Defence response in plants and animals against a common fungal pathogen, *Fusarium oxysporum*

Papri Nag, Sathi Paul, Surbhi Shriti, Sampa Das*

Division of Plant Biology, Bose Institute, P/12 C.I.T. Scheme VII M, Kolkata, West Bengal 700054, India

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SUMMARY

Plant pathogens emerging as threat to human and animal health has been a matter of concern within the scientific community. *Fusarium oxysporum*, predominantly a phytopathogen, can infect both plants and animals. As a plant pathogen, *F. oxysporum* is one of the most economically damaging pathogens. In humans, *F. oxysporum* can infect immunocompromised individuals and is increasing being considered as a problematic pathogen. Mycotoxins produced by *F. oxysporum* suppress the innate immune pathways in both plants and animals. Hence, *F. oxysporum* is the perfect example for studying similarities and differences between defence strategies adopted by plants and animals. In this review we will discuss the innate immune response of plant and animal hosts for protecting against *F. oxysporum* infection. Such studies will be helpful for identifying genes, protein and metabolites with antifungal properties suitable for protecting humans.

1. Introduction

*Fusarium oxysporum* is an important phytopathogen, infecting many crop plants (Edel-Hermann and Lecomte, 2019). Based on its host specificity in plants, *Fusarium oxysporum* species complex (FOSC) has been divided into several groups or *formae specialis* (f. sp.). *F. oxysporum* infecting tomato are classified as f. sp. *lycopersici* (Fol), those infecting pea are classified as f. sp. *pisicerci* (Foc), those infecting f. sp. *ciceri* (Foc), f. sp. *conglutinans* infects plants within the Brassica oleracea species and *F. oxysporum* f. sp. *cubense* infecting banana. In addition to plants, some of the members of FOSC can infect both invertebrate and vertebrate animals including human beings. *F. oxysporum* are frequently isolated from clinical samples (Debourgogne et al., 2016), which often leading to severe infection and sometimes death in human. *F. oxysporum* f. sp. *lycopersici* (Fol) can also infect immunodepressed mice (Ortoneda et al., 2004; Lopez-Diaz et al., 2018). *F. oxysporum* f. sp. *ciceri* (Foc) can infect *C. elegans* (Nag et al., 2017). Several human isolates can also colonize tomato and cucumber (Wang et al., 2020).

In human, *F. oxysporum* is an opportunistic pathogen infecting individuals with compromised immunity. One of the most severe eye infection, ocular keratitis, is caused by either *Aspergillus* or *Fusarium*. Any disruption in the integrity of the corneal epithelium may predispose the individual to ocular keratitis. With the increase in the use of contact lenses, *F. oxysporum* has become one of the major causes of ocular keratitis (Ananthi et al., 2008; Sun et al., 2010). *Fusarium* infection of the skin and nail are common in the developing countries (Nucci and Anaissie, 2002, 2007). In deeply invasive infections, *F. oxysporum* can cause 100% lethality (Nucci and Anaissie, 2002). Several cases of pulmonary infection by *F. oxysporum* has also been recorded (Sander et al., 2009). *F. oxysporum* infecting human or animals has not been designated any *formae specialis*. However, the human pathogenic isolates have also been found to be carrying a unique set of lineage specific chromosomes with characteristic genes which are known to help in pathogenicity (Zhang et al., 2020).

The *Fusarium* genome is compartmentalised into two regions- core genome (containing genes for primary metabolism and reproduction) and the dispensable adaptive genome (containing genes for pathogen virulence and host specialisation). The Adaptive genome is located in the supernumerary or lineage-specific (LS) or accessory chromosomes. Along with other proteins required for host-specific interaction, LS chromosomes code for the rapidly evolving effector proteins which are required for the (full) pathogenicity towards a specific host (De Vries et al., 2020; Zhang et al., 2020). LS chromosomes are also considered to be important for adaptation and speciation (Ma et al., 2010; Sperschneider et al., 2015; Li et al., 2020). Several studies has shown that transfer of pathogenicity related traits can convert non-pathogenic *F. oxysporum* f. sp. *lycopersici* to pathogenic *F. oxysporum* f. sp. *lycopersici*, but pathogenicity transfer did not occur between different *formae*

* Corresponding author.
E-mail address: sampa@jcbose.ac.in (S. Das).

