JMBFS
Journal of Microbiology, Biotechnology and Food Sciences
International peer-reviewed scientific online journal
Published by Faculty of Biotechnology and Food Sciences

TOXICOLOGICAL PROPERTIES OF MYCOTOXIN CITRININ

Ivana Bovdisova[1], Katarina Zbynovska[1], Anna Kalafova[1], Marcela Capcarova[1]*

Address(es):
[1]Slovak University of Agriculture in Nitra, Faculty of Biotechnology and Food Sciences, Department of Animal Physiology, Tr. A. Hlinku 2, 949 76 Nitra, Slovak Republic.

*Corresponding author: bovdis.ivana@gmail.com

doi: 10.15414/jmbfs.2016.5.special1.10-13

ARTICLE INFO

Received 18. 12. 2015
Revised 19. 1. 2016
Accepted 26. 1. 2016
Published 8. 2. 2016

Review

OPEN ACCESS

ABSTRACT

Citrinin (CTN) is a secondary product of fungal metabolism and contaminant of various food and feed materials. This mycotoxin is produced by several fungal strains belonging to the genera *Penicillium, Aspergillus* and *Monascus. In vitro* and *in vivo* studies have shown clear evidence for reproductive toxicity and teratogenic, nephrotoxic, hepatotoxic and embryotoxic effects of citrinin. Mycotoxins can interfere in the cascade of cell machinery and thus affect cellular function. Citrinin is known mycotoxin that is spread over the world, however the mechanism of its action and other functions are still not known properly. Thus, the aim of this review paper is to summarize knowledge about mycotoxin citrinin, to describe its properties and effects on animal organism. In particular, known mechanism of toxicity is shown. In addition levels of exposure and bioaccessibility of citrinin is discussed. In the future, strategies for preventing the contamination by citrinin and the possibilities of its elimination should be investigated.

Keywords: Mycotoxins, citrinin, toxicity

INTRODUCTION

Mycotoxins are a group of structurally diverse secondary metabolites produced by various fungal species. These toxic compounds can contaminate foodstuffs, crops or human foods. The ingestion of these contaminated materials may be pathogenic in animals and humans as they may lead to serious health problems, such as liver, kidney or nervous system damage, immunosuppression and carcinogenesis. Mycotoxins can be classified as hepatotoxins, nephrotoxins, neurotoxins, immunotoxins and so forth. Cell biologists put them into generic groups such as teratogens, mutagens, carcinogens and allergens **(Bennett and Klich, 2003)**.
The amount of mycotoxins needed to produce adverse health effects varies widely among toxins, as well as for each animal or person's immune system. Two concepts are needed to understand the negative effects of mycotoxins on human health: *acute toxicity*, what is the rapid onset of an adverse effect from a single exposure. The second one- *chronic toxicity*, that means the slow or delayed onset of an adverse effect, usually from multiple, long-term exposures. Mycotoxins can be acutely or chronically toxic, or both, depending on the kind of toxin and the dose. Membrane-active properties of various mycotoxins determine their toxicity. Incorporation of mycotoxins into membrane structures lead to alterations in membrane functions. In general, mycotoxins effects on DNA, RNA, protein synthesis and the pro-apoptotic action causing changes in physiological functions including growth, development and reproduction **(Surai *et al.*, 2008)**.

General characteristics of citrinin

Citrinin [C13H14O5, IUPAC: (3R,4S)-4,6-dihydro-8-hydroxy-3,4,5-trimethyl-6-oxo-3H-2-benzopyran-7- carboxylic acid] (Figure 1) is an acidic lemon-yellow crystal with maximal UV absorption at 250 nm and 333 nm (in methanol), melting at 172 °C. It is sparingly soluble in water but soluble in dilute sodium hydroxide, sodium carbonate, or sodium acetate; in methanol, acetonitrile, ethanol and most of other polar organic solvents **(Deshpande, 2002)**. It is capable of forming chelate complexes and can be degraded in acidic or alkaline solution, or by heating. It is a quinone methide with two intramolecular hydrogen bonds. Citrinin crystallizes in a disordered structure, with the p-quinone and o-quinone two tautomeric forms in a dynamic equilibrium in the solid state. In methanol or methanol/methylene chloride mixtures, citrinin undergoes a Michael-type nucleophilic addition reaction. This reaction is reversible and the equilibrium shifts toward the normal citrinin if temperature is increased in methylene chloride **(Poupko *et al.*, 1997)**.

