We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 3

Mycotoxins-Induced Oxidative Stress and Disease

Hossam El-Din M. Omar

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/51806

1. Introduction

Mycotoxins are pharmacologically active mold metabolites produced in a strain-specific way that elicit some complicated toxicological activities **[1]**. More than 300 secondary metabolites have been identified while only around 30 have true toxic properties **[2]**. The chemical structures of mycotoxins vary significantly, but they are low molecular mass organic compounds **[3]**. Mycotoxins are small and quite stable molecules which are extremely difficult to remove and enter the food and feed chain while keeping their toxic properties **[4]**. So, the occurrence of mycotoxins is regulated by legal limits in all developed countries **[5]**. Mycotoxin contamination of the feed and food is a global problem because more than 25% of world grain production is contaminated by mycotoxins **[6]**. The synthesis of mycotoxins by moulds is genetically determined and closely related to primary metabolic pathways, such as amino acid and fatty acid metabolism. However, the actual toxin production is modulated by environmental factors such as substrate composition and quality, humidity and temperature. The occurrence of mycotoxins in animal feed exhibits a geographic pattern, for example *Aspergillus* species meet optimal conditions only in tropical and subtropical regions, whereas *Fusarium* and *Penicillium* species are adapted to the moderate climate. Worldwide trade with food and feed commodities results in a wide distribution of contaminated material **[7]**.

Plant selections for mycotoxin resistance have not created any significant results in protection against grain mycotoxins. The major problem comes from the fact that there are no safe levels of mycotoxins, because of synergistic interactions of many mycotoxins **[2]**. There is sufficient evidence from animal models and human epidemiological data to conclude that mycotoxins cause an important hazard to human and animal health **[1]**. The toxic effect of mycotoxins on animal and human health depends on the type of mycotoxin; level and duration of the exposure; age, health, and sex of the exposed individual, genetics,

dietary status, and interactions with other toxic insults. Thus, the severity of mycotoxin toxicity can be complicated by factors such as vitamin deficiency, caloric deprivation, alcohol abuse, and infectious disease **[1,3,8].**

Mycotoxins according to their chemical structure exert a broad variety of biological effects. The nature and intensity of these effects depend on the actual concentration of an individual mycotoxin and the time of exposure **[7]**. Cell proliferation of all mycotoxin treated blood mononuclear cells was significantly decreased at the highest concentrations of mycotoxins, but this decrease was significantly stronger for different mixtures of mycotoxins **[9]**. In addition, feed commodities are often contaminated with more than one mycotoxin, as mould species produce different mycotoxins at the same time. These co-occurring mycotoxins can exert additive effects, as for example various trichothecenes, but may also act antagonistically, as for example, observed with feeds containing trichothecenes and zearalenone, and commodities, containing aflatoxins and cyclopiazonic acid **[7]**.

Mycotoxicoses are more common in underdeveloped countries and often remain unrecognized by medical professionals, except when huge numbers of people are involved **[3]**. In general, mycotoxin exposure is more likely to occur in parts of the world where poor methods of food handling and storage are common, where malnutrition is a problem, and where few regulations exist to protect exposed populations. The incidence of liver cancer varies widely from country to country, but it is one of the most common cancers in China, Philippines, Thailand, and many African countries. Worldwide, liver cancer incidence rates are 2 to 10 times higher in developing countries than in developed countries **[10]**. The occurrence of fumonisin B1 was correlated with the occurrence of a higher incidence of esophageal cancer in regions of Transkei (South Africa), China, and Northeast Italy **[3]**. In Africa and Asia where the occurrence of mycotoxins is common and a high percentage of the population is infected with hepatitis B or C mycotoxin reduction is obligatory **[8]**. One of the strategies for reducing the exposure to mycotoxins is to decrease their bioavailability by including various mycotoxins-adsorbing agents in the compound feed, which lead to reduction of mycotoxins uptake as well as distribution to the blood and target organs. Another strategy is the degradation of mycotoxins into non-toxic metabolites by using biotransforming agents such as bacteria/fungi or enzymes **[4]**.

Diagnosis of animal mycotoxicosis is based on experimental studies with specific toxins and specific animals, very often under well-defined toxicological laboratory conditions, so that the results of such studies can be far from real-life or natural situations. Furthermore, 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 **[11]**. The economic costs of mycotoxins are impossible to determine accurately **[12]**, but the US Food and Drug Administration (FDA) estimated that in the US the mean economic annual cost of crop losses from the mycotoxins aflatoxins, fumonisins, and deoxynivalenol are $932million USD **[13].** While mycotoxin associated losses in industrial countries are typically market losses as a result of rejected crops, developing countries suffer additionally from health impacts **[14]**. Diagnosis is very

much dependent on receiving a sample of feed that was ingested prior to intoxication, but also on data from another representative group of animals of the facility and the results of a post-mortem examination **[11, 13]**.

In the following table, the mycotoxins of major concern as feed contaminants are aflatoxins, ochratoxin A, Fusarium toxins (trichothecenes like, deoxynivalenol, diacetoxyscipenol, nivalenol, T2-toxin/HT2-toxin, zearalenone and fumonisins) **[4]**. Moreover, the most predominant mycotoxigenic species in wheat grain were *A. flavus* with the ability to produce mycotoxins (aflatoxins B1, B2, G1 and G2 and sterigmatocystin) **[15]**.

Fungal species	Mycotoxin
Aspergillus flavus; A. parasiticus	Aflatoxins
A. flavus	Cyclopiazonic acid
A. ochraceus; Penicillium viridicatum; P. cyclopium;	Ochatoxin A
P. expansum	Patulin
Fusarium culmorum; F. graminearum; F. sporotrichioides	Deoxynivalenol
F. sporotrichioides; F. poae	T-2 toxin
F. sporotrichioides; F. graminearum; F. poae	Diacetoxyscirpenol
F. culmorum; F. graminearum; F. sporotrichioides	Zearalenone
F. moniliforme	Fumonisins
Acremonium coenophialum	Ergopeptine alkaloids

Table 1. The major toxigenic species of fungi and their mycotoxins [16]

2. Route of mycotoxins exposure

The most common route of exposure to mycotoxins is ingestion, but it may also involve dermal, respiratory, and parenteral routes, the last being associated with drug abuse **[17]**. In general, animals are directly exposed to mycotoxins through the consumption of mouldy feedstuffs, eating contaminated foods, skin contact with mould infected substrates and inhalation of spore-borne toxins **[1]**. Human exposure can be via one of two routes; direct exposure due to the consumption of mouldy plant products, or indirect exposure through the consumption of contaminated animal products containing residual amounts of the mycotoxin ingested by the food producing animals **[18]**. Human exposure to mycotoxins is further determined by environmental or biological monitoring. In environmental monitoring, mycotoxins are measured in food, air, or other samples; in biological monitoring, the presence of residues, adducts, and metabolites is assayed directly in tissues, fluids, and excretory products **[19]**. The risk of systemic toxicity resulting from dermal exposure increases in the presence of high toxin concentrations, occlusion, and vehicles which enhance penetration **[20]**. The main human and veterinary health load of mycotoxin exposure is related to chronic exposure **[2]**.

3. Mycotoxins metabolism and induction of oxidative stress

Biodegradation of mycotoxins with microorganisms or enzymes is considered as the best strategy for detoxification of feedstuffs. This approach is considered as environmental friendly approach in contrast to physicochemical techniques of detoxification. Ruminants are potential source of microbes or enzymes for mycotoxins biodegradation **[21].** In vertebrate, mycotoxin is metabolized by cytochrome P450 enzymes to metabolite-guanine-N7 adduct **(Fig 1)**. The carcinogenic potency is highly correlated with the extent of total DNA adducts formed *in vivo* **[22].**

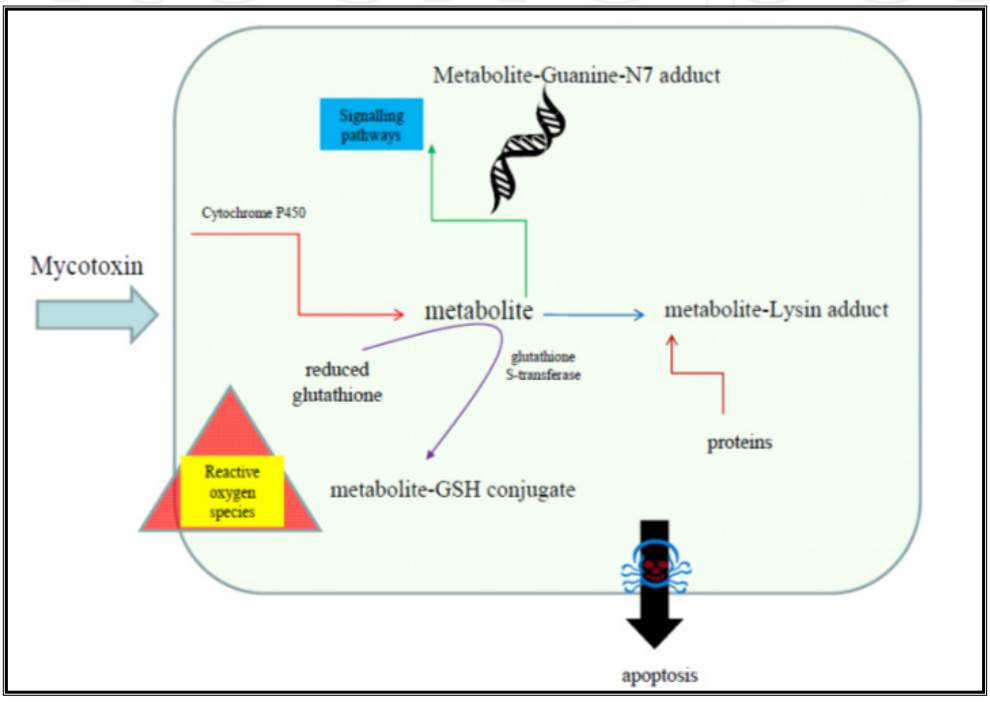

Figure 1. Mycotoxin metabolism in vertebrates **[23]**

Cytotoxicity and ROS generation are mechanisms of mycotoxins mediated toxicity. ROS 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 **[24]**. 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 **[25]**. 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 **[26]** as in **Fig (2)**. Moreover, the cell can tolerate a small to moderate amount of oxidative stress by producing antioxidant molecules e.g vitamin A, C &E and GSH and activates enzymes e.g. CAT, SOD, GPx, glutathione reductase (GR) and glutathione S transferase (GST) to counteract the excess oxidants **[27**]. LPO may bring about protein damage and inactivation of membrane-bound enzyme either through direct attack by free radicals or through chemical modification by its end products [**28]**. Reduction of cellular viability by mycotoxins was correlated with increases of ROS generation and MDA formation in concentration and time dependent manner [**29**]. The importance of oxidative stress and LPO in mycotoxins toxicity was confirmed by the protective effects of natural antioxidants **[2].** Sporidesmin, the mycotoxin responsible for 'facial eczema' in ruminants, contains a disulphide group which appears to be intimately involved in its toxic action. The dithiol form of sporidesmin has been shown readily to undergo autoxidation *in vitro* in a reaction which generates superoxide radical (O_2^-) **[30]**. GST found in the cytosol and microsomes catalyzes the conjugation of activated aflatoxins with GSH, leading to the excretion of aflatoxin **[31]**. Variations in the level of the GST as well as variations in the cytochrome P450 system are thought to contribute to the differences observed in interspecies aflatoxin susceptibility **[22, 32]**.

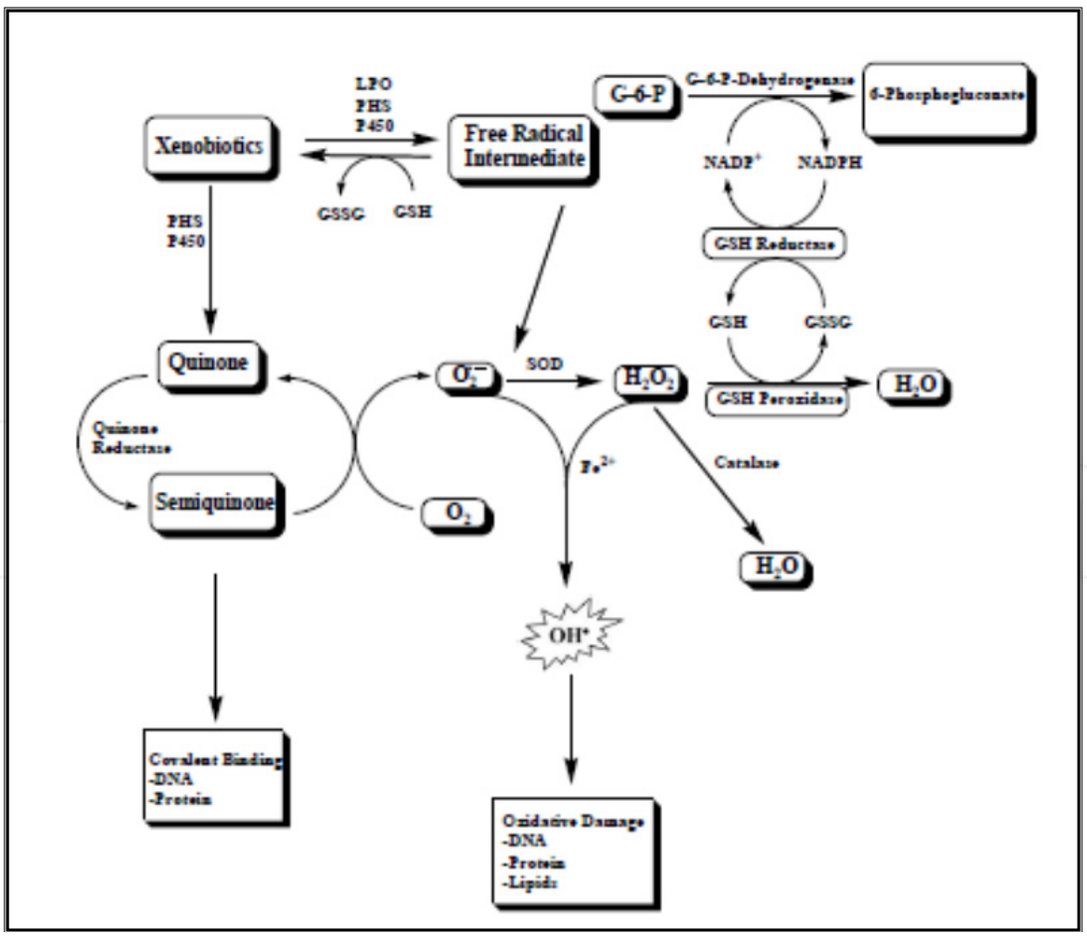

Figure 2. General pathways of ROS production and clearance **[26]**

4. Mycotoxin toxicity

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*, the rapid onset of an adverse effect from a single exposure. *Chronic toxicity*, 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 **(Fig. 3)** causing changes in physiological functions including growth, development and reproduction **[2].** Clinicians often arrange mycotoxins by the organ they affect. Thus, 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 **[1]**.

