Organic Compounds and Fusarium oxysporum

Subjects: Virology
Contributor: Diego Quiroga

The design and the synthesis of novel synthetic antifungal agents used against FOX have been broadly studied in recent years. This review article presents a compendium of the synthetic methodologies during the last ten years as promissory, which can be used to afford novel and potential agrochemical agents. The entry is addressed from the structural core of the most active synthetic compounds against FOX. The synthetic methodologies implemented strategies based on cyclo condensation reactions, radical cyclization, electrocyclic closures, and carbon–carbon couplings by metal–organic catalysis.

Keywords: vascular wilt ; antifungal agent ; FOX ; IC50 ; MIC ; organic synthesis

1. Introduction

The genus *Fusarium* is considered one of the most adaptable and versatile in Eumycota. One of its most economically important species is *FOX*, an invasive phytopathogen responsible for vascular wilt and cortical rot in more than a hundred crops of commercial interest. *FOX* is responsible for a large percentage of economic losses in the agricultural sector worldwide. These phytopathogens have host specialization capacity and high virulence, becoming a broad complex of *FOX* species with a high probability of new pathogens [1]. This complexity of species has gained considerable attention in the scientific community in recent years. The Molecular Plant Pathology Journal has included *FOX* among the “Top 10” of the phytopathogenic fungi based on its scientific and economic importance [2].

FOX complexes are distributed worldwide. The pathogen accumulates in sufficient inoculums, and then a susceptible cultivar is planted. The symptoms of the plant can be evidenced through chlorotic flakes, which undergo curvature and lose structural stability. The plant eventually wilts which can be evidenced by acquiring a yellowish-brown color while the vascular system changes color from light yellow to brick red. Most of the forms in *FOX* complexes exist as chlamydospores, which remain latent in the host’s tissue and soil until they stimulate germination, with exudates from the roots responsible for their germination. Various pathogenic forms of *FOX* can enter the host root through wounds or directly through the root tips [3][4].

The impact of the *FOX* species complex has generated millions of economic losses. In banana crops [5][6][7], the losses caused by the TR4 race of *F. oxysporum f.* sp. were estimated at USD 2000 million during the “Gros Michel” era. TR4 is currently expected to cause even more significant losses eventually: in Latin America, from 1995, the disease of Panama was reported in most banana producing regions, except Papua New Guinea, the South Pacific Islands, and some of the countries bordering the Mediterranean; in Indonesia, Taiwan, Malaysia, China, and the Philippines, losses of around USD 253 million were estimated between 2011 and 2013 [8][9]. In tomato, the only vegetable crop cultivated globally, vital for the daily diet and consumed as freshly unprocessed fruits, millions of losses have been reported due to vascular wilt caused by *FOX* [10]. A reduction in 50% of Africa production has been reported for oil palm due to vascular wilt caused by *FOX* [3][11].

Moreover, huge losses have been reported in melon crops caused by *FOX*, carnation, and chrysanthemum flowers and cotton [12]. In countries such as the USA, China, and India, which provide approximately 35% of the total fiber use globally, *FOX f.* sp. *vasinfectum* diseases caused losses between 0.4 and 1.0% [13]. In Colombia, the cape gooseberry (*Physalis peruviana* L.) production suffered significantly from 2009–2013 due to the *FOX* complexes’ proliferation [14].

In addition to the enormous impact caused in agriculture and the economy, it is known that the toxins secreted by *FOX* complexes can cause alteration in animals and humans health [15]. The disease caused by eating food with mycotoxins is called mycotoxicosis. Several hundred compounds have been described as toxic or potentially toxic secondary metabolites of *FOX* complexes with high toxicity, demonstrated in bioassays or feeding studies. Some mycotoxins, such as enniatins, fusaric acids—inducers of cell death in tomato plants—and moniliformin, have been linked to toxicosis in humans or livestock animals immunocompromised infections in humans [16][17]. A risk factor for fusariosis

can occur in immunocompetent patients due to tissue degradation caused by trauma, severe burns, or foreign bodies in the body. Infections in humans with *FOX* complexes can cause local, focally invasive, or disseminated diseases. Skin lesions can be seen in approximately 75% of cases and are usually located on the trunk and extremities, causing keratitis and onychomycosis. *Fusarium* can also affect deep skin ulcers, third-degree burns, and surgical wounds. In other cases, the infection remains localized in the immunocompetent or immunosuppressed host, causing manifestations such as septic arthritis, skin infection, central line sepsis, endophthalmitis, osteomyelitis, cystitis, and brain abscess [18][19][20][21].