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sugar. Similarly, Van Dam et al. showed that *F. oxysporum* f.sp. *radicis-cucumerinum* can transfer its disease causing traits to a non-pathogenic strain of the same *F. sp.* by horizontal chromosome transfer (HCT) (Van Dam et al., 2017). Based on the studies of HCT of LS or accessory chromosomes in *F. oxysporum*, it is apparent that the transfer of pathogenicity occurs only between strain having high similarities in their core genome. However, the ability of some plant pathogenic FOSC infecting animals including humans warrants an appraisal of what is known about the host-*F. oxysporum* interaction both in plants and animals (Ortoneda et al., 2004; Nag et al., 2017; Wang et al., 2020).

The parallels in plant and animal innate immunity start with the ability to sense the pathogen using receptors at the point of contact and the ability to transmit this signal downstream via calcium signalling and reactive oxygen species (ROS) mediated pathways, activation of defence-related genes by specific transcription factors (TFs), production of antimicrobials and evasion at the organismal level (Sexton and Howlett, 2006). However, comparative studies on mechanism of host responses at molecular level to pathogens infecting both plants and animals are still limited to few, viz., in *Pseudomonas syringae*, *Burkholderia cepacia*, *Fusarium oxysporum*, *Fusarium solani*, *Alternaria solani*. In this review we discuss the innate immune response of plants and animals to the ubiquitous *F. oxysporum* species complex (FOSC).

### 2. *F. oxysporum* infection in plants

Genome analysis of plant pathogenic *Fusarium* revealed the presence of several enzymes which can degrade the cell wall of plants and help in the direct entry of the pathogens (Table 1). The presence of naturally occurring chickpea and garden pea land races with varying degrees of resistance has facilitated studies of *F. oxysporum* infection. In chickpea, after penetration into the root epidermis, the fungus moves towards the vascular bundle through the intercellular spaces. In the susceptible genotype of Chickpea (JG-62 and P-2245), Foc race 1 can easily penetrate the epidermis and reach the intercellular spaces within 2 days after infection (dai) and can cause wilting; whereas, in the resistant genotype (WR-315), it takes 8 days to reach the cortex and is restricted before reaching the vascular bundles (Jiménez-Fernández et al., 2013; Upasani et al., 2016). In tomato, entry is through the root tip or elongation zone during hydroponic culture and root hairs or grooves between the root epidermal cells of the collar region during soil culture (Jagopodi et al., 2002; Nahalkova et al., 2008). Like Foc, Fop race 2 could not reach the vascular tissues in resistant pea accessions. Lignification and suberization of cell walls and papillae like structures were noticed at the site of penetration in the resistant genotype of pea (Bani et al., 2018). In banana *F. oxysporum* f. sp. *cubense* has been shown to invade the host by penetrating the epidermis and growing through the intracellular spaces to reach the vascular bundles (Li et al., 2017). *F. oxysporum* f. sp. *cubense* infection outbreak in banana cultivar, Cavendish, is a serious threat to this crop as it is grown in monoculture (Dita et al., 2018). However, till date none of the members of this *formae speciales* has been reported to infect animals.

