

REVIEW

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Emerging mycotoxins and preventive strategies related to gut microbiota changes: probiotics, prebiotics, and postbiotics – a systematic review†

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Recent research has focused on the involvement of the gut microbiota in various diseases, where probiotics, prebiotics, synbiotics, and postbiotics (PPSP) exert beneficial effects through modulation of the microbiome. This systematic review aims to provide insight into the interplay among emerging mycotoxins, gut microbiota, and PPSP. The review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. In this review, unregulated yet highly recurrent mycotoxins are classified as emerging mycotoxins. The most frequently observed mycotoxins included those from the *Fusarium* genus—enniatins ($n = 11$) and beauvericin ($n = 11$)—and the *Alternaria* genus—alternariol monomethyl ether, altertoxin, and tentoxin ($n = 10$). Among probiotics, the most studied genera were *Lactobacillus*, *Bifidobacterium*, and the yeast *Saccharomyces cerevisiae*. Inulin and cellulose were the most found prebiotics. Data on synbiotics and postbiotics are scarce. Studies have shown that both the gut microbiota and PPSP can detoxify and mitigate the harmful effects of emerging mycotoxins. PPSP not only reduced mycotoxin bioaccessibility, but also counteracted their detrimental effects by activating health-promoting pathways such as short-chain fatty acid production, genoprotection, and reduction of oxidative stress. However, both quantitative and qualitative data remain limited, indicating a need for further *in vivo* and long-term studies. The formulation of PPSP as functional foods, feeds, or nutraceuticals should be considered a preventive strategy against the toxicity of emerging mycotoxins, for which, there is no established regulatory framework.

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1. Introduction

Mycotoxins are secondary metabolites produced by various species of fungi, primarily belonging to the genera *Aspergillus*, *Penicillium*, and *Fusarium*. They are estimated to be present in up to 80% of food and feed. Animal feed contamination is particularly concerning, as in developed countries, up to 70% of cereal harvest—a primary source of mycotoxins—is utilized in the daily diet of animals. Mycotoxin regulation for feed is less restrictive than for food. These toxins pose significant public health risks due to their widespread occurrence and their toxic properties in both animals and humans. They can induce immunotoxicity, neurotoxicity, hepatotoxicity, nephrotoxicity, reproductive and developmental toxicity, and carcinogenicity.¹

Currently, the legislative framework on maximum limits on mycotoxins is established by the recently updated Commission Regulation (EU) 2023/915 of April 25, for aflatoxin B1 (AFB1),

aflatoxin B2 (AFB2), aflatoxin G1 (AFG1), aflatoxin G2 (AFG2), aflatoxin M1 (AFM1), ochratoxin A (OTA), patulin (PAT), deoxynivalenol (DON), zearalenone (ZEA), fumonisin B1 (FB1), fumonisin B2 (FB2) and citrinin (CIT), the last one being applied only in food supplements.² In addition, there are other recent recommendations for emerging or unregulated mycotoxins such as alternariol (AOH), alternariol monomethyl ether (AME), tenuazonic acid (TeA) and the trichothecenes T-2 and HT-2 toxins (T-2 and HT-2).^{3,4}

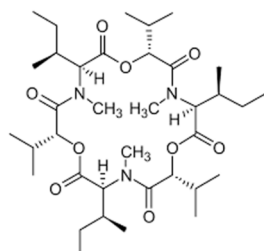
The term “emerging mycotoxins” was first introduced in 2008 and initially referred primarily to *Fusarium* metabolites such as fusaproliferin (FP), beauvericin (BEA), enniatins (ENs), and moniliformin (MON). However, more recent scientific publications have defined emerging mycotoxins as those that are neither routinely detected nor regulated by legislation, despite growing evidence of their prevalence. This work is focused on the 22 emerging mycotoxins included in Fig. 1 and 2 that have been recognized for over 20 years, continue to be widespread, and are not yet subject to regulatory oversight, even though their toxic effects are increasingly documented. The mycotoxins covered in this review are: enniatin A (ENA), enniatin (ENB), enniatin A1 (ENA1), enniatin B1 (ENB1), BEA,

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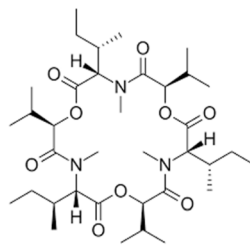
† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d4fo01705f>



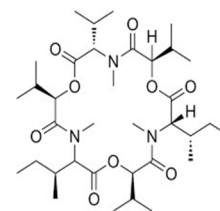
Fusarium



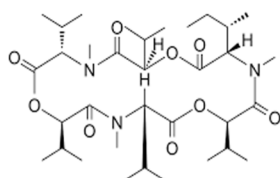
Enniatin A



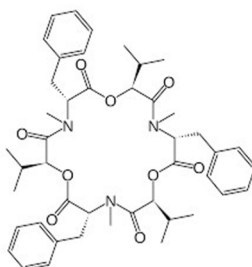
Enniatin B



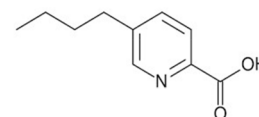
Enniatin A1



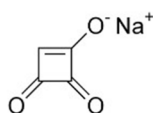
Enniatin B1



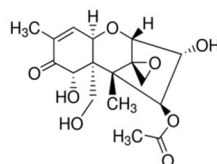
Beauvericin



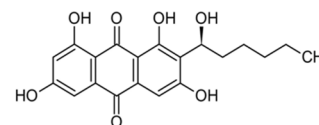
Fusaric acid



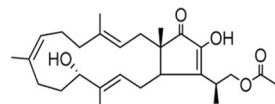
Moniliformin



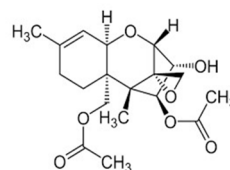
Fusarenon X



Aurofusarin



Fusaproliferin



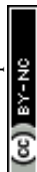
Diacetoxyscirpenol

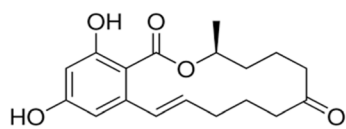
Fig. 1 Chemical structures of the emerging mycotoxins of *Fusarium* included in the bibliographic search ($n = 11$).

fusaric acid (FA), MON, fusarenon X (FX), aurofusarin (AUR), FP, diacetoxyscirpenol (DAS), altuene (ALT), AME, TeA, altertoxin (ATX), tentoxin (TEN), CIT, sterigmatocystin (STE), neosolaniol (NEO), citreoviridin, rugulosin and phomopsis.

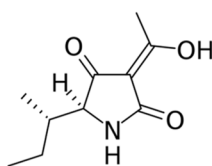
To better understand the relevance of these emerging mycotoxins, the occurrence and co-occurrence of most of them have been studied by Mihalache *et al.* (2023),⁵ who evidenced 38

different combinations in foodstuff (maize, rice, wheat, and flours). These combinations changed from binary mixtures (AME + AOH or AME + TeA) to include 12 different emerging mycotoxins (AOH + AME + TeA + TEN + ENA1 + ENB + ENB + BEA + MON + DAS + NIV + STE). Furthermore, the rising of new data regarding their presence in foodstuff has been highly relevant to enhance multiple risk assessment methodologies,

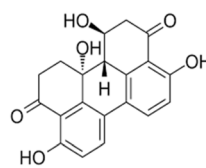


Alternaria

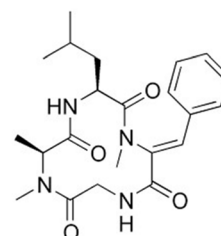
Alternariol monomethyl ether



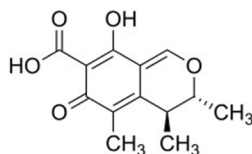
Tenuazonic acid



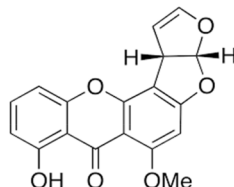
Altertoxin



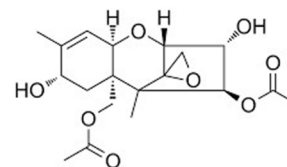
Tentoxin

Monascus

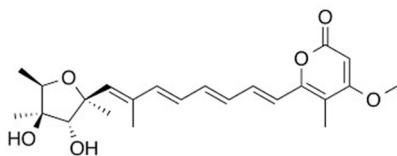
Citrinin



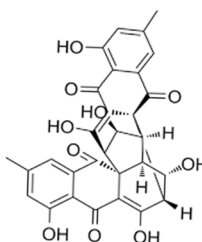
Sterigmatocystin



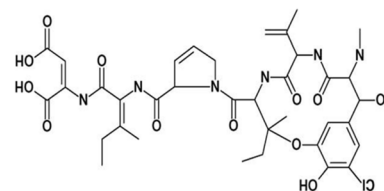
Neosolaniol

Penicillium

Citreoviridin

Diaporthe

Rugulosin



Phomopsis

Fig. 2 Chemical structures of the emerging mycotoxins of *Alternaria*, *Monascus*, *Penicillium* and *Diaporthe* included in the bibliographic search ($n = 10$).

developing future evidence-based regulations and public health.⁵ As shown in Table 1, these emerging mycotoxins are of significant concern due to their involvement in various severe health issues, including cell apoptosis, chromosomal abnormalities, acute cardiac distress, genotoxicity, hemorrhages in legs, skull, and feet, liver injury, cardiovascular collapse, chlorosis, embryotoxicity, teratogenesis, cancer, liver cirrhosis, hepatocellular carcinoma, Shoshin-kakke (acute cardiac beriberi), fatty degeneration, liver cell necrosis and cell death. Although not all emerging mycotoxins were considered in this research, the spectra covered are expected to encompass most of them.

