Food Research International 137 (2020) 109505

Contents lists available at ScienceDirect

Food Research International

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

In vitro and *in vivo* capacity of yeast-based products to bind to aflatoxins B_1 and M_1 in media and foodstuffs: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Yeasts
AFB_1
AFM_1
Binding
Food products
Meta-analysis

ABSTRACT

The aflatoxins are hepatotoxic and carcinogenic metabolites produced by *Aspergillus* species during growth on crop products. In this regard, a systematic review to collect the quantitative data regarding the *in vitro* capacity of yeasts-based products to bind to aflatoxin B_1 (AFB_1) and/or aflatoxin M_1 (AFM_1) was performed. After screening, 31 articles which met the inclusion criteria was included and then the pooled decontamination of aflatoxins in the defined subgroups (the type of foods, pH, contact time, temperature, yeast species, and aflatoxin type) was calculated by the random effect model (REM). The overall binding capacity (BC) of aflatoxins by yeast was 52.05% (95%CI: 49.01–55.10), while the lowest and highest aflatoxins' BC were associated with Yeast Extract Peptone (2.79%) and ruminal fluid + artificial saliva (96.21%), respectively. Regarding the contact time, temperature, pH and type of aflatoxins subgroups, the binding percentages varied from 50.83% (> 300 min) to 52.66% (1–300 min), 50.71% (0–40 °C) to 88.39% (> 40 °C), 43.03% (pH: 3.1–6) to 44.56% (pH: 1–3) and 59.35% (pH > 6), and 48.47% (AFB_1) to 69.03% AFM_1, respectively. The lowest and highest aflatoxins' BC was related to *C. fabianii* (18.45%) and *Z. rouxii* (86.40%), respectively. The results of this study showed that variables such as temperature, yeast, pH and aflatoxin type can be considered as the effective factors in aflatoxin decontamination.

1. Introduction

Mycotoxins are toxic secondary metabolites produced by some species of fungi mainly *Aspergillus*, *Penicillium*, *Fusarium* and *Alternaria* genera with high toxic activity and great stability (de Oliveira & Corassin, 2014; Gonçalves, Corassin, & Oliveira, 2015; Khaneghah, Fakhri et al., 2018; Khaneghah, Martins et al., 2018). All mycotoxins with different degrees of toxicity are cytotoxic, resulting in rupture of cell membranes and other structures or interfering in vital processes such as protein synthesis of RNA or DNA, immunosuppression, nervous and hemorrhagic frames, decreased productive and reproductive efficiency, metabolic and biochemical deficiencies, gastroenteritis, autoimmune diseases, deficiencies in vitamins and/or minerals, genetic alterations, teratogenicity, carcinogenicity, and death in some cases (Fink-Gremmels, 2008).

Among the mycotoxins, the aflatoxins are hepatotoxic and carcinogenic metabolites produced by *Aspergillus* species, mainly *A. flavus*, *A. parasiticus*, and *A. nomius*, especially on grains and cereals such as corn, wheat, and peanuts (de Oliveira & Corassin, 2014; Amirahmadi, Shoeibi, Rastegar, Elmi, and Mousavi Khaneghah, 2018; Rastegar et al., 2017; Nabizadeh et al., 2018). However, twenty different types of aflatoxins were identified, only aflatoxins B_1 (AFB_1), B_2 (AFB_2), G_1 (AFG_1) and G_2 (AFG_2) are frequently found as natural contaminants among food products (Heshmati, Zohrevand, Mousavi Khaneghah, Nejad, & Sant'Ana, 2017; Mousavi Khaneghah et al., 2018; Heshmati, Ghadimi, Ranjbar, & Mousavi Khaneghah, 2019). AFB_1 is the most toxic natural compound identified up to now, being considered as a causative agent of primary hepatocellular carcinoma (Ramalho et al., 2018). It is

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https://doi.org/10.1016/j.foodres.2020.109505
Received 6 April 2020; Received in revised form 1 June 2020; Accepted 26 June 2020
Available online 04 July 2020
0963-9969/

categorized as Group 1, a human carcinogen, by the International Agency for Research on Cancer. (2002) (2002) (2002). Importantly, AFM_1 is the main hydroxylated compound originated from the ingested AFB_1 by lactating animals, being excreted in their milk through contaminated food (Campagnollo et al., 2016; International Agency for Research on Cancer, 2002; Khaneghah, Fakhri, Gahruie, Niakousari, & Sant'Ana, 2019; Rahmani et al., 2018). AFM_1 also preserves several toxic properties of the parent compound including the hepatocarcinogenic effect (Campagnollo et al., 2016). While aflatoxins are highly heat resistant, and small or almost no destruction is observed towards usual food processing technologies like pasteurization, cooking or roasting (Campagnollo et al., 2016; Khaneghah, Fakhri, Raeisi, Armoon, & Sant'Ana, 2018.

While good agricultural practices (GAP) and adequate storage conditions are considered as the best strategies to prevent aflatoxin contamination in food commodities, several methods have been proposed to reduce the issue of mycotoxin contamination including physical, chemical or biological treatments for elimination, inactivation or reduction their bioavailability (Ismail et al., 2018; Mahmood Fashandi, Abbasi, & Mousavi Khaneghah, 2018). Among the biological approaches, the use of microorganisms able to bind to aflatoxins provides an alternative to reduce the bioavailability of the toxin in the organism (Mousavi Khaneghah, Chaves, & Akbarirad, 2017). In this context, yeast species including *Saccharomyces cerevisiae* or *Kluyveromyces lactis* and derived products have been extensively studied *in vitro* (Bovo et al., 2015; Corassin, Bovo, Rosim, & Oliveira, 2013; Hamad, Zahran, & Hafez, 2017). Therefore, the inclusion of appropriate strains in the contaminated diet reduces the absorption of aflatoxins during their passage in the gastrointestinal tract, being eliminated in the feces (Bueno, Casale, Pizzolitto, Salvano, & Oliver, 2007).

