

Effect of Fungal Toxins on Immunodeficient Indicators

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Received: 10 /Aug. / 2021 , Accepted: 13 /Sep. /2021

Abstract

Mycotoxins are natural toxins generally caused by some types of mold (fungi) that may be found in foods. Mold (Fungi) grows on (grains, nuts, spices, dried fruits, apples, and coffee seeds). Due to their effective impact on humans and animals, mycotoxins have gained a great deal of attention as studies have shown that mycotoxins are among the most significant causes of human cancer, in particular liver and kidney cancer, in addition to their impact on the suppression of the immune system, as well as inducing genetic defects and congenital malformations. The Codex Alimentarius Commission develops “international standards and codes of practice” to reduce contact to mycotoxin in some foods. The spectrum of effects ranges from severe poisoning to continuing harmful effects such as immunodeficiency and cancer. This work aims to summarize a comprehensive review of the effects and toxicity of the mycotoxins on Immunodeficient Indicators. We collect almost 150 published papers from Science direct, PubMed, Elsevier, nature, Wiley, and research gate. Then extract 60 papers, which included quality research (experimental and descriptive study) to write this review paper based. Mycotoxins produced from fungi and know the effect of these toxins on immune indicators. Mycotoxins are fungal metabolism produced and effect on immunity. According to the body's resistance to these toxins, the type of mushroom produced from it and its lethal ability. “Mycotoxins” can contaminate a number of raw materials and affect animals to be at serious health risk. Regulations or guidelines apply at the European level for 6 mycotoxins.

Key words: Fungal Toxins, Immune System, Pathogenic fungi, Immunodeficient Indicators.

Introduction

“Mycotoxins” are secondary metabolic compounds produced by many fungi, which can cause disease, or fatal to human's beings and animals, and the production of mycotoxins is restricted to a number of types of fungi. There are over 100 forms of pathogenic fungi that are capable of producing toxic compounds that cause apparent pathological effects in humans and animals (1). Many fungi, especially *Aspergillus*, *Fusarium*, *Penicillium*, and *Alternaria*, produce mycotoxins and comprise a group of several hundred different chemically distinct toxic compounds. Aflatoxin, Ochratoxin, Zearalenone, Trichothecium and Arcot are the most common mycotoxins (2). In addition to the fact, mycotoxins have a cumulative impact that does not occur immediately, but occurs after 10-20 years of consuming contaminated food, heat tolerance to the degree to which it is difficult for these toxins to be killed by conventional thermal treatments used in cooking and production processes. The degree of the availability of conditions in terms of temperature, humidity,

oxygen, pH and mycotoxins vary depending on the type of mushroom growing and the food content.etc. From here, attention started to work at all stages of development and storage on the reduction of food contamination with fungi, and consequently with mycotoxins (3-7).

Therefore, due to their effective impact on humans and animals, mycotoxins have gained a great deal of attention as studies have shown that mycotoxins are among the most significant causes of human cancer, in particular liver and kidney cancer, in addition to their impact on the suppression of the immune system, as well as inducing genetic defects and congenital malformations (8).

Some mycotoxins, including aflatoxins, which are the most significant mycotoxins, have been shown to contribute to liver cancer in other studies, as it was found that there is a link between certain diseases and aflatoxin toxins. The hepatitis B virus is one of these diseases, so infection with this disease leads to liver cancer in the presence of aflatoxins, as aflatoxins and hepatitis B viruses have been shown to be both

carcinogenic (9,10). Their presence raises the risk of developing liver cancer, and the toxicity of aflatoxins and other toxins has been detected by dissecting laboratory animals to study the effects after consuming mycotoxin-contaminated diets. The toxin causes many diseases such as tissue death in the liver, blood congestion in the kidneys, and hemorrhagic disorders because of aflatoxins (11).