Furthermore, climate change is anticipated to become a major environmental concern in the 21st century. Higher

temperatures combined with extreme precipitation or prolonged droughts increase the stress experienced by plants, making all plant-based foods more susceptible to fungal infection and mycotoxin contamination. *Fusarium* mycotoxins are expected to shift towards Northern Europe, while *Aspergillus* species will primarily affect southern and central Europe. Indeed, it is estimated that in Europe, over the next 50–100 years, mycotoxins will become a significant concern. This includes not only the most common mycotoxins, such as aflatoxins and OTA, but also emerging *Fusarium* mycotoxins like ENs and BEA.^{6,7}

Recent research has focused on the involvement of the gut microbiota in a considerable number of diseases such as anxiety, depression, inflammatory bowel disease, dementia,



Table 1 Emerging mycotoxins, food sources, sample, dose administration, exposure time, target organ, toxicological mechanism, damage, and references

Mycotoxin	Food sources	Sample	Dose administration	Exposure time	Target organ	Toxicological mechanism	Damage	Ref
<i>Fusarium</i>								
ENA	Wheat, barley, maize, and rice	Caco-2 and SH-SY5Y cells	0.66–66.70 $\mu\text{g mL}^{-1}$	24–48 h	Intestine, liver	Generation of ROS and mitochondrial depolarization	Apoptosis	8 and 9
ENB	Wheat, barley, maize, and rice	Caco-2 and SH-SY5Y cells	0.63–63.60 $\mu\text{g mL}^{-1}$	24–48 h	Intestine, liver	Generation of ROS and mitochondrial depolarization	Apoptosis	8 and 9
ENA1	Wheat, barley, maize, and rice	Caco-2 and SH-SY5Y cells	0.66–66.70 $\mu\text{g mL}^{-1}$	24–48 h	Intestine, liver	Generation of ROS and NADPH oxidase activation	Apoptosis	8 and 9
ENB1	Wheat, barley, maize, and rice	Caco-2 and SH-SY5Y cells	0.63–63.60 $\mu\text{g mL}^{-1}$	24–48 h	Intestine, liver	Generation of ROS and NADPH oxidase activation	Apoptosis	9
BEA	Wheat, maize, nuts, and coffee	Caco-2 cells	1.17–19.6 $\mu\text{g mL}^{-1}$	24–72 h	Intestine, liver	Generation of ROS	Apoptosis	10
FA	Wheat, barley, corn, and rice	<i>Allium cepa</i> L. bulbs and HepG2 cells	0.18–1.8 $\mu\text{g mL}^{-1}$	24–168 h	Liver	Inhibition of cytochrome oxidase, decrease in ATP synthesis, change in the electrochemical gradient in the plasma membrane and increase in electrolyte loss	Chromosomal abnormalities	11 and 12
MON	Maize, wheat	Male Sprague-Dawley rats	500 $\mu\text{g mL}^{-1}$	28 days	Heart	Pyruvate substitution and carbohydrate metabolism interference	Death and acute cardiac distress	13
FX	Wheat, barley, and cereal-based products	Male and female mice	3–15 mg per kg b.w.	48 h	Liver, kidneys, spleen	Inhibition of protein and DNA synthesis	Apoptosis	14 and 15
AUR	Maize, barley, oats, and wheat	CHO-K1 cell line	0.57–5.7 $\mu\text{g mL}^{-1}$	48 h	Intestine	Enhanced levels of p53 protein	Genotoxicity	16
FP	Maize	Chicken embryo	0.45–2.22 $\mu\text{g mL}^{-1}$	21 days	Chicken embryos	Reduction in cell viability	Hemorrhages on the surfaces of legs, skull, and feet	17 and 18
DAS	Wheat, corn, rice, and maize	Newborn chickens and Wistar rats	1–3 mg per kg bw	6–24 h	Liver, gallbladder, and small intestine	DNA synthesis and protein biosynthesis inhibitor and heterophil extracellular trap release	Liver injury	19 and 20
Apicidin	NR	HepG2 cells	0.06–62.3 $\mu\text{g mL}^{-1}$	24 h	Liver	Cytotoxicity	Cell death	21
<i>Alternaria</i>								
AME	Wheat and its derivatives, rapeseed oil and peas	Male Sprague-Dawley rats	7.35 $\mu\text{g per kg bw per day}$	28 days	Liver, kidneys, spleen	DNA adducts and production of ROS	Genotoxicity	21
TeA	Tomatoes, apples, beer, and cereal foods	Mice	238 $\mu\text{g per kg per day}$	56 days	Liver, kidneys	Generation of ROS	Cardiovascular collapse and gastrointestinal hemorrhage	22
ATX	Cereals, oilseeds, fruits, and vegetables	Male Sprague-Dawley rats	5.51 $\mu\text{g per kg w per day}$	28 days	Liver, kidneys, spleen	Nuclear factor erythroid-derived 2-like 2/antioxidant response element (Nrf2/ARE)	Genotoxicity	16 and 23



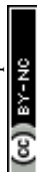
Table 1 (Contd.)

Mycotoxin	Food sources	Sample	Dose administration	Exposure time	Target organ	Toxicological mechanism	Damage	Ref
TEN	Rice	Male Sprague Dawley rats	0.4–41.45 pg mL ⁻¹	10 min	Liver	ATP synthesis reduction	Chlorosis	24 and 25
<i>Monascus</i> CIT	Cheese, sake, and soy sauce	ProTox-II in humans	105 mg per kg weight	24 h	Kidneys	Inhibition of malate dehydrogenase, glutamate dehydrogenase and ATP synthase	Genotoxic, embryotoxic, teratogenic, carcinogenic	26
<i>Aspergillus</i> STE	Maize and peanuts	HepG2 cells	0.16–2.27 µg mL ⁻¹	24–48 h	Liver, kidneys	Generation of ROS	Liver cirrhosis hepatocellular carcinoma	27
NEO	Maize, wheat, and oats	Porcine Langerhans cells	143.4 mg mL ⁻¹	24 h	Leydig cells	Decrease in the ATP content, overproduction of ROS, reduction in mitochondrial membrane potential	Cellular apoptosis	28
Emodin	NR	HepG2 cells	0.027–27 µg mL ⁻¹	24 h	Liver	Cytotoxicity	Cell death	21
<i>Penicillium</i> Citreoviridin	Maize, pecan nuts, and wheat products	Mice	1–10 mg L ⁻¹	15 days	Heart	Inhibition of mitochondrial ATPase	Shoshin-kakke (acute cardiac beriberi)	29
Rugulosin	Rice	Mice	67 mg per kg b.w.	21 days	Liver	Inhibition <i>in vivo</i> and <i>in vitro</i> of DNA replication, transcription, and reparation	Fatty degeneration and liver cell necrosis	30 and 31
Cyclopiazonic acid	Corn, peanuts and cheese	Caco-2 cells	0.014–42 ng mL ⁻¹	24–48 h	Intestine	Cytotoxicity	Cell death	33 and 34
<i>Diaporthe</i> Phomopsis	Lupins	Sheep	0.5 mg kg ⁻¹	4 days	Liver	Cell cycle arrest	Cell death	32 and 33
<i>Phoma</i> Cytochalasin B	Potatoes	EL4	2 mg mL ⁻¹	4 h	Blood	DNA fragmentation	Apoptosis	36
Cytochalasin D	Potatoes	Mice	0.3 mg kg ⁻¹	17 days	Neural tube	Teratogenicity	Fetal death	37
Cytochalasin E	Potatoes	Brine shrimp	0.01–5 µg mL ⁻¹	16–24 h	NR	Cytotoxicity	Cell death	38

Deoxyribonucleic acid (ADN), alternariol monomethyl ether (AME), adenosine triphosphate (ATP), altertoxin (ATX), aurofusarin (AUR), beauvericin (BEA), body weight (b.w.), citrinin (CIT), diacetoxyscirpenol (DAS), enniatin A (ENA), enniatin A1 (ENA1), enniatin B (ENB), enniatin B (ENB), fusaproliferin (FP), fusarenol X (FX), fusaric acid (FA), moniliformin (MON), neosolaniol (NEO), nicotinamide adenine dinucleotide phosphate oxidase (NADPH), NF-E2-related factor 2/antioxidant responsive element (Nrf2/ARE), not reported (NR), reactive oxygen species (ROS), sterigmatocystin (STE), tenuazonic acid (TeA), and tentoxin (TEN).

Parkinson's disease, diabetes, obesity, and cancer.^{39–43} To understand how important the gut microbiota is, it should be said that there are around 26 600 human genes, whereas bacterial genes are more than 4 000 000 in our body. What is more, the bacterial density in the colon is around 10¹¹–10¹² mL⁻¹, being the highest density in any ecosystem on Earth.⁴⁴ On the other hand, there are some factors, such as diet,⁴⁵ stress,⁴⁶ exercise⁴⁷ and medication,⁴⁸ having a notable impact on gut microbiota modulation. Among these factors, this systematic review focuses on emerging mycotoxins and probiotics, prebiotics, synbiotics and postbiotics (PPSP); PPSP is a term recently coined by Li *et al.* (2021).⁴⁹

PPSP has shown to regulate the abundances of some intestinal bacteria such as *Akkermansia*, *Bacteroidetes*, *Blautia*, *Bifidobacteria*, *Bifidobacterium* (B.) and gut microbial metabolites, such as lactic acid, acetate, butyrate and propionate, while suppressing the bile acid pools and decreasing the production of trimethylamine *N*-oxide and lipopolysaccharides.⁴⁹ The significance of PPSP, mainly probiotics and prebiotics, gave rise to the International Scientific Association for Probiotics and Prebiotics (ISAPP) in 2002. ISAPP is a non-profit organization that works to advance the science of probiotics, prebiotics and related substances, such as synbiotics, postbiotics and fermented foods,⁵⁰ contributing to a better under-



standing of how biotics are connected to health and disease. Regarding definitions, prebiotics are described as “a substrate that is selectively utilized by host microorganisms, conferring a health benefit”.⁵¹ Traditionally, they have been defined as “nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already resident in the colon, thus attempting to improve host health”.⁵² Certainly, probiotics are defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host”.⁵² Recently, there has been an emerging trend to investigate synbiotics and postbiotics. Synbiotics are considered “a mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host”, whereas postbiotics are described as “a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host”.^{53,54}

It has been shown that there are three main strategies for alleviating the harm caused by mycotoxins transmitted by microorganisms: (I) directly degrading mycotoxins in food, thanks to microbial pretreatment, and decreasing toxin intake; (II) by boosting probiotic colonization, the creation of bacterial-toxin complexes is suppressed, consequently inhibiting toxin absorption in the intestinal tract; and (III) by modulating the intestinal microecology with probiotics or prebiotics, enhancing the intestinal barrier, remodeling the intestinal microflora, improving intestinal toxicity, and decreasing toxin penetration.⁵⁵ Previously, the interactions between the gut microbiota and regulated mycotoxins^{6,56} and the detoxifying capacity of PPSP on some mycotoxins^{57–61} have been studied. Notwithstanding, the interplay among emerging mycotoxins, gut microbiota and PPSP still remains a framework to systemize.

The aim of this systematic review is to shed light on the potential of PPSP in mitigating the harmful effects of emerging mycotoxins. In addition, it aims to enhance our understanding of the reciprocal relationship between emerging mycotoxins and the gut microbiota, elucidating how emerging mycotoxins can influence the gut microbiota and *vice versa*. Furthermore, this review aims to contribute to future research endeavors by proposing the development of new functional foods and/or nutraceuticals as a strategy for mitigating toxicity associated with emerging mycotoxins.

2. Materials and methods

2.1 Search strategy

The scientific rigor of this systematic review and the minimization of potential bias were ensured through adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement protocol for screening titles, abstracts, and full texts.⁶² A comprehensive literature search was conducted in November–December 2023, utilizing three databases (PubMed, Web of Science, and Scopus). The search

encompassed the period from January 2012 to December 2023, aiming to include recent data on emerging mycotoxins within the context of the gut microbiota and PPSP. In addition, other relevant terms, such as “bacteria”, were considered in combination with “*in vitro*” or “*in vivo*” to capture additional relevant information.

The systematic review was conducted using the following search strings:

(1) Refined research of Pubmed, Web of Science and Scopus. Period: all years.

(“Enniatins” OR “Enniatin A” OR “Enniatin B” OR “Enniatin A1” OR “Beauvericin” OR “Fusaric acid” OR “Moniliformin” OR “Fusarenon X” OR “Aurofusarin” OR “Fusaproliferin” OR “Diacetoxyscirpenol” OR “Alternariol monomethyl ether” OR “Tenuazonic acid” OR “Alteartoxin” OR “Tentoxin” OR “Citritin” OR “Sterigmatocystin” OR “Neosolaniol” OR “Citroviridin” OR “Rugulosin” OR “Phomopsis”) AND (“bacteria”) AND (“*in vitro*” OR “*in vivo*”).

(2) Refined research of Pubmed, Web of Science and Scopus. Period: 2012–2023.

