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***Corresponding author:** Massoud Attarianshandiz, Independent Researcher, No. 18, Haft e Tir 40, Mashhad, Post Code: 9178186584, Iran, Tel: +98 933 606 24 64, +98 915 231 4546; E-mail: masood.64@gmail.com

ORCID: <https://orcid.org/0000-0002-2787-7502>

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Research Article

Enhancing immunity against carcinogens through probiotics: A literature review

Massoud Attarianshandiz*

Independent Researcher, No. 18, Haft e Tir 40, Mashhad, Post Code: 9178186584, Iran

Abstract

This literature review explores various aspects of using probiotics as a dietary practice to mitigate the effects of toxic compounds. The discussion highlights the importance of considering factors such as timing and composition of probiotic consumption for maximum benefits. Studies have demonstrated the potential of probiotics to inhibit Deoxyribonucleic Acid (DNA) damage and reduce the occurrence of aberrant crypts in animal models when administered before exposure to toxicants. Furthermore, probiotics have been found to metabolize genotoxic compounds into inactive forms, indicating their potential role in detoxification processes. The binding activity of probiotics against toxicants has been widely studied, but there is a need for further research on the metabolites produced during these interactions. Additionally, the presence of other compounds in the food matrix and their competitive effects on probiotic binding should be investigated to understand the full picture. The strain-dependent nature of the probiotic activity and the variability of their antimutagenic properties for different mutagens further highlight the complexity of their functionality. Considering these findings, it is recommended to conduct a careful risk assessment to evaluate the safety of probiotics and their metabolites, taking into account the potential risks and benefits associated with their use. This will help ensure the responsible application of probiotics in food safety and human health initiatives.

Key points

1. The presence of other compounds in food matrices can influence the binding and absorption of toxicants by probiotics, emphasizing the importance of studying the functioning of probiotics in the presence of competitors.
2. Limited research exists on the binding principles and the impact of other compounds on the release of bound toxicants, highlighting the need for further investigation in this area.
3. Variations in the antimutagenic activity of probiotics against different mutagens and the strain-dependent nature of their binding abilities emphasize the complexity of probiotic functionality and the need for comprehensive studies to identify optimal probiotic strains for specific toxic compounds.

Introduction

The objective of this research was to identify a combination of probiotics that can effectively combat various common food toxicants in a synergistic manner. This literature review will explore the advancements made in utilizing probiotics for reducing the presence of diverse toxic substances. Examining the current challenges associated with the occurrence of acrylamide in food products. Proposing optimal dietary

recommendations for incorporating probiotics into the daily intake. Deliberating on potential areas for future research and identifying existing gaps in the current literature.

The term “lactic acid bacteria” refers to a diverse group of non-spore-forming, Gram-positive bacteria that ferment carbohydrates and primarily produce lactic acid as a byproduct [1]. These bacteria are typically non-motile, often catalase-negative, and generally thrive in acidic environments [1]. Various

genera, including *Lactobacillus*, *Leuconostoc*, *Pediococcus*, and *Streptococcus*, are associated with lactic acid bacteria [1]. They have been genetically modified to adapt to different growth conditions [1]. Lactic acid bacteria are widely distributed in nature and can be found in milk, dairy, fermented foods, meat products, vegetables, and bread, as well as in the intestinal tracts and mucous membranes of both humans and animals [1]. The ability of these bacteria to produce organic acids, diacetyl, hydrogen peroxide, or bacteriocins enables the bio-preservation of food by inhibiting the growth of other harmful bacteria [1,2]. Alongside fermented foods, gastrointestinal tract contents and feces are the primary sources of lactic acid bacteria [3].

Probiotics are nonpathogenic live microorganisms, typically lactic acid-producing strains, that, when consumed in sufficient quantities, confer health benefits on the host by improving the gut microflora [3,4]. Probiotics have also been associated with the prevention and treatment of various gastrointestinal disorders [4]. While most probiotics available on the market are derived from lactic acid bacteria, probiotics from other bacterial classes also exist [5]. Well-studied probiotics include *Lactobacillus* GG, *Bifidobacterium*, and *Saccharomyces* species [4].

The beneficial role of bacteria in functional foods and ingredients

Lactic acid bacteria have been associated with a wide range of beneficial effects, contributing to both food production and human health. Familiar examples of lactic acid bacteria used in food include yogurt and cheese [6]. Bacteriocin production is another advantageous effect of bacteria, extending the shelf life of food products. Fermented sausages, with their long-standing tradition, serve as a prime example [7]. Bacteriocins are antimicrobial peptides produced by certain bacteria that exhibit inhibitory effects against other microorganisms, including food spoilage and pathogenic bacteria [8,9]. The mechanism by which bacteriocins extend the shelf life of foods involves several key aspects.

Firstly, bacteriocins can directly inhibit the growth and survival of spoilage and pathogenic bacteria by disrupting their cellular membranes, leading to cell lysis and death [8,9]. This inhibitory action helps to control microbial populations and prevent the spoilage of food products.

Secondly, bacteriocins can interfere with the metabolic activities of target bacteria. They may disrupt essential cellular processes such as DNA, RNA, or protein synthesis, impairing bacterial growth and viability [8,9]. By targeting specific cellular components or metabolic pathways, bacteriocins exert their antimicrobial effects, thereby preserving the quality and safety of food.

Furthermore, bacteriocins can have a bacteriostatic effect [9], inhibiting the growth and proliferation of bacteria without causing cell death. This can slow down microbial spoilage and increase the shelf life of food by reducing the overall bacterial load.