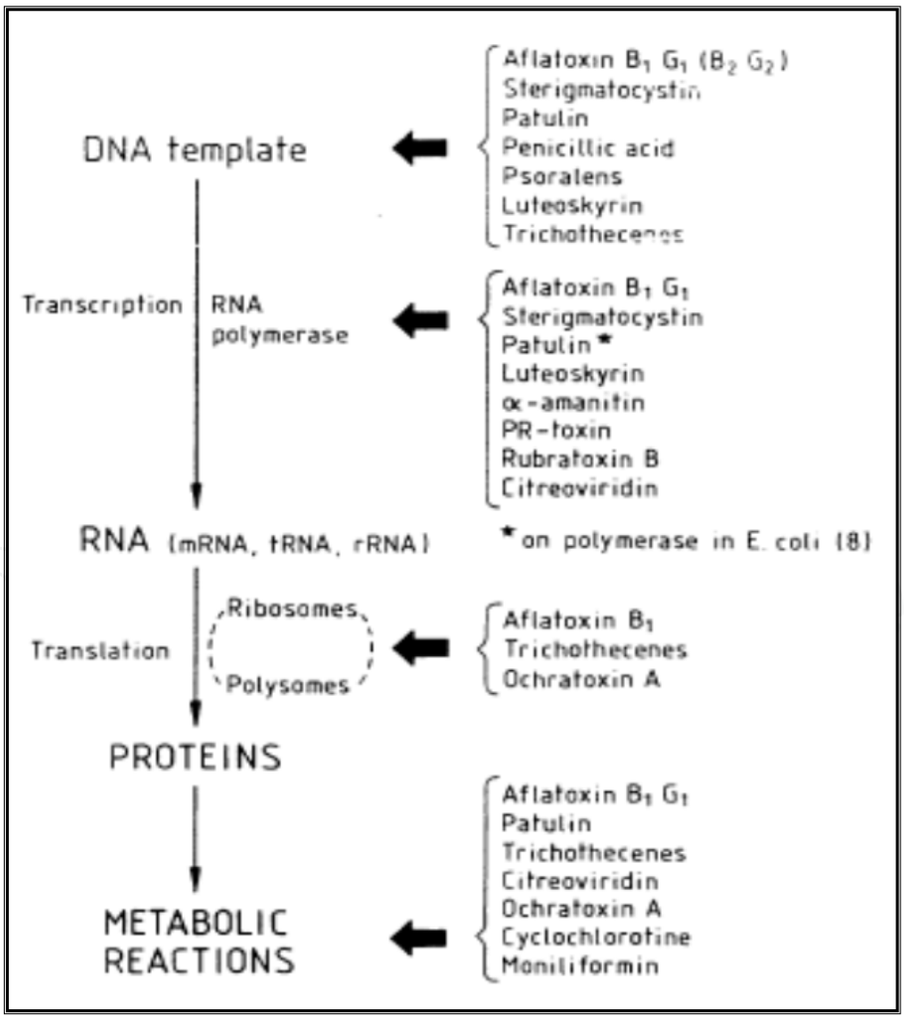

Figure 3. Mycotoxins affecting major sites in RNA and protein synthesis **[33]**

Aflatoxins

Aflatoxins occur in nuts, cereals and rice under conditions of high humidity and temperature. The two major *Aspergillus* species that produce aflatoxins are *A. flavus*, which produces only B aflatoxins, and *A. parasiticus*, which produces both B and G aflatoxins. Aflatoxins M1 and M2 are oxidative metabolic products of aflatoxins B1 and B2 produced by animals following ingestion, and so appear in milk, urine and faeces. Aflatoxicol is a reductive metabolite of aflatoxin B1. Aflatoxins are acutely toxic, immunosuppressive, mutagenic, teratogenic and carcinogenic compounds (classified as group 1 carcinogens according to the **International Agency for Research on Cancer (IARC) [34]**. Aflatoxins have been detected in the blood of pregnant women, in neonatal umbilical cord blood, and in breast milk in African countries, with significant seasonal variations **[35]**. The geographical and seasonal occurrence of aflatoxins in food and of kwashiorkor shows a remarkable similarity **[36]**. It has been hypothesized that kwashiorkor, a severe malnutrition disease, may be a form of pediatric aflatoxicosis **[37]**. Aflatoxins exposure accounts for about 40% of the load of disease in developing countries where a short lifespan is prevalent. Food systems and economics in developed country make the advance in aflatoxins management impossible **[38]**. The prevention of mycotoxins toxicity involves reduction of mycotoxin levels in foodstuffs and increasing the intake of diet components such as vitamins, antioxidants and substances known to prevent carcinogenesis **[39]**. The prevention of mycotoxin contamination of human foods could have a significant effect on public health in low-income countries due to enhanced food safety **[40]**. Chemoprotection against aflatoxins has been confirmed with the use of a number of compounds that either increase an animal's detoxification processes **[41]** or prevent the production of the epoxide that leads to cytotoxicity **[42]**. For the animal feed industries, a major focus has been on developing food additives that provide protection from the mycotoxins. One approach has been the use of esterified glucomanoses and other yeast extracts that provide chemoprotection by increasing the detoxification of aflatoxin **[41]**.

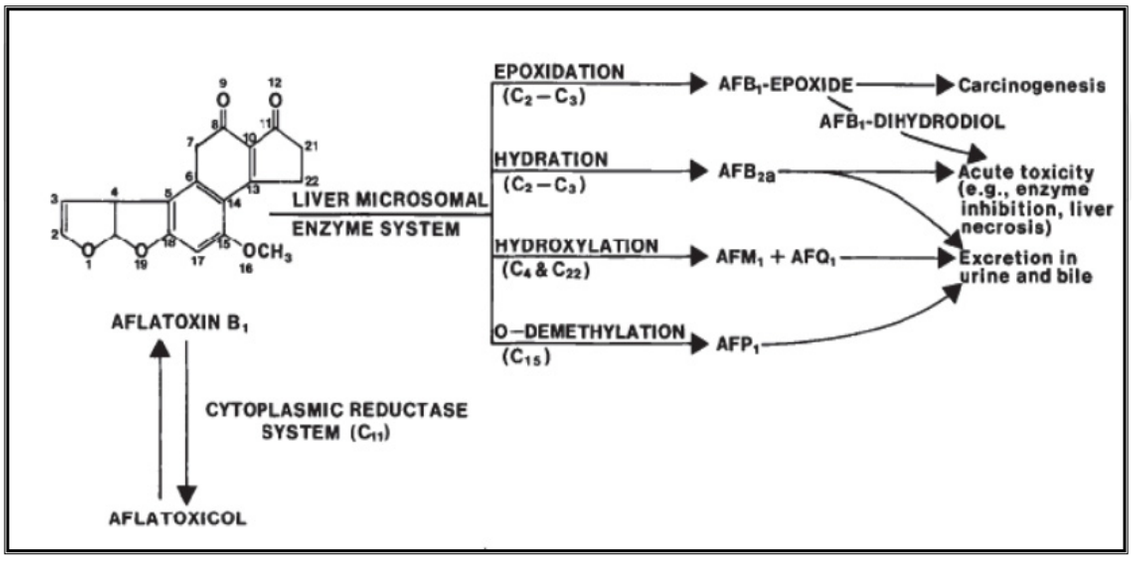

Figure 4. Metabolism of aflatoxin in liver **[46]**

After the absorption, highest concentration of the toxin is found in the liver **[43]**. Once in liver, aflatoxin B1 is metabolized by microsomal enzymes cytochrome P-450 3A4 to different metabolites through hydroxylation, hydration, demethylation and epoxidation. Variations in its catalytic activity of P-450 3A4 are important in issues of bioavailability and drug-drug interactions **[44]**. As in Fig (4) the hydroxylation of AFB1 at C4 or C22 produces, AFM1 and AFQ1, respectively. Hydration of the C2 – C3 double bond results in the formation of AFB2a which is rapidly formed in certain avian species **[45]**. AFP1 results from o-demethylation while the AFB1 – epoxide is formed by epoxidation at the 2,3 double bond Aflatoxicol is the only metabolite of AFB1 produced by a soluble cytoplasmic reductase enzyme system **[46]** .

The putative AFB1 epoxide is generally accepted as the active electrophilic form of AFB1 that may attack nucleophilic nitrogen, oxygen and sulphur heteroatoms in cellular constituents **[47]**. This highly reactive substance may combine with DNA bases such as guanine to produce alterations in DNA **[36]**. However, both humans and animals possess enzymes system, which are capable of reducing the damage to DNA and other cellular constituents caused by the 8,9-epoxide. For example GST mediates the conjugation reaction of the 8,9-epoxide to the endogenous compound GSH, this essentially neutralizes its toxic potential (**Fig. 5)**. Animal species such as the mouse that are resistant to aflatoxin carcinogenesis have 3-5 times more GST activity than susceptible species such as the rat. Humans have less GST activity or 8,9-epoxide conjugation than rats or mice suggesting that humans are less capable of detoxifying this important metabolite **[48].**

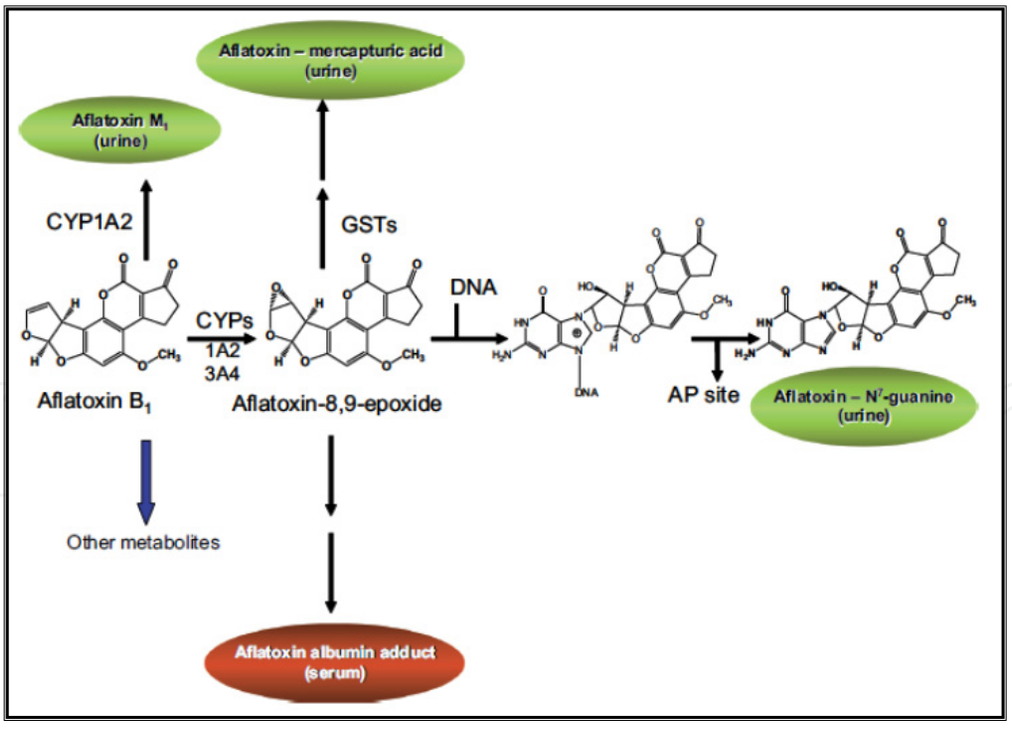

Figure 5. Biomarkers of aflatoxin exposure in an internal dose and a biologically effective dose. Biomarkers of exposure include aflatoxin M1, the internal dose includes the aflatoxin-mercapturic acid and aflatoxinalbumin adduct, and the biologically effective dose is reflected by the excretion of the aflatoxin-N7-guanine adduct formed by depurination leading to an apurinic (AP) site in DNA **[49].**

The diseases caused by aflatoxin consumption are called aflatoxicosis. Acute aflatoxicosis results in death, however, chronic aflatoxicosis results in immune suppression and cancer **[19]**. Suppression of the cell-mediated immune response was mediated by altered cytokine expression **[50]**. Aflatoxins caused hepatotoxicity, nephrotoxicity and genotoxicity in somatic and germ cells, resulted in mitotic and meiotic delay in mice **[51]**. An increase in AFB1-8, 9-epoxide cause a significant increases in hepatic LPO level **[52]**. Peroxidation of membrane lipids initiated loss of membrane integrity; membrane bound enzyme activity and cell lysis **[53]**. LPO was significantly increased in the liver, kidney **[54]** and testis **[55]** of aflatoxin-treated mice as compared to controls. However, GSH levels declined significantly in the liver, kidney and testis after 45 days of aflatoxin treatment **[56]**. Moreover, AFB1 intake and expression of enzymes involved in AFB1 activation/detoxification may play an important role in hepatitis B virus-related hepatocarcinogenesis **[57]**. The results of a clinical trial suggest that chlorophyllin may have a role in preventing dietary exposure to aflatoxin B_1 by reducing its oral bioavailability **[58]**.