#### 2.1. Pathogen perception and signalling

One of the first reactions to pathogen- or damage-associated molecular patterns (PAMPs and DAMPs) recognition by host receptors is eliciting reactive oxygen species (ROS) in the apoplastic spaces. This is done via the induction of NADPH oxidases (respiratory burst oxidase homologues, RBOHs), peroxidases and polyamine oxidases in a temporal manner (Jaud et al., 2012; Kadota et al., 2015; Wszczak et al., 2015; Gupta et al., 2013). During Foc infection in Chickpea, production of ROS and scavenging proteins were upregulated in the resistant genotype WR-315 compared to susceptible JG-62 (Gupta et al., 2013). Consequently, the ROS-scavenging proteins were also upregulated in the resistant genotype (Chatterjee et al., 2014). RBOHF and RBOH, NADH cytchrome b5 reductase, cationic peroxidase 3 (OCP3), flavodoxin-like quinone reductase 1 (FQR1) and iron superoxide dismutase 1 were deregulated in an opposing manner in the resistant genotype WR-315 as recovery is initiated but continues in JG-62 causing further damage and collapse of vascular tissues in the susceptible genotype. In *Arabidopsis thaliana* two class III peroxidase, At3g49120 (AtHPL) and At3g49110 (AtPCa), generate H2O2 in response to elicitors from *F. oxysporum* (Bindschedler et al., 2006). The ROS production in the extracellular matrix may play an important role in cell wall reprogramming by promoting cell wall loosening or crosslinking (Schmidt et al., 2016). Activation of calcium channels located in the plasma membrane leads to increase in Ca2+ concentration in the cytoplasm, activating the calcium-dependent protein kinases (CDPKs), which in turn, relays the signal to the cell nucleus. This leads to a transcriptional, translational and metabolic change in the host plant for initiation of structural or biochemical immune response. Ashraf et al. (2018) could identify several components of calcium signalling in both resistant and susceptible genotypes during Foc infection. Calmodulin, which is part of the Ca2+ signalling system, also plays an important role in
chickpea during *Fusarium* infection (Gupta et al., 2013). Cell suspension culture of *Arabidopsis thaliana* produces an oxidative burst in presence of *Fusarium oxysporum* elicitors, which is enhanced by addition of CaCl₂, may play a role in basal resistance (Davies et al., 2006).

The effector proteins of the pathogen are recognized by receptors like the membrane-anchored I (Immunity) gene, first identified from *Solanum pimpinellifolium* (Catanzariti et al., 2017; Bohn and Tucker, 1939). Consequently several receptor proteins have been identified: I and Iγ gene encode for a membrane bound leucine-rich repeat receptor-like proteins (LRR-RLP) (Gonzalez-Candales et al., 2016; Catanzariti et al., 2017), I₂ encodes for an intracellular coiled-coil nucleotide-binding leucine-rich repeat (CC-NB-LRR) protein (Simons et al., 1998) and I₃ for a membrane bound S-receptor-like kinase (Catanzariti et al., 2015). Many receptor proteins of tomato interact with kinase-containing proteins for relaying the signal further downstream. The Avr1 recognising I₂ interacts with LRR-receptor-like kinase (RLK), suppressor of BAK1-interacting RLK1 (SOBIR1), and Somatic embryogenesis receptor kinase 3/brassinosteroid insensitive 1 associated kinase 1 (SERK3/BAK1) (Catanzariti et al., 2017) (Fig. 1A). Several LRRs (IRF1259, IRF731 and IRF314) and the subsequent MAP kinases have been implicated to be differentially expressed in chickpea during *Foc* infection (Catanzariti et al., 2015; Kumar et al., 2016; Chatterjee et al., 2014; Chakraborty et al., 2019). In banana, *Fusarium oxysporum* f. sp. *cubense* infection upregulates the Flagellin-sensitive 2 (FLS2) LRR transcripts (Li et al., 2012; Bai et al., 2013). In *Arabidopsis*, a recently identified leucine-rich repeat receptor-like kinase, MDIS1-INTERACTING RECEPTOR-LIKE KINASE 2 (MIK2), can bind SERINE-RICH ENDogenous PEPTIDE 12 (SCOOP12) like peptides of *Brassica* and SCOOP-LIKE peptides of *Fusarium oxysporum* (Coleman et al., 2021). Perception of *Fusarium oxysporum* SCOOP12-like peptides by the extra-cellular domain of MIK2 induces its association with and the co-receptors SERK3 and SERK4 in *Arabidopsis*. This in turn relays the signalling through the cytosolic receptor-like kinases BOTRYTIS-INDUCED KINASE 1 (BKI) and AVRPPHB SUSCEPTIBLE1 (PBS1)-LIKE 1 (PBL1) (Hou et al., 2021). The BAK1 homologue in banana and soybean was also upregulated following *Fusarium oxysporum* f. sp. *cubense* infection (Li et al., 2012; Bai et al., 2013) and *Fusarium oxysporum* f. sp. *pisi* infection, respectively (Lanubile et al., 2015).

