* 7FM10 was separated from the customary Japanese food Saba-narezushi, which showed superoxide radical scavenging capacities (Kanno *et al.* 2012). Gram-positive bacteria, particularly *Bacillus* spp., possess an elevated absorption capacity due to their high teichoic acid and peptidoglycan in cell walls (Younan *et al.* 2016). Gram-negative bacterial cell membranes are more modest and less fortunate in these heavy metal adsorbents. *Bacillus* spp. have been shown to contain high Cr-binding activity, as well as the ability to export metal from cells and diminish damage to the body by reducing cell concentrations (Monachese *et al.* 2012).

The information arranged shows the capacity of food-grade microorganisms to diminish the toxicity of chemical pollutants. A portion of the fundamental mechanisms for these valuable impacts are being concentrated; however, there are as yet numerous neglected systems, and it is important to accomplish a superior portrayal of the pollutants/microorganism communication, particularly in food tests. In most studies, *in vitro* and *in vivo* media have been used by standard solutions of toxic complexes, and little attention has been paid to the food milieu when attempting to affirm the adequacy of these microorganism-based methodologies. Accordingly, to affirm the legitimacy of these procedures in the absorption, chelation, and toxicity of pollutants, studies are needed in which pollutants are not just dosed utilizing aqueous solutions yet, in addition, conveyed through debased food.

The utilization of artificial systems imitating the GI entry gives a significant apparatus to strain testing and choice before *in vivo* trials in animals, and last trials in exposed populaces are embraced. Future exploration needs to set up how these microorganisms can be conveyed to the exposed populaces; as enhancements, after their fuze in food definitions, by utilizing them in food fermentations, or whether they can be utilized in decontamination cycles of the fundamental dietary wellsprings of these pollutants. Moreover, it is important to guarantee that these systems do not involve related dangers, particularly in constant openings, like a decrease in the bioavailability of other significant nutrients (e.g. oligo-components or minerals). These examinations will supplement the proof base accessible up until now and permit the choice of fitting procedures for every blend of food and pollutants.

3. Detoxification of pesticides by probiotics

3.1. Sources and distribution of pesticides and their toxicity on humans

One of the biggest and most significant economic activities on the planet is the production of agricultural crops; since the 1950s, the utilization of compounds to prevent crop pests has developed constantly (Alvarez *et al.* 2017). Pesticides are broadly employed in agriculture to oppose bugs, weeds, and plant microbes to enhance plant growth. Numerous pesticide residues have been monitored by industry or because of their widespread use in agriculture (Feng *et al.*, 2019). Pesticides are classified into four main groups based on working principles, chemical

structure, method of activity, and possible toxicity, including organophosphorus (OP), organochlorine (OC), carbamates (CB), and pyrethroids (PY) (Mohammadi *et al.* 2021). The most toxic pesticides (respectively) are OP [malathion, chlorpyrifos, fenitrothion, formothion, parathion, and methyl parathion], CB, and OC classes [dichlorodiphenyltrichloroethane (DDT), hexachlorobenzene (HCB), and hexachlorocyclohexane (HCH)]. These mixtures are powerful synthetics that act essentially by disrupting the function of the nervous system (Alvarez *et al.* 2017). OP and CB insecticides act as inhibitors of acetylcholinesterase, which in turn increases acetylcholine levels and affects various organs such as the central and peripheral nervous system, liver, muscles, brain, and pancreas. While OC insecticides play a role in neurotoxicity in changing ion channels. As a common mechanism, OP, OC, and CB pesticides cause cellular oxidative stress by influencing mitochondrial function and thus disturb the body's neurological and hormonal status (Alvarez *et al.* 2017).

Exposure to minimal amounts of pesticides can cause long-term adverse effects on the skin, endocrine glands, and particularly the nervous system via causing free radicals that may result in DNA damage, lipid peroxidation, cell death, and conceivable carcinogenic impacts (Villarini *et al.* 2008, Sarwar 2015). Indeed, pesticide contamination plays a role in increasing "cancer villages". The term alludes to a spot where cancer mortality rates are significantly above average, possibly due to widespread contamination of pesticides, mainly in water (Lu *et al.* 2015). People are generally influenced because of the pesticides that result in different undesirable impacts, for instance, headaches, nausea (Qi *et al.* 2018), chronic diseases and respiratory problems, and neurodegenerative disorders (Hernández *et al.* 2013). Thusly, fundamental measures are basic to eliminate pesticides from horticultural products.

The chief concern about the utilization of pesticides is their devastating impact on human health, the environment, and wildlife populations. Combinations of pesticides, when used on harvests, leave residues in food, and drinking water sources and furthermore influence the aquatic environment. Exposure to pesticides is high in fresh vegetables and fruits, which represent 30% of a person's diet because they are ingested raw or processed (Qi *et al.* 2018). As the need to consume vegetables and fruits increases, reaped agricultural products are brought right to the market saturated with vast amounts of insecticides (Misra 2015). Fresh produce, when utilized in

processed food, possibly will likewise be contaminated with pesticides, which surges its concentration and affects the composition of the finished product. In addition, throughout food preparation, residual pesticides are converted into different metabolic products that are further toxic than maternal pesticides (Pandiselvam *et al.* 2020).

Ideally, a pesticide should be deadly to the objective pest, but, not lethal to non-target species, counting people. Shockingly, this is not the situation, and insufficient pesticide management poses expected word-related risks and environmental hazards to ecosystems (Lake *et al.* 2012). In addition, pesticide residues can straight affect community health through food consumption. The World Health Organization (WHO) has revealed that word-related poisoning by pesticides has led to about 1,000,000 cases worldwide and given proof that pesticides have a significant impact on various aspects of human health (WHO 1990).

3.2. Biodegradation of pesticides using probiotics

The utilization of organisms for the remediation of pesticides has been very much considered. A few microorganisms, particularly soil bacteria, can endure these contaminants. In addition, certain bacterial strains are equipped to restrict pesticides or alter them into fewer toxic structures (Huët and Puchooa 2017). Probiotics contain pesticide-degrading genes encoded by enzymes with degradation activity, such as OP hydrolase, OP acid anhydrase, and methyl parathion hydrolase, and gene expression in probiotics is excreted within the sight of pesticides (Mohammadi *et al.* 2021). In the biodegradation of OP pesticides by probiotics, several enzymes, including phosphatases, organophosphate hydrolase carboxylesterases, and phosphodiesterase, are involved through the hydrolysis of phosphoric acid esters (Mohammadi *et al.* 2021). LAB degrades OP pesticides by expressing the gene encoding organophosphorus enzyme hydrolase (Bo *et al.* 2011). Acid and alkaline phosphatases produced by probiotics corrupt OP pesticides by hydrolyzing the C-O-P link of an extensive assortment of phosphate esters (Mohammadi *et al.* 2021). Phosphatase released by LAB may also be a significant reason for the interruption of pesticides in the fermentation process (Zhang *et al.* 2014b).

3.3. Protective role of probiotics in mitigating pesticides

In spite of the fact that pesticides assume a significant part in agriculture and food creation, however, it

ought to be seen that their improper and unreasonable use can prompt accumulation in the environment and posture extreme health hazards (Narendran *et al.* 2020). Harmless agricultural methods and inventive technologies may lessen the requirement for chemicals (Asghar *et al.* 2016). Quite possibly, the most efficient and practical technique for the corruption of pesticides is employing microorganisms. Bacteria can separate pesticides in ecologically polluted water and soil in a process referred to as bioremediation and utilize them as wellsprings of energy, carbon, and nitrogen (Barman *et al.* 2014, Mohammadi *et al.* 2021). In addition, some techniques have been utilized in food processing to decrease pesticides in food items. At any rate, a portion of these cycles causes an improvement of residues because of concentration impact as well as a proclivity for lipid moiety (Bajwa and Sandhu 2014).

Recently, the usage of microorganisms, for example, probiotics as detoxification instruments, have opened up another possibility of intoxicants decrement procedures, and a few investigations have been led by utilizing diverse probiotic strains in various media (Mohammadi *et al.* 2021). Fermentation is an old food process that has been accounted for to be an efficient way to reduce pesticide levels. The most studied pesticides are OP pesticides. Microorganisms have been added to various foods for years, for example, yogurt, cheese, or kefir, to improve technological processes or as a result of their dietary benefit. In most cases, recent investigations have shown that various probiotics, predominantly *Lactobacillus* from dairy and wheat products, are able to degrade OP enzymatically with phosphohydrolase (Chiocchetti *et al.* 2019). The protective impacts of probiotics against pesticides toxicity have been broadly examined (Table 2)

Many studies have been performed to reduce the level of pesticides in food utilizing LAB or *Saccharomyces* on OP-contaminated foodstuffs and depend on their capacity to corrupt this kind of pesticide. The part of LAB in eliminating them is typically connected with a cycle of bacterial corruption. In the study of Shaker *et al.* (1988), chlorpyrifos metabolism was described by two LAB (*L. bulgaricus* and *S. thermophilus*). The culture medium in which the bacteria grew primarily contained 7.4 mg/L chlorpyrifos, but 72–83% of the pesticide was removed after 96 h. In another study on Kimchi (fermented cabbage), *L. plantarum*, *Leuconostoc mesenteroides*, *L. sakei*, and *L. brevis* WCP902, were isolated that were additionally able to biologically destroy the pesticides, for instance, comafus, chlorpyrifos, diazinon, and paratin (Cho *et al.*

Table 2. Protective impacts of probiotics against toxicity of pesticides.

