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Mycoviruses in Fungi: Carcinogenesis of Fungal Agents May Not Always Be Mycotoxin Related

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Abstract: Certain viruses have been found to induce diverse biological pathways to carcinogenesis, evidenced by the presence of viral gene products in some tumors. Despite the fact that many fungal agents contain mycoviruses, until recently, their possible direct effects on human health, including carcinogenesis and leukemogenesis, had not been explored. In this regard, most studies of fungal agents have rightly concentrated on their mycotoxin formation and effects. Recently, the direct role of yeasts and fungi in the etiology of cancers, including leukemia, have been investigated. While greater attention has been placed on the carcinogenic effects of *Candida*, the role of filamentous fungi in carcinogenesis has also been explored. Recent findings from studies using the enzyme-linked immunosorbent assay (ELISA) technique indicate that the plasma of patients with acute lymphoblastic leukemia (ALL) uniformly contains antibodies for a certain mycovirus-containing *Aspergillus flavus*, while controls are negative. The exposure of mononuclear leukocytes from patients with ALL in full remission, and long-term survivors, to the product of this organism was reported to result in the re-development of typical genetics and cell surface phenotypes characteristic of active ALL. Mycoviruses are known to be able to significantly alter the biological characteristics and functions of their host. The possible carcinogenic and leukemogenic role of mycoviruses, with and without their host, needs to be further investigated.

Keywords: cancer; leukemia; etiology; mycoviruses; mycotoxins; aflatoxin; viruses; carcinogenesis; leukemogenesis; fungi; parasites

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1. Introduction

All individuals are routinely exposed to a variety of fungal organisms, for the most part without any detectable significant adverse effects. However, this is not universal and varies based on health status, immunity, existence of other disorders, and type of the organism involved. For example, exposure to *Aspergillus* spores routinely occurs in healthy populations without any obvious clinically detectable effects. However, the same exposure can result in serious pathogenic effects in individuals with certain underlying diseases such as cancer or immune deficiency disorders. Until recently, the major known direct pathogenic effects of *Aspergillus* species have included allergies, toxicities, and a variety of infections [1–61] (Table 1). A substantial amount of data, however, has been accumulated, indicating that those working in the occupations with a high degree of fungal exposure generally have a higher rate of cancer [5,62–65]. In contrast, while somewhat controversial [66–72], individuals with allergy-related diseases and asthma have been reported to generally have a lower rate of cancer, including leukemia and a variety of solid tumors, as compared to the general population [73–84]. Some epidemiological data indicates potential roles for IgE, allergy, and atopy in protecting against certain tumors [85,86]. An increased cancer risk in association with IgE immunodeficiency has also been reported [87,88]. Significant information regarding the inverse association between atopic conditions and glioma has been accumulated [89,90].

Table 1. Major non-mycotoxin-related pathogenic effects of *Aspergillus* species.

Allergies [1–5]
Cutaneous infections [6–8],
Rhinosinusitis [9–11],
Wound and craniocerebral infections [12–16],
Keratitis [17–21],
Chronic granulomatous sinusitis [22–25],
Neurotoxicity and meningitis [26–28],
Scleritis [29–31],
Endophthalmitis [32–34],
Otomycosis [35–37],
Pericarditis [38–40],
Endocarditis [41–43],
Mediastinitis [44–46],
Osteoarticular disorders [47–50],
Osteomyelitis [51–53],
Urinary tract infections [54–56],
Bronchopulmonary [57–59]
Local and generalized infections [5,61]

Some microorganisms are known to have the ability to induce tumor initiation and progression, directly through their effects on the cells, or indirectly by their effects on the immune system. Several studies have correlated the possible involvement and association of fungal species, particularly *Candida*, with the development and progression of various types of cancer. While most attention has been directed to yeasts in the so-called blastomycete theory of cancer, more recently, other mechanisms, including the possible role of mycoviruses in fungal organisms, have been suggested [91–99]. In the recent past, it has been shown that the in vitro exposure of mononuclear cells from individuals who have a history of acute lymphoblastic leukemia (ALL) and are in full remission, without any evidence of the disease, including long-term survivors, to a certain mycovirus-containing *Aspergillus flavus* (MCAF) results in the re-development of cell surface phenotypes and genetic markers characteristic of active ALL [91]. Such exposure in controls did not induce any changes [91]. If this is due to the certain genetic or epigenetic background in the ALL patients is not clear. In a related study, unlike controls, patients with ALL were found to have antibodies for the products of MCAF [92]. It is of interest that the mycovirus-containing *Aspergillus flavus* used for these studies was isolated from the home of a patient with ALL and the organism did not produce any aflatoxin [91,92]. A well-known theory for the etiology of ALL in the pediatric age group suggests that the development of this disease is due to a combination of genetic mutations and exposure to infections [100]. This so-called "two-hit" model postulates that ALL evolves in two discrete steps. The first step is in utero initiation by fusion gene formation or hyperdiploidy, which generates a pre-leukemic clone. The second step, which is proposed to only occur in a very small sub-population of the predisposed, is suggested to be exposure to infections and post-natal acquisition of secondary genetic changes that drives conversion to overt ALL. It is postulated that exposure to infections earlier in life are protective, but in their absence, infections later in life trigger the critical secondary mutations [100]. It is suggested that the risk can be further modified by other inherited genetics, and possibly diet, as well as chance. While a number of predisposing genetic factors have been identified, until recent reports [91,92], no certain infectious agents had been proposed. Based on the recent findings, it is postulated that

exposure to mycovirus-containing *Aspergillus flavus* could possibly be one of the post-natal infections that can trigger the second step in the developmental process of ALL [91].

A number of studies have explored the role of viral, bacterial, and fungal organisms in the etiology of a variety of cancers. In the past, many investigations have concentrated on the correlation of viruses with the development of malignant disorders. While such a correlation has been made for many viral agents, less attention has been paid to the fungal organisms, including those containing mycoviruses. Typically, most studies have been based on the statistical relation of the frequency of exposure to a given agent, versus the development of a certain cancer. For example, there is an increased rate of cancer and leukemia [5] in individuals likely be exposed to fungal agents, such as agricultural workers [101]. More recently, experiments have reported direct evidence of some organism's involvement in the development of certain cancers. For example, some experiments have revealed that DNA specific to the human papilloma virus (HPV) is integrated into the host cell genome. This virus is known to be associated with cervical, anal, penile, vulvar, vaginal, oropharyngeal, and head and neck cancers [102]. HPV type 16 and 18 viral DNAs have been found in cervical cancers and two viral dominant oncogenic genes, E6 and E7, are consistently expressed in HPV-positive malignancies and HPV-infected cancer cells. These oncogenes are known to be associated with the malignant transformation of cells and the alteration of the immune system, causing disruption of natural tumor suppressor pathways, culminating in the proliferation of cervical carcinoma cells [103].

Fungi have a worldwide distribution and virtually can be detected in any environment [104–114]. For example, *Aspergilli* are found in soil, water, outdoor and indoor, and may produce numerous conidia which can disperse via air movement and possibly insects [104–106]. While there are seasonal variations, there is a significant amount of spore and diversity of fungi in air particulate matter [107]. The optimum temperature for the growth of these organisms has a wide range, with significant growth occurring in temperatures ranging from approximately 15 to 30 °C [108–111]. Lately, the direct effects of yeast and fungi in the etiology of cancers, including leukemia, have also been further explored. Greater attention has been placed on the so called "blastomycete theory of cancer" and the relation of yeasts, especially the *Candida* species, to carcinogenesis [112]. To a lesser extent, the role of filamentous fungi has also been evaluated. Among the fungal agents, *Aspergillus* and *Candida* species are the most investigated for their possible role in carcinogenesis. *Aspergilli*, due to their widespread distribution and production of mycotoxins, are known for their potential to cause cancer [93,112]. These have been classified and divided into several groups, each with distinct biological and molecular characteristics [93,115–118]. As noted above, *Aspergilli* are known to produce a variety of allergic disorders [1–3,5], toxicities, and infections [17,22–24,54–58,61]. *Aspergillus* can be associated with tissue damage, burn, keratitis and endophthalmitis, or post operative infection [13,16,119–127]. Empyema and pleural aspergillosis, as well as osteomyelitis, can occur, especially in individuals with reduced immunity. The association of *Aspergillus* infections with a foreign body, including peritoneal dialysis catheters and intravenous lines have been reported. Abscesses in various organs and systems, including skin, subcutaneous tissues, sinuses, oropharynx, lungs, brain, and other organs and systems can occur. In many infection entities, *Aspergillus fumigatus* or *A. flavus* are often involved [13,16,119–127]. The effects of mycotoxins produced by fungal agents have been long recognized [113,114].

Normally, *Candida* is located on skin, most of mucosal surfaces, mouth, gastrointestinal tract, and vagina without any detrimental effects. However, *Candida* species in general, and *Candida albicans* in particular, have been found to be associated with the development of certain cancers, including oral, esophageal, and gastrointestinal neoplasms. Some of these carcinogenic effects are through the production of specific hydrolytic enzymes metabolizing ethanol to acetaldehyde (ACH). Acetaldehyde is metabolized from ethanol by alcohol dehydrogenases (ADH). ADH is a cell wall protein necessary for the growth of fungi, its metabolism [128], and interaction with host cell proteins to initiate an immune response [128–130]. Mutations within host DNA degrade protein molecules and impair

their functions which are essential for normal cellular activities and division [131]. ACH, which is a group 1 human carcinogen, can induce the production of pro-inflammatory cytokines and mediators [132–134], causing cellular oxidative stress and damage [134], inducing the formation of covalent adducts in protein or DNA residues [131], DNA cross-linking, or chromosomal aberrations [135,136]. The aberrations described can potentially lead to tumor development and progression [95,137]. There is evidence that pathologically, *C. albicans* can increase the risk of carcinogenesis and metastasis through several other mechanisms, including inflammation, the production of carcinogenic byproducts, the induction of the Th17 response, and molecular mimicry [137–146]. In addition to several clinical reports associating *Candida* spp. to carcinogenesis, there are a number of biomolecular findings indicating its ability to cause dysplasia and malignant neoformation in oral epithelium. *Candida* can produce carcinogens, such as N-nitrosobenzylmethylamine, resulting in the development of malignant disorders including oral cancer [138–141]. The development of pancreatic cancer has also been attributed to inflammation and immune activation due to an increased nitrosamine exposure. Some of the mechanisms of actions suggested for the carcinogenic effects of *Candida* include over-expression of P53, *Ki-67* labeling index, and Prostaglandin-endoperoxide synthase 2 (COX-2), promoting the production of acid aspartyl-proteinase. Other effects include immune-related mechanisms induced by up-regulation in proinflammatory cytokines such as interleukin (IL)-1α, IL-1β, IL-6, IL-8, and IL-18, tumor necrosis factor (TNF)-α, IFN-b [138,142,143], and the production of carcinogenic acetaldehyde [137,144,146] and candidalysin, which is a cytolytic toxin [146].

Mycotoxins

More than 350 types of mycotoxins are found in animal feed but the most important are aflatoxin, ochratoxin, fumonisin, and zearalenone [147–158]. The pathological condition induced by any mycotoxin depends on sex, immune status, type of mycotoxin, duration, and the amount of mycotoxin. Mycotoxins are responsible for the suppression of the quality of the poultry industry. According to the Food and Agriculture Organization (FAO), 25% of cereal grains are found to be affected by mycotoxins. Aflatoxin is one of the most important mycotoxins produced by *A. flavus* and *A. parasiticus*. More than 20 types of aflatoxins are found. The most common derivatives of aflatoxin are B1, B2, M1, and M2. B1 is the most potent carcinogenic mycotoxin and M1 is the most common in milk.