In *Arabidopsis*, three loci have been identified which induces varying degrees of resistance to *Fusarium oxysporum* f. sp. *matthioli* (*Fom*). The cell wall-associated kinase-like 22 (WAK/WAKL), RFO, confers enhanced protection against different *Fusarium oxysporum* f. sp. *matthioli* (*Fom*) and *Verticillium longisporum* isolates (Berrocal-Lobo and Molina, 2007). The RFO2 locus, with extracellular leucine-rich repeats and one receptor-like protein (RLP) domain, provide modest resistance to *Fom* by inducing Tyrosine-Sulfated peptide signalling in *Arabidopsis* (Shen and Diener, 2013). Another locus in *Arabidopsis* Col-0, RFO3, with a receptor-like kinase (RLK) can confer resistance to independent isolates of *Fom* race 2 (Cole and Diener, 2013).

### 2.2. Strengthening of cell wall, a means of defence response to *F. oxysporum*

Transcriptional reprogramming as a result of *F. oxysporum* f. sp. *ciceri* (*Foc*) infection induces changes in lignification, phytoalexins, pathogenesis-related proteins of the host plant and yang cycle involved in ethylene biosynthesis (Kumar et al., 2016; Bindschedler et al., 2006). TFs of the families MYB, bHLH and WRKY families are also deregulated and may play important roles during *Fusarium*-plant interaction (Son et al., 2012; Chen et al., 2014; Lanubile et al., 2015). Lignification and formation of cross-linked matrix of carbohydrate and protein biopolymers pathway proteins may be correlated with the ability to exclude the pathogen from the vascular tissues in chickpea (Elagamy et al., 2017), soybean (Lanubile et al., 2015) and banana (Dong et al., 2020). During *Fusarium* infection in *Arabidopsis*, monolignols, the building block of lignins, are synthesized from phenylalanine via the phenylpropanoid pathway (Kostyn et al., 2012; Xie et al., 2018) and the salicylic acid (Gallego-Giraldo et al., 2011) pathways. In plants, methyl-transferase reactions are important in the lignin biosynthesis and ethylene production pathway. S-adenosyl-L-methionine (AdoMet) from the methane salvage pathway or Yang cycle serves as the major methyl-group donor for numerous highly specific methyl-transferase reactions (Indes et al., 2016). AdoHey hydrolase convert AdoMet to S-adenosyl-L-homocysteine (AdoHey), which is a potent inhibitor of methyltransferases. Hence, AdoHey hydrolase is known to have a role in defence against pathogens by influencing the lignin as well as the ethylene biosynthesis pathway (Kawalleck et al., 1992).

### 2.3. Pathogenesis-related proteins and host secondary metabolites with antimicrobial properties against *F. oxysporum*

The pathogenesis-related (PR) proteins are induced in the host plant...
as a result of pathogen attack and at least few are known to have antifungal and antibacterial properties. PR proteins are induced as a result of systemic acquired resistance after pathogen infection (Van Loon et al., 2006). The antimicrobial peptides (AMP) in plants are small cationic peptides of 45–54 amino acids held together by four disulphide bonds (Parisi et al., 2018). AMPs have been detected in the epidermis of leaves, roots, pods, tubers, fruit, and floral organs, seeds and other possible targets of pathogen contact. In chickpea PR proteins are induced in both the resistant and susceptible varieties during *Fusarium* infection (Kumar et al., 2016; Ashraf et al., 2009). Induction of PR-1 (a and B isoforms), PR-5x, PR-2, PR-4, glucanases, chitinases, peroxidases and xylolignan-specific endoglucanase inhibitor protein (XEGIP) reported for the xylem sap proteome of *Fol*-infected tomato plants (Houterman et al., 2007; Rep et al., 2002). The PRI family, identified initially in tobacco, is represented in every plant species studied to date and homologues have been found in animals, fungi and insects. Lincon et al.