Basic ingredients and dietary supplements containing *S. cerevisiae* are regularly used in animal nutrition since they have functional properties in the diet and present satisfactory results when added to the feed as active cells or as wall components (Shetty & Jespersen, 2006). The beneficial effects of yeasts come from the composition of their cell wall, which is rich in polysaccharides and integrated mainly by complex glucans, mannoproteins and a small percentage of chitin (Susanto, Laconi, Astuti, & Bahri, 2014). The benefits of mannan oligosaccharides (MOS) and β-glucans present in the yeast cell wall include modulation of intestinal microbiota, improvement of intestinal integrity, stimulation of the immune system and adsorption of mycotoxins (Gonçalves et al., 2015). As adsorbing agents, MOS and β-glucans are able to bind to mycotoxins, preventing their absorption in the gastrointestinal system, thus allowing fecal excretion of the adsorbent-toxin complex (Di Gregorio et al., 2014). These beneficial effects open interesting perspectives for using yeast-based products in foodstuffs aiming to reduce human exposure to dietary mycotoxins. However, not all strains or derived products within a given yeast species exhibit similar abilities for aflatoxin removal *in vitro*, hence requiring specific evaluation of each strain for its binding efficacy (Oliveira, Bovo, Corassin, Jager, & Reddy, 2013). Therefore, a systematic review and meta-analysis of the literature reporting quantitative *in vitro* data on the capacity of yeasts-based products to bind to aflatoxins, published in the last 10 years was conducted to evaluate the related affecting factors.

2. Methods

2.1. Searching strategy

A systematic literature search in PubMed, Science Direct and Google Scholar databases was conducted using the following key terms: "Aflatoxin" AND "Yeast" OR "Yeast-based" OR "*Saccharomyces*" OR "*Kluyveromyces*" OR "Biological decontamination" AND "*in vitro*" to retrieve all relevant articles published from 2010 to 2019, that investigated the capacity of yeasts-based products to decontaminate aflatoxins *in vitro*. Additionally, the reference lists of included articles were also manually searched to identify other suitable studies.

2.2. Data collection, inclusion and exclusion criteria

The following information was extracted from each study: type and concentration of the yeast-based product, aflatoxin level, type of medium tested, pH, temperature and contact time. During the primary screening, after excluding unsuitable articles due to irrelevant content, the full texts of potentially eligible articles were downloaded. Then, downloaded citations were examined twice for the inclusion and criteria of final eligibility. Inclusion criteria were: (1) Full-text article available, (2) Original research studies (not reviews) conducted *in vitro*, (3) Aflatoxin binding or adsorption only (not degradation), (4) Expression of exact experimental details, (5) Definition of the type of yeast or derived product examined, (6) The accurate analytical methods mentioned and (7) Articles published in the English language. The citations that did not meet these criteria were excluded.

2.3. Meta-analysis of data

A meta-analysis was conducted based on the binding capacity of aflatoxins by yeast in foods. Binding capacity was calculated by using Eq. (1) (Fakhri, Rahmani, et al., 2019):

$$BC = \frac{F_C - I_C}{I_C} \times 100 \quad (1)$$

In this equation, BC is binding capacity (%); Fc, Final concentration of aflatoxins (μg/kg) and Ic, initial concentration of aflatoxins (μg/kg). The pooled (mean) of BC was calculated via mean and standard error (SE) of BC in the individual study (Higgins, White, & Anzures-Cabrera, 2008; Khaneghah, Fakhri, et al., 2018).

SE of the binding capacity was calculated by using Eq. (2) (Fakhri, Abtahi, et al., 2019; Borenstein, Hedges, Higgins, & Rothstein, 2011):

$$SE = \frac{SD}{\sqrt{n}} \quad (2)$$

In this equation; SD and n are a standard deviation and sample size, respectively.

The weight of individual study was calculated by using Eq. (3) (Fakhri, Abtahi, et al., 2019; Hedges, Gurevitch, & Curtis, 1999):

$$Wi = \frac{1}{Vi} \quad (3)$$

In this equation; Wi and Vi are weight individual study and variance of BC, respectively.

Eq. (4) (Hedges et al., 1999) was used to calculate the relative weight (RW) in any subgroups:

$$RW = \frac{W_i}{\sum W} \times 100 \quad (4)$$

In this equation; W_i and ΣWare relative weight and sum Wi, respectively.

The Chi-square (I^2) test was done to detect the heterogeneity among studies. Heterogeneity is high when I^2 index $>$ 50% and if I^2 index $<$ 50%, heterogeneity is low (Higgins & Thompson, 2002). In this study, I^2 *index* $>$ 50%, therefore, the random effect model (REM) was used for meta-analysis of BC in the defined subgroups (Atamaleki et al., 2020). Subgroups were defined according to the type of foods, pH, contact time (minutes), temperature (°C), yeast species, and type of aflatoxins, as presented in Table 1. pH was classified in ranges of 1–3, 3–6 and $>$ 6, while contact time and temperature were categorized into 1–300 min and $>$ 300 min, and 0–40 °C and $>$ 40 °C, respectively. Yeast species were *S. cerevisiae, K. lactis, D. hansenii, K. marxianus, C. lusitaniae, C. fabianii, P. kudriavzevii, C. tropicalis, A. oncophyllus, K. servazzii* and *Z. rouxii*. Finally, the subgroups for types of aflatoxins were AFB_1 and AFM_1. A meta-analysis was done via STATA 14.0

Table 1
Recent studies (2010 to date) on aflatoxin removal by yeast-based products in prepared media or food products.

Yeast species	Type of product	Level of product (unit)	Type of medium or food	Type of aflatoxin	Aflatoxin concentration (μg/mL or g)	Assay conditions			BC (%)[1]	LOD (μg/mL or g)	Reference
						pH	Time (min)	T (°C)			
S. cerevisiae	Heat-killed cells, dryed at 100 °C, from beer fermentation	0.05 (g/5 mL)	PBS	B_1	1.0	3.0	60	25	55	0.01	Bovo et al. (2015)
						6.0			49		
	Inactive cells from beer fermentation					3.0			56		
						6.0			46		
	Inactive cells from sugarcane fermentation					3.0			53		
						6.0			50		
	Hydrolyzed cells					3.0			69		
						6.0			60		
	Cell wall,					3.0			67		
						6.0			64		
	Active cells from beer fermentation					3.0			45		
						6.0			24		
S. cerevisiae	Heat-killed cells, dryed at 100 °C, from beer fermentation	100 (mg/10 mL)	PBS	B_1	2.0	3.0	60	25	48	0.5	Campagnollo et al. (2015)
						6.0			38		
S. cerevisiae	Commercial dry lager yeast (Saflager W37/70)	10^9 (cells/mL)	UHT skim milk	M_1	0.005	–	30	37	90	0.0001	Corassin et al. (2013)
							60		93		
S. cerevisiae	Dried yeast from sugarcane fermentation	10^{10} (cells/mL)	PBS	B_1	0.005	7.3	5	25	99	0.0001	Gonçalves, Rosim, Oliveira, and Corassin (2014)
							10		98		
							20		98		
							30		97		
	Autolyzed yeast						5		95		
							10		97		
							20		97		
							30		95		
	Cell wall,						5		80		
							10		78		
							20		84		
							30		86		
	Brewery dehydrated residue						5		81		
							10		86		
							20		84		
							30		88		
S. cerevisiae	Dried yeast from sugarcane fermentation	10^{10} (cells/mL)	PBS	B_1	0.5	7.3	5	25	100	0.01	Gonçalves, Rosim, de Oliveira, and Corassin (2015)
							10		96		
							20		96		
							30		93		
	Autolyzed yeast from sugarcane fermentation						5		91		
							10		95		
							20		93		
							30		81		
	Cell wall from sugarcane fermentation,						5		60		
							10		57		
							20		67		

