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REVIEW ARTICLE

The Role of Epigenetic Mechanisms in Modulating Antifungal Resistance in Fungi

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ABSTRACT

The global population's health is significantly and severely threatened by antimicrobial resistance. Consequently, the scientific community allocates substantial of resources and efforts to confront this challenge. By contrast, the majority of these endeavours are focused on antibiotics, and research on antifungal resistance (AFR) is significantly underrepresented. Fungal pathogens acquire drug resistance through a variety of mechanisms. Innovative antifungal treatments and the enhancement of the efficacy of existing antifungals can be facilitated by a comprehensive understanding of the mechanisms by which fungal infections acquire drug resistance. Chromatin structure and gene expression regulation are critical components of fungal species' adaptation to antifungal stress, which suggests a potential therapeutic approach to AFR. This suggests that developing strategies that concentrate on these mechanisms may be a viable approach for controlling antifungal resistance. For the regulation of a diverse array of fungal biology components, epigenetic pathways are indispensable in medical mycology. The development process and the capacity to modify and adapt physical characteristics and resistance to antifungals that are used to treat fungal infections are critically dependent on these methods. The development process and the ability to modify and adapt physical characteristics and resistance to antifungals that are used to treat fungal infections are critically dependent on these methods. A significant concern is increasing resistance to the limited therapeutic options that are available to manage invasive fungal infections, such as histone acetylation and methylation, chromatin remodelling, and gene silencing through heterochromatin, which inhibit prevailing drug-resistance mechanisms. This review discusses the significance of epigenetic pathways in mediating drug resistance in fungi as well as mechanisms of antifungal drug resistance.

Keywords: Epigenetic; Genetic; Candida; Drug Resistance; KDAC inhibitors.

Introduction

Fungal infections kill ~1.6 million people every year [1]. There are approximately 150 million mucosal infections, and 200,000 mortalities caused by *Candida albicans* infections annually in USA. An annual health care cost of nearly $2 billion is expended by the United States due to *Candida* infections [2]. *Candida albicans* is the cause of approximately 75% of all Candida infections, a significant global health concern due to its increased severity [3].

Commensal organisms, such as *Candida* species, colonize the mucous membranes of the gastrointestinal, vaginal, and gastrointestinal tracts without causing any adverse effects. However, this opportunistic pathogen has the capacity to multiply considerably on the surfaces of mucous membranes and to cause systemic disease if the immune system or microbiota of the host are compromised. As medical technology has advanced, the incidence of systemic *Candida* infections and the corresponding mortality rate have both increased. The

most frequently detected species in medical settings is *C. albicans* [4-6].

Systemic and disseminated diseases, as well as severe superficial and mucosal infections, are the most severe clinical symptoms of *Candida* species infections. All of these infections contribute significantly to mortality and morbidity [7]. The prevalence of invasive candidiasis infections caused by non- *C. Albicans* species (NAC) has increased over the past decade [8]. *C. tropicalis, C. glabrata, C. parapsilosis,* and *C. albicans* are the four *Candida* species that are most frequently identified in cases of invasive candidiasis (IC). Although there may be some variation due to age and geography, the most likely cause is variation in antifungal usage and species origin.

As a first-line treatment for IC, only three classes of antifungals that target two distinct pathways are used [9]. Azoles (such as fluconazole), polyenes (such as amphotericin B) specifically target ergosterol, the primary sterol detected in fungi, is echinocandins (anidulafungin) that cause destruction of the fungal cell wall by inhibiting β-1,3-glucan synthase.

In the past two decades, the treatment of bacterial infections has been made possible by the approval of fifteen novel antibiotics [10]. There are five distinct categories into which these antibiotics are categorized. At the same time, echinocandins was the sole approved treatment for fungal infections. In addition, for the past decade, isavuconazole is the sole antifungal drug that has been approved for the treatment of IC [9]. Echinocandins have become the primary treatment option for IC in clinical practice due to their efficacy in eliminating fungi and their drug safety [11].