(“Enniatins” OR “Enniatin A” OR “Enniatin B” OR “Enniatin A1” OR “Beauvericin” OR “Fusaric acid” OR “Moniliformin” OR “Fusarenon X” OR “Aurofusarin” OR “Fusaproliferin” OR “Diacetoxyscirpenol” OR “Alternariol monomethyl ether” OR “Tenuazonic acid” OR “Alteartoxin” OR “Tentoxin” OR “Citritin” OR “Sterigmatocystin” OR “Neosolaniol” OR “Citroviridin” OR “Rugulosin” OR “Phomopsis”) AND (“microbiota” OR “prebiotics” OR “probiotics” OR “postbiotics”).

The criteria to include non-regulated mycotoxins in the list was based on Mihalache *et al.* (2023) and the reports issued by the Spanish Agency for Food Safety and Nutrition (AESAN).^{5,35} It is well known that there are other non-regulated metabolites not been considered when conducting the research. Notwithstanding, it was supposed that the spectra covered would be enough to include all the non-regulated mycotoxins.

2.2 Systematic review process

Among the 811 reports found through the research, 317 were retrieved from PubMed, 295 from Web of Science and 199 from Scopus. After an initial analysis, a total of 401 duplicate records were identified and removed. In addition, during the screening of titles and abstracts, another 381 records were excluded from the systematic review because of different reasons: 124 articles were discarded because they only focused on regulated mycotoxins (AFB1, OTA, fumonisins, *etc.*); 130 were rejected since they included emerging mycotoxins, but they were not assessed in combination with PPSP and 127 were discarded because they analyzed PPSP, but no emerging mycotoxins. Finally, a total of 29 were considered appropriate for inclusion in the present systematic review, assessed and classified based on: the gut microbiota, probiotics, prebiotics, synbiotics and postbiotics (Fig. 3). The selected articles are key to comprehend more deeply the role of the emerging mycotoxins in their combination with microbiota and PPSP.



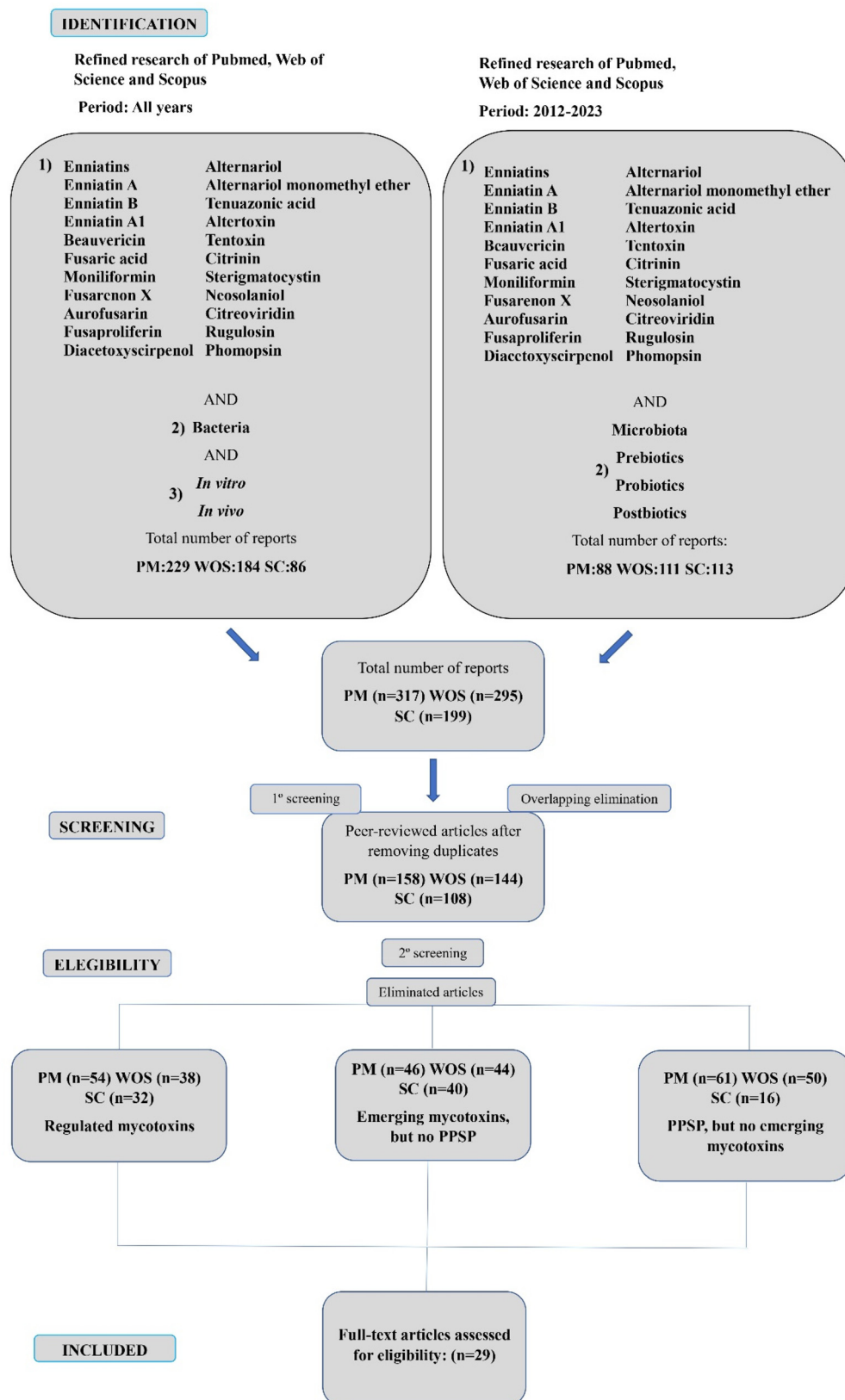


Fig. 3 Graphical representation of the total number of articles screened throughout the two strategies followed for the bibliographic research using the keyword combinations and range of years explained. Number of samples (*n*). Pubmed – PM, Scopus – SC and Web of Science – WOS.



2.3 Data conversion

All data from the studies discussed in this review were converted to $\mu\text{g kg}^{-1}$, mg kg^{-1} , ng mL^{-1} , $\mu\text{g mL}^{-1}$ or mg L^{-1} .

3. Results

3.1 Mycotoxins and the gut microbiota

The bidirectionality between regulated mycotoxins and the gut microbiota has been previously described in mice, pigs, rats, broilers, turkey, and ducks. DON has revealed to up-regulate the relative abundance of pathogens highly related to chronic intestinal diseases at different taxonomical levels (phylum, family, and genus). OTA has disrupted the structure and diversity of gut microbial communities and AFB1 to alter gut microbiota-dependent organic acid metabolism. Meanwhile, some gut microbiota strains, such as probiotics *Lactobacillus plantarum* and *Bacillus shackletonii*, have also shown mitigation effects by metabolizing, binding, and eliminating these regulated mycotoxins.^{67,56}

3.1.1 *In vitro* detoxification of emerging mycotoxins by the gut microbiota. Rumen microbiota has been found to completely detoxify NIV at normal pH after 24 h of incubation, whereas it partially degrades ENB up to 72% after 48 h. In both cases, this degradation depended on microbial activity and was influenced by pH.⁶³ Hedman and Pettersson (1997)⁶⁴ described that the capacity of cow gastrointestinal microflora to metabolize NIV has exerted the same trend. It was shown that 78–82% of anaerobically incubated NIV for 48 h was transformed into de-epoxy-NIV by gastrointestinal microbiota in the fluid rumen.⁶⁴ DAS, also produced by the genera *Fusarium*, has revealed to be deacetylated into 15-monoacetoxyscirpenol (15-MAS) and scirpentriol (SCP) as an additional metabolite by human fecal microbiota, being of utmost importance since deacetylation of mycotoxins results in reduced toxicity, for 15-MAS has been reported to be 8 times less toxic than both DAS and SCP.⁶⁵

The metabolism of *Alternaria* mycotoxins such as AOH, AME and ALT by the microbiota present in feces from three human volunteers has also been studied. As a control for the activity of the fecal microbiota, the isoflavone daidzein was incubated with the fecal cultures and was transformed to its expected metabolites. In contrast, no metabolites of AOH, AME and ALT were detected in the fecal cultures from the same volunteers, showing that the gut microbiota did not possess the capacity to metabolize these compounds. Interestingly, AOH was noted to bind non-covalently to the surface of bacteria where the type and composition of this bacterial cell surface played a notable role in the magnitude of this binding.⁶⁶ An *Alternaria alternata* extract ($5 \mu\text{g mL}^{-1}$), containing among others, AOH, AME, altertoxin-II (ATX-II), stemphytoxin III (STTX-III) and alterperyleneol (ALP), all of which are known as genotoxic, was used to assess the impact of short-term fecal incubation on the DNA-damaging effects. It was shown that microorganisms suppressed the DNA-strand-breaking potential promoted by the applied extract. Besides, in fresh fecal samples, even before anaerobic incubation, the con-

centrations of most of the tested mycotoxins (AOH, AME, ATX-II, STTX-III, and ALP) were lower in those containing microorganisms, especially fecal matter, implying that microbes were engaged in mycotoxin detoxification.⁶⁷

3.1.2 Emerging mycotoxins and the gut microbiota *in vivo*. Novak *et al.* (2021)⁶⁸ fed weaning piglets with different diets for a 14 day-period: DON, ENB + ENB1 + BEA and the four mycotoxins combined. Those piglets receiving the ENs + BEA diet were characterized by possessing a fecal microbiome with a lower diversity compared to the control group, and also compared to the ENs + BEA + DON diet. *L. amylovorus*, which is known to exhibit positive probiotic activities in weaning piglets, was reduced only in the ENs + BEA-fed group, but not in the ENs + BEA + DON one. Furthermore, the relative abundance of *L. reuteri*, which has shown to contribute to diarrhea treatment in piglets by reducing *Cryptosporidium parvum*, was increased in the ENs + BEA-fed group and, to a lesser extent, in the ENs + BEA + DON-fed group, compared to the control and the DON ones.⁶⁸

The ability of the gastrointestinal microflora of pig and chicken to metabolize NIV was studied by Hedman and Pettersson (1997).⁶⁴ On one hand, before pigs were fed with NIV, this mycotoxin was not de-epoxidated or metabolized in any way. However, when the pigs received either 2.5 or $5 \mu\text{g g}^{-1}$ NIV for one week, 97.1% of NIV in feces from five of six pigs was in the de-epoxy-NIV form, while the concentration of unaltered NIV in feces was $0.08 \mu\text{g g}^{-1}$. On the other hand, after three weeks on the NIV feed, even the pig that after one week could not metabolize NIV, was now able to form de-epoxides. In the feces from this pig, 90% of NIV was as de-epoxy-NIV, the concentration of it being NIV $0.17 \mu\text{g g}^{-1}$. Regarding chicken, it was revealed that de-epoxy-NIV was not detected in any samples of feces collected after three weeks of feeding with either 2.5 or $5 \mu\text{g g}^{-1}$ NIV. Interestingly, another unidentified metabolite of NIV was found in all feces samples, except from one bird fed with $5 \mu\text{g g}^{-1}$ NIV.⁶⁴ All the data relating emerging mycotoxins and gut microbiota are shown in Fig. 4 and Table 2. These studies were primarily conducted *in vitro* using feces from humans, pigs, and chickens, or in cow rumen fluids. The most frequently encountered emerging mycotoxins were ENs, BEA, NIV, and *Alternaria* mycotoxins (AOH, AME, ALT-XI, and ALT).