The carcinogenesis and leukemogenesis of many fungal species, in animals and humans, have traditionally been attributed to their production of mycotoxin. Mycotoxins are toxic secondary metabolites that are produced by fungal species, particularly those of filamentous fungi which often grow on plant-based agricultural products. The fungal growth occurs prior to the harvest of the crops and during their storage. Mycotoxins can be found in peanuts, grains, corn, millet, sesame seeds, wheat, and animal-derived foods such as milk, eggs, meat, and other commodities, and are highly toxic to humans and animals. A single fungal species can potentially produce several mycotoxins [148,150]. The hepatotoxicity and hepatocarcinogenic effects of fungal agents secondary to the production of mycotoxins in general, and aflatoxin in particular, are well recognized [91,93]. Some mycotoxins affect DNA replication, and therefore, can have mutagenic or teratogenic effects. Exposure to mycotoxins can result in the impairment of metabolic, nutritional, endocrine, immunological, hepatic, reproductive, and other systems. The four basic toxicities of mycotoxins are acute, chronic, mutagenic, and teratogenic effects. Common acute mycotoxin poisoning effects includes deterioration of liver or kidney function, which can potentially lead to death. Some mycotoxins interfere with protein synthesis, causing disorders ranging from skin sensitivity or necrosis to immunodeficiency, depending on the dose exposed. Mycotoxins are neurotoxic, producing symptoms ranging from trembling to brain damage. An example of the major biotoxins produced by *Aspergillus* species are summarized in Table 2. Aflatoxins, produced by *Aspergillus* spp., are one of the highly toxic secondary metabolites derived from polyketides. These are known to induce acute intoxication, fulminant hepatic failure, and rhabdomyolysis. Chronic exposure to this toxin can result in

cirrhosis of the liver which may lead to hepatocellular and gall bladder carcinoma. Other effects of aflatoxins on human health include disorder of lipid metabolism, depression of protein and enzyme synthesis, and reduced production of hemoglobin and response to vaccines [149,150]. The mycotoxins produced by *Penicillium* and *Fusarium* species have adverse effects on heath, including infertility in males and females, destructive effects on the fetus, impairment of growth and development in children, and undesirable health outcomes in various stages of life. These agents can hamper the division and differentiation of the gametes which can result in infertility due to interference with spermatogenesis. Zearalenone has been linked to precocious puberty in females. In animal models, exposure to mycotoxins can promote adverse effects on spermatozoa, Sertoli and Leydig cell function, oocyte maturation, and uterine and ovarian development and function. These agents have the potential to damage the sex organs. Mycotoxins may disturb the endocrine system and alter steroid hormone homeostasis, resulting in subfertility or infertility. These can exert oxidative stress causing sperm DNA damage and reduced fertilization [151–155]. Based on animal studies, mycotoxins can increase the possibility of stillbirth and can pass through the mother's milk and affect the health of infants [156–159]. Since mycotoxins can negatively alter cell division, they can affect the fetus and decrease the growth and development of children. Neural tube defects in fetuses have been reported. Adverse effects on fetuses and children include abnormal neural development, causing cognitive disability. In addition, these toxins may cause decreased gastrointestinal absorption resulting in malnutrition and reduced growth [160–165].

Table 2. Major biotoxins produced by *Aspergillus* species.

Type of Mycotoxin	Example of Producing Species
Aflatoxins (AFB1, AFB2) *A. flavus* and *A. parasiticus*	(AFG1, AFG2, AFM1) *A. parasiticus*
Ochratoxins *A. carbonarius*, *A. ochraceus*, and *A. niger*	Patulin *A. clavatus*
Citrinin *A. ochraceus* and *A. terreus*	Aflatrem *A. aculeatus*
Secalonic acids *A. aculeatus* and *japonicus*	Cyclopiazonic acid *A. flavus* and *A. oryzae*
Terrein *A. terreus*	Sterigmatocystin *A. versicolor*, *A. nidulans*, and *A. sydowii*
Gliotoxin *A. fumigatus*	*Fumonisins A. welwitschiae* and *A. niger*

2. Metabolism of Aflatoxins

Aflatoxins are furanocoumarins which are produced by various strains of *Aspergillus* species and produce various toxicities in animals and humans [166–171]. The toxicity and mechanism of action of aflatoxins have been explored [166–171]. The carcinogenic and mutagenic activities of aflatoxins are largely attributed to their lactone and difuran rings. Aflatoxins have a furanocoumarin chemical structure, with over 18 types chemically identified. Following ingestion, AFB_1 is metabolized to form AFB_1-8,9-epoxide, which binds to DNA and forms AFB_1-guanine adducts. There are significant individual and age-related differences in the metabolism of AFB_1, resulting in variation noted in its toxicity. In vitro metabolism studies reveal that reduction of AFB_1 results in the production of aflatoxicol (AFL), which its hydroxylation produces AFM_1, its hydration generates AFB_{2a} and its epoxidation AFB_1-2,3-epoxide. Of these, epoxide is the most reactive, and is believed to be responsible for the acute and chronic toxicity of AFB. Aflatoxicol can pass through the placenta and damage the fetus. AFB1 is known to be metabolized in the liver by the cytochrome P450 enzyme system (CYPs). Aflatoxin B1-8,9-epoxide (AFB0), which has *exo* and *endo* isomers, is a carcinogenic derivate of this toxin. The CYP3A4 and CYP1A2 derivates are primarily responsible for the aflatoxin biotransformation, and

the *exo* isomer formed. Studies in birds indicate that CYP2A6 and, to a lesser extent, CYP1A1 are involved in the bioactivation of AFB_1 into AFBO. Regarding DNA, AFB0 binds covalently to the N_7 position on guanine, and forms an AFB1-N_7-guanine adduct. The *endo* isomer has lower affinity than the *exo*; therefore, AFB1-*exo*-8,9-epoxide is likely the major carcinogenic metabolite [158,171]. The production of the various mycotoxins varies based on numerous factors. For example, fungal organisms overwinter as either resistant structures called sclerotia or as mycelium. The difference in the pattern of sclerotia production is associated with different aflatoxin production. An example is that the S strain of *Aspergillus flavus* produces numerous but smaller sclerotia, while the L strain generates fewer but larger sclerotia. The products of these subgroups vary significantly. The S strain isolates, designated SB, make only B aflatoxins while those termed SBG produce B and G aflatoxins. It is suggested that these differences may represent a taxon different from *Aspergillus flavus*.

Some strains of *Aspergillus flavus* do or do not produce aflatoxins B1 and/or B2. Other toxins which may be produced by this organism include cyclopiazonic acid, kojic acid, sterigmatocystin, bnitropropionic acid, aflatrem, aspertoxin, aspergillic acid, and gliotoxin. In addition, *Aspergillus flavus* can potentially produce other secondary metabolites including versicolorin A dihydroxyaflavinine, paspalinine, and indole. Aflatoxins, which are the most potent hepatocarcinogenic agents, are known to be produced by a variety of *Aspergillus* species, predominantly *A. flavus*, *nomius*, and *parasiticus*. Of sixteen structurally related toxins, aflatoxins B1, B2, G1, and G2 are of the most concern [166,167]. The metabolites produced by the hepatic metabolism of aflatoxins are responsible for most of their toxicity. Aflatoxin B1 (AFB1) has the most carcinogenic potential, and its carcinogenicity is classified as group 1 by the International Agency for Research on Cancer (IARC). Exposure to the aflatoxin metabolites results in acute liver damage. Should this be continued, it has a high potential for carcinogenesis due to the damage to DNA through adduct formation and interference with protein metabolism [168]. In pregnant animal models, exposure to AFB1 leads to genotoxic changes which predisposes the offspring to morphological abnormalities, behavioral alterations, reproductive disturbances, cancer, and early death in adult life [170,171]. In humans and animals, the signs and symptoms of aflatoxin toxicity depends on the level and duration of exposure, age, gender, health status, concurrent exposure to other toxins, and a number of other variables. Generally, adults have a higher tolerance for aflatoxin and rarely succumb to acute aflatoxicosis. In contrast, children are less tolerant and their exposure results in stunted growth and delayed development. The latter is common in many developing countries [172–174]. In general, acute aflatoxicosis due to the ingestion or inhalation of high doses of AFB1 results in acute poisoning. These toxins can be transmitted to the fetus through the placenta, and to infants via breast milk [110,111,148,175–183]. Severe damage to the internal organs and systems including liver, kidneys, heart, and the hemopoietic and immune system, along with bleeding, can result in death. For survivors, long-term complications include organ and system failures and carcinogenesis. Post exposure, free AFB1 is present only for a short period of time in the blood. Such exposure can be detected through the measurement of the metabolites of AFB1 including aflatoxin-albumin, aflatoxin M1 (AFM1), aflatoxin P1 (AFP1), aflatoxin Q1 (AFQ1), AFB-N7 guanine, and aflatoxicol (AFL), in blood and biological fluids. In the first 24 h post exposure, the measurement of the breakdown products of AFB1, including AFB_1-guanine, in the urine may reflect exposure to this mycotoxin. Measurement of the AFB_1-albumin adduct level in the serum provides a more integrated measure of the longer-term exposure. AFM1 is classified as agent 2B by IARC for its carcinogenic potential. Metabolites of aflatoxins are present in the tissues, urine, feces, and milk [184–190]. The latter is of importance in infants during breastfeeding because of its effects in infants. Likewise, commercially available milk collected from animals fed with various contaminated agricultural commodities may contain this agent. Various metabolites of mycotoxins can be measured in blood, urine, stool, milk, etc. [184–190]. AFM1 can be utilized as a measurable biomarker in the urine. Immunotoxins with small molecules fail

to induce any response in the human immune system. Therefore, a major potential danger of exposure to mycotoxins in the diet is the human inability to detect them biologically [2].

Another product of AFB1 is the AFB-N7-guanine biomarker which indicates prolonged exposure to this toxin. DNA alkylation or adduct formation is at nucleophilic sites in DNA, including the N7-position of guanine. The N7-guanine adducts are considered non-promutagenic. These are chemically unstable, since the N7-position does not participate in a Watson–Crick base pairing. The N7-guanine adducts have been shown to convert to ring opened lesions (FAPy) which have much more mutagenic potential, persist longer in the body, and have higher mutagenic potency [191]. A variant with a greater carcinogenic potential is fumonisin B1 (FB1), which is classified by the IARC as a 2B product. This is predominantly produced by *Fusarium verticillioides* and *F. proliferatum* and contaminates maize and maize-based foods. FB1 inhibits ceramide synthase and interrupts sphingolipid synthesis via the inhibition of sphingosine-N-acetyltransferase, resulting in oxidative stress, the alteration of DNA methylation, and modulation of autophagy, and results in stress to the endoplasmic reticulum, leading to the reduced production of sphingolipids and the accumulation of sphinganine (Sa) and sphingosine (So). The result is the non-genotoxic mechanism underlying its toxicological and carcinogenic effects. While its effect on human health as yet is not fully discovered, in populations consuming large amounts of contaminated maize-based foods, epidemiological and experimental evidence points to this being a risk factor for esophageal cancer and neural tube defects. In animals, fumonisins can cause leukoencephalomalacia in horses, pulmonary edema in swine, and hepatotoxicity and nephrotoxicity in rats [192–195].