Phenotypic plasticity is a crucial regulatory mechanism that facilitates the rapid adaptation to difficult host environments. Changes in the environment can have a significant impact on the structure of organisms. In order to enhance their pathogenic capabilities and acclimate to their environment, organisms must be able to transition between distinct morphological changes [12, 13]. For instance, *C. albicans* can develop into multicellular hyphae after first growing as a unicellular round yeast cell [14]. Yeast cells are indispensable for the initiation of infections, the dissemination of the infection throughout the body, and the promotion of cell proliferation. Hyphae facilitate the invasion and disintegration of tissues [15].

Epigenetics is the study of heritable changes in gene expression that occur without any modifications to the DNA sequence. Epigenetics is currently transforming our comprehension of the fundamental principles that regulate the occurrence of maladies in individuals and normal development. Nevertheless, the exhaustive examination of the modifications in chromatin structure that occurs during infection, which is a comprehensive examination of the interaction between the fungal and its host, is still incompletely understood. Nevertheless, the recently developed field of research that examines the role of epigenetics in the development of infectious diseases by disrupting the host defence system [16]. Epigenetic regulation influences the expression of virulence attributes and the differentiation of a pathogen [17, 18]. This article discusses the resistance mechanisms of a variety of antifungal drugs and the importance of epigenetic pathways in mediating drug resistance in fungi. In addition, we provide a concise overview of the antifungal properties of Histone deacetylase (HDAC) inhibitors and the results of recent clinical trials that have utilized these drugs.

1. Antifungals and their targets

To effectively manage candidiasis, it is crucial to administer antifungal medications that selectively target an

extensive range of biological processes (Figure 1) [19]. These agents can either completely eradicate the yeast (fungicidal) or inhibit its growth (fungistatic). Cell wall formation, RNA synthesis, and cell membrane synthesis are among the biological targets that are involved. For each of these biosynthetic processes to be carried out, a sequence of enzymes is required [20]. The target and mechanisms of antifungal agents used to treat candidiasis are summarized in Table1.

Table (1): Mechanisms of action and resistance of the main antifungal drugs used for *Candida* species

Antifungal Class	Antifungal Drug	Spectrum of Activity	Mechanism(s) of Action	Mechanism(s) of Resistance	Commonly used drugs	Species reported with resistance	References
Polyenes	Amphotericin B	Fungicidal	In the fungal membrane, polyene molecules form a connection with ergosterol by inserting into the lipid bilayers, resulting in the formation of pores that disrupt the plasma membrane, causing oxidative injury.	Mutations in the *ERG3* gene affect ergosterol biosynthesis and content in the fungal membrane is responsible for a decrease access to the drug target; susceptibility to oxidative damage by increasing catalase activity.	Amphotericin B, nystatin, and natamycin	*C. albicans* *C. krusei* *C.guillermondi* *C. glabrata*	[21, 22]
Pyrimidine analogues	5-Flucytosine	Fungicidal	The incorporation of toxic fluorinated pyrimidine antimetabolites into DNA and RNA causes the inhibition of cellular function and division.	Mutations in the enzyme uracil phosphoribosyl transferase (Fur1p), decreasing the formation of toxic antimetabolites.		*C. albicans* *C. krusei* *C. glabrata* *C.auris* *C. lusitanie* *C.guillermondi*	[21, 23]
Azoles	Fluconazole Voriconazole Posaconazole	Fungistatic	Inhibition of the fungal cytochrome P450 14α-lanosterol demethylase and the accumulation of toxic methylated intermediates, which leads to the disruption of fungal cell membrane function and growth inhibition.	Overexpression of cell membrane efflux pumps, decreasing drug concentration (upregulation or overexpression *CDR* and *MDR* genes); alteration of the target enzyme, decreasing affinity to the binding site (point mutation in *ERG11* gene); upregulation of the target enzyme (overexpression of *ERG11* gene).	Ketoconazole, fluconazole, voriconazole, itraconazole and posaconazole	*C. albicans* *C. glabrata* *C. paraspilosis* *C. auris* *C. dublenisis* *C. krusei* *C. tropicalis*	[24]
Echinocandins	Caspofungin Anidulafungin Micafungin	Fungicidal	Inhibition of β-(1,3) glucan synthase results in a reduction in the production of β-(1,3) glucan, a main component of the fungal cell wall.	Point mutations in *FKS1* and *FKS2* genes	Caspofungin, micafungin and anidulafungin	*C. auris* *C. albicans* *C. glabrata*	[25]

