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Antivirulence drugs against fungal pathogens as a therapeutic alternative to antimicrobial-resistant fungal infections

Moléculas antivirulencia contra patógenos fúngicos como alternativa terapéutica a las infecciones fúngicas resistentes a los antimicrobianos

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Abstract

Fungal infections have become a global public health problem in recent decades, mainly due to the emergence and spread of fungal pathogens resistant to antifungal drugs, which contribute to approximately 1.27 million deaths every year. Therefore, the search for new therapeutic strategies is crucial. Virulence factors of pathogenic fungi are essential mediators in the establishment, invasion and spread of mycoses, so blocking these virulence factors becomes a therapeutic target. In recent years, the development of antivirulence drugs has attracted increasing scientific interest. These molecules have the ability to inhibit the production of one or more virulence factors of pathogens, thereby attenuating their pathogenicity and infectivity, making them a promising therapy. The objective of this review is to describe the antivirulence drugs reported against fungal pathogens of clinical priority by the World Health Organization.

KEY WORDS:
Antifungal agents; mycoses; therapy; virulence; fungi.

Resumen

Las infecciones fúngicas se han convertido en un problema de salud pública a nivel mundial en las últimas décadas, principalmente debido a la aparición y propagación de patógenos fúngicos resistentes a los fármacos antifúngicos; se les atribuye 1,27 millones de muertes al año. Por ello, la búsqueda de nuevas estrategias terapéuticas es crucial. Los factores de virulencia de los hongos patógenos son mediadores esenciales en el establecimiento, invasión y propagación de las micosis, por lo que el bloquear o inhibir a los factores de virulencia se convierte en un objetivo terapéutico. En los últimos años, el desarrollo de fármacos antivirulencia ha suscitado un creciente interés científico. Estas moléculas tienen la capacidad de inhibir la producción de uno o más factores de virulencia de los patógenos, atenuando su patogenicidad e infectividad, lo que las convierte en una terapia prometedora. El objetivo de esta revisión es describir los fármacos antivirulencia reportados contra patógenos fúngicos de prioridad clínica por la Organización Mundial de la Salud.

PALABRAS CLAVE
Antifúngicos; micosis; terapia; virulencia; hongos.

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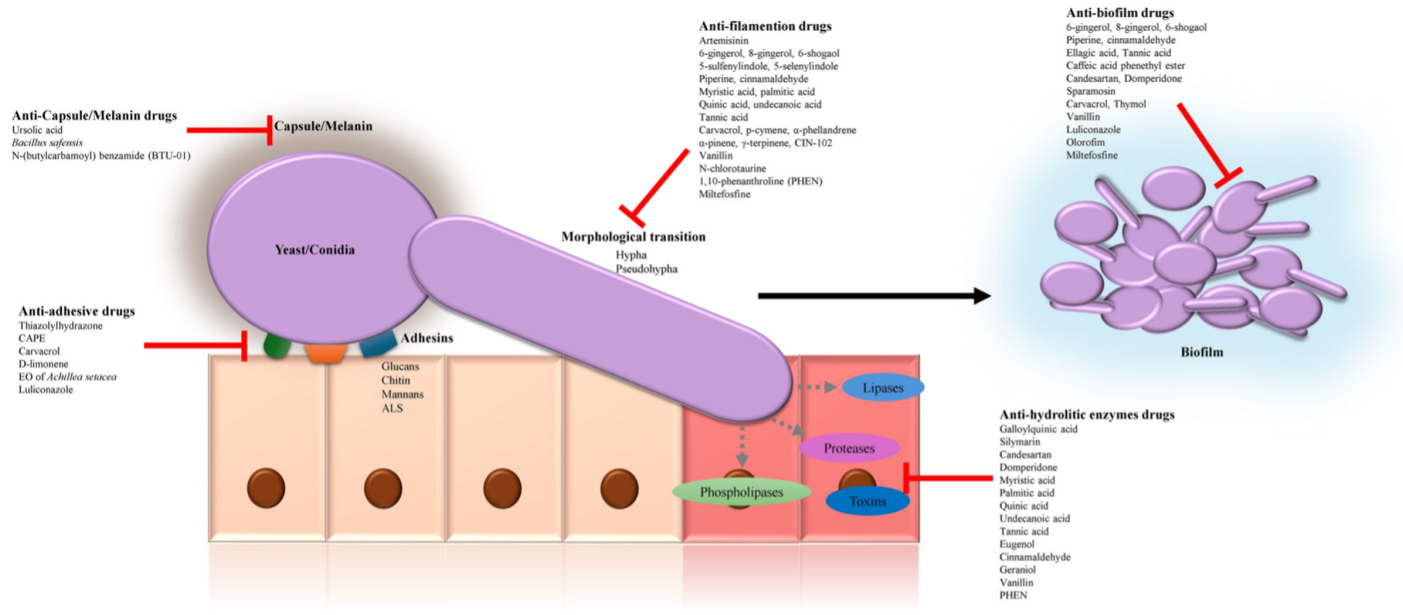
Introduction