Srategies for reducing exposure and risk from aflatoxin in developing countries should be carefully tested and validated using clinical trial designs with biomarkers serving as objective endpoints. Clinical trials and other interventions are designed to translate findings from human and experimental investigations to public health prevention. Both primary (to reduce exposure) and secondary (to alter metabolism and deposition) interventions can use specific biomarkers as endpoints of efficacy. In a primary prevention trial, the goal is to reduce exposure to aflatoxins in the diet. A range of interventions includes planting pest-resistant varieties of staple crops, attempting to lower mould growth in harvested crops, improving storage methods following harvest, and using trapping agents that block the uptake of unavoidably ingested aflatoxins. In secondary prevention trials, one goal is to modulate the metabolism of ingested aflatoxin to enhance detoxification processes, thereby reducing internal dose and subsequent risk **[49] (Fig. 6).**

Ochratoxin A (OTA)

Ochratoxins are the first major group of mycotoxins identified after the discovery of the aflatoxins **[59]**. OTA is found in a variety of plant food products such as cereals. Because of its long half life, it accumulates in the food chain **[60]**. OTA is absorbed passively throughout the gastrointestinal tract and actively in the kidneys. Highest amounts of OTA could be found in the blood and it is distributed in kidney, liver, muscle and adipose tissue in a decreasing order. The toxin is excreted primarily in the urine, and to a lesser degree in bile and also in milk. The half-life of experimentally orally ingested OTA is shorter than intravenously injected OTA **[61]**. According to IRAC **[34]** OTA is classified as group 1 carcinogens. Structure-activity studies suggested that the toxicity of OTA may be attributed to its isocoumarin moiety and lactone carbonyl group. OTA reduces the expression of several genes regulated by nuclear factor-erythroid 2 p45-related factor (Nrf2) and reduces the expression of antioxidant enzymes through inhibition of Nrf2 **[62, 63].** OTA toxicity may be involved in the development of certain kidney diseases through generation of oxidative stress **[64]**. Chronic administration of low dose of OTA caused morphological and functional

changes in proximal tubules and administration of date extract protects against OTA-induced tubule's tissue damage [**65].** However, antioxidant treatment failed to prevent the development of OTA-induced tumors in animal models **[66]**. Indomethacin and aspirin were found to prevent OTA genotoxicity in the urinary bladder and kidney of mice **[67]**. OTA causes acute depletion of striatal dopamine and its metabolites, accompanying evidence of neural cell apoptosis in the substantia nigra, stratum and hippocampus **[68]**.

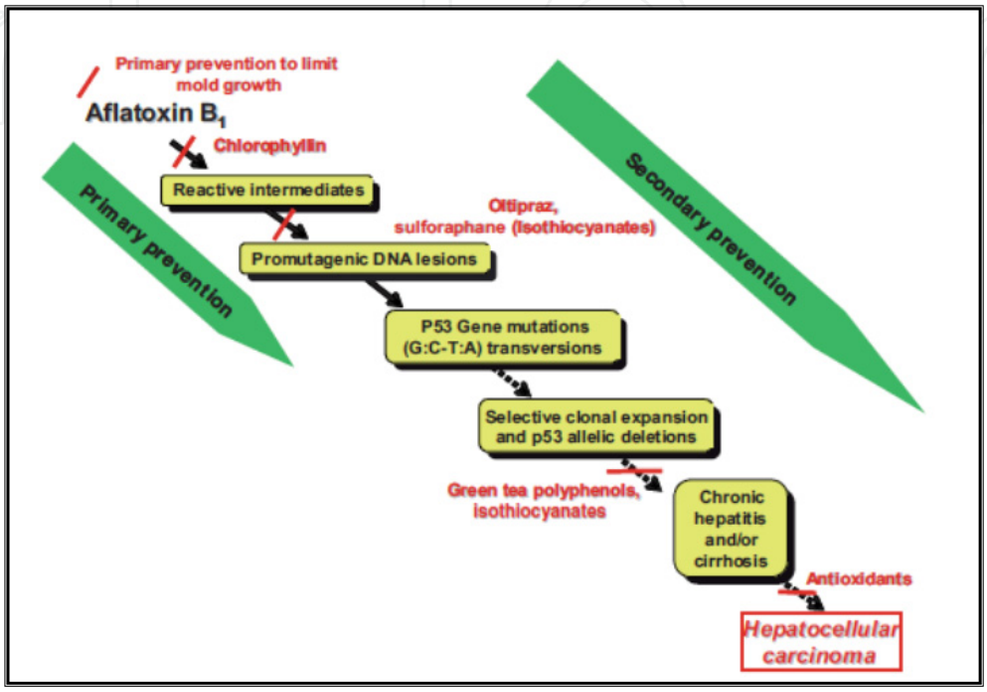

Figure 6. Strategies for reducing exposure and risk from aflatoxin in developing countries **[49]**

OTA has complex mechanisms of action that include oxidative stress, bio-energetic compromise, mitochondrial impairment, inhibition of protein synthesis, production of DNA single strand breaks and formation of OTA-DNA adducts **[69-71]**. OTA induced renal toxicity and carcinogenicity may be mediated by an Nrf2-dependent signal transduction pathway **[63]**. It is a mitochondrial poison causing mitochondrial damage, oxidative burst, LPO and interferes with oxidative phosphorylation **[72, 73]**. OTA was found to chelate ferric ions (Fe^3), facilitating their reduction to ferrous ions (Fe^2), which in the presence of oxygen, provided the active species initiating LPO **[74]**. OTA hydroquinone/ quinone couple was generated from the oxidation of OTA by electrochemical, photochemical and chemical processes resulting in redox cycling and in the generation of ROS **[75]**. OTA impairs the antioxidant defense of the cells making them more susceptible to oxidative damage **[62]** and a reduction in cellular antioxidant defense may contribute to the production of OTA-dependent oxidative damage **[76].**

Studies carried out in several countries including Tunisia, Egypt and France, have indicated a link between dietary intake of OTA and the development of renal and urothelial tumours **[77- 81]**. OTA is known to affect the immune system in a number of mammalian species. The type of immune suppression experienced appears to be dependant on a number of factors,

including the species involved, the route of administration, the doses tested, and the methods used to detect the effects **[82]**. OTA causes immunosuppression following prenatal, postnatal and adult-life exposures. These effects include reduced phagocytosis and lymphocyte markers **[83]** and increased susceptibility to bacterial infections and delayed response to immunization in piglets **[9]**. OTA induces apoptosis in a variety of cell types *in vivo* and *in vitro* that mediated through cellular processes involved in the degradation of DNA **[84]**. Moreover, the immunosuppressant activity of OTA is characterized by size reduction of vital immune organs, such as thymus, spleen, and lymph nodes, depression of antibody responses, alterations in the number and functions of immune cells, and modulation of cytokine production (TNF-α and Il-6). The immunotoxic activity of OTA probably results from degenerative changes and cell death following necrosis and apoptosis, in combination with slow replacement of affected immune cells, due to inhibition of protein synthesis **[85].** Finally, it is proposed that a network of interacting epigenetic mechanisms, including protein synthesis inhibition, oxidative stress and the activation of specific cell signalling pathways is responsible for OTA carcinogenicity [**86] (Fig.7)**

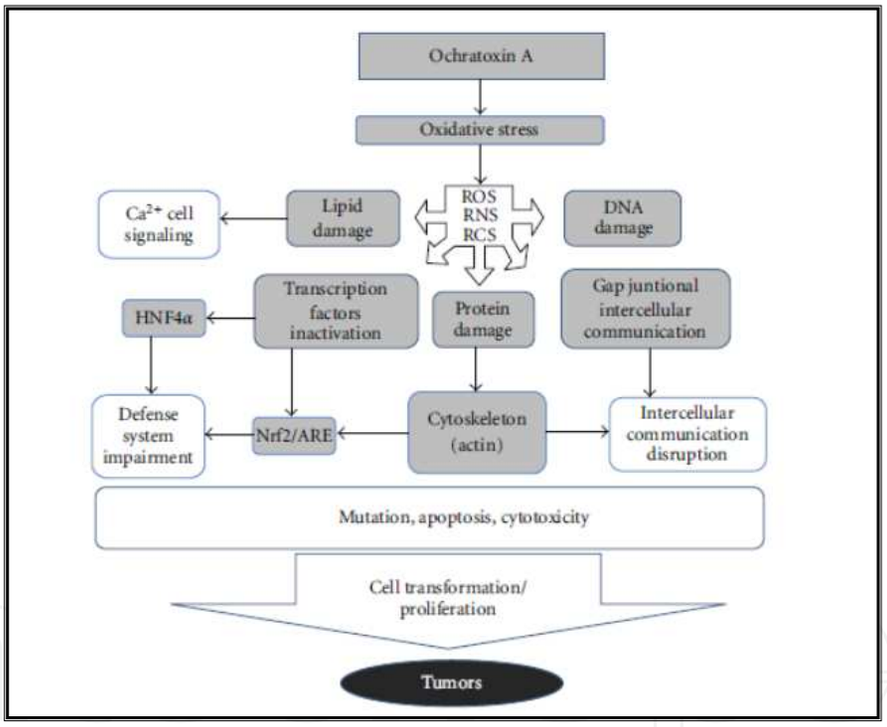

Figure 7. Scheme to illustrate the oxidative stress-mediated mode of action proposed for OTA. Increased production of ROS, RNS, and RCS is likely to originate either from direct redox reactions involving OTA or through the inhibition of cellular defenses such as through the inhibition of transcription factors as Nrf2 which regulates enzymes with antioxidant properties. The generation of radicals will induce macromolecular oxidative damage such as oxidized DNA bases which may be converted into mutation resulting into generation of transformed cells [66].

Trichothecenes

Trichothecenes (TCs) are mycotoxins produced mostly by members of the *Fusarium* genus and other genera (e.g. *Trichoderma*, *Trichothecium*, *Myrothecium* and *Stachybotrys*). By now,

more than 180 different trichothecenes and trichothecene derivatives have been isolated and characterized **[87, 88]**. TCs were found in air samples collected during the drying and milling process on farms, in the ventilation systems of private houses and office buildings and on the walls of houses with high humidity **[89-90]**. They can be divided into four categories according to both their chemical properties and their producer fungi;

1. **Type A:** functional group other than a ketone at C8 position (e.g.; T-2, HT-2, DAS);
2. **Type B:** carbonyl functions at C8 position (e.g.; DON, NIV, FUS-X, 3-acetyl-deoxynivalenol, 15-acetyl-deoxynivalenol);
3. **Type C:** second epoxide group at C7, 8 or C9, 10; (e.g.; crotocin and baccharin);
4. **Type D:** macrocyclic ring system between C4 and C15 with two ester linkages (e.g.; satratoxin G, H, roridin A and verrucarin A) **[87, 91, 92]**.

TCs exposure leads to apoptosis both *in vitro* and *in vivo* in several organs such as lymphoid organs, hematopoietic tissues, liver, intestinal crypts, bone marrow and thymus **[91, 93]**. Acute high dose toxicity of TCs is characterized by diarrhea, vomiting, leukocytosis, haemorrhage, and circulatory shock and death, whereas chronic low dose toxicity is characterized by anorexia, reduced weight gain, neuroendocrine and immunologic changes **[91, 94]**. The myelotoxicity was considered highest for T-2 and HT-2 toxins and lowest for DON and NIV **[94]**. TCs are toxic to many animal species, but the sensitivity varies considerably between species and also between the different TCs **[93].** Cellular effects on DNA and membrane integrity have been considered as secondary effects of the inhibited protein synthesis. The toxin binds to the peptidyl transferase, which is an integral part of the 60S ribosomal subunit of mammalian ribosome. TCs interfere with the metabolism of membrane phospholipids and increase liver LPO *in vivo*. Also, some TCs are shown to change the serotonin activity in the central nervous system, which is known to be related in the regulation of food intake **[88]**.

