Lactic Acid Bacteria against Mycotoxins

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Mycotoxins (aflatoxin, ochratoxin, patulin, zearalenone, fumonisins, trichothecenes) are a large group of chemically diverse, non-protein, low-molecular secondary metabolites produced by molds. They constitute a global threat to human food and health. The generally regarded as safe (GRAS) status and long history as essential ingredients of fermented foods and probiotics make Lactic Acid Bacteria (LAB) a major biological tool against various food-related toxins. Numerous studies have shown LAB to be effective against all major mycotoxins.

Keywords: food ; lactic acid bacteria ; mycotoxins ; detoxification

1. Mycotoxins—Overview and Medical Relevance

Mycotoxins are difficult to define. According to their name, these are toxic substances produced by fungi (“myco” comes from the Greek word for fungus). Apart from that obvious definition, there is little common ground between them except that they are low-molecular secondary metabolites. Target and dose matter. In order to be defined as a mycotoxin, a fungal substance must be toxic to vertebrates and other animals in low concentrations. Many fungi produce compounds toxic to bacteria, but these are called antibiotics (e.g. penicillin); others are dangerous only in high concentrations (e.g. ethanol), and these are not toxins either. As a general rule, mycotoxins are produced by moulds and distinct from the poisons produced by some mushrooms and other macroscopic fungi [1].

The number of people affected by mycotoxins worldwide is unknown due to scarcity of data and difficulty of detection. Moulds and mycotoxins are believed to be minor offenders compared to bacterial, viral and protozoan infections, but they are nevertheless a health hazard that should not be neglected. Mycotoxins in popular culture have gained attention mostly for trivial issues such as their very limited use for bioterrorism as dreamed by Iraqi scientists back in the 1980s or their controversial and not very convincing implication in the so-called “Sick-Building Syndrome”. Mycotoxins have even entered English fiction. Graham Greene’s novel *The Human Factor* (1978) features a character murdered when his whiskey is laced with aflatoxin – a toxicologically improbable plot. Apart from such “mycologically accomplished murderers”, mycotoxin poisoning is accidental and usually comes from consumption of contaminated food [1].

Mycotoxins cause two types of diseases, mycoses and mycotoxicoses. Mycoses are growth of fungi on animal hosts, mostly irritating but potentially life-threatening if they become invasive. Mycotoxicoses are examples of poisoning as a result of exposure (mostly dietary but sometimes respiratory or even dermal) to mycotoxins. They may be acute or chronic and generally affect more people in the developing countries where they can worsen the effects of vitamin deficiency and malnutrition [1]. Mycotoxins are absorbed in the upper parts of the GIT, but in greatly different degree that varies between more than 80% (aflatoxins) to less than 10% (fumonisins) [2]. Many mycotoxins can permeate the skin, although not, it seems, in sufficient doses to cause serious health problems [3].

The number of mycotoxins currently known varies between sources, but it is probably between 400 and 500. They are extremely diverse chemically but, unlike many bacterial toxins, are not proteins. Most of them are produced by relatively few genera of fungi. Those most hazardous to human health are briefly described below and summarised in **Table 1**.

Table 1. Most harmful mycotoxins that often contaminate human food.

Type *	Genus	Foods	Clinical Picture	Molecular Mechanisms	References
Aflatoxin B_1 (AFB_1)	***Aspergillus***	**Nuts, peanuts, maize**	**Extremely potent carcinogen, strongly linked with liver cancer; immunosuppression; stunted growth**	**Mutagenic and genotoxic effects: binds N7 of guanine; GC to TA transversions; (–) transcription, (+) oxidative stress**	[1][4][5]
Ochratoxin A (OTA)	***Aspergillus***	Cereals, coffee, figs, raisins, pork kidneys	**Nephrotoxic effects in all species tested; liver damage, immune suppression, and teratogenic effects in animals**	**(–) Phe metabolism; (–) mitochondrial ATP production; (–) tumor-suppressor gene *dmrt-1* in mice; (+) lipid peroxidation**	[5][6]
Zearalenone (ZEA)	***Fusarium***	Maize, corn, other cereals	**Reduced fertility, stillbirths in females; testicular atrophy and reduced spermatogenesis in males; hemato- and hepatoxic effects**	**ZEA-estrogen receptor complex is translocated into the nucleus which regulates the transcription of many genes**	[5][7]
Fumonisins	***Fusarium***	Maize, rice, beans, beer, soybeans	**Suppression of the immune response; pulmonary edema, esophageal cancer**	**(–) Sphingolipid synthesis; (–) mitochondrial ETC; (+) ROS generation; (+) cytotoxicity**	[1][5]
Trichothecenes	*Fusarium*, *Cephalosporium*, *Myrothecium*, *Stachybotrys*, *Trichothecium*	Grains: rice, barley, oats, maize; eggs, milk, meat	**Alimentary toxic aleukia (ATA): fever, diarrhea, nausea, vomiting, agranulocytosis, necrotic angina, bleeding; reduced serum levels of WBC and Ig in mice**	**(–) Translation; (–) mitochondrial ETC; (+) lipid peroxidation and membrane remodeling; (+) apoptosis**	[1][6][8][9]
Patulin	***Penicillium***	Apples, pears, other fruits	**Neurotoxic and immunotoxic effects reported in animals**	**As yet unknown**	[5]
Citrinin	***Penicillium, Aspergillus, Monascus***	Cereals, Italian sausages	**Nephrotoxic effects in all species tested; reproductive toxicity and chromosome aberrations in mice**	**(–) DNA and RNA synthesis; (–) microtubules assembly; (–) HSP90 multichaperone complex; (+) ROS generation**	[1]
Ergot alkaloids	***Claviceps***	**Various grasses and grains**	**Ergotism, convulsions, ataxia, gangrene, abortion**	**As yet unknown**	[1][5]

