COMPREHENSIVE REVIEW OF PATULIN CONTROL AND ANALYSIS IN FOODS

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ABSTRACT

Patulin is a mycotoxin produced by a number of fungal species that include *Penicillium*, *Aspergillus*, and *Byssochlamys* genera. Several adverse health effects have been attributed to patulin—it is suspected of being clastogenic, mutagenic, teratogenic, and in higher concentrations cytotoxic, hence the importance of prevention, timely detection, and mitigation of contamination by this toxic fungal metabolite. The primary dietary origin of patulin is apples and its products, with the occasional contamination of other fruits, vegetables, and products thereof. The persistence and stability of the molecule allow it to survive processing, poses a major issue for the safety of susceptible foods. This challenge calls for techniques that will allow us to properly identify and eliminate the metabolite from food products. This paper reviews prior research on patulin focusing on detection, control, and level-reduction methods of patulin in several stages of production of these products.

BIOGRAPHICAL SKETCH

Ana Cristina Barsallo Cochez is pursuing a Master of Professional Studies in Food Science and Technology, immediately after the completion of her Doctorate of Veterinary Medicine from the University of Panama. Her interest in food safety grew while in vet school from bromatology courses, as well as an internship in the Food Safety Authority of Panama on her senior year. After finishing her MPS degree, Ana will join the Master of Public Health program at Cornell University.

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INTRODUCTION

Patulin, 4-hydroxy-4H-furo [3,2c] pyran-2(6H)-one, is a metabolic byproduct of many different fungi, that was initially isolated as an antimicrobial active compound during the 1940s. Later on, in the 1950s and 1960s, it was discovered to be toxic to plants and animals, therefore ruling out its use as an antibiotic. The greatest concern within the food industry for patulin contamination are apples and their respective products. Other vegetable and fruit products have been found to contain patulin and/or patulin-producing organisms, however, the incidence of patulin contamination are less frequent than with apple products (Reddy et al. 2016). The effects attributed to this mycotoxin are based on studies performed in the last fifty years, which suggested that patulin may be neurotoxic, immunotoxic, immunosuppressive, genotoxic, teratogenic and carcinogenic (Gonzalez-Osnaya et al. 2007). Children are more susceptible to patulin toxicity than adults, due to their high consumption of apple products in their first year of life, along with their physiology and fairly restricted diet (Barreira, Alvito, and Almeida 2010). Due to its potential toxicity, WHO established a maximum recommended concentration of 50 µg/L of patulin in apple juice, along with the establishment by the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) of a provisional maximum tolerable daily intake (PMTDI) for patulin of 0.4 µg/kg body weight/day (WHO 1995). Likewise, the European Commission established a maximum

concentration of 50 μg/kg of patulin in drinks derived from apples or containing apple juice, 25 μg/kg for solid apple products, and a maximum level of 10 μg/kg allowed for apple products intended for infants and young children (European Comission 2003). Given the extensive list of health risks posed to consumers by this toxin, the development of techniques for its rapid and simple detection is imperative, as well as the application of different methods in food production to prevent, eliminate or reduce contamination levels by this metabolite. The purpose of this review is to examine prior research from 2005 to date on available detection and control methods for patulin before, during and after processing. In addition, we present an overview of the presence of this mycotoxin in several food products around the world.

PREVALENCE

The natural presence of patulin in foods, mostly in apple-based products, has gained international attention. A great amount of studies around the world have examined the breadth and rate to which apples, other fruits, vegetables and their products have been contaminated by patulin. Surveys at a global scale serve as evaluations for countries to know if they face the problem of probable patulin toxicity in its population due to high concentration of the toxin in a wide range of products available to the public.

Several studies have found the contaminant in concentrations above the permitted levels. In Argentina, a study detected that 21.6% of 51 solid and semi-solid apple and pear products were contaminated, with the highest levels found in apple puree with 50% contaminated samples (Funes and Resnik 2009). A study carried out in Northeast China showed that the level of patulin found was higher than 50 µg/kg in 16% of 95 evaluated apple products (Yuan et al. 2010). In Iran, a study on the incidence of patulin in apple juices produced in the West Azerbayjan Province revealed all samples had patulin contamination with 29% of samples containing levels higher than 50 µg/L (Forouzan and Madadlou 2014). An Italian study detected patulin in 26% conventional and 45% organic products samples with a higher mean concentration in the organic products and four samples of juice contained patulin above the limit of 50 µg/kg (Piemontese, Solfrizzo, and Visconti 2005). A second study showed an overall incidence of 34.4% in 125 samples of fruit juices with no sample exceeding 50 µg/kg, but 19 samples contained more