### Table 2

| Antifungal | Source of isolation of antifungal compound | Functions against | Mechanism of action | Refs. |
|------------|-------------------------------------------|------------------|---------------------|-------|
| Pd1        | *P. digitatum* CECT 20,796 (PHI26)         | *F. oxysporum*   | Has the ability to bind fungal membranes | Games et al. (2008) |
| AfB        | *P. digitatum* CECT 20,796                 | *F. oxysporum*   | Not known           | Garrigues et al. (2018) |
| Pr-1       | *Cucurbita moschata*                      | *F. oxysporum*   | Not known           | Park et al. (2010) |
| Cn-p1      | *Cucurbita moschata*                      | *F. oxysporum*   | Not known           | López-Abargrategui et al. (2012) |
| Thaumatin-like protein, Osmotin, Zeamatin | *Zeae mays* | *F. oxysporum* | Not known | Van der Weerden et al. (2013) |
| Plant hormone |                                              |                  | By inducing increase in the levels phenolic compounds such as salicylic acid (SA), kaempferol and quercetin in the plant. No bioassay was done | Ketli et al. (2015) |
| Methyl jasmonate (Me-JA) | Jasmonic acid is produced by all plant; Me-JA is a derivative | *F. oxysporum* | By inducing increase in the levels phenolic compounds such as salicylic acid (SA), kaempferol and quercetin in the plant. No bioassay was done | Steinkellner and Mammerler (2007) |
| Plant Secondary metabolites | ![Plant Secondary metabolites](image1) |                  | Biassay was done. Mechanism of inhibition not known | Zhang et al. (1993) |
| Gossypium hirsutum | *F. oxysporum* f. sp. vasiinfectum |                  | Biassay was done. Mechanism of inhibition not known | Steinkellner and Mammerler (2007) |
| Naringenin,morin, quercetin, glycitin, apigenin, luteolin, kaempferol, rutin, myricetin, daidzein, genistein and coumestrol | Plant derived | *F. oxysporum* f. sp. lycopersici | Biassay was done. Mechanism of inhibition not known | Steinkellner and Mammerler (2007) |
| Plant extracts | ![Plant extracts](image1) |                  | Biassay was done. Mechanism of inhibition not known | Steinkellner and Mammerler (2007) |
| Adhatoda vasica, Eucalyptus globulus, Lantana camara, Nerium oleander, Ocimum basilicum, Thymus atlanticus, Datura metel, and many more | *F. oxysporum* f. sp. lycopersici race 3, *F. oxysporum* f. sp. albedinis, *F. oxysporum* f. sp. cubense | Not known | Isaac and Tahan (2014), Boushali et al. (2020), Akila et al. (2011) |
| Animal derived compound showing antifungal activity | ![Animal derived compound showing antifungal activity](image1) |                  | Not known | Games et al. (2008) |
| Cercropin A and Cercropin B | *Hypospora cercripa* | *A. flavus, A. niger, A. fumigatus, F. moniliforme, and F. oxysporum* | Binds to cell wall ergosterol and cholestrol | De Lucca et al. (1997) |
| Drosomycin | *D. melanogaster* | *F. oxysporum* | Not known | Tian et al. (2008) |
| Metchnikowin | *D. melanogaster* | Pathogenic asconycyota, including *F. graminarum* | Not known | Moghaddam et al. (2017) |
| Thanatin | *Podius malaciveris* | *Neurospora crassa, Botrytis cinerea, Nectria haematococca, Trichoderma viride, Alternaria brassicola, Fusarium culmorum, Ascochyta pisi, Fusarium oxysporum, A. fumigatus and T. mentagrophytes* | Inhibition of spore germination and formation of hyphae | Fehlbaum et al. (1996) |
| Dermaseptins | *Phylomedusa sauvagii* | *F. oxysporum* and *F. moniliforme*, *Aspergillus flavus, A. fumigatus, A. niger* | Binds to cell wall ergosterol and cholestrol | De Lucca et al. (1997) |
| Myticin A and Myticin B | *Mytilus galloprovincialis* | *F. oxysporum* and *Eichhornia crassipes* | Not known | Mitta et al. (1999) |
| Anti-fungal compound identified from other sources | ![Anti-fungal compound identified from other sources](image1) |                  | Not known | Cao et al. (2018) |
| Iritin | *Bacillus velezensis* | *Ralstonia solanacearum* and *Fusarium oxysporum* | Not known | De Lucca et al. (1999) |
| Syringomycin-E | *Pseudomonas* sp. | *A. flavus, A. niger, A. fumigatus, F. moniliforme, and F. oxysporum* | Syringomycin-E can bind chitin, b-1,3 glucan, and mannan | De Lucca et al. (1999) |
| Myricin | *Bacillus amyloliquefaciens* | *Fusarium oxysporum* f. sp. niveum | Myricin destroyed membrane integrity | Wang et al. (2021) |
| Fengycin | *Bacillus amyloliquefaciens* | *F. oxysporum* f. sp. radicidylcopersici | Myricin destroyed membrane integrity | Wang et al. (2021) |
| Gepacilides (A1 and A2) | *Burkholderia cepacia* | *F. oxysporum* | Not known | De Lucca and Walsh (1999) |
| Atroviolrins (A, B, C) | *Trichoderma atroviride* F80317 | *F. oxysporum* | Not known | Oh et al. (2002) |
demonstrated that tomato roots expressing PR1 from plant, human and microbial sources survive Fumonisin B1 better than wild type plants (Lincon et al., 2018). In soybean three PR10, one PR9, four PR5 one PR4 and one PR1 were upregulated after *F. oxysporum* *f. sp. pisi* infection (Lanubile et al., 2015).