To perform effective control of *FOX* complexes is one of the most difficult to achieve. Therefore, various methods have been developed, such as cultural, biological, botanical, genetic, and chemical controls. Some fungi have been evaluated more frequently in biological control methodologies than bacteria, such as *Trichoderma* (53% of fungi) [22][23]. Non-pathogenic *Fusarium* species (23%) and *Penicillium* (10%) are other used microorganisms. Concerning the bacteria uses, *Pseudomonas* (44%), followed by *Bacillus* (13%) and *Streptomyces* (9%), has been broadly employed [24]. Despite the advantages of biological control, microorganisms and botanicals can show a low range of efficiency levels. Nearly a third of the tested microorganisms have been shown to reduce the disease by only 10% to 40%. As for botanicals, most of the reported studies were performed only in vitro tests. These considerations lead to the question of the level of efficiency required to consider the marketing of a biological control product and restrict their field of application [12].

Genetic investigations on *FOX* complexes have shown promissory results towards phytopathogen control. Recent comparative analysis of the *FOX* genomes provided information on the genome's organization and the genomic region that governs pathogenicity, revealing that each specialist form's effector repertoire probably determines the specificity of the host [25]. Through comparative analysis, pathogenicity-related chromosomes have been identified in *FOX* that contain genes for host-specific virulence [26]. On the other hand, genetic engineering advances have been possible using new resistant genotypes of several plants through gene editing and high-performance phenotyping. These success factors depend on the genotype and are related to the level of resistance to *FOX* complexes. Strategies for integrated management should consider increasing plant defenses and suppressing *FOX* complexes in the soil once the disease is present [9][27][28]. However, the productivity and market acceptance for somaclones is lower, and there is low and expensive productivity, especially in small markets for other cultivars. Due to these considerations, pests' chemical control through chemical products (agrochemicals as pesticides) is the most profitable and effective alternative for crops in large areas.

Fungicides with a benzimidazole group in their structure, such as benomyl, carbendazim, and thiabendazole, have demonstrated their capacity to control *FOX* complexes in vitro and under greenhouse conditions. Other agrochemicals such as cyproconazole, propiconazole, and prochloraz showed reduced *Fusarium* wilt disease of about 80% in banana plants. Soil fumigated with methyl bromide effectively reduced Panama disease in South Africa for a few months. However, the fungus was able to repopulate these soils and infect susceptible banana plants. Phosphonate compounds are potent against this phytopathogen as they reduce fungal growth under in vitro conditions. Carbendazim injections into the corm tissue of Rasthali cultivars in India provided short-term tolerance, but the results were erratic with the same treatments in other parts of the world. The disinfection processes of contaminated machinery and agricultural implements used sodium hypochlorite and detergents effectively against conidia and chlamydospores of *F. oxysporum f.* sp. However, they do not apply to large plantations, and it is known that they cause some environmental risks and even harm farmers [9][29][30]. In some countries, prochloraz and azoxystrobin replaced benomyl to control various ornamental *Fusarium* wilts and bulb cultures. However, prochloraz has never been registered for ornamental plants in the USA. The price of azoxystrobin has limited its use in many bulb crops [5].