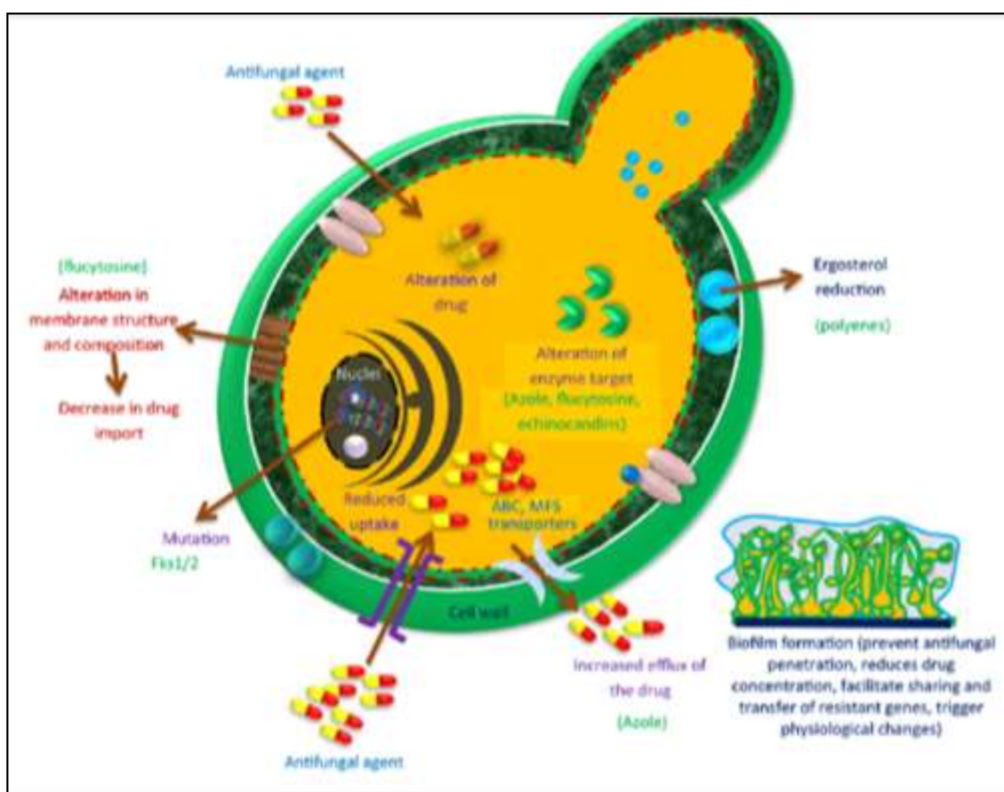

Figure 1: Different mechanisms of drug resistance adapted by *Candida* species [19]

