REVIEW

Toxicological effects of patulin mycotoxin on the mammalian system: an overview

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The mycotoxin PAT (4-hydroxy-4*H*-furo[3,2c]pyran-2[6*H*]-one) is a secondary metabolic product of molds such as *Penicillium*, *Aspergillus*, and *Byssochlamys* species. PAT is a common contaminant of fruit and vegetable based products, most notably apples. Despite PAT's original discovery as an antibiotic, it has come under heavy scrutiny for its potential to impart negative health effects. Studies investigating these health effects have proved its toxic potential. PAT occurrence in the food commodities poses a serious threat and necessitates novel and cost-effective mitigation methods to remove it from food products. It also creates a demand to improve handling and food processing techniques. With this being the case, several studies have been devoted to understanding the key biological and chemical attributes of PAT. While past research has elucidated a great deal, PAT contamination continues to be a challenge for the food industry. Here, we review its influence within the mammalian system, including its regulation, incidences of experimental evidence of PAT toxicity, its interaction with intracellular components, and the effects of PAT induced systemic toxicity on vital organs. Finally, key areas where future PAT research should focus to best control the PAT contamination problem within the food industry have been addressed.

Introduction

Mycotoxins have been known to exist since humans started the cultivation of crops. Mycotoxins are the secondary metabolites of fungi, so they do not have any direct effect on the growth and development of fungi. They are primarily produced by the mycelium of filamentous fungi, specifically molds. Around 200 filamentous fungi are known to produce mycotoxins, such as *Penicillium*, *Aspergillus*, *Fusarium*, and *Claviceps* species.[1] Mycotoxins contaminate a very large range of food and feedstuff, hence they affect a vast population across the globe. Their occurrence in food, feed and beverages has been recognised as a potential threat to human and animal health, either caused by direct contamination of plant materials or products thereof or by "carry over" of mycotoxins and their metabolites into animal tissues, milk, and eggs after the intake of contaminated feed.[2] Due to their inevitable presence, mycotoxins also impose an agro-economical burden which annually accounts for the loss of millions of dollars worldwide. Studies show that exposure to mycotoxins in food (*e.g.* ochratoxin and aflatoxin) may cause severe damage to vital organs like the liver and kidney, although the toxic effect of mycotoxins depends upon their chemical structure, concentration, and the degree of exposure; interestingly, all secondary metabolites of molds do not impart toxicity.

Their toxic manifestation imposes a diverse range of toxic effects, maybe because of their diverse chemical structures. Chemically most of the mycotoxins are stable so they tend to survive during processing and storage, even through high temperature cooking such as that applied during baking bread or producing breakfast cereals. Mycotoxicosis like all toxicological syndromes can be categorized as acute or chronic. Acute effects exhibit a rapid onset in the presence of high amounts, the incidence of which is usually restricted to under-developed nations where resources for controlling food or livestock are limited. Chronic toxicity can be described as being caused by low-dose exposure over a long period of time, which may result in life-threatening medical conditions such as cancers and other generally irreversible effects. Due to all these properties of mycotoxins, there is a big concern related to health and food safety. Various national and international organisations are constantly evaluating the mycotoxin related risk which may have serious health implications to mankind.

Patulin

PAT (4-hydroxy-4*H*-furo{2,3-*C*}pyran-2{6*H*}-1) (clavacin; PAT), (molar mass 154.12) (molecular formula $C_7H_6O_4$) is a mycotoxin

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produced by many different moulds such as *Penicillium*, *Aspergillus*, and *Byssochlamys* species and are mainly produced by *Penicillium patulum* and *Penicillium expansum*; earlier in mid 1900s PAT was recognized for its use as an antimicrobial and anticancer compound and a drug to treat common cold from *Penicillium patulum* (later called *Penicillium urticae*, now *Penicillium griseofulvum*). The toxic aspect of PAT became quite apparent in the era 1950–1960, in addition to its antibacterial, antiviral, and antiprotozoal activities; during the 1960s, PAT was reclassified as a mycotoxin known to be produced by several species of *Penicillium*, *Aspergillus*, and *Byssochlamys*,[3] thus PAT was classified as a toxic secondary metabolite of fungal origin. The chemical and biochemical attributes of PAT are extensively studied by Fliege and Metzlar which entail the electrophilic properties of PAT.[4] It is thought to exert its toxicity through covalent binding to the sulfhydryl group of various amino acids in proteins. In biological systems the formation of adducts of PAT takes place, although adducts have lower toxicity than PAT. Glutathione is considered as the scavenger of PAT induced toxicity. Chemically PAT is a colorless, crystalline, water-soluble polyketide lactone. PAT is thought to exert its toxicity by reacting with thiol groups in the cellular system. These molds are vegetated upon various food commodities, such as apples, pears, and grapes, as a common post harvest pathogen. It is particularly associated with apples exhibiting "brown rot" or other rotting characteristics and is now known to occur worldwide in apples and apple products.

