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Review

Patulin – a contaminant of food and feed: A review

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Contamination of food and agricultural commodities by various types of toxigenic molds (microscopic filamentous fungi) is a serious and widely neglected problem. Poor harvesting practices, improper drying, handling, packaging, storage and transport conditions contribute to fungal growth and increase the risk of mycotoxin production. Patulin is a toxic chemical contaminant produced by several species of microscopic filamentous fungi. It is the most common mycotoxin found in apples, apricots, grapes, grape fruit, peaches, pears, olives and cereals. Patulin has been reported to be a genotoxic, reprotoxic, embryotoxic, and immunosuppressive compound. Further research needs to be focused on the generation of data dealing with epidemiological and toxicity effects, especially in humans.

Keywords: mycotoxin, patulin, toxicity

1 Mycotoxin patulin

Mycotoxins are low-molecular-weight toxic chemical compounds with low volatility, representing secondary metabolites produced by certain filamentous fungi that colonize crops, in the field or post-harvest, capable of causing disease and death in humans and animals through the ingestion of contaminated food products (Cunha et al., 2014). Contamination of food and agricultural commodities by various types of toxigenic molds (microscopic filamentous fungi) is a serious and widely neglected problem. Regardless of decades of extensive research, mold infection still remains a challenging problem (Munkvold, 2003). Poor harvesting practices, improper drying, handling, packaging, storage and transport conditions contribute to fungal growth and increase the risk of mycotoxin production (Bhat et al., 2010).

Patulin, 4-hydroxy-4H-furo[3,2c]pyran-2(6H)-one, is produced by many different molds but was first isolated as an antimicrobial active principle during the 1940s from *Penicillium patulum* (later called *Penicillium urticae*, now *Penicillium griseofulvum*) (Birkinshaw et al., 1943). The same metabolite was also isolated from other species and given the names clavacin, claviformin, expansin, mycoin c, and penicidin (Ciegler et al., 1971). A number of early studies were directed towards harnessing its antibiotic activity. For example, it was tested as both a nose and throat spray for treating the common cold and as an ointment for treating fungal skin infections (Chalmers et al., 2004; Ciegler, 1977). However, during the 1950s and 1960s, it became apparent that, in addition to its antibacterial, antiviral, and antiprotozoal activity, patulin was toxic to both plants and animals, precluding its clinical use as an antibiotic. During the 1960s, patulin was reclassified as a mycotoxin (Bennet and Klich, 2003).

1.1 Producers and occurence of patulin

Patulin is a metabolite produced by a large number of microscopic filamentous fungi within several genera such as *Bysochlamys*, *Eupenicillium*, *Penicillium*, *Aspergillus* and *Peacylomyces* in a variety of food products, e.g. apricots, grapes, grape fruit, peaches, pears, apples, olives and cereals (Askar and Siliha, 1999; Arici, 2000; Gokmen and Acar, 2000; Yurdun et al., 2001; Kadakal and Nas, 2002; Moreau, 2002). Nowadays, *Penicillium expansum*, the blue mold that causes soft rot of apples, pears, cherries, and other fruits, is recognized as one of the most common offenders in patulin contamination.

Several studies have shown that patulin is stable in dry cereals, and in apple and grape juice, but that it is decomposed in wet cereals and during production of cider (Armentia et al., 2000; Trucksess and Tang, 2001; Most and Long, 2002). Residues of patulin can cause particular safety issues in products sucha s juices derived from apples and citrus fruits (Verger et al., 1999; Beretta et al., 2000).

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Today, patulin belongs to a short list of mycotoxins (aflatoxins, ochratoxin A, zearalenone, fumonisins and trichothecenes) whose level in food is regulated in many countries around the world, with European countries being among the first to propose limits in the levels. Since 2003, European regulation 1425/3003 sets a maximum level of 50 μg L^{-1} for fruit juices and derived products, 25 μg L-1 for solid apple products and 10 μg L^{-1} for juices and foods destined for babies and young infants (Chalmers et al., 2004). The US Food and Drug Administration (FDA) limits patulin to 50 μg L^{-1} (Puel et al., 2010). Since patulin persists in heated juices, it has been suggested that its presence in processed apple products may be a good indicator of the quality of fruits used for their production (Jackson and Dombrink-Kurtzman, 2006).

Occurrence of patulin in different fruit products had been determined and summarised here in Table 1. Food commodities that have been contaminated with patulin-producing microscopic filamentous fungi are listed in Table 2.