Pesticides	Name of probiotics	Health benefits	Reference
Pirimiphos-methyl	Wheat fermentation containing <i>L. plantarum</i>	81% reduction of pesticides Lack of effect of pesticides on bacterial growth and fermentation activity	(Dordević <i>et al.</i> 2013a)
Pyrethroid	Milled wheat during fermentation by <i>L. plantarum</i>	Reduction of bifenthrin in milled wheat; Metabolism of bifenthrin via hydrolysis of carboxyl ester bond	(Dordević <i>et al.</i> 2013b)
Dimethoate, malathion, monocrotophos, fenthion, methyl parathion, trichlorphos and phorate	Milk containing <i>L. paracasei</i> , <i>L. Plantarum</i> , <i>L. bulgaricus</i>	<i>L. plantarum</i> and <i>L. bulgaricus</i> displayed a robust effect than <i>L. paracasei</i> . Dimethoate and methyl parathion were generally steady whereas malathion was normally labile.	(Zhao and Wang 2012)
Methoate, monocrotophos, malathion, trichlorphos, fenthion, methyl parathion and phorate	Bovine milk during processing of yogurt with commercial directed vat set starters	Degradation of pesticides was upgraded via one or both of the culture starters, apart from malathion	(Bo <i>et al.</i> 2011)
Endosulfan intoxication on liver and kidneys of pregnant rats	<i>L. plantarum</i> BJ0021	Significantly lower cholesterol levels and considerably depletes hepatic enzymes, reduces apoptosis.	(Bouhafs <i>et al.</i> 2015)
Hlorpyrifos, phorate, trichlorphos and dichlorvos in cured Chinese cabbage	<i>L. plantarum</i>	Disintegrate 96.2–99.7% of four OP pesticides	(Zhou and Zhao 2015)
Whole corn contaminated with chlorpyrifos and phorate	<i>L. plantarum</i> strains	25–33% reduction in pesticide levels for 10 weeks	(Zhang <i>et al.</i> 2016)
Rice straw contaminated with chlorpyrifos	<i>L. casei</i> WYS3	Reduction in pesticide level	(Wang <i>et al.</i> 2016)
Skimmed milk contaminated with methyl, malathion, diazinon, fenitrothion, parathion and chlorpyrifos	<i>L. plantarum</i> 1.0624, <i>L. plantarum</i> 1.066, <i>L. plantarum</i> 1.0317, <i>L. helveticus</i> 1.0203, <i>L. lactis</i> 4.0611, <i>L. plantarum</i> 1.0315, <i>L. bulgaricus</i> L6, <i>L. brevis</i> 1.0209, <i>L. helveticus</i> 1.9204, <i>S. thermophilus</i> 3.0503	Various capacities in pesticide degradation, <i>L. brevis</i> 1.0209 possesses the highest activity of pesticide degradation	(Zhang <i>et al.</i> 2014b)
Chlorpyrifos deltamethrin	<i>L. plantarum</i> strains LB-1 and LB-2 the isolated from brines of naturally fermented black olives	After three days, 96% and 90% of chlorpyrifos and 24% and 53% of deltamethrin were destroyed by strains LB-1 and LB-2, respectively.	(Kumral <i>et al.</i> 2020a)
OC (HCB, α -HCH, γ -HCH, α -chlordane and γ -chlordane) throughout manufacture of cheese and yogurt	<i>L. delbrueckii</i> subsp. <i>bulgaricus</i> , <i>L. rhamnosus</i> , <i>L. acidophilus</i> , <i>L. plantarum</i> , <i>L. casei</i> , <i>B. bifidum</i> and <i>S. thermophilus</i>	Significant impact on reducing these OC pesticides	(Duan <i>et al.</i> 2018)
Cow and goat milk contaminated OC pesticides (α -hexachlorocyclohexane, α HCH, β HCH, heptachlor, β -hexachloro cyclohexane, γ HCH - γ -hexachloro cyclohexane, dieldrin, heptachlor epoxide isomer B, endrin, op'DDD/DDT, op'DDE, pp'DDT, pp'DDE, pp'DDD,) during fermentation	<i>B. animalis</i> subsp. <i>lactis</i> BB-12 and <i>L. acidophilus</i> LA5 alongside a commercial yogurt culture (<i>L. delbrueckii</i> subsp. <i>bulgaricus</i> and <i>S. thermophilus</i>)	Levels of OC pesticides (5.39–20.7%) in yogurt samples decreased significantly after 14 days.	(Witczak and Mituniewicz-Małek 2019)
Diazinon cytotoxicity in human umbilical vein endothelial cells (HUVEC) <i>in vitro</i>	<i>L. casei</i>	Decreased cytotoxicity of diazinon in HUVEC cells	(Shamloo <i>et al.</i> 2016)
Endosulfan in liver and kidneys of pregnant rats	<i>L. plantarum</i> BJ0021	Reduced apoptosis, improved biochemical parameters, and a protective role in reducing endosulfan toxicity.	(Bouhafs <i>et al.</i> 2015)
Glyphosate during the breadmaking process	<i>S. cerevisiae</i>	21% average reduce after 1 h	(Low <i>et al.</i> 2005)
Wheat grains with various concentrations of chlorpyrifos-methyl	<i>S. cerevisiae</i>	Major pesticide losses occurred during autoclaving (up to 80%), while fermentation independently reduced the concentration of CP-methyl by 14 to 19%.	(Dordević and Đurović-Pejčev 2015)

(continued)

Table 2. Continued.

Pesticides	Name of probiotics	Health benefits	Reference
Dimethoate	Milk containing <i>L. plantarum</i> CICC20261	Degradation of more than 81% dimethoate by probiotic strain	(Yuan <i>et al.</i> 2021)
Beta-cypermethrin	<i>L. pentosus</i> 3–27	Degrade 96% of beta- cypermethrin (50 mg/L) after 4 days of culture in medium	(Liu <i>et al.</i> 2022)
deltamethrin, dimethoate, and imidacloprid	<i>Lactobacillus plantarum</i> strains 112 and 123	After the end of the 60-day fermentation, 66–68% of dimethoate, 53–61% of deltamethrin, and 42–50% of imidacloprid were reduced in the fermented black olive naturally and the fermented black olives with both starter.	(Kumral <i>et al.</i> 2020b)
Diazinon	<i>L. acidophilus</i>	<i>L. acidophilus</i> (at 9 log CFU/mL) caused a significant decrease in diazinon concentration in apple juice after fermentation.	(Rezaei <i>et al.</i> 2021)
Beta-cypermethrin	<i>Bacillus cereus</i> GW-01	The administration of this probiotic strain decreased β -cypermethrin levels by 18–53% in different parts of the mice's body.	(Jiang <i>et al.</i> 2023)

2009). In a similar study, a decrease in residual OP levels during yogurt production was reported after adding 7 to 65% LAB or 7–19% yogurt starter culture to skim milk samples (Zhou and Zhao 2015). Higher phosphatase creation of the strains caused more corruption of pesticides in milk. Degradation of OP pesticides is associated with phosphatase activity (an enzyme formed via LAB). OP pesticides are destroyed over the phosphatase created via LAB, which alters OP pesticides to di-alkyl phosphate and aryl alcohol within sight of water (Mohammadi *et al.* 2021). Another study stated the ability of *L. plantarum* to disseminate 96.2–99.7% of OP pesticides (chlorpyrifos, dichloros, folate, and trichlorophone) in pickled Chinese cabbage (Zhou and Zhao 2015).

According to Zhang *et al.* (2014b), the more phosphatase is produced, the more prominent the breakdown of pesticides in milk. The use of LAB during cereal silage has been confirmed to be an operative method to eliminate pesticides. Adding a blend of *L. plantarum* strains to CP- contaminated whole corn reduces the level of pesticides by 25 to 33% within the silo at room temperature for 10 weeks (Zhang *et al.* 2016). In the study of Wang *et al.* (2016), rice straw inoculated with *L. casei* expanded evacuation of CP in the wake of ensiling. The researchers found the expression of the OP hydrolase gene in LAB was three times higher in the groups grown in the sight of CP than in the control group. The use of *S. cerevisiae* during food fermentation gets likewise a training that decreases the levels of certain pesticides. Low *et al.* (2005) researched the capacity of *S. cerevisiae* to

corrupt herbicide glyphosate throughout the fermentation cycle of bread production, indicating an average reduction of 21% after 1 h of incubation. The investigators stated the decrease was because of herbicide destruction, but they did not adopt any measures to confirm it (Low *et al.* 2005, Dorđević and Đurović-Pejčev 2015).