In a study of ziralenone toxin, it has been shown that toxin results in tumors in some rat organs that have lived for more than a year, especially in the uterus and pituitary gland, as well as an increase in uterine weight in immature rat and mice individuals. The presence of tumors in prostate cells and testicles has been observed in men. Zyralinone toxin has been reported to have mineralocorticoid gland anti-fertility and steroidal hormones (12-15).

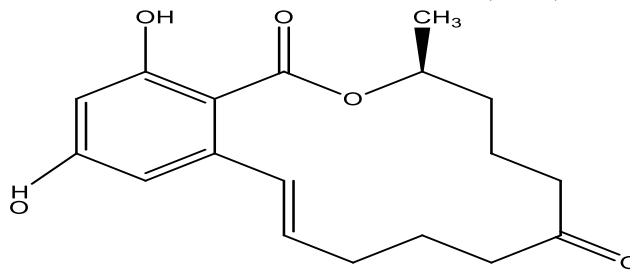


Figure (1): Chemical structure of ziralenone toxin (16)

Ochratoxin toxin is a mycotoxin with an important and direct effect on humans and animals as it has numerous effects found in many kinds of living organisms. It is mainly a nephrotoxin, similar in its action to aflatoxin B1 toxin, affecting the liver and causing embryo deformation, which is both a carcinogen and a system inhibitor. The Mechanism of the Immune (17). These toxins must therefore be avoided by the storage of field crops in warehouses, which meet the required heat, humidity, ventilation and periodic sterilization conditions of grain stores and feed silos. And the use of such anti-fungal contaminants such as organic acids (formic acid, acetic acid) or colloidal substances applied to the food in the treatment of grains (18). This is distinguished by its ability to absorb some of the surface mycotoxins and thereby decrease its toxicity, Usage of chemical methods that cause the decomposition of certain toxins, such as ammonia and weight, with the need for an awareness campaign to demonstrate the hazards of mycotoxins by the Ministry of Health, civil society organisations and various media outlets

Definition of Fungal Toxins and Immunodeficient Indicators

Fungal Toxins (Mycotoxins)

Mycotoxins are naturally occurring toxins that can be contained in food created by certain forms of mold (fungi).

Molds are grown on several distinct crops and food products, which include *i.e.*, (cereals, coffee seeds, nuts, herbs, dried fruits and apples),

(19). Mycotoxins are both contaminants that, while of different sources, are harmful to the health of manufactured animals. In reality, mycotoxins are secondary metabolites formed during storage by molds grown on field crops or on feed ingredients. Mycotoxins are absorbed by infected food and cause a variety of health issues, including reduced immune function, damage to organs, and issues with the nervous and reproductive system. Endotoxins, on the other hand, are a part of Gram-negative bacteria's cell wall (20-24).

When bacteria reproduce or die, they are released into the atmosphere and, most significantly, into the digestive system. They activate a reaction once endotoxins reach the intestinal barrier that absorbs energy and nutrients intended for growth and development. Mycotoxins and endotoxins also co-exist in the animal production digestive system and cause significant economic losses. Furthermore, its adverse effect on animal welfare and efficiency can be cooperatively enhanced (25,26).

typically under high temperature and humidity circumstances (27).

A variety of harmful health disease can be triggered by mycotoxins and pose significant health threats to people and livestock.

Mycotoxins extend from acute toxicity to continuing long lasting symptoms such as immunodeficiency and cancer across the continuum of adverse health effects Figure (2).

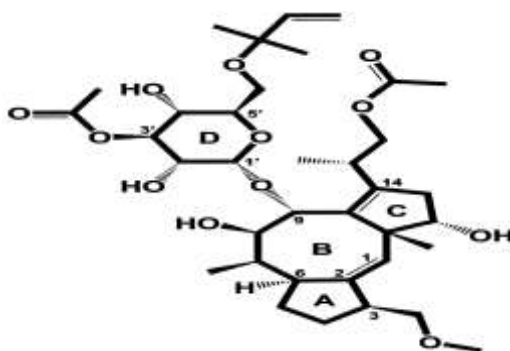


Figure (2): “The structure of the fungal toxin fusicoccin” (28)

Based on calculations of the “Joint Expert Committee on Food Additives” (29-33), the Codex Alimentarius Commission establishes international guidelines and codes of practice to reduce the exposure of mycotoxins in certain foods.