https://link.springer.com/article/10.1007/s11274-020-02940-0

2. Mechanism of drug resistance in *Candida* species

Pyrimidine analogues

Pyrimidine analogues are a specific type of antifungal drugs that inhibit of DNA and RNA synthesis [26]. Flucytosine (5FC) is a pyrimidine analogue that is frequently used to treat fungal infections. Previous studies [27, 28] have demonstrated that the 5FC is effective in suppressing the proliferation of numerous yeasts, such as *Candida* species and *Cryptococcus neoformans*. However, the efficacy of antifungal drugs has been diminished due to the widespread incidence of resistance in many fungal species. 5FC was used in combination with other antifungals, such as fluconazole and amphotericin B [29]. The cytosine deaminase enzyme converts the 5FC to 5-fluorouracil (5FU) after it is introduced into the fungal cell via a permease enzyme. 5-fluorouridylic acid (FUMP) is produced by the enzyme UMP pyrophosphorylase, which converts 5FU to FUMP. Protein synthesis is impeded by FUMP after it is phosphorylated and incorporated into RNA [30]. The antifungal susceptibility test has been used according to the National Committee for Clinical Laboratory Standards (NCCLS), to ascertain the minimum inhibitory concentration for 90% of fungal isolates (MIC90), which varies from 0.12 to 1 ug/mL depending on the species [31]. Thus, it is an effective agent for numerous critical *Candida* species, such as *C. albicans, C. glabrata,* and *C. dubliniensis*, at relatively small doses. However, *C.krusei* exhibits a significantly higher intrinsic resistance, as evidenced

by the MIC_{90} threshold of 32 µg/mL and the limited sensitivity of cells to 5FC [32].

The resistance to 5-FC may be induced by a mutation or loss of any of the three essential enzymes (FCY1, FCY2, or FUR1), as was observed in *Saccharomyces cerevisiae* [33]. It is also feasible for the fungal cell to avoid deleterious antifungal activity by enhancing pyrimidine production [34]. In 1991, Kern et al. were among the first to establish a correlation between a point mutation (Arg134Ser) in the *S. cerevisiae FUR1* gene and 5-FC resistance [35]. 5-FC-resistant clinical *Candida* isolates contain nonsynonymous mutations in the *FUR1, FCY1/FCA1,* and *FCY2* loci [36].

Azoles

Azoles are heterocyclic compounds that contain a nitrogen atom in their ring structure. The common azoles are used as antifungal agents including triazoles as (Fluconazole, voriconazole, and posaconazole). Lenosterol 14α-demethylase is the cytochrome P450 enzyme that is responsible for the conversion of lanosterol to ergosterol. These compounds function by inhibiting the cytochrome P450 enzyme lanosterol 14α-demethylase, which is responsible for the conversion of lanosterol to ergosterol. In yeast, the *ERG11* gene encodes this enzyme., Ergosterol is the primary sterol, like cholesterol in mammals, in the cellular membrane of the fungus species. It is crucial for the regulation of the membrane's elasticity [37]. Azoles exert their effects on the cell membrane of *Candida* through the reduction of ergosterol levels and the accumulation of other detrimental 14α-methylated sterols. Subsequently, this leads to a decrease in the cell membrane's adaptability and impaired cell proliferation [38].

The rise of azole-resistant candida isolates has been linked to the long-term and widespread use of azoles, such as fluconazole [39]. Among the molecular mechanisms underlying acquired resistance to azoles is the involvement of mutations or changes in the expression of the *ERG11* gene [40]. An increase in the synthesis of the encoded enzyme, lanosterol 14α-demethylase, which is the main target of azole drug, is the consequence of overexpressing *ERG11* above normal. The intracellular concentration of azoles is not high enough to prevent the function of the enzyme due to the higher levels of the enzyme [41].

Azole resistance in human fungal pathogens is the consequence of a diverse array of mechanisms, with the overexpression of multidrug efflux pumps and membrane-associated transporters from the ATP-binding cassette transporter (ABC-T) and major facilitator transporter (MFS-T) superfamily occupying the central stages, respectively. The concentration of the drug within the cell is considerably reduced as a result of the active pumping of azoles out by these transporters [42]. Gene amplification and/or gain-of-function mutations in the transcriptional activator (Zn-cluster proteins)-encoding genes (*TAC1* and *MRR1* in *C. albicans* and *PDR1* in *C. glabrata* and *C. auris)* contribute to the overexpression of azole transporters. [43]. Pleiotropic drug resistance (PDR) or multidrug resistance (MDR) is the regulatory network to which this mechanism belongs [44].