3.2 Emerging mycotoxins and probiotics

Studies *in vitro* and *in vivo* have shown the ability of probiotic cultures to bind to and/or even degrade many toxic substances, mitigating their toxicity.^{64,69} Not only has it been reported that single strain or combination of lactic acid bacteria (LAB) are very useful for removal of heavy metals (copper, lead, cadmium, chromium and arsenic) and cyanotoxins (microcystin-LR, -RR and -LF), but also regarding mycotoxins (AFB1, AFB2, AFM1, aflatoxin M2 (AFM2), AFG1, AFG2, PAT, OTA, DON, FB1 and FB2), 3-acetyldeoxynivalenol, NIV, HT-2 and T-2, ZEA and its derivatives, *etc.*, and their harmful effects.^{58,61,70}

3.2.1 Emerging mycotoxins and probiotics *in vitro*. The strains *L. johnsonii* CECT 289, *L. rhamnosus* CECT 288,



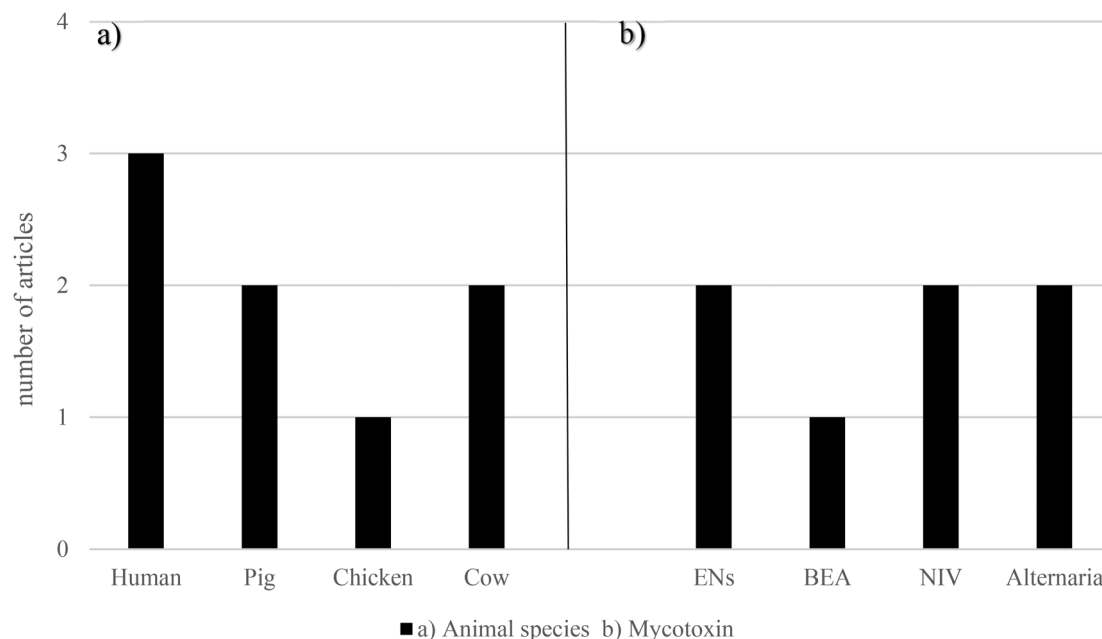


Fig. 4 Graphical bars of the gut microbiota publications ($n = 6$) according to (a) the animal species and (b) emerging mycotoxins studied. Beauvericin – BEA, enniatins – ENs and nivalenol – NIV.

L. plantarum CECT 220, *L. reuteri* CECT 725, *L. casei* CECT 475, *B. breve* CECT 4839 T, *B. adolescentis* CECT 5781 T, *B. bifidum* CECT 870 T and *B. longum* CECT 4551 have exerted to degrade different types of ENs during a simulated gastrointestinal digestion process for 4 h. It was reported that all the bacteria reduced ENA, ENA1, ENB and ENB1 mean bioaccessibility (ranging from 21.0% to 31.2%) in comparison with the control (33.4%–39.6%).⁷¹ The antimicrobial activity of *B. longum*, *B. bifidum*, *B. breve*, *B. adolescentis*, *L. rhamnosus*, *L. casei-casei*, *L. plantarum*, *L. paracasei*, *L. ruminis*, *Streptococcus thermophilus*, twenty-two strains of *Saccharomyces cerevisiae* and nine of *Bacillus subtilis* has been assessed against the minor *Fusarium* mycotoxin ENs (ENA, ENA1, ENA2, ENB, ENB1 and ENB4). The most active mycotoxins were ENA1 and ENB, mainly against *B. adolescentis* 5871 and *S. thermophilus*. Conversely, ENA1 and ENB1 have been reported to inhibit the growth of the cultivated *B. subtilis* strain with a minimum inhibitory concentration (MIC) of 16 and 8 $\mu\text{g mL}^{-1}$, respectively, and to be active against *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Enterococcus faecalis* with MIC values ranging from 2 to 8 $\mu\text{g mL}^{-1}$.⁷³ Another nine bacterial strains characteristic of the gastrointestinal tract like *B. longum*, *B. bifidum*, *B. breve*, *B. adolescentis*, *L. rhamnosus*, *L. casei-casei*, *S. thermophilus*, *L. ruminis*, *L. casei* and twenty-two strains of *S. cerevisiae* have been studied to conduct EN metabolism. The fermentation processes were carried out in a liquid medium of De Man Rogosa Sharpe under anaerobic conditions and in a potato dextrose broth, and the degradation of the EN bioactive compounds was assessed in a food system made of naturally contaminated wheat flour. The results showed ENA, ENA1, ENB and ENB1 degradation ranging from 5.2% to 99.5%. The

highest reduction was caused by *S. thermophilus* CECT 986 in ENA and the lowest by *B. breve* CECT 4839 in ENB. Furthermore, degradation products were identified for all the studied mycotoxins in both the liquid medium and the food system.⁷⁴

Apart from ENs, the interaction between BEA and probiotics is also well documented. Nine yeast strains of *S. cerevisiae* (LO9, YE-2, YE5, YE-6, YE-4, A34, A17, A42 and A08) have shown a BEA mean degradation of 86.2%. The highest degradation activity (98.8%) was due to *S. cerevisiae* LO-9, whereas the lowest (39.7%) by *S. cerevisiae* LS100.⁷⁵ The protective effect of *L. acidophilus* against BEA toxicity has been assessed on a Caco-2 cell line. It was revealed that, in the presence of BEA, *L. acidophilus* significantly increased cell viability at 12 h and 24 h.⁷⁶ *L. paracasei* CECT 277, *L. casei* CECT 4180, *L. rhamnosus* CECT 278T, *L. plantarum* CECT 220, *L. ruminis* CECT 4061T, *L. casei casei* CECT 277, *B. breve* CECT 4839T, *B. adolescentis* CECT 5781T, *B. bifidum* CECT 870T, *B. longum* CECT 4551, *Corynebacterium vitae* CECT 537, *Eubacterium crispatus* CECT 4840 and *S. cerevisiae* CECT 1324 have proven to exert a notable impact on BEA bioaccessibility. The highest bioaccessibility decrease was carried out by *B. longum* showing 45.4%, whereas the lowest data were revealed with the strain *L. rhamnosus* (27.5%).⁷⁷ Other 13 bacterial strains belonging to the gastrointestinal tract (*B. longum*, *B. bifidum*, *B. breve*, *B. adolescentis*, *L. rhamnosus*, *L. casei-casei*, *L. plantarum*, *Eubacterium crispatus*, *Salmonella fecalis*, *Salmonella thermophilus*, *L. ruminis*, *L. casei* and *L. animalis*) were fermented under anaerobic conditions in the liquid medium of De Man–Rogosa–Sharpe agar for 4 h, 12 h, 16 h, 24 h and 48 h at 37 °C. It was revealed that BEA reduction ranged from 66.5% to



Table 2 Collection of the most important characteristics of the studies found regarding emerging mycotoxins and the gut microbiota *in vitro* and *in vivo*. For each study, the studied mycotoxin, type of sample, mycotoxin dose administration, exposure time, experimental assay, results and references are described

Mycotoxin	Sample	Dose administration	Exposure time	Experimental assay	Results	Ref.
<i>In vitro</i>						
ENB	Cow rumen fluid	1 mg kg ⁻¹ ENB	0–48 h	<i>In vitro</i> rumen simulation	ENB degradation up to 72% after 48 h and NIV completely detoxified at normal pH (6.8) after 24 h of incubation. In both cases, the degradation was dependent of the microbial activity	63
NIV	Cow rumen fluid	60 mg kg ⁻¹ NIV	48 h	Anaerobic fecal culture	78–82% of incubated NIV was transformed into de-epoxy-NIV by the gastrointestinal microbiota in the fluid rumen	64
DAS	Human feces	0.7 ng mL ⁻¹	2–72 h	Fecal batch culture	Anaerobic incubation of NIV with cow rumen fluid produced de-epoxide at a high proportion DAS was deacetylated into 15-MAS and SCP as an additional metabolite by human fecal microbiota	65
AOH	Human feces	12.9 µg mL ⁻¹	72 h	Anaerobic fecal culture	AOH, AME and ALT were not metabolized by the gut bacteria. AOH bound non-covalently to the bacteria in function according to the type and composition of its surface	66
AME	Human feces	50 µg mL ⁻¹	48 h	Fecal anaerobic incubation	Microorganisms suppressed the DNA-strand-breaking potential promoted by the applied extract. AOH, AME, ATX-II, STTX-III, and ALP were lower in the samples containing microorganisms, especially fecal matter, implying that microbes were engaged in detoxification	67
ALT						
AOH						
AME						
ATX-II						
STTX-III						
ALP						

Mycotoxin	Sample	Mycotoxin dose administration	Exposure time	Experimental assay	Results	Ref.
<i>In vivo</i>						
ENB	Weaning piglets' feces	1.345 mg kg ⁻¹ (ENB)	14 days	Metagenomic analysis of the fecal microbiome	<i>L. amylovorus</i> was reduced only in the BEA-fed group, but not in the BEA + DON group	68
ENB1		1.830 mg kg ⁻¹ (ENB1)			The relative abundance of <i>L. reuteri</i> was increased in the BEA group and, to a lesser extent, in the BEA + DON group compared to the control and the DON group	
BEA		2.570–3.578 mg kg ⁻¹ (BEA)				
NIV	Pig and chicken feces	2.5–5 mg kg ⁻¹	1–3 weeks	Chemical analysis of feces	After one week, 97.1% of NIV was in the de-epoxy-NIV form in the feces from five of six pigs. After three weeks, this pig was now able to form de-epoxides (90%)	64
					No de-epoxide of NIV, but another unidentified metabolite was found in the feces from chicken fed with 2.5 or 5 µg g ⁻¹ NIV for three weeks	

Alternariol (AOH), alternariol methyl ether (AME), alterperyleneol (ALP), alterperyleneol I (ATX-I), alterperyleneol II (ATX-II), alterperyleneol III (STTX-III), alterperyleneol IV (DON), enniatin B (ENB), *Lactobacillus* (L), nivalenol (NIV), scirpentriol (SCP), stemphytoxin III (STTX-III), and 15-monoacetylscripenol (15-MAS); both SCP and 15-MAS are the products of DAS deacetylation.