While most studies focus on a single mycotoxin and its effects on human health, animal studies reveal a complex and possibly additive, synergistic, or antagonistic effect [196–199]. The association of aflatoxins classified as group1 by the IARC, including aflatoxin B1 (AFB1), aflatoxin B2 (AFB2), aflatoxin G1 (AFG1), aflatoxin G2 (AFG2), and aflatoxin M1 (AFM1), with liver cancer is well documented. Various malignant disorders due to rice and cereal contamination with AFB1, including breast, cervical and esophageal cancers, have been reported [200–207]. A significant amount of data regarding carcinogenicity of mycotoxins, alone or in conjunction with unrelated viruses are available; however, the possible effects of mycoviruses singularly or in combination with their fungal host has not been fully explored.

3. Mycoviruses and Cancer

For several decades, viruses affecting fungal organisms, known as mycoviruses, have been known to exist [208,209]. However, except for occasional reports, their human pathogenicity and possible role in health has not been fully evaluated. It is estimated that from 30 to 80% of all fungal species, predominantly endophytic fungi, contain mycoviruses. The existence of mycoviruses in *Aspergillus* species is well recognized. The modulation of fungal toxins such as the loss of aflatoxin production in *A. flavus* infected with mycovirus has been reported [210,211]. Mycoviruses possess various forms of viral genomes which include double-stranded RNA (dsRNA), single-stranded RNA (ssRNA), and single-stranded DNA (ssDNA). Currently, the International Committee for the Taxonomy of Viruses (ICTV) records 17 taxa, 16 families, and one genus that does not belong to a family. While most mycoviruses have ds RNA linear genomes, positive-sense ss RNA linear genomes including reverse transcribing RNA linear genomes, negative-sense ssRNA linear genomes, or ssDNA circular genomes also exist [212]. Of these, dsRNA segments most commonly affect fungal organisms. Taxonomically, the fungal dsRNA viruses are classified into seven families which include *Endornaviridae*, *Chrysoviridae*, *Megabirnaviridae*, *Quadriviridae*, *Partitiviridae*, *Reoviridae*, and *Totiviridae*. The transmission of mycoviruses occurs vertically during cell division, forming asexual and sexual spores called sporogenesis, and/or horizontally via mating or hyphal anastomosis through cytoplasmic exchange, and not during the extracellular phase of the viral life cycle. The latter, however has been disputed [212]. Some viruses have a unique self-protective or aggressive ability, producing

defensive substances. These products can have a growth-inhibitory activity against several bacterial and fungal species. The term 'killer strains' describes yeast and fungal species that can produce 'killer toxins' with antimycotic activity for lethal function or self-protection. This killer phenotype is usually associated with double-stranded (ds)RNA mycoviruses and linear dsDNA plasmids. It can also be chromosomally encoded. For example, viruses of the family *Totiviridae* have a unique ability to produce a killer toxin which is capable of lysing susceptible neighboring strains, while they themselves remain immune to the toxin. Four killer toxins, i.e., K1, K2, K28, and Klus, have been reported.

Some dsRNA mycovirus-containing fungal agents have been shown to alter the expression of genes involved in the ribosomal synthesis and programmed cell death of the fungal host. Mycoviruses affecting a human pathogen may also have an effect on the infected individual. For example, *Malassezia* species produce various skin diseases including dandruff, seborrheic dermatitis, and atopic dermatitis. In one study, this organism was found to contain MrV40 mycovirus, which belongs to the family *Totiviridae*. In a reported study, the viral nucleic acid from MrV40 had induced a Toll-like receptor 3 (TLR3)-mediated inflammatory immune response in the bone-marrow-derived dendritic cells. This finding may indicate a role for the included mycovirus in the pathogenicity of *Malassezia* [213,214].

Mycoviruses are known to be able to alter their fungal host's phenotype, including but not limited to pigmentation, morphology, sexual and asexual sporulation, the production of toxins, and growth. As noted before, the loss of aflatoxin production in *A. flavus* infected with mycovirus has been reported [210,211]. If these organisms can exert any changes in humans or animals infected with mycovirus-containing fungi has not, as yet, been significantly explored. Viral dsRNA is recognized by Toll-like receptor 3 (TLR-3) and several cytosolic sensors and can provoke interferon production in a TLR-3 dependent or independent fashion [215]. An increased rate of cancer in occupations with higher rate of exposure to fungi, such as agricultural and construction workers, have been found [5,101]. Individuals with allergies have been reported to have a decreased risk of certain cancers compared with the general population. In allergic individuals, lower rate of glioma, laryngeal, esophageal, oral, pancreatic, gastric, colorectal, uterine body cancers, and non-Hodgkin lymphoma have been reported. Reports regarding leukemia, thyroid, lung, melanoma, and breast cancer in this group are conflicting. An increased risk of bladder cancer, lymphoma, myeloma, and prostate cancer in individuals with allergies is reported [68,84,101,215]. It is not clear if in those individuals with allergies and decreased rates of cancer, their allergens include fungi. On the other hand, those with greater exposure to fungi have a higher rate of this disorder. As noted before, patients with acute lymphoblastic leukemia were found to have antibodies to a certain mycovirus-containing *Aspergillus flavus* and the exposure of mononuclear blood cells from patients with ALL in full remission to its products resulted in the redevelopment of genetic and cell surface phenotypes characteristic of ALL [91,92]. Based on these findings, it has been postulated that this organism may potentially have a correlation with leukemogenesis [91,92]. Research regarding mycovirus-containing organisms and cancer may have etiological value.

4. Conclusions

The possible role of various organisms in carcinogenesis and leukemogenesis has been suspected. While the role of viral agents in the development and progress of a variety of cancers has often been the subject of these investigations, the carcinogenic effects of fungal agents have also been explored. Until recently, the latter has been mostly concentrated on the contamination effects of mycotoxins. These effects result in major toxicities which are of health and commercial concern. Demonstration of the effects of various viral agents in carcinogenesis is exemplified by cervical carcinoma. Experiments reveal that DNA specific to the human papilloma virus is integrated into the host cell genome, and viral oncoproteins E6 and E7 consequently cause the disruption of natural tumor suppressor pathways, culminating in the proliferation of cervical carcinoma cells. Mycoviruses have been shown to alter the biology of their fungal host, such as the secession of aflatoxin

production in *Aspergillus* spp. as well as the expression of genes involved in ribosomal synthesis and programmed cell death in several species. The effects of mycoviruses alone or in conjunction with their fungal host in human health is poorly evaluated. Recent studies reveal that patients with acute lymphoblastic leukemia in full remission, and long-term survivors, uniformly have antibodies to a certain mycovirus-containing *A. flavus*. Furthermore, exposure of the mononuclear leukocytes from these patients to the products of the above organism results in the redevelopment of genetic and cell surface phenotypes characteristic of active acute lymphoblastic leukemia pointing to the possible cause and effect relationship. The role of mycoviruses, with and without their hosts in human disorders, particularly in carcinogenesis and leukemogenesis, needs to be explored.

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References

1. Akiyama, K.; Takizawa, H.; Suzuki, M.; Miyachi, S.; Ichinohe, M.; Yanagihara, Y. Allergic Bronchopulmonary Aspergillosis due to Aspergillus oryzae. *Chest* **1987**, *91*, 285–286. [CrossRef] [PubMed]
2. Chakrabarti, A.; Sethi, S.; Raman, D.S.V.; Behera, D. Eight-year study of allergic bronchopulmonary aspergillosis in an Indian teaching hospital. *Mycoses* **2002**, *45*, 295–299. [CrossRef]
3. Sehgal, I.S.; Choudhary, H.; Dhooria, S.; Aggarwal, A.N.; Bansal, S.; Garg, M.; Behera, D.; Chakrabarti, A.; Agarwal, R. Prevalence of sensitization to *Aspergillus flavus* in patients with allergic bronchopulmonary aspergillosis. *Med. Mycol.* **2018**, *57*, 270–276. [CrossRef] [PubMed]
4. Tebbi, C. Etiology of Acute Leukemia: A Review. *Cancers* **2021**, *13*, 2256. [CrossRef]
5. Taj-Aldeen, S.J.; Hilal, A.A.; Chong-Lopez, A. Allergic Aspergillus flavus rhinosinusitis: A case report from Qatar. *Eur. Arch. Oto-Rhino-Laryngol.* **2003**, *260*, 331–335. [CrossRef] [PubMed]
6. Singh, S.A.; Dutta, S.; Narang, A.; Vaiphei, K. Cutaneous Aspergillus flavus infection in a neonate. *Indian J. Pediatr.* **2004**, *71*, 351–352. [CrossRef]
7. Grossman, M.E.; Fithian, E.C.; Behrens, C.; Bissinger, J.; Fracaro, M.; Neu, H.C. Primary cutaneous aspergillosis in six leukemic children. *J. Am. Acad. Dermatol.* **1985**, *12*, 313–318. [CrossRef]
8. Estes, S.A.; Hendricks, A.A.; Merz, W.G.; Prystowsky, S.D. Primary cutaneous aspergillosis. *J. Am. Acad. Dermatol.* **1980**, *3*, 397–400. [CrossRef]
9. Montone, K.T. Pathology of Fungal Rhinosinusitis: A Review. *Head Neck Pathol.* **2016**, *10*, 40–46. [CrossRef] [PubMed]
10. Deutsch, P.G.; Whittaker, J.; Prasad, S. Invasive and Non-Invasive Fungal Rhinosinusitis—A Review and Update of the Evidence. *Medicina* **2019**, *55*, 319. [CrossRef]
11. Rai, G.; Ansari, M.A.; Dar, S.A.; Datt, S.; Gupta, N.; Sharma, S.; Haque, S.; Ramachandran, V.G.; Mazumdar, A.; Rudramurthy, S.; et al. Serum Cytokine Profile in Patients with Chronic Rhinosinusitis with Nasal Polyposis Infected by *Aspergillus flavus*. *Ann. Lab. Med.* **2018**, *38*, 125–131. [CrossRef]
12. Pasqualotto, A.; Denning, D. Post-operative aspergillosis. *Clin. Microbiol. Infect.* **2006**, *12*, 1060–1076. [CrossRef]
13. Kandhavelu, J.; Demonte, N.L.; Namperumalsamy, V.P.; Prajna, L.; Thangavel, C.; Jayapal, J.M.; Kuppamuthu, D. Aspergillus flavus induced alterations in tear protein profile reveal pathogen-induced host response to fungal infection. *J. Proteom.* **2017**, *152*, 13–21. [CrossRef]
14. Rudwan, M.; Sheikh, H. Aspergilloma of paranasal sinuses—A common cause of unilateral proptosis in Sudan. *Clin. Radiol.* **1976**, *27*, 497–502. [CrossRef]
15. Miceli, M.H. Central Nervous System Infections Due to Aspergillus and Other Hyaline Molds. *J. Fungi* **2019**, *5*, 79. [CrossRef] [PubMed]
16. Barrios, N.; Tebbi, C.K.; Rotstein, C.; Siddiqui, S.; Humbert, J.R. Brainstem invasion by Aspergillus fumigatus in a child with leukemia. *N. Y. State J. Med.* **1988**, *88*, 656–658. [PubMed]
17. Zhu, W.-S.; Wojdyla, K.; Donlon, K.; Thomas, P.; Eberle, H. Extracellular proteases of Aspergillus flavus: Fungal keratitis, proteases, and pathogenesis. *Diagn. Microbiol. Infect. Dis.* **1990**, *13*, 491–497. [CrossRef] [PubMed]
18. Rosa Jr, R.H.; Miller, D.; Alfonso, E.C. The changing spectrum of fungal keratitis in south Florida. *Ophthalmology* **1994**, *101*, 1005–1013. [CrossRef] [PubMed]
19. Gugnani, H.C.; Gupta, S.; Talwar, R.S. Role of opportunistic fungi in ocular infections in Nigeria. *Mycopathologia* **1978**, *65*, 155–166. [CrossRef]