Polyenes

Furthermore, these antifungal drugs prioritize the inhibition of ergosterol synthesis in the plasma membrane, which results in the fungus's death. They have the capacity to develop holes or pores and bind to ergosterol [45]. Fungal cells are destroyed by the rapid discharge of monovalent ions (e.g., K^+, Na^+, H^+, and Cl^-) that is facilitated by porous formation. Polyenes include nystatin and amphotericin B. The sole antifungal drug employed for systemic treatment is amphotericin B. As a result,

amphotericin B has a more potent effect on ergosterol, the primary sterol in fungi, than on cholesterol, the most prevalent sterol in mammals. To mitigate the adverse effects of amphotericin B three distinct variants were modified as following: the cholesteryl sulfate complex (ABCD), the lipid complex (ABLC), and the liposomal formulation (LAMB). Comparatively to these formulations, conventional amphotericin B may demonstrate distinctive pharmacokinetic properties [46].

Mutations in the *ERG 2* and *ERG 3* genes, which encode two critical enzymes (C-8 sterol and C-5 sterol) that are involved in the synthesis of ergosterol, are the cause of resistance to amphotericin B. There have been reports of clinical isolates of *C. albicans* that are resistant to amphotericin B and have a reduced ergosterol content because of defective *ERG2* and *ERG* 3 genes [47].

Resistance to azoles is generally observed at a substantially higher frequency in clinical settings than resistance to echinocandins, whereas resistance to polyenes is uncommon [48]. Even though *Candida albicans* is the most common agent to cause bloodstream *Candida* infections, *C. auris* and *C. glabrata* are drug-resistant *Candida* species. *C. auris* is resistant to all three antifungal classes, whereas *C. glabrata* is resistant to azoles and echinocandins [49, 50]. Notably, azole and echinocandin resistance has been reported in approximately 8% of clinical isolates of *C. glabrata* [51]. On the other hand, 41% and 4% of C. auris isolates were discovered to be resistant to two and three antifungal classes, respectively [52].

Echinocandins

Candida spp. is often targeted by antifungal agents that disrupt the cell wall and prevent the synthesis of ergosterol [53]. Cell wall is the primary defence of fungal cells that serves as a rigid exterior barrier and protects against osmotic stress [54]. For antifungal pharmaceutical treatments, it is crucial to target the enzymes responsible for cell wall synthesis, as mammalian cells lack cell walls. Echinocandins selectively target the cell wall. This group comprises anidulafungin, micafungin, and caspofungin [55]. The activity depends primarily on the enzyme β1-3 glucan synthase, which is encoded by three distinct genes: *FKS1, FKS2*, and *FKS3*. The *FKS1* and *FKS2* genes encode the subunits of β (1, 3) D-glucan synthase, a critical component of fungal cell walls that contributes to the synthesis of β (1,3) D-glucan. By inhibiting the activity of this enzyme, echinocandins decrease the quantity of glucans in the cell wall [56]. The synthesis of matrix is a critical mechanism of resistance for a variety of Candida species, including *C. albicans, C. glabrata, C. parapsilosis, C. tropicalis,* and *C. dubliniensis*, and it is strictly regulated. The synthesis of β-1, 3-glucan, a critical component of biofilms, is facilitated by glucan synthase [57]. Β-1,3-glucan biosynthesis and biofilm matrix development are regulated by the yeast Protein kinase C (PKC) pathway through downstream components such as Smi1, Rlm1, Rho1, and Fsk1 [58]. Several mutations that are linked to resistance to echinocandins were identified in the *FKS1* and *FKS2* regions of *C. albicans* and other non-*Candida* species. Their designations were "hot spots" 1 and 2 (HS1 and HS2). The "hot spots" in the *C. albicans FKS1* gene are the amino acids 641-649 and 1,345-1,365 [59].