* Trichothecenes mycotoxins are classified in groups A (T-2, HT-2); B (Deoxynivalenol, DON); C (Crotocin), and D (Verrucarins, Roridin, Satratoxins). Designations: (–), inhibits; (+), stimulates; WBC, white blood cells; Ig, immunoglobulins; ROS, reactive oxygen species; ETC, electron-transport chain; Phe, Phenylalanine.

1.1. Aflatoxins

This is the most important group of mycotoxins in relation to human health. Over a dozen different aflatoxins are known, the four major ones being B_1, B_2, G_1 and G_2, classified according to their green or blue fluorescence under UV light. *Aspergillus flavus* and a few others from the same genus are the best-known producers of aflatoxins. Aflatoxin B_1 (ABF_1) is usually the major aflatoxin produced by toxigenic strains. It is one of the most potent carcinogens yet discovered, especially associated with liver cancer in chronic aflatoxicosis. Acute poisoning with aflatoxin is rare, but may be fatal [1]. The death of thirteen children in northwestern Malaysia in 1988 from acute hepatic encephalopathy and of at least 125 people (from 317 cases) in Kenya in 2004 were traced to Chinese noodles and homegrown maize, respectively, contaminated with aflatoxins [5].

1.2. Ochratoxins

Ochratoxin A (OTA) is the most prominent member of this group, the only one comparable in importance to the aflatoxins, usually produced by many *Aspergillus* and at least two *Penicillium* spp. (*P. nordicum* and *P. verrucosum*). It is often found in infected barley, oats, rye, wheat, coffee beans and other plants of commercial value. OTA is a potent nephrotoxin to all animal species, associated with porcine nephropathy in Denmark and endemic nephropathy in Balkan countries such as Bulgaria, Romania and former Yugoslavia [1]. OTA half-life in humans can be as long as 35 days, considerably longer than in mice, pigs or rats. Acute renal failure in humans has been associated with long-term exposure to ochratoxins in an agricultural setting [5][6].

1.3. Zearalenone

Produced by *Fusarium* spp. and most often found in cereals (especially maize), zearalenone (ZEA) is a structural analogue of 17b-estradiol. Widely studied in various animal models (pigs, ruminants, mice), ZEA is best-known for its strong estrogenic and anabolic effects, to a lesser extent hemato- and hepatotoxic effects. Data in humans are harder to come by and more speculative. In pregnant women, long-term consumption of foods contaminated with zearalenone presumably leads to reduced fetal weight and milk production, even changes in uterine tissue morphology have been suggested [5][7].

1.4. Fumonisins

First described and characterized in 1988, fumonisin B_1 is the most prominent and the most toxic member of this group produced by *Fusarium* spp. which grow as corn endophytes. The toxins inhibit the synthesis of sphingolipids and cause various diseases depending on the species and the dose. In humans, fumonisins are strongly associated with esophageal cancer, especially in South Africa, China and northeast Italy. Unusually for mycotoxins, most of which are soluble in organic solvents, the fumonisins are hydrophilic and therefore harder to study [1][5]. Together with deoxynivalenol, fumonisins have also been implicated in suppression of the immune response, for instance significantly decreased levels of IL-8, IL-1β, IL-6 and macrophage inflammatory protein (MIP)-1β in piglets [10].

1.5. Trichothecenes

A large family hard to classify, trichothecenes are usually divided into four groups. Groups A and B, produced by *Fusarium* spp., include all trichothecenes of major importance, namely T-2, HT-2 and deoxynivalenol (DON); groups C and D include less important members like crotocin, verrucarins and others. DON (aka vomitoxin or food refusal factor) may cause nausea, vomiting and diarrhea in farm animals if ingested in high doses. Trichothecenes are commonly found in various grains (corn, barley, rye, wheat) and strongly associated with alimentary toxic aleukia (ATA) whose acute phase is characterized by necrosis of the oral cavity, bleeding from various organs (nose, mouth, vagina) and CNS disorders. It was common in 19^{th}-century Russia and the former Soviet Union, for instance in the Orenburg district during the Second World War when a large number of people got sick from eating overwintered grain infected with *Fusarium* [1][5][8].

1.6. Patulin

Patulin was first isolated in the 1940s from *Penicilium patulum* (later renamed *P. urticae* and *P. griseofulvum*), tested as an antibiotic in the 1950s, and classified as a mycotoxin in the 1960s. Nowadays, patulin contamination most often comes from *Penicillium expansum*, the blue mould that causes soft rot of apples, pears, cherries and other fruits [1][5].

1.7. Citrinin

Originally isolated from *Penicillium citrinum*, later also from a dozen of other *Penicillium* spp. (incl. *P. camemberti* of cheese fame) and several *Aspergillus* (incl. *A. oryzae* used to make sake, miso and soy sauce), citrinin is a nephrotoxin in

all species tested, although toxic doses vary greatly. It is found in many cereals as well as in some naturally fermented sausages in Italy [1].