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Table 1 (*continued*)

Yeast species	Type of product	Level of product (unit)	Type of medium or food	Type of aflatoxin	Aflatoxin concentration (μg/mL or g)	Assay conditions			BC (%)[1]	LOD (μg/mL or g)	Reference
						pH	Time (min)	T (°C)			
							30		72		
	Brewery dehydrated residue						5		62		
							10		78,0		
							20		67,4		
							30		79,6		
NI	Y1 – Yeast cell wall from brewer's yeast	5 (mg/mL)	Citrate buffer	B_1	0.5	3.0	15	37	40	NI	Joannis-Cassan, Tozlovanu, Hadjeba-Medjdoub, Ballet, and Pfohl-Leszkowicz (2011)
	Y2 – Yeast cell wall from brewer's yeast								17		
	Y3 – Inactivated baker's yeast								17		
	Y4 – Yeast cell wall from baker's yeast								25		
	Y5 – Inactivated baker's yeast								44		
	Y6 – Yeast cell wall from baker's yeast								17		
	Y7 – Yeast cell wall from brewer's yeast								25		
	Y8 – Alcohol yeast								34		
S. cerevisiae	Dried yeast from brewery	0.75 (mg/mL)	PBS	B_1	1.0	1.5	60	37	9	0.0004	Pinheiro et al. (2017)
						7.5			9		
		1.5 (mg/mL)				1.5			12		
						7.5			13		
		2.25 (mg/mL)				1.5			13		
						7.5			16		
		3.0 (mg/mL)				1.5			12		
						7.5			22		
S. cerevisiae	Heat-killed baker's yeast	10^{10} (cells/g)	PBS	B_1	0.5	7.3	30	25	6	NI	Aazami, Nasri, Mojtahedi, and Mohammadi (2018)
							1440		10		
							1440		14		
	Cell wall of baker's yeast						30		22		
							300		28		
							1440		27		
	Cell wall (1 → 3)-β-D-glucan						30		44		
							300		45		
							1440		46		
S. cerevisiae	Heat-killed cells	10^9 (cells/mL)	PBS	M_1	0.05	6.8	720	37	51	NI	Abdelmotilib, Hamad, and Salem (2018)
Kluyveromyces lactis							1440		55		
							2880		57		
							4320		65		
		3×10^9 (cells/mL)					720		59		
							1440		61		
							2880		66		
							4320		73		
		5×10^9 (cells/mL)					720		66		
							1440		73		
							2880		75		
							4320		79		
	Heat-killed cells	10^9 (cells/mL)					720		50		

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Table 1 (*continued*)

Yeast species	Type of product	Level of product (unit)	Type of medium or food	Type of aflatoxin	Aflatoxin concentration (μg/mL or g)	Assay conditions			BC (%)[1]	LOD (μg/mL or g)	Reference
						pH	Time (min)	T (°C)			
							1440		55		
							2880		59		
							4320		60		
		3×10^9 (cells/mL)					720		51		
							1440		58		
							2880		62		
							4320		68		
		5×10^9 (cells/mL)					720		55		
							1440		62		
							2880		67		
							4320		69		
S. cerevisiae	Lyophilized mannoprotein	25 (mg/mL)	water:methanol (60:40)	B_1	1.0	–	720	25	14	0.03	Abdolshahi, Tabatabaie Yazdi, Shabani, Mortazavi, and Monjazeb Marvdashti (2018)
		50 (mg/mL)							33		
		100 (mg/mL)							54		
		150 (mg/mL)							56		
		200 (mg/mL)							65		
		25 (mg/mL)	pistachio		0.18		5		63		
		50 (mg/mL)							84		
S. cerevisiae	Mixture of yeast extract and HSCAS (MycoPurge®)	6 (g/30 mL)	Ruminal fluid + artificial saliva	B_1	0.006	–	180	39	94	0.0006	Akkaya and Bal (2012)
							360		97		
							720		97		
							1440		97		
S. cerevisiae	Viable cells of strain RC008	10^7 (cells/mL)	PBS	B_1	0.05	3.0	60	37	73	1.0	Dogi et al. (2011)
						6.0			50		
						8.0			82		
	Viable cells of strain RC009					3.0			85		
						6.0			42		
						8.0			84		
	Viable cells of strain RC016					3.0			95		
						6.0			56		
						8.0			89		
S. cerevisiae	Immobilized, heat-killed strain ATCC 9763 cells on perlite	10^8 (cells/mL)	milk	M_1	0.08	milk pH	20	4	75	0.004	Foroughi, Jamab, Keramat, and Foroughi (2018)
							40		100		
							80		100		
					0.13		20		80		
							40		85		
							80		88		
					0.18		20		72		
							40		80		
							80		80		
					0.23		20		75		
							40		74		
							80		8		
S. .cerevisiae	Mycosorb_Japan_1 (yeast > 60%, HSCAS, $CaCO_3$)	10 (mg/5 mL)	Citrate buffer (pH 3.0)	B_1	0.2	3.0	60	37	100	NI	Fruhauf, Schwartz, Ottner, Krska, and Vekiru (2012)
			Phosphate buffer (pH 6.5)			6.5			100		

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Table 1 (*continued*)

Yeast species	Type of product	Level of product (unit)	Type of medium or food	Type of aflatoxin	Aflatoxin concentration (μg/mL or g)	Assay conditions			BC (%)[1]	LOD (μg/mL or g)	Reference
						pH	Time (min)	T (°C)			
			Real gastric juice (pH 5.0)			5.0			75		
	Integral_Canada_1 (Yeast by-product)					3.0			30		
						6.5			35		
						5.0			25		
	Microbond_USA (β-glucans, MOS, digestive enzymes)					3.0			55		
						6.5			70		
						5.0			35		
	Nutricell® Polysorb (> 45% β-glucans + MOS)					3.0			100		
						6.5			100		
						5.0			75		
	ActiveMOS (MOS 25%, β-glucans 30%)					3.0			20		
						6.5			19		
						5.0			8		
	Betamune (β-glucan > 70%)					3.0			3		
						6.5			1		
						5.0			3		
	Biolex® MB40 (β-glucan 35–30%, MOS 20–25%)					3.0			13		
						6.5			11		
						5.0			12		
S. cerevisiae	Yeast cell based product (Mycosorb®)	10 (g/kg)	animal feed	B_1	0.008	–	4	25	10	0.0002	Gallo, Masoero, Bertuzzi, Piva, and Pietri (2010)
					0.015				20		
		20 (g/kg)			0.008				14		
					0.015				30		
Kluyveromyces lactis *S. cerevisiae*	Yeast strain ATCC 64712	10^9 (cells/mL)	PBS	B_1	0.025	6.8	360	37	23	0.0001	Hamad et al. (2017)
							720		31		
							1440		37		
							2880		47		
							4320		49		
		3×10^9 (cells/mL)					360		27		
							720		35		
							1440		41		
							2880		45		
							4320		1		
		5×10^9 (cells/mL)					360		35		
							720		43		
							1440		50		
							2880		58		
							4320		62		
	Yeast strain CBS 2359	10^9 (cells/mL)					360		19		
							720		23		
							1440		29		
							2880		33		
							4320		37		