Probiotic species that possess degrading genes can be disengaged from traditional fermented food varieties and added to food products. Likewise, they can be utilized as a supplement to adjust the intestinal microflora and support the GI lumen to reduce the pesticides after absorption. In the field of environmental science, biodegradation of heavy metals and substance pesticides via LAB is, as of now, viewed as one of the least expensive and most secure methods of decontamination without toxic residues. Albeit there are few studies evaluating the capacity of probiotics to degrade counter to pesticides, most of these studies are associated with OP pesticides, and most *in vitro* and *in vivo* explores are expected to put light on basic mechanisms and to distinguish more proficient species on various pesticides. In any case, further examination is as yet expected to comprehend the mechanisms associated with the decontamination cycle and the component to potentiate the inherent decontaminate impact of the probiotic, with the aim of assessing recent creative innovations that are monetarily fit for utilizing LAB in food sources planned for people and animals, pointing most extreme viability of the microorganism. In addition, it can be appropriate to control the expression of pesticide-degrading genes in

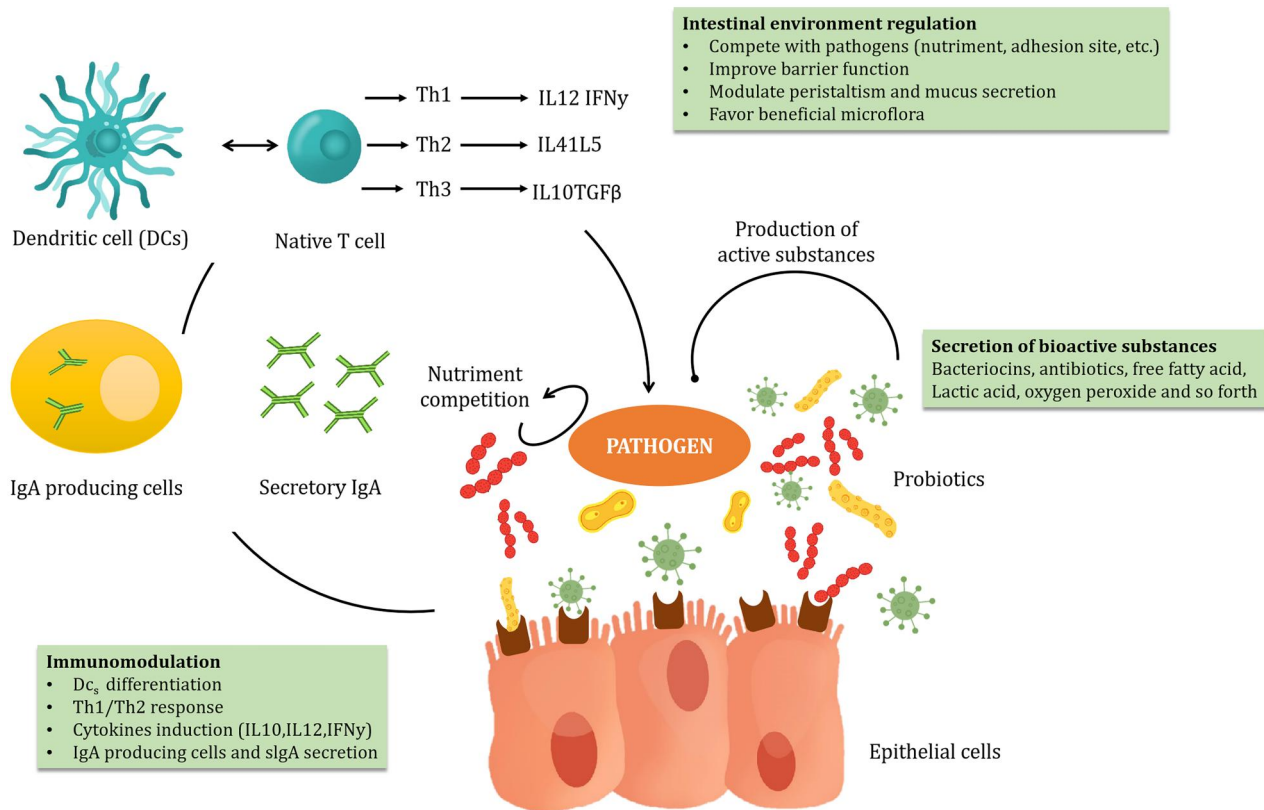


Figure 1. Some mechanistic ways of modulation/control of parasites by probiotics. IgA, immunoglobulin A; sIgA, secretory immunoglobulin A; Th, T helper cells; IL, interleukin; IFN γ , interferon gamma; TGF β , transforming growth factor beta.

probiotic microorganisms or to make genetically engineered bacteria with pesticide-removing activity as a salient option for reducing pesticides.

4. Role of probiotics in the elimination of antiparasitic/antibiotic drug residues and oxidants

Among residues found in food products, especially meats, the biogenic amines (BA) are known for their food poisoning, or “scombroid poisoning”, and influence the freshness and other organoleptic characteristics of meats and their products due to the production of amino acids (Ashaolu and Fernández-Tomé 2021). For instance, in a study involving the probiotic action of *Lactococcus lactis* subsp. *cremoris* CTC 204 and CTC 483, *L. lactis* subsp. *hordinae* CTC 484, and *L. plantarum* CTC 368 and CTC 469, originally obtained from meats, it was found that biogenic amines were produced (Moreno *et al.* 2018). The study showed that the probiotics did secret compounds associated with the safety of the products but did not clarify or justify the production of BA. Probiotics also play crucial roles in the adsorption/detoxification of food contaminants such as oxidants, antibiotics, and antiparasitic drug residues.

4.1. Antiparasitic drug residues

Parasites are a very important nemesis of both plant- and animal-based food products, which inadvertently affect host organisms. Several mechanistic routes of modulation/control of parasites by probiotics are represented in Figure 1.

4.1.1. In humans

The human gut is a complex entertaining interaction of pathogens, intestinal microbiota, and the immune system. This is an ecosystem in which the components exert an essential effect on homeostasis. Maintaining this balance is also critical for the host’s health. However, the human gut is the key target for soil-transmitted helminths (STHs) infections, affecting more than one-fifth of the world’s population (Rosa *et al.* 2018). Protozoans and helminths are popular parasites of the intestines that participate in a microbial relationship in order to modify host-commensal microbiota balance. It was thus speculated that probiotics could contribute a paramount role to the reduction of parasitic pathogenicity, a premise justifying the ever-growing discussions on the links of the microbiota-immunity-inflammation-intestinal parasites complex (Berrilli *et al.* 2012). Efforts to comprehend the

complex cross-kingdom interactions have not yielded many expected results. Nonetheless, Rosa *et al.* (2018) recently found out that probiotics and other fermented foods may reduce gut parasitic worm infections and re-infections usually transmitted from soil and foods. The study was a cross-sectional geographical analysis where the findings provided an interesting perspective on the interactions between kingdoms in the gut ecosystem while associating the taxon, genetics, and functions of the microbiome with their crucial involved mechanisms.

Some probiotics are known for their inhibitory effects on pathogens development and parasites, including protozoans (*Cryptosporidium*, *Eimeria*, etc.) and helminths (*Ascaris*, *Trichuris*, etc.). They are used to efficiently treat GI disorders, respiratory infections, and allergic symptoms while utilizing strain-specific mechanisms of competitive exclusion, molecular secretions, and immune induction, among others (Travers *et al.* 2011).

4.1.2. In animals

Different strain types of probiotics have been reportedly effective against *Giardia duodenalis*, including *L. acidophilus* strains, *L. johnsonii* La1, and *L. casei* in *in vitro* and *in vivo* systems (Humen *et al.* 2005, Shukla *et al.* 2010a, Shukla *et al.* 2010b, Shukla and Sidhu 2011, Shukla *et al.* 2012). Oral treatment of mice with *L. casei* led to a reduction in the parasite *Trichinella spiralis* burden (Bautista-Garfias *et al.* 2001). *Enterococcus faecalis* CECT7121 is a probiotic that possesses antibiotic properties and was later demonstrated to show larvicidal effects on *Toxocara canis* in the murine liver and lungs (Basualdo *et al.* 2007, Chiodo *et al.* 2010). All these investigations need more clarity, such as existing interactions between the microbiome, processes of inflammation, and intestinal parasites-probiotics mechanisms and therapeutic prospects. In addition, exciting novel areas such as parasitome and gut metabolome in persistent parasitic infections and their association with the immunomodulatory processes of the host should involve an integrated approach framework (Berrilli *et al.* 2012).

Probiotic effective microorganisms demonstrated antiparasitic activity in Nile tilapia fish (*Oreochromis niloticus*) that was experimentally challenged with *Trichodina* species (Abdel-Aziz *et al.* 2020). This dietary supplementation has the propensity to prevent infection of *Trichodina* protozoan parasites in Nile tilapia. Distinctive and comprehensive studies in other biological and ecological settings have not been reported yet regarding antiparasitic activities. In piglets, a

probiotic bacterium was modified for the expression of cystatin (AvCys), which is an immunomodulator found in *Acanthocheilonema viteae* (Whelan *et al.* 2014). Upon its administration to the piglets, the post-weaning gut inflammatory response was suppressed, indicative of a potent therapeutic intervention for inflammatory bowel disease (IBD) management in humans (Devaney 2014, Whelan *et al.* 2014).

The poultry's GI tract serves a paramount digestive role and protection, of which a disruption by *Eimeria* spp. parasite could cause a disbalance in the health status of the intestines and lead to an increased number of pathogens like *Clostridium* species whilst creating *Coccidiosis* infection (Madlala *et al.* 2021). This infection disrupts the makeup and activity of the microbiome, well-being, and productivity of poultry. To curb coccidiosis, anticoccidial drugs were developed. These drugs proved to be efficacious, except that resistance and residues in meat lingered. A major alternative strategy is the use of probiotics meant to modify and restore poultry gut microbiota whilst inhibiting drug resistance. Probiotics are included in broilers' feeds in order to improve weight and health, resulting from an improved balance of the intestinal microbes (Awais *et al.* 2019). Probiotics such as *Lactobacillus*, *Bacillus*, *Pediococcus*, *Saccharomyces cerevisiae*, and *Enterococcus faecium* could challenge parasites by adhesion to the gut mucosa while absorbing the receptors of epithelial cells, thus preventing invasion, perforation, and secretion of sporozoites (Jarujareet *et al.* 2018, Erdoğan *et al.* 2019).