1.2 Absorbtion, distribution, metabolism, excretion and biochemical processes of patulin

Patulin administered via the diet is not representative of the human intake as most of that intake comes from drinks containing patulin (Wouters and Speijers, 1996; Fliege and Metzler, 1999). Distribution and metabolism studies of patulin are limited, and no metabolic products have yet been identified. It is quite likely that metabolic fragments or conjugated metabolites of patulin either are bound to the cell membranes or become incorporated

Table 1 Patulin concentrations in fruit products quantified in stable isotope dilution assays using GC/HRMS (Rychlik, 2005)

Product	Samples	Patulin concentration (μg L^{-1})
Apple juices, commercial products	10	5–26.0
Apple juices, home-made	2	11.4 23.9
Apple juice, specially prepareda	1	<0.02
Apple-acerola juice, commercial product	1	0.7
Grape juice, commercial products	2	4.9–5.2
Sour cherry juice, commercial product	1	0.2
Blackcurrant juice, commercial product	1	0.1
Orange juice, commercial product	1	0.1
Plum pulp, commercial product	1	0.8[b]
Apple pulp, commercial product	1	<0.02[b]
Raspberry syrup, commercial product	1	<0.02[b]

[a] peel and core were removed before pressing the apples, [b] values in μg kg^{-1}

Table 2 Food commodities contaminated with patulin-producing microscopic filamentous fungi (Deshpante, 2002)

Commodity	Patulin-producing microscopic filamentous fungi
Wheat flour	*Aspergillus terreus*, *A. clavatus*, *P. patulum*, *P. cyclopium*
Refrigerated dough products	*A. terreus*, *P. urticae*
Cereals and legumes	*Penicillium expansum*, *P. urticae*, *A. terreus*, *A. clavatus*, *Byssochlamys nivea*
Pecans	*P. expansum*
Fruits (apricots, crab apples, persimmons, pears, grapes, apples)	*P. expansum*, *B. nivea*
Fruit juices	*B. nivea*
Meat	*P. expansum*, *P. urticae*, *P. melinii*, *P. clavifonne*
Poultry feed	*P. patulin*, *P. cyclopium*
Cheese, Swiss	*Penicillium* spp.
Cheese, Cheddar	*Penicillium* spp.
Bread	*P. patulum*, *P. cyclopium*

into the cellular components. Results of metabolic studies of C-patulin show that it is excreted principally via the faeces and urine. The major retention and storage site is the erythrocyte (Dailey et al., 1977; McKinley and Carlton, 1991). Patulin has an inhibiting effect on several biochemical parameters such AT-Pase, alkaline phosphatase, aldolase and hexokinase activity. Patulin was able to activate glycogen phosphorylase in the liver, and blood glucose levels increased by 60%. It inhibits aerobic respiration in several systems (Singh, 1967; Stott and Bulleman, 1975; Wouters and Speijers, 1996). Patulin inhibits protein synthesis. As a result, the concentration of glycogen in liver, kidney and intestinal tissues was reduced by high intakes of patulin. The decrease in hepatic glycogen indicated glucose intolerance, which may be due to insulin insufficiency. On the other hand gluconeogenesis was stimulated as evidenced by increased glucose-6-phosphatese and fructose 1,6-diphosphase activity (Wouter and Speijers, 1996). It is amazing how little is known yet on the pharmacokinetic behaviour and metabolism of patulin. Nevertheless no data on these aspects have been published recently.

1.3 Toxicyty of patulin

Patulin has a strong affinity for sulfhydryl groups. Patulin adducts formed with cysteine are less toxic than the unmodified compound in acute toxicity, teratogenicity, and mutagenicity studies. Its affinity for SH-groups explains its inhibition of many enzymes (Puel et al. 2010).

Patulin has been demonstrated to be acutely toxic, genotoxic, teratogenic, and possibly immunotoxic to animals. Although the toxicity of patulin in humans has not been demonstrated conclusively and the effects of long-term exposure are still unknown, to limit its concentration in foodstuffs is taken as a precautionary measure (Cunha et al., 2014).

Animal studies and observations in human have shown that patulin has toxic properties. Acute toxicity after high dosing in animals is expressed as agitation, convulsions, dyspnoea, pulmonary, congestion, oedema, ulceration, hyperaemia and gastrointestinal tract distension (Escuola et al., 1977; Dailey et al., 1977b; Hayes et al., 1979). Nausea, vomiting, gastrointestinal disturbances and kidney damage have been reported for humans (Drusch and Ragab, 2003; Ito et al., 2004). Patulin has been reported to be a genotoxic, reprotoxic, embryotoxic, and immunosuppressive compound (Rol et al., 1990; Hopkins, 1993; Sharma, 1993; Selmangolu and Kockaya, 2004; Selmangolu, 2006; FAO-WHO, 1995; JECFA, 1996). IARC classified patulin in Group 3 (not classifiable as to carcinogenity to humans) (IARC, 1986).

Patulin is toxic at high concentration in laboratory settings, but evidence for natural poisoning is indirect and inconclusive. Nevertheless, the Joint Food and Agriculture Organization-World Health Organization Expert Committee on Food Additives has established a provisional maximum tolerable daily intake for patulin of 0.4 mg kg^{-1} of body weight per day (Puel at al., 2010; JEFCA, 1996).

2 Conclusions

The occurrence of mycotoxins in the food chain is an unavoidable and serious problem the world is facing (Bhat et al., 2010). In recent years, only a few studies have been published on the *in vivo* toxicity of patulin. Most of the toxicological studies have used *in vitro* models and focused on the immunotoxic and genotoxic effects of the toxin (Puel et al., 2010). Wide gaps still exist on the toxicological effects of feeding animals mycotoxin-contaminated feeds. Research in this field is a necessity as there is every possibility that the toxins will enter the human food chain. Further research also needs to be focused on the generation of data dealing with epidemiological and toxicity effects, especially in humans.

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