Fungal pathogens are a growing public health concern worldwide; it is estimated that fungal diseases contribute to approximately 1.5 million deaths annually, but the global burden may be higher due to gaps in diagnosis and clinical understanding. In addition to the human cost, the economic burden of mycoses is estimated to be approximately $11 billion every year. A major causes of this global health threat is the emergence of antifungal resistance in several genera of fungal pathogens, coupled with limited effective and safe treatment options.[1,2] In 2022, the World Health Organization (WHO) published the first global list of fungal pathogens for research, development and public health action to mitigate antifungal resistance, which included the following pathogens: *Candida* spp, *Cryptococcus* spp, *Aspergillus fumigatus*, *Mucor* spp, *Fusarium solani, Scedopsorium* spp, *Lomentospora prolificans*, *Coccidioides* spp and *Paracoccidioides* spp.[3] The challenges posed by these pathogens highlight problems in the treatment of infections, including the prevention of mycosis in hospitals. Therefore, the search for new therapeutic strategies is crucial.

In addition to antifungal resistance, priority fungal pathogens possess a wide arsenal of virulence factors essential for colonization, invasion, tissue damage, immune evasion and mycosis spread. In general, the virulence factors of yeasts and moulds can be divided into: 1) Surface molecules such as glucans, mannans, chitin, lipoproteins, glycoproteins, agglutinin-like sequence (ALS), hyphal wall-specific protein (Hwp) and integrin-like proteins, which are essential for fungal adhesion. 2) Secreted molecules such as toxins and hydrolytic enzymes (proteases, lipases, phospholipases, hyaluronidases, nucleases) whose function is to degrade components of the extracellular matrix and tissues facilitating invasion. 3) Morphological transition is one of the main virulence factors of some yeasts such as Candida species and filamentous fungi, allowing invasion, dissemination and tissue destruction. 4) Melanin and fungal capsules that evade the action of phagocytic cells and 5) fungal biofilms to evade antifungals, the immune system and persist in the environment.4 The action of these virulence factors determines the pathogenicity and severity of the disease, so the development of drugs with inhibitory or attenuating action on virulence becomes a novel strategy in the fight against antifungal infections (Figure 1).

Figure 1

Virulence factors of fungal pathogens as potential therapeutic targets



Fungal pathogens exhibit a repertoire of virulence factors such as adhesins, morphological transition, secretion of toxins and hydrolytic enzymes, capsule, melanin and biofilm production, essential for colonization, establishment and dissemination of an infection, so blocking these physiological mechanisms of fungal pathogens becomes a promising therapeutic target. The red lines represent potential therapeutic targets and examples of molecules with antivirulence activity against fungal pathogens.
Source: own elaboration.

Thus, blocking pathogen virulence factors is a new approach that has emerged in the last decade. Antivirulence drugs are molecules that have the ability to inhibit one or more virulence factors, disarming pathogens rather than killing them or inhibiting their growth, thereby interfering with the pathogen's interaction with the host and limiting ability to establish infections. Currently, most antivirulence strategies focus on various bacterial targets, such as quorum sensing, bacterial biofilms, bacterial motility, bacterial toxins, bacterial pigments, bacterial enzymes and bacterial surfactants, highlighting their potential as targets for attenuating bacterial virulence.[5,6] In recent years, there has been increasing interest in the search for molecules that attenuate the virulence of pathogenic fungi in the fight against antifungal resistance.