20. Erdem, E.; Yagmur, M.; Boral, H.; Ilkit, M.; Ersoz, R.; Seyedmousavi, S. Aspergillus flavus Keratitis: Experience of a Tertiary Eye Clinic in Turkey. *Mycopathologia* **2016**, *182*, 379–385. [CrossRef] [PubMed]
21. Leema, G.; Jayaraman Kaliamurthy, P.G.; Thomas, P.A. Keratitis due to Aspergillus flavus: Clinical profile, molecular identification of fungal strains and detection of aflatoxin production. *Mol. Vis.* **2010**, *16*, 843. [PubMed]
22. Gupta, A.K.; Gupta, A.K. Postgraduate institute management protocol for invasive Aspergillus flavus sinusitis: Is it effective? *Int. J. Infect. Dis.* **2009**, *13*, 134–139. [CrossRef] [PubMed]
23. Jariwal, R.; Heidari, A.; Sandhu, A.; Patel, J.; Shoaepour, K.; Natarajan, P.; Cobos, E. Granulomatous Invasive Aspergillus flavus Infection Involving the Nasal Sinuses and Brain. *J. Investig. Med. High Impact Case Rep.* **2018**, *6*. [CrossRef]
24. Alarifi, I.; Alsaleh, S.; Alqaryan, S.; Assiri, H.; Alsukayt, M.; Alswayyed, M.; Alromaih, S.; Aloulah, M.; Alroqi, A.S.; AlQahtani, A.; et al. Chronic Granulomatous Invasive Fungal Sinusitis: A Case Series and Literature Review. *Ear Nose Throat J.* **2020**, *100*, 720S–727S. [CrossRef]
25. Raz, E.; Win, W.; Hagiwara, M.; Lui, Y.W.; Cohen, B.; Fatterpekar, G.M. Fungal sinusitis. *Neuroimaging Clin.* **2015**, *25*, 569–576. [CrossRef]
26. ElSawy, A.; Faidah, H.; Ahmed, A.; Mostafa, A.; Mohamed, F. Aspergillus terreus Meningitis in Immunocompetent Patient: A Case Report. *Front. Microbiol.* **2015**, *6*, 1353. [CrossRef] [PubMed]
27. Verweij, P.E.; Brinkman, K.; Kremer, H.P.H.; Kullberg, B.-J.; Meis, J.F.G.M. *Aspergillus* Meningitis: Diagnosis by Non-Culture-Based Microbiological Methods and Management. *J. Clin. Microbiol.* **1999**, *37*, 1186–1189. [CrossRef]
28. Antinori, S.; Corbellino, M.; Meroni, L.; Resta, F.; Sollima, S.; Tonolini, M.; Tortorano, A.M.; Milazzo, L.; Bello, L.; Furfaro, E.; et al. Aspergillus meningitis: A rare clinical manifestation of central nervous system aspergillosis. Case report and review of 92 cases. *J. Infect.* **2012**, *66*, 218–238. [CrossRef]
29. Fincher, T.; Fulcher, S.F. Diagnostic and therapeutic challenge of Aspergillus flavus scleritis. *Cornea* **2007**, *26*, 618–620. [CrossRef]
30. Carlson, A.N.; Foulks, G.N.; Perfect, J.R.; Kim, J.H. Fungal Scleritis After Cataract Surgery. Successful outcome using itraconazole. *Cornea* **1992**, *11*, 151–154. [CrossRef]
31. Baharani, A.; Reddy, A.K.; Reddy, R.R.P. *Aspergillus Flavus* Necrotising Scleritis following Pars Plana Vitrectomy. *Ocul. Immunol. Inflamm.* **2019**, *28*, 772–774. [CrossRef] [PubMed]
32. Aydin, S.; Ertugrul, B.; Gultekin, B.; Uyar, G.; Kir, E. Treatment of two postoperative endophthalmitis cases due to *Aspergillus flavus* and *Scopulariopsis* spp. with local and systemic antifungal therapy. *BMC Infect. Dis.* **2007**, *7*, 87. [CrossRef]
33. Lance, S.E.; Friberg, T.R.; Kowalski, R.P. Aspergillus flavus Endophthalmitis and Retinitis in an Intravenous Drug Abuser a Therapeutic Success. *Ophthalmology* **1988**, *95*, 947–949. [CrossRef]
34. Bodoia, R.D.; Kinyoun, J.L.; Qingli, L.; Bunt-Milam, A.H. Aspergillus necrotizing retinitis a clinico-pathologic study and review. *Retina* **1989**, *9*, 226–231. [CrossRef] [PubMed]
35. Ozcan, M.; Ozcan, M.K.; Karaarslan, A.; Karaarslan, F. Concomitant otomycosis and dermatomycoses: A clinical and microbiological study. *Eur. Arch. Oto-Rhino-Laryngol.* **2003**, *260*, 24–27. [CrossRef]
36. Aneja, K.; Sharma, C.; Joshi, R. Fungal infection of the ear: A common problem in the north eastern part of Haryana. *Int. J. Pediatr. Otorhinolaryngol.* **2010**, *74*, 604–607. [CrossRef] [PubMed]
37. Moslem, M.; Mahmoudabadi, A.Z. The high efficacy of luliconazole against environmental and otomycosis Aspergillus flavus strains. *Iran. J. Microbiol.* **2020**, *12*, 170. [CrossRef] [PubMed]
38. Gokahmetoglu, S.; Koc, A.N.; Patiroglu, T. Case Report. Fatal Aspergillus flavus pericarditis in a patient with acute myeloblastic leukaemia. *Mycoses* **2000**, *43*, 65–66. [CrossRef] [PubMed]
39. Walsh, T.J.; Bulkley, B.H. Aspergillus pericarditis: Clinical and pathologic features in the immunocompromised patient. *Cancer* **1982**, *49*, 48–54. [CrossRef] [PubMed]
40. Sergi, C.; Hofmann, W.; Sinn, P.; Schnabel, P.; Otto, H.; Weitz, J.; Otto, G.; Eckart, A. Aspergillus endocarditis, myocarditis and pericarditis complicating necrotizing fasciitis. *Virchows Arch.* **1996**, *429*, 177–180. [CrossRef]
41. Kalokhe, A.S.; Rouphael, N.; El Chami, M.F.; Workowski, K.A.; Ganesh, G.; Jacob, J.T. Aspergillus endocarditis: A review of the literature. *Int. J. Infect. Dis.* **2010**, *14*, e1040–e1047. [CrossRef] [PubMed]
42. Gumbo, T.; Taege, A.J.; Mawhorter, S.; McHenry, M.C.; Lytle, B.H.; Cosgrove, D.M.; Gordon, S.M. Aspergillus Valve Endocarditis in Patients without Prior Cardiac Surgery. *Medicine* **2000**, *79*, 261–268. [CrossRef] [PubMed]
43. Khan, Z.U.; Sanyal, S.C.; Mokaddas, E.; Vislocky, I.; Anim, J.T.; Salama, A.L.; Shuhaiber, H. Endocarditis due to *Aspergillus flavus*. *Mycoses* **1997**, *40*, 213–217. [CrossRef] [PubMed]
44. Ahmad, M.; Weinstein, A.J.; Hughes, J.A.; Cosgrove, D.E. Granulomatous mediastinitis due to Aspergillus flavus in a nonimmunosuppressed patient. *Am. J. Med.* **1981**, *70*, 887–890. [CrossRef]
45. Chatterjee, D.; Bal, A.; Singhal, M.; Vijayvergiya, R.; Das, A. Fibrosing mediastinitis due to Aspergillus with dominant cardiac involvement: Report of two autopsy cases with review of literature. *Cardiovasc. Pathol.* **2014**, *23*, 354–357. [CrossRef]
46. Vaideeswar, P.; Chaudhari, J.; Goel, N. Fungal fibrosing mediastinitis in pregnancy—Case report with review of literature. *J. Postgrad. Med.* **2019**, *65*, 52–55. [CrossRef]
47. Kumashi, P.; Safdar, A.; Chamilos, G.; Chemaly, R.; Raad, I.; Kontoyiannis, D. Fungal osteoarticular infections in patients treated at a comprehensive cancer centre: A 10-year retrospective review. *Clin. Microbiol. Infect.* **2006**, *12*, 621–626. [CrossRef]
48. Papachristou, S.G.; Iosifidis, E.; Sipsas, N.V.; Gamaletsou, M.N.; Walsh, T.J.; Roilides, E. Management of osteoarticular fungal infections in the setting of immunodeficiency. *Expert Rev. Anti-Infect. Ther.* **2020**, *18*, 461–474. [CrossRef]