Importantly, bacteriocins produced by some bacteria have a narrow spectrum of activity [8,9], meaning they specifically target certain microorganisms while sparing others. This selectivity allows for the preservation of desirable microbial populations, such as beneficial bacteria involved in food fermentation, while suppressing the growth of undesirable bacteria.

Overall, the mechanism of action of bacteriocins involves direct antimicrobial effects, interference with bacterial metabolism, and selective targeting of specific microbial populations. By employing these mechanisms, bacteriocins contribute to extending the shelf life of foods by inhibiting spoilage and pathogenic bacteria. Many lactic acid bacteria produce numerous heat-stable bacteriocins, such as glycine, which aids in reducing acrylamide in bread [10,11]. These instances showcase how bacteria contribute to food production and enhance its quality. However, bacteria also have a direct impact on our bodies and overall health when incorporated as probiotics in functional foods [4]. Probiotics offer various benefits, from combating carcinogens to preventing infections [12,13]. In terms of using probiotics to prevent infectious diseases, *in vitro* assays have proven to be reliable predictors for *in vivo* experiments [13]. Consuming probiotics alone or in combination with food has demonstrated antioxidant activity [14]. Furthermore, several studies have indicated the ability of probiotics to reduce toxicants and carcinogens [12].

Acrylamide: A common compound in everyday foods

Acrylamide ($\text{CH}_2=\text{CH}-\text{CONH}_2$) is extensively produced in industries and primarily utilized in the form of polyacrylamide, serving various applications such as wastewater treatment, paper production, and petroleum recovery [15,16]. It is also employed as a grout and soil stabilizer in the construction industry when used as a monomer [16].

This colorless and odorless crystalline compound, acrylamide, can also be found in our daily food items, ranging from potato crisps and cookies to crispbread and even coffee [17-19]. The formation of acrylamide occurs during the Maillard reaction, which is triggered by heat treatment [20,21]. Amino acids (such as Asparagine, Glutamine, Methionine, and Cysteine) and reducing sugars (such as D-fructose, D-galactose, lactose, or sucrose) act as precursors to acrylamide production when exposed to temperatures above 100 °C or 120 °C [20,21]. Notably, the amino acid asparagine has been strongly associated with acrylamide formation in bread, with a clear correlation between its content and the amount of acrylamide present [11]. Three key elements - heat, a carbonyl group (from carbohydrates), and an amine group (from L-asparagine) - are essential for the formation of acrylamide [22]. The presence of water appears to facilitate the reaction, as the reactants are more thoroughly mixed in the presence of a solvent [20,21]. Besides manufacturing conditions, several other factors can influence the presence and quantity of acrylamide in final products, including soil conditions, nitrogen fertilizers, storage conditions, cutting, soaking, and blanching processes, additives like amino acids and proteins, salt, asparaginase, organic acids, and even probiotics [22].

Acrylamide: absorption, distribution, and risks

Acrylamide is rapidly absorbed and widely distributed throughout the body following oral intake in various animal species [23]. *In vitro*, simulations of the gastric system by Tomás, et al. [24] have demonstrated an increase in the soluble fraction of acrylamide after gastric digestion. Autoradiography studies in mice have revealed the accumulation of acrylamide or its metabolites in male reproductive organs and developing fetuses in pregnant females [23]. Haemoglobin adducts of acrylamide with the N-termini of globin chains have been observed in rats fed with fried feed [25]. Investigations into the maternal dietary intake of acrylamide among pregnant women have shown negative effects on fetal growth, birth weight, and head circumference [26,27]. Acrylamide and its metabolites are rapidly and extensively eliminated from the body, primarily through urine, with smaller amounts excreted via feces and exhalation [23].

Despite polyacrylamide being non-toxic, oral exposure to acrylamide poses significant risks, including the potential for cancer, genotoxicity, neurotoxicity, induction of cellular transformation, and growth retardation [17,25,28,29]. Inhibition of acrylamide oxidative metabolism has shown no change in the incidence of cell transformation [28].

As mentioned earlier, acrylamide is primarily a byproduct of the Maillard reaction and is more likely to be found in foods with low moisture content. Tareke, et al. [25] reported that acrylamide could not be detected in unheated or boiled foods. However, on the contrary, Mottram, et al. and Stadler, et al. [20,21] suggested that the presence of water favors the reaction due to the better mixing of reactants in a solvent. While alternative pathways and precursors have been proposed for acrylamide formation, roasted, toasted, and baked foods such as coffee, potato chips, and biscuits are generally among the most contaminated (Raffan & Halford, 2019). This implies that producers of these food types must exercise caution when implementing new processes to ensure that changes do not promote acrylamide formation. For example, some bakeries have added steam to their production line, claiming that it makes their products healthier. However, such claims should be substantiated by analytical assessments to ensure their accuracy.

Analytical assessment of acrylamide detection

For the separation, detection, and quantification of acrylamide, gas or liquid chromatography methods can be employed. Gas Chromatography (GC) requires a derivative such as bromine, while High-Performance Liquid Chromatography (HPLC) allows for the direct measurement of purified extracts [18]. Detection can be achieved using both Ultraviolet (UV) and Mass Spectrometry (MS) detection methods [18]. Tandem Mass Spectrometry (MS/MS) detection offers the advantage of minimizing chromatographic separation while maintaining high selectivity [18]. While Gas Chromatography/Mass Spectrometry (GC/MS) is a more cost-effective option, Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS) is simpler to implement [22].

