

EFFECT OF PATULIN POISONING ON TNF - α LEVELS IN MOUSE LIVERS

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ABSTRACT

Patulin is a mycotoxin mainly produced by *Penicillium expansum*, widely distributed in the environment, and commonly found in spoiled fruits, especially apples. This compound exhibits multiple toxic effects, including hepatotoxic, nephrotoxic, neurotoxic, and immunosuppressive activity. The aim of this study was to evaluate the effect of patulin on the concentration of the pro-inflammatory cytokine TNF- α in the livers of Albino Swiss mice following intoxication with various doses of the toxin. The animals were divided into six groups and administered patulin intraperitoneally in both acute and chronic doses. Analysis of TNF- α levels showed a significant increase in this cytokine in groups receiving a single dose of 0.5 LD50 and 0.2 LD50 of patulin. No significant changes were observed after chronic administration of a 0.1 LD50 dose. The results suggest that patulin toxicity may be associated with an enhanced inflammatory response in the liver, depending on the magnitude and nature of the dose.

Keywords: patulin, tumor necrosis factor alpha, hepatotoxicity.

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INTRODUCTION

Mycotoxins are a group of toxic compounds widely distributed in the environment. Among them, different groups have been distinguished based on their diverse effects on living organisms. Six main groups have been identified: aflatoxins, ochratoxin A, patulin, fumonisins, trichothecenes, and zearalenone [1,2,3].

Patulin exhibits, among other effects, hepatotoxic, nephrotoxic, teratogenic, and immunomodulatory activity [1,2,3]. Due to their prevalence in the environment and food, mycotoxins represent a significant clinical concern. Patulin was first isolated by Birkinshaw and colleagues in 1943 from cultures of *Penicillium patulum* as an antibiotic [4]. In subsequent years, this compound was described under various names, including penicydine, claviformin, harwinin, expansin, and gigantol acid [4,5,6,7]. Many species of *Penicillium* and *Aspergillus* produce patulin, but *Penicillium expansum* is the most significant. These fungi can be present in a wide range of food products, including fruits, vegetables, cereal grains, meat and meat products, bread, and cheese. Optimal growth occurs at 80–90% relative humidity [4]. Animals are also exposed to mycotoxins through feed or their environment, and toxins may accumulate in tissues intended for human consumption, such as milk or meat. This process is referred to as transfer along the food chain [8].

No safe concentration of mycotoxins in food has been established [9]. *Penicillium expansum* is particularly common in decaying fruits such as apples, pears, and grapes and is also frequently found in vegetables, especially tomatoes. Products made from contaminated fruits and vegetables, including apple juice, apple-based wine, jams, and compotes, can also contain this mycotoxin. Some strains of this fungus can produce large amounts of patulin [2,5,6,10,11,12]. Fruit contamination occurs through direct penetration of *P. expansum* into the fruit via mechanical damage to the skin or secondary infection following contamination by other fungi. Fungal growth within fruit cells is rapid, leading to radial expansion, cell destruction, and the formation of a brown spot on the skin known as "blue rot." The fruit's consistency changes, resulting in juice leakage [10,12]. The maximum allowable levels of patulin in food products in the European Union are regulated by Commission Regulation (EC) No 1831/2003 of 19 December 2003 (amending the 2003 regulation), primarily concerning industrially processed apple products [13,14]. Some studies indicate that patulin levels in apple products may exceed these limits, such as Szymczyk et al., which found excessive concentrations in 1.1% of tested Polish apple juices [15]. International studies confirm similar findings; for example, Shahzad Z Iqbal et al. analyzed 442 fruit samples (apples, oranges, apricots, lemons, guavas) at different stages of the supply chain and found patulin in 17–28% of samples, with the highest concentrations in transport and market samples. The average patulin intake per person was 0.11 µg/kg body weight per day [16].

Patulin, a bicyclic lactone known as 4-hydroxy-4H-furo-3,2-c-pyran-2/6H-one, binds strongly to proteins and nucleic acids such as DNA, disrupting cellular function and contributing to its toxicity [4,6]. Patulin is resistant to pasteurization and sterilization and is stable in acidic environments [3,15].

Food poisoning from mycotoxins can be acute, subacute, or chronic. Acute poisoning results from high-dose exposure over a short period, while subacute and chronic poisonings arise from lower doses administered over longer periods [4]. Patulin toxicity has been shown to be 3–6 times higher when administered intravenously, intraperitoneally, or subcutaneously [12].