3. Fungal Epigenetics

Epigenetic modifications alter the observable characteristics of an organism without affecting the actual DNA sequences, thereby altering the genes expression. In an effort to endure adverse conditions, pathogens frequently implement epigenetic mechanisms as an evolutionary strategy [60]. Both RNA and

chromatin can be modified to influence epigenetic changes. RNA is responsible for the modification of the epigenome through the processes of RNA interference (RNAi) and noncoding RNAs. Fungi utilize epigenetic pathways as a mechanism to adapt to their environment and effectively mitigate a variety of stressors, such as that induced by antifungal drugs [21].

Epigenetic mechanisms of drug resistance in fungi

Some examples of chromatin modifications include chromatin remodelling, which involves the modification of the chromatin structure, and interactions between DNA molecules. This comprises chemical transformations, including post-translational modifications (PTMs) of histone proteins and the methylation of nucleotide bases in the DNA. The N-terminal region of nucleosomal histones is particularly susceptible to PTMs [61]. As well as, a variety of epigenetic modifications, including acetylation, methylation, phosphorylation, ubiquitination, and sumoylation, among other processes [62, 63]. Examples of these epigenetic modifications are listed below.

1. RNA interference (RNAi): sRNAs, or short RNAs, facilitate RNA interference (RNAi). The RNA-dependent RNA polymerases and the endonuclease Dicer synthesize sRNAs [64]. The selective targeting of complementary RNAs is accomplished by the Argonaut complex and due to their processing; the Argonaut complex forms an association with these small RNAs (sRNAs). RNAi can either eradicate the target RNAs or delay the translation process [65].

2. DNA methylation: A 5-mC base alteration is produced when a methyl group is incorporated into the cytosine bases of DNA [66]. This mutation is frequently observed in both human genome and a specific fungus. In some organisms, adenine base methylation can occur and perform essential and critical functions [67]. The process of DNA methylation is carried out in prokaryotes to prevent the attack of phages and to facilitate the replication and restoration of chromosomes. In insects, DNA methylation is not as well-known, and it serves a distinct function in comparison to other organisms. However, in fungi, DNA methylation is investigated to analyse transcriptional alterations. In mammals, DNA methylation is associated with various types of malignancies and is crucial for the development of the placenta. Abnormal DNA methylation is associated with diseases such as rheumatoid arthritis, autoimmune diseases, and cancer (Figure 2).

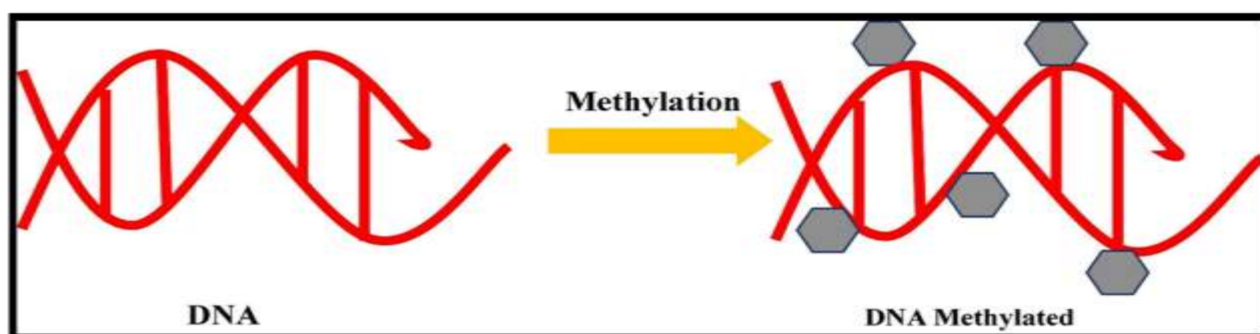

Figure 2: Epigenetic modulation showing DNA methylation: attachment of methyl group at 5′-carbon atom of cytosine ring [68; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9043899]

3. Histone modifications: Histones are crucial constituents of nucleosomes and serve as targets for many PTMs [69]. Methylation, acetylation, and phosphorylation are PTMs that are frequently investigated and extensively reported (Figure 3) [70]. Although certain examples are consistent, most of these modifications are subject to variation. Furthermore, the attachment of additional modifications can be inhibited by the addition of a single PTM to the same or adjacent amino acid residues, primarily due to steric factors [71].

