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Review

The characteristics, occurrence, and toxicological effects of patulin

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ABSTRACT

Mycotoxins are the secondary metabolites secreted by different types of fungi to which humans can get exposed mainly via ingestion. Patulin ($C_7H_6O_4$) is a polyketide lactone produced by various fungal specifies, including *Penicillium expansum* as the main producer. *P. expansum* can infect different fruits and vegetables yet it has preference to apples in which they cause blue rot. Therefore, apples and apple-based food products are the main source of Patulin exposure for humans. Patulin was first identified in 1943 under the name of tercinin as a possible antimicrobial agent. Although it is categorized as a non-carcinogen, Patulin has been linked, in the last decades, to neurological, gastrointestinal, and immunological adverse effects, mainly causing liver and kidney damages. In this review, the characteristics of and possible human exposure pathways to Patulin are discussed. Various surveillance and toxicity studies on the levels of Patulin in various food products and effects of Patulin on cells and animal models have been documented as well. Importance of epidemiological studies and a summary of the possible toxicity mechanisms are highlighted with a case study. The commonly used control methods as described in the literature are also discussed to guide future researchers to focus on mitigating mycotoxins contamination in the food industry.

1. Introduction

Human fungal infections are a public health concern, especially, in immunocompromised patients, such as HIV patients, some cancer patients, patients on immunosuppressive medicines such as organ recipients and bone marrow transplant recipients, in addition to underweight newborn babies. Exposure to any xenobiotic, including radioactive materials, hydrocarbons, heavy metals, and mycotoxins, is a human health risk, specifically resulting in immune system problems, digestive system and nervous system abnormalities, kidney and liver dysfunctions, and cancers (Rahmani et al., 2018). Mycotoxins producing fungi are a major public health concern as accumulative mycotoxins in the body can be toxic, carcinogenic, mutagenic, and they might affect various systems in the body. The most concerning mycotoxins are aflatoxins, ochratoxin A, patulin, fumonisins, zearalenone, T-2 and HT-2 toxins, and deoxynivalenol. Most mycotoxins' adverse health effects are based on individual mycotoxin analysis, however, multiple mycotoxins might occur at the same time in food, which increases the level of concern (Leyva Salas et al., 2017; van Egmond et al., 2007). Once mycotoxins are formed, it will be difficult to manage their amounts, as they are stable in storage and very insensitive to physical and chemical treatments. Therefore, the best way to limit mycotoxins' exposure is to lessen their formation in the first place (Copetti et al., 2014).

Patulin is a mycotoxin produced by various fungi, in particular by *Aspergillus, Byssochlamys*, and *Penicillium*. It was first isolated from *Penicillium griseofulvum* in 1943 by Harold Raistrick (1943). Soon after its identification, Patulin was studied at the British Medical Research Center under the name of "tercinin" as an antimicrobial agent against some gram positive and gram negative bacteria, however, it was not long until the researchers at the center has identified its toxic effects in 1944 (Chalmers and Clarke, 2004). Patulin has been identified in a variety of food products, including fruits and vegetables. However, it is mostly found in apples, in which its level is applied as a quality indicator of apples used in juice or compost production (Zhong et al., 2018).

In this review, the characteristics of "Patulin" are discussed together with the possible human exposure pathways. The review intends to provide toxicologists and food science specialists a detailed surveillance on the levels of Patulin in apple-based foods around the word. Various toxicity studies of Patulin on cells and animal models have been also documented. The review highlights also the possible toxicity mechanisms of Patulin and discusses different control mechanisms that have been evaluated so far in controlling the levels of Patulin in fruits and fruits-based products. The review aims to guide future researchers to focus on mitigating mycotoxin contamination in the food industry.

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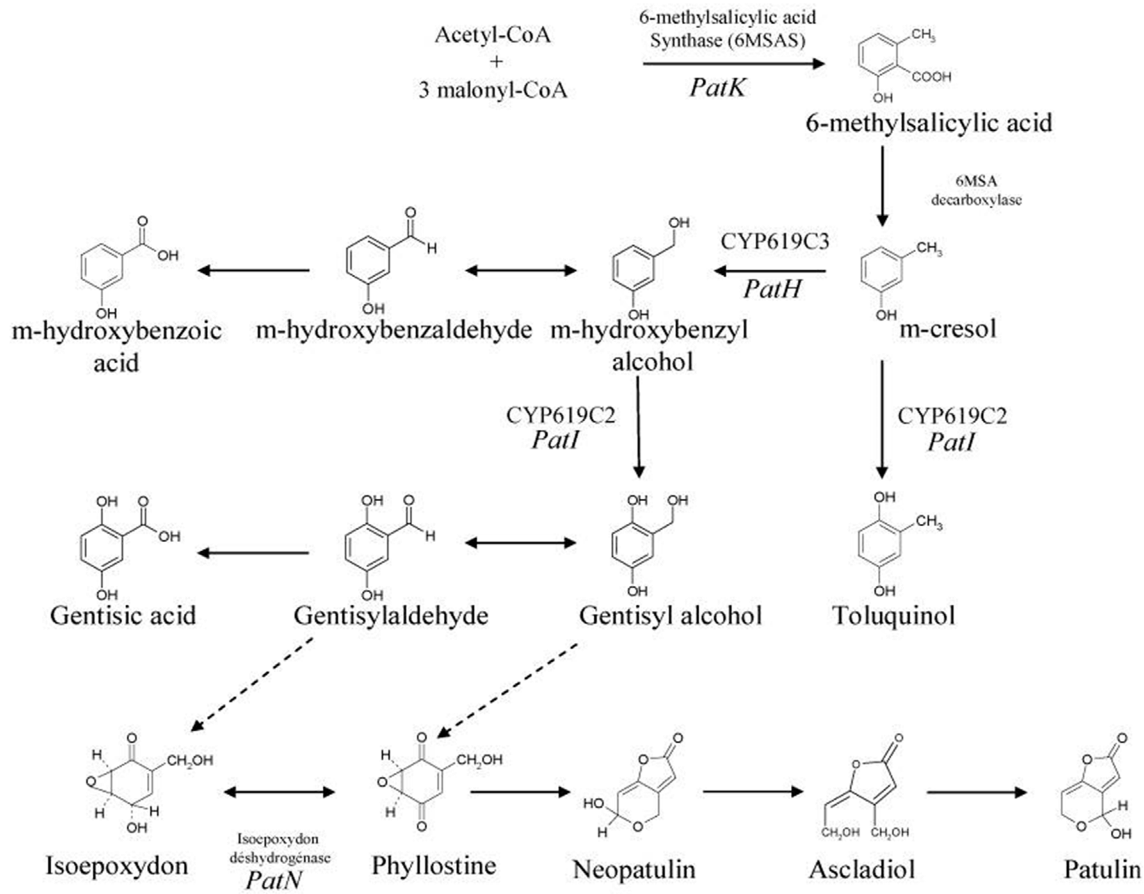

Fig. 1. Patulin biosynthesis pathway (Puel et al., 2010).