Patulin significantly affects gastrointestinal function, damaging the intestinal mucosa, leading to epithelial cell degeneration, chronic inflammation, ulceration, and gastrointestinal bleeding [17,18]. The toxin can impair digestive enzyme production, gastrointestinal motility, and liver cell function, altering hepatic enzyme activity. It also exhibits antibiotic properties against intestinal flora [1,19,20,21,22]. Patulin is nephrotoxic, damaging cell membranes, including glomerular basement membranes and renal tubular cells, resulting in impaired kidney function [23,24,25]. Neurotoxic effects have also been reported, with acute and subacute intoxication leading to behavioral disturbances such as hyperactivity or seizures [4,26]. Moreover, a review published in *Molecules* indicates that patulin can damage enteric neurons, causing neurotoxicity and neuronal degeneration in the brain [27]. The gut-brain axis, linking cognitive and emotional brain regions with intestinal functions, is considered a therapeutic target in psychiatric disorders [28]. Chronic patulin exposure also exerts gonadotoxic effects. For instance, administration of 0.1 mg/kg body weight to rats for 90 days caused testicular tubular damage and reduced sperm production, along with gonadal fibrosis due to chronic inflammation [29,30]. Patulin can disrupt the hypothalamic-pituitary-thyroid axis, with chronic oral exposure at 0.1 mg/kg in rats leading to interstitial thyroid tissue changes, glandular cell edema, and impaired hormone synthesis, particularly thyroxine (T₄) [30]. It affects vascular endothelium, potentially causing mucosal congestion in the respiratory tract and pulmonary edema, and may promote bronchial asthma via immunomodulatory effects [31]. Patulin is mutagenic, genotoxic, teratogenic, immunosuppressive, and carcinogenic [4,32]. It damages DNA, induces oxidative stress, causes chromosomal aberrations, disrupts translation and transcription processes, interferes with tRNA synthesis, and impairs protein synthesis, thus promoting mutations and potentially inducing carcinogenesis [4,33,34,35,36]. Embryotoxic and teratogenic effects include compromised oocyte quality, affecting embryonic development and fertility [4,36]. Additionally, Pillay et al. reported that patulin disrupts insulin signaling and metabolic flexibility in hepatic (HepG2) and renal (HEK293) cells, suggesting mechanisms of insulin resistance [37]. Patulin also exhibits cardiotoxicity by inducing oxidative stress, DNA damage, and activating endoplasmic reticulum stress-mediated apoptosis in human cardiomyocytes [38]. Patulin modulates the immune system by altering lymphocyte production and function. It increases T-cell proliferation, disrupts immunoglobulin production (particularly IgG), and elevates neutrophil and monocyte counts. It inhibits macrophage activity, cytokine production, and secretion of interferon-gamma and interleukins (IL-4, IL-10, IL-13) by human monocytes and T-cells, impairing systemic cellular and humoral immunity [39,40,41].

Tumor necrosis factor (TNF-α) is a pro-inflammatory cytokine with diverse biological effects. Produced mainly by monocytes and macrophages, it stimulates acute-phase protein production, phagocytosis,

and differentiation of B, T, and NK lymphocytes. TNF- α also increases intracellular free radicals in cancer cells, inducing apoptosis [42,43]. Conversely, studies indicate that TNF- α may promote tumor progression by activating collagenases and other enzymes that facilitate cancer cell invasion and adhesion to vascular endothelium [44,45,46].

OBJECTIVE OF THE STUDY

The aim of this study was to analyze the toxicity of patulin with respect to varying TNF- α levels in the liver tissue of Albino Swiss mice.

This objective was addressed through the following specific aims:

- To evaluate the effect of chronic patulin exposure at a dose of 0.1 LD₅₀ on TNF- α levels in the liver tissue of experimental animals.
- To assess the effect of acute patulin exposure at different doses (0.5 LD₅₀; 0.2 LD₅₀; 0.1 LD₅₀) on TNF- α levels in the liver tissue of Albino Swiss mice.
- To perform a comparative analysis of changes in TNF- α concentration in the liver tissue of mice exposed to different doses of patulin.
- To evaluate the relationship between TNF- α levels in liver tissue following acute exposure to various doses of patulin and chronic exposure.

MATERIALS AND METHODS

Tab. 1

Distribution of substances and doses administered to each animal group.