Antivirulence strategies against priority fungal pathogens

Anti-adhesive drugs

Adhesion of fungal pathogens to biotic and abiotic surfaces is the first step in colonization and establishment of infection, so blocking this stage is crucial to prevent mycoses. Several molecules have been reported to attenuate adhesion of *Candida* species, for example Thiazolylhydrazone inhibits adhesion of *Candida albicans* to human buccal epithelial cells reducing oral candidiasis in a murine model.[7] Likewise, Caffeic acid phenethyl ester (CAPE) and carvacrol decrease the adhesion of *C. albicans* and *Candida auris* to lung epithelial cells.[8,9] While D-limonene blocks adhesion of *Candida parapsilosis* to oral cells.[10] The essential oil of *Achillea setacea* was shown to inhibit microbial adhesion of *Candida glabrata*, *Aspergillus niger*, *Rhizopus nigricans*.[11] On the other hand, luliconazole decreased adhesion rate of *L. prolificans* and *Scedosporium* spp (Figure 1).[12] However, further studies are needed to understand the mechanism of action of these molecules to prevent fungal adhesion.

Fungal morphological transition blocker drugs

Morphological transition is a factor that increases the virulence and pathogenicity of pathogenic fungi allowing penetration, invasion and tissue damage. Liang et al. demonstrated that artemisinins inhibit the Ras1-cAMP-Efg1 pathway, suppressing *C. albicans* hyphal formation and reducing oral candidiasis.[13] On the other hand, molecules such as 6-gingerol, 8-gingerol, 6-shogaol, 5-sulfenylindole, 5-selenylindole, piperine, cinnamaldehyde myristic acid and palmitic acid attenuate *C. albicans* hyphae formation by reducing the expressions of specific hyphae genes (*HWP1*, *ECE1* and *CPH1*).[14-17] Similarly, quinic acid and undecanoic acid have shown activity in blocking hyphal growth of *C. albicans* and *Candida tropicalis*.[18] Recently, Flores-Maldonado et al. reported that tannic acid decreases hyphal formation of *C. albicans*, *C. tropicalis* and *C. parapsilosis,*[19] and inhibits conidia germination of *A. fumigatus* and *F. solani*.[20] Several studies have shown that essential oils and their pure components such as carvacrol, *p*-cymene, α-phellandrene, α-pinene, γ-terpinene, CIN-102 and vanillin interfere with spore production and conidia germination of *A. fumigatus* and *F. solani*.[20-22] Sheehan et al. demonstrated that N-chlorotaurine induces an oxidative stress response in *A. fumigatus* by altering the growth of conidia and mycelia.[23] Metallopeptidase inhibitors such as 1,10-phenanthroline (PHEN) completely blocked the transformation of conidia into hyphae in *Scedosporium apiospermum,*[24] similarly, miltefosine affected the development of hyphae of *Scedosporium* species and *L. prolificans* (Figure 1).[25]

Antivirulence targeting hydrolitic enzymes

The production and secretion of hydrolytic enzymes and toxins by pathogenic fungi is crucial in the invasion and spread of infection, these virulence factors have the ability to disrupt components of the extracellular matrix, cell membranes and tissues facilitating fungal damage. Al-Madboly *et al*. demonstrated in a preclinical study that galloylquinic acid inhibits the proteinase and phospholipase activity of *C. albicans* by downregulate the expression of *SAP1*, *PLB1* and *LIP1*, in addition to its potential therapeutic use during vaginal candidiasis.[26] Similarly, silymarin exhibits antivirulence activity by inhibiting the proteinase activity of *C. albicans* by blocking the expression of the *SAP4* gene.[27] Candesartan and domperidone have been shown to reduce the activity of *C. albicans* hemolysins, phospholipases, lipases and proteases by inhibiting the expression of genes specific to these hydrolytic enzymes.[28] Moreover, myristic acid, palmitic acid, quinic acid, undecanoic acid and tannic acid attenuate the secretion of aspartyl proteases and lipases in *C. albicans*, *C. auris*, *C. tropicalis* and *C. parapsilosis*.[15,18,19] On the other hand, natural extracts from plants or invertebrates have been used as antivirulence agents against *Cryptococcus neoformans* by inhibiting the production of hydrolytic enzymes such as peptidases or PLB1 phospholipases and decreasing the intracellular replication of cryptococci in phagocytic cells.[29,30] Likewise, plant-derived compounds such as eugenol, cinnamaldehyde, geraniol, vanillin and tannic acid reduce the protease and elastase activity of *A. fumigatus* and *F. solani*.[20,31] Silva *et al*. showed that PHEN and Ethylene glycol-bis(β-aminoethyl ether) inhibit the secretion of polypeptides and metallopeptidases from *S. apiospermum* (Figure 1).[24]