Probiotics also reduce parasite colonization, compete for attachment sites, co-aggregate with parasites, and secrete antimicrobial chemical substances or cytokines that stimulate the immune system or inhibit siderophores production, thereby making iron unavailable for invading parasites (Madlala *et al.* 2021). This property protects probiotics against the prevalence of parasitic infections like coccidiosis, which then confer several health benefits on the human consumer. Still, other residues found in poultry meat after consumption require further exploration. In mice, the antiparasitic activity of probiotic strains against zoonotic *Trichinella spiralis* infection using six bacteriocinogenic strains, including *Enterococcus faecium* EF55, *E. faecium* 2019 = CCM7420, *E. faecium* AL41 = CCM8558, *E. durans* ED26E/7, *L. fermentum* AD1 = CCM7421, and *L. plantarum* 17L/1 was studied ((Bucková *et al.* 2018). The probiotics were administered daily at a dose of 10^9 CFU/mL against 400 *T. spiralis* larvae introduced into the mice. All strains reduced the fecundity of the parasites at the end of the study (Bucková *et al.* 2018).

Table 3. Most used probiotics in animal feeding as an alternative to antibiotics.

Genus	Species	Type of breeding	Effects	Reference	
<i>Lactobacillus</i>	<i>L. fermentum</i>	Piglets	<ul style="list-style-type: none"> Increased growth Lowered levels of <i>E. coli</i> and reduced rate of diarrhea in infants 	(Huang <i>et al.</i> 2004)	
		Mature pigs Poultry	<ul style="list-style-type: none"> Enhanced SOD, GPx, and CAT Regulation of gut mucosal immunity and reduction of <i>Clostridium perfringens</i>-induced inflammation 	(Wang <i>et al.</i> 2009) (Cao <i>et al.</i> 2012)	
	<i>L. sobrius</i> <i>L. salivarius</i>	Piglets Swine and poultry	<ul style="list-style-type: none"> limited <i>E. coli</i> invasion of the intestine Improved immunity and reduced pathogenic bacteria influence in swine and poultry 	(Konstantinov <i>et al.</i> 2008) (Chaves <i>et al.</i> 2017)	
	<i>L. rhamnosus</i>	Fish	<ul style="list-style-type: none"> Reduced death in RTF and Tilapia based on <i>A. salmonocida</i> and <i>E. tarda</i> colonization 	(Nikoskelainen <i>et al.</i> 2003; Pirarat <i>et al.</i> 2006)	
	<i>L. reuteri</i> <i>L. plantarum</i>	Piglets Fish	<ul style="list-style-type: none"> Benefits TJs expression in piglets Reduced occurrence of <i>Lc. garvieae</i>-induced deaths in RTF 	(Yang <i>et al.</i> 2015) (Vendrell <i>et al.</i> 2008)	
	<i>L. acidophilus</i>	Mature pigs Chickens	<ul style="list-style-type: none"> Enhanced SOD, GPx, and CAT Increased production and quality of eggs Reduced contamination with <i>Salmonella</i> 	(Wang <i>et al.</i> 2012) (Haddadin <i>et al.</i> 1996; Kurtoglu <i>et al.</i> 2004; Van Immerseel <i>et al.</i> 2006)	
		Piglets	<ul style="list-style-type: none"> Increased growth Decreased levels of <i>E. coli</i> and diarrhea in infants 	(Huang <i>et al.</i> 2004)	
	<i>L. amylovorus</i>	Pigs	<ul style="list-style-type: none"> Inhibited pathogen-associated diarrhea Regulated cytokines in piglets against ETEC 	(Finamore <i>et al.</i> 2014; Bajagai <i>et al.</i> 2016)	
	<i>L. paracasei</i>	Piglets	<ul style="list-style-type: none"> limited <i>E. coli</i> colonization of the intestines 	(Bomba <i>et al.</i> 2002)	
	<i>L. pentosus</i>	Fish	<ul style="list-style-type: none"> Improved immunity and Japanese eel survivability against <i>E. tarda</i> 	(Lee <i>et al.</i> 2013)	
	<i>L. brevis</i>	Fish	<ul style="list-style-type: none"> Reduced Tilapia death associated with <i>A. hydrophila</i> 	(Liu <i>et al.</i> 2013)	
	<i>L. casei</i>	Piglets	<ul style="list-style-type: none"> Increased growth Decreased levels of <i>E. coli</i> and diarrhea in infants 	(Huang <i>et al.</i> 2004)	
			<ul style="list-style-type: none"> Activate innate immunity in OFF Reduced coccidiosis in <i>E. tenella</i> infected broiler chickens 	(Kim <i>et al.</i> 2013) (Giannenas <i>et al.</i> 2012; Jungersen <i>et al.</i> 2014)	
	<i>Bifidobacterium</i>	<i>B. thermophilum</i>	Poultry	<ul style="list-style-type: none"> Protection against <i>Salmonella</i> and <i>Listeria in vitro</i> and against chicken <i>E. coli</i> 	(Tanner <i>et al.</i> 2016)
		<i>B. longum</i> <i>B. pseudolongum</i> <i>B. licheniformis</i>	Poultry Piglets Pig	<ul style="list-style-type: none"> Anti-<i>Campylobacter</i> effect in poultry Increased FCR Reduced ETEC-induced diarrhea in piglets 	(Santini <i>et al.</i> 2010) (Afonso <i>et al.</i> 2013) (Kyriakis <i>et al.</i> 1999)
<i>Bacillus</i>	<i>B. subtilis</i>	Fish	<ul style="list-style-type: none"> Reduced infection rate in IMC Increased RTF survivability Reduced channel/striped catfish deaths 	(Newaj-Fyzul <i>et al.</i> 2007; Liu <i>et al.</i> 2012; Ran <i>et al.</i> 2012)	
		Broilers	<ul style="list-style-type: none"> Enhanced grouper fish survivability Improved production of broilers and eradication of <i>Salmonella</i> Reduced pathogens (<i>Salmonella gallinarum</i>) 	(Park <i>et al.</i> 2014; Upadhaya <i>et al.</i> 2016)	
	<i>B. pumilus</i> <i>B. circulans</i>	Fish Fish	<ul style="list-style-type: none"> Enhanced Tilapia immunity Enhanced CCF immunity and survivability 	(Aly <i>et al.</i> 2008) (Bandyopadhyay <i>et al.</i> 2009)	
	<i>Enterococcus</i>	<i>E. faecalis</i> <i>E. faecium</i>	Fish Tuckey	<ul style="list-style-type: none"> protection against <i>Lc. Garvieae</i> Stimulation of lactobacilli and other LAB members in the small intestine 	(Baños <i>et al.</i> 2019) (Vahjen <i>et al.</i> 2002)
Chicken Broilers			<ul style="list-style-type: none"> Significant FCR and weight gain Efficient control and reduction of <i>S. Minnesota</i> levels Enhanced growth Benefits intestinal morphology and cecal microbiota 	(Samli <i>et al.</i> 2007; Kuritza <i>et al.</i> 2011) (Cao <i>et al.</i> 2013)	
		Fish	<ul style="list-style-type: none"> Reduced European eel's Edwardsiellosis 	(Chang <i>et al.</i> 2002)	

(continued)

Table 3. Continued.