than the maximum level for baby food of 10 µg/kg of patulin (Spadaro, Garibaldi, and Gullino 2008). Patulin surveillance results for apple cider samples originating from Michigan cider mills, as well as apple juice and cider samples from retail grocery stores in Michigan, showed that patulin was present in 18.7% and 23.3% of samples, with levels above 50 µg/liter in 11 and 18 samples, respectively (Harris, Bobe, and Bourquin 2009). A study in Qatar showed a patulin occurrence in 100% of sampled apple juices and baby foods, with 5 and 6 samples, respectively, above the maximum recommended limit (Hammami et al. 2017). A survey of apple juices in Navarra, Spain, showed that in 11% of samples the patulin contamination exceeded the maximum permitted level of 50 µg/L (Murillo-Arbizu et al. 2009). In Valencia, another study detected patulin in 23 % of fruit concentrate samples, with levels as high as 126 µg/kg in pear and apple concentrates (Marín et al. 2011). Tunisian studies found patulin to be a concern for the country; one showed that the incidence of patulin was 35%, along with 18% of apple juice samples and 28% of baby food samples exceeding the recommended limit, and a second study found contamination in 50% of 214 samples of various fruit products and 22% of them surpassed the limit of 50 µg/kg of patulin (Zaied et al. 2013; Zouaoui et al. 2015). Lastly, an evaluation of the occurrence of patulin in different fruits, juices and smoothies in Punjab, Pakistan reported that out of 237 samples about 33.8% had concentration levels of patulin above the permissible regulations of 50 µg/kg (Iqbal et al. 2018).

Other evaluations reported the presence of patulin at acceptable levels. Only 3% of sampled apple-based drinks in the State of São Paulo, Brazil, had a patulin concentration of 3-7 µg/L, suggesting that patulin isn't a problem in the region or control methods are effective (Iha and Sabino 2008). In Greece, patulin was found in 100% of 90 samples of fruit juices, however only one sample surpassed the PMTDI for patulin (Moukas, Panagiotopoulou, and Markaki 2008). In Japan, in products marketed in the Tohoku district, patulin was detected in 3 of 143 samples of domestic fruit juices and in 6 of 45 samples of imported juices and juices produced with imported apple juice concentrate in concentrations lower than the maximum limit of 50 µg/liter currently adopted by many countries, including Japan. (Watanabe and Shimizu 2005). A survey of 144 apple-based-foods in Portugal revealed an incidence of positive samples to be 23% with a maximum detected value of 42 µg/kg (Barreira, Alvito, and Almeida 2010). In a later study, patulin levels in apple juices ranged from 1.86 to 45.47 µg/kg, results consistent with those previously reported in Portugal (Cunha et al. 2014). Cunha *et al. (*2014), also carried out the first survey in tomato products that showed that 37.5% of the samples contained patulin in levels ranging from 3.22 to 47.72 µg/kg. Another Portuguese study found a patulin incidence of 75% in cereal-based foods with a maximum level of 4.50 µg/kg (Assunção et al. 2016). Torović et al. (2017) reported for the first time the occurrence of patulin in apple-based food for infants and children marketed in Serbia, finding patulin in 43.8% of infant juices and 16.7% of infant puree, with all values below the legal limit of 10 µg/

kg. Furthermore, 43.0% of the juices for children samples were contaminated with the highest patulin concentration at 30.2 µg/kg, not exceeding the maximum allowed level of 50 µg/kg (Torović et al. 2017). A review of mycotoxin contamination of foods in Southern Africa mentioned two studies of apple juice samples, where they detected toxin ranges of <10 to 75.2 µg/kg in 2007 and <10 to 1,650 µg/kg in 2010 (Misihairabgwi et al. 2017). Finally, studies carried out in the regions Catalonia and Valencia, Spain, sampled an array of apple products, including infant foods, and patulin levels were below the maximum levels fixed by the European Union (Cano-Sancho et al. 2009; Marín et al. 2011). A summary of patulin occurrence in various foodstuffs is given in Table 1.

Table 1. Patulin occurrence in various products (results published from 2005).