49. Roilides, E.; Dotis, J. Osteoarticular and Epidural Infections. In *Aspergillosis: From Diagnosis to Prevention*; Springer: Berlin/Heidelberg, Germany, 2009; pp. 853–862.
50. Gamaletsou, M.N.; Rammaert, B.; Bueno, M.A.; Sipsas, N.V.; Moriyama, B.; Kontoyiannis, D.P.; Roilides, E.; Zeller, V.; Taj-Aldeen, S.J.; Henry, M. Aspergillus arthritis: Analysis of clinical manifestations, diagnosis, and treatment of 31 reported cases. *Med. Mycol.* **2017**, *55*, 246–254.
51. Gabrielli, E.; Fothergill, A.W.; Brescini, L.; Sutton, D.A.; Marchionni, E.; Orsetti, E.; Staffolani, S.; Castelli, P.; Gesuita, R.; Barchiesi, F. Osteomyelitis caused by Aspergillus species: A review of 310 reported cases. *Clin. Microbiol. Infect.* **2014**, *20*, 559–565. [CrossRef]
52. Chi, C.-Y.; Fung, C.-P.; Liu, C.-Y. Aspergillus flavus epidural abscess and osteomyelitis in a diabetic patient. *J. Microbiol. Immunol. Infect.* **2003**, *36*, 177–180.
53. Beluffi, G.; Bernardo, M.E.; Meloni, G.; Spinazzola, A.; Locatelli, F. Spinal osteomyelitis due to Aspergillus flavus in a child: A rare complication after haematopoietic stem cell transplantation. *Pediatr. Radiol.* **2008**, *38*, 709–712. [CrossRef]
54. Khan, Z.U.; Gopalakrishnan, G.; Al-Awadi, K.; Gupta, R.K.; Moussa, S.A.; Chugh, T.D.; Krajci, D. Renal Aspergilloma Due to Aspergillus flavus. *Clin. Infect. Dis.* **1995**, *21*, 210–212. [CrossRef]
55. Pérez-Arellano, J.; Angel-Moreno, A.; Belón, E.; Francès, A.; Santana, O.; Martín-Snchez, A. Isolated Renoureteric Aspergilloma Due to Aspergillus flavus: Case Report and Review of the Literature. *J. Infect.* **2001**, *42*, 163–165. [CrossRef] [PubMed]
56. Kueter, J.C.; MacDiarmid, S.A.; Redman, J.F. Anuria due to bilateral ureteral obstruction by Aspergillus flavus in an adult male. *Urology* **2002**, *59*, 601. [CrossRef]
57. Harada, K.; Oguma, T.; Saito, A.; Fukutomi, Y.; Tanaka, J.; Tomomatsu, K.; Taniguchi, M.; Asano, K. Concordance between Aspergillus-specific precipitating antibody and IgG in allergic bronchopulmonary aspergillosis. *Allergol. Int.* **2018**, *67*, S12–S17. [CrossRef] [PubMed]
58. Asano, K.; Kamei, K.; Hebisawa, A. Allergic bronchopulmonary mycosis-pathophysiology, histology, diagnosis, and treatment. *Asia Pac. Allergy* **2018**, *8*, e24. [CrossRef] [PubMed]
59. Maurya, V.; Gugnani, H.C.; Sarma, P.U.; Madan, T.; Shah, A. Sensitization to Aspergillus antigens and occurrence of allergic bronchopulmonary aspergillosis in patients with asthma. *Chest* **2005**, *127*, 1252–1259.
60. Hadrich, I.; Makni, F.; Neji, S.; Cheikhrouhou, F.; Bellaaj, H.; Elloumi, M.; Ayadi, A.; Ranque, S. Amphotericin B in vitro resistance is associated with fatal Aspergillus flavus infection. *Med. Mycol.* **2012**, *50*, 829–834. [CrossRef]
61. Sabino, R.; Veríssimo, C.; Viegas, C.; Viegas, S.; Brandão, J.; Alves-Correia, M.; Borrego, L.-M.; Clemons, K.V.; Stevens, D.A.; Richardson, M. The role of occupational *Aspergillus* exposure in the development of diseases. *Med. Mycol.* **2019**, *57*, S196–S205. [CrossRef]
62. Tizek, L.; Schielein, M.; Berger, U.; Ege, M.; Schneider, S.; Zink, A. Skin cancer risk and shade: Comparing the risk of foresters with other outdoor workers. *J. Eur. Acad. Dermatol. Venereol.* **2020**, *34*, 2526–2533. [CrossRef] [PubMed]
63. Kawachi, I.; Pearce, N.; Fraser, J. A New Zealand cancer registry-based study of cancer in wood workers. *Cancer* **1989**, *64*, 2609–2613. [CrossRef] [PubMed]
64. Brito-Marcelino, A.; Duarte-Tavares, R.J.; Marcelino, K.B.; Silva-Neto, J.A. Cervical cancer related to occupational risk factors: Review. *Rev. Bras. Med. Trab.* **2020**, *18*, 103–108. [CrossRef] [PubMed]
65. McWhorter, W.P. Allergy and risk of cancer. A prospective study using nhanesi followup data. *Cancer* **1988**, *62*, 451–455. [CrossRef]
66. Shadman, M.; White, E.; De Roos, A.J.; Walter, R.B. Associations between allergies and risk of hematologic malignancies: Results from the VITamins and lifestyle cohort study. *Am. J. Hematol.* **2013**, *88*, 1050–1054. [CrossRef]
67. Liu, X.; Hemminki, K.; Forsti, A.; Sundquist, J.; Sundquist, K.; Ji, J. Cancer risk and mortality in asthma patients: A Swedish national cohort study. *Acta Oncol.* **2015**, *54*, 1120–1127. [CrossRef]
68. Eriksson, N.E.; Mikoczy, Z.; Hagmar, L. Cancer incidence in 13,811 patients skin tested for allergy. *J. Investig. Allergol. Clin. Immunol.* **2005**, *15*, 161–166. [PubMed]
69. Talbot-Smith, A.; Fritschi, L.; Divitini, M.L.; Mallon, D.F.J.; Knuiman, M.W. Allergy, Atopy, and Cancer: A Prospective Study of the 1981 Busselton Cohort. *Am. J. Epidemiol.* **2003**, *157*, 606–612. [CrossRef]
70. Zhu, J.; Song, J.; Liu, Z.; Han, J.; Luo, H.; Liu, Y.; Jia, Z.; Dong, Y.; Zhang, W.; Jiang, F.; et al. Association between allergic conditions and risk of prostate cancer: A Prisma-Compliant Systematic Review and Meta-Analysis. *Sci. Rep.* **2016**, *6*, 35682. [CrossRef]
71. Kozłowska, R.; Bożek, A.; Jarząb, J. Association between cancer and allergies. *Allergy Asthma Clin. Immunol.* **2016**, *12*, 39. [CrossRef]
72. Kantor, E.D.; Hsu, M.; Du, M.; Signorello, L.B. Allergies and Asthma in Relation to Cancer Risk. *Cancer Epidemiol. Biomark. Prev.* **2019**, *28*, 1395–1403. [CrossRef]
73. Källén, B.; Gunnarskog, J.; Conradson, T.B. Cancer risk in asthmatic subjects selected from hospital discharge registry. *Eur. Respir. J.* **1993**, *6*, 694–697. [CrossRef] [PubMed]
74. Carneiro, B.G.M.C.; Petroianu, A.; Machado, J.A.N.; Dos Anjos, P.M.F.; Da Silva, F.R.; Alberti, L.R.; Resende, V.; Barrientos, S.C. Clinical and immunological allergy assessment in cancer patients. *Sci. Rep.* **2021**, *11*, 1–9. [CrossRef]
75. Rava, M.; Czachorowski, M.J.; Silverman, D.; Márquez, M.; Kishore, S.; Tardón, A.; Serra, C.; García-Closas, M.; Garcia-Closas, R.; Carrato, A.; et al. Asthma status is associated with decreased risk of aggressive urothelial bladder cancer. *Int. J. Cancer* **2017**, *142*, 470–476. [CrossRef]

76. Gandini, S.; Lowenfels, A.B.; Jaffee, E.M.; Armstrong, T.D.; Maisonneuve, P. Allergies and the Risk of Pancreatic Cancer: A Meta-analysis with Review of Epidemiology and Biological Mechanisms. *Cancer Epidemiol. Biomark. Prev.* **2005**, *14*, 1908–1916. [CrossRef] [PubMed]
77. Cotterchio, M.; Lowcock, E.; Hudson, T.J.; Greenwood, C.; Gallinger, S. Association between Allergies and Risk of Pancreatic Cancer. *Cancer Epidemiol. Biomark. Prev.* **2014**, *23*, 469–480. [CrossRef] [PubMed]
78. Lowcock, E.C.; Cotterchio, M.; Ahmad, N. Association between allergies, asthma, and breast cancer risk among women in Ontario, Canada. *Cancer Causes Control* **2013**, *24*, 1053–1056. [CrossRef]
79. Jacobs, E.J.; Gapstur, S.M.; Newton, C.C.; Turner, M.C.; Campbell, P.T. Hay Fever and Asthma as Markers of Atopic Immune Response and Risk of Colorectal Cancer in Three Large Cohort Studies. *Cancer Epidemiol. Biomark. Prev.* **2013**, *22*, 661–669. [CrossRef] [PubMed]
80. Olson, S.H.; Hsu, M.; Satagopan, J.M.; Maisonneuve, P.; Silverman, D.T.; Lucenteforte, E.; Anderson, K.E.; Borgida, A.; Bracci, P.M.; Bueno-De-Mesquita, H.B.; et al. Allergies and Risk of Pancreatic Cancer: A Pooled Analysis from the Pancreatic Cancer Case-Control Consortium. *Am. J. Epidemiol.* **2013**, *178*, 691–700. [CrossRef]
81. Merrill, R.M.; Isakson, R.T.; Beck, R.E. The association between allergies and cancer: What is currently known? *Ann. Allergy Asthma Immunol.* **2007**, *99*, 102–117. [CrossRef]
82. Karim, A.F.; Westenberg, L.E.H.; Eurelings, L.E.M.; Otten, R.; Van Wijk, R.G. The association between allergic diseases and cancer: A systematic review of the literature. *Neth. J. Med.* **2019**, *77*, 42–66. [PubMed]
83. Wang, H. Diepgen TL. Is atopy a protective or a risk factor for cancer? A review of epidemiological studies. *Allergy* **2005**, *60*, 1098–1111. [CrossRef]
84. Cui, Y.; Hill, A.W. Atopy and Specific Cancer Sites: A Review of Epidemiological Studies. *Clin. Rev. Allergy Immunol.* **2016**, *51*, 338–352. [CrossRef]
85. Linos, E.; Raine, T.; Alonso, A.; Michaud, D. Atopy and Risk of Brain Tumors: A Meta-analysis. *Gynecol. Oncol.* **2007**, *99*, 1544–1550. [CrossRef]
86. Ferastraoaru, D.; Jordakieva, G.; Jensen-Jarolim, E. The other side of the coin: IgE deficiency, a susceptibility factor for malig-nancy occurrence. *World Allergy Organ. J.* **2021**, *14*, 100505. [CrossRef] [PubMed]
87. McCraw, A.J.; Chauhan, J.; Bax, H.J.; Stavraka, C.; Osborn, G.; Grandits, M.; López-Abente, J.; Josephs, D.H.; Spicer, J.; Wagner, G.K.; et al. Insights from IgE Immune Surveillance in Allergy and Cancer for Anti-Tumour IgE Treatments. *Cancers* **2021**, *13*, 4460. [CrossRef]
88. Amirian, E.S.; Zhou, R.; Wrensch, M.R.; Olson, S.H.; Scheurer, M.E.; Il'yasova, D.; Lachance, D.; Armstrong, A.G.; McCoy, L.C.; Lau, C.C.; et al. Approaching a scientific consensus on the asso-ciation between allergies and glioma risk: A report from the Glioma International Case-Control Study. *Cancer Epidemiol. Biomark. Prev.* **2016**, *25*, 282–290. [CrossRef]
89. Schwartzbaum, J.; Ding, B.; Johannesen, T.B.; Osnes, L.T.N.; Karavodin, L.; Ahlbom, A.; Feychting, M.; Grimsrud, T.K. Association between Prediagnostic IgE Levels and Risk of Glioma. *Gynecol. Oncol.* **2012**, *104*, 1251–1259. [CrossRef] [PubMed]
90. Tebbi, C.K.; Badiga, A.; Sahakian, E.; Powers, J.J.; Achille, A.N.; Patel, S.; Migone, F. Exposure to a mycovirus containing Aspergillus flavus reproduces acute lymphoblastic leukemia cell surface and genetic markers in cells from patients in remission and not controls. *Cancer Treat. Res. Commun.* **2021**, *26*, 100279. [CrossRef] [PubMed]
91. Tebbi, C.K.; Badiga, A.; Sahakian, E.; Arora, A.I.; Nair, S.; Powers, J.J.; Achille, A.N.; Jaglal, M.V.; Patel, S.; Migone, F. Plasma of Acute Lymphoblastic Leukemia Patients React to the Culture of a Mycovirus Containing Aspergillus flavus. *J. Pediatr. Hematol.* **2020**, *42*, 350–358. [CrossRef]
92. Tebbi, C.K.; Kotta-Loizou, I.; Coutts, R.H. Mycovirus Containing Aspergillus flavus and Acute Lymphoblastic Leukemia: Carcinogenesis beyond Mycotoxin Production. In *The Genus Aspergillus—Pathogenicity, Mycotoxin Production and Industrial Applications*; IntechOpen: London, UK, 2021.
93. Huët, M.A.L.; Lee, C.Z.; Rahman, S. A review on association of fungi with the development and progression of carcinogenesis in the human body. *Curr. Res. Microb. Sci.* **2021**, *3*, 100090. [CrossRef]
94. Kaźmierczak-Siedlecka, K.; Dvořák, A.; Folwarski, M.; Daca, A.; Przewłócka, K.; Makarewicz, W. Fungal Gut Microbiota Dysbiosis and Its Role in Colorectal, Oral, and Pancreatic Carcinogenesis. *Cancers* **2020**, *12*, 1326. [CrossRef] [PubMed]
95. Chung, L.-M.; Liang, J.-A.; Lin, C.-L.; Sun, L.-M.; Kao, C.-H. Cancer risk in patients with candidiasis: A nationwide population-based cohort study. *Oncotarget* **2017**, *8*, 63562–63573. [CrossRef]
96. Zhang, D.; Wang, Y.; Shen, S.; Hou, Y.; Chen, Y.; Wang, T. The mycobiota of the human body: A spark can start a prairie fire. *Gut Microbes* **2020**, *11*, 655–679. [CrossRef] [PubMed]
97. Wainwright, M. Do fungi play a role in the aetiology of cancer? *Rev. Med. Microbiol.* **2002**, *13*, 37–42. [CrossRef]
98. Tebbi, C.K. Carcinogenesis and Leukemogenesis of Microorganisms: A Review. *21st Century Pathol.* **2022**, *2*, 109–120.
99. Greaves, M. Author Correction: A causal mechanism for childhood acute lymphoblastic leukaemia. *Nat. Rev. Cancer* **2018**, *18*, 526. [CrossRef]
100. Blair, A.; Zahm, S.H. Agricultural Exposures and Cancer. *Environ. Health Perspect.* **1995**, *103* (Suppl. 8), 205–208. [PubMed]
101. Ljubojevic, S.; Skerlev, M. HPV-associated diseases. *Clin. Dermatol.* **2014**, *32*, 227–234. [CrossRef] [PubMed]
102. Yugawa, T.; Kiyono, T. Molecular mechanisms of cervical carcinogenesis by high-risk human papillomaviruses: Novel functions of E6 and E7 oncoproteins. *Rev. Med. Virol.* **2009**, *19*, 97–113. [CrossRef]