2. Physical and chemical characteristics and biosynthesis of patulin

Patulin ($C_7H_6O_4$) is a polyketide lactone, which is a water soluble white powder. This organic compound is classified as a heat-stable lactone that cannot be thermally denatured. The molar mass of Patulin is 154.12 g/mol and its melting point is 110 °C. According to many biochemical studies, the pathway of Patulin biosynthesis consists of 10 steps (Fig. 1) (Puel et al., 2010). Recently fifteen genes involved in Patulin biosynthesis have been identified by Li et al. (2019) among those genes PatE and PatH are proved necessary in Patulin production. In addition, three of the velvet family proteins have been identified as genes in charge of regulating Patulin levels (VeA, VelB and Vel C) (Zhai et al., 2019).

Penicillium expansum is the main food contaminant known to produce Patulin. As different spoilage microorganisms have different nutrient requirements, specific fungal types contaminate select food products and even fruits. *P. expansum* has preference to pome and stone fruits, such as peaches, cherries, and fruits in which they cause “blue rot” (Moss, 2008; Tannous et al., 2018). Patulin production depends on different factors, such as temperature, pH, and other physiological parameters (Tannous et al., 2018). It is still not clear when fungi secrete Patulin. For example, the level of Patulin secreted by *P. expansum* during apples’ infection can vary from 2 to 100 µg/g; however, the exact level is not related to the infectious characteristics of the fungal species, neither to its pathogenicity (Ballester et al., 2015).

3. Environmental fate of patulin

Patulin is heat stable and not likely to be metabolized by animals. Its environmental fate is not well understood. Many studies showed that plants could defend themselves against xenobiotics by changing the chemical structure of toxicants including mycotoxins. A study conducted on Patulin showed that it might bind to the solid part of the apple due to its electrophilic characteristics (Bissessur et al., 2001). This form of bound Patulin will not be experimentally detected during the chemical purification. There is sufficient evidence that this bound Patulin derivative or “masked Patulin” is not toxic on its own and; therefore, not important to be detected, yet masked mycotoxins might be hydrolyzed in the digestive system of the mammals back to their toxic form. As a result, further analysis is required to understand the toxicity of “masked Patulin” and its fate in the environment (Berthiller et al., 2013).

4. Route of exposure to patulin

Human get exposed to Patulin mainly via infected food products. Foods get the chemical toxin through fungal infections. Many factors affect the food fungal spoilage, including temperature, humidity, chemicals availability, and others. Chemical and physical conditions affect not only fungal growth but also the levels of mycotoxins production. Different types of food products might get fungal contamination via different pathways. Since the main source of Patulin for human comes from fruits, specifically apples and apple-based products as discussed earlier, only fruits’ fungal contamination pathways are discussed in this review.

Microbial contamination could be originated from the soil, air and/or irrigation water. Pre-harvesting infection occurs when microorganisms infect fruits through the calyx or along the stem (Mahajan et al., 2014). Fruit contamination might occur, on the other hand, during harvesting and post-harvesting steps, such as storage, packaging, transportation, and processing of fruits (Tournas, 2005). It is worth noting that *Penicillium* species have the capability to grow in fridges, which increases Patulin production possibility during storage (Altunatmaz et al., 2012). If the skin of the fruit is damaged during any of the harvesting and post-harvesting stages either mechanically or by insects or animal bites, or even by chilling injuries, the fruit becomes more prone for microbial spoilage as it gives the bacteria and fungi access to the soft tissue of the fruit. Animals like birds, rodents, and insects can carry microorganisms so they should be kept away from fresh fruits at all time (Tournas, 2005). In addition, some spoilage microorganisms can infect undamaged fruits and cause lesions that allow their own penetrations and other microorganisms' penetration (Barth et al., 2010). Inappropriate display of fruits in the market can lead also to cross contamination among goods. Workers poor hygienic practices can lead to contamination during the displaying and the final marketing processes. Finally, any inappropriate manufacturing practices is considered a possible contamination pathway (Mailafia et al., 2017). If fruits are not sold raw, contamination might occur during any stage of their processing. In the case of apple juice, the final product could get Patulin contamination at any stage of the juice production as indicated by Sant'Ana et al. (Sant'Ana et al., 2008). Other routes of Patulin exposure have been studied and they were proven to cause toxicity yet they are not likely to occur; therefore, only the ingestion route was considered as the major exposure pathway to Patulin (Pal et al., 2017).

5. Tolerable levels of patulin

Patulin is among a list of mycotoxins of which levels in food products are regulated. This list includes aflatoxins, ochratoxin A, fumonisins, trichothecenes, and zearalenone. According to the World Health Organization (WHO, 2005), the maximum acceptable level of Patulin in apple juice is set at 50 μg/L. This number is in congruence with the FDA and the European Union (EU) recommendations, the latter has also limited the level of Patulin in solid apple to 50 μg/kg, and in kids and babies apple-based foods to 10 μg/L (EU, 2002; FDA, 2005; WHO, 2005).

According to the European Commission's recommendation and based on the established NOEL level of Patulin (43 μg/kg body weight), the provisional maximum tolerable daily intake of Patulin (PMTDI) was set to be 0.4 μg/kg bw. This level has been adopted by most health risk assessment analyses conducted on Patulin (EC, 2006).

6. Populations at risk of patulin exposure

Mycotoxins related risks affect the entire populations in geographic areas where proper hygienic measures during food productions are not followed. High levels of Patulin affect all races, genders, and age groups. However, some age groups are more sensitive when it comes to exposure to toxicants. For instance, Nursing infants are another at risk population, consumption of the toxicant by the mother might lead to the presence of this toxicant in the breast milk in levels higher than the tolerable daily intake (TDI) for this age group even if the mother is exposed to the adults TDI only. A study conducted in 2017 showed that the level of Patulin in breast milk after a single dose exposure of the mother (mathematical model was used) and after multiple exposures were not at risk levels, yet other mycotoxins were risky (Degen et al., 2017).