Product	Origin	No. of positive samples/total samples	LOD	LOQ	Range of positive samples (µg/kg) (µg/liter)	Average of positive samples (µg/kg) (µg/liter)	References
Apple juice, including clear and cloudy juices, and nectars	Sold in Belgium	12/90	5.2	8.1	6.6-13.8	10.2	(Baert et al. 2006)
	Sold in Brazil	4/134	3	7	3-7	ng	(Iha and Sabino 2008)
	China	1941/1987	0.82	2.72	ng-78	8.44	(Y. Guo et al. 2013)
	China	15/15	1.2	1.8	<1.2-90.3	22.8	(Yuan et al. 2010)
	Sold in Argentina	1866/4634	3	10	ng-19,662	26	(Oteiza et al. 2017)
	Sold in Greece	29/29	0.23	1.20	0.9-11.8	5.50	(Moukas, Panagiotopoulou, and Markaki 2008)
	Sold in Italy	16/33	ng	0.5	ng-53.4	3.14	(Piemontese, Solfrizzo, and Visconti 2005)
	Sold in Italy	9/14	1.5	ng	1.7-4.5	2.5	(Versari, Parpinello, and Mattioli 2007)
	Sold in Japan	9/188	4.0	10.0	ng	8	(Watanabe and Shimizu 2005)
	Sold in Michigan, US	ng/141	4.0	ng	8.8-2,700.4	257.5	(Harris, Bobe, and Bourquin 2009)
	Sold in Portugal	28/68	1.2	3.9	ng-42	ng	(Barreira, Alvito, and Almeida 2010)
	Sold in Portugal	5/9	ng	ng	1.86-45.47	ng	(Cunha et al. 2014)
	Sold in Qatar	20/20	1.0	5.0	5.8-82.2	35.37	(Hammami et al. 2017)
	Sold in Serbia	43/100	0.4	1.0	ng-30.2	5.6	(Torović et al. 2017)
	Sold in Spain	30/71	2.08	6.25	ng-15.0	8.1	(Cano-Sancho et al. 2009)
	Sold in Spain	68/100	0.7	2.5	0.7-118.7	19.4	(Murillo-Arbizu et al. 2009)
	Sold in Spain	2/28	2.1	ng	2.9-6.0	ng	(Marín et al. 2011)
	Sold in Tunisia	27/42	0.01	0.05	4-122.36	45.71	(Zouaoui et al. 2015)
	Iran	72/72	5.0	15.0	29.6-151.2	ng	(Forouzan and Madadlou 2014)
	Sold in Iran	39/76	ng	ng	<3-39.5	ng	(Poostforoushfard et al. 2017)
Organic apple juice, including clear and cloudy juices, and nectars	Sold in Belgium	8/65	8.6	16.0	6.2-80	43.1	(Baert et al. 2006)
	Sold in Italy	12/24	ng	0.5	ng-69.3	7.11	(Piemontese, Solfrizzo, and Visconti 2005)
	Sold in Italy	3/8	1.5	ng	1.0-22	9.8	(Versari, Parpinello, and Mattioli 2007)