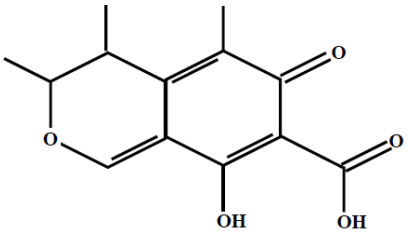

Figure 1 Chemical structure of citrinin

Toxicity of citrinin

Citrinin (CTN) is a secondary metabolite generally produced by various fungi, including *Penicillium*, *Monascus* and *Aspergillus* **(Bennett and Klich, 2003).** CTN is the one of the well-known mycotoxins, which is possibly spread all over the world and it is a natural contaminant of various types of feed and food, occurs mainly in stored grains, corn, wheat, rice, barley and nuts **(CAST, 2003)**. Red chilli, black pepper and dry ginger are the most contaminated spices in which aflatoxins, ochratoxin A and citrinin were present in high concentration. Fennel, caraway and cumin are the spices which can be considered a bit resistant to mycotoxigenic fungi and mycotoxin contamination (**Punam and Kumar, 2015**).
Although citrinin is one of the well-characterized mycotoxins, information on its mechanism of toxic action is limited. Clinically, citrinin was shown to cause renal disease in poultry, pigs, dogs and rats **(Reiss, 1977; Yu *et al.*, 2006)**. CTN has antibiotic properties against grampositive bacteria, but it has never been used as a drug due to its high nephrotoxicity. The kidney is the major target organ of CTN toxicity, but other target organs such as liver and bone marrow have also been reported **(Gupta *et al.*, 1983)**. Historically, CTN is one of the first isolated mycotoxins; however, the data on the mechanism of its toxicity are still controversial and most have been obtained *in vitro*. Like other mycotoxins, CTN could be implicated in porcine nephropathy **(Krogh *et al.*, 1973)**.
The effect of CTN on cell viability was tested with the MTT assay on Vero cells from the green monkey kidney treated with increasing CTN concentrations from 0 μmol.l^{-1} to 250 μmol.l^{-1} **(Bouslimi *et al.*, 2008)**. Up to the concentration of 60 μmol.l^{-1} no significant change in cell viability was observed, and the estimated half maximal inhibitory concentration (IC_{50}) of citrinin was about 220 μmol.l^{-1} after 48 hours of exposure. With the same exposure time, the IC_{50} of CTN for human embryonic cell line was 120 μmol.l^{-1}. At 24 hours of exposure, the IC_{50} of

CTN for human promyelocytic leukaemia (HL-60) cells and porcine kidney PK15 cells was 50 µmol.l^{-1} and 68 µmol.l^{-1}, respectively **(Yu *et al.*, 2006; Šegvić Klarić *et al.*, 2007)**.
In chronic tests, CTN (i) inhibits one of the key enzymes of cholesterol synthesis, leading to a reduced concentration of serum testosterone and hypocholesterolaemia (**Endo and Kuroda, 1976**); (ii) induces multiple immune modulator effects (**Quingqing *et al.*, 2012**); and (iii) triggers nephropathy, hepato- and foetotoxicity and renal adenoma formation in various animal models (**Carlton *et al.*, 1974; Xu *et al.*, 2006**).

