Mycobiology

Mini-review

Influence of Temperature and Water Activity on Deleterious Fungi and Mycotoxin Production during Grain Storage

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Abstract Cereal grains are the most important food source for humans. As the global population continues to grow exponentially, the need for the enhanced yield and minimal loss of agricultural crops, mainly cereal grains, is increasing. In general, harvested grains are stored for specific time periods to guarantee their continuous supply throughout the year. During storage, economic losses due to reduction in quality and quantity of grains can become very significant. Grain loss is usually the result of its deterioration due to fungal contamination that can occur from preharvest to postharvest stages. The deleterious fungi can be classified based on predominance at different stages of crop growth and harvest that are affected by environmental factors such as water activity (a_w) and eco-physiological requirements. These fungi include species such as those belonging to the genera *Aspergillus* and *Penicillium* that can produce mycotoxins harmful to animals and humans. The grain type and condition, environment, and biological factors can also influence the occurrence and predominance of mycotoxigenic fungi in stored grains. The main environmental factors influencing grain fungi and mycotoxins are temperature and a_w. This review discusses the effects of temperature and a_w on fungal growth and mycotoxin production in stored grains. The focus is on the occurrence and optimum and minimum growth requirements for grain fungi and mycotoxin production. The environmental influence on aflatoxin production and hypothesized mechanisms of its molecular suppression in response to environmental changes are also discussed. In addition, the use of controlled or modified atmosphere as an environmentally safe alternative to harmful agricultural chemicals is discussed and recommended future research issues are highlighted.

Keywords Aflatoxin, Aflatoxin biosynthesis gene cluster, Mycotoxin, Storage fungi, Temperature, Water activity

Cereal grains, including wheat, rice, and corn, are the hard and dry seeds typical of the family of grasses (Gramineae). Grains are one of the most important staple food sources for humans. For example, rice is the major food for Asians, sorghum and millet for Africans and Indians, wheat, rye, and barley for Europeans, and corn for Americans [1]. Historically, the ability to store and distribute food grains has been the foundation of urbanization, as urban societies depend on the effective supply of grains throughout the year. Hence, food grains must be safely stored, after harvesting at specific times of the year, to ensure supply throughout the remainder of the year [2]. The estimated global production of cereal grains in 2017 was 2,593 million metric tons (MMT). Of this amount, the production of coarse grains, wheat, and rice, was 1347, 743, and 502 MMT, respectively [3]. Owing to the growing human population, food shortages have been predicted. For instance, it was estimated that more than one billion people would be malnourished and facing hunger in 2009. Therefore, continuous enhancement of food production and minimization of crop losses are needed to meet the demands of the growing human population [4].

Increased grain production has resulted in extended grain storage period. During storage, grain deterioration by fungal contamination includes discoloration, musty odors, dry matter loss, tissue disintegration, nutritional and processing quality losses, and mycotoxin accumulation [5]. The estimated losses by different causes in cereal grains during storage vary widely. The National Academy of Science [6] estimated the minimum overall losses as around 10% worldwide, with losses of up to 50% in tropical regions. The main cause of quality loss and spoilage is the action of deleterious

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microorganisms, which interact among themselves, with the grain, and with the environment of the storage facilities [7]. The concept of stored-grain ecosystem is used to describe all these interrelated biotic and abiotic factors affecting the grains, with the goal of preserving the harvested grains with minimum losses in their quantity and quality [7]. A better understanding of all these interacting factors has paved way for the development of efficient grain storage systems in the last decade [8].

Historically, thousands of years ago, the ancient Egyptians were known to store harvested grains. The Bible and Quran describe the famous story of Jacob's son, Joseph, who ordered the storage of harvested grains in ancient Egypt in the years of abundance to overcome seven years of severe grain shortage. Old scriptures have also described the details of several practices used by the ancient Egyptians for protection of stored grains from pests using dusting, fumigation, volatilization, or pyrolysis of incense [9]. More recently, several methods have been developed for efficient mass storage of grains. Efforts to reduce or eliminate the use of harmful chemicals to control deleterious fungi and mycotoxin production in stored grains include the screening and selection of antagonistic bacterial strains with antifungal and anti-mycotoxin activities [10-12]. Environmental control by manipulation of the ecological factors at the storage facilities remains a basic and efficient measure for controlling fungal contamination in stored grains. Fungal growth on stored grains is an obvious signs of poor quality grains from the aspects of diminished sensory quality and nutritional value. Mycotoxins produced by the grain fungi also pose a health hazard to animals and humans.

In this review, we discuss (1) the different groups of fungi contaminating grains at different time periods from preharvest to postharvest stages, (2) mycotoxins and their related fungi, (3) the effects of environmental conditions such as temperature and water activity (a_w) on deleterious fungi and a detailed consideration of the major mycotoxins with a focus on molecular aflatoxin suppression, and (4) controlled or modified atmosphere conditions for the management of deleterious fungi and mycotoxin production during grain storage.

CLASSIFICATION OF FUNGI CONTAMINATING STORED GRAINS

The fungi that contaminate grains are divided into two main groups and a third intermediate group based on their predominance at different stages of crop growth and harvest as affected by environmental conditions (Fig. 1) [5, 13-15]. The first group is field fungi that can colonize the ripening grains on standing crops in the field prior to harvesting. This group includes species of the genera *Alternaria* and *Fusarium*. Most of the field fungal species do not infect the crops after harvesting; however, they can produce mycotoxins before or just after harvesting [5, 16]. The second group is the storage fungi that can be present in small numbers prior to harvesting, or can contaminate grains during harvesting and increase in numbers during storage as the environmental conditions favor the growth of these fungi over the growth of other groups. Storage fungi mainly include species of the genera *Aspergillus* and *Penicillium* [17, 18]. In Korea, *Aspergillus candidus*, *Aspergillus flavus*, *Aspergillus fumigatus*, *Penicillium fellutanum*, and *Penicillium islandicum* are the most predominant fungal species observed in stored rice grains [19-22]. The intermediate fungal group comprises of fungi that continue to develop in storage if a_w remains high. This group includes species of the genera *Cladosporium*, *Fusarium*, and *Trichoderma* [13-15]. Wilson *et al.* [23] argued that location must be considered in the classification of field versus storage fungi because the occurrence of storage fungi in the field might increase in lower latitudes. As a consequence, a specific fungal species could be