Apple juice concentrate	China	20/20	1.2	1.8	<1.2-94.7	28.6	(Yuan et al. 2010)
	Turkey	23/23	0.23	1.20	2.6-36.8	11.60	(Moukas, Panagiotopoulou, and Markaki 2008)
	China	14/14	0.23	1.20	3.8-16.2	8.50	(Moukas, Panagiotopoulou, and Markaki 2008)
	Sold in Spain	14/33	2.1	ng	9.3-74.4	ng	(Marín et al. 2011)
	Sold in Tunisia	24/30	0.01	0.05	4.5-889	158.1	(Zouaoui et al. 2015)
Apricot juice	Sold in Argentina	1/22	3	10	ng-16	0.7	(Oteiza et al. 2017)
	Sold in Italy	7/27	1.2	1.7	ng-32.4	3.6	(Spadaro, Garibaldi, and Gullino 2008)
Apricot juice concentrate	China	2/2	0.23	1.20	12.2-15.3	13.70	(Moukas, Panagiotopoulou, and Markaki 2008)
Grape juice	Sold in Argentina	5/50	3	10	ng-13,808	283	(Oteiza et al. 2017)
Orange juice	Sold in Argentina	0/17	3	10	-	-	(Oteiza et al. 2017)
	Sold in Greece	3/3	0.23	1.20	3.1-10.8	6.80	(Moukas, Panagiotopoulou, and Markaki 2008)
Peach juice	Sold in Argentina	9/93	3	10	ng-24	5	(Oteiza et al. 2017)
	Sold in Italy	2/30	1.2	1.7	ng-5.0	0.3	(Spadaro, Garibaldi, and Gullino 2008)
Peach juice concentrate	Sold in Spain	4/15	2.1	ng	9.4-21.3	ng	(Marín et al. 2011)
Pear juice	Sold in Argentina	122/1138	3	10	ng-1749	54	(Oteiza et al. 2017)
	Sold in Italy	1/7	ng	0.5	ng-1.1	0.22	(Piemontese, Solfrizzo, and Visconti 2005)
	Sold in Italy	25/39	1.2	1.7	ng-33.4	5.1	(Spadaro, Garibaldi, and Gullino 2008)
	Sold in Tunisia	20/42	0.01	0.05	5-231	62.5	(Zouaoui et al. 2015)
Organic pear juice	Sold in Italy	4/8	ng	0.5	ng-61.0	11.46	(Piemontese, Solfrizzo, and Visconti 2005)
Pear juice concentrate	Sold in Spain	5/10	2.1	ng	90.4-126.9	ng	(Marín et al. 2011)
Pineapple juice	Sold in Argentina	0/6	3	10	-	-	(Oteiza et al. 2017)
Pineapple juice concentrate	Sold in Greece	1/1	0.23	1.20	7.7	7.7	(Moukas, Panagiotopoulou, and Markaki 2008)
Mixed fruit juices	China	30/30	1.2	1.8	<1.2-91.8	13.1	(Yuan et al. 2010)
	Sold in China	3/20	3.5	8.0	ng-16.8	13.1	(Ji et al. 2017)
	Sold in Greece	12/12	0.23	1.20	2.8-11.2	5.60	(Moukas, Panagiotopoulou, and Markaki 2008)
	Sold in Italy	8/45	ng	0.5	ng-0.7	0.19	(Piemontese, Solfrizzo, and Visconti 2005)
	Sold in Italy	9/29	1.2	1.7	ng-25.4	4.9	(Spadaro, Garibaldi, and Gullino 2008)
	Sold in Tunisia	17/34	0.01	0.05	10-55.7	28.5	(Zouaoui et al. 2015)
	Sold in Pakistan	136/237	0.04	0.12	0.04-1100	ng	(Iqbal et al. 2018)
Organic mixed fruit juices	Sold in Italy	6/12	ng	0.5	ng-13.5	2.10	(Piemontese, Solfrizzo, and Visconti 2005)
Baby apple juice	Sold in Qatar	6/6	1.0	5.0	7.7-61.3	30.67	(Hammami et al. 2017)
	Sold in Serbia	21/48	0.4	1.0	ng-8.3	3.6	(Torović et al. 2017)
Baby foods	China	19/30	1.2	1.8	<1.2-67.3	9.3	(Yuan et al. 2010)
	Sold in Greece	3/3	0.23	1.20	4-6.9	5.10	(Moukas, Panagiotopoulou, and Markaki 2008)
	Sold in Qatar	7/7	1.0	5.0	1.02-24.57	1.92	(Hammami et al. 2017)
	Sold in Serbia	11/66	0.4	1.0	ng-7.7	3.4	(Torović et al. 2017)
	Sold in Spain	42/124	2.08	6.25	ng-9.6	7.1	(Cano-Sancho et al. 2009)
	Sold in Spain	0/17	1.4	ng	-	-	(Marín et al. 2011)
Apple Cider	Sold in Michigan, US	ng/18	4.0	ng	15.3-35.2	24.2	(Harris, Bobe, and Bourquin 2009)
Organic apple vinegar	Sold in Italy	2/6	ng	1.25	ng-4.2	1.52	(Piemontese, Solfrizzo, and Visconti 2005)
Grape must	Germany	52/96	ng	ng	3.5-80	10.7	(Majerus, Hain, and Kölb 2008)
Solid apple-based products, including marmalade, puree, sweet and jam	Sold in Argentina	6/26	2.8	4.7	17-39	27.0	(Funes and Resnik 2009)
	Sold in Argentina	0/7	2.8	4.7	-	-	(Funes and Resnik 2009)
	Sold in Argentina	0/4	2.8	4.7	-	-	(Funes and Resnik 2009)
	Sold in Argentina	4/8	1.7	6.3	22-221	123.0	(Funes and Resnik 2009)
	Sold in Portugal	5/76	1.2	3.9	ng-5.7	ng	(Barreira, Alvito, and Almeida 2010)
	Sold in Spain	4/77	2.08	6.25	ng-17.6	13.5	(Cano-Sancho et al. 2009)