T-2 Toxin

T-2 toxin is a cytotoxic secondary fungal metabolite that belongs to TCs family produced by various species of *Fusarium* (*F. sporotichioides*, *F. poae*, *F. equiseti*, and *F. acuminatum*), which can infect corn, wheat, barley and rice crops in the field or during storage **[95]**. T-2 toxin is a well known inhibitor of protein synthesis through its high binding affinity to peptidyl transferase resulting in trigger of ribotoxic stress response that activate mitogen-activated protein kinases [**96]**. Moreover, T-2 toxin interferes with the metabolism of membrane phospholipids and increases liver LPO **[97]**. Also, T-2 toxin suppresses drug metabolizing enzymes such as GST **[98]**. T-2 toxin treated mice showed a time-dependent increase in ROS generation, depletion of GSH, increases in LPO and protein carbonyl content in the brain. Moreover, the gene expression profile of antioxidant enzymes showed a significant increase in SOD and CAT via the dermal route and GR and GPx via the subcutaneous route **[99]**. General signs of T-2 include nausea, emesis, dizziness, chills, abdominal pain, diarrhea, dermal necrosis, abortion, irreversible damage to the bone marrow, reduction in white blood cells and inhibition of protein synthesis **[100, 101].** Moreover, the effects of T-2 toxins on the immune system include changes in leukocyte counts, delayed hypersensitivity,

depletion of selective blood cell progenitors, depressed antibody formation and allograft rejection **[39]**. Also, T-2 toxin has a direct lytic effect on erythrocytes **[102]**. T-2 toxin can induce apoptosis in many types of cells bearing rapid rates of proliferation [**103]** and increased the expression of both oxidative stress and apoptosis related genes in hepatocytes of mice **[104]**. T-2 toxin induces neuronal cell apoptosis in the fetal and adult brain **[68].** In this aspect, it suggested that dysfunction of the mitochondria and oxidative stress might be the main factor behind the T-2 toxin-induced apoptosis in the fetal brain **[105]**. ROS activate caspase-2 which play a crucial role in the control of apoptosis **[106, 107]**. Moreover, it was demonstrated that T-2 toxin induced cytotoxicity in HeLa cells is mediated by generation of ROS leading to DNA damage and trans activation of p53 protein expression which leads to shift in the ratio of Bax/Bcl-2 in favour of apoptosis and subsequent release of Cyt-c from mitochondria followed by caspase cascade **[99]**.

Fumonisins

Fumonisins produced by the fungus *Fusarium verticillioides*, a widespread fungal contaminants of various cereals, predominantly corn **[2, 108]**. Fumonisn B1 (FB1) and B2 are of toxicological significance, while the others (B3, B4, A1 and A2) occur in very low concentrations and are less toxic **[3].** FB1 is poorly absorbed and rapidly eliminated in feces. Minor amounts are retained in liver and kidneys. FB1 does not cross the placenta and is not teratogenic *in viv*o in rats, mice, or rabbits, but is embryotoxic at high, maternally toxic doses [**109]**. FB1 has been linked to a number of diseases in humans and animals **[1, 40]**. FB1 increases oxidative DNA damage, as measured by increased DNA strand breaks and malondialdehyde adducts in rat liver and kidney *in vivo* **[111]**. As shown in Fig. (9) an alternative mechanism of action of FB1 involves the disruption of the de novo sphingolipid biosynthesis pathway by inhibition of the enzyme ceramide synthase **[68, 112]**. The inhibition of sphingolipid biosynthesis disrupts numerous cell functions and signaling pathways, including apoptosis and mitosis, thus potentially contributing to carcinogenesis through an altered balance of cell death and replication [**113]**. Disruption of sphingolipid metabolism leads to changes in the sphinganine to sphingosine ratio **[114**] as demonstrated in rat liver and mouse kidney at carcinogenic doses of FB1 **[115]**.

FB1-induced DNA damage and hepatocarcinogenesis in experimental models can be modulated by a variety of factors including nutrients, chemopreventive agents, and other factors such as food restriction and viral infection, as well as genetic polymorphisms **[118]. I**n rat C6 glioma cells, FB1 inhibits protein synthesis, causes DNA fragmentation and cell death, increases 8-hydroxy-2'-deoxyguanosine, induces LPO, and cell cycle arrest **[119].** Also, the signs of apoptosis were increased caspase-3 like protease activity and internucleosomal DNA fragmentation [**120]**. Furthermore**,** the disruption of membrane structure, the enhancement of membrane endocytosis, and the increase in membrane permeability caused by FB1 in macrophages provide additional insight into potential mechanisms by which the fumonisins might enhance oxidative stress and cellular damage **[121]**.

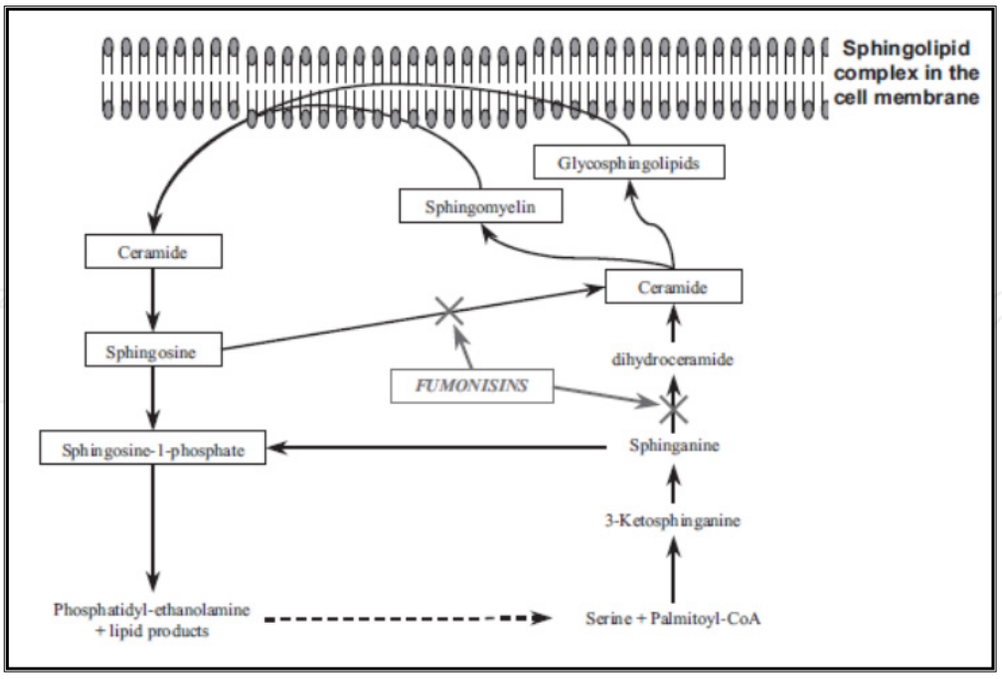

Figure 8. Pathway of de novo synthesis (not in boxes) and turnover of sphingolipids (boxed) in animal cells, and their inhibition by fumonisins. Fumonisns inhibit the synthesis of ceramides by specifically binding to sphingosine and sphinganine **[116, 117]**

Zearalenone

Zearalenone (ZEA) is produced mainly by *Fusarium graminearum* and related species, principally in wheat and maize. ZEA and its derivatives produce estrogenic effects in various animal species **[3].** The structure of the ZEA similar to steroids and binds to ER as an agonist. There are two major biotrasformation pathways for ZEA in animals (1) hydroxylation catalyzed by 3α- and 3β- hydroxysteroid dehydrogenase (HSDs) resulting in the formation of α- and β-ZOL; (2) conjugation of ZEA and its metabolites with glucuronic acid, catalyzed by uridine diphosphate glucuronyl transferase. Consequently, ZEA is a substrate for 3α-HSD and 3β-HSD present in many steroidogenic tissues, such as liver, kidney, testis, prostate, hypothalamus, pituitary, ovary, intestine **[122, 123]**. The adverse effects of ZEA are partly determined by the processes of elimination, because the biliary excretion and entero-hepatic cycling are important processes affecting the fate of ZEA and explaining a different sensitivity between animals **[124]**. α and β Zearalenol metabolites caused cytotoxicity by inhibiting cell viability, protein and DNA syntheses and inducing oxidative damage and over-expression of stress proteins. However, the ZEA metabolites exhibited lower toxicity than ZEA, with β zearalenol being the more active of the two metabolites **[125].** In addition**,** oxidative damage is likely to be evoked as one of the main pathways of ZEA toxicity which may initiate event at least in part contribute to the mechanism of ZEA induced genotoxic and cytotoxic effects **[126].** ZEA and its derivatives compete effectively with 17 β-E2 for the specific binding sites of the oestrogen receptors (ERs) occurring in different organs. Two subtypes of ER exist, ER-α and ERβ that are differently distributed in the body. Binding of ZEA and its derivatives initiate a sequence of

events known to follow estrogen stimulation of target organs **[127, 128]**. So, the effect of ZEA and its metabolites depends upon the reproductive status (prepubertal, cycling or pregnant) of the affect animals **[123].** ZEA do not induce apoptosis in porcine ovaries [**129]**, however, apoptosis is the principal mechanism contributing to germ cell depletion and testicular atrophy following ZEA exposure **[130].** Moreover, ZEA has potent effects on the expression of chicken splenic lymphocytes cytokines at the mRNA level **[131]**.

Patulin

Patulin (PAT) is a toxic chemical contaminant produced by several species of mould, especially within *Aspergillus*, *Penicillium* and *Byssochlamys*. It is the most common mycotoxin found in apples and apple-derived products such as juice, cider, compotes and other food intended for young children. Exposure to this mycotoxin is associated with immunological, neurological and gastrointestinal outcomes **[132]**. PAT-induced nephropathy and gastrointestinal tract malfunction have been demonstrated in animal models **[133]**. The toxic effects of PAT on various cells related to its activity on SH groups **[134]**. Moreover, it suggested that PAT-induced apoptosis is mediated through the mitochondrial pathway without the involvement of p53 **[12]**. The interaction with sulfhydryl groups of macromolecules by PAT and the subsequent generation of ROS plays a primary role in the apoptotic process. The genotoxic effects might be related to its ability to react with sulfhydryl groups and to induce oxidative damage **[135]**. PAT was found to reduce the cytokine secretion of IFN-γ and IL-4 by human macrophages **[136]** and of IL-4, IL-13, IFN-γ, and IL-10 by human peripheral blood mononuclear cells and human T cells **[137]**. The clinical signs of PAT toxicosis are typical of the nervous syndrome. Animals present hyperaesthesia, lack of coordination of motor organs, problems with ingestion and digestion. At the molecular level, PAT alters ion permeability and/or intracellular communication, causing oxidative stress and cell death (**116)**.

Citrinin

Citrinin is a toxic metabolite produced by several filamentous fungi of the genera *Penicillium, Aspergillus* and *Monascus*, which has been encountered as a natural contaminant in grains, foods, feedstuffs, as well as biological fluids. Some analytical systems have been developed for its detection and quantification [**138]**. As one of mycotoxins, citrinin possesses antibiotic, bacteriostatic, antifungal and antiprotozoal properties. While it is also known as a hepato-nephrotoxin in a wide range of species **[139]**, *in vitro* studies have demonstrated that citrinin produced multiple effects on renal mitochondrial function and macromolecule biosynthesis that ultimately resulted in cell death **[140]**. Citrinin inhibited the oxygen consumption rate by about 45 % and inhibited the glucose utilization of BHK-21 cells by about 86 % due to alterations in mitochondrial function and in the glycolytic anaerobic pathway **[141]**. Citrinin occurred frequently together with another nephrotoxin–ochratoxin A in foodstuffs such as cereals, fruits, meat **[142]** and cheese **[143].** Citrinin can act synergistically with ochratoxin A to depress RNA synthesis in murine kidneys **[144, 145]**. The simultaneous exposure of rabbits to citrinin with OTA even at sub-clinical dietary levels potentiated the OTA induced nephrotoxicity at ultrastructural level **[146].** To avoid the

direct/indirect intake of citrinin, it is important to develop detoxification methods for citrinin during food processing. So far, there have been several reports on the detoxification of citrinin. The investigation on thermal decomposition and detoxification showed that, in the presence of a small amount of water, heating citrinin at 130°C caused a significant decrease in its toxicity to Hela cells **[147]**; whereas heating at 150°C in water caused formation of highly toxic compounds **[148]**.

Ergot Alkaloids

The ergot alkaloids are among the most fascinating of fungal metabolites. They are classified as indole alkaloids and are derived from a tetracyclic ergoline ring system **[149]**. These compounds are produced as a toxic cocktail of alkaloids in the sclerotia of species of *Claviceps*, which are common pathogens of various grass species. Ergotism is still an important veterinarian problem. The principal animals at risk are cattle, sheep, pigs, and chickens. Clinical symptoms of ergotism in animals include gangrene, abortion, convulsions, suppression of lactation and hypersensitivity **[150]**. More recently, pure ergotamine has been used for the treatment of migraine headaches. Other ergot derivatives are used as prolactin inhibitors, in the treatment of Parkinsonism, and in cases of cerebrovascular insufficiency [**149]**. The therapeutic administration of ergot alkaloids may cause sporadic cases of human ergotism **[151].** Ergotism is extremely rare today, primarily because the normal grain cleaning and milling processes remove most of the ergot so that only very low levels of alkaloids remain in the resultant flours. In addition, the alkaloids that are the causative agents of ergotism are relatively labile and are usually destroyed during baking and cooking **[3]**.