In addition, the level of Patulin in apple-based foods for kids has been set to be 5 times lower than the acceptable level for adults, which indicates that children below the age of 12 are considered as population at risk (WHO, 2005). Besides having higher exposure per kilogram body weight, children have different physiology from those of adults, making them more vulnerable (Bruckner, 2000; Raiola et al., 2015).

Many studies have focused also on the exposure levels of pregnant women to various contaminants, as toxicants consumed by the mother can immediately affect the development of the fetus; therefore, pregnant women are another population at risk. Direct epidemiological studies on human are rare, a study conducted in France evaluated the exposure of pregnant women to Patulin showed that the daily intakes of food products involved in Patulin exposure is higher during pregnancy (Chan-Hon-Tong et al., 2013). Since Patulin is mainly detected in fruits (apple in particular), vegetarian mothers who consume higher amounts of fruits per day are expected to be another population at risk for mycotoxins including Patulin. According to a large scale study conducted in France, the average French population's Patulin daily intake was determined to be at 18–30 ng/kg bw, while the vegetarian population of the same study showed a significantly higher estimated average intake (34–50 ng/kg bw) (Leblanc et al., 2005).

Patulin is a possible proteotoxic molecule, studies have proven that toxicants that can affect organisms at the proteomic level should be studied in both genders and their response is usually sex-dependent (Guerra-Moreno and Hanna, 2017). The sex-dependent adverse effect of mycotoxins is often overlooked in related toxicology studies, yet many researchers have shown that males are more sensitive than females (Andretta et al., 2012). Patulin has been proven to have endocrine disrupting activity, in hormonal related studies in particular, both male and female models must be used to obtain correct interpretation of results (Soler and Oswald, 2018). The male population sensitivity to Patulin effect has also been proven in a study on the effect of intramuscular injection of Patulin in the bones' of rabbits, in which male rabbits have shown more intensive bone remodeling (Duranova et al., 2015).

7. Food contamination levels (chemical surveillance studies)

Adverse effects of Patulin can mainly be observed after prolonged exposure via consumption of contaminated food products. Many studies around the world surveyed the level of Patulin in various food products, especially in apples and apple-based foodstuffs. Table 1 summarizes the findings of published studies.

The highest maximum Patulin average contamination level was detected in Iran (620 μg/kg) by Montaseri et al. (2014) followed by Czech Republic (328.5 μg/kg) in the European Union as detected by Ostry et al. (2018). Data from other European countries showed the average Patulin levels within the acceptable range (Murillo-Arbizu et al., 2009; Piemontese et al., 2005; Sirot et al., 2013; Tangni et al., 2003; Thuvander et al., 2001). It is worth noting that a study in South Africa showed also an average Patulin level above the maximum acceptable level (Shephard et al., 2010). Finally, Gokmen and Acar (2000) showed also in one of their screening analyses in Turkey that 52% of the samples collected had Patulin concentrations above the recommended level.

8. Patulin-related adverse health effects

Acute exposure to Patulin might cause gastrointestinal symptoms including nausea, vomiting, ulcers, intestinal hemorrhages, and lesions in the duodenum. According to the International Agency of Research on Cancer (IARC), Patulin is a group 3 carcinogen, which means that there is not enough animal research based studies or epidemiological studies to support its carcinogenesis (IARC, 2018). Patulin's affinity to sulfhydryl groups has been widely described explaining its inhibitory effect towards many enzymes (ATPase, lysosomal enzymes, RNA polymerase etc.) (Puel et al., 2010). Nowadays, Patulin is known to be linked with neurological, gastrointestinal, and immunological adverse effects (Pal et al., 2017). In addition, WHO considers Patulin as a possible genotoxic compound (WHO, 2005). Toxicity assessments of Patulin showed damages in the vital organs and systems including liver, kidney, and others (Pal et al., 2017). Lately, the adverse effects of mycotoxins in general and of Patulin in particular on the susceptible structures of the intestines has been widely studied and Patulin toxicity on the function of the intestinal barrier was demonstrated (Akbari et al., 2017). Intestinal barrier has two other partners in the digestive system, the

Table 1
The Concentration of Patulin in various food products.

Sample type	Number of samples	Country	Contamination levels (μg/kg for solid and μg/L for liquid)	Average contamination level (SD)	Percentages of samples with contamination level above recommendations	Reference
Apples	12	Qatar	ND-17.3	3.71 (0.6)	Adult level→ 0% Children level → 16.6%	Hammami et al. (2017)
Apple juice	20	Qatar	5.8–82.2	35.37 (1.66)	Adult level→ 25%	
Baby apple juice	6	Qatar	7.7–61.3	30.67 (6.7)	Adult level→ 50%	
Baby apple compost	7	Qatar	1.02–24.57	10.92 (1.21)	Adult level→ 42.8%	
Apple leather	35	Iran	< 10-2259	620	Adult level→ 91.4% Children level → 94.2%	Montaseri et al. (2014)
Apple leather	36	China	ND-58.4		Adult level→ 2.7% Children level → 25%	Maragos et al. (2015)
Grapes	10	Czech Republic	119–644	328.5	Adult level→ 100% Children level → 100%	Ostry et al. (2018)
Apple juice	55	Iran	0–39.5		0	Poostforoushfard et al. (2017)
Apple	30	South Africa	< 10-1650	73(300)	Not calculated	Shephard et al. (2010)
Apple juice	36	Iran	0–190.7	52.8 (15.6)	Not calculated	Rahimi and Rezapoor
Apple juice concentrate	28	Iran	0–41.3	24 (4.9)	Not calculated	Jeiran (2015)
Apples	351	Portuguese	3–80.5	20.5	Not calculated	Martins et al. (2002)
Apples	29	Portuguese	2.1–12.6	5.6	0	Cunha et al. (2009)
Apple juice	50	Romania	0.7–101.9		Adult level→ 6%	Oroian et al. (2014)
Apple juice	45	Turkey	19.1–732.8		Adult level→ 44%	Yurdun et al. (2001)
Apple juice	30	Tunisia	0–167	80		Zaied et al. (2013)
Mixed fruits juice	30	Tunisia	0–125	55	Adult level→ 18%	
Apple compost baby food	25	Tunisia	0–165	68	Adult level→ 28%	
Apple juice	234	Turkey	5–376	63	Adult level→ 52%	Gokmen and Acar (2000)
Apple juice	119	Turkey	8–153	43	Adult level→ 34%	
Apple juice	67	Turkey	< 5-103	19	Adult level→ 8%	
Apple juice	62	Turkey	< 5-119	31	Adult level→ 8%	
Grapes	10	Czech Republic	119–644	328.5	Adult level→ 100% Children level → 100%	Ostry et al. (2018)
Apples	39	France	–	0.042	Not calculated	Sirot et al. (2013)
Apple juice	25	France	–	0.115	Not calculated	
Fruits juices (conventional)	100	Italy	0.5–53.4	1.15	Not calculated	Piemontese et al. (2005)
Fruits juices (Organic)	69	Italy	0.5–69.3	4.78	Not calculated	
Apples (conventional)	13	Italy	0.5–81.7	11.14	Not calculated	
Apples (Organic)	9	Italy	0.5–50.8	11.27	Not calculated	
Apple juice	100	Spain	0.7–118.7	19.4	Adult level→ 11% Children level → 41%	Murillo-Arbizu et al. (2009)
Apple juice	43	Belgium	0.67–38.8	9	0	Tangni et al. (2003)
Apple juice	39	Sweden	–	2.2	0	Thuvander et al. (2001)

