Chapter 1

Introductory Chapter: *Fusarium* - Pathogenicity, Infections, Diseases, Mycotoxins and Management

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1. Introduction

The genus *Fusarium* contains pathogens that can cause significant harm to humans, animals and plants by infecting vegetables, grains and seeds and causing diseases in humans and animals. *Fusarium oxysporum*, *F. solani* and *F. fujikuroi* complexes are of great importance worldwide especially as a plant, human and animal pathogen.

Identifying Fusarium species is not easy. Currently, scientists are focused on identifying *Fusarium* species using molecular techniques, such as genetic markers and polymerase chain reaction-restriction fragment length polymorphism, for analyzing the rDNA internal transcribed spacer region.

The aim of this book is to highlight the new information reported by numerous studies on *Fusarium* species. The primary aims of this book are the following:

(a) To provide an overview of historical importance and taxonomy of *Fusarium* species

(b) To understand the mechanism of *Fusarium* infections and the factors that cause the infections

(c) To discuss *Fusarium* species-caused diseases, pathogen diversity and host range in plants

(d) To discuss mycotoxin contaminations in cereals

(e) To discuss plant secondary metabolites as well as anti-fungal and anti-mycotoxigenic compounds

(f) To discuss plant-*Fusarium* interactions

(g) To discuss the antagonistic activity of *Trichoderma* and *Fusarium* species

h) To discuss genetic diversity, genetic resistance and molecular markers to investigate population diversity

(i) To discuss the environmental conditions that enable the opportunistic growth of *Fusarium*

(j) To discuss the distribution and evolution of the genes responsible for mycotoxin biosynthesis

(k) To discuss the steps that can be taken to prevent toxin production

(l) To discuss suitable approaches for *Fusarium* species disease management

(m) To discuss development of *Fusarium*-resistant cultivars to reduce the diseases caused by *Fusarium* species on a wide scale

2. Plant pathogens and cereals

Fusarium attacks numerous plants and cereals that are important for human and animal nutrition. It specifically infects certain parts of them, such as grains, seedlings, heads, roots or stem, and causes various diseases, reduced commercial yield, and decrease in product quality [1]. *Fusarium* head blight (FHB) [2, 3], foot (FR) and root rot (RR) [4] and crown rot (CR) are among the major diseases caused by them. FHB produced by *F. graminearum* (teleomorph Gibberella zeae, Schwabe) causes starch and protein losses in cereals [5]. *Fusarium* species are saprophytic and are found commonly growing on the plants as a pathogen. *F. proliferatum* is a plant pathogen that is capable of infecting many important crops. *F. oxysporum* f.sp. *cubense* (FOC) causes *Fusarium* wilt, which is the most destructive disease of banana [6]. Many *Fusarium* species from the *F. solani* species complex (FSSC) are pathogenic and virulent. FSSC causes diseases in many agriculturally important crops, such as FR and/or RR of the infected host plant and causes necrosis. Symptoms, such as wilting, stunting and chlorosis, vary widely according to FSSC pathogenesis and the host plant species. Necrosis depends on the severity of fungal development [4]. Two of the most serious diseases of wheat known globally are *Fusarium* CR and *Fusarium* FHB.

Stephens et al. [7] investigated the CR disease in wheat infected by *F. graminearum* and reported that CR developed in three stages. In the first stage, the *F. graminearum* biomass significantly increased within 2 days after inoculation. At this stage, there was germination of spores and superficial hyphal growth on the leaf sheath. In the second stage, the fungal biomass significantly decreased over 2 weeks. At this stage, the fungus penetrated from the outer parts of the leaf sheath to the leaf sheath base. In the third stage, biomass of *F. graminearum* increased significantly, and this increase correlated with fungal colonization on wheat and showed that the fungal biomass was being formed as fungal colonization on wheat crown parenchyma.

3. Fusarium infections in humans

Fusarium species cause superficial, locally invasive and diffuse infections in humans. Although *Fusarium verticillioides*, including *F. moniliforme* and *F. fujikuroi* species complex [8],

are opportunistic pathogens, the species in the *F. solani* complex include pathogenic species [9]. *F. solani*, *F. oxysporum*, *F. verticillioides* and *F. proliferatum* infect the immune-compromised patients. Sidhu et al. [10] reported that prevalent meningospondylodiscitis in an elderly diabetic patient caused by *F. oxysporum*. *F. sacchari*, *F. anthophilum*, *F. chlamydosporum* and *F. dimerum* was also thought as related to human disease. Guendouze-Bouchefa et al. [11] reported a rare case of perinephric abscess in a child caused by *F. chlamydosporum*.