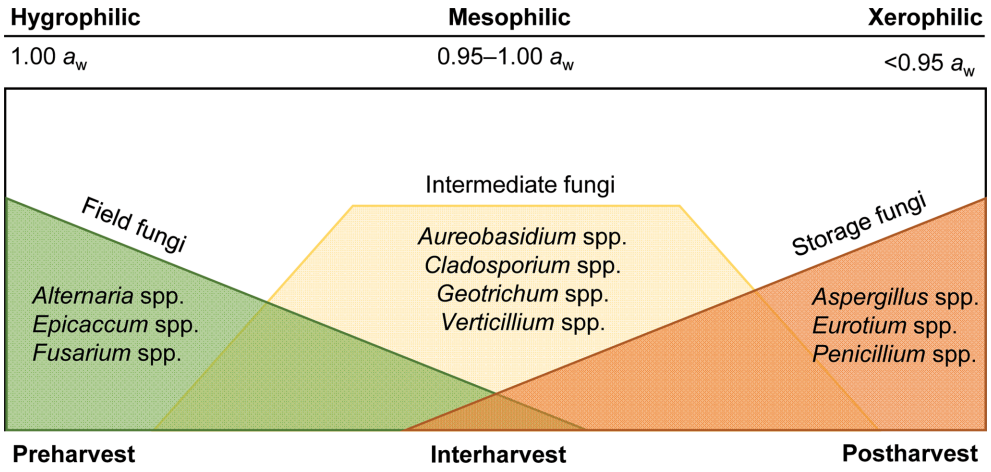

Fig. 1. Classification of fungal groups based on their stages of occurrence and dominance from preharvest to postharvest stages of field crops. The top scale represents the alternate classification of fungal species on grains based on their water activity requirements (i.e., optimum water activity [a_w]) for fungal growth [5, 13-15].

classified as a storage fungus in one location and as a field fungus in another. More information is needed about field and storage fungi from different latitudes to define the effect of location, along with the environmental factors responsible for fungal contamination of grains [23]. Fungal contamination at the preharvest stage is governed mainly by interactions with host plants, genotype, soil types, and biological factors. At the postharvest stage, fungal growth and development are governed by the substrate status (grain damage and nutritional constituents), environmental factors (temperature and moisture), and biotic factors (insect pests and microorganisms) [18, 24].

The main environmental factors governing the predominance of fungal groups on grains are a_w and the eco-physiological requirements of each fungal group. On standing crops before harvest, hygrophilic fungal species dominate and generally disappear after a few months in storage. After harvest, these fungal species are replaced by mesophilic fungal species that persist during storage as long as a_w supports their growth. Finally, xerophilic fungal species are the dominant species present under storage conditions, when a_w drops beyond the limits of growth for hygrophilic and mesophilic fungal species. The most xerotolerant fungal group is the genus *Aspergillus* followed by the genus *Penicillium* [15]. The fungal groups were categorized based on optimum a_w for growth of xerophiles, mesophiles, and hygrophiles being < 0.95, 0.95 to < 1.00, and 1.00, respectively [13]. The mesophilic fungal group, in this case, is confusing because this term is usually used to describe temperature requirements of microorganisms rather than a_w. Hocking and Pitt [25] suggested a slight modification to the above a_w criteria, with xerophiles considered to be fungi capable of growth at $a_w \leq 0.85$.

Miller [18] identified four different types of pathogenic and mycotoxigenic fungi. The first type comprises fungi that are pathogenic to plants (e.g., *Fusarium graminearum*); the second type includes fungi that infect stressed and weak plants (e.g., *Fusarium moniliforme*); the third type comprises fungi that contaminate standing plants and produce mycotoxins after harvest (e.g., *A. flavus*); and the fourth type includes fungi that are present in soil or decaying plant debris, contaminate developing grains on standing plants, and develop during storage when conditions are suitable for their growth (e.g., *Aspergillus ochraceus* and *Penicillium verrucosum*). This classification is somewhat confusing, particularly since types 3 and 4 can be combined due to their similar eco-physiological requirements. Nevertheless, the classification is valuable since it emphasizes the role of environmental factors in determination of the dominant fungi at different stages of grain crop growth and harvest.

MYCOTOXINS IN STORED GRAINS

Mycotoxins are low molecular-weight, secondary metabolites that are produced by certain fungal species mainly belonging to the genera *Aspergillus*, *Fusarium*, and *Penicillium*. Mycotoxins are toxic to humans and animals, and cause a wide range of disorders from gastroenteritis to cancer [26]. Mycotoxin contamination of food and feed was first verified in the 1960s after a large number of turkeys were supplied with *A. flavus*-contaminated feed [27]. However, in 1881, as described by Pitt [28], extracts from rice infected with *P. islandicum* were reported to induce animal mortality. The term mycotoxicosis is used to describe the non-infectious, non-contagious, and non-transferable fungus-related toxic effects on humans or animals upon ingestion of mycotoxin-contaminated food or feed [29].

Mycotoxins have been a health threat for millennia. For example, ergotism, originally known as "St. Anthony's fire," resulted in massive death in Europe during the middle ages. It was shown to be related to toxins (*i.e.*, ergot alkaloids) produced by the ergot fungus (*Claviceps purpurea*), having various toxic effects on humans and animals [30]. In 1891, toxicity of rice grains contaminated with mold was observed in Japan; this was later referred to as "yellow rice." This term describes the rice grains contaminated with certain species of *Penicillium* that are toxic to several animals and cause grain discoloration in rice [31]. Another infamous historic outbreak of a mycotoxin-induced disease or mycotoxicosis is alimentary toxic aleukia (ATA) associated with the *Fusarium* toxin T-2, in Russia during the World War II. Thousands of ATA cases resulted from the consumption of poor quality and overwintered grains left in the field [18]. Subsequently, the disease was determined to be caused by the T-2 toxin produced by a *Fusarium* sp. during growth on wet grains overwintered in the fields [32]. More recently, in western India and Kenya, outbreaks of hepatitis with rapidly developing symptoms affected several hundred people and caused many deaths. The culprit was aflatoxicosis, which is developed due to the consumption of grains heavily contaminated with aflatoxins [33, 34].

Of the thousands of reported fungal species, only around 100 species can produce various mycotoxins. The mycotoxin-producing fungi primarily belong to the genera *Aspergillus*, *Fusarium*, and *Penicillium*. Several hundred mycotoxins have been isolated and chemically characterized; however, relatively low numbers of mycotoxins can develop on foods and feeds. Among these aflatoxins, ochratoxins, deoxynivalenol, zearalenone, fumonisin, trichothecenes, and patulin significantly contaminate stored grains [35]. According to the Food and Agriculture Organization (FAO), 25% of the world's food crops are contaminated with significant amounts of mycotoxins, mainly in tropical regions [26]. The major mycotoxins, causal fungi, and biological activities are summarized in Table 1 [26, 29, 36, 37]. High humidity and temperature in the tropical and subtropical regions than in the temperate regions increase the susceptibility of crops to mycotoxin contamination [38]. Therefore, global climate changes are expected to cause a more serious problem when some mycotoxigenic fungal species are likely to dominate others. For example, *A. flavus* is likely to dominate other

Table 1. Major mycotoxins and their related fungi and toxicity to humans and animals