Mycotoxins are toxic complexes which are easily formed through several kinds of mold

(fungi). For several foods, i.e., (grains, dried fruits, nuts, and spices, mould), which can create mycotoxins, grows. Prior to or after harvesting and during storage, mold may form. On / in the food itself (34), it can shape. This typically occurs in conditions that are hot, wet and humid. The majority of mycotoxins are chemically stable and withstand the processing of foods (35).

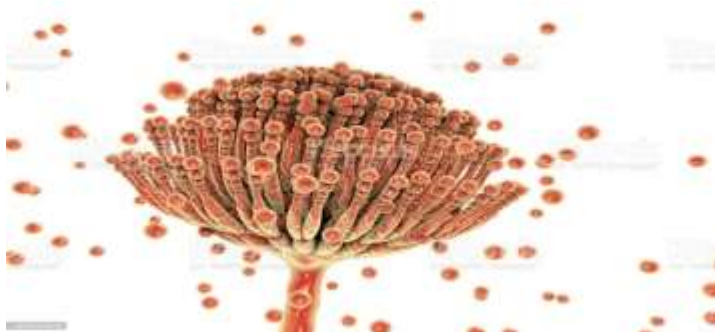


Figure (3): Mycotoxins (Aspergillus) (36).

Several hundred different mycotoxins have been identified, but aflatoxins, ochratoxin A, patulin, pheomonescence, zyaralenone, nevanol, and deoxy-nephallinol are the most common mycotoxins that are a source of interest for the health of human and livestock. Because of seed contamination with mold both before and after harvesting, mycotoxins occur in the food chain. Mycotoxin exposure can occur straight by the intake of contaminated food and indirect intake of

animals fed with contaminated feed, especially the milk of those animals (37,38).

Method of action of the fungal protein PAF

By permeabilization of the membrane of plasma and pore formation activity, several antimicrobial proteins apply their function. Detail study with (PAF) showed (excluded this hypothesis) the completely different “mode of action” Figure (4).

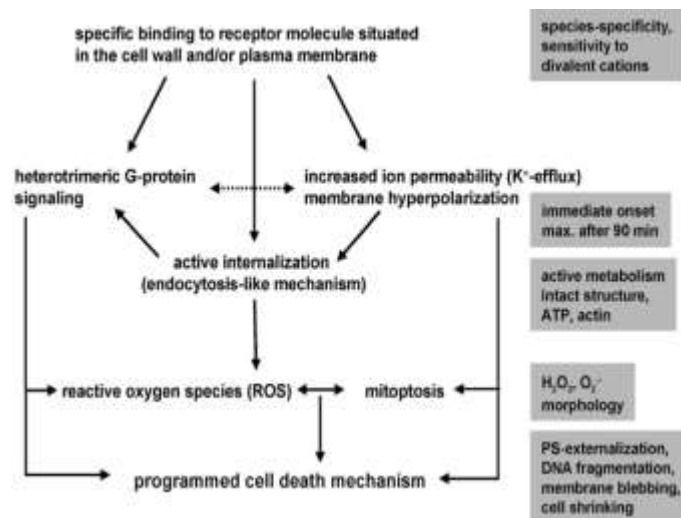


Figure (4): Schematic diagram for the hypothetical mechanism of action of the antifungal protein PAF (Penicillium chrysogenum antifungal protein) (39)

Onychomycosis

This is the term used for mycotoxin exposure-related toxicity. Via i.e., (ingestion, skin touch, inhalation, and access into the bloodstream and lymphatic system), mycotoxins may have both acute and chronic health effects. They inhibit the synthesis of proteins, damage the pharyngeal system, prevent the removal of lung particles, and increase bacterial endotoxin sensitivity. The indications of infection with a fungus vary by the kind of mycotoxin, also on the concentration and as well as the time of exposure, and the exposed individual's age, fitness, and gender. There have been poorly researched harmonious effects correlated with many additional variables, such as biology, diet, and associations to more toxins. Therefore, mycotoxin (40) can have a compound impact on vitamin deficiency, calorie deprivation, alcoholism, and infectious disease status.