mucus and the microbiota. Chronic exposure to mycotoxins including Patulin might significantly modify the normal intestinal flora composition. Patulin's effect on the intestinal microbiota clearly demonstrated that there is a need for further investigation (Robert et al., 2017).

9. Adverse health effects identified by animal models

The toxicity of Patulin has been widely explored using animal models including mice, hamsters, chicken, and monkeys. The exposure route was mainly through ingestion, the mycotoxin was added in many studies to the food or water of the animals, while in other studies gavaging was used (Table 2).

10. Patulin adverse effects on cell models and possible toxicity mechanisms

Many studies have evaluated the effect of Patulin on cells. The accumulative data of cells' toxicity clearly suggests that Patulin has adverse effects on various cells as summarized in Table 3.

Patulin is a highly reactive molecule with preference to sulfhydryl containing compounds. It is able to make covalent adducts with electrophilic chemicals (Fliege and Metzler, 2000). Intracellularly, Patulin targets cysteine and causes its depletion. It can also react with lysine and histidine containing proteins. This adduct formation is the main toxicity pathway of Patulin (Song et al., 2014b).

Among the toxicity mechanisms described, the overexpression of Rpn4 gene through activation of Rpn4 transcription factor that controls the expression of proteasome (in charge of protein degradation) is an important mechanism of Patulin toxicity. Once Rpn4 is overexpressed, it leads to protein destruction and proteotoxicity. However, this mechanism is reversible by removal of Patulin as demonstrated by an experiment conducted on yeast cells (Guerra-Moreno and Hanna, 2017).

Moreover, many studies focused on the oxidative damage pathway of Patulin as the main toxicity pathway. Reactive chemicals containing oxygen are known as reactive oxygen species (ROS), including peroxides, hydroxyl radicals, superoxide, and others. ROS are usually the byproducts of mitochondrial electron transport during aerobic respiration; they might also be produced by oxidoreductase enzymes and during metal catalyzed oxidation. Naturally, ROS play important roles in cell signal transduction and cell cycling. Cells might produce ROS as a response to xenobiotics, cytokines, and microbial invasion. When the amount of ROS is above the cell's capacity to show an effective antioxidant response, the cell would be under oxidative stress. Oxidative stress might result in damaging some macromolecules (proteins, DNA and lipids). High levels of ROS have been demonstrated in various diseases including diabetes, cancer, neurodegeneration, and aging. Oxidative stress in cells is usually the result of over expression of

Table 2
Patulin adverse health effects determined by using animal models.

Animal model	Dose/route of exposure	Exposure type/ Duration	End Point	Level of risk	Dose causing adverse effect	Reference
Mice	35–65 mg/kg bw	Acute/72h	Death		48 mg/kg bw (LD50)	McKinley and Carlton (1980a)
			Gastrointestinal disorders	Intestinal and gastric Hyperaernia	35 mg/kg bw	
		Chronic/2 weeks	Death		24 mg/kg bw	
			Gastrointestinal disorders	Intestinal and gastric Hyperaernia	24 mg/kg bw	
Rats		Acute	Death		55 mg/kg bw (LD50)	McKinley et al. (1982)
			Gastrointestinal disorders	Intestinal and gastric Hyperaernia	55 mg/kg bw	
Hamsters		Acute/24h	Death		31.5 mg/kg bw (LD50)	McKinley and Carlton (1980b)
			Gastrointestinal disorders	Intestinal and gastric Hyperaernia	15.75 mg/kg bw	
Rats	0.1 mg/kg bw/gavage	Chronic/5–6 weeks	Hormonal problems	Increase level of testosterone and decrease level of T4 Sperm count decrease	0.1 mg/kg bw 0.1 mg/kg bw	(Selmanoglu, 2006; Selmanoglu and Kockaya, 2004)
Rats	1.5–15 mg/kg bw/gavage	Chronic/10–23 weeks	Death		7.5 mg/kg bw	Dailey et al. (1977)
Mice (NMRI)	1–3.75 mg/kg bw/oral for mothers	Sub-chronic	Embryogenesis effects	Cleft palates	3.75 mg/kg bw	Roll et al. (1990)
Rats	1–55 μM/rat serum of cultured embryos	Acute	Embryo lethality		55 μM	Smith et al. (1993)
Mice (B6C3F1) females	0.08–2.56 mg/kg bw	Chronic/28 days	Immunological effect	Cytotoxic T-cells, natural killer, monocyte increase		LLewellyn et al. (1998)
Heifers and bulls	504 μg/kg of feed samples	Outbreak	Neurological signs	knuckling over at the fetlocks, muscle fasciculation, hyperaesthesia, ataxia, stumbling and recumbency		Botha et al. (2014)
Dairy cows	728 μg/kg of feed samples	Outbreak	Neurological signs	Aggressive behavior and paralysis		
Mice	1 mg/kg/intraperitoneal injection	Chronic/7 days	Hepatotoxicity	High levels of hepatic ROS, bone marrow chromosomal aberration		(Song et al., 2014b)
Mice	1 mg/kg/intraperitoneal injection	Chronic/8 weeks	Neurological signs	Brain oxidative damage, increase ROS.		(Song et al., 2014a)
Mice	40–160 μg/animal/dermal exposure	Acute/4–6 h	Skin cells apoptosis	DNA damage		Saxena et al. (2009)
Mice BalbC males	1 mg/kg/intraperitoneal injection	Sub-chronic/3 days	Hepatotoxicity	High level of ROS		Jayashree et al. (2017)
Mice BalbC	3.75 mg/kg bw	Acute	Hepatotoxicity And kidney problems	DNA fragmentation in liver and kidney. Renal dysfunction. Liver and kidney cells apoptosis.		(Boussabbeh et al., 2016a)
Mice BalbC	3.75 mg/kg bw	Acute	Cardiotoxicity	High levels of oxidative stress indicators		(Boussabbeh et al., 2015a)

Table 3
Adverse effects on Patulin on cell cultures.