These modifications are accelerated by enzymes such as protein arginine methyltransferases (PRMT), histone methyltransferases (HMT), and lysine acetyltransferases (KAT). Lysine deacetylases (KDAC) and lysine demethylases (KDM) are enzymes that are essential for the elimination of these modifications [72]. histone acetyltransferases (HATs) and histone deacetylases (HDACs) are the names of the enzymes that modulate histones. Histone modifications can either facilitate or inhibit the binding of transcription factors, enhancers, or chromatin remodelling proteins, thereby altering gene expression levels. Acetylated histones induce an unfolded structure, which facilitates transcription, whereas deacetylated histones increase chromatin compaction, thereby restricting transcription. Both histone deacetylases (HDACs) and histone acetyltransferases (HATs) are involved in reversible mechanisms that actively regulate transcription [73, 74].

***A.** Histone Methyl transferases and Demethylases*

In contrast to the extensive research conducted on histone acetyltransferases (HATs) and histone deacetylases (HDACs), the ongoing investigation into the role of histone methyltransferases (HMTs) and lysine demethylases (KDMs) in drug resistance in pathogenic fungi is still under investigation. New research has demonstrated that the resistance to azoles is reduced in *C. glabrata* cells when the alleles responsible for the production of histone H3K4 methyl transferase (*CgSet1*) and H3K36 methyl transferase (*CgSet2*) are removed [75, 76]. The regulation of azole resistance can be represented by the distinct functions of lysine 4 and 36 methylations in histone H3. Furthermore, the emergence of azole resistance, which is contingent upon *CgSet1* has been attributed to the activation of *ERG* genes, including the specific gene *ERG11*. Conversely, the *Cgset2Δ* mutant demonstrated a slight increase in the expression of *PDR1*-network genes, which may have contributed to its reduced susceptibility to fluconazole [76]. In accordance with this concept, the expression of *PDR1*-network genes is regulated by the histone demethylase *CgRph1* in *C. glabrata*. The basal expression of the *CgPDR1* and *CgCDR1* genes was reduced in the *Cgrph1Δ* mutant, and the susceptibility to fluconazole was significantly increased.

***B.** Histone Acetyltransferases*

Antifungal drug resistance in *C. albicans* and *C. glabrata* has been attributed to histone acetylation. [77, 78]. The deletion of the gene that encodes histone acetyltransferase 1 (Hat1) led to a change in the acetylation of histone H4 at lysines 5 and 12 before its integration into the chromatin [79]. The enhancement of *C. albicans'* susceptibility to caspofungin was demonstrated to be associated with an elevated release of reactive oxygen species (ROS) as a consequence of the modification [80]. The deletion of HAT1 or HAT2, which encode regulatory subunits of the chromatin assembly associated acetyltransferase complex NuB4, led to a reduction in resistance to voriconazole and itraconazole [78]. *HAT1* may play two distinct roles in regulating echinocandin and azole resistance. *GCN5* is present in a variety of multi-subunit

regulatory complexes, including the (Spt-Ada-Gcn5 acetyltransferase) SAGA and yeast SAGA-like SLIK complexes. Recent research has found a correlation between *C. albicans* resistance to caspofungin, but not to azole, and the fungal lysyl acetyltransferase, *GCN5* [81]. Furthermore, the higher susceptibility of the *GCN5Δ/Δ* mutant to caspofungin was not a result of elevated levels of reactive oxygen species (ROS) within the cell. As a result of the *ADA2* component's absence from the SAGA/ADA coactivator complex, the *ADA2Δ/Δ* mutant exhibited reduced lev els of H3K9 acetylation at the *MDR1* gene and faced challenges in the expression of the *MDR1* gene when *C. albicans* were subjected to fluconazole.