1.8. Ergot alkaloids

This toxic cocktail of alkaloids is found in the sclerotia of *Claviceps* spp., common pathogens on various grasses and grains, and probably known from antiquity as testified by Assyrian tablets c. 600 BC which refer to “noxious pustule in the ear of grain”. Ergotism, usually caused by eating cereals infected with *Claviceps*, has also been known since antiquity. It was a scourge in Europe during the Middle Ages when its two forms, gangrenous and convulsive, were responsible for high-mortality outbreaks; some 20,000 people are believed to have died from the disease only in the Aquitaine region in 944–945 AD. The disease is even implicated it witch trials, including the notorious Salem Witch Trials in Massachusetts in late 17th century. Though rare in humans nowadays, ergotism remains a major veterinarian problem [1][5].

2. LAB Detoxification of Mycotoxins – effectiveness, mechanisms, perspectives

Biological detoxification of food can be achieved with various bacteria degrading, metabolizing or adsorbing mycotoxins and thus effectively neutralizing them. The practice goes back to the 1960s, but the last twenty years have seen a significant increase in the number of studies [11]. On the whole, biological methods for decontamination seem more promising than chemical or physical methods such as, respectively, alkalisation and oxidation or milling and irradiation. It is easier, safer and cheaper to use the right bacteria for the purpose. Novel propositions for prevention of mycotoxin contamination include nanoparticles to modify their biosynthesis and the breeding of mould-resistant crops, but these methods have their own limitations as well [12].

Mycotoxins are highly resistant to harsh conditions, including high temperatures during cooking, which makes them particularly difficult to eliminate from contaminated foods. Crops may be affected in the field but usually are during prolonged and poor storage. No actual or precise figures about the worldwide loss due to fungal growth and mycotoxin production are available, but 25% of feed and food annually sounds like a reasonable estimation, which makes mycotoxins almost as much an economic threat as they are a health hazard [12].

Their generally regarded as safe (GRAS) status and ancient history as essential ingredients of fermented foods make LAB one of the strongest candidates for a biological weapon against mycotoxins [12]. Synthetic antifungal preservatives like benzoate, sorbate and propionate have been implicated in health issues ranging from irritability and inattentiveness to cancer and damage to the nervous system. There is a growing body of experimental evidence that LAB, in addition to being healthier, are more effective antifungal preservatives than synthetic analogues [13]. Possible disadvantages of LAB include changes in the sensory properties or the nutritional value of the foods [14]. The antifungal properties of LAB are two major and essentially different types: inhibition of fungal growth and neutralization of mycotoxins. A number of studies [15][16] have reported a broad spectrum of antifungal activity by many *Lactobacillus* spp. due to various organic acids (e.g. lactic, phenyllactic, acetic) which inhibit the fungal growth but are not involved in toxin neutralisation.

The present discussion concentrates on LAB as an antidote to mycotoxins. There is a large and steadily growing literature on the subject, further enhancing the well-documented role of LAB as probiotics. The mechanisms by which LAB exert their anti-mycotoxin action remain largely elusive. The only one studied in some detail is adsorption on the cell surface where a complex network of teichoic and lipoteichoic acids, S-layer proteins and exopolysaccharides plays a vital role in the process. The peptidoglycan layer has also been implicated in the process. However, the binding capacity is highly variable: species- and strain-specific, greatly affected by pH and temperature, and mostly reversible [15][17]. Other mechanisms such as degradation of mycotoxins or their conversion to less toxic metabolites are still waiting for proper experimental support [12]. Whatever the mechanism, LAB have been instrumental in some remarkable feats of detoxification (**Table 2**).

Table 2. Major studies of LAB-mediated mycotoxin-related detoxification.

Target Toxin	LAB Strain	Mechanism of Action	Maximum effectiveness	References
Aflatoxin B_1				
	L. amylovorus* CSCC 5197 and CSCC 5160, *Lc. rhamnosus Lc1/3	**Probable adsorption on the cell surface**	**>50% AFB_1 bound from solution, but reversibly**	**[18]**
	***Lc. rhamnosus* LBGG and LC-705**	**None proposed**	**80% removal from liquid media, very rapidly**	**[19]**