The members of *F. solani* and *F. oxysporum* species complexes are known to include the agents that cause human infections worldwide. *F. solani* can adhere to and damage the corneal membrane [12]. Some *Fusarium* species, such as *F. dimerum*, are associated with keratomycosis, particularly in the bad hygiene conditions.

4. Fusarium diseases in animals

Fusarium mycotoxins affect the growth, reproduction and hormonal condition of the animal. The effect of these mycotoxins on animals depends on the quantity of mycotoxin intake. After intake, these mycotoxins arrive at the gastrointestinal epithelial cell layer which is covered by the mucous secreted from goblet cells [13, 14].

Although deoxynivalenol (DON) and fumonisin-B1 (FB1) increase the permeability of intestinal epithelial cell layer in humans, animals and birds, they worsen the viability and proliferation of intestinal epithelial cells. High doses of mycotoxins may cause abdominal distress, diarrhea, cardiac insufficiency, emesis and even death in pigs and equine leukoencephalomalacia (ELEM) in horses [15]. Through *in vivo* and *in vitro* experimental studies, Cortinovis et al. [16] demonstrated that ZEN and its metabolites markedly up-regulated estrogen secretion in the reproductive organs.

ZEN is closely associated with infertility, decreased milk production and hyperestrogenism [17]. Cortinovis et al. [16] reported that ZEN directly affect ovarian cells and alter oocyte maturation under in vitro conditions; conversely, under in vivo conditions, this mycotoxin affected ovulation and puberty onset and caused morphological and functional disorders. T-2 toxin (T-2) causes cutaneous lesions in the mount and intestinal membrane and reduces egg production in poultry [18].

5. Mycotoxins and mycotoxin-producing conditions

Fusarium mycotoxins are very common worldwide. They exist in many plants and in various compositions. The major *Fusarium* mycotoxins are FB1, trichothecenes [e.g. DON, nivalenol (NIV), T-2 and ZEN] [19–21]. The most important species that is common in Europe is *F. graminearum*. In the past, *Fusarium* genus members were mostly not considered as pathogens in the field. However, *F. proliferatum* and *F. verticillioides* are of great importance as the main producers of the most dangerous *Fusarium* mycotoxins [22, 23]. Worldwide mycotoxin occurrence in maize and wheat/bran samples with their median and maximum levels were given in **Figure 1** [24, 25].

Shi et al. [5] evaluated the mycotoxins from 20 of the most common *Fusarium* species and sorted them into the following three groups based on their molecular characterization (**Figure 2**). Group-1 comprised fusaric acid producers and was further divided into two subgroups. Subgroup-I comprised *F. fujikuroi*, *F. solani*, *F. verticillioides* and *F. proliferatum* that produce fusaric acid and fumonisins; subgroup-II comprised *F. musae*, *F. equiseti*, *F. temperatum*, *F. subglutinans*, *F. tricinctum*, *F. oxysporum*, *F. concentricum*, *F. sacchari* and *F. andiyazi* that produce only fusaric acid. According to the classification of *Fusarium* mycotoxins, type-A trichothecene producers comprising *F. polyphialidicum*, *F. sporotrichioides* and *F. langsethiae* formed the Group-II, and type-B trichothecene producers comprising *F. meridionale*, *F. culmorum*, *F. graminearum* and *F. poae* formed Group-III.

In the presence of *Fusarium* species in plants, the contamination with fumonisins was shown in wheat [26], garlic [27], and asparagus [28]. The most affected plants, that is, maize, beans, soybean [29], rice [30], and sorghum [31] were specifically infected by *Gibberella fujikuroi* species complex (*F. proliferatum, F. verticillioides* and *F. andiyazi*) [29, 32].

Guidance values for *Fusarium* mycotoxins were set in Commission Recommendation 2006/576/EC [33]. Recommended values for the *Fusarium* mycotoxins DON, ZEA and fumonisins were set in "Commission Recommendation 2006/576/EC" [33]. For T-2 and HT-2 toxin, indicative