Satratoxin G

Satratoxin G is one of the most potent macrocylclic TCs produced by *Stachybotrys chartarum* **[152]**. Roridin A is a commercially available macrocyclic TC used as a stratoxin G substitute, and roridin L2 is a putative biosynthetic precursor of satratoxin **[153]**. Satratoxin G is potent inhibitors of eukaryotic translation that are potentially immunosuppressive. It rapidly binds small and large ribosomal subunits in a concentration- and time-dependent manner that was consistent with induction of apoptosis **[154]**. A signal transduction pathway in satratoxin-induced apoptosis in HL-60 cells involves, caspase-3 activation through activation of both caspase-8 and caspase-9 along with cytosolic release of cytochrome c and fragmentation of nucleosomal DNA by DFF-40/CAD **[155]**.

Roridin E

Roridin E is a well-known macrocyclic trichothecene mycotoxin possessing potent anti-proliferative activity against cancer cell lines **[156].** Four new isolated from a marine-derived fungus, *Myrothecium roridum* strain 98F42 **[157]**. One of them, 12-deoxy derivative of roridin E, showed reduced cytotoxicity about 80-fold less than that of roridin E against human promyelocytic (HL-60) and murine leukemia (L1210) cell lines **[158]**. Treatment of rats with roridin E caused minimal toxicity on the hepatic and renal tissue, however, co administration of linoleic acid with roridin E resulted in increase toxicity due to increased incorporation to the cell membrane or inhibit its biotransformation **[159]**.

5. Mmycotoxins and apoptosis

Apoptosis is a process for maintenance of tissue homeostasis. Several processes, such as initiation of death signals at the plasma membrane, expression of pro-apoptotic oncoproteins, activation of death proteases and endonucleases combine to cause cell termination. ROS may play a major role in apoptosis. GSH depletion increases the % of apoptotic cells **[160]**. In general, apoptosis is considered as a common mechanism of toxicity of various mycotoxins **[68]**. TCs induce apoptosis response via mitochondrial and non-mitochondrial mechanisms **[161]**. The amphophilic nature of TCs facilitates their cytotoxic effect on cell membranes and inside the cell interact with ribosome and mitochondria causing inhibition of protein synthesis **[162]**. FB_1 and OTA are able to induce apoptosis and necrosis in porcine kidney PK15 cells **[163]**. This is because the structure of FB_1 resembles sphingoid bases which regulate cell growth, differentiation, transformation and apoptosis, and so it is not surprising that FB_1 can alter growth of certain mammalian cells. The involvement of the TNF signal transduction pathway in FB1 induced apoptosis in African green monkey kidney fibroblasts has been shown **[164]**. Moreover, TNF-α production is responsible for FB1 induced apoptosis in mice primary hepatocytes **[165]**. Over expression of cytochrome P450-sensitized hepatocyte to TNFα-mediated cell death was associated with increased LPO and GSH depletion **[166]**. FB1 was reported to increase induction of cytochrome P450 isoforms and caused peroxidation of membrane lipids in isolated rat liver nuclei as well as GSH depletion of in pig kidney cells **[167-169].** GSH depletion is known to activate c-Jun N-terminal kinase through redox inhibition of GST, which normally binds to and inhibits stress kinases **[170]**. Stimulation of apoptosis and necrosis in porcine granulosa cells by ZEA is dose-dependent manner via a caspase-3- and caspase-9-dependent mitochondrial pathway [**171]**. At the molecular level, fumonisins inhibit ceramide synthase and disrupt sphingolipid metabolism therefore influence apoptosis and mitosis **[109]**. The immunotoxic activity of OTA probably results from degenerative changes and cell death following necrosis and apoptosis in combination with slow replacement of affected immune cells due to inhibition of protein synthesis **[85].** Moreover**,** PAT induce DNA damage and cell cycle arrest along with intrinsic pathway mediated apoptosis which may have dermal toxicological implications **[172]**.

Satratoxin H is thought to induce apoptosis of PC12 cells through the activation of p38 mitogen activated protein kinase and c-Jun N-terminal kinase in GSH-sensitive manner **[173]**. Chemoprotective effects of flavonoid compounds against aflatoxins were confirmed in hens **[174]**. Moreover, cysteine and GSH has protective effect against PAT in the incident of rumen microbial ecosystem, however vitamin C and ferulic acid did not demonstrate an effect [**175]**. Metallothioneins (MTs) are four major isoforms found in cytoplasm, lysosomes, mitochondria and nuclei of mammalian cells **[176]**. MT-1 and 2 have ubiquitous tissue distribution particularly in liver, pancreas, intestine, and kidney, whereas MT-3 is found in brain and MT-4 in skin **[177]**. MT can play important role in the process of mycotoxins detoxification probably by redistribution of significant ions to transcriptional factors and interactions with oxygen radicals that may be generated by mycotoxins **[23].** Nivalenol, a

trichothecene mycotoxin induces apoptosis in HL60 cells and that intracellular calcium ion plays a role in the nivalenol-induced secretion of IL-8 from this cell line **[178].**

6. Mycotoxins as therapeutics compound

Cumulative knowledge about toxins structure and mechanism of action, as well as recent progress in the fields of cell biology, immunology, molecular biology and nanotechnology, enabled the development of different targeting strategies that are vital for converting a lethal toxin into a therapeutic agent**. Fig. 9** showed three targeting strategies in toxin based therapy. i- Ligand targeted toxins upon administration to patients are internalized and intoxicate diseased cells, sparing healthy cells that do not display the target on their surface. ii- protease activated toxins: the toxin is engineered to be cleaved and activated by a disease-related intracellular or extracellular protease. Toxin cleavage may enhance cell-binding and/or translocation, stabilization or catalytic activity of the toxic moiety specifically in protease expressing cells, leading to their suppression. iii- toxin based suicide gene therapy: a DNA construct, encoding for a toxic polypeptide whose expression is regulated by a specific transcription regulation element, is delivered to a heterogeneous cell population **[179]**.

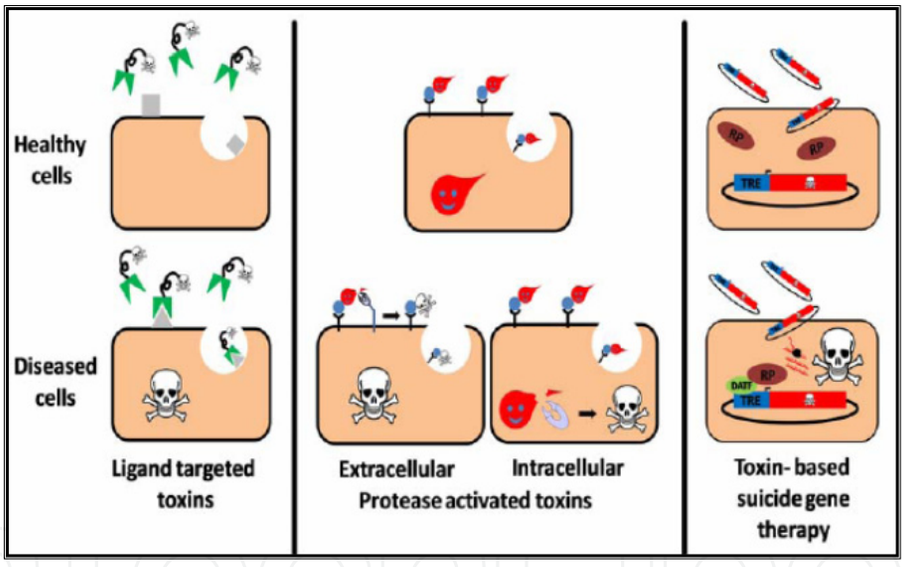

Figure 9. Three targeting strategies in toxin based therapy **[179]**.

Because of their pharmacological activity, some mycotoxins or mycotoxin derivatives have found use as antibiotics, growth promoters, and other kinds of drugs. Ergocryptine is an ergot alkaloid that affects dopaminergic activity principally by interacting with D2-type receptors **[180]**. The bromation derivative has increased dopamine agonist activity, and is used against Parkinsonism and to reduce growth hormone secretion and milk production **[181]**. Ergotamine was among the most effective available agents for relieving migraine attacks **[182]**. Ergometrine and the semi-synthetic methylergometrine have been widely used for the prevention and treatment of excessive uterine bleeding following birth and also to initiate delivery **[183]**. Lysergic acid diethylamide is a serotonin receptor agonist **[184]** and can also interact with dopamine receptors to make it a useful tool for probing the

biochemical basis for behaviour **[185]**. Methysergide a semi-synthetic ergot alkaloid is a serotonin antagonist used in the treatment of migraine and is used for daily preventive therapy rather than in acute cases **[184]**. The TCs have been associated with various biological properties, such as antiviral especially as inhibitors of the replication of Herpes, antibiotic, antimalarial, antileukemic and immunotoxic **[59,186].** Mycoestrogenic zearalenone is suspected to be a triggering factor for central precocious puberty development in girls. Due to its chemical resemblance to some anabolic agents used in animal breeding, ZEA may also represent a growth promoter in exposed patients **[187]**. Development of cyclosporine A as immunosuppressive drug has been traced back to the stimulus derived from the first highly-active cyclopeptides from *Amantia mushrooms* **[188]**.

7. Conclusion

Mycotoxins are produced in a strain-specific way, and elicit some complicated and overlapping toxigenic activities in sensitive species that include carcinogenicity, inhibition of protein synthesis, immunosuppression, dermal irritation, and other metabolic perturbations. Mycotoxins usually enter the body via ingestion of contaminated foods, but inhalation of toxigenic spores and direct dermal contact are also important routes. There is sufficient evidence from animal models and human epidemiological data to conclude that mycotoxins pose an important danger to human and animal health. Trichothecenes cause protein synthesis inhibition via binding to the 18s rRNA of the ribosomal large subunit as a major mechanism underlying induction of cell apoptosis. T-2 toxin triggers a ribotoxic response through its high binding affinity to peptidyl transferase which is an integral part of the 60 s ribosomal subunit and interferes with the metabolism of membrane phospholipids and increases liver lipid peroxides. SH is thought to induce caspase-3 activation and apoptosis through the activation of MAPK and JNK in a GSH-sensitive manner. FB_1-induced inhibition of ceramide synthesis can result in a wide spectrum of changes in lipid metabolism and associated lipid-dependent pathways. OTA has complex mechanisms of action that include mitochondrial impairment, formation of OTA-DNA adducts and induction of oxidative stress and apoptosis through caspase activation. Accordingly, the strict control of food quality, in both industrialized and developing countries, is therefore necessary to avoid mycotoxicosis.

Author details

Hossam El-Din M. Omar
Zoology Department, Faculty of Science, Assiut University, Egypt

8. References

[1] Bennett JW, Klich M. Mycotoxins. Clinical Microbiology Reviews 2003; 16 (3): 497–516.
[2] Surai PF, Mezes M, Melnichuk SD, Fotina TI. Mycotoxins and animal health: From oxidative stress to gene expression. *Krmiva 2008; 50*: 35–43.
[3] Peraica M, Radic B, Lucic A, Pavlovic M. Toxic effects of mycotoxins in humans. Bull. WHO 1999; 77:754–766.

[4] EFSA (2009): Annual Report of European Food Safety Authority, ISBN: 978-92-9199-211-9 doi:10.2805/3682.
[5] Reverberi M, Ricelli A, Zjalic S, Fabbri AA, Fanelli C. Natural functions of mycotoxins and control of their biosynthesis in fungi. Appl Microbiol Biotechnol 2010; 87:899–911.
[6] Fink-Grenmels J, Georgiou NA. Risk assesment of mycotoxins for the consumer. In: Ennen G, Kuiper HA, Valentin A, eds. Residues of Veterinary Drugs and Mycotoxins in Animal Products. NL-Wageningen Press 1996 p 159-74.
[7] Fink-Grenmels, J . Mycotoxins: Their implications for human and animal health. Veterinary Quarterly 1999; 21(4):115-120.
[8] Bryden WL.Mycotoxins in the food chain: human health implications. Asia Pac J Clin Nutr 2007; 16(1):95-101.
[9] Stoev S, Denev S, Dutton M, Nkosi B. Cytotoxic effect of some mycotoxins and their combinations on human peripheral blood mononuclear cells as measured by the MTT assay. The Open Toxinology Journal 209; 2: 1-8.
[10] Henry SH, Bosch FX, Troxell TC, Bolger PM. Reducing liver cancer-global control of aflatoxin. Science 1999; 286:2453–2454.
[11] Binder EM, Tan LM, Chin LJ, Handl J, Richard J. Worldwide occurrence of mycotoxins in commodities, feeds and feed ingredients. Animal Feed Science and Technology,2007; 137: 265–282.
[12] Wu TS, Liao YC, Yub FY, Chang CH, Liu BH. Mechanism of patulin-induced apoptosis in human leukemia cells (HL-60). Toxicology Letters 2008; 183:105–111.
[13] CAST Report. Mycotoxins: risks in plant, animal, and human systems. In: J.L. Richard, G.A. Payne (Eds.), Council for Agricultural Science and Technology Task Force Report 2003; No. 139, Ames, Iowa, USA. ISBN 1-887383-22-0.
[14] Wu F. Mycotoxins risk assessment for the purpose of setting International Regulatory Standards. Environ. Sci. Technol. 2004; 38 (15): 4049–4055.
[15] Afifi MM, Abdel-Mallek AY, El-Shanawany AA, Khattab SMR .Fangal populations and myctotoxins of wheat grains imported to Egypt. Ass.Univ. Bull.Envir. Res.2012; 15(1):31-52.
[16] D'mello, JPE, Macdonald AMC. Mycotoxins. Animal Food Sci. Technol. 1997; 69, 155-166.
[17] Peraica M, Domijan AM. Contamination of food with mycotoxins and human health. Arh. Hig. Rada. Toksikol. 2001; 52: 23–35.
[18] Boutrif E, Bessy C. Global significance of mycotoxins and phycotoxins. In: *Mycotoxins and phycotoxins in perspective at the turn of the millennium*. Koe, W.J., Samson, R.A., van Egmond, H.P., Gilbert, J. and Sabino, M. (eds.). Ponsen and Looyen, Wageningen, The Netherlands 2001,p. 3-16.
[19] Hsieh D . Potential human health hazards of mycotoxins. In: Natori S, Hashimoto K, Ueno Y (Eds.). Mycotoxins and Phytotoxins. Third Joint Food and Agriculture Organization/ W.H.O./United Nations Environment Program International Conference of Mycotoxins. Elsevier, Amsterdam, The Netherlands 1988; p. 69-80.
[20] Kemppainen RJ, Thompson FN, Lorenz MD, Munnell JF, Chakraborty PK. Effects of prednisone on thyroidal and gonadal endocrine function in dogs. *Journal of Endocrinology*, 1983; 96:293-302.