Aflatoxins

These are forms of mycotoxin that *Aspergillus* mushrooms, such as *A. Flavus*. The collective term aflatoxin refers to the development of four separate mycotoxins, namely (G1, G2, B1 and B2). "Aflatoxin B1" the highly toxic, is a powerful carcinogen which, in many animal species, is specifically related to harmful health issues, such as liver cancer. Aflatoxins are primarily associated with commodities i.e., (cotton, peanuts, spices, pistachios and maize) that are produced in tropical and subtropical regions (41).

Ochratoxin

It is a fungal toxin found in three types of secondary metabolites: A, B and C. It contains all forms of "Penicillium and Aspergillus". The three forms are different since the "non-chlorinated" form of "Ochratoxin A (OTA)" is "Ochratoxin B (OTB)" and the Australian form of "Ochratoxin A" is "Ochratoxin C (OTC)". For a large variety of goods, that include drinks i.e., (beer and wine), *Aspergillus ochraceus* has been described as a contaminant. The key type present in grapefruit, *Aspergillus carbonarius*, releases toxins during making procedure of the juice (41).

Citrine

This type of toxins was separated from "*Penicillium citrinum*" for the first time but has been identified in more than 10 *Penicillium* species and many *Aspergillus* species. Any of these animals, i.e., (cheese, which is *Penicillium camembert*, sake, soy sauce which is *Aspergillus oryzae* and miso), are used to manufacture human food. In Japan, citrine is related to "yellow rice disease" and functions as a "nephrotoxin" in all of the tested animal species. While several human foods which include i.e., (wheat, rice, maize, barleycorn, cereals, rye whiskey, and colored foods) are associated to them, their complete importance for human health is still not known. In order to minimize RNA synthesis in rat kidneys, citrine can also function synergistically with Ochratoxin A (42).

Oregon

These toxins are compounds that are natural pathogens of various types of grass, developed as a toxic combination of “alkaloids” in the ergot of the Debussy fungus. Ergot ingestion from tainted grains, typically in the shape of bread, which made from filthy flour, induces ergot, a human illness generally known as “St. Fire Anthony”. There are two kinds of ergotoxicity: gangrene that affects the flow of blood to the limbs and spasticity that affects the central nervous system. As a human illness, new cleaning techniques for birth control pills have greatly reduced ergot poisoning. It remains an important veterinary concern, though. The pharmaceutical ergot alkali was used (42).

Patulin

This toxin was developed by “*P. expansum*”, *Aspergillus*”, *Paecilomyces*”, and “*Penicillium*”. A category of rotten products (fruits and vegetables), particularly in rotten fruits (apples and figs), is especially associated with *P. expansum*. The fermentation procedure kills it is

absent in apple beverages *i.e.*, apple juice. While “patulin” has not considered as a carcinogen, animals have documented damage to the natural defenses. In 2004, the “European Community” set limits for the concentrations of “patulin: in food items. 50 mcg / kg in all concentrations of fruit juice, 25 mcg / kg in strong apple manufactured goods employed for direct use, and 10 mcg / kg in baby apple crops, including apple juice, are present (43).

More than 50 varieties of mushrooms develop “Fusarium” and have a record of infecting growing grains, *i.e.*, (wheat and maize). They consist of a group of mycotoxins, *i.e.*, fumonsin, that affect horses' (nervous system) and can cause rodent cancer. Near association of trichothecenes with persistent and lethal toxic influence on creatures (animals and humans) and zearalenone with no lethal toxic influence on animals or humans. “Pubvercin, inatin, butenolide, equisten, and fusarin” are some of the other predominant sources of fusarium toxins.