Phytoalexins are low molecular mass secondary metabolites with antimicrobial activity produced by the plant as a result of pathogen infection or abiotic stress (Ahuja et al., 2012). Phytoalexins have been reviewed at great length by Ahuja et al. (2012) and will not be discussed here in detail. To compensate for the high rates of immune reactions occurring after *Foc* infection in *Cicer*, nitrogen and carbon metabolism of the host plant is reprogrammed (Kumar et al., 2016; Gupta et al., 2010). In addition dysregulation of phytoalexins- genistein, luteolin, clotrimazole and quinone- occur in both the resistant and susceptible genotypes of chickpea during *Foc* infection (Kumar et al., 2016). Table 2 lists some of the antimicrobial and secondary metabolite products from plants which have been tested against *F. oxysporum*.

### 2.4. Plant immune suppression by *F. oxysporum* toxins

Like effectors, toxins are also thought to reduce ROS production in the host plant by suppressing the immune reactions (Perinberry et al., 2019). Mycotoxins are also produced during the saprophytic phase of the fungi. Fusaric acid (FA), produced by FOSC, is known to be associated with wilting in plants, even external application of FA results in wilt-like symptoms in *tomato* (Singh et al., 2017). It is also known to cause hypersensitive reaction in tomato by interfering with the antioxidants like catalase and peroxidase (Singh and Upadhyay, 2014). Plant defence responses are activated by FA application in subtoxic doses (Bouizgarne et al., 2006). López-Diaz et al. (2018) showed that mutants of *F. oxysporum* with reduced capacity of producing FA led to reduced virulence in tomat plants.

### 3. *F. oxysporum* infection in animals

The major pathways for entry of *Fusarium* inside the human body are airways, damaged skin tissue and mucosal membranes (Nucci and Anaissie, 2007). In immunocompetent individuals, *Fusarium* isolates cause allergic fungal sinusitis (Wicken, 1993), keratitis (cornea opacity leading to blindness, and even loss of the eyeball), onychomycosis (infection of the toenails or fingernails) and locally invasive infections (Nucci and Anaissie, 2007), which may become disseminated infections in immune-compromised patients (Marr et al., 2002). Fusariosis, like many other invasive fungal infections share similar features in its manifestation in patients receiving high doses of corticosteroids and those with neutropenia (Smith and Kauffman, 2012). In order to study Fusariosis, several animal models have been identified, e.g., mice (Mayayo et al., 1999), *Drosophila* (Lamaris et al., 2007), *Caenorhabditis elegans* (Muhammed et al., 2012).

Host innate immunity against FOSC shares defence mechanism which are similar against other fungi (Schafer et al., 2014; Lionakis et al., 2017). In a broad prospective, the effector cells- neutrophils, monocytes and macrophages have anti-fungal roles and are recruited at the site of fungal infection. Phagocytes are more effective against spores and non-filamentous fungi. Phagocytes release anti-fungal peptides and oxygen-intermediates against fungi. The dendritic cells, which link the innate and adaptive immunity, are also important defence against fungal infections.