[21] Upadhaya SD, Park MA, Ha JK. Mycotoxins and Their Biotransformation in the Rumen. A review. Asian-Aust. J. Anim. Sci.2010; 23 (9): 1250-1260.
[22] Eaton DL, Groopman DJ, ed.; 1994). The toxicology of aflatoxins: human health, veterinary, and agricultural significance. Academic Press, San Diego, Calif.
[23] Vasatkova A, Krizova S, Adam V, Zeman L, Kizek R. Changes in metallothionein level in rat hepatic tissue after administration of natural mouldy wheat. Int. J. Mol. Sci., 2009; 10: 1138-1160.
[24] Devasagayam TPA, Tilak JC, Boloor KK, Sane Ketaki S, Ghaskadbi Saroj S, Lele RD ."Free Radicals and Antioxidants in Human Health: Current Status and Future Prospects". *Journal of Association of Physicians of India 2004;* 52: 796.
[25] Sies H. Oxidative stress: from basic research to clinical application. *Am. J. Med.*, 1991; *91*: 31S–38S.
[26] Tafazoli, S. Mechanisms of drug-induced oxidative stress in the hepatocyte inflammation model, Doctor of Philosophy, Department of Pharmaceutical Sciences, University of Toronto, 2008.
[27] Halliwell B, Gutteridge JMC. Free Radicals in Biology and Medicine. Fourth Edition, Oxford University Press, Oxford, UK, 2007.
[28] Halliwell B, Gutteridge JMC. *Free Radicals in Biology and Medicine*, 3rd ed.; Oxford University Press: New York, NY, USA, 1999.
[29] Ferrer E, Juan-Garcia A, Font G, Ruiz MG. Reactive oxygen species induced by beauvericin, patulin and zearalenone in CHO-K1 cells. Toxicology *in Vitro;* 2009, 23: 1504–1509
[30] Munday R. Studies on the mechanism of toxicity of the mycotoxin, sporidesmin. I. Generation of superoxide radical by sporidesmin.Chemico-Biological Interactions; 1982, 41(3): 361-374.
[31] Raj HG, Prasanna HR, Mage PN, Lotlikar PD. Effect of purified rat and hamster hepatic glutathione S-transferases on the microsome mediated binding of aflatoxin B1 to DNA. Cancer Lett.; 1986, 33:1–9.
[32] Eaton DL, Ramsdel HS. Species and diet related differences in aflatoxin biotransformation, p. 157–182. *In* D. Bhatnagar, E. B. Lillehoj, and D.K. Arora (ed.), Handbook of applied mycology, vol. 5, mycotoxins in ecological systems. Marcel Dekker, Inc., New York, N.Y.;1992.
[33] Kiessling KH. Biochemical mechanism of action of mycotoxins. Pure & Appl. Chem.;1986, 58(2): 327-338.
[34] IARC. Overall evaluations of carcinogenicity: an updating of IARC Monographs volumes 1 to 42. Report of an IARC Expert Committee. Lyon, International Agency for Research on Cancer, 1987 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Supplement 7).
[35] Maxwell SM, Apeagyei F, de Vries HR, Mwanmut DD, Hendrickse RG. Aflatoxins in breast milk, neonatal cord blood and sera of pregnant women. J. Toxicol. Toxin. Rev.; 1989, 8: 19-29.
[36] Hendrickse RG. Kwashiorkor: the hypothesis that incriminates aflatoxins. Pediatrics; 1991, 88: 376-379.

[37] Hendrickse RG. Of sick turkeys, kwashiorkor, malaria, perinatal mortality, heroin addicts and food poisoning: research on the influence of aflatoxins on child health in the tropics. Ann. Trop. Med. Parasitol.; 1997, 91:787– 793.
[38] Williams JH, Phillips TD, Jolly PE, Stiles JK, Jolly CM, Aggarwal D. Human aflatoxicosis in developing countries: a review of toxicology, exposure, potential health consequences, and interventions. Am.J.Clin.Nutr.; 2004, 80:1106-1122.
[39] Creppy EE. Update of survey, regulation and toxic effects of mycotoxins in Europe. Toxicology Letters; 2002, 127: 9–28.
[40] Murphy PA, Hendrich S, Landgren C, Bryant CM. Food mycotoxins: an update. Journal of Food Science; 2005, 71: 52-R65.
[41] Kensler TW, Davis EF, Bolton MG. Strategies for chemoprotection against aflatoxin-induced liver cancer. In: Eaton D, Groopman JD, eds. The toxicology of aflatoxins:humanhealth, veterinary, and agricultural significance. London: Academic Press; 1993, p. 281–306.
[42] Hayes JD, Pulford DJ, Ellis EM, McLeod R, James RF, Seidegard J. Regulation of rat glutathione S-transferase A5 by cancer chemopreventive agents: mechanisms of inducible resistance to aflatoxin B1. Chem Biol Interact; 1998, 112:51–67.
[43] Mintzlaff HJ, Lotzsch R, Tauchmann F, Meyer W, Leistner L. Aflatoxin residues in the liver of broiler chicken given aflatoxin-containing feed. Fleischwirtschaft; 1974, 54: 774-778.
[44] Guengerich FP. Cytochrome P450s and other enzymes in drug metabolism and toxicity. *The AAPS Journal* ; 2006, 8 (1) Article 12 (http://www.aapsj.org).*pp.E101-E110*.
[45] Patterson DSP, Allcroft R. Metabolism of aflatoxins in susceptible and resistant animal species. Fd. Cosmet. Toxicol 1970, 8: 43.
[46] Dhanasekaran D, Shanmugapriya S, Thajuddin N Panneerselvam A. Aflatoxins and aflatoxicosis in human and animals. In aflatoxins - biochemistry and molecular biology, Guevara-Gonzalez, R.G. (editor), ISBN 978-953-307-395-8, InTech, Published, 2011, PP.221-254.
[47] Guengerich FP, Johnsen WW, Ueng YF, Yamazaki H, Shimada T. Involvement of cytochrome P450, glutathione S-transferase and epoxide hydrolase in the metabolism of aflatoxin B1 and relevance to risk of human liver cancer. Environ Health Persp, 1996, 104: 557-562.
[48] Verma RJ. Aflatoxin Cause DNA Damage. Int J Hum Genet; 2004, 4(4): 231-236.
[49] Groopman JD, Thomas W, Kensler TW, Wild CP. Protective interventions to prevent aflatoxin-induced carcinogenesis in developing countries. Annu. Rev. Public Health; 2008, 29:187–203.
[50] Meissonnier GM, Pinton P, Laffitte J, Cossalter AM, Gong YY, Wild CP, Bertin G, Galtier P, Oswald I. Immunotoxicity of aflatoxin B1: impairment of the cell-mediated response to vaccine antigen and modulation of cytokine expression. Toxicol. Appl. Pharmacol.; 2008, 231, 142–149.
[51] Deabes MM, Darwish HR, Abdel-Aziz KB, Farag IM, Nada SA, Tawfek N S. Protective effects of *Lactobacillus rhamnosus GG* on aflatoxins-induced toxicities in male albino mice. J Environment Analytic Toxicol.; 2012, 2:132. doi:10.4172/2161-0525.1000132.

[52] Toskulkao C, Taycharpipranai S, Glinsukon T. Enhanced hepatotoxicity of aflatoxin B1 by pretreatment of rats with ethanol. Res Comm Chem Pathol Pharmacol; 1982, 36: 477-482.
[53] Toskulkao C, Glinsukon T. Hepatic lipid peroxidation and intracellular calcium accumulation in ethanol potentiated aflatoxin B1 toxicity. J Pharmacobio Dyn, 1988, 11:191-197.
[54] Verma RJ, Nair A. Vitamin E prevents aflatoxin induced lipid peroxidation in liver and kidney. Med Sci Res; 1999, 27: 223.
[55] Verma RJ, Nair A. Ameliorative effect of vitamin E on aflatoxin-induced lipid peroxidation in the testis of mice. Asian J Androl; 2001, 3: 217.
[56] Patel JW. Stimulation of cyclophosphamide induced pulmonary microsomal lipid peroxidation by oxygen. Toxicology; 1987, 45: 71.
[57] Yu MW, Lien JP, Chiu YH, Santella RM, Liaw YF, Cher CJ. Effect of aflatoxin metabolism and DNA adduct formation on hepatocellular carcinoma among chronic hepatitis B carriers in Taiwan. Journal of Hepatology; 1991, 27: 320-330.
[58] Sudakin DL. Dietary Aflatoxin Exposure and Chemoprevention of Cancer: A Clinical Review. Clinical Toxicology; 2003, 41(2):195-204.
[59] Bra¨se S, Encinas A, Keck J, Nising CF. Chemistry and Biology of Mycotoxins and Related Fungal Metabolites. Chem. Rev. 2009, *109*, 3903–3990.
[60] Pfohl-Leszkowicz A, Manderville RA. Ochratoxin A: An overview on toxicity and carcinogenicity in animals and humans. Mol. Nutr. Food Res. 2007, *51*, 61–99.
[61] Marquardt RR, Frohlich AA. A review of recent advances in understanding ochratoxicosis. Journal of Animal Science, 1992, 70, 3968-3988.
[62] Cavin C, Delatour T, Marin-Kuan M, Holzhauser D, Higgins L, Bezencon C, Guignard G, Junod S, Piguet D, Richoz-Payot J, Gremaux E, Hayes JD, Nestler S, Mantle P, Schilter B. Reduction in antioxidant defences may contribute to ochratoxin A toxicity and carcinogenicity. Toxicol. Sci.; 2007, 96 (1), 30–39.
[63] Boesch-Saadatmandi C, Wagner AE, Graeser AC, Hundhausen C, Wollram S, Rimbach G. Ochratoxin A impairs Nrf2-dependent gene expression in porcine kidney tubulus cells. J. Anim. Phys. Anim. Nutr;.2009, *93*: 547–555.
[64] Krogh P. Role of ochratoxin in disease causation. Fd Chem Toxic; 1992, 30: 213–224.
[65] Ali A, Abdu S.Antioxidant protection against pathological mycotoxins alterations on proximal tubules in rat kidney. Functional Foods in Heals and Disease; 2011, 4:118-134.
[66] Marin-Kuan M, Ehrlich V, Delatour T, Cavin C, Schilter B. Evidence for a role of oxidative stress in the carcinogenicity of ochratoxin A. Journal of Toxicolog, 2011: 1-15.
[67] Obrecht-Pumio S, Grosse Y, Pfohi-Leszkowicz A, Dirheimer G. Protection by indomethacin and aspirin against genotoxicity of ochraoxin A, particularly in the urinary bladder and kidney. Arch Toxicol. 1996; 70:244-248
[68] Doi K, Uetsuka K. Mechanisms of mycotoxin-induced neurotoxicity through oxidative stress-associated pathways. Int. J. Mol. Sci.;2011, *12*: 5213-5237
[69] Dirheimer G, Creppy EE. Mechanism of action of ochratoxin A, IARC Sci. Publ., 1991, 115: 171-175.
[70] Gautier JC, Holzhaeuser D, Markovic J, Gremaud E, Schilter B, Turesky RJ. Oxidative damage and stress response from ochratoxin exposure in rats. Free Radic. Biol. Med.,2001, *30*: 1089–1098.

[71] Bryan NS, Rassaf T, Maloney RE, Rodriguez CM, Saijo F, Rodriguez JR, Feelisch M. Cellular targets and mechanisms of nitros(yl)ation: An insight into their nature and kinetics *in vivo.* Proc. Natl. Acad. Sci. USA; 2004, *101*: 4308–4313.

[72] Mantle PG. Risk assessment and the importance of ochratoxins. International Biodeterioration and Biodegradation, 2000, 50: 143-146.

[73] Petzinger E, Ziegler K. Ochratoxin A from a toxicological perspective. Journal of Veterinary Pharmacolocy Therapeutics, 2000, 23, 91-98.