(*continued on next page*)

Table 1 (*continued*)

Yeast species	Type of product	Level of product (unit)	Type of medium or food	Type of aflatoxin	Aflatoxin concentration (μg/mL or g)	Assay conditions			BC (%)[1]	LOD (μg/mL or g)	Reference
						pH	Time (min)	T (°C)			
		3×10^9 (cells/mL)					360		23		
							720		27		
							1440		31		
							2880		37		
							4320		43		
		5×10^9 (cells/mL)					360		27		
							720		31		
							1440		35		
							2880		39		
							4320		45		
	Yeast mix (S. cerevisiae + K. lactis)	10^{10} (cells/mL)					360		36		
							720		46		
							1440		49		
							2880		57		
							4320		66		
Saccharomyces pastorianus	Active cells	1 (g/200 mL)	Beer – bottom fermentation	B_1	0.01	4.0	10,080	10	18	NI	Inoue, Nagatomu, Uyama, and Mochizuki (2013)
S. cerevisiae	Active cells	80 (mg/200 mL)	Beer – top fermentation			4.0	10,080	20	25		
	Wine must	87.5 (mg/350 mL)	Wine			3.0	10,080	25	70		
S. cerevisiae	Heat-killed cells from strain HR 125a	10^7 (cells/mL)	milk	M_1	0.005	milk pH	60	25	42	0.00002	Ismail et al. (2017)
		10^8 (cells/mL)							54		
		10^9 (cells/mL)							74		
		10^{10} (cells/mL)							100		
		10^7 (cells/mL)			0.001				28		
		10^8 (cells/mL)							45		
		10^9 (cells/mL)							73		
		10^{10} (cells/mL)							92		
Debaryomyces hansenii	Yeast pool for kefir preparation	0.01 (g/L)	kefir	M_1	0.15	4.6	10,080	4	69	NI	Kamyar and Movassaghghazani (2017)
Kluyveromyces marxianus subsp. *Marxianus*					0.2				45		
					0.25				65		
S. cerevisiae	Viable cells from strain PTCC 5177 + starter bacteria	2.1×10^9 (cells/mL)	yoghurt	M_1	0.0005	4.5	1440	4	77	NI	Karazhiyan, Sangatash, Karazhyan, Mehrzad, and Haghighi (2016)
							10,080		71		
							14 20,160		74		
							30,240		75		
	Acid-treated (2 M HCl, 37 °C, 1 h) cells from strain PTCC 5177 + starter bacteria						1440		78		
							10,080		81		
							14 20,160		73		
							30,240		75		
	Heat-treated cells (121oC, 15 min) from strain PTCC 5177 + starter bacteria						1440		73		
							10,080		75		
							14 20,160		74		

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Table 1 (*continued*)

Yeast species	Type of product	Level of product (unit)	Type of medium or food	Type of aflatoxin	Aflatoxin concentration (μg/mL or g)	Assay conditions			BC (%)[1]	LOD (μg/mL or g)	Reference
						pH	Time (min)	T (°C)			
							30,240		84		
	Ultrasound-treated cells (sonication for 15 min, 50 °C) cells from strain PTCC 5177 + starter bacteria						1,440		79		
							10,080		76		
							14 20,160		75		
							30,240		74		
–	Yeast cell wall product	0.5 (g/100 g)	PBS	B_1	2.0	2.06.8	24	39	93	NI	Kong, Shin, and Kim (2014)
Clavispora lusitaniae	Viable cells	10^5 (cells/mL)	PBS	B_1	0.05	6.0	60	37	13	0.001	Magnoli et al. (2016)
Cyberlindnera fabianii		10^6 (cells/mL)							15		
Pichia kudriavzevii		10^7 (cells/mL)							15		
Candida tropicalis		10^5 (cells/mL)			0.1				17		
		10^6 (cells/mL)							20		
		10^7 (cells/mL)							26		
Cyberlindnera fabianii	Viable cells	10^5 (cells/mL)			0.05				13		
		10^6 (cells/mL)							16		
		10^7 (cells/mL)							20		
		10^5 (cells/mL)			0.1				17		
		10^6 (cells/mL)							22		
		10^7 (cells/mL)							25		
Clavispora lusitaniae	Viable cells	10^5 (cells/mL)			0.05				12		
		10^6 (cells/mL)							15		
		10^7 (cells/mL)							16		
		10^5 (cells/mL)			0.1				26		
		10^6 (cells/mL)							29		
		10^7 (cells/mL)							30		
Pichia kudriavzevii	Viable cells	10^5 (cells/mL)			0.05				13		
		10^6 (cells/mL)							14		
		10^7 (cells/mL)							21		
		10^5 (cells/mL)			0.1				23		
		10^6 (cells/mL)							26		
		10^7 (cells/mL)							31		
Candida tropicalis	Viable cells	10^5 (cells/mL)			0.05				13		
		10^6 (cells/mL)							14		
		10^7 (cells/mL)							21		
		10^5 (cells/mL)			0.1				19		
		10^6 (cells/mL)							23		
		10^7 (cells/mL)							29		
S. cerevisiae	Strain RC016	10^7 (cells/mL)	PBS	B_1	0.05	7.3	30	37	82	0.001	Pizzolitto et al. (2012)
					0.1				49		
					0.5				65		
	Strain 01				0.05				39		
					0.1				32		
					0.5				33		
	Strain 03				0.05				47		
					0.1				35		
					0.5				26		
	Strain 05				0.05				33		
					0.1				24		
					0.5				18		
	Strain 08				0.05				46		
					0.1				59		
					0.5				37		

(*continued on next page*)

Table 1 (*continued*)