For HPLC analysis, the defatting of samples using n-hexane, extraction with water, sonication, centrifugation, and purification with solid-phase extraction is performed. The purified extracts are transferred to the vial of the HPLC system [18]. The analysis involves injecting the sample into a reversed-phase column with a pre-column and eluting with a mobile phase. Acrylamide is detected using a selective ion monitoring mode, with separate monitoring for acrylamide and the internal standard. The identification of acrylamide is done by comparing the retention times with the labeled acrylamide [18].

Regarding GC analysis, the sample is ground and mixed with the internal standard and water. After centrifugation and filtration, the eluate is collected. Subsequently, bromination and phase separation procedures are carried out. The organic layer is then centrifuged, and the liquid phase is decanted. The pooled fraction is evaporated, and the residue is dissolved in ethyl acetate with triethylamine. The final solution is transferred into the insert in an amber vial [30].

Probiotics and acrylamide

An *in vivo* experiment involving four different probiotics and two carcinogens, including acrylamide, demonstrated that certain probiotic strains, specifically *Bifidobacterium* species (*B. bifidum*, *B. breve*, *B. longum*, *B. infants*), significantly reduced DNA damage induced by acrylamide in the liver [31]. In this study, the probiotic strains were administered 3 hours prior to the genotoxin treatment [31]. This *in vivo* experiment, along with another study conducted by Szekér, et al. [32], highlights the presence of probiotic strains that can effectively adhere to the gastrointestinal tract [31,32]. Furthermore, additional *in vivo* experiments support the use of lactic acid bacteria in protecting against carcinogens [33].

Under simulated gastrointestinal conditions, two lactic acid bacteria, *Lactobacillus reuteri* NRRL 14171 and *Lactobacillus casei* Shirota were observed to survive and remove up to 73% of acrylamide from commercial potato chips [19]. Moreover, immobilized cells demonstrated faster acrylamide degradation compared to free cells [34]. Oral consumption of *Enterococcus faecium* NCIM 5593 was found to improve neuronal dysfunction and reduce oxidative stress induced by acrylamide in mice [35].

Serrano-Niño, et al. [36] conducted an *in vitro* experiment using a mixture of 14 different probiotics and acrylamide in phosphate buffer saline. They discovered that lactic acid strains were capable of removing between 11.89% and 29.12% of the known concentration of acrylamide [36].

This reduction in acrylamide content was attributed to the formation of a stable bacterial-toxin complex and was influenced by the concentration and pH of the solution [36]. Based on their findings, the researchers concluded that the small intestine is the most favorable site for the binding of mutagens [36].

All bacteria in the study demonstrated the ability to bind with acrylamide, with *Lactobacillus reuteri* Northern Regional Research Laboratory 14171 (USDA-ARS) and *Lactobacillus casei*

Shirota exhibiting the highest efficiency by reducing 24.01% and 24.95% of 5 µg/ml acrylamide, respectively [36].

These results suggest that the binding capacity of probiotics to acrylamide could potentially be enhanced through the addition of natural antioxidants. For instance, Zhang and Zhang [37] found that incorporating bamboo leaves or green tea extract as antioxidants can reduce acrylamide formation by approximately 82.9% and 72.5%, respectively, without significantly altering the sensory characteristics of fried bread sticks.

Taher and Hassouna [38] reported that lactic acid fermentation of bread, particularly with 4% *Lactobacillus plantarum*, resulted in a 27.4% decrease in acrylamide content [38]. Additionally, the combined use of lactic acid bacteria and *Nigella sativa* oil led to a 56% reduction in acrylamide content [38].

The interaction between baker's yeast (*Saccharomyces cerevisiae*) and lactic acid bacteria (*Lactobacillus bulgaricus* and *Lactobacillus brevis*) was found to have a synergistic effect, improving the organoleptic properties and extending the shelf life of bread [39,40]. The inclusion of lactic acid bacteria and yeast in bread production resulted in higher loaf volume compared to bread made solely with baker's yeast [41].

These findings collectively indicate that probiotics and lactic acid bacteria can reduce the levels of free acrylamide compounds in food, and their presence does not negatively affect bacterial growth [42].

It is important to note that the outcomes of different studies can be highly dependent on the specific strains of bacteria used, as suggested by Shah and Wu [43]. They found varying detoxification abilities among different bacterial groups [43].

Shen, et al. 2019 [44] conducted a comprehensive molecular study to investigate the adsorption mechanism of acrylamide by lactic acid bacteria. Using scanning electron microscopy and atomic force microscopy, the researchers explored the role of different components in the adsorption process. They found that peptidoglycan and cell wall proteins are crucial for the adsorption of acrylamide by lactic acid bacteria [44]. This finding is in agreement with other studies which have found the cell wall skeleton, protein molecules on the cell surface or peptidoglycan had a more adhering effect on the mutagens [45-47].

Furthermore, other studies have demonstrated the potential of bacterial biofilms and planktonic cells in the degradation and utilization of organic compounds. For instance, Aneez Ahamad and Mohammad Kunhi [48] investigated the enhanced degradation of phenol by *Pseudomonas* sp. CP4 immobilized in agar and calcium alginate beads. The study showed that the immobilized cells in agar beads outperformed both free cells and Ca-alginate-entrapped cells, enabling the degradation of higher phenol concentrations [48].

Similarly, Maksimova, et al. [49] explored the biodegradation capabilities of the *Alcaligenes faecalis* 2 strain

toward acrylamide and acrylic acid. The study revealed that the strain could completely utilize both compounds as the sole sources of carbon and energy, with the transformation of acrylamide into acrylic acid occurring before bacterial growth initiated. Notably, when *A. faecalis* 2 cells were immobilized on specific materials, such as a type of basalt fibers and Carbofon-B-aktiv, they exhibited enhanced acrylamide transformation rates [49].