Genus	Species	Type of breeding	Effects	Reference
		Piglets	<ul style="list-style-type: none"> • Modulated fecal microbiome of piglets • Increased diversity of beneficial bacteria 	(Pajarillo <i>et al.</i> 2015)
	<i>E. gallinarum</i>	Fish	<ul style="list-style-type: none"> • Increased daily gain 	(Sorroza <i>et al.</i> 2013)
	<i>E. casseliflavus</i>	Fish	<ul style="list-style-type: none"> • Protection of Sea bass • Enhanced growth of RTF and resistance to <i>S. iniae</i>-induced disease 	(Safari <i>et al.</i> 2016)
<i>Lactococcus</i>	<i>Lc. lactis</i>	Fish	<ul style="list-style-type: none"> • When BT is infected with <i>A. salmonicida</i>, • Improved survivability • Activation of phagocytes • Reduced proliferation of intestinal pathogenic organisms 	(Balcázar <i>et al.</i> 2009)
		Swine	<ul style="list-style-type: none"> • Efficacious vaccine component against swine erysipelas 	(Cheun <i>et al.</i> 2004)
<i>Leuconostoc</i>	<i>L. mesenteroides</i>	Fish	<ul style="list-style-type: none"> • BT improved survivability, phagocytes activation, and intestinal pathogens reduction 	(Balcázar <i>et al.</i> 2009)
		Poultry	<ul style="list-style-type: none"> • IMO of the probiotic enhances <i>Bifidobacterium</i> and <i>Lactobacillus</i> growth without serving as substrate for <i>Salmonella</i> or <i>E. coli</i> 	(Chung <i>et al.</i> 2004)
<i>Pediococcus</i>	<i>P. acidilactici</i>	Chickens	<ul style="list-style-type: none"> • FCR of broiler chickens is improved 	(Harimurti <i>et al.</i> 2015)
<i>Streptococcus</i>	<i>S. thermophilus</i>			
	<i>S. phocae</i>	Fish	<ul style="list-style-type: none"> • Enhanced growth and anti-<i>V. harveyi</i> 	(Swain <i>et al.</i> 2009)
<i>Aspergillus</i>	<i>A. oryzae</i>	Chickens	<ul style="list-style-type: none"> • Enhanced feeding and weight gain 	(Kim <i>et al.</i> 2003)
	<i>A. niger</i>	Broilers	<ul style="list-style-type: none"> • Enhanced growth • Decreased muscle protein catabolism, and plasma fat/cholesterol contents 	(Saleh <i>et al.</i> 2010; 2011)
<i>Saccharomyces</i>	<i>S. cerevisiae</i>	Sows and piglets	<ul style="list-style-type: none"> • Improvement of sows' reproduction cycles • Elevated IgGs in piglets' colostrum and plasma • Improved growth and intestine health • Restored the mucosa of intestines 	(Heugten <i>et al.</i> 2003; LeMieux <i>et al.</i> 2010; Jang <i>et al.</i> 2013)
		Fish	<ul style="list-style-type: none"> • Improved growth, hematology, antioxidation, and immunity of Nile tilapia • Improved fungal resistance in Nile tilapia • Enhanced innate immunity of gilthead seabream 	(Ortuño <i>et al.</i> 2002; Hoseinifar <i>et al.</i> 2018; Abdel-Tawwab <i>et al.</i> 2020)
<i>Kluyveromyces</i>	<i>K. fragilis</i>	Piglets	<ul style="list-style-type: none"> • Improved innate immunity and fecal scores 	(Keimer <i>et al.</i> 2018)
	<i>K. marxianus</i>	Fish	<ul style="list-style-type: none"> • Source of protein for Atlantic Salmon 	(Øverland <i>et al.</i> 2013)
		Broilers	<ul style="list-style-type: none"> • Improved feed intake • Improved immunity and structural make up of broilers' intestines • Feed efficiency and immunity 	(Wang <i>et al.</i> 2017)
Combinations	BioPlus 2B: <i>B. licheniformis</i> and <i>B. subtilis</i> spore	Sow and piglets	<ul style="list-style-type: none"> • Improved health status and sows fertility • Increased sow feeding • Decreased diarrhea scores in piglets • Increased piglets number • Increased body weight of piglets • Decreased sow weight loss in the period of suckling • Decreased mortality in the pre-weaning period 	(Alexopoulos <i>et al.</i> 2004)
	Dietary probiotics <i>Lc. lactis</i> BFE920 and <i>Lactobacillus plantarum</i> FGL0001	Fish	<ul style="list-style-type: none"> • Improved OFF innate immunity and weight gain • Increased survivability against <i>S. iniae</i>-induced disease in OFF 	(Beck <i>et al.</i> 2015)
	Dietary <i>Lactobacillus reuteri</i> , <i>L. salivarius</i> and <i>Streptococcus salivarius</i> ab	Piglets	<ul style="list-style-type: none"> • Enhanced growth performance, blood parameters, and IgGs 	(Dlamini <i>et al.</i> 2017)
	LACTINA®: <i>L. acidophilus</i> , <i>L. helveticus</i> , <i>L. bulgaricus</i> , <i>Lc. lactis</i> , <i>S. thermophiles</i> and <i>E. faecium</i>	Piglets	<ul style="list-style-type: none"> • Increased suckling piglets' body weight 	(EFSA, 2013)
	Dietary supply of <i>Lactobacillus pentosus</i> ITA23	Chickens	<ul style="list-style-type: none"> • Enhanced weight gain • Improved daily gain 	(Jahromi <i>et al.</i> 2016)

(continued)

Table 3. Continued.

Genus	Species	Type of breeding	Effects	Reference
	and <i>Lactobacillus acidophilus</i> ITA44		<ul style="list-style-type: none"> • Increased sugar transporter genes (GLUT2, GLUT5, SGLT1, and SGLT4) expression • Improved beneficial cecal microbiota population 	

SOD: superoxide dismutase; GPx: glutathione peroxidase; CAT: catalase; RTF: rainbow trout fish; TJPs: tight junction proteins; ETEC: enterotoxigenic *E. coli*; *E. tarda*: *Edwardsiella tarda*; OFF: olive flounder fish; *E. tenella*: *Eimeria tenella*; FCR: feed conversion ratio; IMC: Indian major carp; CCF: Catla catla fish; *S. Minnesota*: *Salmonella minnesota*; BT: Brown Trout (*Salmo trutta*); *A. salmonicida*: *aeromonas salmonicida*; IMO: Isomaltooligosaccharides; *V. harveyi*: *Vibrio harveyi*.

This is applicable to humans, except that similar research in a clinical setting is lacking.

4.2. Antibiotic residues

Antibiotics are used during animal/poultry farming and other cropping systems for food products meant for human consumption. Despite the need for safe food production during animal rearing, the well-being and environment of the animals must also be taken into consideration. Derivation of healthy foods from animals entails controlling or preventing bacterial infections, usually with the help of antibiotics. The bans imposed on the antibiotic compounds used as growth promoters have created some issues in animal breeding, rendering their usage limited in application, often to only treat and prevent infections from bacteria. Unfortunately, they are excessively and abusively used, leading to more problems with precarious consequences on the health of consumers, including antibiotic resistance and lingering residues in foods (Arsène *et al.* 2021). Therefore, probiotics proffer a mild or suitable alternative in this regard based on their antipathogenic and immunomodulatory functions. In feeds, they also have the ability to promote growth factors with or without prebiotics.

During animal farming, antibiotic residues evolve. These residues are pharmacologically active substances such as active ingredients, auxiliary substances, degradation products, and metabolites that occur in the environment or remain in feed for animals being administered the drug (Arsène *et al.* 2021). Resistance, allergy, disruption of normal gut flora, carcinogenicity, mutagenicity, and teratogenicity are among the environmental and published health risks associated with antibiotic residues (Beyene 2016). Expected antibiotic doses excretable from animals into the ecosystem of soil, water, and atmosphere can cause chemical pollution of the environment, and microbial or commensal flora, just as dairy products from the animals and other fermented foods could be interfered with (Pawar *et al.* 2012). Numerous reports indicate that probiotics such as *S. cerevisiae* and *Aspergillus oryzae*

classified as yeasts/fungi are more effective in adult ruminants than bacterial probiotics, as the latter show better effects in chickens, pigs, and young calves (Markowiak and Śliżewska 2018). Table 3 shows a list of the most used probiotics in animal feeding, which exert impacts on antibiotic residues.

Lactobacilli are usually included in dairy and non-dairy foods as main probiotics and are now recently used as feed additives based on their mortality reduction and immunity enhancement in fish (Nikoskelainen *et al.* 2003, Pirarat *et al.* 2006, Kim *et al.* 2013), growth performance enhancement in piglets (Huang *et al.* 2004), poultry eggs production and quality (Haddadin *et al.* 1996, Kurtoglu* *et al.*, 2004, Van Immerseel *et al.* 2006). In spite of all these benefits, some *Lactobacilli* such as *L. casei* and *L. rhamnosus*, may contribute to pathogenic attacks, though *Lactobacilli* are generally regarded as safe (GRAS), along with some other groups like *Bifidobacteria* (Vesterlund *et al.* 2007).

Strains of *Bifidobacteria* are mostly host-specific (Mattarelli *et al.* 2017). *B. pseudolongum* showed remarkable impacts on food conversion ratio (FCR) without changes in the final weight, weight gain, and feed intake when used as a feed additive in piglets (Afonso *et al.* 2013). *B. animalis*, *B. thermophilum*, and *B. longum*, when used as an additive in poultry, could mitigate coccidiosis caused by *Eimeria tenella* in broiler chickens (Giannenas *et al.* 2012, Jungersen *et al.* 2014) to protect against *Salmonella* and *Listeria* species *in vitro* and against *E. coli* in chicken, and an anti-*Campylobacter* activity, respectively (Santini *et al.* 2010, Tanner *et al.* 2016). Although *Bifidobacteria* have been widely researched for their potential use in feed additive studies and as an alternative to conventional antibiotics in breeding, the findings should not be mistaken as authoritatively describing the probiotic group as completely safe against all pathogens and antibiotic residues.

Lactococcal and *Enterococcal* strains are also important in the exertion of probiotic benefits to reduce the excessive use of antibiotics. *Lactococcus lactis* could exert antibacterial activities while improving immunity and furunculosis in various fish types (Balcázar *et al.* 2009,

Heo *et al.* 2013, Hoseinifar *et al.* 2018). *Enterococcus* species were reported alternatives to sub-lethal antibiotics in poultry and swine feed additives, especially *E. faecium*. For instance, when a microencapsulated *E. faecium* SF68 (NCIMB 10415) strain was investigated for anti-*Chlamydia* infection in pigs at 9×10^9 CFU, infection severity and rate were reduced (Pollmann *et al.* 2005). A similar observation was reported in the small intestine of turkey and chicken (Vahjen *et al.* 2002, Samli *et al.* 2007). Regarding the safety of both groups, both *Lactobacilli* and *Enterococci* have been linked to resistance to antibiotics and infections, including urogenital tract and endocarditis (Anadón *et al.* 2006, Heikens *et al.* 2007, Protonotariou *et al.* 2010, Rodrigues *et al.* 2016). Therefore, irrespective of their benefits, regular trial studies must be conducted prior to use in animal feeds and additives in order to block the possibility of residue transfer or any other danger to both animal and human consumer health.

Bacilli like *B. subtilis* remain popular in food supplementation for poultry and fish farming with demonstrated health benefits and high prospects for immunomodulation in animal rearing and disease bio-control (Kumar *et al.* 2006, Newaj-Fyzul *et al.* 2007, Liu *et al.* 2012, Park and Kim 2014, Upadhaya *et al.* 2016). *B. licheniformis* also showed antibacterial potential by blocking diarrhea caused by enterotoxigenic strains of *E. coli* in piglets within the period of 3–10 days after weaning (Kyriakis *et al.* 1999). Again, the safe production of these probiotics is essential.