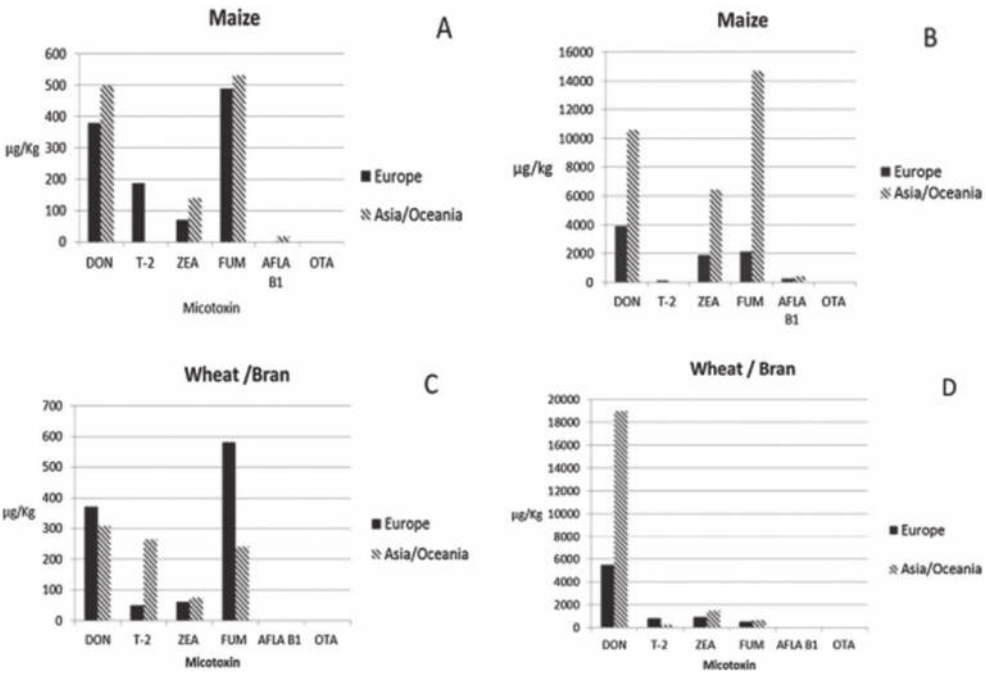

Figure 1. Worldwide mycotoxin occurrence (µg/kg) in maize and wheat/bran samples (A, C: Median of positive samples; B, D: Maximum levels) [24, 25].

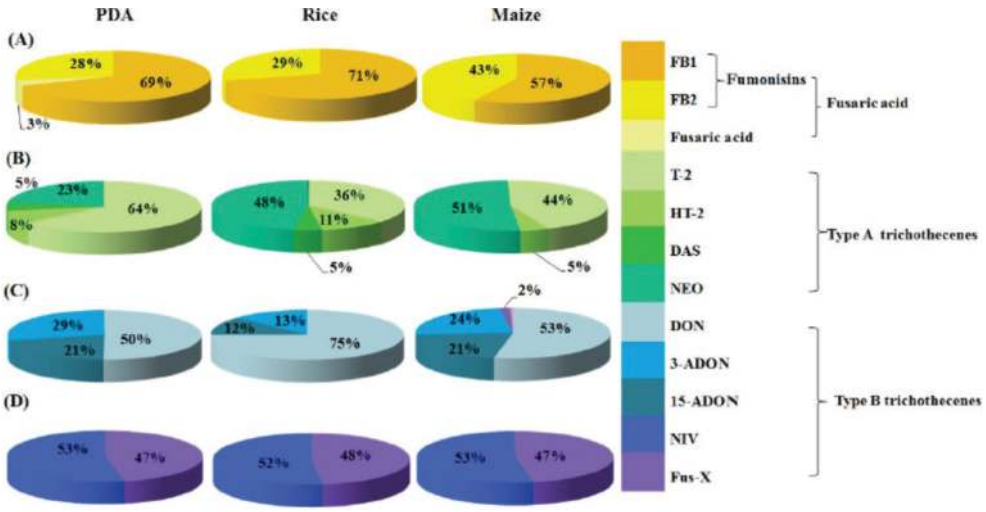

Figure 2. Mycotoxin classification according main four *Fusarium* species (A) *F. proliferatum* (B) *F. langsethiae* (C) *F. graminearum* and (D) in PDA, rice and maize medium [5].

levels for cereals and cereals products were set in "Commission Recommendation 2013/165/EU" [34]. Maximum limits for DON, ZEA, fumonisins, T-2 and HT-2 toxins have been set for cereals and by-products according to the production technology used [35].

6. Fungal resistance

Resistance of *Fusarium* to antifungal drugs has been defined by many researchers. It is known that many FSSC members cause fusarial onychomycosis [36]. *F. solani* showed more resistance to antifungal agents than others [37]. The effect of azole antifungals used clinically is depend on a particular site, lanosterol-14α-demethylase. While imidazole or triazole rings are important for conferring the therapeutic effect in animals, epoxiconazole, propiconazole, difenoconazole, bromuconazole and tebuconazole are used for plants. *Fusarium* spp. are resistant to azoles [38].