Toxicity, carcinogenicity, and teratogenicity

Acute LD_{50} (median lethal dose) of CTN varies with the route of administration, physiological conditions and animal species. Oral LD_{50} for rats is 50 mg.kg^{-1} b.w. **(Sakai, 1955)**, while subcutaneous LD_{50} is 67 mg.kg^{-1} b.w. **(Ambrose and DeEds, 1945)**. The subcutaneous treatment of pregnant rats with 35 mg.kg^{-1} on days 6, 9, and 10 of pregnancy resulted in 50 % or higher maternal mortality **(Reddy *et al.*, 1982)**. Acute lethal doses administered to rabbits, guinea pigs, rats and swine caused swelling of the kidneys and acute tubular necrosis **(Ambrose and DeEds, 1946; Friis *et al.*, 1969; Krogh *et al.*, 1970)**.
Subchronical oral treatment of rats with water suspension isolated from a strain of *Penicillium viridicatum* Westling caused CTN-induced kidney damage characterized by enlarged kidney, hydropic degeneration, loss of brush border and pyknotic nuclei in the proximal tubules **(Friis *et al.*, 1969)**. Treatment of mice with weekly injections of CTN (20 mg.kg^{-1}) for six weeks resulted in a significant decrease in total bone marrow cells, red blood cell precursors, white blood cell precursors, megakaryocytes, decrease in spleen weight and decrease in the total spleen cell count **(Gupta *et al.*, 1983)**. The electron transport system of the kidney and liver mitochondria were considered as the target of the toxic action of citrinin **(Da Lozzo *et al.*, 1998)**.
CTN is embryocidal and foetotoxic in mice **(Hood *et al.*, 1976)**. In pregnant Sprague-Dawley rats, CTN given subcutaneously (35 mg.kg^{-1} b.w.) on gestation day 3 to 15 did not decrease the number of implants and no gross or skeletal malformations were found, but the foetuses were about 22 % smaller than control **(Reddy *et al.*, 1982)**. CTN injected to pregnant rats of the same strain at a dose of 30 mg.kg^{-1} on gestation days 5 to 14 resulted in a few foetal resorptions and minimal malformations **(Mayura *et al.*, 1984)**.

Genotoxic and nephrotoxic effects of citrinin

Genotoxicity of CTN has not been unequivocally established because various test systems gave both positive and negative results. An increase in DNA damage was detected using single cell gel electrophoresis (comet test) in Vero cells exposed 24 h to CTN **(Bouslimi *et al.*, 2008).** However, the same method gave negative results in human-derived liver cells (HepG2) **(Knasmüller *et al.*, 2004)** and human embryonic kidney cells (HEK293) **(Liu *et al.*, 2003)** no matter if Fpg was present or not. This suggests that CTN-induced oxidative stress did not affect DNA. In contrast to negative results, various cell cultures exposed to CTN showed a significant increase in micronucleus frequency **(Šegvić Klarić *et al.*, 2007)**.
Citrinin has been shown to be nephrotoxic when pigs were fed doses of 200-400 mg citrinin/kg for 1 to 2 months **(Harwig and Munro, 1975)**. Another characteristic of citrinin toxicity is polyuria resulting in injury and cell death in the proximal renal tubule **(Lurá *et al.*, 2001)**. *In vitro* studies with renal cortical explants from swine synthesis indicated that DNA, RNA and protein synthesis were inhibited at 0.01 mM citrinin, inhibition of respiration was seen at 1 mM citrinin and organic iron transport was inhibited at 0.01 mM citrinin **(Braunberg *et al.*, 1992)**. CTN along with ochratoxin A (OTA) has been implicated as a potential causative agent in human endemic Balkan nephropathy **(Vrabcheva *et al.*, 2000).** It is revealed that OTA-induced cytotoxicity is mediated by direct DNA damage whereas CTN caused ROS-mediated DNA damage. Cells suffering from DNA damage directly or through ROS take to intrinsic pathway of apoptotic cell death **(Gayathri *et al.*, 2015).**