Mycotoxin	Major food	Mycotoxin-producing fungal spp.	Toxicity to humans and animals	Reference
Aflatoxins	All cereal grains	*Aspergillus flavus*, *Aspergillus parasiticus*	Acutely toxic, immunosuppressive, mutagenic, teratogenic, carcinogenic	[26, 29]
Alternaria toxins	All cereal grains	*Alternaria*	Esophageal cancer	[36]
Deoxynivalenol	All cereal grains	*Fusarium graminearum*	Vomiting, feed refusal	[26]
Trichothecenes	All cereal grains	*Fusarium*	Alimentary toxic aleukia, decrease in immune responses, nausea, vomiting	[26, 29]
Ergot alkaloids	Rye, wheat	*Claviceps purpurea*, *Aspergillus*, *Penicillium*, *Rhizopus*	Neurotoxic, gangrenous, edema, causing severe pains, paresthesias	[26, 37]
Fumonisin	Maize, rice	*Fusarium moniliforme*	Possible carcinogen for humans, equine encephalomalacia pulmonary edema in pigs, esophageal carcinoma	[26]
Ochratoxin	All cereal grains	*Penicillium verrucosum*, *Aspergillus ochraceus*	Nephrotoxic, immunosuppressive, carcinogenic, teratogenic	[26, 29]
Patulin	Rice	*Penicillium expansum*	Hemorrhage, possibly carcinogenic	[26]
Sterigmatocystin	All cereal grains	*Aspergillus versicolor*	Hepatotoxic, carcinogenic	[26]
Zearalenone	Wheat, corn, rice	*Fusarium graminearum*	Estrogenic not acutely toxic	[26]

fungal species that have a lower optimum temperature for growth [39]. Thus, aflatoxin produced by this fungus might become the major mycotoxin of concern. Several studies have indicated that climatic changes could affect important crops and mycotoxigenic fungal contamination [39-41].

Human and animal health hazards associated with mycotoxin contamination of food and feed have prompted about 100 countries to formulate regulations concerning the allowable levels of mycotoxins [42]. In general, the allowed level of aflatoxins in food destined for human consumption is 4–30 parts per billion (ppb) [43]. The strictest level of total aflatoxin (4 μg/kg body weight [BW]) is in the European Union (EU). In the United States, the acceptable limit is 20 μg/kg BW [42]. On the other hand, for ochratoxin A, the provisional tolerable weekly intake is 100 ng/kg BW [44]. Strict control of food and feed contamination are crucial to reduce the human and animal health risks due to mycotoxins [29]. In the following section, the effect of environmental factors on mycotoxigenic fungi and major mycotoxins found in cereal grains are discussed.

FACTORS AFFECTING FUNGAL GROWTH AND MYCOTOXIN PRODUCTION IN STORED GRAINS

In the stored-grain ecosystem, several intrinsic and extrinsic factors interact and affect the etiology, dominance, and toxin production of mycotoxigenic fungi. It is important to note that the conditions favorable for fungal growth and development in stored grains are not always conducive for

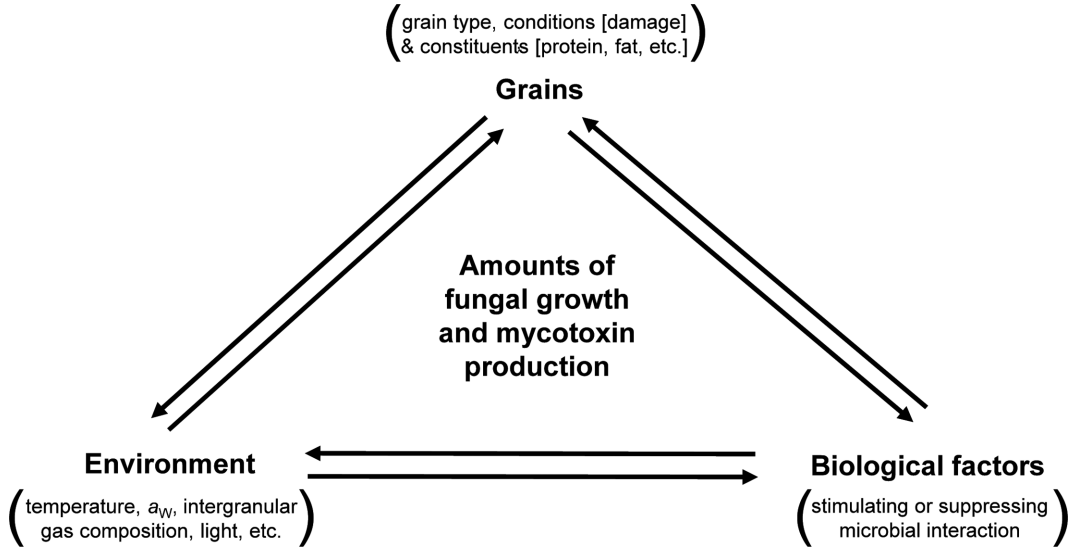

Fig. 2. Illustration of the main interrelated factors affecting fungal growth and mycotoxin production in the stored-grain ecosystem. The interactions among the three main factors (grain type, biological factors, and environment) can control the occurrence and dominance of fungal species on grains, and the type and amounts of the mycotoxins produced.

mycotoxin production. The general factors influencing fungal growth and mycotoxin production on stored grains are illustrated in Fig. 2. Fungal growth and mycotoxin production are principally controlled by various environmental or ecological factors including temperature, water availability, pH, light, and nature of substrate. These conditions vary immensely among different fungal species, and even within isolates of the same species. Therefore, it is difficult to describe a single set of optimum conditions for fungal growth and mycotoxin production [45]. The minimum and optimum temperatures and a_w for growth and mycotoxin production of the major mycotoxigenic fungal species are summarized in Table 2 [15, 24, 46-53].

Environmental factors also affect several physiological processes that are important for fungal survival and competition. The expressions of hydrolytic enzymes including β-D-galactosidase, α-D-galactosidase, *N*-acetyl-β-D-glucosaminidase, β-D-fucosidase, and β-D-xylosidase are affected by a_w, particularly during the early stages of development. These enzymes play an important role in the establishment of fungal populations on substrates [54]. In addition, carbon source utilization is affected by environmental conditions. The use of carbon sources and niche overlap index (NOI) of individual fungal species depend on a_w and temperature [50, 55]. The NOI is based on the difference between the number of carbon sources utilized by an individual fungal species and those commonly utilized by the coexisting fungal species. This index is a useful tool to illustrate the competition ability of a fungal species in a given ecosystem [54].

The main environmental determinants affecting grain fungi and mycotoxin production during storage are water availability and temperature [7]. Estimation of the water content of grains is not sufficient to indicate the water available for microbial growth. However, equilibrium relative humidity (ERH), a_w, or water potential (Ψ) can be used to measure water availability. ERH and a_w are the main parameters used in the studies for evaluating the effect of water availability on grain fungi. ERH represents the percent relative humidity of the air between grains in equilibrium

Table 2. Minimum and optimum temperatures (Tm) and water activity (a_w) for fungal growth and mycotoxin production