### 3.1. Pathogen perception at the barrier tissues of animals

Fungal infections can occur when abrasions and wounds occur in the epidermal layer, making the animal vulnerable (Coates et al., 2018). FOSC frequently infect the barrier tissues at the cutaneous layer of skin following skin breakdown (Nucci et al., 2002), however, FOSC infection can also occur through an intact skin layer in mice (De Paulo et al., 2013). Once the pathogen crosses the structural barrier provided by the skin, pathogen recognition receptors (PRRs) in the sub-epidermis can identify the pathogen- or damage- associated molecular patterns to initiate innate immunity. *Drosophila* Toll and human interleukin-1 receptors (TLRs) and interleukin-1 receptor (IL-1R) belongs to the same family of transmembrane receptor family with cytoplasmic TIR domains. However, TLRs contain leucine-rich repeats (LRs) in its endodomain while IL-1R possess Ig-like domains (Nünnberger et al., 2004). TLR-4 and IL-1R seem to be functional in conjunction with MyD88 during *Fusarium* kratitis (68) (Tarahishy et al., 2008) (Fig. 1B). MyD88 is the common adaptor for most TLRs and IL-1 receptors (Krishnan et al., 2007). TLR-4, IL-1R and MyD88 are distributed in almost all cells of the immune system and activation of MyD88 leads to the induction of innate immune cells via MAPK pathway (to induce different TFs) or through other kinases (to induce NF-κx) leading to the production of cytokines, chemokines and other immunomodulatory molecules (Nünnberger et al., 2004). Correia et al. (2020) showed that even the crude extract of *F. oxysporum* induced pro-inflammatory IL-6, IL-17, TNF-α and anti-inflammatory TGF-β1 cytokinines. TLRs are conserved among many phyla including human, *Drosophila* and *C. elegans*. Disease development starts in *C. elegans* with force feeding of microconidia (Muhammed et al., 2012) leading to the induction of a unique set of molecular signatures independent of Tol-1 but dependent on Daf-16, TGF-β1 (Nag et al., 2017) and MAPK pathways (Muhammed et al., 2012).

In addition to TLRs, fungal recognition also involves C-type lectin receptors (CLRs) (Van de Veerdonk et al., 2008; De Figueiredo et al., 2011) present in many tissues like macrophages, monocytes, neutrophils, mast cells, dendritic cells (DCs), bronchial epithelial cells and pulmonary epithelium of the respiratory system, corneal epithelial cells as transmembrane receptors and body fluids. Dectin-1, Dectin-2, Mince, mannos receptor (MR), and DC-SIGN are some of the CLRs known to recognize mannan, glucans, and chitin present on the fungal cell wall (Goyal et al., 2018) (Fig. 1B).

Th17 cells organise at the barrier membranes and protect against external pathogens. Th17 cells are important not only for mucosal immunity, it also acts a bridge for adaptive immunity, and often is a double edged sword as its balance can decide the outcome from defence to pathogenesis (Khader et al., 2009). Th17 cells are activated by *F. oxysporum*, *Aspergillus* and *Candida* infection (Taylor et al., 2014). Th17 cells are also important defence during fungal keratitis in mice (Taylor et al., 2014).

### 3.2. Small peptides and host secondary metabolites with antimicrobial against *F. oxysporum*

Small proteins with antimicrobial (AMP) or antifungal activity are secreted by the host cells to inhibit the growth of bacterial, fungal and viral pathogens. AMPs are mostly produced by members belonging to different kingdoms in response to pathogen attack. AMPs are gene encoded and maybe also be produced constitutively expression (Hilgediis and Marx, 2013). β-defensins connect innate immunity with the adaptive immunity by recruiting via Toll pathway (Biragyn et al., 2002). Drosomycin and metchnikowin produced by *Drosophila* are active against *Fusarium* and other filamentous fungi (Tian et al., 2008). Metchnikowin acts selectively against pathogenic ascomycota, including *F. graminearum* (Moghaddam et al., 2017). The *C. elegans* genome encodes for several types of AMP gene clusters and neuropeptide-like proteins (NLPs), caenacsin family proteins (CNs), antibacterial factor (ABF) peptides and caenopores or saposin-like proteins (SPP). However, only SPP-11 has been found to be upregulated during *F. oxysporum* infection compared to uninfected controls (Nag
In mice, antimicrobials which are either induced upon *F. oxysporum* infection or expressed constitutively, seems to be involved in the destruction of fungus inside macrophages, neutrophils and dendritic cells (Schafer et al., 2014). Although, not much is known about the recognition and uptake of *F. oxysporum* by macrophages, engulfing more than three spores seems to cause lysis of the macrophage (Schafer et al., 2014). It has been recently demonstrated that β-1,6-linked Galactofuranose- rich peptidogalactomannan present in the cell wall of *F. oxysporum* is responsible for uptake spores by macrophage (de Oliveira et al., 2019).