[74] Omar RF, Hasinoff BB, Mejilla F, Rahimtula AD. Mechanism of ochratoxin A stimulated lipid peroxidation. Biochemical Pharmacology, 1990, 40: 1183-1191.

[75] Dai J, Park G, Wright MW, Adams M, Akman SA, Manderville RA. Detection and characterization of a glutathione conjugate of ochratoxin A. Chem. Res. Toxicol., 2002, 15 (12), 1581–1588.

[76] Stemmer K, Ellinger-Ziegelbauer H, Ahr HJ, Dietrich DR. Carcinogen- specific gene expression profiles in short-term treated Eker and wild-type rats indicative of pathways involved in renal tumorigenesis. Cancer Res., 2007, 67: 4052–4068.

[77] Abdelhamid AM. Occurrence of some mycotoxins (aflatoxin, ochratoxin, citrinin, zearalenon and vomitoxin) in various Egyptian feeds. Archive in Animal Nutrition, 1990, 40, 647.

[78] Maaroufi K, Achour A, Hammami M, el May M, Betheder AM, Ellouz F, Creppy EE Bacha H. Ochratoxin A in human blood in relation to nephropathy in Tunisia. Human and Experimental Toxicology, 1995, 14, 609-614.

[79] Fillastre JP. Néphrotoxicité expérimentale et humaine des ochratoxines. Bulletin Académie Nationale de Médecine, 1997, 181, 1447.

[80] Godin M, Fillastre JP, Le Gallicier B, Pauti MD. Ochratoxin-induced nephrotoxicity in animals and humans, Semaine des Hopitaux, 1998, 74, 800-806.

[81] Wafa EW, Yahya RS, Sobh MA, Eraky I, El Baz H, El Gayar HAM, Betbeder AM, Creppy, EE. Human ochratoxicosis and nehropathy in Egypt: a preliminary study. Human and Experimental Toxicology, *1998,* 17, 124-129.

[82] [82]- O'Brien E, Dietrich DR. Ochratoxin A: The continuing enigma. Critical Reviews in Toxicology, 2005, 35:33–60.

[83] Müller G, Kielstein P, Rosner H, Berndt A, Heller M, Köhler H. Studies on the influence of combined administration of ochratoxin A, fumonisin B1, deoxynivalenol and T-2 toxin on immune and defence reactions in weaner pigs. Mycoses, 1999, 42, 485–493.

[84] Seegers JC, Boehmer LH, Kruger MC, Lottering ML, De Kock M. A comparative study of ochratoxin A induced apoptosis in hamster kidney and HELA cells. Toxicol. Appl. Pharmacol., 1994, 129:1–11.

[85] Alanati, L., Petzinger, E. Immunotoxic activity of ochratoxin A. J. Vet. Pharmacol. Therap., 2006, 29: 79–90.

[86] Marin-Kuan M, Cavin C, Delatour T, Schilt B. Ochratoxin A carcinogenicity involves a complex network of epigenetic mechanisms. Toxicon, 2008, 52:195–202 .

[87] Sudakin DL. Trichothecenes in the environment: Relevance to human health. *Toxicol. Lett.*,2003, *143*: 97-107.

[88] Eriksen GS, Pettersson H. Toxicological evaluation of trichothecenes in animal feed. Anim. Feed Sci. Technol., 2004, *114*: 205-239.

[89] Croft WA, Jarvis BB, Yatawara CS. Airborne outbreak of trichothecene toxicosis. Atmospheric Environment, 1986, 20, 549-552.
[90] Nikulin M, Pasanen AL, Berg S, Hintikka EL. Stachybotrys atra growth and toxin production in some building materials and fodder under di!erent relative humidities. Applied and Environmental Microbiology, 1994, 60: 3421-3424.
[91] Pestka JJ. Deoxynivalenol:toxicity, mechanisms and animal health risks. Anim. Feed Sci.Technol., 2007, *137*, 283-298.
[92] Yazar S, Omurtag GZ. Fumonisins, Trichothecenes and Zearalenone in Cereals. Int. J. Mol. Sci.,2008, *9*, 2062-2090.
[93] Eriksen GS. *Metabolism and Toxicity of Trichothecenes*, Doctoral thesis, Uppsala, Sweden, 2003.
[94] Larsen JC, Hunt J, Perin I, Ruckenbauer P. Workshop on trichothecenes with a focus on DON: Summary report. Toxicol. Lett., 2004, 153: 1-22.
[95] Desjardins AE, Hohn TM, McComic SP. Trichothecene biosynthesis in *Fusarium* species: chemistry, genetics, and significance. Microbiol. Mol. Biol. Rev., 1993, *57*: 595–604.
[96] Shifrin VI, Anderson P. Trichothecene mycotoxins trigger a ribotoxic stress response that activates c-jun N-terminal kinase and p38 mitogen-activated protein kinase and induces apoptosis. J. Biol. Chem., 1999, *274*: 13985–13992.
[97] Chang IM, Mar WC. Effect of T-2 toxin on lipid peroxidation in rats: Elevation of conjugated diene formation. Toxicol. Lett., 1988, *40*: 275–280.
[98] Guerre P, Eeckhoutte C, Burgat V, Galtier P. The effects of T-2 toxin exposure on liver drug metabolizing enzymes in rabbit. Food Addit. Contam., 2002, *17, 1019-1026.*
[99] Chaudhary M, Rao PV. Brain oxidative stress after dermal and subcutaneous exposure of T-2 toxin in mice. Food Chem. Toxicol., 2010, *48*: 3436–3442.
[100] Pacin A, Reale C, Mirengui H, Orellana L, Boente G. Subclinic effect of the administration of T-2 toxin and nivalenol in mice. Mycotoxin Research, 1994, *10*: 34-46.
[101] Moss MO. Mycotoxin review-2. *Fusarium*. Mycologist, 2002, *16*, 158-161.
[102] Gyongyossy-Issa MIC, Khanna V, Khachatourians GC. Characterisation of hemolysis induced by T-2 toxin. Biochim. Biophys. Acta.,1985, 838: 252-256.
[103] Shinozuka J, Suzuki M, Noguchi N, Sugimoto T, Uetsuka K, Nakayama H, Doi K. T-2 toxin-induced apoptosis in hematopoietic tissues of mice. Toxicol. Pathol.,1998, *26*: 674–681.
[104] Shinozuka J, Miwa S, Fujimura H, Toriumi W, Doi K. Hepatotoxicity of T-2 Toxin, Trichothecene Mycotoxin. In *New Strategies for Mycotoxin Research in Asia (Proceedings of ISMYCO Bangkok '06)*; Kumagai, S., Ed.; Japanese Association of Mycotoxicology: Tokyo, 2007, pp. 62–66
[105] Sehata S, Kiyosawa N, Makino T, Atsumi F, Ito K, Yamoto T, Teranishi M, Baba Y, Uetauka K, Nakayama H, Doi K. Morphological and microarray analysis of T-2 toxin-induced rat fetal brain lesion. Food Chem. Toxicol., 2004, *42*: 1727–1736.
[106] Annunziato L, Amoroso S, Pannaccione A, Cataldi M, Pignataro G, D'Alessio S, Sirabella R, Second A, Sibaud L, DiRenzo GF. Apoptosis induced in neuronal cells by oxidative stress: role played by caspases and intracellular calcium ions. Toxicol. Lett.,2003, *139*: 125–133.

[107] Huang P, Akagawa K, Yokoyama Y, Nohara K, Kano K, Morimoto K. T-2 toxin initially activates caspase-2 and induces apoptosis in U937 cells. Toxicol. Lett., 2007, *170*: 1–10.

[108] Wild CP, Gong YY. Mycotoxins and human disease: a largely ignored global health issue. Carcinogenesis, 2010, 31(1):71–82.

[109] Voss KA, Riley RT, Norred WP, Bacon CW, Meredith FI, Howard PC, Plattner RD, Collins TF, Hansen DK, Porter JK. An overview of rodent toxicities: liver and kidney effects of fumonisins and *Fusarium moniliforme*. Environ Health Perspect.,2001,109 (2):259–266.

[110] Howard PC, Eppley RM, Stack ME, Warbritton A, Voss KA, Lorentzen RJ, Kovach RM, Bucci TJ. Fumonisin B1 carcinogenicity in a 2-year feeding study using F344rats and B6C3 F1 mice. Environ. Health Perspect., 2001,109: 277–282.

[111] Abel S, Gelderblom WCA. Oxidative damage and fumonisin B1-induced toxicity in primary rat hepatocytes and liver *in vivo*. Toxicology, 1998,131, 121 - 131

[112] Merrill AH, Sullards MC, Wang E, Voss KA, Riley RT. Sphingolipid metabolism: roles in signal transduction and disruption by fumonisins. Environ. Health Perspect., 2001, 109(2):283–289.

[113] Stockmann-Juvala H, Savolainen A. A review of the toxic effects and mechanisms of action of fumonisin B1. Hum. Exp. Toxicol., 2008, 27: 799–809.

[114] Riley RT, Enongene E, Voss KA, Norred WP, Meredith FI, Sharma RP, Spitsbergen J, Williams DE, Carlson DB, Merrill AH, Jr. Sphingolipid perturbations as mechanisms for fumonisin carcinogenesis. Environ. Health Perspect., 2001, 109: 301–308.

[115] Voss KA, Howard PC, Riley RT, Sharma RP, Bucci TJ, Lorentzen RJ. Carcinogenicity and mechanism of action of fumonisin B1: a mycotoxin produced by *Fusarium moniliforme* (=*F. verticillioides*). Cancer Detect. Prevent., 2002, 26: 1-9.

[116] Riley RT. Mechanistic interactions of mycotoxins: theoretical consideration. In: Sinha KK, Bhatanagar D (Eds.), Mycotoxins in Agriculture and Food Safety. Marcel Dekker, Inc, Basel, New York, 1998, pp. 227–254.

[117] Yiannikouris A, Jouany JB. Mycotoxins in feeds and their fate in animals: a review. Anim. Res., 2002, 51: 81–99.

[118] Wang JS, Groopman DJ. DNA damage by mycotoxins. Mutation Research,1999, 424: 167–181.

[119] Mobio TA, Anane R, Baudrimont I, Carratū MR, Shier TW, Dano SD, Ueno Y, Creppy EE. Epigenetic properties of fumonisin B1: cell cycle arrest and DNA base modification in C6 glioma cells. *Toxicol. Appl. Pharmacol.* 2000, *164*, 91–96.

[120] Stockmann-Juvala H, Mikkola J, Naarala J, Loikkanen J, Elovaara E, Savolainen K. Fuminisin B1-induced toxicity and oxidative damage in U-118MG glioblastoma cells. Toxicology, 2004, *202*: 173–183.

[121] Ferrante MC, Meli R, Raso GM, Esposito E, Severino L, Carlo GD, Lucisano A. Effect of fumonisin B1 on structure and function of macrophage plasma membrane. Toxicology Letters, 2002, 129: 181–187.

[122] Olsen M. Metabolism of zearalenone in farm animals. In *Fusarium mycotoxins, taxonomy and pathogenicity*, 1st Ed.; Chelkowsi, J., Ed.; Elsevier: Amsterdam-Oxford-New York, 1989, pp. 167–177.

[123] Minervini F, Dell'Aquila MD. Zearalenone and reproductive function in farm animals. Int. J. Mol. Sci, 2008, *9*: 2570-2584.

[124] D'Mello JPF, Placinta CM, MacDonald AMC. *Fusarium* mycotoxins: A review of global implications for animal health, welfare and productivity. Anim. Feed Sci. Technol., 1999, *80*: 183-205.

[125] Ben Othmen ZO, El Golli E, Abid-Essefi S, Bacha H. Cytotoxicity effects induced by zearalenone metabolites, α zearalenol and β zearalenol, on cultured vero cells. Toxicology, 2008, 252: 72–77.

[126] Hassen W, Ayed-Boussema I, Oscoz AA, Lopez AD, Bacha H. The role of oxidative stress in zearalenone-mediated toxicity in Hep G2 cells: Oxidative DNA damage, gluthatione depletion and stress proteins induction. Toxicology, 2007, 232: 294-302.

[127] Kuiper-Goodman T, Scott PM, Watanabe H. Risk assessment of the mycotoxin zearalenone. Reg. Toxicol. Pharmacol., 1987, *7*: 253–306.

[128] Kuiper-Goodman T, Hilts C, Billiard SM, Kiparissis Y, Richard ID, Hayward S. Health risk assessment of ochratoxin A for all age-sex strata in a market economy. Food Addit. Contam. Part A Chem. Anal. Control Expo. Risk Assess., 2010, *27*: 212–240.

[129] Wasowiczi K, Gajecja M, Calka J, Jakimiuk E, Gajecki M. Influence of chronic administration of zearalenone on the processes of apoptosis in the porcine ovary. Vet. Med. Czech, 2005, *50 (12): 531–536*.

[130] Kim II-H, Son HY, Cho SW, Chang-Su Ha, CS, Kang BH. Zearalenone induces male germ cell apoptosis in rats. Toxicology Letters, 2003, 138: 185-192.

[131] Wang YC, Deng JL, Xu SW, Peng X, Zuo ZC, Cui HM, Wang Y, Ren ZH. Effects of zearalenone on IL-2, IL-6, and IFN-γ mRNA levels in the splenic lymphocytes of chickens. The Scientific World Journal, 2012: 1-5.