Target Toxin	LAB Strain	Mechanism of Action	Maximum effectiveness	References
	Lc. paracasei LOCK 0920, *Lev. brevis* LOCK 9044, *Lp. plantarum* LOCK 0945	None proposed	39–55% decrease, depending on the initial concentration of AFB_1	[20]
	Lactococcus lactis, *Lp. plantarum*	Low-molecular proteins involved, possibly bacteriocins	81% combined, 27–46% separately	[21]
	L. kefiri KFLM3	Toxin-binding on the cell surface	80% decrease in milk, 0% in MRS	[22]
	Lev. brevis NM101-1, *Lc. paracasei* ABRIINW.F58	Antifungal compounds caused 52–80% transcriptional inhibition of the *omt-A* gene, a key player in the biosynthesis of AFB_1	90–96% reduction of the AFB_1 production by *A. flavus* and *A. parasiticus*	[23]
	Levilactobacillus spp. 2QB383, *Lp. plantarum* 1QB147, 1QB314 and 3QB350	Toxin binding is assumed for the reduced amounts; no mechanism proposed for the reduced production	>50% reduced amount by inactivated strains in PPB *; >50% reduced production in YES broth at 25 °C	[24]
Ochratoxin A				
	Str. thermophilus T4, *L. delbrueckii* subsp. *bulgaricus* LB-51	None proposed	Complete elimination of 0.5 mg/L in milk; 36 and 26% drop with 1.0 and 1.5 mg/L	[25]
	L. bulgaricus 259/2 and 171/2	None proposed	Up to 94% detoxification, but very much strain-dependent	[26]
	Lc. rhamnosus GG, *L. acidophilus* CH-5, *L. helveticus* 8, *Lactococcus lactis* 202	Toxin binding on the cell surface is assumed, another mechanism hypothesized	60–87% decrease, rapid process but partially reversible	[27]
	L. acidophilus VM 20	Toxin-binding on the cell surface	96–97% decrease for 4 h	[28]
	P. parvulus UTAD 473	Degradation by putative peptidase	100% degradation in MRS for 7 days at 30 °C	[29]
	Lb. kefiri KFLM3	Toxin-binding on the cell surface	81% decrease in milk, 15% in MRS	[22]
	Lc. rhamnosus CECT 749, Lp. plantarum CECT 749 and CECT 288, *Lc. casei* CECT 4045, *Lc. casei* CECT 4040, *L. bulgaricus* CECT 4005	>90% degradation by proteolytic activity; very little adsorption	97–99% in MRS at pH 6.5	[30]
	Lp. plantarum 3QB361	Toxin-binding on cell surface assumed	~60% reduced amount by inactivated strain in PPB	[24]
Patulin				
	Lev. brevis 20023	Adsorption on the cell wall	65% adsorption	[31]
	Lp. plantarum ATCC 8014	Adsorption on the cell wall, proteins mediated	96% decrease in apple juice during 6 weeks of cold storage	[32]
	L. kefiranofaciens JKSP109	Adsorption on the cell wall	93% removal at pH 4.6 and 15° Brix	[33]
Deoxynivalenol				
	Lp. plantarum GT III	Adsorption assumed; metabolic degradation suggested	67% reduction by unviable cells (sterilized)	[34]

Target Toxin	LAB Strain	Mechanism of Action	Maximum effectiveness	References
	***Lc. paracasei* LHZ-1**	**Cell wall adsorption confirmed as the major mechanism**	**40.7% reduction by the cell wall fraction, only 10.5 & 8.9% by SN or cellular lysate**	[35]
Fumonisins				
	Lactococcus lactis*, *L. delbrueckii	**Toxin-binding on the cell surface**	**75% recovery from spiked maize meal after 4 days**	[36]
	***Lp. paraplantarum* CNRZ 1885, *Str. thermophilus* RAR1**	**Toxin binding was assumed; the role of peptidoglycan confirmed**	**19–37% bound FB_1, 65–76% FB_2, both after TCA treatment**	[37]
Zearalenone				
	Lactococcus lactis*, *L. delbrueckii	**Toxin binding assumed**	**68% recovery from spiked maize meal after 4 days**	[36]
	***Lp. plantarum* A1**	**Toxin-binding on the cell surface**	**99% immediately, 77% after 72 h**	[38]
	***Lb. kefiri* KFLM3**	**Toxin-binding on the cell surface**	**100% decrease in milk, 60% in MRS**	[22]
	Lactococcus lactis	**Surface adsorption assumed, interactions with surface proteins and intracellular uptake**	**90% bound in the first 20 min**	[39]
	***Lp. plantarum* 3QB361**	**Toxin-binding on the cell surface**	**70–80% amount reduction by inactivated strain in PPB**	[24]

* Abbreviations: PPB, Potassium Phosphate Buffer; YES, Yeast Extract Sucrose; MRS, De Man, Rogosa and Sharpe medium; AFB_1, aflatoxin B_1; SN, supernatant; FB_1 and FB_2, fumonisins B_1 and B_2; TCA, Trichloroacetic Acid.

2.1. LAB against Aflatoxin B1 (AFB1)

AFB_1 in grains and grain-based products, to a lesser degree its less toxic but still dangerous metabolite AFM_1 in milk and fermented milk products, remain the major health concern worldwide as far as mycotoxins are concerned. The combination of high toxicity and wide exposure makes them especially dangerous during chronic dietary intake. Since they are mostly produced by moulds in hot and humid regions, the climate change is expected to have an impact on the presence of aflatoxins in European foods [4].

Binding on the cell wall is the major mechanism by which LAB neutralise aflatoxins. Much work has been done on the subject in the last several decades, but it has brought little real understanding. On the contrary, the accumulated evidence has rather stressed the extreme dependence of the process on the LAB strain in question, the medium, and the physical conditions.