In vivo toxicity assessment shows damage to vital organs and systems including the liver, kidney, intestinal tissues, and immune system.[5] Several studies have revealed its mutagenicity, teratogenicity, chromosomal aberration, DNA strand damage, and micronuclei formation in mammalian cells.[6,7] However, pieces of evidence for the carcinogenic potential of PAT in the animal model are not sufficient and there are no promising results on the revertant frequency by PAT in the Ames test. Based on the available data, the presence of PAT can be used as a quality control parameter, as its detection in apple derived food such as juices, ciders and concentrates indicated that moldy apples were used in the production of juices and the accumulation of PAT within the body may pose toxicological threats. For this reason, the problem of detecting even low levels of PAT in apple juices continues to receive attention. Because apple juice is such a popular beverage and the possibility for life-long exposure exists, PAT will likely remain important to apple processors and governments interested in monitoring the quality of apple juices and products.

Regulations

PAT has been classified as a group 3 carcinogen by the International Agency for Research on Cancer, this group includes the compounds for which there are no enough data to allow their classification.[8] However, on the basis of available data regulatory authorities have established 50 µg L^{-1} (50 ppb) as the maximum recommended concentration in apples and its products.[9–11] The ingestion of PAT exposed fruits and vege-

tables can lead to several health complications, like immune suppression, carcinogenesis, gastrointestinal inflammation, ulcers, bleeding, PAT mutagenicity, carcinogenicity, embryotoxicity and teratogenic effects. Recent advances in studies have reported the genotoxic effect of PAT on human cells through the induction of reactive oxygen species.[6]

PAT incidence

PAT can withstand various processing events such as heating and milling. Its highest concentration has been reported in apples and apple derived products at concentrations up to 16 milligrams per kilogram [16 parts per million (ppm)], although this should be considered as an exception. Although the incidence of PAT contamination is fairly high, the level of contamination is generally low with usual levels of less than 10 µg L^{-1} [10 parts per billion (10 ppb)] in commercial apple juices.[12]

Otezia and co-workers analyzed the incidence of PAT in various juices and pulp derived from different fruits like apples, oranges, pears, and grapes, which were found to have the mean PAT concentration >50 µg kg^{-1}, the limit set by European legislation.[13] Similarly, in China, about 17.5% of samples (dry fruits, juices, and jam) were reported to exceed (50 µg kg^{-1}) the European limit.[14]

PAT incidence data clearly establish its regular association with human foods; although its significance for human health is yet to be understood, PAT incidence raises a serious health concern especially among children; to date there have been very few epidemiological data regarding PAT exposure. PAT contamination in various commercial food items around the world is summarized in Table 1.

Patulin toxicity

The oral LD50 value of PAT in mice and rats varies from 20–100 mg per kg BW. This value is much higher than the actual concentration of PAT to which living beings get exposed. The intravenous and intraperitoneal routes are more toxic than the oral route. In acute studies, PAT causes hemorrhages, formation of edema and dilation of the intestinal tract in experimental animals.[32] In subchronic studies, hyperemias of the epithelium of the duodenum and kidney function impairment were observed as the main effects. Toxic signs consistently reported in all studies were agitation, in some cases convulsions, dyspnea, pulmonary congestion, edema, ulceration, hyperemia and distension of the gastrointestinal tract.[33]

Experimental studies on patulin

Experimental observation suggests that the major retention sites of PAT are erythrocytes and blood-rich organs (spleen, kidney, lung and liver).[34] At the cellular level, PAT has been shown to have effects including plasma membrane disruption,