Cell line	Patulin Dose	Exposure type/ Duration	End Points	Levels of Risk	Reference
Mice lymphoma	0.5 µM	Acute	Cell death		(Schumacher et al., 2005b)
Chinese hamster v79	0.3 µM	Sub-chronic	Genes mutations		(Schumacher et al., 2005a)
Chinese hamster ovaries	15 µM	Acute	DNA damage		Liu et al. (2003)
human peripheral blood mononuclear cells (PBMC)	64.8 ng/ml	Acute	Immunological effect	Reduce interferon-gamma production	Wichmann et al. (2002)
PBMC	50 ng/ml	Acute	Immunological effect	Reduce production of: interferon-gamma, IL-4, IL-13, IL10	Luft et al. (2008)
HepG2 cells	0.45–7.5 µM IC50 = 1.17–2.66 µM	Acute/72h	Hepatic Cell death		Fernandez-Blanco et al. (2018)
HepG2 cells	LC50-7.2 mM	Acute	Hepatic cells autophagy	Increase Reactive Oxygen Species (ROS), collapses of mitochondrial membrane potential.	Yang et al. (2018)
HEK293 cells	8 µM	Acute/10h	Kidney cells apoptosis		Zhong et al. (2017)
HEK293 cells	5–25 µM IC50 = 15 µM	24h	Cell death	Endoplasmic reticulum stress	(Zhang et al., 2015)
HCT116 cells	5–25 µM IC50 = 20 µM	24h	Cell death	Endoplasmic reticulum stress	(Boussabbeh et al., 2015b)
S. cerevisiae	50 µg/ml	Acute/4h	Proteotoxicity	Induction of the transcription factor Rpn4	Guerra-Moreno and Hanna (2017)
Caco-2 cells (intestinal epithelial cells)	100 µM	Acute/5h	Intestinal barrier impairment	Transepithelial electrical resistance (TEER) decrease. Increase permeability. Decrease protein expression.	McLaughlin et al. (2009)
Caco-2 cells	50 µM	Acute/72h	Intestinal barrier impairment	TEER decrease. Decrease protein expression.	Kawauchiya et al. (2011)
Caco-2 cells	50 µM	Acute/36h	Intestinal barrier impairment	TEER decrease. Increase permeability.	Katsuyama et al. (2014)
Caco-2 cells	50 µM	Acute/24h	Intestinal barrier impairment	TEER decrease. Decrease protein expression.	Assuncao et al. (2016)
PBMC	0.5 nM-25 µM	Acute/24h	Immunological disorder	T-cells proliferation reduction starting 10 nM	
Caco-2 cells and HT-29-D4 cells	1–100 µM	Acute/24h	Intestinal barrier impairment	TEER decrease.	Mahfoud et al. (2002)
Rat colonic explants	100–500 µM	Acute/2h	Intestinal barrier impairment	TEER decrease. Increase permeability.	Mohan et al. (2012)
RAW264.7 Mice leukemic monocyte macrophage	1–100 µM	Acute/2h	Immunological disorder	Innate response suppression. IL6 expression reduced starting 5 µM	Tsai et al. (2016)
Neuro-2a	1–100 µM	Acute/24h	Neurological cell death	IC10 = 3–3.2 µM IC50-52-82.6 µM	Malekinejad et al. (2015)
H295R cells	0.0032–32 µM	Acute	Hormonal problems	Cells death at 32 µM. Inhibition of transcription. Increase of estradiol and progesterone levels. Decrease in testosterone level.	Frizzell et al. (2014)
Human erythrocytes	10 µM	Acute	Cell death	Increase of calcium ions levels which leads to cells suicide	Lupescu et al. (2013)

reactive oxygen species (ROS), dysfunction of mitochondria, impaired antioxidant system, or a combination of all of these together (Ray et al., 2012; Yang et al., 2018).

Excessive ROS might induce autophagy in cells. The autophagic system activation involves the bulk degradation of some cytoplasmic proteins in addition to selective degradation of cytoplasmic organelles. Such mechanism has been observed in hepatic cells (HepG2) exposed to Patulin, treatment of the cells with an inhibitor of autophagosome formation (3-methyladenine) has lessened Patulin toxicity, which indicated that Patulin toxicity pathway might go through autophagy by oxidative stress (Sun et al., 2018). Related study showed higher levels of ROS in cells exposed to Patulin in addition to an over expression of autophagy markers (LC3-II and LC31). The level of the protein P62 was also proven to decrease upon Patulin treatment, P62 is one of the bulk proteins degraded by autophagy and; therefore, its degradation is used as an autophagy marker (Lee et al., 2012). Among the autophagy induction mechanisms investigated by Yang et al. (2018), the inhibition of PI3K/AKT/mTOR signaling pathway was determined to be vital in regulating transcription, translation, migration and cell survival. The levels of p-AKT and p-mTOR were proven to decrease upon Patulin treatment, indicating the validity of this possible mechanism. Many studies imply that excessive amounts of ROS might lead to autophagy by affecting the PI3K/AKT/mTOR pathway (Loos et al., 2014; Yang et al., 2018; Zhang et al., 2012).

Among the mechanisms of Patulin toxicity, apoptosis was widely investigated (Kwon et al., 2012). For example, Zhang et al. (2015) investigated apoptosis as a possible mechanism of Patulin induced cell death in human embryonic kidney cells (HEK293). As the levels of antioxidants (glutathione and catalase) decreased upon Patulin exposure, the concentration of the oxidative stress marker known as malondialdehyde (MDA) increased. Although the potential of Patulin dose dependent cell death caused by apoptosis or autophagy was not clarified using fluorescent microscopy, it was clear that oxidative stress plays a major role in Patulin induced cell death (Zhang et al., 2015).