Animal Group	Dose Administered During Study
Group 1	Control group: 0.9% NaCl, once daily for 28 days
Group 2	0.1 LD ₅₀ /day for 28 days
Group 3	Single dose 0.5 LD ₅₀
Group 4	Single dose 0.2 LD ₅₀
Group 5	Single dose 0.1 LD ₅₀
Group 6	Single dose 0.9% NaCl

On the 29th day of the experiment, the animals were euthanized via decapitation. Liver tissue samples (250 mg) were collected and homogenized in concentrated, buffered PBS (Phosphate-Buffered Saline, GIBCO®) at a ratio of 0.5 g tissue per 2 mL buffer. The homogenates were centrifuged at 14,000 rpm for 15 minutes at 4°C. TNF- α levels were determined in the supernatants using an ELISA reader and a kit from Cloud-Clone Corp., USA, according to the manufacturer's instructions.

LD₅₀, or lethal dose 50, refers to the dose that causes death in 50% of exposed animals [47,48].

STATISTICAL ANALYSIS

Results were processed statistically and presented as tables and graphs. The arithmetic mean $\pm$ standard deviation, minimum, and maximum values were calculated. Normality of data distribution was assessed to determine the appropriate statistical tests. Nonparametric methods were applied when data did not follow a normal distribution or when variances were unequal. Differences

The study was conducted on female Albino Swiss mice. A total of 36 mice were randomly assigned to six groups (four experimental and two control groups). The initial body weight of the mice ranged from 20 to 24 g. Male mice were excluded due to their strong territorial behavior and production of unpleasant odors. Animals were maintained under standard laboratory conditions, with a 12/12-hour light-dark cycle, constant ambient temperature, controlled humidity, and low noise levels. The study was approved by the Local Ethical Committee (LEC No. 22/2013).

Patulin was administered intraperitoneally to the animals according to the following scheme:

1. Group I (Control): Received 0.9% NaCl solution once daily for 28 days.
2. Group II: Received 0.1 LD₅₀/day for 28 days.
3. Group III: Received a single dose of 0.5 LD₅₀.
4. Group IV: Received a single dose of 0.2 LD₅₀.
5. Group V: Received a single dose of 0.1 LD₅₀.
6. Group VI: Received a single dose of 0.9% NaCl. [Table 1]

in TNF- α levels between patulin-exposed and control animals were analyzed using the Mann-Whitney U test. Differences in TNF- α levels among experimental groups exposed to different doses of patulin were assessed using the Kruskal-Wallis ANOVA test. Post-hoc pairwise comparisons between groups were performed using Dunn's test. Statistical significance was set at $p < 0.05$. Analyses were conducted using Statistica 10.0 (StatSoft, academic license, Medical University of Lublin).

RESULTS

The TNF- α concentration in the liver tissue of animals from the control group, which received intraperitoneal 0.9% NaCl for 28 days, ranged from 446.90 ng/mL to 1254.00 ng/mL, with a mean value of 857.70 ng/mL. In animals chronically administered patulin at a dose of 0.1 LD₅₀ for 28 days, TNF- α levels ranged from 422.50 ng/mL to 1215.00 ng/mL, with a mean of 752.87 ng/mL. Statistical analysis using the Mann-Whitney test showed no significant differences in TNF- α levels between the control group and animals chronically exposed to 0.1 LD₅₀ of patulin.

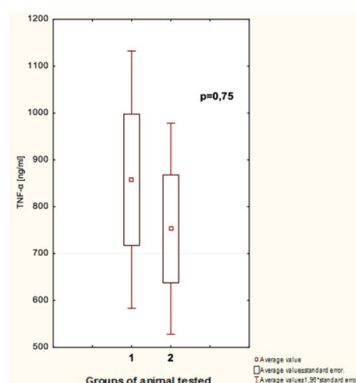


Fig. 1 TNF- α concentrations in liver tissue of animals after chronic exposure to 0.1 LD₅₀ of patulin and in the control group.

In the group of animals receiving a single dose of 0.5 LD₅₀ of patulin, TNF- α concentrations in liver tissue ranged from 432.20 ng/mL to 1164.00 ng/mL, with a mean of 767.10 ng/mL. In animals receiving 0.2 LD₅₀, TNF- α levels ranged from 432.80 ng/mL to 658.90 ng/mL, with a mean of 554.47 ng/mL. In animals administered a single dose of 0.1 LD₅₀, TNF- α concentrations ranged from

307.70 ng/mL to 550.60 ng/mL, with a mean of 423.10 ng/mL. In the control group receiving a single intraperitoneal dose of 0.9% NaCl, TNF- α concentrations ranged from 123.80 ng/mL to 573.00 ng/mL, with a mean value of 373.00 ng/mL.