Table 1 PAT content in various foods

Ref.	Range or mean of contamination	Positive samples	Commodity	Country
15	5–190.7 µg kg^{-1}	16% of 161 samples	Fruit juices	Iran
16	29.58–151.2 µg l^{-1}	72/72	Apple juices	
17	10–2559 µg kg^{-1}	35/35	Patulin leather	
18	>4 µg l^{-1}	18.7%	Apple cider	Michigan
19	19.1–732.4 µg l^{-1}	60% of 45	Apple juices	Turkey
20	10 µg l^{-1}	8/31	Fruit juice	South Africa
	5–20 µg l^{-1}	2/6	Whole fruit products	
		6/10	Infant juices	
21	9.32 µg kg^{-1}	34% of 53	Pure apple juice	Italy
	4.54 µg kg^{-1}	8% of 82	Mixed juice	
22	0.11–3.14 µg kg^{-1}	26/100	Conventional fruit juices	
	0.18–7.11 µg kg^{-1}	31/69	Organic juices	
23	21–1839 µg l^{-1}	12/50	Apple juice and fruit juice	India
24	17–221 µg kg^{-1}	11/51	Apple and Pear (solid and semi solid products)	Argentina
25	2.5–38.8 µg l^{-1} and 2.8–6.1 µg l^{-1}	35/43 and 3/7 respectively	Local and imported apple juice and cider	Belgium
		22/177	Organic, conventional and handcrafted juices	
26	0–167 µg l^{-1}	30/85	Apple juice, mixed juice and baby food	Tunisia
27	6–15 µg l^{-1}	188	Apple juice and mix juice	Japan
28	2.8–8.9 ng ml^{-1}	3/24, 2/24, 4/24	Apple juice, orange juice and grape juice	South Korea
	9.9–30.9 ng ml^{-1}			
	5.2–14.5 ng ml^{-1}			
29	0.7–101.9 µg l^{-1}	50/50	Apple juice	Romania
30	1.2–42 µg l^{-1}	33/144	Apple based foods	Portugal
31	1–94 µg kg^{-1}	83/95		China

inhibition of protein synthesis, inhibition of Na+-coupled amino acid transport, disruption of transcription and translation, inhibition of DNA synthesis,[35–43] and inhibition of interferon γ producing T-helper type 1 cells.[5] Furthermore, loss of free glutathione in living cells is associated with PAT exposure,[44,45] and treatment with exogenous cysteine and glutathione prevented its toxicity within the intestinal epithelium.[35] PAT has also been shown to induce inter and intramolecular protein cross-linking. This reaction is preferential with the thiol group of cysteine, but also occurs with the side chains of lysine and histidine, and α-amino groups.[46] Other observations have also noted PAT's reactivity with NH$_2$ groups.[47] Similarly, PAT has been shown to inhibit protein prenylation, a necessary post-translational protein modification involved in the activation of many proteins, including numerous oncogenes, such as Ras, that must be prenylated for proper function.[38] Finally, PAT's inhibition of transcription and translation appears to be through direct interaction with RNA and DNA.[40–42] Thus, while PAT toxicity may result from the thiol related interaction in a number of cases, there appear to be exceptions to this rule. Therefore the basis of these various toxic effects appears to be mixed. However, in a recent study, human promyelocytic leukemia (HL-60) cells were used to elucidate the mechanism and death mode associated with PAT. So collectively all the observations suggest that PAT may induce apoptosis either through the mitochondrial pathway or without the involvement of p53; the interaction with the sulfhydryl groups of macromolecules by PAT and the subsequent generation of reactive oxygen species (ROS) play a primary role in the apoptotic process.[48,49] The systemic exposure of PAT affects the vital organs by damaging DNA.[50]