Furthermore, apoptosis is a programmed cell death that has two pathways (extrinsic and intrinsic), the intrinsic mitochondrial pathway is usually triggered by signals from other organs such as the endoplasmic reticulum (ER) (Sharaf El Dein et al., 2009). Unfolder protein response (UPR) is a mechanism induced by stressed ER, if normal conditions are not restored, ER stress would lead to mitochondrial apoptosis (Hetz, 2012). Boussabbeh et al. (2015a,b) have demonstrated that human colon carcinoma cells (HCT116) and embryonic kidney cells (HEK293) exposed to Patulin showed accumulation of unfolded protein, high level of ER chaperon protein known as GRP78, increase in the expression of GADD34 (DNA damage inducible protein), in addition to the up-regulation of the transcription factor CHOP that plays a key role in ER stress induced apoptosis. Active caspase-3 level was also shown to increase as a response to Patulin, which indicates the role of those protease enzymes in this Patulin-mediated apoptotic response. The study further demonstrated mitochondrial apoptosis by proving that cells that lack the pro-apoptotic protein Bax and Bak respond less to Patulin exposure. The levels of ROS have been demonstrated high in both cells lines exposed to Patulin. Pre-treatment of cells with the free radical scavenger NAC showed decrease in all the ER oxidative stress markers, which proves that when cells are exposed to Patulin, ROS levels increase which triggers ER stress that signal for mitochondrial apoptosis (Boussabbeh et al., 2015a,b).

Among the proteins involved in Patulin induced mitochondrial apoptosis, p53 and Bcl-2 family members were identified in the signaling pathways (Zhong et al., 2017). A study conducted on two types of cell lines, wild-type p53 embryonic kidney cells (HEK) and p53 knockout mouse embryonic fibroblast (MEF), has demonstrated that p53 plays an important function in Patulin oxidative stress and in increasing ROS generation. As wild-type p53 cells expressed higher levels of ROS, more DNA damages in wild-type cells when exposed to Patulin compared to the knockout cells were observed (Jin et al., 2016). Different mechanisms have been discussed yet Patulin induced cellular toxicity requires obviously further investigations. However, it can be inferred from the literature that ROS and their oxidative stress are major components of the Patulin induced cell toxicity mechanism. Fig. 2 summarizes many of the possible mechanisms involved in Patulin induced oxidative stress induced by apoptotic and autophagic responses (Ramalingam et al., 2019).

11. Patulin carcinogenicity and anti-tumor effects

The first study establishing the link between the tumor development and Patulin exposure was carried out by Dickens and Jones (1961), who demonstrated the development of sarcoma after administrating Patulin subcutaneously into two months old female rats. The carcinogenicity of Patulin was then evaluated on female Sprague-Dawley rats over a period of 64 weeks, during which rats were given Patulin twice a week by gavage (Osswald et al., 1978). In spite of the development of benign tumors in exposed animals, Patulin did not show actual carcinogenic effect during this study. In 1982, a six weeks analysis on F344 male rats showed that rats given Patulin in their diets significantly increased the areas and the numbers of hyperplastic nodules in their livers, demonstrating the tumor initiating potential of Patulin in rats' liver (Imaida et al., 1982). A more recent study has shown that the topical application of Patulin (400 nM) on Female Swiss albino mice skin has resulted in increased ROS production and doubled the rate of cells' proliferation, which has led to the formation of tumor in three of the seven treatment groups in two weeks (Saxena et al., 2011). Since the animal model studies did not show sufficient evidence of carcinogenicity, the International Agency of Research on Cancer (IARC) has considered Patulin as not carcinogenic to human (Group 3 carcinogen) (IARC, 2018).

On the other hand, various studies have evaluated Patulin as a possible anti-tumor agent. An analysis on colon cancer cell line, HCT116, showed that treatment with Patulin increased ROS production and stimulated the expression of the pro-apoptotic protein ATF3,

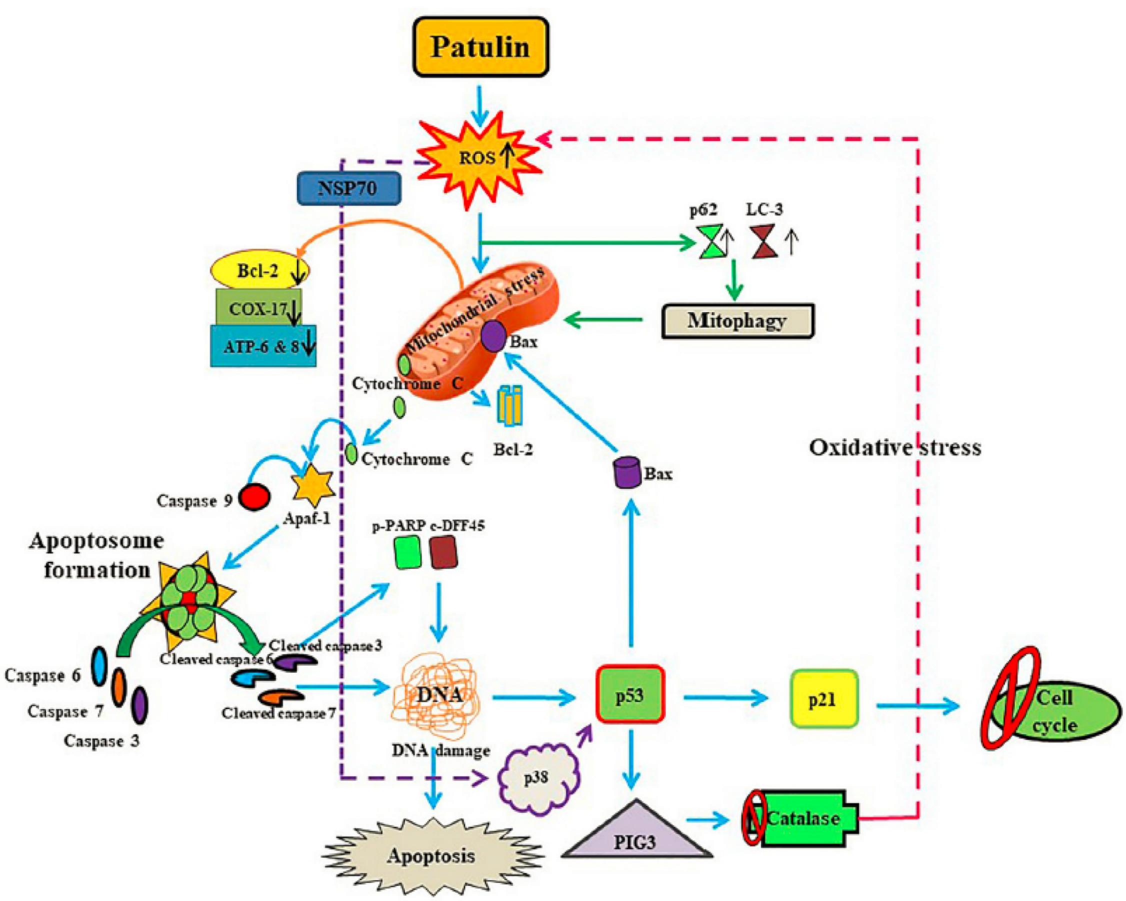

Fig. 2. Possible mechanisms involved in Patulin induced oxidative stress responses (Ramalingam et al., 2019).