Yeast species	Type of product	Level of product (unit)	Type of medium or food	Type of aflatoxin	Aflatoxin concentration (μg/mL or g)	Assay conditions			BC (%)[1]	LOD (μg/mL or g)	Reference
						pH	Time (min)	T (°C)			
S. cerevisiae	Viable cells from strain RC009	10^7 (cells/mL)	artificial intestinal fluid	B_1	0.02	8.0	60	37	34	0.0001	Poloni et al. (2015)
					0.05				24		
	Viable cells from strain RC012				0.02				33		
					0.05				82		
	Viable cells from strain RC016				0.02				71		
					0.05				61		
S. cerevisiae	Viable cells from strain LL74 (from bakery by-products)	10^8 (cells/mL)	simulated gastric conditions	B_1	1.26	3.0	60	37	31	NI	Poloni et al. (2017)
			simulated intestinal conditions			8.0			11		
	Viable cells from strain LL83 (from bakery by-products)		simulated gastric conditions						36		
			simulated intestinal conditions						28		
S. cerevisiae	Viable cells from strain ATCC 9763	$1{,}8 \times 10^{10}$ (cells/mL)	pistachio	B_1	0.01	6.0	90	25	22	NI	Rahaie, Emam-Djomeh, Razavi, and Mazaheri (2012)
							180		41		
							480		40		
							720		38		
					0.02		90		61		
							180		68		
							480		65		
							720		60		
	Heat-treated (120 °C, 20 min) cells from strain ATCC 9763				0.01		90		32		
							180		55		
							480		41		
							720		39		
					0.02		90		66		
							180		73		
							480		70		
							720		70		
	Acid-treated cells (25 °C, 2 M HCl, 90 min) cells from strain ATCC 9763				0.01		90		36		
							180		56		
							480		56		
							720		49		
					0.02		90		60		
							180		72		
							480		70		
							720		63		
S. cerevisiae	Viable cells from commercial baker yeast	10^9 (cells/mL)	milk	B_1	0.01	milk pH	720	37	54	NI	Rayes (2013)
							1,440		57		
							2,160		67		
							4,320		82		
		5×10^9 (cells/mL)					720		86		
							1,440		84		
							2,160		89		
							4,320		99		
		7×10^9 (cells/mL)					720		75		

(*continued on next page*)

Table 1 (*continued*)

Yeast species	Type of product	Level of product (unit)	Type of medium or food	Type of aflatoxin	Aflatoxin concentration (μg/mL or g)	Assay conditions			BC (%)[1]	LOD (μg/mL or g)	Reference
						pH	Time (min)	T (°C)			
							1,440		79		
							2,160		87		
							4,320		98		
		10^9 (cells/mL)					60	5	19		
								37	63		
								50	74		
								100	85		
		5×10^9 (cells/mL)						5	24		
								37	77		
								50	82		
								100	91		
		7×10^9 (cells/mL)						5	23		
								37	84		
								50	96		
								100	95		
S. cerevisiae	Glucomannan yeast product (Mycosorb®)	41 (mg/40 mL)	Gastro-intestinal fluid of chicken	B_1	0.008	–	120	39	120	0.002	Susanto et al. (2014)
		82 (mg/40 mL)							21		
		123 (mg/40 mL)							42		
		164 (mg/40 mL)							46		
Amorphophallus oncophyllus		41 (mg/40 mL)			0.007				4		
		82 (mg/40 mL)							29		
		123 (mg/40 mL)							37		
		164 (mg/40 mL)							89		
S. cerevisiae	Viable cells from strain A18	2×10^8 (cells/mL)	PBS	B_1	2.0	6.0	30	37	45	NI	Tabari, Kermanshahi, Golian, and Heravi (2018)
	Heat-killed (120 °C, 20 min) cells from strain A18								73		
	Strain A18 cell wall	10 (mg/mL)							73		
Kazachstania servazzii	Viable cells from strain KFLY1 (from kefir milk)	2.0 (Optical density at 600 nm)	Yeast extract peptone dextrose (YPD) broth	B_1	1.0	–	1,440	25	4	0.004	Taheur et al. (2017)
			UHT milk			–			61		
	Viable cells from strain KFLY3 (from kefir milk)		Yeast extract peptone dextrose (YPD) broth						3		
			UHT milk						72		
	Viable cells from strain KFLY4 (from kefir milk)		Yeast extract peptone dextrose (YPD) broth						2		
			UHT milk						29		
	Viable cells from strain KFLY5 (from kefir milk)		Yeast extract peptone dextrose (YPD) broth						5		
			UHT milk						64		
	Viable cells from strain KFLY6 (from kefir milk)		Yeast extract peptone dextrose (YPD) broth						0		
			UHT milk						70		
	Viable cells from strain KFLY1 (from kefir milk)		Yeast extract peptone dextrose (YPD) broth						7		
			UHT milk						71		
	Viable cells from strain KFLY3 (from kefir milk)		Yeast extract peptone dextrose (YPD) broth						8		

(*continued on next page*)

Table 1 (*continued*)

Yeast species	Type of product	Level of product (unit)	Type of medium or food	Type of aflatoxin	Aflatoxin concentration (μg/mL or g)	Assay conditions			BC (%)[1]	LOD (μg/mL or g)	Reference
						pH	Time (min)	T (°C)			
			UHT milk						20		
	Viable cells from strain KFLY4 (from kefir milk)		Yeast extract peptone dextrose (YPD) broth						0		
			UHT milk						65		
	Viable cells from strain KFLY5 (from kefir milk)		Yeast extract peptone dextrose (YPD) broth						0.5		
			UHT milk						7		
	Viable cells from strain KFLY6 (from kefir milk)		Yeast extract peptone dextrose (YPD) broth						3		
			UHT milk						32		
	Viable cells from strain KFGY7 (from kefir grains)		Yeast extract peptone dextrose (YPD) broth						0		
			UHT milk						74		
Zygosaccharomyces rouxii	Viable cells	10^9 (cells/mL)	peanut meal	B_1	0.115	10.0	10	40	67	NI	Zhou, Chen, Kong, Ma, and Liu (2017)
								60	79		
								80	84		
								100	95		
								110	95		
							5	100	79		
							10		95		
							15		97		
							20		98		

T: Temperature; BC: Binding capacity; LOD: Limit of detection; PBS: Phosphate buffer saline; RT: Room temperature; NI: Not informed.

[1] Values are related to the initial concentration of aflatoxins.