### 3.3. Immune suppression in animals by *F. oxysporum* toxins

Mycoxicosis in humans and animals following ingestion of food contaminated by toxin-producing *Fusarium* spp. has been reported a long time ago (Nelson et al., 1994). In the case of *F. oxysporum*, the mycoxicosis responsible may be Fusaric acid. It has also been recently demonstrated that fub1Δ mutants of *F. oxysporum* with reduced FA production has significantly reduced virulence in immunodepressed mice (Lopez-Diaz et al., 2018). *F. oxysporum* secreted FA has been shown to increase the levels of neurotransmitters like serotonin, 5-hydroxyindooleacetic acid, tyrosine, and dopamine in rat pineal cell cultures (Porter et al., 1995). FA causes inhibition of noradrenaline synthesis, reduces the luteinizing releasing hormone and prolactin from the basal hypothalamus in animals (Tobias et al., 1983). In pigs acute doses of FA causes vomiting and lethargy (Smith and MacDonald, 1991) and narcolepsy in chicks (Bungo et al., 1999). FA is immunotoxic to peripheral blood mononuclear cells (PBMCs) and acute monocyctic leukemic (Thp-1) cell line, inciting cell death in both cases. In Thp-1 cells the extracellular receptor kinase (ERK) proteins are upregulated and the c-Jun N-terminal kinase (JNK) proteins are downregulated, which regulate the mitochondrial apoptosis control protein, Bcl-2. Contrastingly, in PBMCs both ERK and JNK proteins are upregulated and p38 MAPK expression is downregulated inducing paraptosis (Dhani et al., 2017). High doses of FA may be toxic for the cells while controlled doses may be of therapeutic use. FA administration in controlled doses had a hypotensive effect by inhibiting Dopamine-β-hydroxylase, thus, reducing the level of noradrenaline, which controls the blood pressure in humans (Hidaka et al., 1969).

### 4. Conclusions

*Fusarium oxysporum* is an opportunistic pathogen of plants and can infect animals only when the structural integrity is damaged. During plant infection, the main defence against *F. oxysporum* is the reinforcement of cell wall by augmenting lignin and cell wall carbohydrates. After the fungus successfully establishes itself inside the plant host, production of antimicrobials and secondary metabolites is initiated. Unlike plants, defence against *F. oxysporum* infection in animals does initiate any reinforcement of cell structures. In animals, production of antimicrobials, destruction of fungus inside the macrophages, neutrophils and dendritic cells are the main defence mechanisms. The commonality in plants and animals against *F. oxysporum* appear to be the production of antimicrobial peptides.

### Outlook

Several antimicrobial peptides, phytoalexins and secondary metabolites from plants and invertebrates have been tested against *F. oxysporum* to understand whether these antimicrobials have the potentiality to be used as novel therapeutics during human infection. Table 2 lists some of the antimicrobial products from animals which have been tested against *F. oxysporum*. Since the *F. oxysporum* strains capable of infecting human and plant differ mostly in the accessory genomic level; while the core genome is predominantly conserved (Van Dam et al., 2017). It may be useful to test the antimicrobials, phytoalexins and secondary metabolites produced by the plants and animals which target the products of the essential genes which are usually located on the core genome of the strains which can infect humans.

### Ethics approval and consent to participate

Not applicable to review article.

### Consent for publication

All authors consent to participate in this review article.

### Availability of data and material

This manuscript does not have any data and material.

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### Declaration of Competing Interest

None declared.

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