	Sold in Spain	0/5	1.4	ng	-	-	(Marín et al. 2011)
	Sold in Tunisia	7/35	0.01	0.05	2-76.75	32.26	(Zouaoui et al. 2015)
	Sold in Tunisia	5/15	0.01	0.05	4.7-554	302	(Zouaoui et al. 2015)
Pear marmalade and jam	Sold in Argentina	1/6	3.8	2.9	25	25	(Funes and Resnik 2009)
	Sold in Tunisia	7/16	0.01	0.05	17-325	123.7	(Zouaoui et al. 2015)
Mixed fruit jams and purees	Sold in China	2/20	2.6	8.6	ng-11.0	10.8	(Ji et al. 2017)
	Sold in Italy	1/15	ng	0.5	ng-0.7	0.11	(Piemontese, Solfrizzo, and Visconti 2005)
Organic fruit purees	Sold in Italy	9/25	ng	0.5	ng-13.0	0.18	(Piemontese, Solfrizzo, and Visconti 2005)
Tomato pulps, juices and jellies	Sold in Portugal	10/28	ng	ng	3.22-47.72	ng	(Cunha et al. 2014)
Dried longans	Sold in China	19/21	3.2	10.0	ng-194.3	75.0	(Ji et al. 2017)
Dried figs	Sold in China	13/20	7.5	15.0	ng-276.9	130.7	(Ji et al. 2017)
Dried hawthorn	Sold in China	2/20	2.7	8.9	ng-11.5	11.1	(Ji et al. 2017)
Mixed dried fruit products	Sold in China	3/36	3.8	12.5	ng-68.0	42.5	(Ji et al. 2017)
Cereal-based foods	Sold in Portugal	15/20	0.9	2.9	ng-4.50	2.33	(Assunção et al. 2016)

LOD, limit of detection, LOQ, limit of quantification and ng, not given.

DETECTION AND ANALYSIS

The presence of patulin in surveillance studies conducted around the world highlight the global issue and risk that patulin contamination of apple and other fruit products poses to consumers worldwide. This growing concern calls for the development of simple and fast detection techniques to ensure the effective and timely determination of patulin levels in foods. A recent review of current sample preparation and analytical methods for patulin detection in apple-based food matrices has been published by Li et al., (Xianjiang Li et al. 2017).

According to Association of Official Analytical Chemists Intl., the official method to quantify patulin in apple juice is high-performance liquid chromatography (HPLC) with ultraviolet (UV) detection, using clean-up with ethyl acetate and sodium carbonate, method 995.10. However, there are several drawbacks (e.g. intricate sample preparation processes prior to analysis, expensive instruments and equipment) of this method, as well as

other conventional analytical methods, that have sparked interest in developing alternative methods.

A study conducted by Yang et al. (2017) developed an analytical method based on the 96-Well Plate purification and LC-MS/MS determination for patulin analysis. Sample preparation was optimized by carrying out purification in MAX 96-Well plate and using an ammonium hydroxide concentration in the eluate of 0.8%. This method obtained acceptable accuracy and precision, and its limit of detection and limit of quantification were 0.30 and 1.0 μg/L, respectively. Li et al., (Xianjiang Li et al. 2018) developed a rapid and simple methodology for measuring patulin in apple juice by combining single-drop liquid-liquid-liquid microextraction (SD-LLLME) with isotope dilution ultra-high-performance liquid chromatography-mass spectrometry (LC-MS/MS). The SD-LLLME method used had an extraction time of 20 min, consumed less organic solvent, and showed great advantage in sample throughput compared to other extraction methods. The separation was performed on a 1.7 μm C18 column (2.1 x 50 mm), at a flow rate of 0.3 mL/min with gradient elution. Detection was carried out with a triple quadrupole MS, with optimized parameters to get the best sensitivity of patulin (capillary voltage, −2.5 kV; corn voltage, 10 V; source offset voltage, 30 V), and to reach the highest response of daughter ion, m/z 109 (collision gas follow rate, 0.05 mL/min; collision energy, 8). The established method had a limit of detection of 0.5 μg/L, a limit of quantification of 2 μg/L, and demonstrated many advantages like short

preparation time, easy manipulation, low solvent consumption and high accuracy.