3.2.2 Emerging mycotoxins and probiotics *in vivo*. To study the influence of fermentation on feed acidity and microbiological parameters, two different diets were prepared: (i) non-fermented basal feed and (ii) fermented basal feed. A fermented basal diet was characterized by including some microbial starters (*L. uvarum* LUHS245, *L. casei* LUHS210, *Pediococcus acidilactici* LUHS29 and *Pediococcus pentosaceus* LUHS183). Piglets were fed using these diets for 36 days and feces microbiota,

BEA bioaccessibility was decreased, ranging from 15.7% to 60.5%, compared to the control (93.2%), with the addition of the following prebiotics: galactomannan 5%, glucomannan high-molecular weight (HMW) 1%, glucomannan HMW 5%, glucomannan fine powder 1%, glucomannan fine powder 5%, citrus fiber 1%, citrus fiber 5%, bamboo fiber 1%, bamboo fiber 5%, carrot fiber 1%, carrot fiber 5%, pie fiber 1%, pie fiber 1%, β -glucan 1%, β -glucan 5%, xilan 1%, xilan 5%, cellulose HMW 1%, cellulose HMW 5%, cellulose medium-molecular weight (MMW) 1% and cellulose MMW 5%.⁷² BEA has also shown to be decreased by β -1,3 glucan, chitosan LMW, chitosan MMW, FOS, galactomannan, inulin, and pectin at both concentrations (1% and 5%). Each sample was contaminated, reaching a BEA concentration of both 5 and 25 mg L⁻¹.

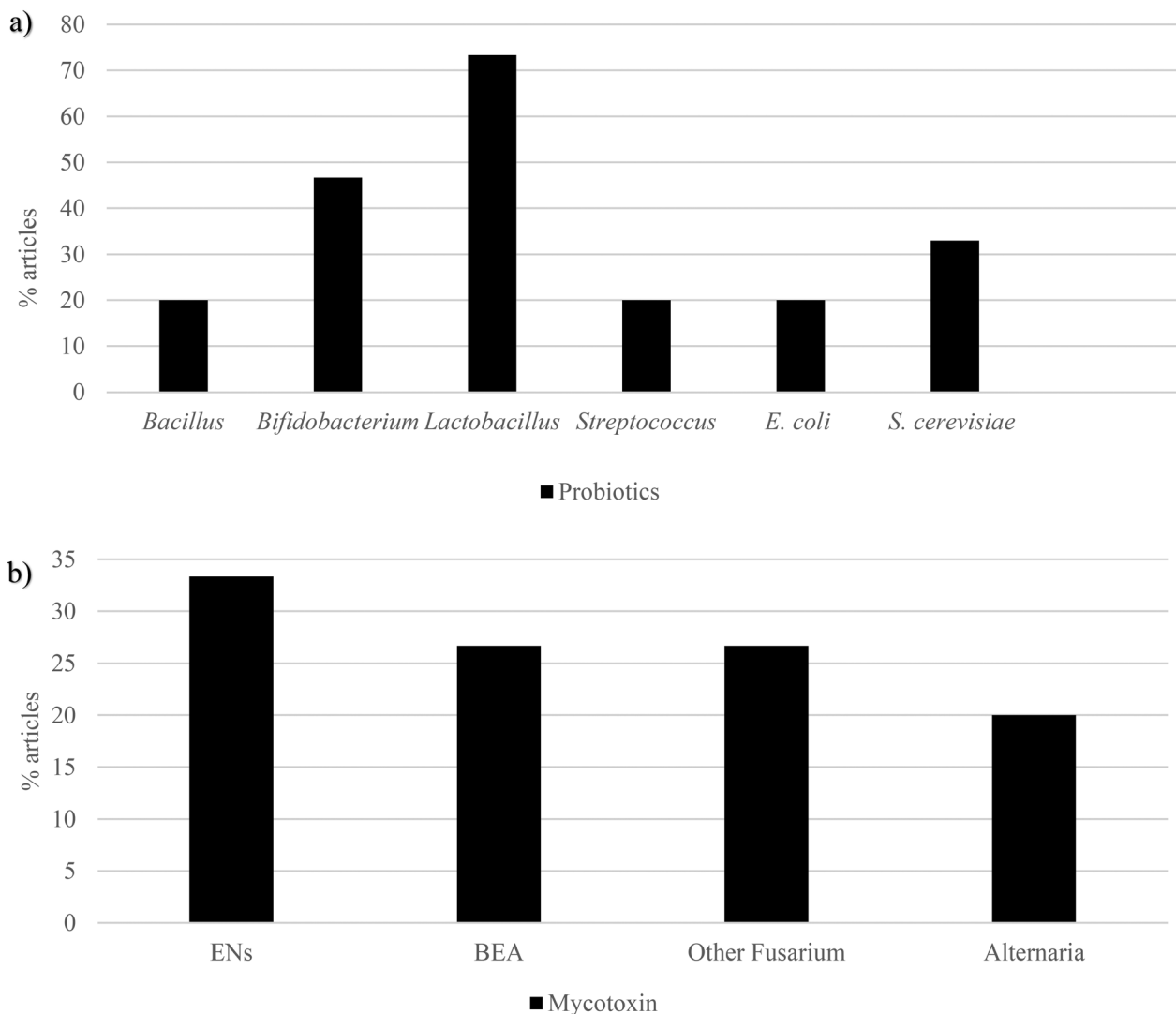


Fig. 5 Graphical bars of the probiotic publications ($n = 15$) according to the (a) microbial species and (b) the emerging mycotoxins studied. In the reports, *Bacillus*, *Bifidobacterium*, *Lactobacillus*, *Streptococcus*, *E. coli* and *S. cerevisiae* were the most recurrent probiotics, whereas enniatins, beauvericin, other *Fusarium* mycotoxins and *Alternaria* mycotoxins were the most used emerging mycotoxins. Beauvericin – BEA, enniatins – ENs, *Escherichia coli* – *E. coli* and *Saccharomyces cerevisiae* – *S. cerevisiae*.

While the mean control bioaccessibility was 92.6% and 90.0% for both BEA concentrations, respectively; when adding prebiotics, it was 13.2% and 50.4%, respectively, galactomannan being the most reducing one (5.2%).⁹³

Similar results have been obtained with *Alternaria* mycotoxins. AOH, AME, ATX-II, STTX-III, and ALP have been found to be decreased, already before anaerobic incubation, in the samples containing particulate fecal matter. These samples were supposed to be also composed of indigestible fiber fractions.⁶⁷ The antifungal effects of the volatile compound 2-phenylethyl isothiocyanate (2-PEITC) against *A. alternata* and its mycotoxins TEN, AOH, AME, and ALT were assessed. 2-PEITC is found in some vegetables and contributes to gastrointestinal health.⁹⁴ After a 2 h treatment, these four mycotoxins were extracted and detected by high performance liquid chromatography-tandem mass spectrometry (HPLC-TOF-ESI-MS) in the

mycelium of *A. alternata*. The concentrations of TEN, AOH, AME, and ALT at the MIC of 2-PEITC-treated groups were only 27%, 90%, 90%, and 88% of the corresponding control groups, respectively.⁹⁵ The anthocyanidin delphinidin (30.3 $\mu\text{g mL}^{-1}$) has exerted to strongly antagonize the genotoxic properties of ATX-II by significantly suppressing the level of DNA strand breaks by up to 75% in HT-29 colon carcinoma cells.⁸⁴ Conversely, AOH and AME degradation has been assessed after cinnamaldehyde treatment in centrifuge tubes under rotary shaking conditions (150 rpm) at 25 °C for 120 min. It was found that AOH and AME degradation rates were 16.8% and 7.3%, respectively.⁹⁶ The results are shown in Table 4.

3.4 Mycotoxins and synbiotics

The use of synbiotics has been previously proved to be effective in the removal of PAT.^{97,98} The deleterious effects of



Table 3 Collection of the most important characteristics of the studies found regarding the emerging mycotoxins and probiotics *in vitro* and *in vivo*. For each study, the studied mycotoxin, type of probiotic, mycotoxin dose administration, exposure time, experimental assay, results and references are described

Mycotoxin	Probiotic	Dose administration	Exposure time	Experimental assay	Results	Ref.
<i>In vitro</i>						
ENA	<i>L. johnsonii</i> CECT 289	<i>B. breve</i> CECT 4839 T	Not reported	4 h	Dynamic gastrointestinal <i>in vitro</i> digestion	71
ENA1	<i>L. rhamnosus</i> CECT	<i>B. adolescentis</i> CECT 5781 T				
ENB	<i>L. plantarum</i> CECT 220	<i>B. bifidum</i> CECT 870 T				
ENB1	<i>L. reuteri</i> CECT 725 <i>L. casei</i> CECT 47	<i>B. longum</i> CECT 4551				
ENA	<i>B. longum</i>	<i>L. ruminis</i>	0.2–20.000 ng per disc	24 h	Antimicrobial analyses carried out the disc-diffusion method	72
ENA1	<i>B. bifidum</i>	<i>Streptococcus thermophilus</i>				
ENA2	<i>B. breve</i>	22 strains of <i>S. cerevisiae</i>				
ENB	<i>B. adolescentis</i>	9 strains of <i>Bacillus subtilis</i> .				
ENB1	<i>L. rhamnosus</i>					
ENB4	<i>L. casei-casei</i> <i>L. plantarum</i> <i>L. paracasei</i>					
EN1	<i>Bacillus subtilis</i> 168 trpC2		2–8 µg mL ⁻¹	3 weeks	Cocultivation media	73
ENB1	<i>Staphylococcus aureus</i> ATCC 29213 <i>Streptococcus pneumoniae</i> ATCC 49619 <i>E. coli</i> ATCC 25922 <i>Staphylococcus aureus</i> 25697 <i>Enterococcus faecalis</i> UW 268 <i>Pseudomonas aeruginosa</i> B 63230					
ENA	<i>B. longum</i>	<i>Streptococcus thermophilus</i>	Not reported	48 h	<i>In vitro</i> degradation under an anaerobic atmosphere	74
ENA1	<i>B. bifidum</i>	<i>L. ruminis</i>				
ENB	<i>B. breve</i>	<i>L. casei</i>				
ENB1	<i>B. adolescentis</i>	22 strains of <i>S. cerevisiae</i>				
BEA	<i>L. rhamnosus</i> <i>L. casei-casei</i> <i>S. cerevisiae</i> LO9 <i>S. cerevisiae</i> YE-2 <i>S. cerevisiae</i> YE5 <i>S. cerevisiae</i> YE-6 <i>S. cerevisiae</i> YE-4 <i>S. cerevisiae</i> YE5	<i>S. cerevisiae</i> YE-6 <i>S. cerevisiae</i> A34 <i>S. cerevisiae</i> A17 <i>S. cerevisiae</i> A42 <i>S. cerevisiae</i> A08	5 mg L ⁻¹ ; 5 mg kg ⁻¹	48–72 h	Biological degradations under aerobic conditions in the liquid medium of PDB	75
BEA	<i>L. acidophilus</i>		0.8–15.7 µg mL ⁻¹	24–72 h	Cell viability assay	76
BEA	<i>L. paracasei</i> CECT 277 <i>L. casei</i> CECT 4180 <i>L. rhamnosus</i> CECT 278T <i>L. plantarum</i> CECT 220 <i>L. ruminis</i> CECT 4061T <i>L. casei casei</i> CECT 277 <i>B. breve</i> CECT 4839T	<i>B. adolescentis</i> CECT 5781T <i>B. bifidum</i> CECT 870T <i>B. Longum</i> CECT 4551 <i>Corynebacterium vitæruminis</i> CECT 537 <i>Eubacterium crispatus</i> CECT 4840 <i>S. cerevisinas</i> CECT 1324	5–25 mg kg ⁻¹	48 h	<i>In vitro</i> dynamic digestion model	77



Table 3 (Contd.)