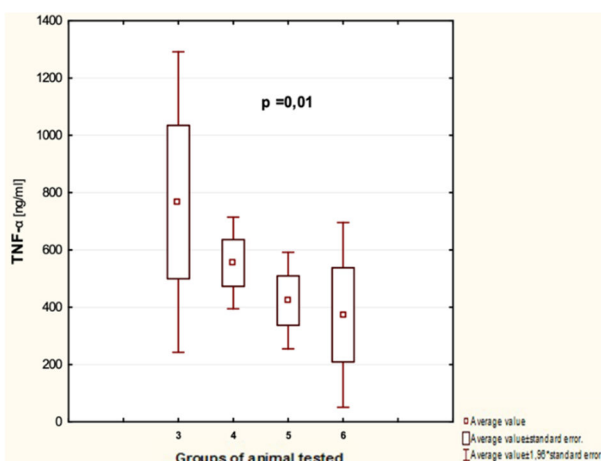


Fig. 2 TNF- α concentrations in liver tissue of animals exposed to single doses of patulin at different concentrations.

The highest TNF- α concentration in liver tissue was observed in mice receiving a single dose of 0.5 LD₅₀. Animals exposed to single doses of 0.2 LD₅₀ or 0.1 LD₅₀ showed lower TNF- α levels. Statistical analysis using the Kruskal-Wallis's test confirmed that these differences were significant ($H = 11.09$; $p = 0.01$). Post-hoc multiple comparison analysis (Dunn's test) indicated statistically significant differences in TNF- α concentrations between the following groups: 3 and 6; 4 and 6; 3 and 5; and 3 and 4 ($p < 0.05$). The results are shown graphically in Figure 2.

TNF- α levels in the liver of mice exposed to a single dose of 0.2 LD₅₀ were also significantly higher than in the control group ($p = 0.04$). TNF- α concentrations in the liver of animals receiving a single 0.5 LD₅₀ dose were significantly higher than in animals receiving 0.1 LD₅₀ ($p = 0.002$) and significantly higher compared with animals receiving 0.2 LD₅₀ ($p = 0.04$). No statistically significant differences were observed between TNF- α levels in

animals exposed to single doses of 0.2 LD₅₀ and 0.1 LD₅₀ ($p = 0.19$), nor between animals receiving 0.1 LD₅₀ and the control group ($p = 0.81$).

DISCUSSION

Mold fungi are widely distributed in the human environment, with food being the primary source of intoxication [4,49]. Increasingly, scientists are focusing on mycotoxins, their toxicity to humans and animals, and the determination of harmful concentrations in food products. Mycotoxin poisoning usually occurs in a chronic manner [4], resulting from the accumulation of toxins in the body over long periods. Numerous publications describe the harmful effects of various mycotoxins on humans and animals [1,4,19,27,36,50–53], but only a few address patulin intoxication.

Patulin is among the most prevalent mycotoxins in the human environment, mainly produced by *Penicillium expansum*, though it is also synthesized by other fungal species. Its most common sources are spoiled fruits, such as apples, pears, and grapes [10,50]. Initially, studies focused on the phytotoxic and antibiotic properties of patulin; it was even used as an aerosol treatment for upper respiratory infections. However, the drug was withdrawn after its toxicity was confirmed [1]. Patulin's toxicity arises from its strong interactions with nucleic acids and proteins [4]. Numerous harmful effects on humans and animals have been described, including teratogenic, embryotoxic, gonadotoxic, mutagenic, carcinogenic, neurotoxic, cardiotoxic, nephrotoxic, immunosuppressive, hepatotoxic, and gastrointestinal effects, as well as disruption of the hypothalamic-pituitary-thyroid axis [16,22,27,28,35,37,38,48,51,54,55]. During intoxication, patulin disrupts organismal homeostasis, leading to an acute-phase response, with IL-6 and TNF- α acting as primary inducers of acute-phase protein synthesis. Many authors have described the effects of patulin on cytokine production [1,18,40,41,56,57], yet studies evaluating TNF- α concentrations in liver tissue are limited. Bouhet et al. [1] demonstrated that patulin induces the expression of genes encoding TNF- α , IL-6, IL-1, and IL-8.