Main mycotoxins

Below is the main mycotoxin produced by fungi and Contaminated commodities:

Table (1): Main mycotoxins, produced by fungi and contaminated commodities (44).

Status	Mycotoxins	Mold (Fungi) produced	Polluted commodities
Regulated toxins	Ochratoxin A	<i>Penicillium</i> <i>Aspergillus</i> ,	cereal and products made of cereal, resins, coffee, pork meat
	Zearalenone	<i>Fusarium</i>	cereal and products made of cereal
	Trichothecenesb: “deoxynivalenol, nivalenol, T-2 toxin, diacetoxyscirpenol”	<i>Fusarium</i>	Beer, cereal and products made of cereal
	Patuline	<i>Byssochlamys</i> <i>Penicillium</i> , <i>Aspergillus</i> ,	Cereal and products, fruits, and fruit juices,
	Aflatoxin	<i>Aspergillus</i>	Milk, dry fruits <i>i.e.</i> , nuts, cereal, and products made of Cereals
Non-regulated mycotoxins	Alternariol	<i>Alternaria</i>	Cereal, vegetables, and fruits
	Kojic acid	<i>Aspergillus</i>	Dry fruits
	Sterigmatocystin	<i>Aspergillus</i>	Cereals and nuts
	Penitrem	<i>Penicillium</i>	Cheese, cereals, nuts, and fruits
	Mycophenolic acid	<i>Penicillium</i> , <i>Byssochlamys</i>	Silage
	Satratoxin	<i>Stachybotrys</i>	Straw

Immunodeficient Indicators

One of the most important processes in the human body is the immune system, since it is a complex network of cells and proteins by which the body will protect itself against foreign bodies that continuously invade it. As the immune system consists of a series of protection lines against microbes such as bacteria, viruses and fungus that cause diseases. It is as follows: the first line of protection: (I) innate, non-specialized line of defense that is born with humans, as it consists of: ^{a)} skin: as it is a shield against the entry into the body of water and pathogenic microbes (45). ^{b)} Mucous membranes in the cavities of the body; they contain a sticky mucus, like the nose and mouth, to which different microbes adhere. ^{c)} Digestive juices in the stomach: since they are marked by a high acidity level that helps to destroy much of the bacteria in the food. ^{d)} Saliva: Helps minimize the number of bacteria and other organisms in the mouth that are present (46).

(II) The second line of defense; adaptive immune responses are a specialized line of defense that evolves with a person's development, because if the microbes can bypass the first line of defense, they face the second line of defense, this line consists of: ^{a)} all types of advanced white blood cells that protect the body against infection, providing the body with resistance and immunity to different pathogens. ^{b)} The lymphatic system, consisting of a network of vessels containing specialized lymphocytes that fight viruses and other pathogens and make antibodies that, when the body is exposed to them again, aid kill microbes (47).

Bias living things exist on various animals, biodiversity, biodiversity, large-scale area. The return of radiation from excess cells to ultraviolet radiation warns of a rise in bacterial malignancy melanin-3, including that of many disease-

Immune response against fungal infections

Immunity means the normal protection of the human body against attacks by live pathogens. In particular, those caused by micro-organisms, like human fungi, and the absence of this immunity prepares the body for infection with diseases simply by parasitic and opportunistic fungi (thrush fungi that live on dead substances in the

causing fungi. Its involvement in those with infection 4 can also induce immunity, but it was not understanding how. Stubbers and colleagues named them a normal protein in the first episode of the second week to differentiate between melanin formed by the *Aspergillus fumigatus* fungus. "Their results highlight the" restoration of the immune system, "such as those undergoing immune system suppression, such as those undergoing immune system suppression (48).

They are free radicals, labeled, tiny insoluble melanin substances, immune to degradation by acids, pigment melanin substances. Maybe the penny is an explanation for the complexity of evaluating, not completely understanding the structure of these materials. Because of the alternate copies of the house, the following copies are from the other copies (49).