These findings collectively highlight the potential of both bacterial biofilms and planktonic cells in the fight against acrylamide. The adsorption and degradation capacities of lactic acid bacteria, along with the advantages conferred by immobilization techniques, offer promising avenues for the development of efficient treatment technologies targeting acrylamide in various applications [44,48,49].

Heterocyclic amines

Heterocyclic Amines (HCAs) are formed during the cooking process of meat and fish, resulting from the heating of a mixture containing creatinine, sugars, and amino acids [50]. These compounds have been identified as mutagenic and are known to exhibit higher mutagenic properties compared to other common mutagens and carcinogens [50].

In light of the mutagenicity of HCAs, there is growing interest in exploring potential strategies to mitigate their harmful effects. One such avenue of investigation involves the use of probiotics, which are beneficial microorganisms that have been shown to possess various health-promoting properties.

Table 1 listed the number of studies showing the binding ability or antimutagenicity of probiotics against toxic agents. There, researches indicate that certain probiotic strains exhibit promising binding ability or antimutagenic effects against toxic agents, including HCAs. These probiotic species, such as *Bifidobacterium longum*, *Lactobacillus gasseri*, *Streptococcus thermophilus*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, *Streptococcus cremoris*, *Enterococcus faecium*, *Enterococcus faecalis*, *Lactobacillus acidophilus*, and *Lactobacillus plantarum*, have demonstrated positive outcomes in terms of reducing the mutagenic potential of toxic compounds [31,46,52-54].

By exploring the binding ability or antimutagenicity of probiotics against HCAs, researchers aim to identify potential strategies for minimizing the adverse health effects associated with the consumption of cooked meat and fish. Understanding the interactions between probiotics and HCAs can contribute to the development of novel approaches to reduce the mutagenic properties of these harmful compounds and promote food safety.

When examining the binding ability of different probiotic strains to Heterocyclic Amines (HCAs), some interesting findings have emerged. For instance, two strains of *B. longum* exhibited binding percentages of 91.7 and 82.6% to Tryptophan-P-1 [54]. In a study by the same researchers, 28 strains of *L. gasseri* were tested for their ability to bind to



Table 1: lists a number of studies showing the binding ability or antimutagenicity of probiotics against toxic agents.

Microorganisms	Genera	Species	Strains	Type of the Hazardous Compound	Carcinogen	Media / Condition	Initial Dosage	Reduction Percent	Reference
Bacteria	Bifidobacterium	<i>B. bifidum</i>			16 different Polycyclic aromatic hydrocarbons	in-vitro, in yogurt	0.25µg of each/ml medium).	46.6,3.46	(Arab et al, 2010)
Bacteria	Bifidobacterium	<i>B. infantis</i>	1912	Aflatoxin	Aflatoxin B1	distilled water	50 ng of aflatoxin B1 /ml	40	(Shah and Wu , 1999)
Bacteria	Bifidobacterium	<i>B. longum</i>	2 different strains	heterocyclic amines	pyrolysates (Trp-P-1)	In vitro	100 µg/ml	82.6 - 91.7	(Sreekumar and Hoson, 1998)
Bacteria	Enterococcus	<i>E. faecalis</i>	D66	heterocyclic amines	Trp-P-1 and Trp-P-2			55.1 and 78.5	(Sung, 2014)
Bacteria	Enterococcus	<i>E. faecium</i>	D12	heterocyclic amines	Trp-P-1 and Trp-P-2			52.8 and 62.7	(Sung, 2014)
Bacteria	Lactobacillus	<i>L. acidophilus</i> , <i>L. casei</i> and <i>L. rhamnosus</i>			1,2-dimethylhydrazine	rat fed with fermented milk	30 mg/kg	colorectal cancer prevention	(Desrouillères et al., 2015)
Bacteria	Lactobacillus	<i>L. gasseri</i>	28 different strains	heterocyclic amines	pyrolysates (Trp-P-1)	In vitro	100 µg/ml	48.5 - 95.4	(Sreekumar and Hoson, 1998)
Bacteria	Lactobacillus	<i>L. rhamnosus</i>	IMC501	heterocyclic aromatic	4-Nitroquinoline-1-Oxide	in vitro - SOS Chromotest	1 mg/ml		(Bocci et al, 2015)
Bacteria	Lactobacillus	<i>L. plantarum</i>	21 different strains	heterocyclic aromatic	4-Nitroquinoline-1-Oxide	in vitro - SOS Chromotest	0.1 mM	more than 75% genotoxicity inhibition	(Prete et al, 2017)
Bacteria	Lactobacillus	<i>L. bulgaricus</i>			16 different Polycyclic aromatic hydrocarbons	in-vitro , in yoghurt	0.25µg of each/ml medium).	91.5, 3.46	(Abou-Arab et al., 2010)
Bacteria	Lactobacillus	<i>L. bulgaricus</i>			4-Nitroquinoline-1-Oxide or 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide	cultured milk	AF2 (.018 µg/ml) or 4NQO (.025 µg/ml)	genotoxicity inhibition	(Hosono and Kashina, 1986)
Bacteria	Lactobacillus	<i>L. acidophilus</i>	D38	heterocyclic amines	Trp-P-1 and Trp-P-2			67 and 40.6	(Sung, 2014)
Bacteria	Lactobacillus	<i>L. plantarum</i>	D70	heterocyclic amines	Trp-P-1 and Trp-P-2			74.3 and 58.3	(Sung, 2014)
Bacteria	Lactobacillus	<i>L. delbrueckii subsp. bulgaricus</i>	2038	heterocyclic amines	Trp-P-1 and MeIQx	distilled water	10 µg/ml	94.1 and 60.8	(Terahara et al., 1998)
Bacteria	Lactobacillus	<i>L. sakei</i>			acrylamide	bread with fermented lupine			(Bartkiene et al., 2013)
Bacteria	Lactobacillus	<i>L. plantarum</i>	1.0065		acrylamide	extracted peptidoglycan	6 µg/mL	87	(Zhang et al., 2017)
Bacteria	Lactobacillus	<i>L. casei</i>	Shirota		acrylamide	simulated gastrointestinal conditions	10 µg AA/mL	68	(Rivas-Jimenez et al, 2016)
Bacteria	Lactobacillus	<i>L. reuteri</i>	NRRL		acrylamide	simulated gastrointestinal conditions	10 µg AA/mL	(R et al, 2008)	(Rivas-Jimenez et al, 2016)
Bacteria	Lactobacillus	<i>L. acidophilus</i>	SBT0274	heterocyclic amines	pyrolysates (Trp-P-1)	vitro	100 µg/ml	95.4	(Sreekumar and Hoson, 1998)
Bacteria	Lactobacillus	<i>L. acidophilus</i>	SBT1703	heterocyclic amines	pyrolysates (Trp-P-1)	vitro	100 µg/ml	94.7	(Sreekumar and Hoson, 1998)
Bacteria	Lactobacillus	<i>L. acidophilus</i>	SBT10239	heterocyclic amines	pyrolysates (Trp-P-1)	vitro	100 µg/ml	95.3	(Sreekumar and Hoson, 1998)
Bacteria	Lactobacillus	<i>L. acidophilus</i>	SBT10241	heterocyclic amines	pyrolysates (Trp-P-1)	vitro	100 µg/ml	94.9	(Sreekumar and Hoson, 1998)
Bacteria	pediococcus	<i>P. acidilactici</i>	D19	heterocyclic amines	heterocyclic amines				(Sung, 2014)
Bacteria	pediococcus	<i>P. pentosaceus</i>			acrylamide				(Bartkiene et al., 2013)