A validated and sensitive HPLC with diode array detection (DAD) method for patulin determination in complex fruit matrices, like strawberries, was developed by Sadok, Szmagara, and Staniszewska (2018). They applied a modified version of QuECheRS (Quick, Easy, Cheap, Effective, Rugged and Safe) procedure for sample preparation to extract patulin from strawberries. They optimized the extraction process by employing acetonitrile with glacial acetic acid (AA) (1%, v/v) as the solvent; the sample purification by conducting the cleanup on tubes containing 150 mg $MgSO_4$, 25 mg primary secondary amine (PSA) and 7.5 mg Carbon; and the residue reconstitution by using an acidified acetonitrile and water phase (10:90, v/v). The method developed uses a C18 Rapid resolution HT 3.5 µm column (4.6 x 150 mm) coupled with a 5 µm C18 Narrow Bore Guard column (2.1 x 12.5 mm), a mobile phase composed of two solvents (0.1% (v/v) AA in water, 0.1% (v/v) AA in acetonitrile) applied in a gradient program during a 25 min run at 0.5 µL/min and monitoring of the eluted material at 276 nm wavelength. The protocol presented a limit of detection of 1.5 µg/kg, a limit of quantification of 5 µg/kg, and yielded good precision, excellent extraction efficiency and recovery results.

One technique that has been gaining popularity as a promising method for rapid patulin detection is molecularly imprinted polymer (MIP), due to its low cost, simplicity, reliability and wide choice of templates and functional monomers (W. Guo et al. 2017). The development of a magnetic molecularly

imprinted stir-bar (MMISB) for patulin isolation was reported by Regal et al. (2017). Its applicability was tested in spiked apple samples with subsequent detection with HPLC-MS/MS. A non-covalent approach was used to prepare the polymer, as well as, bulk polymerization with a pre-polymerization mixture of methanol and toluene (90:10) as solvents and EGDMA as the cross-linker. The extraction protocol consisted of adding and removing solvents from a beaker and only required a magnetic stirrer and an external magnet. Recoveries were 60%-70% in a minimum loading time of 45 min under stirring and the polymer coat showed no deterioration after several hours of use. The limit of detection was 10 ng/g and the limit of quantification was 50 ng/g. In a study conducted by W. Guo et al. (2017) a MIP and electropolymerization technology-based electrochemical sensor was constructed. The electrode was modified with carbon dots (CDs), chitosan (CS) and gold nanoparticles (AuNPs), to enhance its sensitivity. To optimize the synthesis conditions of the molecularly imprinted polymer, they evaluated different ratios of template to monomer and a ratio of 1:6 was selected as the most suitable due to its superior current response. The limit of detection was 7.57 x 10^{-13} mol/L and recovery rates ranged from 96%-98.7% when tested in apple juice samples.

Giovannoli et al. (2017) screened a 256-member combinatorial polymeric library to identify polymer formulations with good binding properties towards patulin. The library was based on the use of 16 functional monomers, four cross-linkers and four porogenic solvents. The desired properties were good binding in acidic buffer (bound-to-total (B/T) ≥ 0.95) and almost negligible

binding in acetonitrile (B/T ≤ 0.05). Retention of patulin was strongly influenced by the environment in which the library screening took place. Screening performed in an acidic buffer led to patulin being completely retained by most of the polymers (200/256 with B/T ≥ 0.95), while, contrarily, when performed in acetonitrile complete retention of patulin was observed in a small number of polymers (13/256 with B/T ≥ 0.95) and a greater number showed no retention (33/256 with B/T ≤ 0.05). Twenty-five polymers were identified to possess the desired properties, and one of the polymers was randomly selected and used to set up a solid-phase extraction procedure of patulin from apple juice. Samples were analyzed with reverse phase HPLC and UV detection. The proposed extraction protocol was successful in simplifying the clean-up step and yielded good extraction results.

The development of a novel and optical detection method for patulin in apple juice combining the phosphorescence properties of Mn-doped ZnS quantum dots (QDs) with the high selectivity of MIPs has been reported by Zhang et al., (W. Zhang et al. 2017). The surface imprinting process used to build the nanosensor (MIP-QDs) was carried out using 6-HNA as the dummy template, due to the high specificity these showed for patulin, 3-aminopropyltriethoxysilane (APTES) as the functional monomer and tetraethoxysilane (TEOS) as the cross-linker. Evaluation of phosphorescence quenching parameters determined that pH 6.0 and the solvent of water were optimal for adsorption. Selectivity tests showed that the MIP-QDs were able to competitively bind patulin from the interferents. Phosphorescence sensing of

patulin was performed with an optimized MIP-QDs concentration of 0.04 mg/mL in a 30 min incubation time. The limit of detection was 0.32 µmol/L. The developed method achieved consistent accuracy compared to HPLC.