Involvement of reactive oxygen species

In several studies, it has been concluded that reactive oxygen species (ROS) is a key player in PAT mediated toxicity. Earlier in 1996 Barhoumi and Burghardt demonstrated that glutathione (GSH) depletion by PAT results in the generation of ROS in a rat hepatocyte cell line. PAT being electrophilic in nature forms covalent adducts with nucleophilic moieties particularly cellular thiols including GSH, which is important in neutralizing free radicals and oxidants.[4] Furthermore, PAT treatment in HEK293 and HL-60 cultures also rapidly generated ROS, including superoxide anions.[51] Simultaneously lipid peroxidation levels were significantly increased in HL-60 cells and mouse kidney homogenates treated with PAT. Furthermore, in the same study, PAT-mediated ROS was also correlated with the activation of the ERK signaling pathway.[51] PAT induced ROS reported to cause cell death through the activation of the endoplasmic reticulum stress pathway and disruption in mitochondrial function in HCT116 and HEK293.[52] In addition, it is concluded that lipid peroxidation of the cell membrane caused by PAT treatment may also lead to the formation of ROS capable of inducing oxidative DNA damage.[53] Intraperitoneal administration of PAT has been reported to show a significant increase in SOD and catalase activity and a rise in protein carbonyl and malondialdehyde levels.[52]

Interaction of patulin with DNA

PAT did not increase the revertant number in the Ames test using several strains of *Salmonella typhimurium*, but some studies have shown mutagenic activity in *Saccharomyces cerevisiae*

and in *Bacillus subtilis*.[54] There are studies that have described the clastogenic potential of PAT. In Chinese hamster ovary cells (CHO-K1), blood lymphocytes and human embryonic kidney cells PAT increases the gap and strand breakage in DNA and sister chromatid exchange frequency. This suggests that in human cells, PAT is a potent clastogen with the ability to cause oxidative damage to DNA. In other studies chromosomal aberration and micronuclei formation are reported to be induced by PAT in V79-E Chinese hamster cells and in human lymphocytes.[55,56] Roll and co-workers suggested the PAT induced chromosomal damage in Chinese hamster bone marrow cells.[57] Nevertheless, the induction of gene mutations was observed in cultured mouse mammary carcinoma FM3A cells, Chinese hamster lung fibroblast V79 cells and mouse lymphoma L5178Y cells.[58–60] At cytotoxic concentrations of PAT, an increase of strand breaks was observed in a variety of different cell types.[58,61,62] As a further mechanism, the induction of oxidative DNA damage is discussed.[11] This discussion is based on the observation that PAT reacts with the important cellular antioxidant glutathione[4] and could thus decrease the antioxidant capacity. At concentrations that induced mutations and micronuclei in V79 cells (0.5–2.5 µM), PAT significantly induced DNA–DNA cross-linking, thus showing the direct reactivity of PAT towards DNA in a cellular system.[63] A study by Fliege and Metzler (2000b) revealed the ability of PAT to induce protein–protein and DNA–DNA cross-linking suggesting the induction of DNA–DNA cross-linking by PAT as a possible mechanism of PAT mutagenicity.[64] Experiments conducted in human embryonic kidney (HEK293) cells indicated the genotoxic potential of PAT *via* the induction of oxidative DNA damage.[6] In contrast *in vitro* studies in a similar cell type revealed PAT induced ERK phosphorylation that contributes to DNA damage, through the MEK pathway in HEK293 cells.[65] Nonetheless, PAT is also shown to cause the G2/M phase arrest of V79 cell lines and primary human skin fibroblasts,[59,66] that might allow cells to repair DNA damage prior to continuing into the S-phase or undergoing mitosis. PAT also causes DNA damage in the skin of mice at the concentration of 160 µg per 100 µl of acetone for 24–72 hours which leads to cell cycle arrest and apoptosis.[67]

Inhibition of different enzymes

PAT forms an adduct with thiol containing cellular components such as glutathione and cysteine-containing proteins.[45,68] Indeed, many enzymes with a sulfhydryl group in their active site are sensitive to PAT. Na^+-K^+ dependent ATPase, RNA polymerase, aminoacyl-tRNA synthetase, and muscle aldolase[40,41,69–71] have all been shown to be inhibited by PAT. However, enzymes that lack the sulfhydryl group are also sensitive to PAT, like urease.[72]