Aspergillus called the flight to the human disease caused by a fungus of the genus *Aspergillus*. The head of an individual who inhaled *Aspergillus* fuming spores is given to a female head; it spreads to other places in the body. The host cells can induce a pathway of cell degeneration, called cytophagia, which helps kill the fungus, but fungal melanin can inhibit cellular autophagy 7, in addition to melanin's inflammation binding (50). Cells supplemented by lung infection with the fungus milia fungus.

The melanin phenomenon, in this case increases the host's defenses. It plays in the molecule in the fungi 'malignancy, asking if it is possible to detect virus infection. Stubbers and colleagues have examined this by researching members of the Lentin C family protein, which was previously investigated for a role in antifungal defense. Therefore, the ability to attach spores from *Aspergillus* is the form. Smokers, or they're not. And by doing this, it was engineered in the form of proteins that they studied, and they named it Mail Pool (51).

human body and do not cause damage except for infection with diseases) (52).

Knowledge about the body's immunity to fungal infections is limited to the same knowledge as information about the body's bacterial and viral infections.

In general, however, it is understood that infection with such microorganisms increases the immunity of the body to these or other organisms.

As for the fungi in the first negative or acquired protection, there are no special variables. In general, immunity comprises two forms of desirability and responses to any external attack on the body: 1) active, which is the immunity that does not exist in the body until friction exists between the living organism and the body, and 2) second, passive, which is hereditary immunity, or Which is present in the body with the presence or absence of the living organism.

1. Phagocytic drug
 - a. Neutrophils Neutrophils A
 - b. About Moncutis
 - c. Macrophages
2. Lymphocytis
 - a. Lymphocytis T
 - b. Lymphocytis B

Lymphocytes (Macrophages Neutrophils, Moncutis and T&B) are thought to function together to protect the host body, and these vary

according to the individual and the form of injury in general (53).

There are also no particular factors that play a significant role in primary fungal infections. Because the surface of the body is usually known to be the key resistance to fungal infection, as well as fatty acids, a fatty substance present in Sebum that is secreted by the sebaceous glands that gives the body immunity to fungi because it contains anti-fungal substances.

Also, a non-specific immune system reaction operation that involves:

1. Phagocytic cells that deal with the interference or parasitism of tiny fungal cells.
2. Similar to alveolar macrophages, which are essential for the ingestion of pulmonary cells. The liver and spleen macrophages have the potential to kill certain fungi from the blood stream Figure (5).

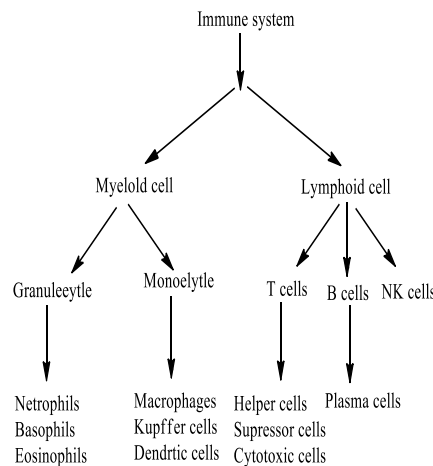


Figure (5): Schematic diagram of immune system (54).

Damage to mycotoxins (Impact of The Immune System)

Mycotoxins exert their immunotoxin effects through different mechanisms, such as damaging the intestinal barrier, altering the production and function of different immune organs, reducing

immune cell phagocytic ability, and reducing immune responses mediated by cells (55).

Therefore, mycotoxin-induced immune deficiencies result in inadequate inactivation of endotoxins and a stronger inflammatory response to endotoxins, leading to decrease animal health and efficiency Figure (6).

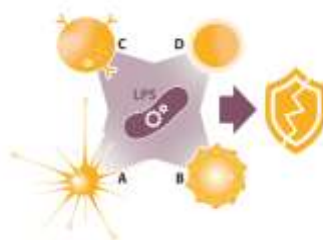


Figure (6): immunotoxic effects (56).

Mycotoxins induce immunosuppression, resulting in sufficient endotoxin inactivation. A: core cell, B: macrophage, C: cell in B, D: cell in T.