103. Scheidegger, K.; Payne, G. Unlocking the secrets behind secondary metabolism: A review of Aspergillus flavus from pathogenicity to functional genomics. *J. Toxicol. Toxin Rev.* **2003**, *22*, 423–459. [CrossRef]
104. Gonçalves, A.B.; Paterson, R.R.M.; Lima, N. Survey and significance of filamentous fungi from tap water. *Int. J. Hyg. Environ. Health* **2006**, *209*, 257–264. [CrossRef] [PubMed]
105. Gibson, A.M.; Baranyi, J.; Pitt, J.I.; Eyles, M.J.; Roberts, T.A. Predicting fungal growth: The effect of water activity on Aspergillus flavus and related species. *Int. J. Food Microbiol.* **1994**, *23*, 419–431. [CrossRef]
106. Fröhlich-Nowoisky, J.; Pickersgill, D.A.; Després, V.R.; Pöschl, U. High diversity of fungi in air particulate matter. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 12814–12819. [CrossRef]
107. Sautour, M.; Sixt, N.; Dalle, F.; L'Ollivier, C.; Fourquenet, V.; Calinon, C.; Paul, K.; Valvin, S.; Maurel, A.; Aho, S.; et al. Profiles and seasonal distribution of airborne fungi in indoor and outdoor environments at a French hospital. *Sci. Total. Environ.* **2009**, *407*, 3766–3771. [CrossRef] [PubMed]
108. Hedayati, M.T.; Pasqualotto, A.C.; Warn, P.A.; Bowyer, P.; Denning, D.W. Aspergillus flavus: Human pathogen, allergen and mycotoxin producer. *Microbiology* **2007**, *153*, 1677–1692. [CrossRef] [PubMed]
109. VandenBergh, M.F.; Verweij, P.E.; Voss, A. Epidemiology of nosocomial fungal infections: Invasive aspergillosis and the environment. *Diagn. Microbiol. Infect. Dis.* **1999**, *34*, 221–227. [CrossRef]
110. Mousavi, B.; Hedayati, M.T.; Hedayati, N.; Ilkit, M.; Syedmousavi, S. Aspergillus species in indoor environments and their possible occupational and public health hazards. *Curr. Med. Mycol.* **2016**, *2*, 36–42. [CrossRef]
111. Schoental, R. Moses and mycotoxins. *Prev. Med.* **1980**, *1*, 159–161. [CrossRef]
112. Marr, J.S.; Malloy, C.D. An epidemiologic analysis of the ten plagues of Egypt. *Caduceus* **1996**, *12*, 7–24. [PubMed]
113. Varga, J.; Due, M.; Frisvad, J.C.; Samson, R.A. taxonomic revision of Aspergillus section Clavati based on molecular, morphological and physiological data. *Stud. Mycol.* **2007**, *59*, 89–106. [CrossRef] [PubMed]
114. Samson, R.A.; Visagie, C.M.; Houbraken, J.; Hong, S.-B.; Hubka, V.; Klaassen, C.H.; Perrone, G.; Seifert, K.A.; Susca, A.; Tanney, J.B. Phylogeny, identification and nomenclature of the genus Aspergillus. *Stud. Mycol.* **2005**, *53*, 1–27.
115. Frisvad, J. A critical review of producers of small lactone mycotoxins: Patulin, penicillic acid and moniliformin. *World Mycotoxin J.* **2018**, *11*, 73–100. [CrossRef]
116. Frisvad, J.C.; Hubka, V.; Ezekiel, C.N. Taxonomy of Aspergillus section Flavi and their production of aflatoxins, ochratoxins and other mycotoxins. *Stud. Mycol.* **2019**, *93*, 1–63. [CrossRef]
117. James, M.J.; Lasker, B.A.; McNeil, M.M.; Shelton, M.; Warnock, D.W.; Reiss, E. Use of a Repetitive DNA Probe to Type Clinical and Environmental Isolates of *Aspergillus flavus* from a Cluster of Cutaneous Infections in a Neonatal Intensive Care Unit. *J. Clin. Microbiol.* **2000**, *38*, 3612–3618. [CrossRef] [PubMed]
118. Borgohain, P.; Barua, P.; Dutta, P.J.; Shaw, D.; Rudramurthy, S.M. Onychomycosis Associated with Superficial Skin Infection Due to Aspergillus sydowii in an Immunocompromised Patient. *Mycopathologia* **2019**, *184*, 683–689. [CrossRef]
119. Vandecasteele, S.J.; Boelaert, J.R.; Verrelst, P.; Graulus, E.; Gordts, B.Z. Diagnosis and Treatment of *Aspergillus flavus* Sternal Wound Infections after Cardiac Surgery. *Clin. Infect. Dis.* **2002**, *35*, 887–890. [CrossRef]
120. Myoken, Y.; Sugata, T.; Fujita, Y.; Kyo, T.-I.; Fujihara, M.; Kohara, T.; Katsu, M.; Mikami, Y. Molecular epidemiology of invasive stomatitis due to Aspergillus flavus in patients with acute leukemia. *J. Oral Pathol. Med.* **2003**, *32*, 215–218. [CrossRef]
121. Lutz, B.D.; Jin, J.; Rinaldi, M.G.; Wickes, B.L.; Huycke, M.M. Outbreak of Invasive *Aspergillus* Infection in Surgical Patients, Associated with a Contaminated Air-Handling System. *Clin. Infect. Dis.* **2003**, *37*, 786–793. [CrossRef]
122. Kradin, R.L.; Mark, E.J. The pathology of pulmonary disorders due to *Aspergillus* spp. *Arch. Pathol. Lab. Med.* **2008**, *132*, 606–614. [CrossRef]
123. Bangash, M. Aspergillus flavus Brain Abscess in Immunocompetent Teenagers: A Case Series with Review of Literature. *J. Case Rep.* **2017**, *7*, 8–12. [CrossRef]
124. Jensen, J.; Guinea, J.; Torres-Narbona, M.; Muñoz, P.; Peláez, T.; Bouza, E. Post-surgical invasive aspergillosis: An uncommon and under-appreciated entity. *J. Infect.* **2010**, *60*, 162–167. [CrossRef]
125. Gage, A.A. Aspergillus Infection after Cardiac Surgery. *Arch. Surg.* **1970**, *101*, 384–387. [CrossRef]
126. Liu, Y.; Ou, Y.; Sun, L.; Li, W.; Yang, J.; Zhang, X.; Hu, Y. Alcohol dehydrogenase of Candida albicans triggers differentiation of THP-1 cells into macrophages. *J. Adv. Res.* **2019**, *18*, 137–145. [CrossRef] [PubMed]
127. Klotz, S.A.; Pendrak, M.L.; Hein, R.C. Antibodies to α5β1 and αvβ3 integrins react with Candida albicans alcohol dehydrogenase. *Microbiology* **2001**, *147*, 3159–3164. [CrossRef] [PubMed]
128. Chaffin, W.L. Candida albicans cell wall proteins. *Microbiol. Mol. Biol. Rev.* **2008**, *72*, 495–544. [CrossRef] [PubMed]
129. Setshedi, M.; Wands, J.R.; De la Monte, S.M. Acetaldehyde Adducts in Alcoholic Liver Disease. *Oxidative Med. Cell. Longev.* **2010**, *3*, 178–185. [CrossRef]
130. Reyes-Gordillo, K.; Shah, R.; Arellanes-Robledo, J.; Hernández-Nazara, Z.; Rincón-Sánchez, A.R.; Inagaki, Y.; Rojkind, M.; Lakshman, M.R. Mechanisms of action of acetaldehyde in the up-regulation of the human α2 (I) collagen gene in hepatic stellate cells: Key roles of Ski, SMAD3, SMAD4, and SMAD7. *Am. J. Pathol.* **2014**, *184*, 1458–1467.
131. Hernández, E.; Bucio, L.; Souza, V.; Escobar, M.C.; Gómez-Quiroz, L.E.; Farfán, B.; Kershenobich, D.; Gutiérrez-Ruiz, M.C. Pentoxifylline downregulates α (I) collagen expression by the inhibition of Iκbα degradation in liver stellate cells. *Cell Biol. Toxicol.* **2008**, *24*, 303–314. [CrossRef] [PubMed]