4.3. Oxidants

Oxidants are free radicals, for example, reactive nitrogen species (RNS), reactive oxygen species (ROS), and reactive sulfur species (RSS), which are produced inside cells over various metabolic processes or outside living systems through food production processes like heat treatment or storage (Ashaolu 2020a). Antioxidants such as tocopherols, carotenoids, flavonoids, amino acids, glutathione (GSH), thioredoxin, ascorbic acid, and enzymes such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) aid in reducing oxidative stress and protecting lipids, proteins, and DNA. Moreover, consumers' demand for healthful foods like those fortified with antioxidants and probiotics is ever-increasing (Ali *et al.* 2020).

Probiotics like strains of *Lactobacillus* and *Bifidobacterium*, as well as their isolated ingredients and secreted materials, exert various anti-proliferative, pro-apoptotic, and antioxidant compounds via

expression and secretion of antioxidant enzymes, binding to ROS, releasing small molecular weight antioxidants and chelation of transition metals, and prevention of detrimental actions of many carcinogens (Nowak *et al.* 2019). There are sufficient literature and studies on the use of probiotics to douse oxidants responsible for oxidative stress, among other health issues. For example, *in vitro*, studies involving 2,2-diphenyl-1-picrylhydrazyl (DPPH), ABTS, and β -carotene bleaching assays showed the probiotic strain, *Levilactobacillus brevis* KU15147 isolated from kimchi, possess antioxidant potentials (Kim *et al.* 2021). *In vitro* and *ex vivo* investigations have also confirmed that probiotics can target oxidants/radicals for detoxification. For instance, among 17 selected probiotic strains employed in a recent study, *Bifidobacterium bifidum* MG731 and *B. lactis* MG741 showed the highest DPPH free radical chelating activity (90.6% and 59.6%, respectively), while *B. lactis* MG741, *L. plantarum* MG989 (98.9%), *L. salivarius* MG242, and *B. bifidum* MG731 showed the highest ABTS free radical scavenging activity (99.5%, 97.1%, and 96.1%, respectively) (Kang *et al.* 2021). The study also showed that nitric oxide was produced in low amounts by *B. bifidum* MG731, *B. lactis* MG741, *L. salivarius* MG242, and *L. plantarum* MG989, among others through, suppression of inducible nitric oxide synthase and cyclooxygenase 2, which were upregulated via LPS-stimulated RAW 264.7 macrophages (Kang *et al.* 2021).

In animals meant for food, the effect of *L. farciminis* supplementation in quail diets on performance, blood antioxidant capacity, and intestinal health showed a positive response (Aydin *et al.* 2021), similar to *Paenibacillus polymyxa* LM31 supplemented diet (Alagawany *et al.* 2021). A similar feat was attained in weaned piglets when *Saccharomyces boulardii* mafi-1701 was used, and the researchers concluded that the supplemented diets associated with enhanced antioxidant activity, anti-inflammatory responses, and improved intestinal microbial ecology could be linked to improvement in feed conversion ratio and reduction in diarrhea rate (Zhang *et al.* 2020). In a recent mice study, *L. fermentum* CQPC07 modulated antioxidant capacity and lipid metabolism in high-fat diet-induced obese mice, leading to attenuated obesity, inflammation, and dyslipidemia (Wu *et al.* 2021). In this case, probiotics do not only target oxidants for overall health status improvement; they specifically reduce the risks of obesity.

In humans, oxidative stress biomarkers are usually the focal point. Most studies on probiotic supplementation led to a positive effect on different health

outcomes; as several of them indicated that probiotics supplementation improved antioxidant status, some did show conflicting findings (Zamani *et al.* 2020).

5. Role of probiotics in adsorption/detoxification of synthetic/unauthorized food additives

5.1. Nitrite and nitrate

The inorganic anions nitrate (NO_3^-) and nitrite (NO_2^-) are normally found in the human body and some nutrients, such as vegetables and fruits. Nitrates and nitrites are usually added to processed meats, such as sausages, bacon, hot dogs, and ham, because this food additive can provide antimicrobial activity and improve red or pink color and salty flavor in meat products. Processed meats do not turn brown and spoil quickly because the addition of nitrites is converted into nitric oxide (NO) to interact with protein and nitric oxide synthases in meats bringing about color changing and preservation of meat products (Macdougall *et al.* 1975). Both nitrate and nitrite have been regarded as hazardous chemical compounds to human healthiness with adverse influence on daily drinking water and food products because carcinogenic N-nitrosamines can be produced by nitrite-mediated nitrosation with low molecular weight amines. Nitrates are a relatively low health risk, inert, and more stable in comparison with nitrites.

However, many bacteria and enzymes in the human body can easily convert nitrates to nitrites which involve the production of NO and N-nitrosamines, especially under acidic pH in the mouth or stomach. Nitrates and nitrites metabolism produces NO and other bioactive nitrogen oxides in blood and tissues (Kone *et al.* 2003). NO is endogenously synthesized, while L-arginine is converted to L-citrulline and NO with nitric oxide synthases (Tang *et al.* 2011). NO is a colorless gas with free radical properties and also a signaling molecule in many physiological and pathological processes, such as causing vasodilation by the relaxation of the blood vessels in inner muscles to increase blood circulation (Luiking *et al.* 2010, Hord 2011). The decrease in NO production is associated with diabetes, high blood pressure, and cardiovascular disease (Liu and Huang 2008, Monti *et al.* 2012, Hobbs *et al.* 2013, Ashworth *et al.* 2015).

During food preparation and processing, nitrosamines and/or their precursors are produced unintentionally as by-products resulting in commonly being found in a variety of processed foods, including processed meats, cosmetics, alcoholic beverages, and even

cigarette smoke (Cogliano *et al.* 2004). The formation of nitrosamines in low concentration was determined in drinking water with the disinfection of dichloramine (Krasner *et al.* 2013, Kadmi *et al.* 2015, West *et al.* 2016). N-nitrosodimethylamine, as the predominant nitrosamine form, exhibited a potential carcinogen that causes diverse cancers in various organs and tissues such as the liver, nasal sinus, kidney, brain, bladder, esophagus, and stomach (Jakszyn and González 2006, Fishbein *et al.*, 2020, Huang *et al.* 2021).

The ability of probiotics, vitamin C, or vitamin E plus selenium to overcome the influences of nitrate in drinking water was investigated in forty-two New Zealand White male rabbit bucks at 16 to 61 weeks of age. Their kidney and liver functions (nutritious values, digestibility coefficients), feed and water intake, hepatic and renal histology, productive performance, and digestive were evaluated after the combination treatment of 700 ppm nitrate and 1000 ppm probiotic comprising *L. acidophilus*, *S. cerevisiae*, sodium bicarbonate, monobasic potassium phosphate, dextrose, and sodium chloride. The result indicated that 700 ppm nitrate not only increased liver enzymes (alanine aminotransferase and aspartate aminotransaminase) activity and urea concentration but also decreased dry matter intake and nutrient digestibility. However, there is no important impact of nitrate on the body and organ weight of rabbits since animals may already adapt to high nitrate feeds by using some nitrate as a non-protein nitrogen source. The supplementation of probiotics, 200 ppm vitamin C, or 200 ppm vitamin E plus selenium have significant potential to increase testosterone, fertility, the number of offspring, and the total offspring weight of rabbits sired by bucks (Attia *et al.* 2013). In the subsequent research, the results also revealed that these antioxidants or a probiotic supplement with 700 ppm of nitrate treatment significantly improved the negative influence of 700 ppm nitrate on rabbits on the digestive system and the function of the liver and kidney (Attia *et al.* 2018).

The application of *Nitrosomonas* sp. and *Nitrobacter* sp. probiotics are commonly used in the aquaponic system to improve water quality in the aquaculture system. High production of Nile tilapia causes a high accumulation of harmful organic waste, including toxic ammonia and nitrite compounds in feces and leftover feed, because of the high feed amount and mass stock in the intensive culture system. The chemoautotrophic *Nitrosomonas* sp. and *Nitrobacter* sp. can be found in soil and water environment. *Nitrosomonas* sp. is responsible for the oxidation of ammonium to nitrite, and then *Nitrobacter* sp. can potentially oxidize

nitrite into nitrate under the nitrification process to improve water quality. This study included five treatments repeated four times by using the method of Rancangan Acak Lengkap (RAL) when culturing Nile tilapia in the aquaponic system for 29 days. The probiotics containing 10^7 CFU/g of both *Nitrosomonas* and *Nitrobacter* bacteria were added into the aquaponic system every once a week. The result exhibited that the reduction of nitrite level and the rise of nitrate level were detected significantly when adding 1.5 mg/L *Nitrosomonas* and *Nitrobacter* probiotic into the aquaponic system with Nile tilapia culturing (Setiawan and Rahardja, 2021).