Bacteria	Streptococcus	<i>S. thermophilus</i>			16 different Polycyclic aromatic hydrocarbons	in-vitro , in yoghurt		87.7, 3.46	(Abou-Arab et al., 2010)
Bacteria	Streptococcus	<i>S. thermophilus</i>			4-Nitroquinoline-1-Oxide or 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide	cultured milk	AF2 (.018 µg/ml) or 4NQO (.025 µg/ml)	genotoxicity inhibition	(Hosono and Kashina, 1986)
Bacteria	Streptococcus	<i>S. thermophilus</i>	1131	heterocyclic amines	Trp-P-1 and MeIQx	distilled water	10 µg/ml	83.2 and 32.2	(Terahara et al., 1998)
Bacteria	Streptococcus	<i>S. cremoris</i>	Z.25	heterocyclic amines	Trp-P-1	Vitro Binding	1000 ppm	86.65	(Zhang and Ohta, 1991)
Bacteria	Streptococcus	<i>S. cremoris</i>	Z.25	heterocyclic amines	Trp-P-2	Vitro Binding	1000 ppm	84.78	(Zhang and Ohta, 1991)
Bacteria	Streptococcus	<i>S. cremoris</i>	C-25	heterocyclic amines	Trp-P-1 and Trp-P-2, Glu-P-1.	Vitro Binding - Freeze-dried cells	50 µg each in .05 ml	98.23,96.31,25.36	(Zhang and Bin, 1990)
yeast		<i>Debaryomyces hansenii</i>	LG2, LG15		4-Nitroquinoline-1-Oxide	in vitro - SOS Chromotest	0.1 mM	more than 75% genotoxicity inhibition	(Prete et al., 2017)
yeast		<i>Wickerhamomyces anomalus</i>	LUL14 TO8		4-Nitroquinoline-1-Oxide	in vitro - SOS Chromotest	0.1 mM		
yeast		<i>Torulaspora delbrueckii</i>	TO2, TO3		4-Nitroquinoline-1-Oxide	in vitro - SOS Chromotest	0.1 mM		
yeast		<i>Hanseniaspora uvarum</i>	TO5		4-Nitroquinoline-1-Oxide	in vitro - SOS Chromotest	0.1 mM		
yeast		<i>Metschnikowia aff. Fructicola</i>	RIB1, RIB3		4-Nitroquinoline-1-Oxide	in vitro - SOS Chromotest	0.1 mM		
yeast		<i>Metschnikowia raukaufii</i>	LAM3		4-Nitroquinoline-1-Oxide	in vitro - SOS Chromotest	0.1 mM		
yeast		<i>Candida apicola</i>	UV10		4-Nitroquinoline-1-Oxide	in vitro - SOS Chromotest	0.1 mM		
yeast		<i>Meyerozyma guilliermondii</i>	PR1		4-Nitroquinoline-1-Oxide	in vitro - SOS Chromotest	0.1 mM		
yeast		<i>Saccharomyces boulardii</i>	Codex		4-Nitroquinoline-1-Oxide	in vitro - SOS Chromotest	0.1 mM		

Trp-P-1, and five strains demonstrated binding capacities exceeding 94% [54]. Notably, a strong correlation between antimutagenicity and binding was observed, with the lowest binding percentage recorded at 48.5% [54].