[132] Puel O, Galtier P, Oswald IP. Biosynthesis and toxicological effects of patulin. Toxins, 2010, *2*: 613-631.

[133] Mahfoud R, Maresca M, Garmy N, Fantini J. The mycotoxin patulin alters the barrier function of the intestinal epithelium: mechanism of action of the toxin and protective effects of glutathione. Toxicol. Appl. Pharmacol., 2002, 181: 209–218.

[134] Liu F, Ooi V, Chang S. Free radical scavenging activities of mushroom polysaccharides extracts. Life Sci., 1996, 60(10): 763- 771.

[135] [135]- Liu BH, Wu TS, Yu FY, Su CC. Induction of oxidative stress response by the mycotoxin patulin in mammalian cells. Toxicol. Sci., 2007, 95(2):340-347.

[136] Wichmann G, Herbarth O, Lehmann I.: The mycotoxins citrinin, gliotoxin, and patulin affect interferon-gamma rather than interleukin-4 production in human blood cells. Environ. Toxicol., 2002, *17*: 211–218.

[137] Luft P, Oostingh GJ, Gruijthuijsen Y, Horejs-Hoeck J, Lehmann I, Duschl A. Patulin Influences the Expression of Th1/Th2 Cytokines by Activated Peripheral Blood Mononuclear Cells and T Cells Through Depletion of Intracellular Glutathione. Environ. Toxicol., 2008, *23*: 84–95.

[138] Yu FY, Liao YC, Chang CH and Liu BH. Citrinin induces apoptosis in HL-60 cells via activation of the mitochondrial pathway. Toxicology Letters, 2006,161: 143-151

[139] Berndt WO. Ochratoxin–citrinin as nephrotoxins. In Llewellyn GC, Rear PCO (Eds.), Biodeterioration Research 3 New York, USA: Plenum Press, 1999, PP.55-56.

[140] Chagas GM, Oliveira MBM, Campello AP, Kluppel MLW. Mechanism of citrinin-induced dysfunction of mitochondria. III. Effects on renal cortical and liver mitochondria swelling. Journal of Applied Toxicology, 1995, 15: 91–95.
[141] Chagas GM, Kluppel MLW, Oliveira MBM. Citrinin affects the oxidative metabolism of BHK-21 cells. Cell Biochem and Function, 1995, 13(4):257-271.
[142] Nishijima, M. In Kurata H & Ueno Y (Eds.), Toxigenic fungi. Amsterdam, Netherlands, 1984, PP.172-181.
[143] Vazquez BI, Fente C, Franco C, Cepeda A, Prognon P, Mahuzier G. Simultaneous high-performance liquid chromatographic determination of ochratoxin A and citrinin in cheese by time-resolved luminescence using terbium. Journal of Chromatography A, 1996, 727: 185–193.
[144] Sansing GA, Lillehoj EB, Detroy RW. Synergistic toxic effect of citrinin, ochratoxin A and penicillic acid in mice. Toxicon, 1976, 14:213-220.
[145] Glahn RP, Shapiro RS, Vena VE, Wideman RF, Huff WE. Effects of chronic ochratoxin A and citrinin toxins on kidney function of single comb white leghorn pullets. Poultry Science, 1989, 68(9): 1205–1211.
[146] Kumar M, Dwivedi P, Sharma AK, Singh ND, Patil RD. Ochratoxin A and citrinin nephrotoxicity in New Zealand White rabbits: an ultrastructural assessment. Mycopathologia, 2007, 163: 21–30.
[147] Kitabatake N, Trivedi AB, Doi E. Thermal decomposition and detoxification of citrinin under various moisture conditions. Journal of Agricultural and Food Chemistry, 1991, 39(12): 2240–2244.
[148] Trivedi AB, Doi E, Kitabatake N. Toxic compounds formed on prolonged heating of citrinin under watery conditions. Journal of Food science, 1993, 58(1): 229–231.
[149] Bennett JW, Bentley R. Pride and prejudice: the story of ergot. Perspect. Biol. Med., 1999, 42:333-355.
[150] Lorenz K. Ergot on cereal grains. Crit. Rev. Food Sci. Nutr., 1979, 11:311-354.
[151] Cabellero-Granado FJ, Viciana P, Cordero E, Gomez-Vera M.J, del Nozal M, Opez-Cortes LF. Ergotism related to concurrent administration of ergotamine tartrate and ritonavir in an AIDS patient. Antimicrob. Agents Chemother., 1997, 41:1297.
[152] Yang GH, Jarvis BB, Chung YJ, Pestka JJ. Apoptosis induction by satratoxins and other trichothecene mycotoxins: Relationship to ERK, p38 MAPK, and SAPK/JNK activation. Toxicol. Appl. Pharmacol., 2000, 164: 149–160.
[153] Nielsen KF. Mycotoxin production by indoor molds. Fungal Genetics Biology, 2003, 39: 103-117.
[154] Bae HK, Shinozuka J, Islam Z, Pestka JJ. Satratoxin G Interaction with 40S and 60S Ribosomal Subunits Precedes Apoptosis in the Macrophage. Toxicol Appl Pharmacol., 2009, 237(2): 137–145.
[155] Nagase M, Shiota T, Tsushima A, Murshedul M, Fukuoka S, Yoshizawa T, Sakato N. Molecular mechanism of satratoxin-induced apoptosis in HL-60 cells: activation of caspase-8 and caspase-9 is involved in activation of caspase-3. Immunology Letters, 2002, 84: 23-27.
[156] Oda T, Xu JKU, Nakazawa T, Namikoshi M. 12^{-} -Hydroxyl group remarkably reduces Roridin E cytotoxicity. Mycoscience, 2010, 51:317–320.

[157] Xu J, Takasaki A, Kobayashi H, Oda T, Yamada J, Mangindaan REP, Ukai K, Nagai H, Namikoshi M. Four new macrocyclic trichothecenes from two strains of marine-derived fungi of the genus Myrothecium. J Antibiot, 2006, 59:451–455.

[158] Namikoshi M, Akano K, Meguro S, Kasuga I, Mine Y, Takahashi T, Kobayashi H. A new macrocyclic trichothecene, 12,13-deoxyroridin E, produced by the marine-derived fungus Myrothecium roridum collected in Palau. J Nat Prod. 2001, 64:396–398.

[159] Omar HM, El-Sawi NM, Meki ARMA. Acute toxicity of the mycotoxin roridin E on liver and kidney of rats. J. Appl. Anim. Res., 1997, 12:145-152.

[160] Kam PCA , Ferch NI. Apoptosis: mechanisms and clinical implicat. Anaesthesia, 2000, 55: 1081-1093.

[161] Rocha O, Ansari K, Doohan FM. Effects of trichothecene mycotoxins on eukaryotic cells: A review. Food Additives and Contaminants, 2005, 22(4): 369–378.

[162] Pace JG, Watts MR, Canterbury WJ. T-2 mycotoxin inhibits mitochondrial protein synthesis. Toxicon, 1988, 26:77–85.

[163] Klaric MK, Rumora L, Ljubanvic D, Pepeljnjak S. Cytotoxicity and apoptosis induced by fumonisin B1, beauvericin and ochratoxin A in porcine kidney PK15 cells: effects of individual and combined treatment. Arch Toxicol., 2008, 82:247–255.

[164] Jones C, Ciacci-Zanella JR, Zhang Y, Henderson G, Dickman M. Analysis of fumonisin B1-induced apoptosis.Environ Health Perspect., 2001, 109 (2): 315–320.

[165] Sharma N, Suzuki H, He Q, Sharma RP. Tumor necrosis factor α -mediated activation of c-Jun NH2-terminal kinase as a mechanism for fumonisin B1 induced apoptosis in murine primary hepatocytes. J Biochem. Molecular Toxicology, 2005, 19 (6):359-367.

[166] Liu H, Jones BE, Bradham C, Czaja MJ. Increased cytochrome P-450 2E1 expression sensitizes hepatocytes to c-Jun-mediated cell death from TNF-α. Am J Physiol Gastrointest Liver Physiol, 2002, 282:G257–G266.

[167] Martinez-Larranaga MR, Anadon A, Diaz MJ, Fernandez R, Sevil B, Fernandez-Cruz ML, Fernandez MC, Martinez MA, Anton R. Induction of cytochrome P4501A1 and P4504A1 activities and peroxisomal proliferation by fumonisin B1. Toxicol Appl Pharmacol., 1996, 141:185–194.

[168] Kang YJ, Alexander JM. Alterations of the glutathione redox cycle status in fumonisin B1-treated pig kidney cells. J Biochem Toxicol, 1996, 11:121–16.

[169] Sahu SC, Eppley RM, Page SW, Gray GC, Barton CN, O'Donnel Lmw. Peroxidation of membrane lipids and oxidative DNA damage by fumonisin B1 in isolated rat liver nuclei. Cancer Lett, 1998, 125:117–121.

[170] Adler V, Yin Z, Fuchs SY, Benezra M, Rosario L, Tew KD, Pincus MR, Sardana M, Henderson CJ,Wolf CR, Davis RJ, Ronai Z. Regulation of JNK signaling by GSTp. EMBO J; 1999, 18:1321–1334

[171] Zhu L, Yuan H, Guo C, Lu Y, Deng S, Yang Y, Wei Q, Wen L, He Z. Zearalenone induces apoptosis and necrosis in porcine granulosa cells via a caspase-3- and caspase-9-dependent mitochondrial signaling pathway. Journal of Cellular Physiology, 2012, 227(6):1814-1820.

[172] Saxena N, Ansari KM, Kumar R, Dhawan A, Dwivedi PD, Das M. Patulin causes DNA damage leading to cell cycle arrest and apoptosis through modulation of Bax, P53 and P21/waf1 proteins in skin of mice. Toxicology and Applied Pharmacology, 2009, 234:192-201.

[173] Nusuetrong P, Pengsuparp T, Meksuriyen D, Tanitsu M, Kikuchi H, Mizugaki M, Shimazu KI, Oshima Y, Nakahata N, Yoshida M. Satratoxin H generates reactive oxygen species and lipid peroxides in PC12 cells. Biol. Pharm. Bull., 2008, 31: 1115-1120.
[174] Coulombe RA, Guarisco JA, Klein PJ, Hall JO. Chemoprevention of aflatoxicosis in poultry by dietary butylated hydroxytoluene. Anim. Feed Sci. Technol., 2005,*121*: 217-225.
[175] Morgavi DP, Boudra H, Jouany JP, Graviou D. Prevention of patulin toxicity on rumen microbial fermentation by SH-containing reducing agents. J. Agric. Food Chem., 2003, *51*: 6906-6910.
[176] Eckschlager T, Adam V, Hrabeta J, Figova K, Kizek R. Metallothioneins and Cancer. Curr Protein Pept Sci, 2009, 10: 360–375.
[177] Davis SR, Cousins RJ. Metallothionein expression in animals: A physiological perspective on function. J. Nutr., 2000, 130: 1085-1088.
[178] Nagashima H, Nakagawa H, Iwashita K. Mycotoxin nivalenol induces apoptosis and intracellular calcium ion-dependent interleukin-8 secretion but does not exert mutagenicity. In Ikura K et al. (eds.), Animal Cell Technology: Basic & Applied Aspects, 2009, pp.301-306.
[179] Shapira A, Benhar I. Toxin-based therapeutic approaches. Toxins, 2010 *2*: 2519-2583.
[180] Rowell PP, Larson BT. Ergocryptine and other ergot alkaloids stimulate the release of [3H] dopamine from rat striatal synaptosomes. Journal of Animal Science, 1999, 77(7): 1800-6.
[181] Samuelsson G. Drugs of natural origin. 4th ed. Apotekar societeten. Stockholm, 1999.
[182] Eadie MJ. Ergot of rye-the first specific for migraine. Journal of Clinical Neuroscience, 20, 11 (1): 4-7.
[183] De Costa C. St Anthony's Fire and living ligatures: a short history of ergometrine. The Lancet, 2002, 359: 1768-70.
[184] Nichols CD, Garcia EE, Sanders-Bush E. Dynamic changes in prefrontal cortex gene xpression following lysergic acid diethylamide administration. Molecular Brain Research, 2003, 111 (1-2): 182-188.
[185] Nichols CD, Sanders-Bush EA. Single dose of lysergic acid diethylamide influences gene expression patterns within the mammalian brain. Neuropsychopharmacology, 2002, 26 (5): 634-642.
[186] Hart C. Forged in St. Anthony's Fire: drugs for migraine. Modern drug discovery, 1999, 2 (2): 20- 31.
[187] Kupchan SM, Streelman DR, Jarvis BB, Dailey RG, Jr, Sneden ATJ. Isolation of potent new antileukemic trichothecenes from Baccharis megapotamica. J Org Chem., 1977, 42(26):4221-4225
[188] Hughes BJ, Hsieh GC, Jarvis BB, Sharma RP. Effects of macrocyclic trichothecene mycotoxins on the murine immune system. Arh. Environ. Contam. Toxicol, 1989, 18: 388-395.
[189] Massaer F, Meucci V, Saggese G, Soldani G. High growth rate of girls with precocious puberty exposed to estrogenic mycotoxins. J Pediatr; 2008, 152: 690-695.
[190] Kapoor VK. Natural toxins and their therapeutic potential. Indian Journal of Experimental Biology., 2010, 8: 228-237.