Fungi	Toxin	Fungal growth/mycotoxin production				References
		Minimum Tm (°C)	Optimum Tm (°C)	Minimum a_w	Optimum a_w	
Alternaria alternata	Altenuene, alternariol, alternariol monomethyl ether	–	21/25	0.88/0.88–0.89	0.982/>0.97	[24, 46]
Alternaria alternata	Tenuazonic acid	–	21/20	0.88/0.90–0.93	0.982/>0.97	[24, 46]
Alternaria tenuissima	Tenuazonic acid	10/10	20/20	0.85/0.85	1.00/1.00	[24, 47]
Aspergillus amstelodami	Sterigmatocystin	6/–	–	0.70/–	–	[48]
Aspergillus candidus	Kojic acid	10/–	–	0.75/–	–	[48]
Aspergillus carbonarius	Ochratoxin A	8/–	35/25–30	0.80/0.83–0.87	0.93–0.987/0.98	[24]
Aspergillus chevalieri	Gliotoxin, xanthocillin, sterigmatocystin	10/–	–	0.71/–	–	[48]
Aspergillus flavus	Aflatoxin	–/8	35/28	0.78–0.84/0.84	0.95/0.99	[15, 24, 49]
Aspergillus fumigatus	Fumigillin, gliotoxin	12/–	–	0.82/–	–	[48]
Aspergillus nidulans	Kojic acid, sterigmatocystin	12/–	–	0.83/–	–	[48]
Aspergillus niger	Oxalic acid	12/–	35/–	0.85/–	0.99/–	[48, 50]
Aspergillus ochraceus	Ochratoxin A	–	30/25–30	0.77/0.83–0.87	0.96–0.98/0.98	[15, 51, 52]
Aspergillus oryzae	Kojic acid, oryzacidin	–	–	0.86/–	–	[48]
Aspergillus parasiticus	Aflatoxin	–	35/33	0.81–0.82/–	0.95/0.99	[24]
Aspergillus versicolor	Sterigmatocystin	6/–	–	0.83/–	–	[48]
Cladosporium herbarum	Epicladosporic acid	–7/–	–	0.88/–	–	[48]
Fusarium graminearum	Zearalenone	–	–/25–30	–/0.90–0.91	–/0.98	[24]
Fusarium spp.	Fumonisins	4/10	30/15–30	0.90/0.93	_	[53]
Fusarium spp.	Deoxynivalenol	5–10/11	20–25/29–30	0.90–0.91/0.90	0.98–0.99/0.99	[24]
Penicillium aurantiogriseum	Ochratoxin A	–	–	0.82–0.85/0.87–0.90	–	[15]
Penicillium brevicompactum	Mycophenolic acid	–2/–	–	0.81/–	–	[48]
Penicillium citrinum	Citrinin	12/–	–	0.80/–	–	[48]
Penicillium clavatus	Patulin	12/–	–	–	–/0.99	[24]
Penicillium expansum	Patulin	0/1–4	–	0.82–0.85/–	–/0.99	[15, 24]
Penicillium islandicum	Islanditoxin, luteoskyrin	10/–	–	0.83/–	–	[48]
Penicillium patulum	Patulin	4/–	–	0.81/–	–/0.95	[15, 24]
Penicillium verrucosum	Ochratoxin A	0/–	–/25	0.80–0.81/0.83–0.85	0.95/0.90–0.95	[15, 24]
Stachybotrys atra	Stachybotryotoxins	2/–	–	0.94/–	–	[48]

–, not reported.

with water in the grains. On the other hand, a_w is the ratio of the water vapor pressure above the grains to that above pure water at the same temperature and pressure [56]. The a_w as a measurement of water availability has replaced moisture content measurement as a more useful and precise expression of water availability for microbial growth. As the water available for microbial growth is reduced, a_w becomes lower [48]. The significance of the major mycotoxins contaminating stored grains and the influence of temperature and a_w on fungal growth and mycotoxin production are discussed next.

Aflatoxins. Aflatoxins are the most significant mycotoxins that contaminate various agricultural and food products. They are the most potent carcinogens with immunosuppressive, mutagenic, and teratogenic activities in humans and animals [29, 57]. There are several types of aflatoxins. For example, aflatoxins B_1, B_2, G_1, and G_2 are most important; aflatoxins M_1 and M_2 are the metabolic products of oxidation of aflatoxin B_1 in humans and animals following ingestion [29]. Aflatoxin B_1 is the most toxic substance and is classified as a Class 1 carcinogen by the International Agency for Research on Cancer (IARC), based on the evidence of its carcinogenicity in humans after the evaluation of epidemiological and laboratory results [58]. Continuous exposure to low doses of aflatoxins might be carcinogenic and high doses can result in acute toxicity leading to death [59]. Malnutrition, along with the chronic intake of aflatoxin, may also result in immunosuppression, impaired growth, and other diseases [60]. An association between the dietary intake of aflatoxins in contaminated food and high incidence of liver cancer was concluded from epidemiological studies conducted on human subjects exposed to aflatoxin-contaminated food [35].

Aflatoxins are produced by species of *Aspergillus* section *Flavi*, primarily *A. flavus* and *A. parasiticus*. These two species are ubiquitous present in some foods and stored agricultural products. Other species reported to produce aflatoxins include *Aspergillus arachidicola*, *Aspergillus minisclerotigenes*, and *Aspergillus nomius* [61, 62]. The major source of contamination in cereal grains is the conidia of toxin-producing fungi in the field, which can continuously grow and contaminate the grains [63]. The aflatoxin-producing fungi may form sclerotia in damaged grains before harvest, which can be dispersed in the soil during harvesting. The sclerotia can survive in soil and remain viable to regenerate conidiophores and conidia in subsequent growing seasons, leading to repeated contamination of grains [64].

As mentioned above, the optimum conditions for the germination and growth of mycotoxigenic fungi are not always conducive for toxin production. This has been observed in the growth and aflatoxin production by *A. flavus* and *A. parasiticus*. The fungal growth occurs over a narrower range of conditions than germination. Moreover, aflatoxin production occurs over a narrower range of conditions than fungal growth. Hill *et al.* [65] reported that the optimum temperature and a_w for fungal growth were 35°C and 0.95, respectively; however, the optimum temperature and a_w for aflatoxin production by these two species were 33°C and 0.99, respectively. The effects of environmental conditions on aflatoxin production by *A. flavus* and *A. parasiticus* have been studied. Klich [66] reported that the optimum temperature for aflatoxin production can vary between 24–30°C depending on the strain and substrate type. Earlier, Sorenson *et al.* [49] reported that the optimum temperature for aflatoxin production by *A. flavus* on rice grains was 28°C, with considerable toxin production still evident at 32°C. Temperatures above 32°C markedly hinder aflatoxin production even though fungal growth was enhanced. The toxins are not produced at 8°C. Abdel-Hadi *et al.* [67] reported that optimal growth of *A. flavus* is at 30–35°C and 0.99 a_w, whereas the optimum conditions for aflatoxin production are 25–30°C at 0.99 a_w and 30–35°C at 0.95 a_w. The suppression of aflatoxin production at temperatures higher than 32–35°C has been described in several other studies [68-70]. Kheiralla *et al.* [71] demonstrated that aflatoxin production was not correlated to fungal growth at temperatures higher than 30°C. In that study, variations in the optimum temperature for aflatoxin production were observed between different isolates of *A. flavus*. They also reported that maximum aflatoxin production occurred at 25–30°C 14 days after incubation. However, the fungal growth expressed as mycelial dry weight in that study continuously increased with increasing temperature, with maximum growth at 35°C. A recent study on corn grains described the significant increase in aflatoxin production by increasing the temperature from 30 to 37°C [72]. In contrast, Yu *et al.* [73] reported almost complete cessation of aflatoxin production at 37°C on laboratory media. Medina *et al.* [72] suggested that the short incubation period of broth cultures could be responsible for the lack of aflatoxin production at 37°C in the latter study. However, other possible explanations for the two contrary findings are the use of different strains and, in the study by Medina *et al.* [72], use of corn as the substrate. This substrate could possibly create a micro-environment within individual kernels that might offer slightly different conditions than expected. Thus, the comparison of fungal strains cultured in broth might yield different results.