Antivirulence drugs targeting immune evasion mechanisms

The capsule and melanin of fungi are essential virulence factors to persist in the environment and evade host defenses; these molecules are able to prevent phagocytosis, neutralize reactive oxygen species and other radicals, resist UV radiation and produce a physical barrier that defends the fungal cell. For this reason, melanized and capsulated fungi are adapted to be human pathogens: blocking these virulence factors becomes a therapeutic target (Figure 1). Wang *et al*. demonstrated that ursolic acid inhibited the capsule and melanin production of *C. neoformans in vitro*.[32] Similarly, *Bacillus safensis* through its chitinase activity, destabilizes cell wall architecture and changes in morphology by preventing proper anchoring of melanin and polysaccharide components of the capsule, thus disarming the virulence factors of *C. neoformans*.[33] Moreover, N-(butylcarbamoyl) benzamide (BTU-01), alone and in combination with amphotericin B, significantly decreases the size cells and capsules of *C. neoformans*.[34]

Anti-biofilm drugs

Fungal biofilms consist of multicellular communities embedded in a matrix of extracellular polymeric substances that allow fungi to evade antifungals and the immune system and persist in the environment. Several studies have shown that natural compounds such as 6-gingerol, 8-gingerol, 6-shogaol, piperine, cinnamaldehyde, ellagic acid, caffeic acid phenethyl ester and tannic acid inhibit the formation of biofilms of *Candida* species.[8,14,16,19] Similarly, the FDA-approved drugs candesartan and domperidone inhibited *C. albicans* biofilm formation.[28] On the other hand, Chen et al. demonstrated that sparamosin reduced *C. neoformans* biofilm formation.[35] While Korem et al. exhibited the effect of new heterocyclic compounds on *C. neoformans* and *C. gattii* biofilm formation.[36] Regarding filamentous fungi "molds", Ríos-López et al. reported that vanillin and tannic acid attenuated the biofilm formation of *A. fumigatus* and *F. solani*.[20] Likewise, thymol and carvacrol showed anti-biofilm activity against *Fusarium* spp.[37] Finally, molecules such as luliconazole, miltefosfine and olorofim decrease biofilm formation of *Scedosporium* spp and *L. prolificans* (Figure 1).[12,25,38]

Challenges and future perspectives

Currently, the repertoire of new antifungals is limited and therapeutic options to combat antifungal-resistant mycoses are scarce. Therefore, the search for new therapeutic strategies is crucial. In the last decade, antivirulence drugs have generated a growing expectation whose objective is to attenuate the pathogenicity of fungi. One potential advantage of antivirulence drugs is that most of them have the capacity to block multiple virulence factors (Table 1), which could decrease fungal virulence. However, currently there is little information on the mechanisms of action of these molecules. The main challenge of antivirulence drugs is that most of them lack antifungal activity and cannot eradicate the pathogenic fungus, which could cause clinical problems during mycoses. To overcome this challenge, the combination of antivirulence molecules with conventional antifungal drugs has been proposed and has been shown to have synergistic effects.[9,19,20,34] Another future clinical challenge is to assess whether fungal pathogens are able to develop resistance to these drugs in the long or medium term.

Conclusión

Antivirulence drugs are molecules capable of disarming and attenuating the virulence of pathogens, allowing containment and limiting the invasion of infection, which has become a novel and attractive strategy to address emerging antimicrobial resistance. Although experimental findings *in vitro* and *in vivo* experimental models show promising results with antivirulence therapy against multidrug-resistant fungal pathogens, further studies are needed to demonstrate the efficacy of antivirulence drugs in the treatment and prevention of mycoses. Therefore, preclinical or clinical trials are the next step in considering the use of these strategies as an alternative to the uncertain future of antimicrobial resistance.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de interés. Son responsables del contenido y la redacción del artículo.

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