Of 20 strains of LAB and bifidobacteria tested by Peltonen et al., most efficient were two strains *Lb. amylovorus*, CSCC 5160 and CSCC 5197, and one *Lb. rhamnosus* (Lc1/3). They were able to bind more than 50% of AFB_1 from solution (5 µg/mL), 59.7, 57.8 and 54.6% respectively, within 24 hours. The binding was rapid but unstable. Only CSCC 5160 demonstrated a steady increase in the binding capacity, reaching maximum values of 73.2% at 72h. The other strain *Lb. amylovorus*, CS 5197, peaked at 48h. *Lb. rhamnosus* Lc1/3 had the strangest kinetics of all: peaked in the very beginning with the highest binding capacity of all (76.9%), but then declined to only 54.6% at 24h and never recovered for the next 48 hours. This specificity, remarkably different between strains of the same species, suggests that toxin binding capacity in *Lactobacillus* is a complex process depending on multiple factors. Moreover, the binding in this case proved to be easily reversible. Upon incubation in toxin-free solution, various amounts of AFB_1, 48.6, 30.7 and 26.5% for CSCC 5160, CSCC 5197 and Lc1/3 respectively, were dissociated from the bacteria and released back into the medium. Of the five bifidobacteria strains tested, most efficient were *Bb. lactis* CSCC 1906 and *Bb. animalis* CSCC 1941, binding 48.7 and 45.7% AFB_1. Of the three *Lactococcus* strains studied, most efficient proved to be *Lc. lactis* ssp. *cremoris* ARH74 with 41.1% binding of AFB_1 [18].

Favourable binding kinetics are a necessary but in itself not a sufficient condition for a successful anti-mycotoxin probiotic. The cell count and the type of medium are important factors that may have decisive influence.

Lb. rhamnosus LBGG and LC-705 achieved 80% removal of AFB_1 (5 mg/mL) from liquid media. The process was very rapid, reaching maximum in the very beginning and maintaining similar values for the next 72h. Strains of *Lb. gasseri*, *Lb. acidophilus* and *Lb. casei* were also tested, but their binding capacity was significantly lower and less consistent in time. Notably, however, even LBGG and LC-705 required very high cell densities, approximately $2x10^9$ CFU/mL, for effective detoxification. This makes the strains somewhat unsuitable as toxin-protecting food additives [19].

Of 11 LAB strains isolated from kefir, *Lb. kefiri* KFLM3 proved to be the most potent in eliminating AFB_1 (1 mg/mL). Toxin binding, the assumed mechanism, was reversible and very much dependent on the pH and the medium. The AFB_1 binding capacity *Lb. kefiri* KFLM3 improved from 0% in MRS to 80% in milk. The bacteria/mycotoxin complex was found to be more stable at pH 7-8 and more prone to dissociate at pH 3: 12 and 37%, respectively, of the bound AFB_1 were recovered [22]. A less extreme case of medium-dependent detoxification were some LAB strains isolated from Brazilian artisanal cheeses. They were able to reduce the AFB_1 levels much more effectively in phosphate buffer (>80% for some) compared to milk (>50% for all). The binding was time- and pH-dependent as well, on the whole much more effective close to neutral levels (6.5) than in highly acidic environment (3.0) and slightly better for 5 than for 15 min [24].

While probiotic design is difficult under such conditions, it has been attempted in specific settings. *Lb. paracasei* LOCK 0920, *Lb. brevis* LOCK 9044 and *Lb. plantarum* LOCK 0945 achieved dose-dependent detoxification of broiler feed: 55% when contaminated with a low concentration of AFB_1 (1 mg/kg) and 39% when contaminated with a high concentration of AFB_1 (5 mg/kg). These results were obtained after 6h of fermentation and remained stable 12 and 24h after adding the strains which the authors finally evaluated as a promising probiotic supplement for broiler feed [20].

An innovative study of ten LAB strains isolated from Brazilian artisanal cheeses, most notably *Levilactobacillus* spp. 3QB398, *L. plantarum* 3QB350 and *L. brevis* 2QB422, were shown to inhibit the *production* of aflatoxins B_1, B_2, G_1 and G_2 by *Aspergillus parasiticus*. The authors found that the time of inoculation with the LAB strains, simultaneously with the fungus or 24/48h later, was critical for inhibition of the aflatoxin production. Curiously enough, on the whole these LAB strains appeared to be least effective against the most important aflatoxin, AFB_1. Nevertheless, there were some notable exceptions. Three *L. plantarum* strains, 1QB147, 1QB314 & 3QB350, were able to reduce AFB_1 production with more than 50%, yet they all achieved that at different time points (0, 24, 48h) of inoculation and none of them at more than one time point. *Levilactobacillus* spp. 2QB383 was the only strain with something like 100% effectiveness: even when it was inoculated 48h after the fungus, no detectable levels of AFB_1 were observed. The mechanism of this suppressed production remains to be elucidated [24].

One of the few studies to propose a more sophisticated mechanism of LAB action against mycotoxins concluded that it may be due to transcriptional inhibition. Of 38 *Lactobacillus* species isolated from dairy products, *Lb. brevis* NM101-1 and *Lb. paracasei* ABRIINW.F58 were selected for their conventional antifungal activity (i.e. growth inhibition). This was found to be due to antifungal compounds of protein nature which remained active within a large range of temperatures and pH but lost their inhibitory effect upon treatment with proteases. Most interestingly, these antifungal compounds caused significant inhibition on transcriptional level of the *Omt-A* gene which encodes a key enzyme in the biosynthesis of AFB_1. The effect was species-dependent, more pronounced with the compounds from *Lb. brevis* which reached 80 and 64.5% inhibition in *Aspergillus flavus* and *A. parasiticus*, respectively. The antifungal compounds from *Lb. paracasei* were somewhat weaker but still reached 70 and 52% inhibition, respectively, of the *Omt-A* gene in the same two *Aspergillus* spp. [23].