Immunotoxicity

It is a well known established fact that mycotoxins can alter immune responses and PAT is one of them. PAT appreciably reduces the expression of IL-23, IL-10 and TGF-β in bovine macrophages.[73] Balb/c mice, when exposed to PAT, showed increased Th2 cytokine levels and decreased IFN-gamma production. PAT also causes airway hyperactivity and eosinophilic lung inflammation thereby increasing allergic immune response.[74] PAT exposure to male rats for 60 or 90 days caused hemorrhage, plasma cell hyperplasia, a dilation and fibrosis in the cortex, enlarged interstitial tissue between the thymic lobules, enlarged fat tissue, thinning of the cortex, and blurring of the cortico-medullary demarcation in the thymus at the concentration of 0.1 mg per kg bw.[75] Another similar study conducted by the same group shows the loss of cristae in mitochondria and chromatin margination and lysis in the nucleus in the interdigitating dendritic cells of the thymus. They also observed apoptotic body formation and cell apoptosis in dendritic cells.[76] This group also showed the loss of the cytoplasm and mitochondrial cristae of cells, swollen endothelial cells, increased thickness of the basement membrane, closed lumen of capillaries, accumulation of the fibrous material at the periphery of the capillaries and nuclear anomalies in the walls of thymus capillaries.[77] PAT exposure leads to the reduced expression of IL-4, IL-13, IFN-gamma, IL-10 and intracellular GSH depletion in human peripheral blood mononuclear cells.[78]

Patulin induced organ toxicity

Intestinal toxicity

The gastrointestinal (GI) tract is the major organ of an individual's body. The GI tract plays a major role in the absorption of essential nutrients and water. Apart from its role in taking up of nutrients, the GI tract also acts as a barrier to any pathogens or xenobiotics present in food.[79] The GI tract is the primary site of exposure to xenobiotics present in food and that too at the maximum concentrations. Mycotoxins are known to alter several GIT functions such as the decrease in surface area, change in TEER, *etc.*[80] PAT also induces intestinal injury. PAT is reported to cause intestinal ulcers, inflammation and bleeding.[81] There are few *in vitro* studies evaluating the toxicity of PAT towards intestinal cells. Two human intestinal epithelial cell lines (HT29 and Caco-2), when exposed to a micromolar concentration of PAT, showed the reduction in the TEER mediated by inactivation of protein tyrosine phosphatase.[35] A study suggested that PAT may take part in initiating intestinal inflammation. PAT can enhance the passage of commensal bacteria and increased the effect of IL-1 beta on IL-8.[82] Exposure to PAT at a concentration of 95 µM caused the evident reduction in TEER of the human colon cancer cell (Caco-2) monolayer.[83] PAT also affects the distribution of claudin proteins on tight junctions and considerably decreased the expression of ZO-1, thus modifying the tight junctions and increasing the permeability.[84] PAT has the potential to modify epithelial permeability and ion transport in intact mucosal tissue.[85] The phosphorylation of ZO-1 was observed after 24 hours of exposure to Caco 2 cells.[86] PAT exposure decreases the cell viability of Caco 2 cells, downregulates the expression of Zona occludens1 and myosin light

chain 2 and prevents the T-cell proliferation.[87] PAT causes a decrease in goblet cells and an increase in apoptosis, which is extremely toxic to the intestine but on the other hand ascladiol, a metabolite of PAT, is relatively safe for the intestines.[88]

Hepatotoxicity

The liver is the largest glandular organ. This is the place where many of the important proteins are made, like blood clotting factor. It also helps in the biotransformation of xenobiotics. If the GI tract is the primary site for toxicants then the liver is the first organ to come into contact with toxicants absorbed in the gut *via* enterohepatic circulation. The liver transforms the toxicant to a lesser or higher toxic metabolite and then releases into the blood or back to the GIT for absorption. PAT exposure to mice caused an increase in activities of serum alanine transaminase (ALT) and aspartate transaminase (AST) and caused lipid peroxidation which was measured by thiobarbituric acid reactive substances.[89] A separate study showed that PAT treatment (152.5 ppb PAT per ml) of male albino mice orally for up to 6 weeks causes increased serum biochemical markers like ALT, AST, Alkaline Phosphatase (AP), urea, creatinine and uric acid.[90] Primary cultures of adult human hepatocytes were exposed to PAT and it reduced the cell viability. PAT also upregulates the pregnane X receptor gene along with CYP2B6, 3A5, 2C9, and 3A4 expression. PAT also causes the elevation of aryl hydrocarbon receptor (AhR) and CYP1A1 and CYP1A2 mRNA expression.[91]