Despite this, several measures must be considered when using agrochemicals since the side effects can be even more harmful than the pathogen. These effects only appear when the amount of pesticide in the body is more significant than what it can eliminate, so it accumulates and reaches the toxic level [31]. Frequent use of pesticides can harden or stunt cultivars of a species. Combined with the incomplete effectiveness of chemical treatments against *Fusarium* wilt, these considerations have made chemical control disappointing for farmers and the productive sector. Many times, "cocktails" of the mentioned agrochemicals are used, enhancing their effects and causing chemical alterations that originate new chemical substances [32]. The use of these mixtures and their storage without due control has caused severe health disorders for producers and their families, mainly at the reproduction level. The increased risks during pesticide application often result from a lack of information, knowledge, awareness, and inadequate supervision during the application and sale of highly toxic products. Due to this, several alternatives have been sought that allow chemical pest control to be carried out with minimal impact. Specifically, to reduce fungi's presence in the post-harvest stage, studies have been carried out that contemplate the use of extracts from resistant plants [33]. This alternative is impressive considering that the secondary metabolites with biological activity are the terpenoid type, phenolic compounds, phenylpropanoids, stilbenes, alkaloids, saponins, and heterocyclic compounds [34], whose advantage corresponds to their

rapid degradation in the soil. Therefore, new agrochemical agents' synthesis continues to be a profitable one and still to be explored. In this review, we present a compendium of organic compounds active against different species of *FOX*, their synthesis methods, and some recommendations and perspectives of the authors, formulated during the process of consolidation of the information to redirect the search for new molecules active against *FOX* systematically and rationally.

2. Compendium of the Organic Molecules with the Highest Reported Antifungal Activity against *FOX* Species

A bibliographic review was carried out in a time window between 2010 and 2020 to establish the organic molecules with the most significant biological activity against *FOX*. It was evidenced that the expression of the antifungal activity in the manuscripts differs concerning the units used or the property defined for this purpose, for example, half-maximal inhibitory concentration (IC_{50}), half-maximal effective concentration (EC_{50}), minimum inhibitory concentration (MIC), or percentage of inhibition (%) at a specific concentration. This review took the IC_{50}, EC_{50}, or MIC value expressed in micromolar as a criterion to select the interest reports. We discarded those reports where the activity was only reported as a percentage of inhibition. They were not conclusive, or merely the employed method did not provide definitive quantitative information for the corresponding molecules.

3. Conclusions and Perspectives

This review allowed us to establish that most of the synthetic methods published for promising antifungal agents usually employ cyclo condensation reactions. These protocols generally tend to have moderate to good yields, which depend on the structural nature of the precursors, the reaction conditions, and the use of catalysts. Among the most used catalysts, the use of porous materials, composites that can cause acidic or basic catalysis, have recently increased, although both inorganic and organic acids and bases are still being used. In addition, numerous protocols evidenced the use of metal catalysts, which tend to improve performance and selectivity under mild conditions. Regarding the energy sources used, although the use of conventional heating is maintained, many methodologies have more frequently used microwave or ultrasound irradiation to achieve better performance. On the other hand, the manuscripts cited and discussed in this review clearly showed that heterocyclic compounds play an essential role in controlling a phytopathogen such as *FOX*, being benzothiazole derivatives, the most studied compounds with the highest antifungal activity (**Table 1**). Some reports have described biological and environmental effects and their potential activity, degradation pathways, and subproducts characterization of synthetic heterocycles such as podophyllotoxin derivatives [35], rhodamine derivatives and analogs [36], benzothiazole and benzotriazole derivatives—which have emerged as contaminants in aquatic environments and toxic to aquatic organisms [37][38][39][40]—and polycyclic (hetero)aromatic hydrocarbons compounds which recently was demonstrated their predominance in contaminated food samples and their relationship with potential toxicity [41]. However, further studies are necessary to establish these promissory antifungal agents' potential cytotoxicity and environmental risks.