Mechanism of toxicity

In vertebrate, mycotoxin is metabolized by cytochrome P450 enzymes to metabolite-guanine-N7 adduct (Figure 2). The carcinogenic potency is highly correlated with the extent of total DNA adducts formed *in vivo* **(Eaton and Groopman, 1994)**.
Cytotoxicity and ROS generation are mechanisms of mycotoxins mediated toxicity. ROS (reactive oxygen species) are chemically reactive molecules containing oxygen. They are highly reactive due to the presence of unpaired electrons. ROS formed as a natural byproduct of the normal metabolism of oxygen have important roles in cell signaling and homeostasis. However, during times of environmental stress, ROS levels can increase dramatically as a result of oxidative stress **(Devasagayam *et al.*, 2004)**. Oxidative stress occurs when the concentration of ROS generated exceeds the antioxidant capability of the cell. In other words, oxidative stress describes various deleterious processes resulting from an imbalance between the excessive formation of ROS and limited antioxidant defenses **(Sies, 1991)**. Under normal conditions, ROS are cleared from the cell by the action of superoxide dismutase (SOD), catalase (CAT) or glutathione peroxidase (GPx). The main damage to cells results from the ROS-induced alteration of macromolecules such as polyunsaturated fatty acids in membrane lipids, proteins and DNA. Additionally, oxidative stress and ROS can originate from xenobiotic bioactivation by prostaglandin H synthase (PHS) and lipoxygenases (LPOs) or microsomal P450s which can oxidize xenobiotics to free radical intermediates that react directly or indirectly with oxygen to produce ROS and oxidative stress **(Tafazoli, 2008)**.

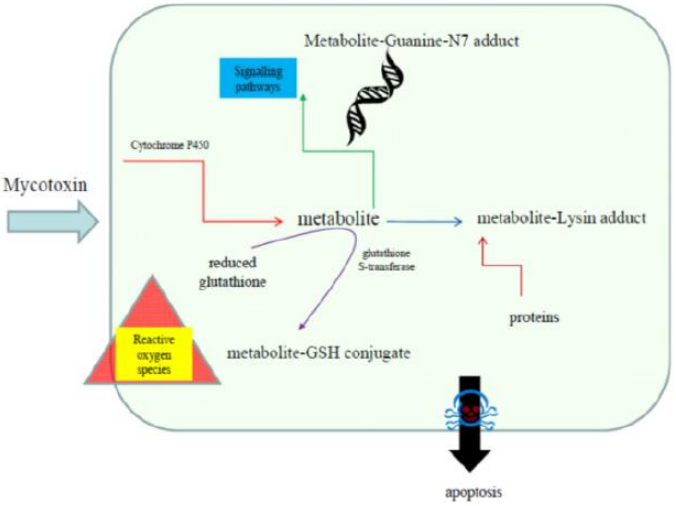

Figure 2 Mycotoxin metabolism in vertebrates **(Vasatkova *et al.*, 2009)**.