While evaluating the effect of a_w on aflatoxin production, Faraj *et al.* [74] reported that a_w has a higher influence on aflatoxin production than temperature. On the contrary, Mousa *et al.* [68] found that temperature had a higher influence on aflatoxin production than a_w. This dichotomy may be due to the different values of a_w used in both studies, which could be below the optimum range for toxin production in the first study. More precisely, Medina *et al.* [72] reported that variations in a_w exert a more profound effect on aflatoxin production, which was confirmed by higher changes in aflatoxin-related gene expression. Mousa *et al.* [68] found that aflatoxins were produced at

temperatures ranging from 20 to 40°C, with continuous increase noted with increasing a_w in the range of 0.82 to 0.92. At 40°C, only a minute quantity of aflatoxins was observed at a_w of 0.92. Cuero *et al.* [75] reported that the optimum growth for *A. flavus* on maize extract agar occurred at 0.95 a_w, while maximum aflatoxins were produced at 0.98 a_w. Similarly, Zhang *et al.* [76] observed more aflatoxin production at 0.99 than at 0.93 a_w, which correlated with the corresponding regulation of the aflatoxin biosynthesis gene cluster.

The characterization of aflatoxin biosynthesis pathway has facilitated the understanding of the roles of different structural and regulatory genes in the aflatoxin production process [77, 78]. Recently, sequencing and annotation of the *A. flavus* genome has paved the way for different molecular approaches, such as reverse transcriptase real-time polymerase chain reaction, microarrays, and RNA-sequencing (RNA-Seq), which are being used to study the behavior of aflatoxigenic fungal species under various environmental conditions [79]. The effect of temperature on aflatoxin production by *A. flavus* and *A. parasiticus* could be explained by understanding the changes in the expression of aflatoxin-related genes in the fungi with temperature [80]. In the latter study, at 37°C, the level of expression of aflatoxin production-related genes was reduced, with the consequent suppression of aflatoxin production. Abdel-Hadi *et al.* [81] confirmed the positive correlation between the expression of an early structural gene (*aflD*) and aflatoxin B_1 production. In a similar study, Schmidt-Heydt *et al.* [82] reported that two transcriptional pathway regulatory genes, *aflR* and *aflS*, are expressed at lower levels at temperatures above 37°C, which results in suppression of aflatoxin production. Additionally, the interactions between temperature and a_w were correlated with the ratio of these transcriptional regulatory genes. Increasing *aflR* and *aflS* ratios were associated with increasing aflatoxin B_1 production [82, 83]. Likewise, Yu *et al.* [73] studied the gene expression and aflatoxin production at 30 and 37°C using RNA-Seq technology. Aflatoxin production was confirmed to be one of the most tightly regulated processes in fungal cells. They

Table 3. Observations and comments regarding the influence of temperature and water activity (a_w) on the regulatory genes governing the transcription of the aflatoxin biosynthesis gene cluster

Observation	Comment	References
High temperature (37°C) resulted in the reduction of aflatoxin production by down-regulation of *aflR* expression, responsible for transcriptional activation of the aflatoxin biosynthesis pathway genes	AFLR protein was also present at low levels at 37°C, which suggests that other factors might also be involved in the transcriptional regulation of the aflatoxin biosynthesis pathway genes	[86]
General up-regulation of aflatoxin biosynthesis-related genes but no difference in the expression levels of two regulatory genes (*aflR* and *aflS*) between 28 and 37°C	Aflatoxin suppression at high temperatures might not be related to the inhibition of transcription of *aflR* or *aflS*, but possibly because AFLR is nonfunctional at high temperatures	[80]
A relationship was observed between the *aflS*:*aflR* ratio and aflatoxin production, which was affected by temperature and a_w	High *aflS*:*aflR* ratios were correlated with the production profile of aflatoxin G_1, while a low ratio was related to aflatoxin B_1 biosynthesis	[83]
Using the highly sensitive RNA-sequencing technology, the expression levels of *aflR* and *aflS* were evaluated to be 5 and 24 times higher at 30°C than at 37°C	Temperature-induced aflatoxin suppression is through the down-regulation of *aflR* and *aflS*, which results in the inactivation of transcription of the structural genes. The authors refuted the contrary results by O'Brian *et al.* [80] stating lower sensitivity associated with microarray gene expression analysis	[73]
Temperature and a_w influenced the relative expression of eight major aflatoxin biosynthesis genes, including the regulatory genes (*aflR* and *aflS*); consequently, aflatoxin production was affected	The optimum conditions for aflatoxin production by *A. flavus* were 25–30°C at 0.99 a_w and 30–35°C at 0.95 a_w	[67]
High expression of the two regulatory genes (*aflR* and *aflS*) was observed at the aflatoxin production conducive (28°C) and non-conducive (20 and 37°C) conditions	Temperature could influence aflatoxin production by inducing the expression of structural biosynthesis genes (*aflD* and *aflO*), but not the regulatory genes (*aflR* and *aflS*)	[84]
A weak correlation was observed between the expression level of *aflR* and aflatoxin production on corn-based media	The *aflR* expression might not be a good indicator of aflatoxin production or possibly the sampling time frame for gene expression in that study did not allow for the detection of changes in *aflR*	[85]
Stress conditions (low a_w and high temperature) resulted in higher expression levels of the biosynthesis genes, in contrast with the previous studies, and aflatoxin production was significantly higher at 37°C than at 30°C on stored corn grains	The contrasting observation by Yu *et al.* [73] might be related to the short incubation period of 24–48 hr in liquid culture, which might be the reason for the lack of toxin production at 37°C	[72]

also reported that higher aflatoxin production was correlated with a 50% increase in the expression of aflatoxin biosynthesis genes at 30°C in comparison to that at 37°C. Moreover, higher expression levels were observed in the two transcriptional regulatory genes, *aflR* and *aflS*, at 30°C than at 37°C. Therefore, it can be concluded that at a temperature higher than 37°C, aflatoxin production is negatively affected by the down-regulation of the transcription of *aflR* and *aflS* [73]. Previously, Chang [87, 88] demonstrated that AFLR proteins encoded by *aflR* in association with AFLS proteins encoded by *aflS* together regulate aflatoxin biosynthesis. They also showed a role of AFLS as a coactivator to the AFLR pathway regulator for transcription of the aflatoxin gene cluster. However, O'Brian *et al.* [80] observed no difference in the expression levels of *aflR* and *aflS* in *A. flavus* between 28 and 37°C. Consequently, they suggested that the aflatoxin biosynthesis regulatory protein does not function at elevated temperatures regardless of its expression level. Further, Gallo *et al.* [84] reported high expression of the *aflR* and *aflS* regulatory genes under conditions non-