Bacteriocins have also been suggested as possible anti-mycotoxin substances produced by LAB. Mixed culture of *Lb. plantarum* and *Lc. lactis* achieved 81% reduction of AFB_1 (0.05 mg/mL = 50 ppb) in MRS broth after only 6h of cultivation, and that level remained stable for another 24 hours. This was considerably better than both species separately (46% and 27%, respectively) or common food preservatives like benzoic and propionic acids (39% and 6%, respectively). The authors speculated that bacteriocins are largely responsible for the effect because they obtained their best detoxification values (90%) with a crude protein extract filtered through a 1,000-Da dialysis membrane [21].

In respect to LAB and AFB_1, it may be concluded that much has been achieved but more remains to be done. Suitable strains for effective detoxification are relatively few and need rigorous testing before they are approved as probiotics.

2.2. LAB against Ochratoxin A (OTA)

Several bacteria have been reported to degrade OTA, most notably *Phenylobacterium immobile* and *Bacillus licheniformis*. Degradation is usually detected by the presence of ochratoxin a, an essentially non-toxic product from the

hydrolysis of OTA. This does not seem to be the case with LAB. Adsorption on the cell wall again appears to be much the most predominant mechanism. Unless some degradation products, ochratoxin a or the opened lactone form of OTA, are detected, toxin-binding on the cell surface must be assumed [6]. Since OTA contains an amide bond between the ochratoxin a and the L-β-phenylalanine moieties, at least in theory it can be degraded by proteolytic enzymes. But data are scarce and inconclusive, limited to commercial proteases which are indeed capable of hydrolysing OTA.

The earliest studies turned towards some of the best characterised LAB from dairy products. Yogurt bacteria seem capable of remarkable reduction of OTA content in milk. *Str. salivarius* subsp. *thermophilus* T4 and *Lb. delbrueckii* subsp. *bulgaricus* LB-51 achieved complete elimination of 0.5 mg/L OTA after 18h of incubation; but 36 and 26% less with 1.0 and 1.5 mg/L, respectively. The strains were less effective separately, 79 and 62% for *Str*. *salivarius* and *Lb*. *delbrueckii*, respectively, at 0.5 mg/L OTA. The authors also reported a change in morphology in the lactobacilli (longer rods, thinner cell walls) at high OTA concentrations (1.0 and 1.5 mg/L) [25].

Strain-dependent detoxifying ability is very often the case here, sometimes to a perplexing degree. It is shown by *Lb. bulgaricus* 259/2 and 171/2: 94 and 28.5% reduced levels of OTA (50 ppb) after 48h incubation in MRS medium. Two strains of *Lb. acidophilus* (1A and 4A) were also compared but showed a difference of only 13.8% (46.5 vs 32.7) in their ability to reduce OTA levels [26]. Another notable illustration of strain specificity concerns four strains *Lb. delbrueckii* subsp. *bulgaricus*, J7, P7, 171_2 and SL, which showed great variability in their binding and nothing very impressive even at their best (6 to 34%) [27].

If different strains do show similar detoxifying rates – for example, *Lb. helveticus* 2A (71.9%) and *Lb. helveticus* 8 (67.1%) [26][27] – this must be regarded as sheer coincidence. Note, also, that these studies used very different OTA concentrations, 50 vs 1000 ppb. While the toxin concentration is critical to make sense of the percentage detoxification, the latter is more prominently, and misleadingly, displayed in most studies. The importance of the medium also tends to be neglected. It can be considerable, as demonstrated by *Lb. kefiri* KFLM3 which achieved 81% decreased OTA (1 mg/mL) in milk, but only 15% in MRS – a startling difference [22].

It appears that most LAB strains do not exhibit remarkable mycotoxin detoxifying abilities. Several relatively large-scale screenings persistently point out to that conclusion.

Of 29 LAB strains, *Lactobacillus* and *Lactococcus* spp., tested for their ability to remove OTA (1000 ppb) from media, only four were able to reach 60% or more: *Lb. rhamnosus* GG (87.5%), *Lb. acidophilus* CH-5 (70.5%), *Lb. helveticus* 8 (67.1%) and *Lc. lactis* 202 (59.6%). The process was relatively rapid, reaching maximum values within 15h, but partially reversible: within the next 25h almost 10% of the bound toxin returned to the medium. Based on calculations of the toxin amount in biomass at several different time points, the authors speculated about an alternative mechanism, in addition to binding, of OTA removal, but went no further than this [27].

Of 30 LAB strains, *Lactobacillus* and *Bifidobacterium* spp., only four proved able to reduce more than 50% OTA (0.5/1.0 mg/mL) for 4h. Only one, *Lb. acidophilus* VM 20, was truly remarkable: 96–97% decrease with both concentrations. However, as is usually the case, the process was heavily dependent on cell density, pH and toxin concentration. Raising the pH from 5 to 7 or lowering the cell count from 1×10^9 to 1×10^8 nearly halved the efficiency of *Lb. acidophilus* VM 20 as OTA reducer. The effect proved to have rather a high threshold of saturation. Only at 50 mg/mL OTA did the level of reduction begin to fall, and then only with 10–15% [28]. Similar or higher amount of OTA per kilogram is seldom found in contaminated foods; it has been reported only in green coffee beans, raisins and spices [6].