Technique of enzyme-connected immune sorbent assays (ELISAs)

ELISA is a technique in which antibodies and color changes used to detect a substance. ELISA is the most widely used test for detecting mycotoxins, such as aflatoxins because its simplicity, sensitivity, and adaptability. One target for GT is transcription factor NF- κ B, which is inhibited in cells. GT significantly reduced the production of bacterial peptidoglycan polysaccharide PG-PS-stimulated TNF- α from the NR8383 cell line at the IC₅₀ 0.14 inhibition concentration and dependently inhibited the nuclear binding of NF-129 in rodent macrophages.

Immunohistochemistry (IHC) technique

Immunohistochemistry (IHC) is a technique for showing the existence and position of protein in tissue parts. It is not as much of receptive as

“immunoassays” *i.e.*, western blotting or ELISA, quantitatively. This includes the analysis of procedure in the form of conserved tissue. It is particularly beneficial for evaluating the progression of and treating diseases *i.e.*, cancer (57).

Effect of Gliotoxin on immunological cells

GT can associate in vitro with various cell types of the immune system that are involved in resistance to fungal infections. Gliotoxin was first identified when workers found that the phagocytic phenomenon of macrophage adherence to plastic was blocked by gliotoxin secreted by *Aspergillus fumigatus*.

It has been recommended that the function of GT in virulence in the animal host depends on the degree of immunosuppression in the animal host. By blocking NF- κ B activation in experimental colitis, it has been shown that GT reduces inflammatory responses and subsequent expression of inflammatory genes.

CONCLUSION

More than 50 varieties of mushrooms develop *Fusarium* and have a record of infecting growing grains, *i.e.*, (wheat and maize). They consist of a group of mycotoxins, *i.e.*, fumonsin, that affect horses' (nervous system) and can cause rodent cancer. Mycotoxins and cause animals to be at grave health risk may infect a variety of raw materials. Aflatoxin B1 the highly toxic, is a powerful carcinogen which, in many animal species, is specifically related to harmful health issues, such as liver cancer. Pigs, a species very

vulnerable to mycotoxin, are genuinely revealed because of a cereal-rich diet. There are many adverse effects of exposure to these toxins on pigs, including alteration of the immune response. The resulting effect raises infectious disease immunity and occurrence and reduces the efficacy of the vaccine. At the European level, legislation or suggestions refer to 6 mycotoxins which are commonly exist in pig feed. The toxin causes many diseases such as tissue death in the liver, blood congestion in the kidneys, and hemorrhagic disorders.

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تأثير السموم الفطرية على مؤشرات المناعة

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الخلاصة

السموم الفطرية هي سموم تنتج بشكل عام من بعض أنواع العفن (الفطريات) التي قد توجد في الأطعمة. ينمو العفن (الفطريات) على (الحبوب والمكسرات والتوابل والفواكه المجففة والتفاح وبذور القهوة). ونظراً لتأثيرها الفعال على الإنسان والحيوان، فقد حظيت السموم الفطرية باهتمام كبير حيث أظهرت الدراسات أن السموم الفطرية من أهم أسباب الإصابة بسرطان للإنسان، وخاصة سرطان الكبد والكلية، بالإضافة إلى تأثيرها على تثبيط جهاز المناعة، وكذلك إحداث أضرار وراثية وتشوهات خلقية. تضع هيئة الدستور الغذائي "معايير وقواعد ممارسات دولية" لتقليل التعرض للسموم الفطرية في بعض الأطعمة. يتراوح نطاق التأثيرات من التسمم الحاد إلى الآثار الضارة المستمرة مثل نقص المناعة والسرطان. يهدف هذا العمل إلى تلخيص مراجعة شاملة لتأثيرات وسمية السموم الفطرية على مؤشرات المناعة.

الكلمات المفتاحية: السموم الفطرية، الجهاز المناعي، الفطريات الممرضة، المؤشرات المناعية.