Mycotoxin	Probiotic		Dose administration	Exposure time	Experimental assay	Results	Ref.
BEA	<i>B. longum</i>	<i>Eubacterium crispatus</i> , <i>Salmonella fecalis</i> and <i>Salmonella thermophilus</i>	5 mg L ⁻¹	4–48 h	Fermentations in the liquid medium of MRS	BEA reduction ranged from 66.5% to 83.1%, the highest decrease value being that caused by the strain of <i>L. casei-casei</i>	78
	<i>B. bifidum</i> <i>B. breve</i> <i>B. adolescentis</i> <i>L. rhamnosus</i> <i>L. casei-casei</i> <i>L. plantarum</i>	<i>L. ruminis</i> <i>L. casei</i> <i>L. animalis</i>					
AUR	<i>E. coli</i> (ATCC 25922)	<i>L. acidophilus</i> (DSMZ 20079)	1.1–146.1 µg mL ⁻¹	6 h	Fast digital time-lapse microscopic method	The most potent compound was AUR against <i>L. acidophilus</i> . Meanwhile, BEA, ENs and FA were characterized by having weak antibiotic effects	79
ENs	<i>Salmonella enterica</i> serovar <i>typhimurium</i> 3389-1 (DT12)	<i>L. acidophilus</i> (20079)	1.4–174.6 µg mL ⁻¹				
BEA	<i>Staphylococcus aureus</i> (ATCC 29213)	<i>L. salivarius</i> (20555)	1.6–200.7 µg mL ⁻¹				
FA		<i>L. sobrius</i> (16698)	0.2–29.7 µg mL ⁻¹				
		<i>B. longum</i> subsp. <i>longum</i> Reuter (20219) <i>B. breve</i> (20213)					
FA	<i>Burkholderia ambifaria</i> T16		0.06 mg mL ⁻¹	72 h	<i>In vitro</i> detoxification	<i>Burkholderia ambifaria</i> has been shown to inhibit the growth of several <i>Fusarium</i> species and possess the unique ability to use the mycotoxin FA as the sole C, N and energy sources, as well as the capacity to detoxify FA in barley seedlings	80
DAS	<i>L. acidophilus</i> 1A <i>L. acidophilus</i> 4A <i>L. helveticus</i> 2A <i>L. bulgaricus</i> 3A	<i>L. bulgaricus</i> 5A <i>Bacillus licheniformis</i> <i>Bacillus subtilis</i> <i>S. cerevisiae</i>	0.5 µg mL ⁻¹	48 h	Biodegradation <i>in vitro</i> in agar plates	DAS appeared to possess an inhibitory effect on the growth of almost all <i>Lactobacillus</i> and <i>Bacillus</i> strains, whereas no effect was observed on yeast strains	81
DAS	<i>Akkermansia muciniphila</i> DSM 22959 <i>B. adolescentis</i> DSM 20083 <i>Bacteroides thetaiotaomicron</i> DSM 2079 <i>Prevotella copri</i> DSM 18205 <i>Faecalitalea cylindroides</i> T2-87 <i>Anaerobutyricum hallii</i> DSM 3353 <i>Anaerostipes hadrus</i> SSC/2 <i>Blautia obeum</i> A2-162	<i>Butyrivibrio fibrisolvens</i> 16/4 <i>Coprococcus</i> sp. ART55/1 <i>Eubacterium rectale</i> DSM 17629 (A1-86) <i>Roseburia intestinalis</i> L1-82 <i>Lactiplantibacillus plantarum</i> NCIMB 7220 <i>Faecalibacterium prausnitzii</i> A2-165 <i>Enterococcus mundtii</i> DSM 4838	0.7 ng mL ⁻¹	0–48 h	Anaerobic incubation	The human microbiome characteristic bacteria <i>Prevotella copri</i> revealed to deacetylate 51.3% of DAS to 15-MAS after 48 h	82
TeA	<i>L. brevis</i> 20023 (LAB-20023)		0.5 µg mL ⁻¹	12 h	Adsorption	<i>L. brevis</i> 20023 (LAB-20023) cells have revealed to adsorb TeA from 12.5% to 90.1%	83



Table 3 (Contd.)

Mycotoxin	Probiotic		Dose administration	Exposure time	Experimental assay	Results	Ref.
AOH	<i>Bacteroides caccae</i>	<i>Alistipes finegoldii</i>	0.5–50 $\mu\text{g mL}^{-1}$	24 h	Absorption assay	Both Gram types were able to adsorb AOH, AME, and AST. Gram-negative bacteria showed higher adsorptive capacities. This tendency was not observed for neither ATX-I nor ALP	84
AME	<i>Bacteroides eggerthii</i>	<i>Alistipes timonensis</i>					
AST	<i>Bacteroides thetaiotaomicron</i>	<i>Ruminococcus bicirculans</i>					
ATX-I	<i>Bacteroides vulgatus</i>	<i>Akkermansia muciniphila</i>					
ALP	<i>Parabacteroides distasonis</i>	<i>L. hominis</i>					
	<i>E. coli</i>	<i>B. Longum</i>					
	<i>Clostridium innocuum</i> (CI)	<i>B. sp.</i>					

Mycotoxin	Probiotic	Mycotoxin dose administration	Exposure time	Experimental assay	Results	Ref.
<i>In vivo</i>						
AME	<i>L. uvarum</i> LUHS245	10.1–17.06 $\mu\text{g kg}^{-1}$	36 days	Fermentation/ biotransformation	AME and ALT were found in 61-day-old control piglets' feces and in fermented feed samples. However, AME was not found in probiotic-treated piglets' feces	85
ALT	<i>L. casei</i> LUHS210					
	<i>Pentosaceus acidilactici</i> LUHS29					
	<i>Pediococcus pentosaceus</i> LUHS183					

Alternariol methyl ether (AME), alterperyleneol (ALP), altertoxin I (ATX-I), alterperyleneol (ALP), altuene (ALT), altersetin (AST), aurofusarin (AUR), beauvericin (BEA), *Bifidobacterium* (B), diacetoxyscirpenol (DAS), enniatin A (ENA), enniatin A1 (ENA1), enniatin A2 (ENA2), enniatin B (ENB), enniatin B1 (ENB), enniatin B4 (ENB4), enniatins (ENS), *Escherichia coli* (*E. coli*), fusaric acid (FA), lactic acid bacteria (LAB), *Lactobacillus* (*L.*), minimal inhibitory concentrations (MICs), De Man–Rogosa–Sharpe agar (MRS), potato dextrose broth (PDB), *Saccharomyces* (*S.*), and tenuazonic acid (TeA).

OTA have also been reversed by using beneficial synbiotics possessing the ability to reduce the number of potential pathogens in the digestive tract and by increasing the activity of α -glucosidase and α -galactosidase, while decreasing the activity of potentially harmful fecal enzymes (β -glucosidase, β -galactosidase and β -glucuronidase).^{60,99}

3.4.1 Emerging mycotoxins and synbiotics. The bioaccessibility of ENs (ENA, ENA1, ENB, and ENB1) and BEA was analyzed by using an *in vitro* static and dynamic simulated gastrointestinal digestion system, imitating the digestive physiological conditions until the colonic compartment. Inulin and FOS at two concentrations (1% and 5%) were first added, and afterwards, the colonic microbial fermentation was carried out by using *L. paracasei* CECT 277, *L. casei* CECT 4180, *L. rhamnosus* CECT 278T, *L. plantarum* CECT 220, *L. ruminis* CECT 4061T, *L. casei casei* CECT 277, *B. breve* CECT 4839T, *B. adolescentis* CECT 5781T, *B. bifidum* CECT 870T, *B. longum* CECT 4551, *Corynebacterium vitaeruminis* CECT 537, *Eubacterium crispatus* CECT 4840 and *S. cerevisiae* CECT 1324. The bioaccessibility of EN and BEA was shown to be higher in the synbiotic prebiotic static model (6.2%–44.9% and 46.7%–61.1%, respectively) than that found in the dynamic one (23.0%–68.9% and 76.2–91.0%, respectively).⁹² Similar results have been revealed in Meca *et al.* (2012),⁹³ where the fibers β -1,3 glucan, chitosan LMW, chitosan MMW, FOS, galactomannan, inulin and pectin (1% and 5%) were combined with the bacteria *L. animalis*

CECT 4060T, *L. casei* CECT 4180, *L. casei rhamnosus* CECT 278T, *L. plantarum* CECT 220, *L. ruminis* CECT 4061T, *L. casei-casei* CECT 277, *B. breve* CECT 4839T, *B. adolescentis* CECT 5781T, *B. bifidum* CECT 870T, *Corynebacterium vitaeruminis* CECT 537, *Streptococcus faecalis* CECT 407, *Eubacterium crispatus* CECT 4840, and *S. cerevisiae* CECT 1324. *In vitro* mean bioaccessibility values of BEA (at both experimental concentrations: 5 and 25 mg L^{-1}) by using synbiotics were 12.9% and 42.4%, respectively – 5.3 and 28.2-fold higher in comparison with the data evidenced with the prebiotic sample treated with duodenal digestion.⁹³

3.5 Mycotoxins and postbiotics

Postbiotics are considered to have positive effects on human health.⁵⁰ Yeast cell wall extract (YCWE) and a post-biotic yeast cell wall-based blend (PYCW) have revealed to reduce the adverse effects related to serum biochemistry, liver function, immune response, altered cecal short chain fatty acids (SCFAs), goblet cell counts and architecture of the intestinal villi. These results were found studying commercial broilers fed with a diet containing DON, T-2 and ZEA at 3.0 mg kg^{-1} , 104 $\mu\text{g kg}^{-1}$ and 79 $\mu\text{g kg}^{-1}$, respectively.⁵⁷ Some characteristic bacterial enzymes, which isolated are considered postbiotics, have exerted to remove AFB1, OTA, DON and ZEA.⁶³ Butyrate, one of the most studied gut microbiota metabolites, has shown to reverse the alterations caused by DON by blocking