Neurotoxicity

In the region of Flanders, Belgium, serious neurotoxicosis was observed amid some herds of beef cattle. *Aspergillus clavatus* was the major contaminant found in fodder after the investigation on diet elements. Moreover, PAT traces were also detected. Animal necropsies showed neuronal degeneration in the CNS, axonal degeneration in the PNS and nervous lesions.[92] Mice exposed to PAT for 8 weeks showed the increased levels of GSSG, reactive oxygen species, thiobarbituric acid reactive substances and protein carbonyl levels and downregulated protein thiol and total thiol groups. Furthermore, PAT also reduces the activities of glutathione peroxidase and glutathione reductase.[93] In neuro-2a cells, PAT causes ATP depletion and mitochondrial and lysosomal dysfunction.[94]

Renal toxicity

Kidneys are required to maintain total body salt, water, acid base balance and excretion of waste products. Kidneys are sensitive to injuries from ingested xenobiotics perhaps due to high renal blood flow. Toxins can be concentrated in renal tissues by the process of tubular reabsorption. Thus, the concentration of the toxic substance in the lumen and surrounding renal cells is fairly high making it a possible target for patulin induced toxicity. PAT exposure to mice elevates the expression of p53, bax, and cytochrome c and downregulates the bcl2 expression in the kidney.[95] 152.5 ppb PAT per ml was given to male albino mice orally for 6 weeks causing the
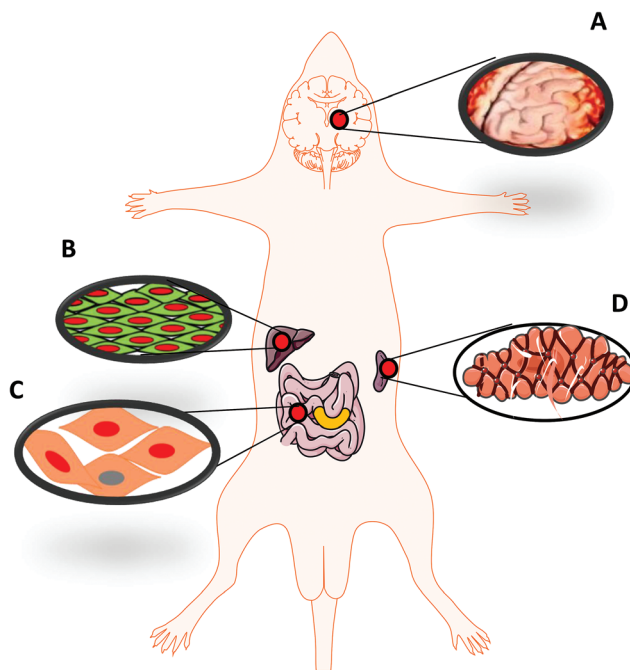

Fig. 1 Systemic changes resulting from patulin exposure. Dietary exposure of PAT leads to the systemic toxicity in the mammalian system after reaching into the intestine along food it causes (C) intestinal injury, intestinal ulcers, inflammation, bleeding and a decrease in transepithelial resistance, through the port vein on coming into contact with (B) hepatocytes it induces rise in ALT, AST and MDA levels further PAT reaches up to (D) the kidney and (A) the brain, where it results into neurotoxicosis, neuronal degeneration, degeneration of glomeruli and renal tubules.

degeneration of glomeruli and hemorrhage in the tubules of the cortical region in kidney tissues.[91] PAT disordered the arrangement of renal cells and reduced the dextran clearance abilities of Zebrafish (Danio rerio) embryos.[96] PAT affects the growth of human embryonic kidney (HEK293) cells suggesting that it causes increased oxidative stress which may lead to apoptosis in HEK293 cells.[97] Overall systemic changes resulting from PAT exposure are summarized in Fig. 1.