The complexity of mutagens appears to influence the binding properties of different probiotic strains, as evidenced by the variety of heterocyclic amines tested in the study [54]. Another study investigated the effects of *S. thermophilus* and *L. delbrueckii* subsp. *bulgaricus* on Trp-P-1 and MeIQx (2-Amino-3,8-dimethylimidazo[4,5-f]quinoxaline), revealing the ability of these bacteria to absorb toxin compounds ranging from 32.2% to as high as 94.1% [52]. Interestingly, when the experimental environment shifted from distilled water to the small intestine of rats, the absorption of Trp-P-1 by the small intestine was significantly reduced by *S. thermophilus*, while the addition of *L. delbrueckii* subsp. *bulgaricus* had no effect [52]. In terms of specific strains, *S. cremoris* cells demonstrated binding percentages of 86.65% and 84.78% for Trp-P-1 and Tryptophan-P-2, respectively, while the binding to the cell wall skeleton was 70.75% and 68.44%, respectively [45]. When subjected to gastric juice, the binding percentages of Trp-P-1 and Trp-P-2 to *S. cremoris* cells decreased to 65.0% and 53.6%, respectively [53].

Additionally, *E. faecium*, *E. faecalis*, *L. acidophilus*, and *L. plantarum* demonstrated binding percentages of 52.8%, 55.1%, 67%, and 74.3% for Trp-P-1, respectively, and 62.7%, 78.5%, 40.6%, and 70.2% for Trp-P-2, respectively [46].

Moreover, an in vivo study conducted by Dominici, et al. [31] demonstrated the protective properties of *Lactobacillus rhamnosus* against the induction of DNA damage on colon cells caused by a specific type of heterocyclic amine.

N-nitroso diethylamine

Nitrosamines, potential carcinogens, may be present in food and beverages in volatile forms. Zhang and Ohta [53,55], observed that among nine tested strains of *S. cremoris*, the cell wall skeleton of strain Z-25 exhibited the highest binding of 37.96 ppm/mg, while the lowest binding was observed for strain Z-31 at 1.48 ppm/mg [45]. *Streptococcus lactis* was also found to possess binding activity to N-nitroso diethylamine.

4-nitroquinoline-1-oxide

The heterocyclic aromatic compound 4-nitroquinoline-1-oxide (4-NQO) is a toxic carcinogen frequently used as a model for toxinogenic studies. Bocci, et al. [56] selected this compound due to its high carcinogenicity and molecular stability and found that *L. rhamnosus* effectively transforms it into inactive forms [56]. In another study, out of 22 different strains of *Lactobacillus plantarum*, 21 strains significantly reduced the genotoxicity of 4-NQO by over 75% [57]. Additionally, among 15 different species and strains of yeasts tested, 12 of them, including *Debaryomyces hansenii*, *Wickerhamomyces anomalus*, *Torulaspora delbrueckii*, *Hanseniaspora uvarum*, *Metschnikowia aff. Fructicola*, *Metschnikowia raukaufii*, *Candida apicola*, *Meyerozyma*

guilliermondii, and *Saccharomyces boulardii*, exhibited more than 75% inhibition of genotoxicity [57]. Hosono and Kashina [58] conducted studies that indicate the antimutagenic properties of yogurt produced by cultivating *S. thermophilus* and *L. bulgaricus* against 4-nitroquinoline 1-oxide (4NQO) and 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide [58]. Interestingly, this antimutagenicity was independent of pH and likely based on other factors, potentially proteins [58].

Polycyclic aromatic hydrocarbons (PAHs)

PAHs are a group of chemicals formed during the incomplete combustion or high-temperature pyrolysis of organic matter, and they can be found in the environment, including air, soil, and food. Some PAHs are known to exhibit toxicity, carcinogenicity, and mutagenic effects on humans and animals [59]. A study on the reduction of PAHs using *Bifidobacterium bifidum*, *Streptococcus thermophilus*, and *Lactobacillus bulgaricus* demonstrated the capability of these bacteria to remove these compounds from their environment [59]. Specifically, *B. bifidum*, *S. thermophilus*, and *L. bulgaricus* reduced these compounds by 46.6%, 87.7%, and 91.5%, respectively [59].

Aflatoxins

Aflatoxins are human carcinogens and are produced as secondary metabolites by *Aspergillus* species [60]. The presence of aflatoxins in foods and feed is a significant concern due to their adverse health effects and contribution to food waste [43]. In a detoxification study, various strains of probiotics, including *B. bifidum*, *B. pseudolongum*, *B. infantis*, *B. bifidum*, and *L. casei*, were tested, and all strains demonstrated some detoxification ability. *B. infantis* exhibited the highest detoxification capacity, while *B. pseudolongum* showed the lowest [43]. However, it should be noted that although bacterial toxin binding ranged from 20% to 50%, washing the organisms with water resulted in the release of the toxin compound, leaving only 10% to 40% bound [43].

Xu, et al. [60] reported the mycotoxin-degradation ability of *B. shackletonii*, marking the first identification of this bacterium's potential in mycotoxin degradation. While *B. shackletonii* may not have been extensively studied as a probiotic, further research can explore its potential uses, including in this project. This bacterium includes a thermophilic strain and is capable of spore formation [61]. Notably, studies have shown that *Bacillus* probiotic spores can germinate in significant numbers in the jejunum and ileum, indicating their ability to colonize the small intestine [62]. This information positions *B. shackletonii* as a promising candidate for use in food processing, particularly in bakery production.