Tupaki-Sreepurna et al. [39] reported that FSSC members, mainly *F. falciforme* and *F. keratoplasticum*, showed multi-drug resistance against caspofungin and azoles. Only a few antifungal agents (voriconazole, posaconazole and amphotericin B) showed *in-vitro* activity against *F. falciforme* and *F. keratoplasticum* [40].

Conversely, the echinocandins are lipopeptide molecules which effectively work by inhibiting 1,3-β-D-glucan synthase of the fungal membrane. If a change occurs in the amino acid residues of β-1,3-glucan synthase enzyme subunits (FKS subunits) in the treatment process, it may lead to increased drug resistance [41, 42].

Polyenes, which are fungicidal, are known as amphipathic drugs, such as nystatin and amphotericin-B. The complexes show efficacy via destroying the proton gradient, allowing for the leakage of ions and removal of ergosterol from phospholipids in the membrane, thus causing fungal cell death in the process [43, 44].

7. Plant disease resistance mechanism

Plants, humans and animals give instant response to the pathogen. In animals, this effect is seen as antibody production, while in plants, it is seen in the form of secretion of various proteins, such as defense-related enzymes and pathogenesis-related proteins [45]. Defense-related enzymes are of great importance in the plant disease resistance mechanism. Immunized plants have rich defense-related enzymes that prevent them from suffering large losses.

If a plant is stimulated by a pathogen, early local defense reactions (a local programmed cell death) are followed by systemic responses (signal is transmitted from infected tissue to the whole plant). At the end, overall defense gene expression gets induced. Consequently, signal perception is essential for plants to combat pathogens [46, 47].

Numerous studies have been done on the transporter genes of plants for improved resistance to *Fusarium* spp. A sucrose transporter gene (IbSWEET10) of the SWEET gene family obtained from the sweet potato line ND98 was tested for this purpose. This overexpression of the gene has been shown to reduce sugar levels and has a potential use to lower carbohydrate levels and increase the resistance of the plant [48].

8. Fungal transporters

Transporters are of great importance in protecting fungi against plant defense compounds. Transporters enable efflux of the plant-originated defense compounds. Although resveratrol (from grape) and camalexin (from Arabidopsis) transport via the transporter BcatrB of *Botrytis cinerea*, pisatin (from pea) transports by the NhABC1 transporter of *F. solani* f. sp. *pisi*, and rishitin (from potato) transports via the GpABC1 transporter of *F. sambucinum* [4, 49–51].

Transporters are divided into two major classes: the ATP-binding cassette (ABC) and the major facilitator superfamily (MFS) transporters. ABC transporters are known to be important for resistance against fungal pathogens, particularly for pleiotropic drug resistance or multidrug resistance domains [52]. Although some transporters produce specific or non-specific toxins, some of them show very specific responses to fungicide sensitivity or resistance [53].

9. Identification, control and management

It is possible to identify the genus *Fusarium* by several methods. On culturing, hyaline, banana-shaped and multicellular macroconidia are very common; however, to identify them at the

species level is not easy. Therefore, molecular methods are needed. Some of the most commonly used molecular methods are the genus-specific PCR, 28 s rRNA gene sequencing, sequence-based PCR, multiplex tandem PCR and automated repetitive sequence-based PCR [54].

As a biological control, Ben Amira et al. [55] showed that when *Trichoderma harzianum* was co-cultured with *F. solani*, the former happened to have an antagonistic effect *in-vitro*. Then, they repeated this experiment by inoculating olive tree roots with the same *T. harzianum* and *F.* solani combination. They reported that the former showed a mycoparasitic reaction and antagonistic effects on *F. solani*. Therefore, mycoparasitic fungi, such as *T. harzianum* may be used as a biocontrol agent against *Fusarium*.

Notably, agricultural and chemical precautions cannot be completely successful in preventing *Fusarium*-related diseases in plants [56]. Therefore, synthetic fungicides are not a true approach for preventing the *Fusarium*-related diseases due to their harmful effects on the ecosystem and environment, and growing disease-resistant species to combat *Fusarium*-related diseases seems a more sustainable approach. Resolving the concern of plant diseases caused by *Fusarium* using biological control methods seems to be a more efficient and eco-friendly approach for agricultural products.

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