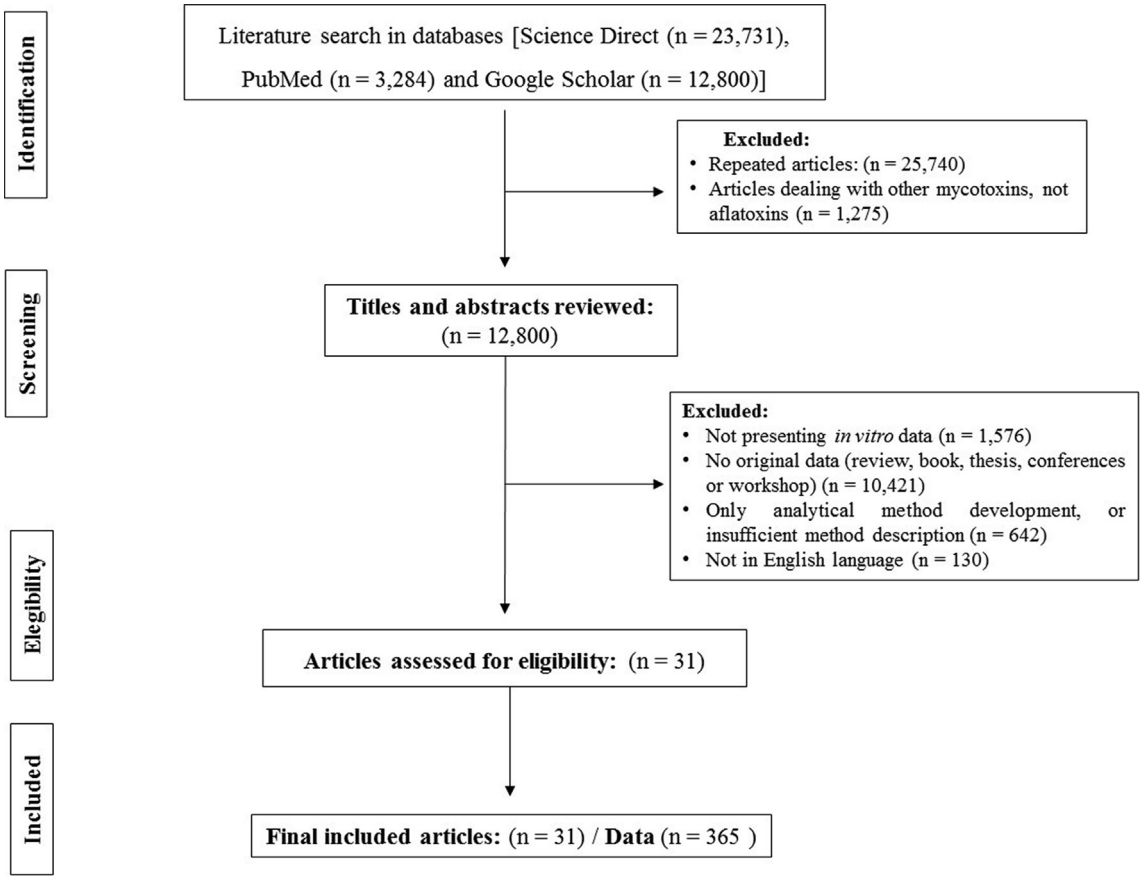

Fig. 1. Flow diagram describing the literature search, inclusion and exclusion criteria, and data collection.

software (Stata Corp, College Station, TX).

3. Key findings and discussion

3.1. Description of the studies

During the identification step, 39,851 articles were obtained from PubMed, Science Direct and Google Scholar (as the gray literature) databases. After screening, 12,800 articles were chosen and evaluated for eligibility, while 12,769 articles were excluded in the initial assessment due to duplication or based on their title and abstract contents. Finally, 31 articles fulfilled the inclusion criteria and were included in the current study, as summarized in Fig. 1.

3.2. In vitro binding of aflatoxins by yeast-based products

The outcomes form studies conducted from 2010 to date on aflatoxin removal by yeast-based products in prepared media or food products are presented in Table 1. Regardless the type of substrate (food or media), the binding process occurs through the cell wall. Moreover, yeast strains are more efficient than the LABs in adsorbing mycotoxins, most likely due to the concentration of β-glucans in its cell wall. β-Glucans are responsible for inactivating mycotoxins through their capacity to selectively bind to polar and non-polar mycotoxins through intermolecular forces such as hydrogen bridges and Van der Waals forces. These properties have great potential to improve performance and decrease animal mortality (Jouany, Yiannikouris, & Bertin, 2005). According to Corassin et al. (2013), the cell walls of yeast (*Saccharomyces cerevisiae*), act as adsorbents, being able to connect efficiently to several mycotoxins such as aflatoxin, fumonisin, and zearalenone, although the bond with T-2 toxin, ochratoxin and citrine are moderate.

The components of the cell walls have a limited number of linkage poles for aflatoxins and other mycotoxins and may not present availability for such connections due to a saturation of these poles (Pizzolitto, Salvano, & Dalcero, 2012). Although more specific information on the mechanism of linking mycotoxins to the cell wall is still scarce, there is a correlation between the amount of β-D-glucans in the cell wall of yeast and the efficacy of sequestrate AFB_1, among other mycotoxins (Armando et al., 2012; Yiannikouris et al., 2004). Thus, the greater the number of β-glucans available in the commercial product, the greater the availability of these bonding poles and consequently more efficient will be the binding of mycotoxins.

It is known that more important than the yeast strain, is the fermentation environment that will actually provide the fundamental differences in the final composition of the product. The strains used in sugarcane processing to obtain ethanol will result in a product with a higher concentration of β-glucans. The yeast culture goes through countless fermentation cycles, which makes the cell wall denser, resulting in higher carbohydrate rates and lower fat content in its composition, making it less digestible in the gastrointestinal tract (Fig. 2). The three-dimensional structure of the polysaccharides constituting the yeast cell wall allows the binding of different mycotoxins and/or their metabolic derivatives (Ringot et al., 2005). The available β-D-glucans in the yeast wall are able to adsorb several mycotoxins while the α-D-mannan inhibit the toxic activity of mycotoxins, probably because they interact with the radicals of these compounds (Madrigal-Bujaidar, Madrigal-Santillán, Pages, Kogan, & Chamorro, 2002).