Denitrobacterium detoxificans is an anaerobic non-fermentative nitro-respiring bacterium that is initially found in the bovine rumen and can provide protection to cattle from nitro-toxins potentially grazed by livestock (Anderson *et al.* 1996, Anderson *et al.* 2000). The nitro-toxins 3-nitro-1-propionic acid and 3-nitro-1-propanol formed via leguminous plants can be metabolized and detoxified by *Denitrobacterium detoxificans* and possibly other bacteria from other GI habitats. Characterization of the nitro-metabolizing activity is determined in the mixed inhabitants of bovine ruminal and equine cecal bacteria. The results indicated that low nitro-toxin-metabolizing, CO_2 , or formate-requiring microbes in the equine cecum might be like *Denitrobacterium detoxificans* microorganisms to offer potential detoxification of 3-nitro-1-propionic acid and 3-nitro-1-propanol (Zhang *et al.* 2014a).

Rumen methane production and successive eructating emission of this potent greenhouse gas can be reduced by providing nitrate-containing feeds to ruminants. However, this may cause a potential risk to unadapted animals because of the high accumulation of nitrite. Nitrate is a more promising electron acceptor thermodynamically for anaerobic respiration by rumen microbes compared to carbon dioxide. A previous *in vivo* study investigated the nitrate- and nitrite-metabolizing ability of a potential rumen probiotic *Paenibacillus* 79R4 in nitrate supplementation of ruminant diets. The result demonstrated that co-administration of nitrite-selected *Paenibacillus* 79R4 bacterium might prevent nitrite toxicity by lessening methemoglobin accumulation and enhancing nitrite metabolism while diminishing methane emission and reducing the negative impacts of nitrate on rumen fermentation in the nitrate-treated Holstein steers (Latham *et al.* 2019).

The probiotic application of *Lactocaseibacillus paracasei* DTA-83 was examined as a nitrite-reducing agent to evaluate the potential probiotic and postbiotic

ability of pre-converted nitrite from celery. The addition of 2.0% of potentially postbiotic celery powders in pork sausages was used to improve the typical reddish color with approximately 80 mg/kg nitrite concentration. The result demonstrated that *L. paracasei* DTA-83 is a favorable functional and natural alternative to meat curing for the production of probiotic or postbiotic meat ingredients to substitute the traditional addition of sodium nitrite because of the promising ability of pre-convert nitrite from celery. Besides, the inhibitory impact against *Salmonella* spp. in the matrix was also detected when using these probiotic or postbiotic celery juice and powder (Oliveira *et al.* 2021). Optical analysis of nanoencapsulation materials by color measurement has been used in various food products (Lee *et al.* 2020). In addition, the addition of *L. plantarum* can reduce nitrate and nitrite reductase as well as improve the color and gel structure of Chinese fermented sausages. Therefore, the mixture of *L. plantarum* and low levels of sodium nitrite may enhance sausage quality with lower nitrite and biogenic amine levels (Zhu *et al.* 2020).

5.2. Acrylamide

The formation of acrylamide in the food industry is commonly induced by carbohydrates and amino acids naturally in a variety of food products during high-temperature processes such as frying, baking, roasting, smoking, and grilling. Potatoes or other vegetables containing the amino acid asparagine under thermal processing can produce acrylamide in the presence of some specific sugars (Mottram *et al.* 2002, Stadler *et al.* 2002). Acrylamide is also a precursor of polyacrylamide and acrylamide copolymers used in many industrial productions, including plastic, paper, dyes, and adhesive. Besides, these chemicals are also used in drinking water and sewage treatment. Acrylamide, as a process-induced food toxicant, can be formed after high-heating in many processed foods, including meat products, cereals, French fries, potato chips, cookies, cakes, coffee, bread, biscuits, and even tobacco (Capuano and Fogliano 2011, Rivas-Jimenez *et al.* 2016).

According to many previous studies, acrylamide presents a potentially teratogenic neurotoxic mutagenic carcinogenic effect (Matoso *et al.* 2019). Hence, acrylamide has been classified as a possible human carcinogen in the 2A group via International Agency for Research on Cancer. After ingestion of acrylamide, it is easily absorbed and distributed between different organs of humans and animals. Therefore, it is

typically found in the human kidney, heart, thymus, brain, placenta, and liver. There are two major pathways of acrylamide formation in food products: the acrolein pathway and the N-glycoside pathway (or Strecker pathway) (Capuano and Fogliano 2011, Hu *et al.* 2014).

In the acrolein pathway, ammonia is formed through the oxidative degradation of asparagine and other amino acids. Acrolein and acrylic acids are derived from the oxidative degradation of lipids and then the dehydration of glycerol. Afterward, acrylamide is produced (Pedreschi *et al.* 2014). On the other hand, in the Strecker pathway, the Schiff base is formed when foods containing certain sugars and proteins with asparagine are heated at a higher temperature than 120 °C. The formation of Amadori compounds or decarboxylated azomethine ylides from the Schiff base leads to the generation of acrylamide due to the β -elimination of decarboxylated Amadori compounds or the hydrolysis of azomethine ylides (Duda-Chodak *et al.* 2016). The formation of acrylamide is not only present in the high quantity of decreasing sugars and free asparagine in raw materials but also can be increased via several exogenous factors, for instance, increasing pH, water content, heating temperature, and processing time (Xu *et al.* 2014).

The removal ability of *L. casei* Shirota and *L. reuteri* NRRL 14171 to acrylamide in commercial potato chips was investigated with simulated GI conditions under a dynamic system. Toxin removal ability was evaluated in different acrylamide levels and bacteria concentrations. Between 32 to 73% of acrylamide removal under different simulated GI conditions was observed in *L. casei* Shirota. The findings confirmed that both *Lactobacillus* strains significantly decrease the bioavailability of dietary acrylamide even though potato chips contained a high level of acrylamide at 34.162 $\mu\text{g}/\text{kg}$, which is exceeded by 34-fold the values recommended by the European Union (Rivas-Jimenez *et al.* 2016).

The binding capability of different peptidoglycan to acrylamide was evaluated with four LAB strains, including *L. plantarum* 1.0065, *L. acidophilus* KLDS1.0307, *L. casei* ATCC393, and *Streptococcus thermophilus* KLDS1.0316. The binding mechanism and interactions were determined among acrylamide and different peptidoglycan components such as functional groups, amino acids, chemical constituents, and surface structure. The results revealed that the amino acid alanine of peptidoglycan provided significant binding capability on acrylamide. Furthermore, several components of peptidoglycan also evidently interacted with acrylamide, such as C=O in amide groups, N-H in amines groups,

and C-O in carboxyl groups aromatic hydrocarbons and polysaccharides. These binding interactions may offer a promising strategy to detoxify acrylamide in food products (Zhang *et al.* 2017).

The behavior of bacteria can be influenced by the various attachment surfaces under different growth environments (Lee *et al.* 2015). Another study also showed that the acrylamide absorption capacity could be enhanced by increasing the roughness of the cell wall of five LAB containing *L. acidophilus* KLDS 1.030, *L. plantarum* 1.0665, *L. plantarum* 806, *L. plantarum* ATCC 8014, and *L. casei* ATCC 393. Moreover, the acrylamide adsorption capability of these five LAB was related to the hydrophobicity on the cell surface, the nitrogen-to-carbon ratio, and functional groups, including C=O, C-O, and N-H groups on peptidoglycan (Shen *et al.* 2019).

Amidases (acylamidase, amidohydrolase, EC 3.5.1.4) play a crucial role in decomposing acrylamide by catalyzing acrylamide hydrolysis into acrylic acid and ammonia. Amidase can be produced by a variety of fungi and bacteria. According to very few previous studies, amidase-produced fungi include mold *Aspergillus* spp. and yeast *Candida* spp. In contrast to fungi, many bacteria species which naturally occur in the human GI tract or foods present the capability of amidase synthesis, such as *E. coli* (Holt and Stewart 1964, Kobayashi *et al.* 1997), *Enterobacter aerogenes* (Buranasilp and Charoenpanich 2011), *Helicobacter pylori* (Skouloubris *et al.* 1997, Bury-Moné *et al.* 2003, Van Vliet *et al.* 2003), *Pseudomonas putida* (Prabu and Thatheyus 2007, Chacko *et al.* 2012), *Bacillus clausii* (Shukor *et al.* 2009, Lippolis *et al.* 2013), and *Rhodococcus* sp. (Nawaz *et al.* 1998). *E. coli*, the typical representative of intestinal microbiota, can catalyze the hydrolysis of non-protein linear molecules on their C-N bonds with the production of amidases and other enzymes (Kobayashi *et al.* 1997). *Helicobacter pylori* in the human stomach can degrade acrylamide into ammonia to cover the cells directly by amidase production. It may protect *H. pylori* from the unfavorable environment containing high gastric acid in the stomach by the combination of urease and amidase ability (Skouloubris *et al.* 1997, Bury-Moné *et al.* 2003). Overall, these bacteria in the human GI lumen might provide a promising strategy to degrade acrylamide potentially inside the body by synthesizing amidases (Khorshidian *et al.* 2020).

5.3. Heterocyclic amines and polycyclic aromatic hydrocarbons

Heterocyclic amines and polycyclic aromatic hydrocarbons (PAH) are commonly formed in cooked fish and

meats during the high-temperature process, such as frying, boiling, roasting, and barbecuing. The formation of heterocyclic amines is caused by the high content of amino acid, sugars, creatine, or creatinine in muscle meats during thermal processing, especially above 150 °C. Also, PAH are produced during meat smoking and grilling when the muscle tissue and fats are heated directly on a hot surface or open fire (Cross and Sinha 2004). Oleogels are defined as liquid oil captured within a thermos-reversible 3D gel network, and they can replace typical fats during food processing to prevent the formation of heterocyclic amines and PAH (Demirci *et al.* 2020). Many studies have indicated that exposure to both heterocyclic amines and PAH could be potential carcinogens in animal models (Sugimura *et al.* 2004, Lili *et al.* 2018). When heterocyclic amines were fed to rodents, the development of a tumor was observed in several organs, counting the skin, breast, colon, lung, prostate, and liver (Ohgaki *et al.* 1984, Kato *et al.* 1989, Ito *et al.* 1991, Shirai *et al.* 1997). Likewise, PAH are undeniably associated with the occurrence of leukemia and tumors in different human organs, such as the lungs, bladder, and digestive tract (Mastrangelo *et al.* 1997, Abdel-Shafy and Mansour 2016).