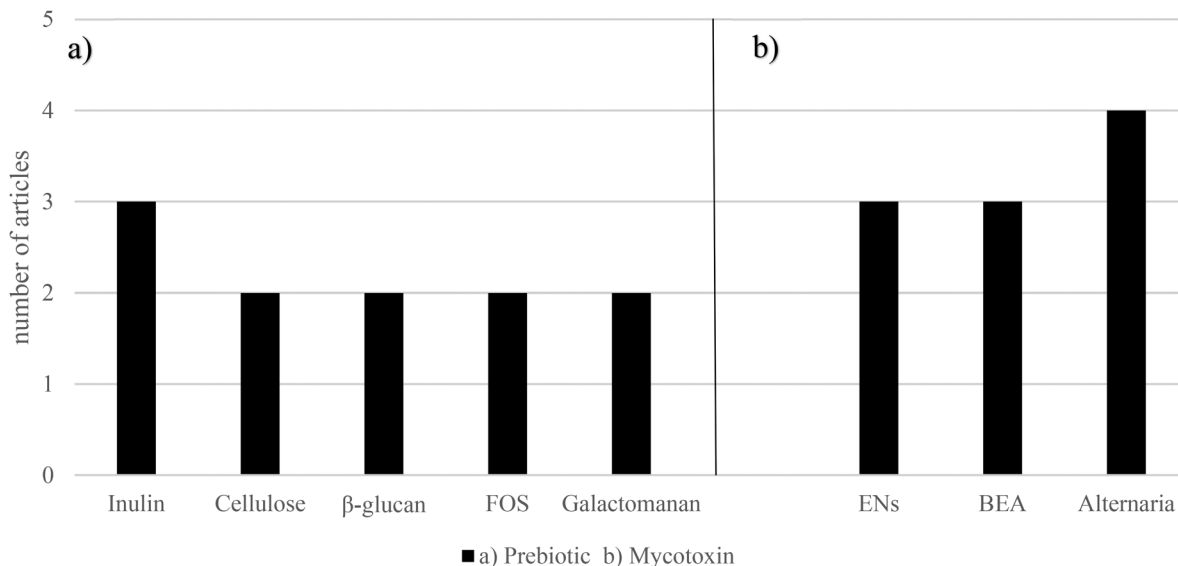


Fig. 6 Graphical bars of the prebiotics ($n = 9$) according to (a) the prebiotic type and (b) the emerging mycotoxins studied. Beauvericin – BEA, enniatins – ENs and fructooligosaccharides – FOS. In the studies, inulin, cellulose, β -glucan, FOS and galactomannan were the most used prebiotics, whereas ENs, BEA and *Alternaria* mycotoxins were the most recurrent emerging mycotoxins.

some genes involved in reactive oxygen species and tumor necrosis factor alpha mediated pathways.¹⁰⁰ Likewise, AFB1 and ZEA have been reported to reduce the content of SCFAs (butyrate, propionate and acetate).^{101,102}

3.5.1 Emerging mycotoxins and postbiotics. The utilization of postbiotics (PYCW) for addressing emerging mycotoxins was first documented in Xu *et al.* (2023).¹⁰³ In contrast to inorganic clay-based adsorbents characterized by presenting some limitations, such as the possible contamination with other detrimental compounds (dioxins, polychlorinated biphenyls, and heavy metals), organic adsorbents such as PYCW have shown to be more efficient and safe product substitutes.¹⁰⁴ In this study, an absorption bioassay was conducted exposing BEA (0.5, 2, 5, 20, 40 and 63 $\mu\text{g mL}^{-1}$) and CIT (0.5, 1, 10, 40, 50 and 68 $\mu\text{g mL}^{-1}$) to PYCW at different concentrations for 2 h. The results showed that PYCW presented an overall mean adsorption efficiency of 70.1% for BEA and 35.1% for CIT.¹⁰³

4 Discussion

The interactions along the gut are very complex due to the quantity of factors, which play a notable role in its physiology, so that there are times where it is so likely not to know completely which specific pathways or molecules are the consequence of a particular fact. However, there are some established correlations which help us to better understand how biological systems work. One of these strong correlations is the preventive role of PPSP and the gut microbiota in disease and its health-promotion effects.⁴⁹ As has already been said,⁶² PPSP and the gut microbiota possess the capacity to bind and metabolize a vast quantity of substances entering the gastrointestinal tract. Therefore, despite theoretically reducing ben-

eficial compounds, PPSP can also decrease the exposure to detrimental ones, such as toxins, including emerging mycotoxins.

As presented, European regulations only encompass a small set of mycotoxins (AFB1, AFB2, AFG1, AFG2, AFM1, OTA, PAT, DON, ZEA, FB1, FB2, CIT, AOH, AME, TeA, T-2 and HT-2 and ergoalkaloids).² Due to their regulation, these mycotoxins tend to be more studied – also including their interactions with the gut microbiota and PSPP. In fact, studies show that studied mycotoxins disrupt the gut microbiota, while concomitant intake of PSPP mitigates the effects of the mycotoxins and contributes to maintain gut microbiota homeostasis.^{56,58,90,99,101} Although similar trends are expected with unregulated mycotoxins, it has to be carried out as a one-on-one mycotoxin analysis, since every mycotoxin possesses a specific chemical structure and a different response in the environment where it is located.⁶² Actually, there are some 400 known mycotoxins, so the vast majority of them are not still regulated and need a more profound comprehension.¹ Furthermore, it should not be forgotten that mycotoxins tend to be found in combinations, so the most common mixtures found in food and feed are the ones interesting to be tested.

4.1 Emerging mycotoxins and the gut microbiota

Regarding the interaction between the gut microbiota and emerging mycotoxins, studies have revealed a clear tendency: the gut microbiota contributes to emerging mycotoxin detoxification through binding and/or metabolism^{63–65,67} and emerging mycotoxins alter the gut microbiota composition.⁶⁸ Despite being the trend confirmed by these studies, the difficulty stems from the heterogeneity of the analyzed samples. The microbiota exhibits significant variability, with the microbiome differing by species. In humans, microbiota changes are influenced by factors such as the level of urbaniz-



Table 4 Collection of the most important characteristics of the studies found concerning the emerging mycotoxins and prebiotics *in vitro*. For each study, the studied mycotoxin, type of prebiotic, mycotoxin dose administration, exposure time, experimental assay, results and references are described

Mycotoxin	Prebiotic		Dose administration	Exposure time	Experimental assay	Results	Ref.
<i>In vitro</i> ENA ENA1 ENB ENB1	Inulin (1.5%–10%)		1.02–2.04 mg mL ^{−1}	8 h	<i>In vitro</i> digestion model	ENA, ENA1, ENB and ENB1 bioaccessibility reduction in a dose-dependent manner at an inulin concentration ranging from 1.5% to 10%	91
ENA ENA1 ENB ENB1 BEA ENA ENA1 ENB ENB1 BEA BEA	Cellulose (1% and 5%)		Not reported	4 h	<i>In vitro</i> digestion model	Cellulose (1% and 5%) decreased ENA, ENA1, ENB and ENB1 bioaccessibility a mean of 26.9% and 44.7%, respectively BEA bioaccessibility reduction ranged from 60% to 80%	71
ENA ENA1 ENB ENB1 BEA ENA ENA1 ENB ENB1 BEA BEA	Inulin and FOS (1% and 5%)		Not reported	4 h	Static gastrointestinal <i>in vitro</i> digestion model	Highest reductions carried out when adding enriched inulin 5% (5.7%) and FOS 5% (3.9%) for ENA and ENA1, respectively	92
BEA	Galactomannan 1–5% Glucomannan HMW 1%–5% Glucomannan FP 1%–5% Citrus fiber 1%–5% Bamboo fiber 1%–5% Carrot fiber 1%–5%	Pie fiber 1%–5% β-Glucan 1%–5% Xilan 1–5% Cellulose HMW 1–5% Cellulose MMW 1–5%	5–25 mg kg ^{−1}	52 h	<i>In vitro</i> digestion model	BEA bioaccessibility reduction ranging from 15.7% to 60.5% comparing to control (93.2%)	77
BEA	β-1,3 glucan Chitosan LMW Chitosan MMW FOS	Galactomannan Inulin Pectin (All 1% and 5%)	5 mg kg ^{−1}	52 h	<i>In vitro</i> digestion model	BEA mean bioaccessibility decrease when adding prebiotics (13.2% and 50.4%, respectively for 1% ad 5%), galactomannan being the most reducing one (5.2%)	94
AOH AME ATX-II STTX-III ALP TEN AOH AME ALT	Particulate fecal matter supposed to be composed also by indigestible fiber fractions		50 µg mL ^{−1}	48 h	Fecal incubation <i>in vitro</i>	AOH, AME, ATX-II, STTX-III, and ALP reduction by samples supposed to be also composed of indigestible fiber fractions	67
	2-PEITC		0.1–1.38 mg kg ^{−1}	2 h	Qualitative analysis performed using a mass spectrometer after incubation for the MIC	TEN, AOH, AME, and ALT concentrations of 2-PEITC-treated groups were only 27%, 90%, 90%, and 88% of the corresponding control groups, respectively	95
ATX-II	Delphinidin		0.35 µg mL ^{−1}	24 h	Coupled SRB/WST-1 cytotoxicity assays	ATX-II genotoxic properties were antagonized by delphinidin (30.3 µg mL ^{−1}) by significantly suppressing the level of DNA strand breaks by up to 75% in HT-29 colon carcinoma cells	89
AOH AME	Cinnamaldehyde		0.81–0.82 µg mL ^{−1}	2 h	Degradation assay	AOH and AME degradation rate was 16.8% and 7.3%, respectively, after 120 min of cinnamaldehyde treatment	96

Alternariol (AOH), alternariol monomethyl ether (AME), alterperyleneol (ALP), altertoxin II (ATX-II), altuene (ALT), beauvericin (BEA), enniatin A (ENA), enniatin A1 (ENA1), enniatin B (ENB), enniatin B1 (ENB), fructooligosaccharides (FOS), high-molecular weight (HMW), low-molecular weight (LMW), medium-molecular weight (MMW), minimum inhibitory concentration (MIC), sulforhodamine B/water-soluble tetrazolium salt (SRB/WST-1), tentoxin (TEN), 2-phenylethyl isothiocyanate (2-PEITC), and stemphyliotoxin III (STTX-III).



ation of the location and even the time of day within the same individual.^{105–107} For example, rumen microbiome is characterized by possessing many enzymes involved in the *de novo* synthesis of vitamin B12.¹⁰⁸

According to experimental feasibility, it has been shown that gut microbiota samples are obtained from feces in most of the experiments, since the fecal microbiota is more accessible than the colon one. Interestingly, it has been revealed that colon microbiota has a different profile than the fecal one, the microbiome in the large intestine being much more diverse than those of the small intestine and feces. For instance, while in the large intestine there were 4080 operational taxonomic units, in the feces only 443 were found.¹⁰⁹ Indeed, bacterial biomass also changes along the gastrointestinal tract and the feces: duodenum (10^3 bacteria per g), jejunum (10^4 g⁻¹), ileum (10^7 g⁻¹), colon (10^{12} g⁻¹) and feces (5^{10} g⁻¹).^{110,111} In addition, short-term trials are likely to hide that long-term mycotoxin exposure may lead to the development of the ability to degrade these mycotoxins despite being unable to do it in the first moment.⁶⁴

There are other limitations that should be highlighted. Although in Debevere *et al.* (2020)⁶³ the incubation time (48 h) was in line with other experiments studying mycotoxin degradation *in vitro*, it is considerably longer than the *in vivo* retention time of the digesta in the rumen, implying that under normal physiological conditions the results would be different. Despite Crudo *et al.* (2020)⁶⁷ having shown that AOH, AME, ATX-II, STTX-III and ALP were lower in the samples containing microorganisms than in those without them, it should be noted that the sample size was very small ($n = 4$). In this study, all donors shared some characteristics: they were healthy omnivorous volunteers (two males and two females) ranging from 26 to 34 years old and with a normal body mass index ($18.5\text{--}24.9$ kg m⁻²), none of them had been treated with antibiotics, probiotics, and prebiotics for the previous three months and they did not present previous intestinal diseases. However, the entire diet, playing a notable role in gut metabolism and in the interactions with mycotoxins, was not considered. Moreover, as mentioned in the same article, there are other limitations such as the short-term trial (3 h) and the fact that the growth media used might alter the initial microbial composition of the feces, contributing to the growth of some microorganisms at the expense of others. Conversely, in Novak *et al.* (2021),⁶⁸ only the mycotoxins ENB, ENB1, BEA and DON were assessed in weaning piglets' feces in contrast to the control. It was shown that *L. amylovorus* and *L. reuteri*, both beneficial microbes, were up-regulated and down-regulated, respectively, when adding BEA in comparison with DON and the control. Furthermore, the combination of ENs and BEA increased the total protein synthesis, but the addition of DON had an inhibitory effect.⁶⁸ Although it is important to know the interactions among these four mycotoxins, the real conditions are more complex, since a meal may contain a variety of contaminants, so the results under normal conditions are so likely to differ from these ones. While microbes could metabolize emerging mycotoxins, these toxins can also influence the composition of the microbiome, creating a potential

double-edged sword scenario. In addition, it is important to consider the varying doses of emerging mycotoxins used in experiments, ranging from nanograms to milligrams.