CTN under *in vivo* condition has the ability to cause oxidative stress and ROS-mediated DNA damage in mouse skin upon topical exposure leading to enhanced expression of p53, p21/waf1 and Bax proteins that causes cell cycle arrest at the G0/G1 as well as G2/M phases and caused apoptosis through the mitochondria-mediated pathway **(Kumar *et al.*, 2011)**. The p53 protein plays a key role in the DNA damage response pathway by transmitting a variety of stress signals associated with antiproliferative cellular responses that lead to apoptosis **(Jiang *et al.*, 2010)**. In response to CTN-induced DNA damage, overexpression of p53 protein leading to upregulation of p21/waf1 was also observed, which results in arrest of the cell cycle progression at the G0/G1 or G2/M phases **(Abbas and Dutta, 2009)**. CTN exposure could lead to toxicity by enhancing apoptosis of normal skin cells which involves a cascade of events including cell cycle arrest at G0/G1 as well as G2/M phases. The cell cycle arrest by CTN may permit DNA repair, but if it is faulty may allow proliferation of mutated cells, which is generally observed in case of tumorigenesis **(Das *et al.*, 2005b).**
The cytotoxic effects of several mycotoxins including CTN on target tissues and cultured cells are thought to correlate with their apoptosis-inducing ability **(Chan, 2007; Yu *et al.*, 2006)**.
The mycotoxin citrinin triggers an immediate and general antioxidant response in yeast cells. Induction of harmful ROS levels might therefore be the prevalent toxicity mechanism of this toxin. In yeast cells, citrinin activates the expression of antioxidant encoding genes and oxidative stress specific reporters. The ROS activated transcription factor Yap1 is critically involved in the adaptive response to citrinin. Additionally, the mutation of specific toxin exporters such as Pdr5, identifies physiologically important citrinin defense systems. Yeast is an efficient model to unravel toxicity and detoxification mechanisms of mycotoxins **(Pascual-Ahuir *et al.*, 2014).**
Factors such as breeding, sex, environment, nutritional status, as well as other toxic entities can affect the symptoms of intoxication and may contribute to the significance of mycotoxin damage on economic output and animal health **(Binder *et al.*, 2007)**.
CTN causes cell injury, including apoptosis. However, its precise regulatory mechanisms of action, particularly in stem cells and embryos, are currently unclear. Recent studies show that CTN has cytotoxic effects on mouse embryonic stem cells and blastocysts, and is associated with defects in their subsequent development, both *in vitro* and *in vivo*. Experiments with the embryonic stem cell line, ESC-B5, disclose that CTN induces apoptosis via several mechanisms, including ROS generation, increased cytoplasmic free calcium levels, intracellular nitric oxide production, enhanced Bax/Bcl-2 ratio, loss of mitochondrial membrane potential, cytochrome C release, activation of caspase-9 and caspase-3, and p21-activated protein kinase 2 and c-Jun N-terminal protein kinase activation. Additional studies show that CTN promotes cell death via inactivation of the HSP90/multi-chaperone complex and subsequent degradation of Ras and Raf-1, further inhibiting anti-apoptotic processes such as the Ras→ERK signal transduction pathway **(Chan, 2008)**.
A recent study from the European Food Safety Authority **(EFSA, 2012)** preliminarily set the maximal citrinin dose of no concern for nephrotoxicity in humans at an exposure level of 0.2 µg/kg body weight per day. For high

consuming individuals, especially children, the critical citrinin concentration ranges between 9 and 53 µg/kg grain-based products and for average consumers between 19 and 100 µg/kg grain-based products. However, the same study concluded that the impact of uncertainties on the risk assessment of citrinin is large, and that more data regarding both the occurrence of citrinin in food and feed in Europe and the toxicity mechanisms of this mycotoxin are needed.

CONCLUSION

The mechanism of CTN toxicity is not fully understood, especially not whether CTN toxicity and genotoxicity are the consequence of oxidative stress or of increased permeability of mitochondrial membranes. There is also a need for toxicological studies in laboratory animal species to further explore the toxicological potential of citrinin and to characterize the dose-response relationships.

Acknowledgement: This work was financially supported by the VEGA project 1/0760/15 and by the APVV project 0304-12.

REFERENCES

ABBAS, T. & DUTTA, A. 2009. p21 in cancer: intricate networks and multiple activities. *Nature Reviews Cancer*, 9, 400–414. http://dx.doi.org/10.1038/nrc2657

AMBROSE, A.M. & DEEDS, F. 1945. Acute and subacute toxicity of pure citrinin. *Proceedings of the Society for Experimental Biology and Medicine*, 59, 289-91.

AMBROSE, A.M. & DEEDS, F. 1946. Some toxicological and pharmacological properties of citrinin. *Journal of Pharmacology and Experimental Therapeutics*, 88, 173-86.

BENNETT, J.W. & KLICH, M. 2003. Mycotoxins. *Clinical Microbiology Reviews*, 16 (3), 497–516.

BINDER, E.M., TAN, L.M., CHIN, L.J., HANDL, J. & RICHARD, J. 2007. Worldwide occurrence of mycotoxins in commodities, feeds and feed ingredients. *Animal Feed Science and Technology*, 137, 265–282.