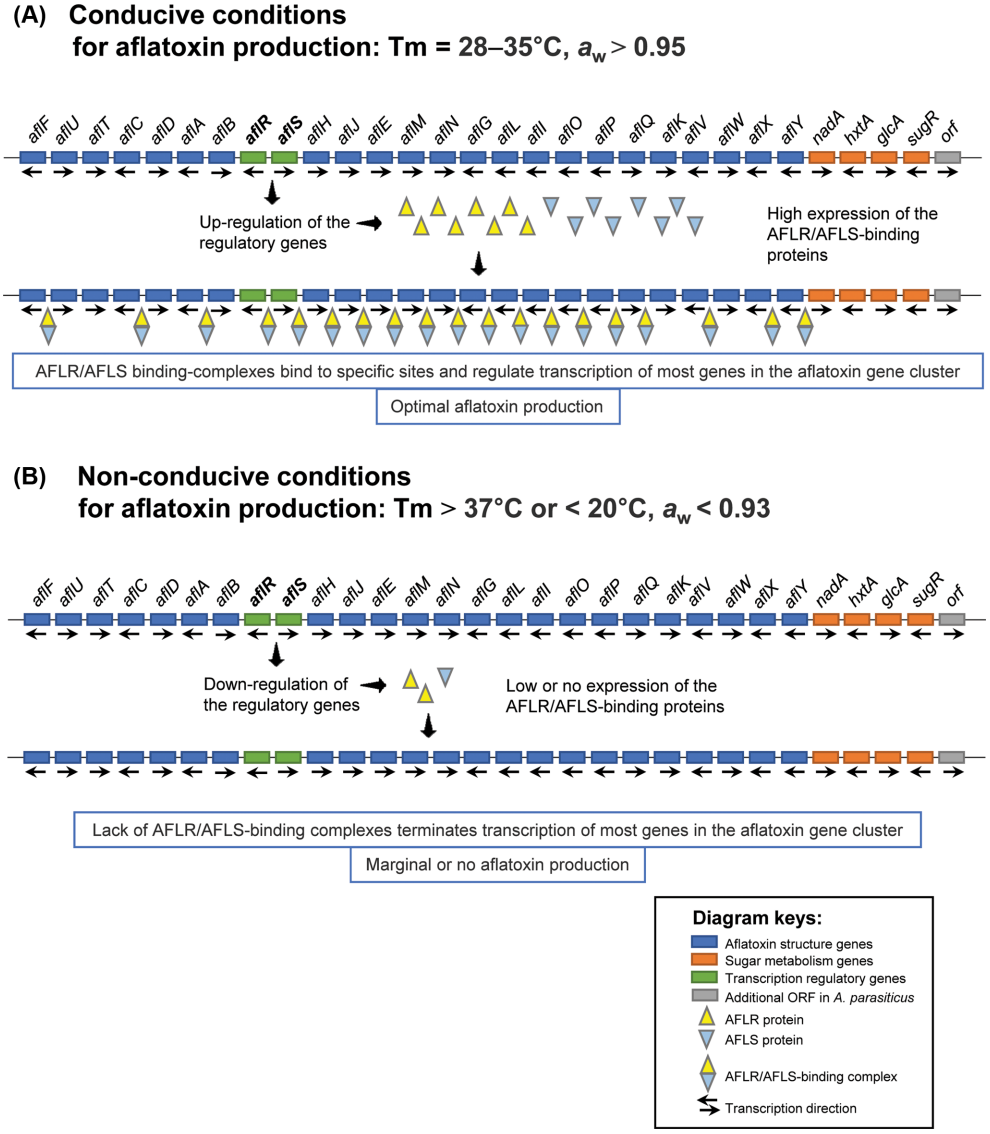

Fig. 3. Influence of temperature (Tm) and water activity (a_w) on the aflatoxin biosynthesis gene cluster (~80 kb DNA region) under conducive production conditions at optimum Tm (28–37°C) and a_w (> 0.95) (A), and non-conducive conditions at high (> 37°C) or low (< 20°C) Tm and low a_w (< 0.93) (B). The diagram shows the aflatoxin gene cluster in the toxin-producing fungi (e.g., *Aspergillus flavus* and *Aspergillus parasiticus*), emphasizing the roles of two transcription regulatory genes, *aflR* and *aflS*, in the regulation of aflatoxin production [78, 89]. The two genes are located in divergently adjacent positions within the gene cluster. It is hypothesized that the AFLR proteins (encoded by *aflR*) in association with AFLS proteins (encoded by *aflS*) bind to specific sites on the aflatoxin gene cluster to activate the transcription of most structural genes [84, 85, 90]. Aflatoxin production is a tightly regulated process that is affected dramatically by changing environmental conditions. The unfavorable conditions cause reduction in expression of the two regulatory genes, *aflR* and *aflS*, which results in the suppression of aflatoxin production.

conducive for aflatoxin production. Likewise, in a more recent study, Bernáldez *et al.* [85] found a weak correlation between the expression level of *aflR* and aflatoxin production. The authors demonstrated that *aflR* expression is not a good indicator for aflatoxin production in *A. flavus*. Further molecular research will be needed to identify other genes as indicators for aflatoxin biosynthesis. A possible explanation for the inconsistency could be that the mycotoxin production pathway-related gene expression levels in response to changing environmental factors may vary between strains. Variable observations and comments on the environment-induced aflatoxin suppression and roles of the regulatory genes in several previous studies are summarized in Table 3 [67, 72, 73, 80, 83, 84-86]. Based on the findings of the previous studies, a hypothetical mechanism of aflatoxin suppression under conducive or non-conducive temperature and a_w conditions highlighting the possible roles of *aflR* and *aflS* in the regulation of transcription of the aflatoxin gene cluster is illustrated in Fig. 3 [78, 87-90]. Further studies are required to confirm the hypothesized mechanism of aflatoxin transcription regulation and to identify novel target sites for controlling aflatoxin production, which may be helpful for the management of aflatoxin levels in food and feed.

***Alternaria* toxins.** Fungal species of the genus *Alternaria* can colonize a wide variety of plants as saprophytes or in some cases as fungal pathogens of specific crops. The most common species include *Alternaria alternata*, *Alternaria arborescens*, *Alternaria radicina*, and *Alternaria tenuissima*, which occur in several crops including cereals [54]. The significance of contamination of cereal grains with *Alternaria* spp. is the production of mycotoxins, particularly on grains that are not appropriately dried or which are damaged after harvesting [91]. Unlike *Aspergillus* and *Penicillium* spp., *Alternaria* spp. might not survive on grains with low moisture content [92]. *A. tenuissima* is the major species that predominates on cereals compared with other *Alternaria* spp. [93]. Several secondary metabolites with toxic activities have been isolated and chemically characterized from *Alternaria* spp. Among them, altenuene, alternariol, and alternariol monomethyl ether occur most frequently on cereal grains [94, 95]. Previously, Liu *et al.* [36] demonstrated that *A. alternata* is the causal agent of esophageal cancer in humans. The fungal isolate was obtained from grains in Linxian County, China, where the incidence of esophageal cancer was high. The extracts of this isolate were shown to be tumorigenic in mice.