One of the few studies so far to concentrate on *degradation* of OTA found that four *Pediococcus parvulus* strains isolated from Douro wines achieved 89–98% degradation of OTA (1 mg/mL) in MRS medium (5 mL) after 5 days of incubation at 30°C with 10^3 CFU/mL. One strain, *P. parvulus* UTAD 473, even reached 100% degradation of OTA under these conditions; sixteen other LAB strains (mostly *Lb. plantarum* and *Oenococcus oeni*) managed only 10-20%. The rate of the process was dependent on the inoculum size (almost five times faster with 10^9 CFU/mL) and the incubation temperature (~30% slower at 37°C). The presence of ochratoxin a was confirmed by LC-MS/MS and a putative peptidase was proposed, but the authors unfortunately did not go further in that direction. Fascinatingly, however, they conducted adsorption studies with dead *P. parvulus* and concluded that only 1.3% of the OTA was actually bound to the cell wall [29].

Another study of OTA degradation compared 27 commercial LAB strains cultivated for 24h at 37°C in 10 mL MRS broth contaminated with 0.6 mg/mL OTA. The authors concluded that among the six strains that showed 97-99% total reduction of OTA at pH 6.5, hydrolysis was by far the predominant mechanism; only 2–4% were due to adsorption. Curiously, the

hydrolysis was less effective in a more acidic medium (pH 3.5). Degradation products ochratoxin a and phenylalanine were confirmed by mass spectrometry [30]. However, no protease was identified or even proposed, much less isolated and characterised.

Interestingly, a study of OTA reduction by *Lb. bulgaricus*, also tested the ability of these *Lactobacilli* to neutralize several different trichothecenes such as nivalenol (1 ppm), deoxynivalenol (1 ppm), diacetoxyscirpenol (500 ppb) and T2 toxin (500 ppb), but no effect was observed [26]. The same lack of correlation between detoxifying capacities was demonstrated for OTA and patulin by *Lactobacillus* and *Bifidobacterium* [28].

On the whole, the efficiency of LAB as OTA scavengers is considerable and reinforces their role as probiotics with anti-mycotoxin action. However, as in the case of AFB_1 detoxification, strains must be selected with great care as regards their capacity to neutralise OTA and their optimal conditions.

2.3. LAB against Patulin

In a pioneering study of patulin removal by LAB in liquid medium, Fuchs and colleagues showed that *Bb. animalis* VM 12 was capable of 80% reduction of patulin (0.5/0.1 mg/mL) for 4h in MRS. As in the case of OTA mentioned above, the process was rather less effective with lower cell densities and in a medium with higher pH [28]. In recent years, perhaps because of its easy availability on mouldy fruits, patulin has attracted some notable attention in the field of LAB detoxification.

An intriguing study with heat-inactivated LAB used methods like Fourier Transform Infrared Spectroscopy (FTIR), Zeta Potential and Contact Angle to confirm the importance of physical and chemical parameters like specific surface area, cell wall volume and N/C ratio for the binding capacity of patulin. Since C–O, OH and NH were the main functional groups involved, probably polysaccharides and/or proteins are the crucial binding molecules. Nothing more specific was established about the patulin-binding mechanism of LAB. *Lb. brevis* 20023 was found to have the highest specific surface area, greatest cell wall volume and, expectedly, highest capacity (65.02%) to adsorb patulin (4 mg/L) from aqueous solution [31].

Central composite design was used to optimise *Lb. plantarum* ATCC 8014 achieved 96% patulin removal from apple juice during 6 weeks of cold storage. The juice was artificially contaminated with 100 mg/L patulin. However, very high cell density was required (3.6×10^{11} CFU/mL) as well as the addition of prebiotic fructooligosaccharide (2.3%), ascorbic acid (213 mg/L) and citric acid (1.4 g/L). SDS-PAGE was used to confirm that S-layer proteins were involved in the adsorption of patulin. The electrophoresis showed a sharp decline in the amount of a 50-kDa fraction on the first day of incubation, which is in agreement with the kinetics of patulin decrease: almost 70% on the first day, then much slower but steady decrease until the 42nd day [32].

A recent study used LAB from Tibetan kefir grains for detoxification of apple juice and went into some detail about the adsorption mechanism. FTIR was used to establish the most important functional groups, and while the result (C–O, OH, C–H, N–O) was somewhat different than the study mentioned above [31], the authors reached the same, admittedly rather general, conclusion: proteins and polysaccharides on the cell surface must be responsible for the patulin adsorption. Of the five strains tested, *Lb. kefiranofaciens* JKSP109 was the finest patulin scavenger – 93% at 100 mg/L, but only 56% mg/L – although two other strains did almost as well. The adsorption capacity was found to depend on pH and the °Brix, the higher the better in both cases [33].

2.4. LAB against Deoxynivalenol (DON)

DON has been a somewhat unpopular research subject in the last few decades, which is surprising considering its prevalence in cereal crops. According to some studies, published and unpublished, 65% of the maize kernels harvested in France during 2004–2006 were contaminated with DON and fumonisins; another study of corn samples from several European countries found that 52 of 67 contaminated samples (78%) contained DON, and while only two of them exceeded the EU recommended values (8 mg/kg in grain and grain products), six others exceeded 1 mg/kg; concentrations from 100 to 1000 mg/kg appeared to be quite common in Europe [10][40]. A couple of recent studies have dealt with LAB as DON detractors in a somewhat illuminating way.