BOUSLIMI, A., BOUAZIZ, C., AYED-BOUSSEMA, I., HASSEN, W. & BACHA, H. 2008. Individual and combined effects of ochratoxin A and citrinin on viability and DNA fragmentation in cultured Vero cells and on chromosome aberrations in mice bone marrow cells. *Toxicology*, 251, 1-7. http://dx.doi.org/10.1016/j.tox.2008.06.008

BRAUNBERG, R.C., GANT, O., BARTON, C. & FRIEDMAN, L. 1992. *In vitro* effects of the nephrotoxins ochratoxin A and citrinin upon biochemical function of porcine kidney. *Archives of Environmental Contamination and Toxicology*, 44, 1768-1773.

CARLTON, W.W., SANSING, G.M., SZCZECH, G.M. & TUITE, J. 1974. Citrinin mycotoxins in Beagle dogs. *Food and Cosmetics Toxicology*, 12, 479-490. http://dx.doi.org/10.1016/0015-6264(74)90061-3

CARTER, W.O., NARAYANAN, P.K. & ROBINSON, J.P. 1994. Intracellular hydrogen peroxide and superoxide anion detection in endothelial cells. *Journal of Leukocyte Biology*, 55, 253-258.

COUNCIL OF AGRICULTURAL SCIENCE AND TECHNOLOGY (CAST). 2003. *Mycotoxins: Risks in Plant, Animal, and Human Systems. Council of Agricultural Science and Technology.* Task force report No. 139. CAST, Ames, IA.

CHAN, W.H. 2007. Citrinin induces apoptosis via a mitochondria-dependent pathway and inhibition of survival signals in embryonic stem cells, and causes developmental injury in blastocysts. *Biochemical Journal*, 404, 317–326. http://dx.doi.org/10.1042/bj20061875

CHAN, W.H. 2008. Citrinin induces apoptosis in mouse embryonic stem cells. *IUBMB Life*, 60 (3), 171-9. http://dx.doi.org/10.1002/iub.30

DA LOZZO, E.J., OLIVEIRA, M.B. & CARNIERI, E.G. 1998. Citrinin-induced mitochondrial permeability transition. *Journal of Biochemical and Molecular Toxicology*, 12, 291-297.

DAS, M., ANSARI, K. M., DHAWAN, A., SHUKLA, Y. & KHANNA, S. K. 2005b. Correlation of DNA damage in epidemic dropsy patients to carcinogenic potential of argemone oil and isolated sanguinarine alkaloid in mice. *International Journal of Cancer*, 117, 709–717. http://dx.doi.org/10.1002/ijc.21234

DESHPANDE, S. S. 2002. *Handbook of Food Toxicology*. Marcel Dekker, Inc., New York, NY, USA, p. 424.

DEVASAGAYAM, T.P.A., TILAK, J.C., BOLOOR, K.K., SANE KETAKI, S., GHASKADBI SAROJ, S. & LELE, R.D. 2004. Free radicals and antioxidants in human health: current status and future prospects. *Journal of Association of Physicians of India*, 52, 796.

EATON, D.L. & GROOPMAN, J.D. 1994. *The Toxicology of Aflatoxins: Human Health, Veterinary, and Agricultural Significance*. San Diego, CA, Academic Press, INC.

ENDO, A. & KURODA, M. 1976. Citrinin, an inducer of cholesterol synthesis. *The Journal of Antibiotics*, 29, 841-843. http://dx.doi.org/10.7164/antibiotics.29.841

EUROPEAN FOOD SAFETY AUTHORITY (EFSA). 2012. Panel on contaminants in the food chain (CONTAM). Scientific Opinion on the risks for public and animal health related to the presence of citrinin in food and feed. *EFSA J. 10, http://www.efsa.europa.eu/en/efsajournal/pub/2605.*

FRIIS, P., HASSELAGER, E. & KROGH, P. 1969. Isolation of citrinin and oxalic acid from *Penicillium viridicatum* Westling and their nephrotoxicity in rats and pigs. *Acta Path Microbiol Scand*, 77, 559-60.