Viewing mycotoxins as toxic compounds or as potential drugs is indeed a question that arises. On the one hand, they can reduce beneficial microorganisms, such as *Lactobacillus*, *S. cerevisiae* and *Bacillus*,^{72,73,79,81} whose depletion is generally connected to disease promotion.¹¹² On the other hand, they can play a role as antibiotics by eliminating microorganisms involved in diseases.^{112–116} For instance, AOH and AME have exerted to be promising inhibitors of glycogen-synthase-kinase 3, being an important target in drug discovery. In fact, this enzyme has revealed to participate in signaling pathways of type 2 diabetes, cancer, neurological disorders, and other diseases.¹¹⁷ In addition, ergotamine with its α -adrenoreceptor-blocking mode of action has also been used for acute migraine treatments for over 50 years.¹¹⁸ Further investigation is needed in the field to clarify the results and assess the real implications of these emerging mycotoxins towards health and diseases, also taking into consideration that the dose and the type of mycotoxin may be decisive in the health or disease-promoting outcomes.

4.2 Emerging mycotoxins and probiotics

The bidirectional fluxes between probiotics and emerging mycotoxins have been widely confirmed. A vast quantity of probiotics (*Lactobacillus*, *Bifidobacterium* and *S. cerevisiae*) has shown to reduce emerging mycotoxins' bioaccessibility (ENs, BEA and *Alternaria*).^{74–78,92,93} At the same time, emerging mycotoxins have exerted to alter probiotic compositions (*B. subtilis* and *Staphylococcus aureus*).^{72,73,79,81} This bioaccessibility decrease may be due to the bacterial mycotoxin binding capacity^{83,84} and/or their ability to contribute to detoxification by originating derivatives characterized by possessing less toxicity.^{82,83} However, in most of these studies, probiotics are not assessed in combination, but one by one and using *in vitro* conditions. Only Vadopalas *et al.* (2020)⁸⁵ assessed probiotics' effects on emerging mycotoxins under *in vivo* conditions. In this study, not only did the addition of some microbial starters modified some blood parameters, but also contributed to modulate the gut microbiota and detoxify AME. Despite these beneficial effects, it should be noted that the experiment only lasted two months and the piglets' organs were not fully mature. Combining probiotics and working *in vivo* would be a more realistic approach to the human environment, since there are a lot of microorganisms that form a part of the gut microbiota.¹¹⁹ What is more, it is very well documented that the interplay along the gut concerns not only different bacteria, but also fungi, archaea, viruses, and helminths.¹²⁰

4.3 Emerging mycotoxins and prebiotics

It has been clearly shown that prebiotics reduce emerging mycotoxin bioaccessibility. Although the term prebiotic is very vast, the collected data cover a high quantity of these types of compounds at a different concentration.^{67,71,77,91–93,95,96} As in the probiotic case, there are two mechanisms explaining this reduction. The first one is the capacity of prebiotics to bind



emerging mycotoxins, and the second one is the ability to metabolize them, and it is very likely to have both processes working at the same time. However, most studies do not consider an analysis of secondary metabolites of emerging mycotoxins, so this metabolism cannot be fully confirmed. Regarding mycotoxin reduction, if the metabolites have not been degraded, it is assumed that they have bound to the structures of the prebiotics, although they are also subject to metabolism anyway. Conversely, apart from reducing bioaccessibility, prebiotics can also directly suppress the detrimental effects of mycotoxins. As it is shown in Aichinger *et al.* (2018), the anthocyanidin delphinidin blocks significantly ATX-II genotoxic properties by suppressing the level of DNA strand breaks.⁸⁹ The action of these prebiotics may derive from blocking the mycotoxin, preventing its action or from having a beneficial agonist impact on some physiological pathways. Furthermore, it should also be noted that in all these experiments, prebiotics are evaluated only one by one. The reality of the human diet includes a wide combination of them, so more research needs to be carried out taking this complexity into account.

4.4 Emerging mycotoxins, synbiotics and postbiotics

The role of synbiotics in the modulation of emerging mycotoxins has been assessed only in two studies.^{92,93} In both, the results showed that the addition of synbiotics increased mycotoxin bioaccessibility when compared to prebiotics. It has been hypothesized that probiotics degraded prebiotics, so that the binding ability of the last ones was lost. Although it may be possible, it cannot be extended as a generality, since only small fractions of prebiotics and probiotics were used in these two trials, and they do not represent either all probiotics or complete prebiotics. Conversely, those synbiotics applied to

non-emerging mycotoxins reveal opposite results. For instance, Zoghi *et al.* (2017)⁹⁷ showed that the removal of PAT by probiotic bacteria from apple juice depended significantly on the FOS content (as a prebiotic) and the addition of ascorbic acid. Under the best conditions, 91.3% of the initial patulin concentration was removed from juice for 6 weeks.⁹⁷ Zoghi *et al.* (2019) also reported that by adding FOS, ascorbic and citric acid to apple juice inoculated with *L. plantarum*, the efficiency of PAT removal was improved to 95.9% for 6 weeks cold storage.⁹⁸ On the other hand, despite being supposed to enhance clinical outcomes compared to probiotics or prebiotics alone due to their synergistic effect, synbiotics are very difficult to formulate and few have shown to possess clinical efficacy. It is also worth mentioning that most clinical trials are not characterized by including relevant probiotic or prebiotic controls, and many have not performed relevant microbiota analyses.¹²¹ Research needs to be expanded to more (emerging) mycotoxins in combination with synbiotics.

Finally, postbiotics have shown to bind, metabolize and alleviate the harmful effects of some emerging and non-emerging mycotoxins^{57,63,100,103} as well as these mycotoxins have revealed to alter the composition of some postbiotics.^{101,102} Notwithstanding, it is needed to extend these experiments to more (emerging) mycotoxins and to more postbiotics, since only the combination of PYCW with BEA and CIT has been assessed. In fact, it will be very interesting to focus on the interplay between (emerging) mycotoxins and SCFAs.

4.5 Interplay between emerging mycotoxins, the gut microbiota and PSPP

Although the results have revealed a clear trend, data on this interaction have only been found in 12 of the 20 emerging mycotoxins investigated. However, apart from these 20 ones,

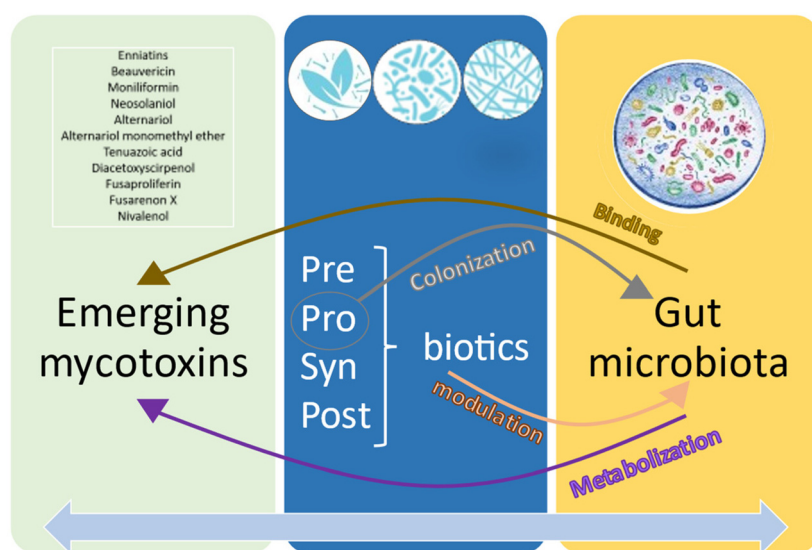


Fig. 7 Detoxification processes of the emerging mycotoxins by probiotics, prebiotics, synbiotics and postbiotics (PPSP) and the gut microbiota. Emerging mycotoxins are metabolized and bound by the gut microbiota. At the same time, PPSP contributes to colonize and modulate the gut microbiota, and also have an indirect impact on the metabolism of the emerging mycotoxins.



other emerging mycotoxins were found. The collected data encompassed a lot of experimental differences (mycotoxin/biotic type and concentration, species, time exposure, assay type, *etc.*), making the comparisons difficult among them. As Fig. 7 illustrates, the interaction between the gut microbiota and emerging mycotoxins involves metabolization and binding processes. The role of PPSP in relation to emerging mycotoxins primarily revolves around colonization (probiotics) and modulation (all). Furthermore, there exists a two-way communication between microbiota and PPSP, where the gut microbiota can degrade and metabolize PPSP, activating secondary bioactive compounds that may contribute to the detoxification and/or alleviation of emerging mycotoxins. Similarly, PPSP can enhance certain gut microbiota strains involved in the removal of emerging mycotoxins. Indeed, this reciprocal relationship can also be applied to the entire spectrum of PPSP, as the addition of probiotics, prebiotics, and synbiotics may enhance the production of certain postbiotics (such as short-chain fatty acids), and *vice versa*.

5 Conclusions

Emerging mycotoxins have been implicated in numerous harmful biological processes. Despite their diverse nature, studies have demonstrated that the gut microbiota and PPSP can detoxify and/or alleviate the adverse effects resulting from exposure to these emerging mycotoxins. *ENS*, *BEA*, *NIV*, and *Alternaria* mycotoxins were among the most frequently encountered emerging mycotoxins. The genera *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces* were the most extensively studied probiotics, while inulin, cellulose, β -glucan, FOS, and galactomannan were among the most evaluated prebiotics. Data on synbiotics and postbiotics were limited. Evidence clearly demonstrates the existence of interplay between the gut microbiota and emerging mycotoxins, as well as between PPSP and emerging mycotoxins, involving processes such as metabolization, colonization, modulation, and binding. In addition, connections between the gut microbiota and PPSP, as well as within the same PPSP, were identified, all contributing to the alleviation of the effects of the emerging mycotoxins.

However, quantitative and qualitative data remain limited. Further *in vivo* and long-term trials are necessary to better comprehend the complexity of these interactions in both animals and humans. The formulation of PPSP as functional food and nutraceuticals should be considered a preventive strategy against the toxicity of emerging mycotoxins in human diets and animal feed.

Author contributions

Á. Lázaro: writing – original draft, methodology, investigation and validation. P. Vila-Donat: methodology, investigation, and review and editing. L. Manyes: investigation, review and editing, project administration, and conceptualization.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

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

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