Carcinogenicity of patulin

There have been very limited data reported regarding the carcinogenic potential of PAT hence it is classified as group 3 as it is not carcinogenic to humans, however, long term exposure of PAT in rats and mice shows the carcinogenic potential of PAT. In rats a significant increase in tumor incidence was observed between control and PAT treated animals leading to sarcoma at the injection site, when administered subcutaneously,[98] although both male and female rats receiving the highest dose (1.5 mg per kg body weight) did not survive for the duration of the study, demonstrating PAT's toxic potential. Single topical application of PAT at a concentration of 400 nM causes tumor formation in mice skin after 14 weeks when followed by topical application of TPA, suggesting its role as a tumor initiator.[99] Osswald and co-workers have reported that the

chronic exposure of PAT causes benign tumors in the region of the fore stomach and glandular stomach in Dawley rats when exposed through gavage.[100] Nonetheless, a six week study suggests that PAT has tumor initiating potential in rat liver when tested *via* a liver carcinogenesis model.[101] PAT induced cell proliferation in primary murine keratinocytes *via* the EGFR-mediated Akt and MAPK signaling pathways.[102] FDA reports revealed that generally, animal studies are considered as appropriate models by safety experts for assessing potential adverse effects in humans. Therefore, based upon the adverse effects due to PAT in animal studies, FDA believes that humans may be at risk of harm at some levels of exposure to PAT.[101,102] But still, there is a lack of consensus among the scientific community about PAT induced carcinogenicity.

Conclusion and future perspective

As depicted in Fig. 2, studies conducted so far have reported that PAT exposure to the cellular system results in the accumulation of p62 and a decrease in intracellular GSH level, which ultimately lead to oxidative stress mediated cell cycle arrest, release of cytochrome c, activation of UPR response[103] and inhibition of catalase activity. Moreover, PAT's intracellular degradation occurs through the formation of the PAT-GSH adduct and its subsequent conversion into ascladiol (Ascl) and desoxypatulinic acid (DPA).[104] Although most of the toxicological studies have been conducted using *in vitro* experimental approaches, studies investigating the PAT effect on human health have remained indecisive, hence there is a need to investigate the PAT toxicity effect more profoundly. Moreover, in the past few years, a great amount of information has been unfolded about the chemical and biological nature of PAT, along with it several advances have been put forward in the development of methods to detect and quantify PAT, however, in developing countries there is a big concern about PAT contamination as it has not been prioritized from a public health perspective. Therefore, there is a need to generate epidemiological data about PAT induced toxicity and its occurrence in developing countries.

Conflicts of interest

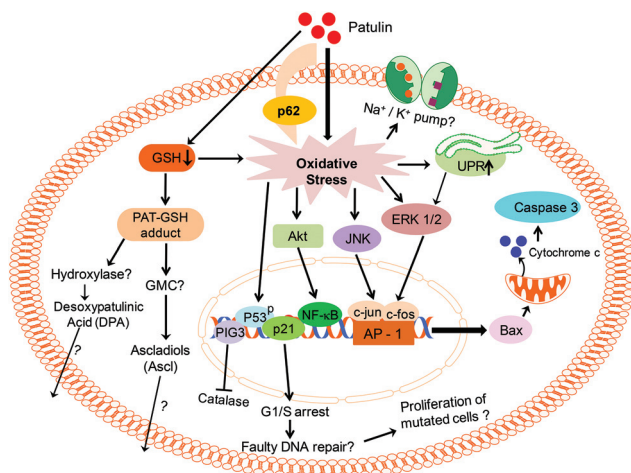The authors have declared no conflicts of interest

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Fig. 2 Model depicting the underlying mechanisms of PAT-induced oxidative stress and its cellular breakdown event based on information reported by various study groups. PAT exposure to the cellular system results in p62 accumulation and a decrease in intracellular GSH level, which ultimately leads to the oxidative stress mediated cell cycle arrest, release of cytochrome c, activation of UPR response[103] and inhibition of catalase activity. Moreover, PAT's intracellular degradation occurs through the formation of the PAT-GSH adduct and their subsequent conversion in ascladiols (Ascl) and desoxypatulinic acid (DPA).[104] GSH is gluthatione; PAT-GSH is the glutathione adduct with PAT, and UPR is unfolded protein response while GMC is glucose methanol choline oxidoreductase. The question marks (?) indicate an unknown function/process.

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