For cereal grains (e.g., wheat), *A. alternata* and *Alternaria triticina* are the causal agents of the black point disease, which results in discoloration of the kernels and reduces grain quality. These *Alternaria* spp. can tolerate low temperatures and cause spoilage in vegetables during cooled transport [24]. Regarding the effects of a_w and temperature, it was reported that the limits for germination are lower than those for *A. alternata* growth, being 0.86 a_w for germination and 0.88–0.89 a_w for fungal growth and toxin production. Moreover, a narrower range of temperature is required for the production of toxic altenuene and alternariol monomethyl ether than for alternariol. Maximum production of the three toxins was observed at 25°C and $a_w > 0.97$ [24]. Studies on the influence of a_w and temperature on tenuazonic acid production by *Alternaria* spp. from sorghum and cottonseeds also revealed that a_w and time affected the optimum production [92]. On sorghum-based media, the minimum a_w for production was about 0.93–0.90. In another study conducted on *A. tenuissima* from cottonseed, the maximum tenuazonic acid production was obtained as 20°C and 37% water content (= 1.00 a_w), and the minimum toxin production was observed at 14.9% water content (= 0.85 a_w) [47]. In the same study, tenuazonic acid production was halved at 0.95 a_w. The results from these studies indicate that conditions for toxin production by different *Alternaria* species may vary immensely with respect to growth.

In an attempt to understand the roles of mycotoxins in a competing environment for fungal species in a given ecosystem, Müller *et al.* [96] incubated wheat kernels with two isolates of *Fusarium* spp. and two isolates of *A. tenuissima.* Before fungal inoculation, the wheat kernels were amended with the mycotoxins, alternariol and tetramic acid (*Alternaria* toxins), and deoxynivalenol and zearalenone (*Fusarium* toxins). Growth of *Alternaria* strains and mycotoxin production in wheat kernels supplemented with *Fusarium* mycotoxins were enhanced. Additionally, enhanced growth of *Alternaria* spp. resulted in degradation of the *Fusarium* mycotoxins on the wheat kernels substrate [96]. These results are meaningful for understanding the complex interactions between fungal populations of different genera and the possible roles of mycotoxins.

Fumonisins. Fumonisins are mycotoxins produced primarily by *Fusarium verticillioides* (formerly *F. moniliforme* = *Gibberella fujikuroi*) and other related fungal species. These mycotoxins were discovered and characterized about 20 years ago [97]. Since then, at least 15 fumonisin compounds were identified. Of these, fumonisins B_1 and B_2 are the most toxic and abundant, whereas fumonisins B_3, B_4, A_1, and A_2 are less toxic and occur in lower amounts [29]. Fumonisins have been associated with increased incidence of human esophageal cancer and a number of animal diseases [98]. It is classified by IARC as a class 2B possible human carcinogen [58].

Corn is the most susceptible host to contamination with fumonisin-producing fungi. A wide range of corn-based foods have been reported to be contaminated with these mycotoxins worldwide [99]. Contamination might initially occur in the field. During harvest, if the grains have a high moisture content, fungal growth can continue after harvest and fumonisins can accumulate to significant levels before drying and storage [24]. Fumonisin B_1 production is also subject to a narrow range of temperature and a_w than that

conducive for growth of the fungus. Although values might vary depending on the isolates, fungal growth was reported to occur between 4–37°C with an optimum temperature of 30°C, whereas fumonisin production can occurs between 10–37°C, with 15–30°C as the optimum temperature. Regarding the a_w required for growth and toxin production, 0.90 and 0.93 were recognized as the minimum values for growth and fumonisin B_1 production, respectively. Increased a_w was correlated with enhanced fungal growth and toxin production [24, 53].

Ochratoxins. Ochratoxin A is a potent nephrotoxin that is teratogenic, immunosuppressive, and carcinogenic. It is classified as a group 2B, possible human carcinogen based on sufficient evidences of its carcinogenicity in animals [58]. Ochratoxin A could increase the mutagenic ability of aflatoxin B_1 in cases of simultaneous occurrence in certain crops [100]. However, other studies showed that detection of ochratoxin A at high level was associated with the absence or reduction of aflatoxin B_1, suggesting a possible competition between these toxin-producing fungi on the substrate [35]. The major ochratoxin A-producing fungi are *Aspergillus carbonarius*, *Aspergillus melleus*, *A. ochraceus*, *Aspergillus sclerotiorum*, *Aspergillus sulphureus*, and *P. verrucosum*. Other species including *Aspergillus niger* and *Penicillium purpurascens* are also considered minor ochratoxin A producers [44].

Most studies related to the influence of temperature and a_w on the production of ochratoxin A have focused on *A. ochraceus*, which belongs to *Aspergillus* section *Circumdati* and is the major ochratoxin A-producing fungus contaminating cereal grains, particularly in temperate and tropical regions [101]. The niche overlap and dominance by *A. ochraceus* and consequent ochratoxin A production are influenced by temperature, a_w, and the interaction and competition with other fungi [102]. In a study on maize grains, at 30°C, the production of ochratoxin A was significantly higher at 0.95 than at 0.995 a_w. Regardless of the a_w level, ochratoxin production was significantly reduced by interaction with other fungal spp., such as *A. candidus*, on maize grains [102]. In another study, the influence of temperature and a_w on *A. ochraceus* growth and ochratoxin A production on barley grains was investigated, in which the toxin production occurred within a narrower range of a_w and temperature than the fungal growth [103]. In this study, the minimum a_w for fungal growth and toxin production was 0.85 and 0.90, respectively; the optimal growth and toxin production conditions were 30°C and 0.99 a_w. The differences in the reported minimum and optimum conditions for growth and ochratoxin production in the different studies could be related to the use of different substrates. The nutrient source can affect the minimum a_w for fungal growth and toxin production [104]. Madhyastha *et al.* [105] suggested that ochratoxin A production is not associated with rapid growth of *A. ochraceus*. Moreover, Häggblom [106] reported that the ochratoxin A production could be reduced at higher growth rates of the fungus.

The other major ochratoxin A-producing species is *P. verrucosum*, which is particularly problematic in cool climatic regions, contaminating inappropriately dried wheat and barley. This fungus can grow over a wide temperature range (0–35°C), with 25°C being the optimum temperature for toxin production on grains. It can produce the toxin at lower temperature (5–10°C) at its optimum a_w. The optimum a_w for ochratoxin A production is between 0.90 and 0.95, whereas the minimum a_w is 0.83–0.85. However, the optimum a_w for fungal colonization of stored grains is 0.95 [24]. Studies on the effects of temperature and a_w on the causal fungi have consistently shown that the range of temperature and a_w for toxin production is narrower than that for growth. However, ochratoxin A production by *P. verrucosum* could be an exception, as the fungus grows and produces ochratoxin A under similar temperature and a_w conditions [107].