132. Simoni-Nieves, A.; Clavijo-Cornejo, D.; Gutiérrez-Ruiz, M.C.; Gomez-Quiroz, L.E. Acetaldehyde Effects on Cellular Redox State. In *The Liver*; Academic Press: Cambridge, MA, USA, 2018; pp. 63–70. [CrossRef]
133. Homann, N.; Jousimies-Somer, H.; Jokelainen, K.; Heine, R.; Salaspuro, M. High acetaldehyde levels in saliva after ethanol consumption: Methodological aspects and pathogenetic implications. *Carcinogenesis* **1997**, *18*, 1739–1743. [CrossRef]
134. Pöschl, G.; Seitz, H.K. Alcohol and cancer. *Alcohol Alcohol.* **2004**, *39*, 155–165. [CrossRef]
135. Alnuaimi, A.D.; Ramdzan, A.N.; Wiesenfeld, D.; O'Brien-Simpson, N.M.; Kolev, S.D.; Reynolds, E.C.; McCullough, M.J. Candida virulence and ethanol-derived acetaldehyde production in oral cancer and non-cancer subjects. *Oral Dis.* **2016**, *22*, 805–814. [CrossRef]
136. Ramirez-Garcia, A.; Rementeria, A.; Aguirre-Urizar, J.M.; Moragues, M.D.; Antoran, A.; Pellon, A.; Abad-Diaz-de-Cerio, A.; Hernando, F.L. Candida albicans and cancer: Can this yeast induce cancer development or progression. *Microbiology* **2016**, *42*, 181–193.
137. Krogh, P.; Hald, B.; Holmstrup, P. Possible mycological etiology of oral mucosal cancer: Catalytic potential of infecting *Candida aibicans* and other yeasts in production of *N*-nitrosobenzylmethylamine. *Carcinogensis* **1987**, *8*, 1543–1548. [CrossRef]
138. Gayathri, K.; Balachander, N.; Malathi, L.; Sankari, S. Candida in potentially malignant oral disorders. *J. Pharm. Bioallied Sci.* **2015**, *7*, 164. [CrossRef]
139. Di Cosola, M.; Cazzolla, A.P.; Charitos, I.A.; Ballini, A.; Inchingolo, F.; Santacroce, L. Candida albicans and Oral Carcinogenesis. A Brief Review. *J. Fungi* **2021**, *7*, 476. [CrossRef] [PubMed]
140. Wang, S.H.; Wang, S.C.; Chen, P.C.; Wang, S.T.; Liu, Y.W. Induction of cyclooxygenase-2 gene by Candida albicans through EGFR, ERK, and p38 pathways in human urinary epithelium. *Med. Mycol.* **2017**, *55*, 314–322.
141. Netea, M.G.; Stuyt, R.J.L.; Kim, S.; Van der Meer, J.W.M.; Kullberg, B.J.; Dinarello, C.A. The Role of Endogenous Interleukin (IL)–18, IL-12, IL-1β, and Tumor Necrosis Factor–α in the Production of Interferon-γ Induced by *Candida albicans* in Human Whole-Blood Cultures. *J. Infect. Dis.* **2002**, *185*, 963–970. [CrossRef] [PubMed]
142. Bombeccaria, G.; Spadaria, F.; Rossia, M.; Porrinia, M.; Bosottia, M.; Giannì, A. Biology of *Candida* spp. in potentially malignant disorders and carcinoma of the oral cavity. *Dent. Cadmos.* **2016**, *84*, 624–634. [CrossRef]
143. Warnakulasuriya, S.; Ariyawardana, A. Malignant transformation of oral leukoplakia: A systematic review of observational studies. *J. Oral Pathol. Med.* **2015**, *45*, 155–166. [CrossRef]
144. Engku Nasrullah Satiman, E.A.F.; Ahmad, H.; Ramzi, A.B.; Abdul Wahab, R.; Kaderi, M.A.; Wan Harun, W.H.A.; Dashper, S.; McCullough, M.; Arzmi, M.H. The role of Candida albicans candidalysin ECE1 gene in oral carcinogenesis. *J. Oral Pathol. Med.* **2020**, *49*, 835–841. [CrossRef]
145. Bennett, J.W.; Klich, M. Mycotoxins. *Clin. Microbiol.* **2003**, *16*, 497–516. [CrossRef] [PubMed]
146. Marin, S.; Ramos, A.; Cano-Sancho, G.; Sanchis, V. Mycotoxins: Occurrence, toxicology, and exposure assessment. *Food Chem. Toxicol.* **2013**, *60*, 218–237. [CrossRef] [PubMed]
147. Gupta, R.C.; Doss, R.B.; Lall, R.; Srivastava, A.; Sinha, A. Aflatoxins, ochratoxins, and citrinin. In *Reproductive and Developmental Toxicology*; Elsevier: Amsterdam, The Netherlands, 2022; pp. 983–1002.
148. Vanhoutte, I.; Audenaert, K.; De Gelder, L. Biodegradation of Mycotoxins: Tales from Known and Unexplored Worlds. *Front. Microbiol.* **2016**, *7*, 561. [CrossRef]
149. Turner, P.C.; Collinson, A.C.; Cheung, Y.B.; Gong, Y.Y.; Hall, A.J.; Prentice, A.M.; Wild, C.P. Aflatoxin exposure in utero causes growth faltering in Gambian infants. *Leuk. Res.* **2007**, *36*, 1119–1125. [CrossRef]
150. Eze, U.; Routledge, M.; Okonofua, F.; Huntriss, J.; Gong, Y. Mycotoxin exposure and adverse reproductive health outcomes in Africa: A review. *World Mycotoxin J.* **2018**, *11*, 321–339. [CrossRef]
151. Erceg, S.; Mateo, E.M.; Zipancic, I.; Jiménez, F.J.R.; Aragó, M.A.P.; Jiménez, M.; Soria, J.M.; Garcia-Esparza, M. Assessment of Toxic Effects of Ochratoxin A in Human Embryonic Stem Cells. *Toxins* **2019**, *11*, 217. [CrossRef] [PubMed]
152. Khoury, D.E.; Fayjaloun, S.; Nassar, M.; Sahakian, J.; Aad, P.Y. Updates on the Effect of Mycotoxins on Male Reproductive Efficiency in Mammals. *Toxins* **2019**, *11*, 515. [CrossRef]
153. Kanora, A.; Maes, D. The role of mycotoxins in pig reproduction: A review. *Vet. Med.* **2009**, *54*, 565–576. [CrossRef]
154. Coppa, C.F.S.C.; Khaneghah, A.M.; Alvito, P.; Assunção, R.; Martins, C.; Es, I.; Goncalves, B.L.; De Neeff, D.V.; Sant'Ana, A.S.; Corassin, C.H.; et al. The occurrence of mycotoxins in breast milk, fruit products and cereal-based infant formula: A review. *Trends Food Sci. Technol.* **2019**, *92*, 81–93. [CrossRef]
155. Fraeyman, S.; Croubels, S.; Devreese, M.; Antonissen, G. Emerging Fusarium and Alternaria Mycotoxins: Occurrence, Toxicity and Toxicokinetics. *Toxins* **2017**, *9*, 228. [CrossRef] [PubMed]
156. Rushing, B.R.; Selim, M.I. Aflatoxin B1: A review on metabolism, toxicity, occurrence in food, occupational exposure, and detoxification methods. *Food Chem. Toxicol.* **2019**, *124*, 81–100. [CrossRef]
157. Ortiz, J.; Jacxsens, L.; Astudillo, G.; Ballesteros, A.; Donoso, S.; Huybregts, L.; De Meulenaer, B. Multiple mycotoxin exposure of infants and young children via breastfeeding and complementary/weaning foods consumption in Ecuadorian highlands. *Food Chem. Toxicol.* **2018**, *118*, 541–548. [CrossRef] [PubMed]
158. Kiarie, G.M.; Dominguez-Salas, P.; Kang'ethe, S.K.; Grace, D.; Lindahl, J. Aflatoxin exposure among young children in urban low-income areas of Nairobi and association with child growth. *Afr. J. Food Agric. Nutr. Dev* **2016**, *16*, 10967–10990. [CrossRef]
159. Smith, L.E.; Prendergast, A.J.; Turner, P.C.; Mbuya, M.N.N.; Mutasa, K.; Kembo, G.; Stoltzfus, R.J. The Potential Role of Mycotoxins as a Contributor to Stunting in the SHINE Trial. *Clin. Infect. Dis.* **2015**, *61*, S733–S737. [CrossRef]

160. Watson, S.; Moore, S.E.; Darboe, M.K.; Chen, G.; Tu, Y.-K.; Huang, Y.-T.; Eriksen, K.G.; Bernstein, R.M.; Prentice, A.M.; Wild, C.P.; et al. Impaired growth in rural Gambian infants exposed to aflatoxin: A prospective cohort study. *BMC Public Health* **2018**, *18*, 1247. [CrossRef]
161. Khlangwiset, P.; Shephard, G.S.; Wu, F. Aflatoxins and growth impairment: A review. *Crit. Rev. Toxicol.* **2011**, *41*, 740–755. [CrossRef]
162. Patel, R.; Hossain, M.A.; German, N.; Al-Ahmad, A.J. Gliotoxin penetrates and impairs the integrity of the human blood-brain barrier in vitro. *Mycotoxin Res.* **2018**, *34*, 257–268. [CrossRef]
163. Herrera, M.; Bervis, N.; Carramiñana, J.J.; Juan, T.; Herrera, A.; Ariño, A.; Lorán, S. Occurrence and Exposure Assessment of Aflatoxins and Deoxynivalenol in Cereal-Based Baby Foods for Infants. *Toxins* **2019**, *11*, 150. [CrossRef]
164. Van Vleet, T.R.; Klein, P.J.; Coulombe, R.A.C., Jr. Metabolism and cytotoxicity of aflatoxin B 1 in cytochrome P-450-expressing human lung cells. *J. Toxicol. Environ. Health Part A* **2002**, *65*, 853–867. [CrossRef]
165. Bren, U.; Fuchs, J.E.; Oostenbrink, C. Cooperative Binding of Aflatoxin B_1 by Cytochrome P450 3A4: A Computational Study. *Chem. Res. Toxicol.* **2014**, *27*, 2136–2147. [CrossRef] [PubMed]
166. Wild, C.; Turner, P. The toxicology of aflatoxins as a basis for public health decisions. *Mutagenesis* **2002**, *17*, 471–481. [CrossRef] [PubMed]
167. Diaz, G.J.; Murcia, H.W.; Cepeda, S.M. Cytochrome P450 enzymes involved in the metabolism of aflatoxin B1 in chickens and quail. *Poult. Sci.* **2010**, *89*, 2461–2469. [CrossRef]
168. Supriya, C.; Reddy, P.S. Prenatal exposure to aflatoxin B1: Developmental, behavioral, and reproductive alterations in male rats. *Sci. Nat.* **2015**, *102*, 1–13. [CrossRef]
169. Fetaih, H.A.; Dessouki, A.A.; Hassanin, A.A.; Tahan, A.S. Toxopathological and cytogenetic effects of aflatoxin B1 (AFB1) on pregnant rats. *Pathol. Res. Pract.* **2014**, *210*, 1079–1089. [CrossRef]
170. Williams, J.H.; Phillips, T.D.; Jolly, P.E.; Stiles, J.K.; Jolly, C.M.; 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. [CrossRef]
171. Chen, C.; Mitchell, N.J.; Gratz, J.; Houpt, E.R.; Gong, Y.; Egner, P.A.; Groopman, J.D.; Riley, R.T.; Showker, J.L.; Svensen, E.; et al. Exposure to aflatoxin and fumonisin in children at risk for growth impairment in rural Tanzania. *Environ. Int.* **2018**, *115*, 29–37. [CrossRef] [PubMed]
172. Tola, M.; Kebede, B. Occurrence, importance and control of mycotoxins: A review. *Cogent Food Agric.* **2016**, *2*, 1191103. [CrossRef]
173. Lamplugh, S.; Hendrickse, R.; Apeagyei, F.; Mwanmut, D. Aflatoxins in breast milk, neonatal cord blood, and serum of pregnant women. *Br. Med. J. Clin. Res. Ed.* **1988**, *296*, 968. [CrossRef]
174. Jonsyn, F.E.; Maxwell, S.M.; Hendrickse, R.G. Human fetal exposure to ochratoxin A and aflatoxins. *Ann. Trop. Paediatr.* **1995**, *15*, 3–9. [CrossRef]
175. Maxwell, S.M.; Familusi, J.B.; Sodeinde, O.; Chan, M.C.K.; Hendrickse, R.G. Detection of naphthols and aflatoxins in Nigerian cord blood. *Ann. Trop. Paediatr.* **1994**, *14*, 3–5. [CrossRef]
176. Groopman, J.D.; Egner, P.A.; Schulze, K.J.; Wu, L.S.-F.; Merrill, R.; Mehra, S.; Shamim, A.A.; Ali, H.; Shaikh, S.; Gernand, A.; et al. Aflatoxin exposure during the first 1000 days of life in rural South Asia assessed by aflatoxin B1-lysine albumin biomarkers. *Food Chem. Toxicol.* **2014**, *74*, 184–189. [CrossRef]
177. Denning, D.; Allen, R.; Wilkinson, A.P.; Morgan, M.R. Transplacental transfer of aflatoxin in humans. *Carcinogenesis* **1990**, *11*, 1033–1035. [CrossRef]
178. Abulu, E.O.; Uriah, N.; Aigbefo, H.S.; Oboh, P.A.; Agbonlahor, D.E. Preliminary investigation on aflatoxin in cord blood of jaundiced neonates. *West Afr. J. Med.* **1998**, *17*, 184–187.
179. Abdulrazzaq, Y.M.; Osman, N.; Yousif, Z.M.; Trad, O. Morbidity in neonates of mothers who have ingested aflatoxins. *Ann. Trop. Paediatr.* **2004**, *24*, 145–151. [CrossRef]
180. Gong, Y.Y.; Cardwell, K.; Hounsa, A.; Egal, S.; Turner, P.C.; Hall, A.J.; Wild, C.P. Dietary aflatoxin exposure and impaired growth in young children from Benin and Togo: Cross sectional study. *BMJ* **2002**, *325*, 20–21. [CrossRef] [PubMed]
181. Gong, Y.Y.; Hounsa, A.; Egal, S.; Turner, P.C.; Sutcliffe, A.E.; Hall, A.J.; Cardwell, K.; Wild, C.P. Postweaning Exposure to Aflatoxin Results in Impaired Child Growth: A Longitudinal Study in Benin, West Africa. *Environ. Health Perspect.* **2004**, *112*, 1334–1338. [CrossRef] [PubMed]
182. Sharma, R.P. Immunotoxicity of Mycotoxins. *J. Dairy Sci.* **1993**, *76*, 892–897. [CrossRef]
183. Mykkänen, H.; Zhu, H.; Salminen, E.; Juvonen, R.O.; Ling, W.; Ma, J.; Polychronaki, N.; Kemiläinen, H.; Mykkänen, O.; Salminen, S.; et al. Fecal and urinary excretion of aflatoxin B1 metabolites (AFQ1, AFM1 and AFB-N7-guanine) in young Chinese males. *Int. J. Cancer* **2005**, *115*, 879–884. [CrossRef]
184. Jager, A.V.; Tonin, F.G.; Baptista, G.Z.; Souto, P.C.; Oliveira, C.A. Assessment of aflatoxin exposure using serum and urinary biomarkers in São Paulo, Brazil: A pilot study. *Int. J. Hyg. Environ. Health* **2016**, *219*, 294–300. [CrossRef] [PubMed]
185. Fernández, A.; Belío, R.; Ramos, J.J.; Sanz, M.C.; Sáez, T. Aflatoxins and their Metabolites in the Tissues, Faeces and Urine from Lambs Feeding on an Aflatoxin-Contaminated Diet. *J. Sci. Food Agric.* **1997**, *74*, 161–168. [CrossRef]
186. Hajmohammadi, M.; Valizadeh, R.; Naserian, A.; Nourozi, M.E.; Rocha, R.S.; Oliveira, C.A. Composition and occurrence of aflatoxin M1 in cow's milk samples from Razavi Khorasan Province, Iran. *Int. J. Dairy Technol.* **2020**, *73*, 40–45.