The aim of this study was to assess the toxic effect of patulin based on TNF- α concentrations in the liver tissue of Albino Swiss mice exposed to different doses of this mycotoxin. Female Albino Swiss mice weighing approximately 20 g were administered patulin intraperitoneally in aqueous solution, modeling both acute and chronic intoxication. One group received 0.1 LD₅₀ for 28 days, while other groups received single doses of 0.5 LD₅₀, 0.2 LD₅₀, and 0.1 LD₅₀. Control groups received intraperitoneal saline either as a single dose or daily for 28 days. A statistically significant increase in TNF- α concentration was observed in the liver tissue of animals exposed to acute doses of 0.5 LD₅₀ and 0.2 LD₅₀ compared with the control group. A single dose of 0.1 LD₅₀ did not cause statistically significant changes. The highest TNF- α concentration was found in liver tissue of mice receiving the highest single dose (0.5 LD₅₀). TNF- α concentrations were significantly lower after administration of 0.2 LD₅₀ or 0.1 LD₅₀ compared with 0.5 LD₅₀. In the chronic 0.1 LD₅₀ exposure group, TNF- α levels were higher than in controls, but this difference was not statistically significant.

Previous studies confirm a correlation between chronic patulin exposure and increased TNF- α in liver tissue. For example, Nagwa et al. [21] demonstrated that 0.2 mg/kg body weight/day induced TNF- α and liver enzyme elevation in rats after just one week. Serum TNF- α and transaminase levels correlated with histopathological changes indicating chronic inflammation and fibrosis.

Gashlan et al. [48] also confirmed hepatotoxicity of patulin, reporting significant increases in transaminases, gamma-glutamyltransferase (GGTP), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) in mice receiving 0.1 mg/kg/day for three weeks.

The liver is essential for survival and exhibits remarkable regenerative capacity. Functional regeneration is possible even after 70% hepatectomy, taking 3–6 months in humans and 7–10 days in rats, with initial functional recovery possible within 5 days post-surgery, though delayed by complications [20, 58–60]. Liver regeneration involves cell proliferation, including DNA replication, with cytokines such as TNF- α and IL-6

playing a key role in priming hepatocytes for proliferation. TNF- α facilitates gene expression during liver regeneration, activates stress-activated kinases including JNK (Janus-activated kinase), and promotes IL-6 production [61, 62]. Studies [61–64] have demonstrated that increased TNF- α levels correlate with signalling induction preparing hepatocytes for proliferation, supporting proper gene expression essential for liver regeneration after intoxication. Analysis of the current results and literature confirms the hepatotoxicity of patulin. Both acute high-dose exposure and chronic low-dose exposure pose risks to humans and animals. Fruits and fruit-derived products are the main sources of patulin intoxication. Even a single moldy fruit can contaminate an entire batch of fruits or fruit- and vegetable-derived products [5]. Early intoxication may go unnoticed due to a lack of clinical symptoms, with full manifestation of mycotoxicosis often occurring only after extensive or irreversible tissue and organ damage. Factors such as nutritional status, chronic illnesses, and medications can affect mycotoxin metabolism and intoxication outcomes. Therefore, monitoring patulin levels in food and animal feed is critical.

CONCLUSIONS

- This study confirmed that patulin exhibits hepatotoxic effects in Albino Swiss mice. Both a single high-dose exposure (0.5 LD₅₀) and chronic low-dose exposure (0.1 LD₅₀/day for 28 days) affected TNF- α concentrations in liver tissue, although the effects of chronic intoxication were less pronounced.
- A statistically significant increase in TNF- α in the liver was observed after single exposure to 0.5 LD₅₀ and 0.2 LD₅₀ compared with controls, with the highest concentration at 0.5 LD₅₀, confirming a dose-dependent toxic effect.
- A single 0.1 LD₅₀ dose and chronic 0.1 LD₅₀ exposure did not produce significant changes in TNF- α compared with controls, suggesting minimal doses have limited impact on hepatic inflammation.
- Increased TNF- α after patulin exposure confirms activation of acute-phase response mechanisms and potential priming of hepatocytes for regeneration. TNF- α thus functions both as a mediator of liver regeneration and as an indicator of toxic stress.
- The results highlight the toxicological hazard of patulin, commonly present in the environment, emphasizing the need for systematic monitoring of patulin in food and animal feed.
- Further research into the mechanisms of patulin toxicity is recommended.

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