Altogether 16 LAB strains, eight commercially available (e.g. Lyofast LPRA, Yo-flex YC-180) and eight isolated from cereals and kefir (mostly *Lb. plantarum*), were tested for anti-fungal activity and DON reduction. Only six of them significantly inhibited the growth (agar halos bigger than 30 mm in diameter) of *Fusarium graminearum* JAPAR 2218, a confirmed DON producer and an economic scourge for grain crops worldwide. DON reduction studies were conducted with 1.5 mg/mL toxin in MRS for 4h and volume of 2 mL with average cell densities in the order of 10^{10} CFU/mL and three

types of bacteria, viable and heat-inactivated by pasteurisation (100°C, 30 min) or sterilization (121°C, 15 min). In all cases, the sterilized cells showed the best ability to reduce DON, usually 20-30% higher than that of the viable cells. There was some correlation between antifungal activity and toxin reduction, but not much. The best of the isolated strains, *Lb. plantarum* GT III (67% DON reduction), was not among the most potent fungicides (27 mm halo) [34].

Lb. paracasei LHZ-1 isolated from yogurt achieved 40.7% reduction of DON (50 mg/mL) by the cell wall fraction in PBS for 24h at 37°C. In contrast, only 10.5 and 8.9% were reduced by culture supernatant or cellular lysate, respectively. Laser scanning confocal microscopy was used to further elucidate the mechanism of DON detoxification. DON was labelled with AMCA-X SE to produce blue fluorescence and thus was obtained visual evidence that DON does form complexes with the bacterial cell wall. As in the study just mentioned (Franco, 2011), pasteurised and sterilised cells removed DON more efficiently than viable cells, only in this case the increase was only 5-6% at most. In addition to heat inactivation, the influence of several chemical agents on the DON removal rate was also tested with the same amount of cells (1 x 10^{10} CFU/mL): 10% trichloroacetic acid (15 min) and 4M HCl (2h) increased it with 2-3% compared to viable cells, while 8M urea (6h) and 20 mg/mL lysozyme (18h) decreased it with about 20–25% [41].

2.5. LAB against Fumonisins

After DON, fumonisins are the next most prominent contaminants of food and feed [40]. Not much has been done so far to combat their toxic effects with LAB, but something has nevertheless been achieved, especially in regard to the elusive mechanism of toxin-binding to the cell wall.

One study found that LAB starter culture (*Str. lactis*, *Lb. delbrueckii*) added to a maize meal could reduce the levels of fumonisin B_1 (2 mg/g meal) with almost 75% for 4 days. This fermented meal was comparatively less toxic to SNO human esophageal carcinoma cell line, but the difference was not significant. The authors perceptively note that the reduction of the toxin level may not necessarily result in reduced toxicity because the LAB fermentation does not alter the bioavailability of the toxin. Chronic complications from trace amounts of the toxin remain a potential problem [36].

Another study provided some insight into the exact components of the LAB cell wall that bind fumonisin B_1 and B_2 (FB_1, FB_2). The importance of peptidoglycan (PG) was confirmed in two different ways. Mutants with defective PG layer were found to have decreased toxin binding, which affected only FB_2, and only with 20-25%. Purified PG bound fumonisins (5 mg/mL each) in similar, but somewhat lower, degree compared to LAB (20% for FB_1, 60% for FB_2, both at 2 mg/mL PG). Mutants with defective synthesis of lipoteichoic acids showed negligible difference (5-10%) compared to the wild type, indicating that this component of the cell wall is unimportant as far as fumonisin binding is concerned. The tricarballylic acid chains of the fumonisins were confirmed to be essential for the toxin-binding, which decreased when the chains were hydrolysed. The authors also claimed that treatment with lipases and proteases had no effect on the toxin binding, and neither did the use of mutants lacking exopolysaccharides, although in both cases they did not show the data [37].

2.6. LAB against Zearalenone (ZEA)

ZEA has been reported in foods and body fluids (animal as well as human) with frequency that is nothing short of alarming [7]. As in the cases of AFB_1 and OTA, a great deal of work has been done on LAB detoxification of ZEA, but the accumulated data are often incomplete or inconsistent, if not downright contradictory, the molecular mechanisms remain elusive, and the application of LAB as ZEA-detoxifying probiotics is problematic, at best.

One promising probiotic of the future against ZEA is *Lb. plantarum* A1. This strain was shown to have potent and rapid ability to bind ZEA (20 mg/mL). The process was partially reversible, dropping from immediate 99% to only 77% after 72h of cultivation in MRS broth, but the relatively small inoculum (10^8 CFU/mL) is a point in the strain's favor [38]. Similar kinetics were obtained with *Lc. Lactis* isolated from milk products and 130 mg/mL ZEA, although in this case the process appeared to be virtually irreversible [39]. LAB starter culture (*Str. lactis*, *Lb. delbrueckii*) added to a maize meal reduced the levels of ZEA (2 mg/g meal) with 68% for 4 days; as in the case of FB_1, the decreased toxicity on the SNO cell line was not significant [36]. *Lb. kefiri* KFLM3 achieved 100% decrease of ZEA (1 mg/mL) in milk, but only 60% in MRS, yet another reminder of the importance of the medium [22]. *L. plantarum* 3QB361, isolated from Brazilian cheese and inactivated in phosphate buffer, managed to reduce ZEA (2 mg/mL) with 70-80% at pH 6.5, but five other strains (from ten tested) hardly managed 20-40% – another timely reminder, this time of species- and strain-specificity [24].

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