3.3. In vivo binding of aflatoxins by yeast-based products

In vitro binding studies are indicative of *in vivo* responses to specific mycotoxins. However, *in vivo* experiments are scarcer, as they are

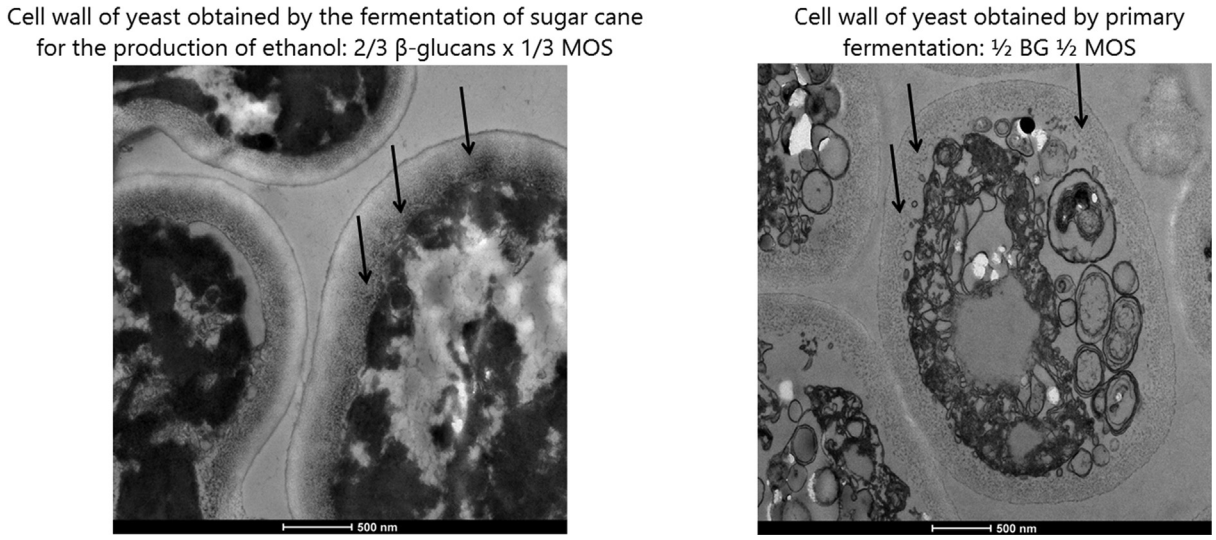

Fig. 2. Electron microscopy images of yeast cell wall resulted after fermentation of sugar cane for ethanol production (left), and cell wall of yeast obtained from primary fermentation (right). The black arrows indicate the differences in the concentration of β-glucans (darker areas) in the two types of cell walls. Authorship: Ricardo L. C. Barbalho, on behalf of ICC Brazil.

usually very difficult to accomplish, although recent studies have successfully demonstrated *in vivo* the efficiency of yeasts as adsorbents of aflatoxins, as presented in Table 2. The β-glucans, besides conferring the adsorbent action, provide immunomodulation of the innate immune system through the stimulation of the production of cytokines that triggers an increase in phagocytic cells. This extra stimulus promotes a faster and more efficient response of the innate and specific animal immune system. Intestinal integrity is an indicator of efficiency for the protective barrier formed by the gastrointestinal tract, which prevents the paracellular translocation of unwanted compounds, such as mycotoxins and pathogens from the lumen of the intestine to the own blade and subsequently into the bloodstream (Franco, Mousavi Khaneghah, Lee, & Oliveira, 2019). Thus, the less permeable the mucosa bowel is present, the lower the passage of these compounds. In this context, the effect of agglutination of the pathogenic bacteria by the yeast MOS contributes for better integrity of the villi, i.e., the intestinal permeability is reduced favoring a protective barrier against bacteria and mycotoxins into the bloodstream.

3.4. Meta-analysis findings

The overall BC of aflatoxins by years was 52.05% (95%CI: 49.01–55.10) (Table 3). The order of effect of each substrate (foods or media) on aflatoxins' BC were summarized as ruminal fluid + artificial saliva (96.21%) > peanut meal (86.39%) > yoghurt (77.54%) > ultra-high temperature milk (75.65%) > pistachio (73.50%) > pasteurized milk (72.60%) > wine (70.00%) > kefir (60.02%) > pistachio (54.30%) > artificial intestinal fluid (50.83%) > phosphate buffer saline (PBS) (48.74%) > gastro-intestinal fluid (48.72%) > phosphate buffer (pH 6.5) (47.95%) > citrate buffer (pH 3.0) (45.81%) > solvent (water: methanol, 60:40) (44.29%) > simulated gastric conditions (33.49%) > real gastric juice (33.28%) > citrate buffer (27.72%) > beer – top fermentation (25.00%) > simulated intestinal (19.46%) > beer – bottom fermented (18.00%) > animal feed (17.65%) > yeast extract peptone broth (2.79%) (Table 3). This order indicates the aflatoxins' BC efficacy of substrates containing natural yeasts (e.g., ruminal fluid, kefir), when compared with food products (e.g., peanuts, dairy products, pistachio and wine). However, based on the findings, there is no absolute preference in terms of aflatoxins' BC efficacy among the two groups of investigated substrates.

The rank order of pH classes based on BC was "6 < (59.35%)" > "1–3 (44.56%)" > "3.1–6 (43.03%)" (Table 4). *S. cerevisiae*, demonstrates to be more effective in surviving the different conditions of the gastrointestinal tract, being more resistant to acidic pH and the presence of bile (Kühle, Skovgaard, & Jespersen, 2005), besides promoting better results in the binding capacity of mycotoxins (Pizzolitto et al., 2012). In a study conducted by Pennacchia, Blaiotta, Pepe, and Villani (2008) it was concluded that more than 50% of the strains of *S. cerevisiae* exposed to the passage simulated by the human gastrointestinal tract, showed 70% of survival.

In relation to the contact time classes based on BC, the rank order was "1–300 min (52.66%)" > "300 min (50.83%)" (Table 4). The binding process of microorganisms to aflatoxins is usually rapid, reaching a maximum binding percentage after 1 min contact (Pizzolitto et al., 2012). This suggests that mycotoxin is not required to pass through a metabolic pathway in the cytoplasm inside the strain so that it is inactivated.

The rank order of temperature classes based on BC was "40 °C < (88.39%)" > "0–40 °C (50.71%)" (Table 4). The percentage of mycotoxins bound to the cell walls of yeast is not a completely linear phenomenon and may vary according to several factors, especially the amount of β-glucans, conformation of the cell wall, which differs between the strains of yeast (Jouany & Diaz, 2005), different animal species, interaction between mycotoxins and other compounds, environment, etc., thus contributing to the differences observed in studies in the literature.

As for the yeast species based on BC, the rank order was *Z. rouxii* (86.40%) > *D. hansenii* (69.00%) > *S. cerevisiae* (59.73%) > *K. Marxianus* (55.29%) > *K. lactis* (47.11%) > *A. oncophyllus* (40.38%) > *K. servazzii*(27.20%) > *P. Kudriavzevii* (20.47%) > *C. lusitaniae* (20.16%) > *C. tropicalis* (20.02%) > *C. fabianii* (18.45%) (Table 4). It is postulated that, within a given genus or species, not all strains exhibit similar abilities for toxin removal. In fact, this capacity is remarkable only in specific strains with variable efficacy (Oliveira et al., 2013). Finally, the rank order of aflatoxin type based on decontamination of aflatoxin was AFM_1 (69.03%) > AFB_1 (48.47%).