Bagheri et al. (2018) reported successful selective determination of patulin in spiked water and apple juice samples by an MIP-capped Ag nanoparticle/flake-like Zn-based metal organic framework nanocomposite (AgNPs@ZnMOF). The flake-like MOF was prepared by complexation of Zn^{2+} and terephthalic acid (TA), followed by a solution impregnation procedure to create Ag NPs in the pores of the MOF. The MIP layer was created on the surface of AgNPs@ZnMOF by self-assembly reaction of APTES as the cross-linker and TEOS as the main monomer with patulin as the template reagent. Specificity experiments that assessed the nanocomposite adsorption affinity towards patulin, its analogue molecules, and additional selected mycotoxins indicated the higher selectivity of the composite for patulin molecules. To reach maximum sensitivity in the fluorometric determination of patulin, several factors were evaluated and the combination of parameters that accomplished the optimum signal was TA: 1.5 mmol/L, H_2O_2: 1 mmol/ L, reaction time: 5 min, pH 7, contact time: 20 min, nanocomposite: 0.1 mg mL− 1 and weight ratio for Ag:MOF of 1:20. The developed method had a detection limit of 0.06 µmol/L, required no special pretreatment of samples except diluting steps and obtained recoveries in the 102.97% to 104.07% range.

A novel bioassay based on the fluorescent resonant energy transfer (FRET) strategy has been proposed by Z. Wu et al. (2018). The aptasensor utilized gold

nanoparticles (AuNPs) as the acceptor and upconversion nanoparticles (UCNPs) as donors. To increase proximity of the molecules, they connected energy donor and acceptor through the complementary DNA strands by conjugating the patulin-specific DNA aptamer reported by S. Wu et al. (2016) with ammino-functionalized UCNPs (AF-UCNPs), and modifying AuNPs with the aptamer partial complementary DNA fragments (pcDNA). An optimized dosage of pcDNA-AuNPs and exonuclease-catalyzed target recycling strategy were used to increase the assay detection sensitivity. Selectivity evaluations using five biotoxins as competitive agents resulted in far less changes in fluorescence intensities for the other toxins compared to that observed for patulin, demonstrating the strong anti-interference capacity of the assay. The method proved reliable with a limit of detection of 0.003 ng/mL and recoveries ranging from 93.33% to 105.21% in spiked apple juice samples. No significant difference was observed between the bioassay results and those obtained through HPLC.

Some of the above-mentioned techniques are simple and controllable, showing promise for their practical application as novel methods for patulin detection.

CONTROL

A recent review on patulin mitigation strategies in food and beverages was published by Ioi et al. (2017). They examine the effects of pre-processing controls, e.g. control of storage conditions, use of fungicides and physical removal of fungi and infected tissue; conventional processing steps, i.e.

clarification/filtration, heat treatment and fermentation; and other patulin reduction techniques, including biological control agents, chemical additives and several physical treatments, on patulin content in food and beverages. Barad, Sionov, and Prusky (2016) published a review of the operons involved in patulin biosynthesis, several environmental, and pre-processing factors affecting patulin activation and accumulation, as well as its involvement in pathogenicity.

As mentioned in the review Ioi et al. (2017), several microorganisms have been found to be capable of biodegrading, detoxifying or binding patulin. The focus is centered mostly in yeasts and lactic acid bacteria. X. Zhang et al. (2016) reported isolation of a new strain of filamentous fungi belonging to *Byssochlamys nivea* that showed the ability to degrade high concentrations of patulin. The *B. nivea* FF1-2 strain proved incapable of patulin production and was shown to reduce patulin in medium at a concentration of 500 μg/mL to undetectable levels. The effects of pH and temperature on patulin degradation were evaluated, achieving a maximum degradation rate of 97.1% at pH 4.0, and optimal performance at 37 ºC. The ability of *B. nivea* FF1-2 to reduce patulin appears to be due to a metabolic conversion process. Degradation of patulin in apple puree resulted in a 97.1% degradation rate on the ninth day and an overall organoleptic acceptability of the treated puree, showing the *B. nivea* FF1-2 potential for patulin reduction in fruit products.