Trichothecenes and zearalenone. Trichothecenes are a group of metabolites produced by a number of fungi, including the genera *Fusarium*, *Myrothecium*, *Phomopsis*, and *Trichoderma*, [27]. More than 148 trichothecenes have been identified; however, only a few toxins, such as deoxynivalenol (also known as vomitoxin), nivalenol, and T-2, are common contaminants of food and feed. Ingestion of contaminated food or feed in high doses can result in immune response reductions, nausea, and vomiting [29]. On the other hand, zearalenone is another mycotoxin produced by several *Fusarium* spp., primarily *F. graminearum* and other related species such as *Fusarium crookwellense*, *Fusarium culmorum*, and *Fusarium equiseti*, which are common contaminants of grains [108]. Zearalenone toxicosis causes estrogenic effects in many animals, which can lead to infertility, vulval edema, and feminization of males [29].

Magan and Lacey [109] studied the effect of temperature and a_w on the growth of several *Fusarium* spp. such as *Fusarium avenaceum*, *F. culmorum*, *Fusarium poae*, and *Fusarium tricinctum*. The optimum temperature for fungal growth was 20–25°C, with reduced growth at 5–10 and 35°C. At the optimum temperature, the optimum a_w was 0.98–0.995 and minimum a_w was 0.90–0.91 and 0.88 for germination. In another study, the optimum temperatures for deoxynivalenol production on corn grains having 30% moisture content was 29–30°C for *F. graminearum* and 25–26°C for *Fusarium roseum*, with about 11°C as the minimum temperature for toxin production by both fungi [110].

Most fungal species produce higher levels of mycotoxins at their optimum growth temperature. However, outbreaks of mycotoxicoses related to *Fusarium* species have occurred after exposure of the substrates to lower temperatures [111]. After the initial growth of *Fusarium* spp. at room temperature, subsequent incubation at a low temperature of 12–14°C resulted in higher toxin productions [112]. In agreement with this finding, Ryu and Bullerman [113]

observed maximum deoxynivalenol and zearalenone production by *F. graminearum* after incubation on rice cultures at 25°C for 2 wk followed by 4 wk at 15°C. These results indicate that low temperature stress on certain *Fusarium* spp. increases toxin production. On the contrary, the same study showed that increased incubation temperature resulted in enhanced fungal growth expressed as the amount of produced free ergosterol, which was not correlated with the production of deoxynivalenol and zearalenone. In another study conducted on a wheat-based agar medium, the optimum conditions for growth, and maximum production of deoxynivalenol and nivalenol by *F. culmorum* were observed to be 25°C and a_w of 0.995 and 0.981, respectively [114]. In this study, the observed difference in optimum a_w for the production of deoxynivalenol and nivalenol was, as claimed by the authors, related to the fungal response to stress conditions by producing the more toxic deoxynivalenol to improve competitiveness. Moreover, the production of both toxins in this study occurred at a narrower a_w range than that for fungal growth [114].

MODIFIED ATMOSPHERE FOR MANAGEMENT OF MYCOTOXIGENIC FUNGI DURING GRAIN STORAGE

Modified atmosphere storage is a method of food preservation that aims to extend the storage life and maintain the quality of food products. This is achieved mainly by creating an atmosphere around the food products that is enriched in CO_2 and low in O_2. These conditions reduce the respiration rate of food products and inhibit the activity of microorganisms [115]. The primarily advantage of this method is the reduction or even elimination of the use of harmful chemicals. However, there are practical, technical, and biological factors that might restrict the use of modified-atmosphere approach [45]. The modified atmosphere is different from controlled-atmosphere storage. The gas composition in the modified atmosphere is initially modified and then changes with the respiration rate or biological activity of the food products. In the controlled atmosphere, the gas composition is continuously controlled throughout the storage period [115].

Several studies have reported the inhibitory effect of modified atmosphere with raised CO_2 and reduced O_2 levels on the growth and mycotoxin production of deleterious fungal species. Earlier, reduction in aflatoxin production by *A. flavus* on peanuts using increased CO_2 concentration was reported [116]. Similarly, Shih and Marth [117] reported that aflatoxin production by *A. parasiticus* in a liquid medium was inhibited by increasing CO_2 or N_2 levels, with complete inhibition of the toxin production at 100% of both gases. Moreover, penicillic acid production was inhibited on corn kernels inoculated with *P. martensii* by increasing the CO_2 concentrations. The level of toxin reduction varied depending on the incubation temperature [118]. Paster *et al.* [119] observed the complete inhibition of ochratoxin A production by *A. ochraceus* at ≥ 30% CO_2, regardless of the O_2 level, with partial inhibition of colony growth at 60% CO_2 and no observed growth at 80% CO_2. A significant reduction was also observed in the T-2 production by *F. tricinctum* at CO_2 levels up to 50% and the O_2 level close to normal atmospheric level. Additionally, at CO_2/O_2 levels of 60%/20% and 80%/20%, the reduction of T-2 production was accompanied with reduction of the fungal growth expressed as colony diameter with 2–4 days delay in the appearance of colonies [120]. In another study, Paster *et al.* [121] observed almost complete inhibition of zearalenone production by *F. equiseti* in high moisture corn grains by increasing the CO_2 levels (20, 40, and 60%). More recently, Samapundo *et al.* [122] reported that increased initial headspace CO_2 concentration resulted in inhibition of fumonisin B_1 production by *F. verticillioides* and also affected *Fusarium proliferatum* growth.

Although most stored-grain fungi seem to be sensitive to elevated CO_2 levels, resistance to high CO_2 has been reported in several fungi, such as *Penicillium roqueforti*, which was found in sealed silos containing barley grain at 0.80–0.87 a_w and high CO_2 levels. Notably, fungal response to a modified atmosphere can vary immensely between different fungal species, and even between strains of the same species [45]. Furthermore, interactions with grain types (substrate), storage temperature, and a_w can also affect the fungal tolerance to low O_2 and high CO_2 [8].

CONCLUSIONS

Cereal grains are a very important source of food for the growing human population worldwide. Improved preservation and quantity and quality control of cereal grains are urgently needed to meet the increasing food demands. Grain contamination with mycotoxigenic fungi often deteriorates the quality of grains and leads to mycotoxin production. Mycotoxins are dangerous metabolic substances produced by deleterious storage fungi and can cause severe outbreaks of diseases in humans and animals. Therefore, they should be eliminated or minimized in food and feed by using various effective control measures. Environmental factors, such as temperature and a_w, can significantly influence fungal growth and mycotoxin production in stored grains. Understanding the effects of such factors on the stored-grain fungi will help in the development of efficient strategies for controlling or managing fungal contamination. In addition, there is a need for conducting studies on the influence of temperature and a_w on the molecular regulatory processes of mycotoxigenic fungi, which will facilitate the development of control measures to minimize mycotoxin production by the identification of targets for molecular control approach such as RNA silencing. The use of controlled or modified atmosphere is a potential alternative for the use of harmful agricultural chemicals during grain storage. Besides, further understanding of fungal interactions with different grain types at different storage temperatures

and a_w will help to improve the storage systems for grains. In this review, results of the considerable research efforts involving different grain types, fungal species, environmental conditions, and locations have been described. Thus, we hope that this review will not only help in the use of controlled or modified environmental conditions during grain storage, but also contribute towards understanding the diverse responses of different mycotoxigenic fungi to the environmental factors. Future studies should consider the integration of various fungal control methods, including environmental and biological measures, which would assure environmentally safe and sustainable storage of grains.

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