GAYATHRI, L., DHIVYA, R., DHANASEKARAN, D., PERIASAMY, V.S., ALSHATWI, A.A. & AKBARSHA, M.A. 2015. Hepatotoxic effect of ochratoxin A and citrinin, alone and in combination, and protective effect of vitamin E: *In vitro* study in HepG2 cell. *Food and chemical toxicology*, 83, 151-163. http://dx.doi.org/10.1016/j.fct.2015.06.009

GUPTA, M., SASMAL, D., BANDYOPADHYAY, S., BAGCH,I G., CHATTERJEE, T. & DEY, S. 1983. Hematological changes produced in mice by ochratoxin A and citirinin. *Toxicology*, 26, 55-62.

HARWIG, J. & MUNRO, I.C. 1975. Mycotoxins of possible importance in diseases of Canadian farm animals. The *Canadian Veterinary Journal*, 16, 125-141.

HOOD, R.D., HAYES, A.W. & SCAMMELL, J.G. 1976. Effects of prenatal administration of citrinin and viriditoxin to mice. *Food and Cosmetics Toxicology*, 14,175-8.

JESWAL, P. & KUMAR, D. 2015. Mycobiota and natural incidence of aflatoxins, ochratoxin A and citrinin in Indian spices confirmed by LC-MS/MS. *International Journal of Microbiology*, 2015, 1-8. http://dx.doi.org/10.1155/2015/242486

JIANG, L., SHEIKH, M. S. & HUANG, Y. 2010. Decision making by p53: life versus death. *Molecular and Cellular Pharmacology*, 2, 69–77.

KNASMÜLLER, S., CAVIN, C., CHAKRABORTY, A., DARROUDI, F., MAJER, B.J., HUBER, W.W. & EHRLICH, V.A. 2004. Structurally related mycotoxins ochratoxin A, ochratoxin B, and citrinin differ in their genotoxic activities and in their mode of action in humanderived liver (HepG2) cells: implications for risk assessment. *Nutrition and Cancer*, 50, 190-7. http://dx.doi.org/10.1207/s15327914nc5002_9

KROGH, P., HASSELAGER, E. & FRIIS, P. 1970. Studies on fungal nephrotoxicity. II Isolation of 2 nephrotoxic compounds from *Penicillium viridicatum* West: Citrinin and oxalic acid. *Acta Pathol Microbiol Scand*, 78, 401-13.

KROGH, P., HALD, B. & PEDERSEN, E.J. 1973. Occurrence of ochratoxin A and citrinin in cereals associated with mycotoxic porcine nephropathy. *Acta Pathologica Microbiologica Scandinavica Series B*, 81, 689-95.

KUMAR, R., DWIVEDI, P.D., DHAWAN, A., DAS, M. & ANSARI, K.M. 2011. Citrinin-generated reactive oxygen species cause cell cycle arrest leading to apoptosis via the intrinsic mitochondrial pathway in mouse skin. *Toxicological sciences* 122 (2), 557–566. http://dx.doi.org/10.1093/toxsci/kfr143

LAURÁ, M.C., FUENTES, M.B., CABAGNA, M., GONZÁLES, A.M., NEPOTE, A.F., GIUGNI, M.C., RICO, M. & LATORRE, M.G. 2001. Actividad de metabolitos de *Penicillium citrinum* sobre ratones *Mus musculus*. *Revista Iberoamericana de Micología*, 18, 183-186.

LIU, B.H., YU, F.Y., WU, T.S., LI, S.Y., SU, M.C., WANG, M.C. & SHIH, S.M. 2003. Evaluation of genotoxic risk on oxidative DNA damage in mammalian cells exposed to mycotoxins, patulin and citrinin. *Toxicology and Applied Pharmacology*, 191, 255-63. http://dx.doi.org/10.1016/s0041-008x(03)00254-0

MAYURA, K., PARKER, R., BERND,T W.O. & PHILLIPS, T.D. 1984. Effect of simultaneous prenatal exposure to ochratoxin A and citrinin in the rat. *Journal of Toxicology and Environmental Health*,13, 553-61.