Future research on this type of heterocyclic compounds could give more promising results in agrochemistry. It is hoped that this information will lead to the design of better molecules with improved antifungal properties and greater specificity as the development of new synthetic strategies. However, there is an urgent need to direct research related to the synthesis and design of new bioactive molecules against *FOX*, considering the described antecedents in this review. The design of novel antifungal agents against *FOX* should be oriented to inhibit specific enzymes, commonly called molecular targets. Thus, Catharina and Carels (2018) performed a systematic identification of specific enzymes for *FOX* [42]. In addition, they described the characterization of enzymatic functionalities associated with protein targets that could be considered for the control of root rots induced by *FOX* such as chitin synthase [43], UDP-N-acetylglucosamine diphosphorylase [44], the decapping scavenger enzyme (DcpS, m7GpppX diphosphatase) [45], carnitine acetyltransferase [46], hydroxyanthranilate 3,4-dioxygenase [47][48], ureidoglycolate lyase [49], and holocytochrome-c synthase (HCCS, also known as cytochrome c heme lyase) [50]. It is necessary to focus on vital processes such as cell membrane stability, respiration, mitosis and cell division, and signal transduction. The cell membrane performs many biological functions: to prevent the entry of large molecules, provide the cell's shape, maintain the water potentials in the cell, and participate in signal transduction. It has been established as adverse effects of fungicides, affecting the membrane of microorganisms, which alter their structure and function [51]. Azole fungicides, such as triazoles, interrupt the biosynthesis of ergosterol, an essential sterol of fungal cell membranes, by inhibiting cytochrome P450 eburicol 14α-demethylase (CYP51). This inhibition prevents the demethylation of eburicol, the primary substrate of CYP51 in most filamentous fungi such as *FOX*, which leads to a depletion of ergosterol and an accumulation of non-functional 14α-methylated sterols [52]. Inhibition of this enzyme could deplete ergosterol and changes the fluidity of the membrane in the lipid bilayer, which leads to a reduction in the activity of crucial membrane enzymes and, if ergosterol levels are low enough, blocks the "sparking" reaction

necessary for the re-initiation of fungus growth [53]. Fungicides that alter cell division processes presumably affect β-tubulin, since these can inhibit the assembly of α- and β-tubulin heterodimers in microtubules, which are vital for various processes such as signaling motility, division cell, and mitosis [54][55]. Moreover, fungicides that become inhibitors of this metabolic process can bind to cytochrome b [56], an enzyme that is part of the bc1 complex, which is present in the internal mitochondrial membrane of eukaryotic organisms and is responsible for catalyzing the transfer of electrons from ubiquinol to cytochrome c [57]. Compounds that inhibit mitochondrial respiration block the electron transfer process in the airway and lead to an energy deficit due to a shortage of ATP [58]. Many of the fungicides can cause damage to process such as DNA replication and transcription in phytopathogenic fungi. Within the enzymes that involve these metabolic processes, topoisomerases are ubiquitous enzymes found in various living organisms, including fungi pathogens [59], as they are necessary for the maintenance of DNA topology [60]. The main goal to direct the design of novel bioactive compounds is the molecular characterization of these enzymatic targets and the determination of their quaternary structure, their active site and mainly, successful protocols for their obtention. However, few reports have been published for *FOX* enzymatic targets making difficult the access to this information.

Despite this, computational tools such as molecular docking, molecular dynamics, and quantitative structure–activity relationship (QSAR) offer an essential alternative for the rational design of new antifungal agents against *FOX*. Recently, in silico molecular docking studies of pyrrolo(1,2-*a*)pyrazine-1,4-diones, hexahydro, and pyrrolo(1,2-*a*)pyrazine-1,4-diones, hexahydro-3(2-methylpropyl)pyrrolo(1,2-*a*)pyrazine-1,4-diones against some enzymatic targets, showed the potential of these compounds as bioactive multitargeting compounds [61]. Hydrazone derivatives bearing imidazole or benzimidazole nucleus were designed, synthesized, and evaluated for their antioxidant, antifungal, and anti-acetylcholinesterase activities. Molecular docking studies of the most active compounds showed reasonable binding modes in the active site of *FOX* FGB1 enzyme and acetylcholinesterase, and in silico predictions of ADME and pharmacokinetic parameters indicated that these compounds should have good oral bioavailability [62]. The structure–antifungal activity relationship studies of fusarubin analogs using molecular docking and simulations-allowed establishing these compounds' possible mechanism against three target enzymes [63]. Finally, molecular docking studies of some Schiff bases derived from 5-(morpholinosulfonyl)indol-2,3-dione and appropriate amines or hydrazide derivatives indicated good binding with the evaluated enzymatic targets lower binding energy of the most promising compounds than a standard drug used [64]. These recent antecedents involving computational tools leading to the generation of structure–activity correlation models will allow the effective obtaining of new agrochemical agents.

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