leading to cell growth arrest. Pre-treatment of the same cells with the antioxidant NAC reduced ATF3 expression, which indicated that the tumor cells' apoptosis is oxidative stress triggered. Treated cells did not show any significant change in ER-stress indicators, proving that Patulin-mediated ATF3 over-expression is not regulated by ER stress. The same experiments were repeated on other cancer cell lines (SW480 and CaCo2) and the results were similar (Kwon et al., 2012). A study conducted on Balb/c mice implanted with B16F10 cells has demonstrated that the intraperitoneal administration of Patulin over 20 days induced regression of melanoma cells. Patulin activated apoptosis in tumor cells, which was demonstrated by over expression of apoptosis-related proteins p53, Bax and caspase-3. In addition, tumor cells exposed to Patulin showed a lower expression level of the Bcl2 protein, in charge of cell death regulation (Boussabbeh et al., 2016b).

In a more recent study, cervical and colorectal cancer cell lines (HeLa, SW-48, and MRC-5) treated with different doses of Patulin exhibited reduced cell growth at 4 μM Patulin concentration (Abastabar et al., 2017). Patulin was also investigated as a lung cancer chemopreventive compound. Lung cancer is among the most lethal cancer type in the world, it is usually accompanied by an over expression of the nuclear factor kappa B (NF-KB). HEK tumor cells treated with 1.5 μM Patulin showed 90% inhibition of the NF-KB activity compared to the control (Monteillier et al., 2018). The same study showed a Patulin dose-dependent cytotoxicity and migration inhibition on adenocarcinomic human alveolar cells (A549), meaning that Patulin induced apoptosis in lung cancer cells.

It is worth mentioning that the mechanisms of tumor cells' growth arrest are similar to those shown on none-tumor cells. Therefore, Patulin's potential as an anti-tumor drug should be considered with caution since the toxin does not differentiate tumor cells from normal cells. As demonstrated by Akbari et al. (2017), the active Patulin level of 4 μM (154.12 μg/L), which is above the acceptable level of Patulin in apple juice, is likely to cause a systemic toxicity *in-vivo* rather than exerting an anti-tumor activity.

12. Factors modifying Patulin's toxicity

Some compounds are known to modify Patulin toxicity. It is well known that fungi are capable of producing many types of mycotoxins at once. Furthermore, food samples might be contaminated with more than one fungal type. Therefore, consumers might get exposed to combinations of mycotoxins. Toxicity of individual mycotoxins has been widely studied. However, interactive effect of mycotoxins including antagonistic and/or synergistic effect of multiple mycotoxins should be further investigated. The synergic effect of Patulin, deoxynivalenol, and toxin T-2 on HepG2 cells was evaluated by Fernandez-Blanco et al. (2018). The highest toxicity levels were observed in the combination of Patulin and toxin T-2 (20 nM Patulin + 34 nM T-2) in exposed HepG2 cells, followed by the combination of the three mycotoxins together. Synergic effect was more pronounced compared to that of individual toxin effect (Fernandez-Blanco et al., 2018; Klarić et al., 2013).

In 2010, Puel et al. reported that Cytochrome P450 inhibitors (proadifen) increase Patulin toxicity, while cysteine decreases it. More recently, the effect of green tea polyphenols (GTP) (50–100 mg/kg BW) on male Kunming mice (22 ± 2 g) and the effect of green tea leaves (GTL) (100–200 mg/kg BW) on male Balb/c mice (30 ± 5 g) exhibited reduction of Patulin-induced hepatotoxicity at 1 mg/kg and 2 mg/kg, respectively (Jayashree et al., 2017; Song et al., 2014b).

The effect of selenium was tested as an antagonist for Patulin toxicity. Supplementation of selenium (0.2 mg/kg) significantly ameliorated the Patulin induced neurological toxicity at 1 mg/kg in 4 weeks old male Kunming mice (Song et al., 2014a). Two forms of selenium (methylseleninic acid (MSeA) and sodium selenite) were also tested by Lu et al. (2017) as inhibitors of Patulin-induced nephrotoxicity and hepatotoxicity *in vitro*. Cell culture assays showed that 3–5 μM of MSeA were capable of protecting the cells from Patulin cytotoxicity. Moreover, in an animal model study, the hepato-protective and nephroprotective effects of MSeA (2 mg/kg body weight, oral administration) from Patulin-induced toxicity (10 mg/kg body weight, intraperitoneal injection) were also demonstrated (Lu et al., 2017).

When 3-methyladenine was added to HepG2 cell culture, it protected the cells against Patulin toxicity (Yang et al., 2018). In the same study, an ROS inhibitor (N-acetyl-L cysteine) was also proven to protect cells from Patulin induced autophagy, which implies that Patulin induces cell death through an ROS dependent pathway (Yang et al., 2018).

Taking into account the burden of Patulin on health, its detoxification has been widely explored. Apigen (API) is a plant extract known as an antioxidant. The addition of API on HEK293 cells inhibited the accumulation of ROS in cells and; therefore, inhibited Patulin induced apoptosis (Zhong et al., 2017). Another natural antioxidant named Crocin (CRO) was also evaluated as Patulin induced toxicity suppressor. CRO succeeded in restoring normal biochemical parameters' levels in kidney and liver of mice as well as cardiac system, and protected their cells from apoptosis (Boussabbeh et al., 2016a).

Wang et al. (2018) investigated the effect of an antioxidant known as glutathione on Patulin induced cytotoxicity in HEK293 cells. Results showed that glutathione increased cells' viability via decreasing the intracellular and the mitochondrial ROS; hence, lessening the oxidative damage, which protects cells from Patulin-induced apoptosis. HEK293 cells pre-treated with glutathione showed higher levels of active antioxidant enzymes, such as superoxide-dismutase (SOD), glutathione-reductase (GR), and glutathione-peroxidase (GPx).