Dimethylhydrazine (DMH)

1,2-dimethylhydrazine (DMH) is a widely recognized colon carcinogen and is frequently used as a model in experimental [63,64]. In a study by Desrouillères, et al. it was observed that a diet supplemented with fermented milk containing three probiotic strains (*Lactobacillus acidophilus*, *L. casei*, and *L. rhamnosus*) reduced the occurrence of colon cancer in rats

fed DMH [5]. This study is intriguing as it demonstrates the potential of using a combination of bacteria to counteract the effects of a toxic compound.

When considering the numerical values, it is important to note that data from different studies are challenging to compare due to variations in several variables. However, these data can indicate whether a bacterial species has exhibited positive effects against common toxicants found in food. For example, *L. plantarum* has shown positive activity against 4-Nitroquinoline-1-Oxide, Trp-P-1, Trp-P-2, and acrylamide [46,47,57]. *L. bulgaricus* and *S. thermophilus* have demonstrated activity against various polycyclic aromatic hydrocarbons, 4-Nitroquinoline-1-Oxide, 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide, Trp-P-1, and MeIQx [52,55,59]. *S. cremoris* has exhibited binding capabilities to Trp-P-1, Trp-P-2, and Glu-P-1 [45,53]. These microorganisms, which have shown activity against a range of compounds, could be promising candidates for further research.

Based on this literature review, several conclusions can be drawn. First, this project is not the first of its kind to investigate the effects of probiotics on toxicants in general and acrylamide in particular. Second, while the number of studies in this area is not extensive, especially regarding probiotics and acrylamide, the results are still limited, albeit positive. This suggests that there is room to identify more effective probiotics compared to other types of carcinogens.

Outline

Using probiotics as a supplement in food is a well-established approach, primarily focusing on their role as live microorganisms within the body. However, there is potential to explore the idea of incorporating probiotics into pre-heated food materials. This raises a few key considerations.

A suitable probiotic candidate should possess specific characteristics. Firstly, it should not interfere with the food production process while retaining its beneficial properties. For example, it should not disrupt the activity of yeast in bakery products. However, it can be beneficial by reducing the formation of acrylamide through the reduction of asparagine. Additionally, probiotics could potentially extend the shelf life of products by producing bacteriocins. Secondly, the implementation of probiotics in food should ensure their survival during the production process, as their most significant benefits occur inside the body. This may require adaptations to the production procedures, and studying gene regulation and transcriptional repressors could provide insights into the bacteria's stress response and resilience [65]. Although probiotics are typically implemented as live organisms, the adsorption ability of lactic acid bacteria against toxins is closely associated with their cell walls. Therefore, non-viable probiotics with intact cell walls may also be worth considering. However, further research is needed as studies have found that purified cell walls from probiotic *L. gasseri* can lead to maladaptive inflammatory responses [66]. In conclusion, the initial objective could be to search for specific *Lactobacillus* strains or probiotics that meet these criteria and can be practically employed.



Is there a perfect combination of probiotics? The effects of probiotics on toxin compounds are highly dependent on bacterial and chemical species. The literature often introduces one or a few microorganism species that are effective against specific groups of compounds, and research involving a combination of organisms targeting different compounds is limited.

It is noteworthy that Terahara, et al. [52] discovered two different bacteria capable of adsorbing toxic compounds within different pH ranges. *Streptococcus thermophilus* exhibited optimum adsorption between pH 4 and 9, while *Lactobacillus delbrueckii* subsp. *bulgaricus* had an optimum pH of 4 [52]. Another study investigated the interaction time between probiotics and toxicants [54]. They found that most mutagenic compounds were immediately bound after adding the microorganism cells, but further incubation led to increased binding, with the optimum incubation time varying among different strains [54]. Furthermore, Desrouillères, et al. [5] observed that a supplemented diet of fermented milk containing three probiotic strains (*Lactobacillus acidophilus*, *L. casei*, and *L. rhamnosus*) reduced the occurrence of colon cancer in rats exposed to DMH [5]. This study is intriguing as it demonstrates the potential of using a combination of bacteria to counteract the effects of a toxin compound. These findings suggest that combining different microorganisms may widen the working window and enhance the efficiency of probiotics. By selecting the right combination, probiotics could potentially exert their beneficial effects beyond the small intestine and enhance their ability to adsorb toxicants. Discovering this perfect combination of probiotics could be an interesting challenge for this project.

Furthermore, as it is stated earlier, studies have shown that *Bacillus* probiotic spores can evolve in substantial numbers in the jejunum and ileum and could colonize the small intestine [62]. Therefore, spores could also be considered as a good candidate for this perfect probiotic combination. By exploring the use of spores in combination with other probiotics, the effectiveness and range of benefits may be enhanced, allowing for a more comprehensive approach to addressing toxin compounds in food.

Good probiotic dietary practice

Understanding the optimal consumption pattern of probiotics is crucial to harness their maximum benefits. Dominici, et al. [31] found that administering a combination of probiotics three hours prior to the intake of toxic compounds in animal models significantly inhibited DNA damage [31]. In another study, rats that consumed 1 to 2 ml of fermented milk containing three different probiotic strains daily for several weeks exhibited a significant reduction in aberrant crypt count, a marker of colon cancer [5]. Similarly, mice treated with a probiotic suspension for 10 days prior to toxicant administration showed significant inhibition of DNA damage [31]. Moreover, Villarini, et al. [33] conducted a study where rats were fed probiotic-supplemented feed for five days, leading to a decrease in DNA damage occurrence, particularly in colon cells [33].