PASCUAL-AHUIR, A., VANACLOIG-PEDROS, E. & PROFT, M. 2014. Toxicity mechanisms of the food contaminant citrinin: application of a quantitative yeast model. *Nutrients*, *6*, 2077-2087. http://dx.doi.org/10.3390/nu6052077

POÓR, M., LEMLI, B., BÁLINT, M., HETÉNYI, C., SALI, N., KŐSZEGI, T. & KUNSÁGI-MÁTÉ, S. 2015. Interaction of citrinin with human serum albumin. *Toxins*, 7, 5155–5166. http://dx.doi.org/10.3390/toxins7124871

POUPKO, R., LUZ, Z. & DESTRO, R. 1997. Carbon-13 NMR of citirnin in the solid state and in solutions. *Journal of Physical Chemistry A*, 101, 5097–5102.

QINGQING, H., LINBO, Y., YUNQIAN, G. & SHUQIANG, L. 2012. Toxic effects of citrinin on the male reproductive system in mice. *Experimental and Toxicologic Pathology*, 64, 465-469. http://dx.doi.org/10.1016/j.etp.2010.10.015

REDDY, R.V., MAYURA, K., HAYES, A.W. & BERNDT, W. 1982. Embryocidal teratogenic and fetotoxic effects of citrinin in rats. *Toxicology*, 25, 150-60.

REISS, J. 1977. Mycotoxins in foodstuffs X. Production of citrinin by *Penicillium chrysogenum* in bread. *Food and Cosmetics Toxicology*, 15, 303-307.

SAKAI, F. 1995. An experimental study on the toxic effect, especially on the kidney of "yellowed rice" polluted by *Penicillium citrinum* Thom, as well as of

citrinin, a pigment isolated from the mould. *Folia Pharmacologica Japonica*, 51, 431-42.

SIES H. 1991. Oxidative stress: from basic research to clinical application. *The American Journal of Medicine*, 91, 31–38.

SURAI, P.F., MEZES, M., MELNICHUK, S.D. & FOTINA, T.I. 2008. Mycotoxins and animal health: From oxidative stress to gene expression. *Krmiva*, 50, 35–43.

ŠEGVIĆ KLARIĆ, M., ŽELJEŽIĆ, D., DOMIJAN, A.-M., PERAICA, M. & PEPELJNJAK, S. 2007. Citotoxicity, genotoxicity and apoptosis induced by ochratoxin A and citrinin in porcine kidney PK15 cells: Effects of single and combined mycotoxins. *Toxicology Letters*,172. http://dx.doi.org/10.1016/j.toxlet.2007.05.170

TAFAZOLI, S. 2008. *Mechanisms of drug-induced oxidative stress in the hepatocyte inflammation model*. Doctor of Philosophy, Department of Pharmaceutical Sciences, University of Toronto.

VASATKOVA, A., KRIZOVA, S., ADAM, V., ZEMAN, L. & KIZEK R. 2009. Changes in metallothionein level in rat hepatic tissue after administration of natural mouldy wheat. *International Journal of Molecular Sciences*, 10, 1138-1160. http://dx.doi.org/10.3390/ijms10031138

VRABCHEVA, T., USLEBER, E., DIETRICH, R. & MARTLBAUER, E. 2000. Co-occurrence of ochratoxin A and citrinin in cereals from Bulgarian villages with a history of Balkan endemic nephropathy. *Journal of Agricultural and Food Chemistry*, 48, 2483–2488. http://dx.doi.org/10.1021/jf990891y

YU, F.Y., LIAO, Y.C., CHANG, C.H. & LIU, B.H. 2006. Citrinin induces apoptosis in HL-60 cells via activation of the mitochondrial pathway. *Toxicology Letters*, 161, 143-151. http://dx.doi.org/10.1016/j.toxlet.2005.08.009

XU, B.J., JIA, X.Q., GU, L.J. & SUNG, C.K. 2006. Review on the qualitative and quantitative analysis of the mycotoxin citrinin. *Food Control*, 17, 271-285. http://dx.doi.org/10.1016/j.foodcont.2004.10.012