4. Conclusion

In order to reduce the mycotoxin contamination in food commodities, several methods have been proposed including physical, chemical or biological treatments. Among them, biological treatments especially by using of yeasts attracted notable attention in view of *in vitro* and *in*

Table 2
Studies on the *in vivo* modulation of aflatoxin bioavailability by yeast-based products.

Type of yeast-based product	Inclusion level (kg/100 kg feed)	Dose (g/animal/day)	Animal species	Aflatoxin concentration (mg/kg)	Main results	Reference
S. cerevisiae-based products [1]	NI	20	Dairy cow	0.48[2]	All tested products reduced the excretion of aflatoxin M_1 into milk, with maximum efficiency (78–89%) by cell wall and autolyzed yeast from sugarcane industry	Gonçalves et al. (2017)
Beer fermentation residue	1.0	NI	Broiler chick	2.0	Reduction of the severity of histological changes in liver and kidney	Bovo et al. (2015)
Yeast cell wall	0.2	NI	Broiler chick	0.02	Improved average daily gain and feed intake	Sun, Park, Guo, Weaver, and Kim (2015)

NI: Not informed.
[1] Products tested: Cell wall, autolyzed and dried yeast from sugarcane industry, and partially dehydrated yeast from brewery industry.
[2] Administered daily to each animal by gavage for 6 consecutive days.

Table 3
The findings of Meta-analysis of absorption capacity of aflatoxins based on type of foods.

Type of foods	Number study	ES* (%)	Lower	Upper	Weight (%)
PBS	181	48.74	44.23	53.26	49.74
Citrate buffer	8	27.72	22.36	33.09	2.21
Water: methanol (60:40)	5	44.29	25.16	63.43	1.38
Pistachio	2	73.50	52.92	94.08	0.55
Ruminal fluid + artificial saliva	4	96.21	94.58	97.85	1.1
Milk	44	72.60	62.69	82.53	12.15
Citrate buffer (pH 3.0)	7	45.81	23.97	67.65	1.93
Phosphate buffer (pH 6.5)	7	47.95	26.32	69.58	1.94
Real gastric juice (pH 5.0)	7	33.28	9.62	56.95	1.94
Animal feed	4	17.65	9.76	25.56	1.09
Beer – bottom fermentation	1	18.00	16.86	19.14	0.28
Beer – top fermentation	1	25.00	19.34	30.66	0.27
Wine	1	70.00	68.86	71.14	0.28
Kefir	3	60.02	47.51	72.53	0.82
Yoghurt	16	77.54	72.66	82.43	3.9
Artificial intestinal fluid	6	50.83	30.15	71.51	1.66
Simulated gastric conditions	2	33.49	28.59	38.39	0.55
Simulated intestinal	2	19.46	2.80	36.12	0.55
Pistachio	24	54.30	48.76	59.84	6.64
Gastro-intestinal fluid of chicken	8	48.72	15.23	82.22	2.18
Yeast extract peptone dextrose (YPD) broth	11	2.79	1.26	4.32	3.04
UHT milk	13	75.65	56.35	94.32	3.54
Peanut meal	8	86.39	79.39	93.40	2.21
Overall	**365**	**52.05**	**49.01**	**55.10**	**100**

* Effect size that in the current study is pooled AC of aflatoxins

vivo evidences indicating the potential application of yeast-based products to bind to aflatoxins. In this regard, the current study provided a first comprehensive and quantitative approach of *in vitro* data on the aflatoxins' BC of yeast-based products and the related factors affecting the binding process. According to findings, temperature, pH, yeast species, type of food matrix and type of aflatoxin are effective variables influencing the BC of yeasts to aflatoxins in food products. However, no preference in terms of aflatoxins' BC was noted between food or media substrates. Although the BC of yeasts to aflatoxins can be improved by further increasing in temperature and pH, particularly in the case of AFM_1 decontamination from foods, no significant difference in aflatoxins removal efficacy was observed among different contact times. Further studies are recommended to evaluate industrial applications of yeast-based products for aflatoxin decontamination based on economical and safety aspects.

CRediT authorship contribution statement

Fernanda B. Campagnollo: Conceptualization, Data curation, Investigation, Validation. **Amin Mousavi Khaneghah:** Data curation, Writing - review & editing. **Liliana L. Borges:** Investigation, Writing - original draft. **Melina A. Bonato:** Investigation. **Yadolah Fakhri:** Investigation. **Caio B. Barbalho:** Investigation. **Ricardo L.C. Barbalho:** Conceptualization, Investigation, Writing - original draft. **Carlos H. Corassin:** Conceptualization, Data curation, Validation, Writing - review & editing. **Carlos A.F. Oliveira:** Conceptualization, Funding acquisition, Project administration, Writing - review & editing.

Declaration of Competing Interest

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

Table 4
The findings of meta-analysis of absorption capacity of aflatoxins based on pH, time contact, temperature, yeast species and type of aflatoxins subgroups.

Subgroups	Class	Number study	ES (%)	Lower	Upper	Weight (%)
pH	1–3	32	44.56	28.70	60.42	8.84
	3.1–6	95	43.03	39.49	46.56	25.70
	6 <	183	59.35	55.24	63.46	50.58
Contact time (Min)	1–300	226	52.66	48.70	56.61	62.13
	300 <	139	50.83	47.21	54.46	37.87
Temperature (°C)	0–40	252	50.71	47.61	53.81	96.41
	40 <	13	88.39	85.02	91.75	3.59
Yeast species	S. Cerevisiae	230	59.73	56.20	63.25	63
	K. Lactis	59	47.11	42.85	51.37	16.31
	D. Hansenii	1	69.00	62.32	75.68	0.27
	K. Marxianus	2	55.29	35.70	74.88	0.55
	C. Lusitaniae	7	20.16	11.94	28.37	1.94
	C. Fabianii	7	18.45	16.05	20.85	1.94
	P. Kudriavzevii	7	20.47	16.01	24.93	1.94
	C. Tropicalis	9	20.02	17.99	22.04	2.49
	A. Oncophyllus	4	40.38	5.73	75.04	1.08
	K. Servazzii	22	27.20	15.68	38.72	6.08
	Z. Rouxii	8	86.40	79.39	93.40	2.21
Aflatoxin type	B1	300	48.47	45.12	51.83	82.57
	M1	65	69.03	61.34	76.73	17.43

Acknowledgments

The authors would like to thank the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, Grant #2017/20081-6) for financial support.

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