Probiotic metabolism of chemicals and the role of metabolites

An important aspect to consider is whether probiotics have the ability to metabolize toxic compounds and what the resulting metabolites are. A study demonstrated that *L. rhamnosus* can effectively transform the genotoxic compound 4-Nitroquinoline-1-Oxide into an inactive form, thereby eliminating its genotoxicity [56]. While several studies have focused on the binding activity and antimutagenic properties of probiotics against toxicants, limited research has been conducted on the metabolites generated by probiotics during the metabolism of these compounds. The aforementioned example highlights the need for further investigation in this area. Although in this particular case, the probiotics were able to neutralize the compound's genotoxicity, it is important to explore the diverse possibilities and potential effects of metabolites. Thus, conducting more studies in this field is crucial, and it could serve as a significant objective for this project.

Functioning of probiotics in the presence of competitors

Many studies have demonstrated the binding effect of probiotics and toxicants in their models, but they often neglect to consider the presence of other potential competitors that could influence the microorganisms' ability to absorb toxin compounds. Food is typically a complex matrix comprising various compounds and chemicals that can bind to the surface of microorganisms, making it challenging for toxicants to bind effectively.

It is crucial to monitor the impact of other present compounds on the absorption and binding of toxicants to the microorganisms. For instance, Zhang & Ohta [53] and Sreekumar & Hosono [54] have investigated the effect of metal salts and found a reduction in binding. Furthermore, it is worth noting that not only can the presence of other compounds compete with binding, but they can also cause the bound compound to be released. In one study, washing cells with distilled water did not result in the release of the attached mutagen, but the addition of a second amino acid pyrolysate partially released the compound [54]. Overall, research in this area is limited, highlighting the need for a better understanding of the binding principles and further investigation.

Table 1 provides a summary of a literature review showcasing the ability of various microorganisms to bind to different toxic compounds. However, it is important to consider that the same organism may not exhibit the same inhibitory activity against different mutagens [67]. For instance, Thyagaraja and Hosono [67] found significant variations in the antimutagenic activity of different lactic acid bacteria toward various food-related mutagens [67,68]. Additionally, as previously mentioned, the ability of different organisms to bind toxins may depend strictly on the specific strain [43].

Conclusion

In conclusion, the literature review reveals significant evidence supporting the potential of probiotics to mitigate the



effects of toxic compounds. Probiotics have shown promising results in protecting against DNA damage and reducing the occurrence of colon cancer markers [5,31,33,51].

Optimal consumption patterns of probiotics play a crucial role in harnessing their maximum benefits. Administering a combination of probiotics prior to the intake of toxic compounds has been shown to inhibit DNA damage [31]. Regular consumption of probiotics, such as fermented milk containing specific strains, has been associated with a significant reduction in colon cancer markers [5].

The ability of probiotics to metabolize toxic compounds and produce specific metabolites is an area that requires further exploration. Limited research has been conducted on the diverse possibilities and potential effects of metabolites generated during the metabolism of toxicants by probiotics [56]. Understanding the role and impact of these metabolites is essential for a comprehensive understanding of probiotic functionality.

Considering the presence of other compounds and competitors in the gut environment is crucial when evaluating the binding and absorption of toxicants by probiotics. Various compounds found in food can influence the microorganisms' ability to bind effectively to toxins [53,54]. The impact of these competitors and the principles governing the binding process require further investigation.

It is important to note that different microorganisms may exhibit varying inhibitory activity against different toxic compounds [67]. The antimutagenic activity of probiotics can vary depending on the specific strain and the mutagen being targeted. Therefore, selecting the appropriate probiotic strain for a specific toxicant is essential for achieving desired results [43].

Overall, the studies reviewed highlight the potential of probiotics in mitigating the effects of toxic compounds. However, further research is needed to explore optimal consumption patterns, understand the role of metabolites, investigate the impact of competitors, and determine strain-specific activity. Advancing our knowledge in these areas will contribute to the development of targeted probiotic interventions and promote their effective use in protecting against the harmful effects of toxic compounds.

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Compliance with ethical standards and conflict of interest

The author, as an independent researcher, unequivocally declares the absence of any conflict of interest. This comprehensive literature review stands as a testament to the author's unwavering commitment to advancing scientific knowledge and understanding. It represents a culmination of diligent efforts expended during the author's pursuit of various Ph.D. applications, which unfortunately did not materialize due to limited external funding sources. Despite this setback, the author persevered and self-financed the research conducted for this manuscript, ensuring the utmost integrity and dedication to scholarly excellence.

It is essential to underscore that there are no financial or personal relationships that could in any way compromise the objectivity, impartiality, or integrity of the work presented herein. The author's sole motivation has been the pursuit of knowledge, and every effort has been made to maintain the highest ethical standards throughout the research process.

As the author seeks to further expand the scope and impact of their research, potential sponsors are invited to join in this noble endeavor. Any prospective collaboration or sponsorship would not only contribute to the advancement of scientific understanding but also facilitate the exploration of new frontiers and the development of innovative solutions to pressing challenges. The author remains open and eager to engage with partners who share a passion for scientific inquiry and a commitment to making a meaningful difference in the world.

In summary, the author extends their sincerest assurance that this manuscript has been prepared with the utmost diligence, intellectual rigor, and ethical consideration. It is a testament to the author's unwavering dedication and serves as an invitation to potential sponsors to join in this exciting journey of discovery and knowledge dissemination.

Ethical approval

This article does not contain any studies with human participants or animals performed by the author.

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