Enzyme treatments are also being considered for their possible use in patulin detoxification. Immobilized porcine pancreatic lipase (PPL) was applied to

aqueous solutions for patulin reduction (Xiaohong Li et al. 2017). After testing several supporting materials, $CaCO_3$ was determined to be the ideal immobilization adsorbent for PPL. Optimum immobilization conditions were set at pH 5.0, temperature of 30 °C, in a 10 mL solution containing 0.5 g of $CaCO_3$ and 0.6 mg/mL of PPL and a 3-hour contact time. The effects of enzyme amount, pH, temperature, initial patulin concentration and time on the batch detoxification experiments were also evaluated, yielding the highest degradation rates at 60 mg/mL immobilized PPL, pH 6.0, temperature of 40 °C, initial concentration of 25 mg/L, and detoxification time of 42 hours. The enzyme was tested for reusability and maintained 65% of its detoxification capacity at the fifth successive batch detoxification experiment. Fourier transformed infrared (FTIR) spectra analysis results propose that patulin detoxification might be due to the lipases catalysis.

Detoxification strategies using Chitosan (CS), a natural polysaccharide produced by deacetylation of chitin, combined with other technologies, have been studied for patulin adsorption. The biosorption of a cross-linked xanthated chitosan resin (CXCR) for patulin from apple juice was investigated by Peng et al. (2016). The chemically modified chitosan resin was prepared by reversed phase suspension cross-linking method, with glutaraldehyde as the cross-linking agent and carbon disulfide as the modification agent. Adsorption conditions of CXCR were optimum at pH 4.0, 30 °C and 18 hours contact time. Experimental data consistent with the Freundlich model suggested that the adsorption mechanism of CXCR was considered as multilayer adsorption and

surface heterogeneity. Luo, Zhou, and Yue (2017) developed nontoxic chitosan-coated Fe_3O_4 particles for patulin adsorption. The magnetic adsorbent particles were prepared by using Triton X-100 as the emulsifier in a reverse-phase water-in-oil microemulsion system. Patulin adsorption was tested by adding 300 μg of chitosan-coated Fe_3O_4 particles to 10 mL of juice-pH simulation aqueous with a patulin concentration of 200 μg/L at pH 4.0 and 30 ºC, reaching a maximum adsorption capacity of 6.67 mg/g in within 5 hours of reaction time, as well as a recovery rate of 99.95% in 60 minutes. Cytotoxicity and acute toxicity studies revealed that the particles were biocompatible with no safety concerns and insignificant cytotoxicity.

Lastly, the reduction of patulin production in wheat tortillas using volatile bioactive compounds from mustard flours was reported by Saladino et al. (2016). Glucosinolates (GLS), the precursors of isothiocyanates (ITCs), known fungal growth inhibitors, were extracted and characterized from oriental and yellow mustard flours. The identified GLS, sinigrin (SN) and sinalbin (SA), are precursors of the antimicrobial compounds allyl isothiocyanate (AIT) and parahydroxybenzyl isothiocyanate (PHITC) respectively, used for growth reduction of inoculated *P. expansum* on wheat tortillas. Two bioactive packaging were evaluated for kinetic volatilization of AIT which achieved maximum volatilization between 1-24 h, depending on the volatilization technique, and remained stable for two months storage. Samples were analyzed with LC-MS/MS and the mean reduction of patulin observed was 92.58%.

CONCLUSIONS

The recognition of patulin as a hazard has risen in the last decade. An increased number of surveys on a variety of food products have revealed a dire situation for some countries. This situation should be a call to action for governments to set regulatory limits for patulin and to devise and implement preventive measures and monitoring programs for food surveillance of this toxin.

The development of fast and efficient detection and analysis methods for patulin is urgently needed. Rapid methods for patulin detection are still absent, hence, the AOAC Intl. standard HPLC-UV method is still the most commonly employed method.

Despite showing encouraging results, current control methods for patulin haven't reached the point of total assurance of safety of food products. There are several new technologies that might be promising alternatives to conventional practices. The great potential of these new methods may lead to the inclusion of some of these techniques in the production process as part of a hurdle approach to patulin reduction. In the future, increased safety will presumably come from an integrated system of conventional and innovative control methods throughout processing.

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