A more recent study has demonstrated that the exposure of Male C57BL/6 mice to *L. plantarum* CCFM8610 probiotics prior to Patulin ingestion protects the animals from Patulin related digestive system adverse effects (Zhai et al., 2019). Additionally, the treatment with the anti-oxidant epicatechin protected erythrocytes against Patulin-induced oxidative stress (Tokarova et al., 2019).

13. Preventive measures used to control patulin exposure

P. expansum infect fruits mainly if the skin is damaged. Additionally, chill bites, physical damages, and rodent and insect bites are other routes of fruits' skin damage. Therefore, appropriate harvesting and storage methods are required to protect fruits' quality (Jackson et al., 2003).

Studies have demonstrated that washing fruits with high-pressure water and elimination of rotten fruits prior to storage help in avoiding fungal contamination and; therefore, Patulin production (Acar et al., 1998). For some fruits, UVC light has proven efficiency in limiting *P. expansum* growth in the post-harvested product without damaging the fruit itself (Syamaladevi et al., 2015).

As *P. expansum* started getting resistance to regular fungicides, scientists begun exploring alternative chemical treatments. Recently, exogenous potassium phosphide treatment has shown promising results in controlling Patulin producing fungi growth (Lai et al., 2017). A treatment with a combination of sodium hypochlorite (NaClO), hydrogen peroxide (H_2O_2), and copper sulfate ($CuSO_4$) has resulted in complete inhibition of *P. expansum* growth, spores germination, and Patulin production (Cerioni et al., 2013). Chlorine dioxide (ClO2) has shown antifungal activity against *P. expansum* in apples sample and in PDB media (Zhang et al., 2018). Propolis, a honeybee product, has been applied as a natural antifungal agent to inhibit the growth of Patulin producing fungi (Matny, 2015). Finally, chemical adsorption of Patulin was recently investigated by Liu et al. (2019), whose team has developed a new metal-organic framework-based adsorbent (UiO-66(NH2) @Au-Cys) that showed a very high efficacy in Patulin removal from apple juice, the developed adsorbent showed treatment capacity ten times higher than that of microbe-based bio-adsorbents (Liu et al., 2019).

A study showed that a nitrogen free media triggered an immediate production of Patulin in *P. griseofulvum*. In addition, when ammonium ions were added to the culture media, the secondary metabolite production stopped directly (Rollins and Gaucher, 1994). Those results open research opportunities for the production of nitrogen based fruits preservative to protect prone fruits from Patulin contamination. Another study showed that the transcription of one of the Patulin biosynthesis pathway genes requires a pH of 5, any increase or decrease in the pH will stop the transcription, which also open the way to use pH modification as a protective measure from Patulin exposure (Puel et al., 2010).

Furthermore, a variety of recent molecular techniques have been developed for the early detection of Patulin producing fungi, the RT-PCR based on the *patF* gene detection has proven a specificity for Patulin production. Rapid and easy detection help in avoiding the importing of contaminated products and it helps in using only fruits of good quality for fruit-based food production, such as jams and juices (Tannous et al., 2018). A new amplification technique known as loop-mediated isothermal amplification (LAMP) has been used to target one of the Patulin biosynthesis pathway genes (isoepoxydon dehydrogenase (*idh*) (Frisch and Niessen, 2019). The developed assay showed high specificity in detecting Patulin producing fungi and it could serve as a quick detection tool in food quality control Beside molecular techniques, nano-technology was also used in Patulin detection in food samples, Xu et al. (2019) have recently developed a sensor containing glassy carbon electrode (GCE) modified with black phosphorus nanosheets, gold nano-particles and Patulin aptamer, which showed a Patulin detecting range between 0.1 nM and 10 μM (Xu et al., 2019).

Corrective measures are also considered to reduce the amount of Patulin once detected in food samples. Patulin and other mycotoxins are known to be stable and resistant to various treatments, yet several methods showed some promising results. UV irradiation was not only used to kill the fungi but also to reduce Patulin levels in contaminated samples. Results were promising for filtered juice. However, it did not work for fresh juice containing a lot of suspended particles that absorb the UV light before it reaches the Patulin particles (Tikekar et al., 2012). In addition, several chemicals showed promising results in Patulin decontamination, such as ammonia, potassium permanganate, vitamin B, sulfur dioxide, ozone, pyridoxine hydrochloride, and calcium D-pantothenate (Diao et al., 2019; Tannous et al., 2018).

For Patulin reduction in apple juice, citric acid, sodium bicarbonate, vinegar, combination of sodium bicarbonate and citric acid, baking powder, and ultraviolet (UV) irradiation were considered to reduce Patulin level. Only the UV irradiation and the sodium bicarbonate treatments showed Patulin reducing effect (Kim et al., 2018). However, UV and sodium bicarbonate had negative effects on the juice quality, yet those effects were reversible by addition of citric acid. Therefore, a combination of sodium bicarbonate and citric acid might be considered as an additive to apple juice to reduce Patulin levels (Kim et al., 2018). Finally, biological agents have also been considered in Patulin decontamination of samples that can be fermented, among those agent, yeast (*Saccharomyces cerevisiae*) is the most commonly used organisms for fermentation (Moss and Long, 2002). *Alicyclobacillus* heat-inactivated bacterial cells and spores were tested for their capacity to adsorb Patulin from contaminated samples (Sajid et al., 2018). Among seven strains tested, *Alicyclobacillus acidocaldarius* showed the best results by adsorbing up to 12.6 μg/g of Patulin from apple juice samples A recent study also showed that the inoculation of the probiotic *Lactobacillus plantarum* ATCC 8014 into Patulin contaminated apple juice increases the efficiency of Patulin removal and improves the safety of juices for human consumption (Zoghi et al., 2019).

14. Conclusion

When different research teams around the world demonstrate the same adverse effect, the toxicant would be strongly the causative agent of the discussed adverse health effects. The consistency of the evidence collected and the findings of studies prove that Patulin exposure causes intestinal barrier impairment and gastrointestinal problems, immunological, neurological, and developmental adverse effects. Various cell culture and animal model studies showed that Patulin has hepatotoxic, genotoxic, and proteotoxic effects. In addition, Patulin in high doses might lead to animals' death. Therefore, Patulin requires attention and further evaluation for its levels in food products and risks on the human health, especially on at risk populations including children. Many surveillance studies showed the levels of Patulin in apple-based food products, yet its exact toxicity mechanisms and factors that affect its production and causes of its adverse effects require further investigations. A better understanding of Patulin as a toxicant will lead in applying the most effective preventive measures to protect human from any possible adverse effect.

Declaration of interests

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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