187. Ahmadi, E. Potential public health risk due to consumption of contaminated bovine milk with aflatoxin M1 and Coxiella burnetii in the West of Iran. *Int. J. Dairy Technol.* **2020**, *73*, 479–485. [CrossRef]
188. Diaz, G.J.; Sánchez, M.P. Determination of aflatoxin M1 in breast milk as a biomarker of maternal and infant exposure in Co-lombia. *Food Addit. Contam. Part A* **2015**, *32*, 1192–1198. [CrossRef] [PubMed]
189. Boysen, G.; Pachkowski, B.F.; Nakamura, J.; Swenberg, J.A. The formation and biological significance of N7-guanine adducts. *Mutat. Res. Toxicol. Environ. Mutagen.* **2009**, *678*, 76–94. [CrossRef]
190. Voss, K.A.; Riley, R.T. Fumonisin Toxicity and Mechanism of Action: Overview and Current Perspectives. *Food Saf.* **2013**, *1*, 49–69. [CrossRef]
191. Chen, C.; Riley, R.T.; Wu, F. Dietary Fumonisin and Growth Impairment in Children and Animals: A Review. *Compr. Rev. Food Sci. Food Saf.* **2018**, *17*, 1448–1464. [CrossRef]
192. Marasas, W.F.; Kellerman, T.S.; Gelderblom, W.C.; Coetzer, J.A.; Thiel, P.G.; Van Der Lugt, J.J. Leukoencephalomalacia in a horse induced by fumonisin B1 isolated from Fusarium moniliforme. *Onderstepoort J. Veter. Res.* **1988**, *55*.
193. Harrison, L.R.; Colvin, B.M.; Greene, J.T.; Newman, L.E.; Cole, J.R., Jr. Pulmonary edema and hydrothorax in swine produced by fumonisin B1, a toxic metabolite of Fusarium moniliforme. *J. Vet. Diagn. Investig.* **1990**, *2*, 217–221. [CrossRef]
194. De Ruyck, K.; De Boevre, M.; Huybrechts, I.; De Saeger, S. Dietary mycotoxins, co-exposure, and carcinogenesis in humans: Short review. *Mutat. Res. Mol. Mech. Mutagen.* **2015**, *766*, 32–41. [CrossRef]
195. Speijers, G.; Speijers, M. Combined toxic effects of mycotoxins. *Toxicol. Lett.* **2004**, *153*, 91–98. [CrossRef]
196. Grenier, B.; Oswald, I. Mycotoxin co-contamination of food and feed: Meta-analysis of publications describing toxicological interactions. *World Mycotoxin J.* **2011**, *4*, 285–313. [CrossRef]
197. Bensassi, F.; Gallerne, C.; Sharaf el Dein, O.; Hajlaoui, M.R.; Lemaire, C.; Bacha, H. In vitro investigation of toxicological interactions between the fusariotoxins deoxynivalenol and zearalenone. *Toxicon* **2014**, *84*, 1–6. [CrossRef]
198. Chhonker, S.; Rawat, D.; Naik, R.; Koiri, R. An overview of mycotoxins in human health with emphasis on development and progression of liver cancer. *Clin. Oncol.* **2018**, *3*, 1408.
199. Steyn, P.S. Mycotoxins, general view, chemistry and structure. *Toxicol. Lett.* **1995**, *82*, 843–851. [CrossRef] [PubMed]
200. El-Kady, I.A.; El-Maraghy, S.S.M.; Mostafa, M.E. Natural occurrence of mycotoxins in different spices in Egypt. *Folia Microbiol.* **1995**, *40*, 297–300. [CrossRef]
201. Ueno, Y.; Hsieh, D.P.H. The Toxicology of Mycotoxins. *CRC Crit. Rev. Toxicol.* **1985**, *14*, 99–132. [CrossRef]
202. Alizadeh, A.M.; Roshandel, G.; Roudbarmohammadi, S.; Roudbary, M.; Sohanaki, H.; Ghiasian, S.A.; Taherkhani, A.; Semnani, S.; Aghasi, M. Fumonisin B1 Contamination of Cereals and Risk of Esophageal Cancer in a High Risk Area in Northeastern Iran. *Asian Pac. J. Cancer Prev.* **2012**, *13*, 2625–2628. [CrossRef] [PubMed]
203. Belhassen, H.; Jiménez-Díaz, I.; Arrebola, J.; Ghali, R.; Ghorbel, H.; Olea, N.; Hedili, A. Zearalenone and its metabolites in urine and breast cancer risk: A case-control study in Tunisia. *Chemosphere* **2015**, *128*, 1–6. [CrossRef] [PubMed]
204. Pillay, D.; Chuturgoon, A.A.; Nevines, E.; Manickum, T.; Deppe, W.; Dutton, M.F. The Quantitative Analysis of Zearalenone and Its Derivatives in Plasma of Patients with Breast and Cervical Cancer. *Clin. Chem. Lab. Med.* **2002**, *40*, 946–951. [CrossRef]
205. Marasas, W.; Wehner, F.; Van Rensburg, S.; Van Schalkwyk, D. Mycoflora of corn produced in human esophageal cancer areas in Transkei, southern Africa. *Phytopathology* **1981**, *71*, 792–796. [CrossRef]
206. Ellis, L.F.; Kleinschmidt, W.J. Virus-like Particles of a Fraction of Statolon, a Mould Product. *Nature* **1967**, *215*, 649–650. [CrossRef] [PubMed]
207. Ghabrial, S.A.; Caston, J.R.; Jiang, D.; Nibert, M.L.; Suzuki, N. 50-plus years of fungal viruses. *Virology* **2015**, *479–480*, 356–368. [CrossRef] [PubMed]
208. Schmidt, F.R.; Lemke, P.A.; Esser, K. Viral influences on aflatoxin formation by Aspergillus flavus. *Appl. Microbiol. Biotechnol.* **1986**, *24*, 248–252. [CrossRef]
209. Kotta-Loizou, I.; Coutts, R.H.A. Mycoviruses in Aspergilli: A Comprehensive Review. *Front. Microbiol.* **2017**, *8*, 1699. [CrossRef]
210. Yu, X.; Li, B.; Fu, Y.; Xie, J.; Cheng, J.; Ghabrial, S.A.; Li, G.; Yi, X.; Jiang, D. Extracellular transmission of a DNA mycovirus and its use as a natural fungicide. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 1452–1457. [CrossRef] [PubMed]
211. Park, M.; Cho, Y.-J.; Kim, D.; Yang, C.-S.; Lee, S.M.; Dawson Jr, T.L.; Nakamizo, S.; Kabashima, K.; Lee, Y.W.; Jung, W.H. A novel virus alters gene expression and vacuolar morphology in Malassezia cells and induces a TLR3-mediated inflammatory immune response. *Mbio* **2020**, *11*, e01521. [CrossRef]
212. Clancey, S.A.; Ruchti, F.; LeibundGut-Landmann, S.; Heitman, J.; Ianiri, G. A Novel Mycovirus Evokes Transcriptional Rewiring in the Fungus *Malassezia* and Stimulates Beta Interferon Production in Macrophages. *Mbio* **2020**, *11*, e01534-20. [CrossRef]
213. Vercammen, E.; Staal, J.; Beyaert, R. Sensing of Viral Infection and Activation of Innate Immunity by Toll-Like Receptor 3. *Clin. Microbiol. Rev.* **2008**, *21*, 13–25. [CrossRef]

214. Vena, J.E.; Bona, J.R.; Byers, T.E.; Middleton, E.; Swanson, M.K.; Graham, S. Allergy-related diseases and cancer: An inverse association. *Am. J. Epidemiol.* **1985**, *122*, 66–74. [CrossRef]
215. Hwang, C.-Y.; Chen, Y.-J.; Lin, M.-W.; Chen, T.-J.; Chu, S.-Y.; Chen, C.-C.; Lee, D.-D.; Chang, Y.-T.; Wang, W.-J.; Liu, H.-N. Cancer risk in patients with allergic rhinitis, asthma and atopic dermatitis: A nationwide cohort study in Taiwan. *Int. J. Cancer* **2011**, *130*, 1160–1167. [CrossRef] [PubMed]