The removal of heterocyclic aromatic amines was examined with eight LAB, including *Bifidobacterium longum*, *L. helveticus*, *L. bulgaricus*, *L. acidophilus*, *L. casei*, *L. plantarum*, *L. kefir*, and *S. thermophiles*. Both *L. helveticus* and *S. thermophiles* exhibited the highest binding capability to heterocyclic aromatic amines, with their inactivation range between 72 and 89%. In contrast, only 4 to 13% of heterocyclic aromatic amines were bound by *L. plantarum* and *L. kefir* (Stidl *et al.* 2008). The adsorption ability of *L. casei* DN 114001 (Actimel strain) was estimated to three heterocyclic aromatic amines, including IQ (2-amino-3-methyl-3H-imidazo[4,5-f]quinoline), MeIQx (2-amino-3,8-dimethyl-3H-imidazo[4,5-f] quinoxaline, and PhIP (2-amino-1-methyl-6-phenyl-1H-imidazo[4,5-b]pyridine). The findings revealed that these three heterocyclic aromatic amines could be decomposed and reduced their genotoxicity significantly under the alkaline comet assay by *L. casei* DN 114001 depending on cell growth, the medium, and the incubation time (Nowak and Libudzisz 2009).

Various mutagenic and toxicological effects on humans and animals were observed from the cause of some PAH. Three LAB (*Bifidobacterium bifidum*, *S. thermophilus*, and *L. bulgaricus*) were used to estimate the biodegradation of PAH during a 2 to 72 h incubation period at 37 °C. The significant reduction of PAH from

these three LAB was observed, and the highest reduction percent reached 91.5% with *L. bulgaricus* at the end of 72 h. On the other hand, the biodegradation of PAH by yogurt starter was investigated during the yogurt-making process. The result showed that the reduction percent is only 3.5% in the final product, and the *in vitro* studies cannot precisely correspond to the actual situation in food manufacturing (Abou-Arab *et al.* 2010, Khorshidian *et al.* 2016).

5.4. Acetamide

Acetamide has been identified as a possible carcinogen and mutagen in humans and animals. Liver carcinomas in rats were developed when their diet contained 2.36% acetamide for one year (Humans *et al.* 1999). Acetamides in ruminants can be converted usually by amidase and other enzymes into acetate and ammonium (Belasco 1954, Simon *et al.* 1973, Mahenthiralingam *et al.* 1993). However, some unmetabolized acetamides could release into their milk and meat tissue (Bals *et al.* 2019). However, ammonization of crop residues has been developed rapidly because it can enhance their nutrient bioaccessibility for animal feeds. When crop residues are treated using the technique of ammonia fiber expansion to release cellulosic sugar polymer, it could improve the availability of hydrolytic enzymes and the inorganic nitrogen content resulting in the increase of the digestibility of crops residues *in vitro* (Bals *et al.* 2010, Griffith *et al.* 2016, Blümmel *et al.* 2018) and *in vivo* (Mor *et al.* 2018). Therefore, the milk and meats from the ruminants would be contaminated by acetamide due to the application of ammonization for crop residues as livestock feed. Acetamide is a food contaminant that can be found in many foods, such as milk, beef, roasted coffee (Vismeh *et al.* 2018), and chicory root (Wei *et al.* 2016). For ammonia production, *H. pylori* produced two aliphatic amidases, including AmiE, a classical amidase, and AmiF, a new type of formamidase. Except for urease and arginase, AmiE and AmiF are responsible for a regulatory network of nitrogen metabolism (Bury-Moné *et al.* 2003).

5.5. Oxalate

Oxalate is found widely in humans and in a variety of foods, including vegetables, fruits, grains, nuts, and legumes. Oxalate is used in plants by binding extra calcium to remove it. However, the human body does not require oxalate as a necessary nutrient.

The overconsumption and excessive absorption of oxalate would cause hyperoxaluria to increase the risk of the formation of urinary tract stones, counting ureteral stones, kidney stones, and bladder stones (Smith *et al.* 1972, Chadwick *et al.* 1973, Earnest and DI 1979). The main components of urinary calculi are crystal structures and contain calcium phosphate, calcium oxalate, cysteine, uric acid, and struvite (Lee and Bariol 2013, Li *et al.* 2013, He *et al.* 2017). The endogenous metabolism of ascorbic acid and glyoxylate provides the majority of urinary oxalate in the human body. By contrast, only 10–20% of urinary oxalate is derived from a daily diet. Further, the primary absorption of oxalate takes place in the human colon, where generally only 3–5% of dietary oxalate would be absorbed (Ratkalkar and Kleinman 2011, Whittamore and Hatch 2017). Because of the oxalate abundance in plants, vegetarians and vegans usually consume considerably more oxalate at approximately between 80 to 2,000 mg/day in comparison to the typical daily intake of 70 to 920 mg (Ferraro *et al.* 2020).

The existence of oxalate-degrading microorganisms was first reported in the human intestine in 1940 (Barber and Gallimore 1940). *Oxalobacter formigenes* was isolated and identified as one anaerobic oxalate-degrading bacteria in 1985 from the rumen and human GI habitats (Allison *et al.* 1985, Allison *et al.* 1986). Another oxalate-degrading microorganism was isolated and identified. The oxalate in black tea could be decomposed significantly by *Eubacterium lentum* WYH-1 (Ito *et al.* 1996). Two enzymes, formyl-CoA transferase, and oxalyl-CoA decarboxylase, were associated with the degradation of oxalate (Ito 1997). Besides, *Enterococcus faecalis* with oxalate-degrading ability was isolated under anaerobic conditions from human stools, and it is frequently used as a probiotic in the human GI tract (Hokama *et al.* 2000). Seventy-nine strains of LAB under screening for the capability of oxalate degradation were determined on MRS agar plates. The probiotic *L. rhamnosus* GG showed the highest efficiency in decomposing oxalate compared to other tested strains. Besides, the presence of glucose enhanced the oxalate degradation significantly (Murru *et al.* 2017).

6. Future prospective of probiotics in the food safety

In the previous sections, we focused on the numerous beneficial impacts of probiotics in the detoxification of toxins and chemicals and in improving the quality and

shelf life of food products. It is of great importance to provide appropriate and safe food for the growing population of the world, so it would be an interesting field for researchers and investors to expand the current knowledge and apply the available knowledge to enhance the accessibility of the population to a secure and safe source of food. We suggest the following areas for future research.

- At first, we need to increase the legislative agencies' and consumers' awareness and desire for the application of natural products and processes in food industries. It will attract funds for research in this field and increase the demand for the products. To reach this goal, the application of knowledge transfer systems is necessary.
- To apply probiotics as a protective culture to prolong the shelf life of raw, cooked, and ready-to-eat foods, it is crucial to define the most suitable probiotic strains, understand their mechanisms, and the strength of their inhibiting activity, and their suitability to the host. It needs innovative examination methods and progressive molecular tools.
- Production of probiotics at a large scale and the development of methods to ensure the maintenance of active and viable probiotics during storage and administration is another field that needs research efforts. Each kind of food has a special environment favoring the maintenance of a special strain of microorganisms. We need to improve our knowledge about the interaction between pathogens and probiotics in the specific condition of each food product, and we require to develop techniques to gain the best condition for the proper action of probiotics. The extremely acidic environment of the stomach and the bile salts are other barriers to the release of sufficient probiotics to the action site (intestine). Microencapsulation and spray drying are techniques that have been proposed for improving the survivability of probiotics during storage and in the digestive tract of the host.
- Probiotics can be used as substitutes for antibiotics in animal feeds and can also decrease the pathogen loads (specifically zoonosis) in animal feed products. Assessing the application of probiotics in different production stages and farm settings, as well as the economic evaluation of the strategy, is of great value.
- Application of probiotics in combination with other materials as pre-biotics or post-biotics.

7. Conclusions

Providing healthy and safe food for human societies is one of the important goals of governments and international organizations such as FAO and WHO. Today, many advances have been made in preventing food contamination with chemical contaminants and unauthorized and unconventional additives. Furthermore, many advances have been made in identifying, detecting, and tracking these contaminants in food products. However, the maintenance of such chemical contaminants in various foods and food frauds such as the use of unauthorized additives or excessive use of permitted additives are unavoidable, making this topic one of the major challenges in the field of food safety and food security.

So far, various methods have been used to eliminate, neutralize, or reduce the effects of chemical contaminants in food and after consumption in the host body. One of the effective methods that is comprehensively discussed in this review is the application of probiotics. Various studies, many of which are mentioned in this article, have shown that different probiotics, depending on the genus and species and the existing conditions, have the potential to neutralize and detoxify various chemical compounds in foods, as well as in the host body after consumption. Although the conclusive proof of many of these studies requires further investigation, it has been shown that probiotics can be used to enhance food safety. It can be concluded that in addition to the well-known health benefits of consuming foods containing probiotics, their detoxifying effects are also significant and deserve further research and consideration.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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