C. albicans enhanced its susceptibility to fluconazole [82]. Similarly, the *CgADA2* gene, which is responsible for H3K9 acetylation, was deleted from *C. glabrata*, which resulted in a sensitivity to all three classes of drugs: azoles, polyenes, and echinocandins. Nevertheless, the *CgPdr1*-mediated regulation of multidrug-resistance (MDR) genes remained unimpaired in the *CgADA2Δ* mutant [83].

C. *Histone Deacetylases*

C. albicans isolates that were resistant to azoles treatments exhibited increased gene expression for histone deacetylase-encoding genes, including *HDA1* and *RPD3* [77]. The sustained azole resistance that was established during the in vitro acquisition of fluconazole resistance ultimately resulted in a decrease in the elevated levels of *HDA1* and *RPD3* gene expressions observed in fluconazole-resistant strains [84].Thereby underscoring a transient requirement of histone acetylation in the antifungal resistance process (Figure 2). Additionally, *HDA1* and *RPD3* are critical for the regulation of azole resistance in *Saccharomyces cerevisiae* by influencing the activity of the heat-shock protein, Hsp90. Hsp90's efficacy was reduced due to the absence of *HDA1* and *RPD3*, as its acetylation is crucial for its activity regulation [85]. There is a substantial degree of conservation in the cellular chaperon in order to eradicate the fluconazole resistance in *C. albicans* that is contingent upon Hsp90, it was necessary to remove four KDACs (*Hos2, Hda1, Rpd3,* and *Rpd31*) [86].

The absence of the NAD^+-dependent histone deacetylase *Hst1* resulted in the development of fluconazole resistance in *C. glabrata*. The resistance was, however, resolved by the deletion of the *CgPDR1* or *CgCDR1* alleles in the *Cghst1Δ* mutant, which encode a critical MDR efflux pump [87]. This implies that the cellular response to azoles is dependent on *CgHst1*, and either *CgCDR1* or *CgPDR1* is essential for this process [88]. In addition, the expression levels of *CgCDR1* and *CgPDR1* transcripts were elevated in the *Cghst1Δ* gene mutant strains [89]. This indicates that *CgHst1* functions as a suppressor of the genes in the *CgPDR1* network [90]. The development of fluconazole resistance in *C. glabrata* cells was the consequence of the consistent increase in transcription of *CgCDR1* and *CgPDR1* genes, which was induced by the use of nicotinamide to inhibit *CgHst1* [91]. In addition, the production of a NAD+-dependent histone deacetylase is facilitated by the deletion of the *CaHST3* gene, which results in the development of resistance to echinocandins in *C. albicans*. In addition, the histone deacetylase Set3 complex regulates the resistance of biofilm-producing *C. albicans* cells to caspofungin and amphotericin B through the actions of four critical components: *CaSet3, CaHos2, CaSnt1,* and *CaSif2* [92].

4. Chromatin remodelling: The structure of chromatin is highly dynamic, which challenges the previous theories that classified it as either euchromatin (loosely condensed and

actively transcribed) or heterochromatin (densely condensed and not transcribed). A critical step in the initiation of transcription is the modification of the arrangement of nucleosomes within the genome by chromatin [93]. Due to the substantial energy demands of chromatin remodelling, ATP-dependent nucleosome remodels are essential [94]. The SWI/SNF and ISWI proteins are the subject of extensive research due to their role as chromatin remodels. Chromatin's degree of compaction or loosening is contingent upon the formation of loops in DNA sequences, which can lead to three-dimensional interactions that can impact transcription. The correlation between enhancers and promoters, which have the ability to recruit transcription factors and initiate the transcription process, is a meticulously researched example of this connection [74].

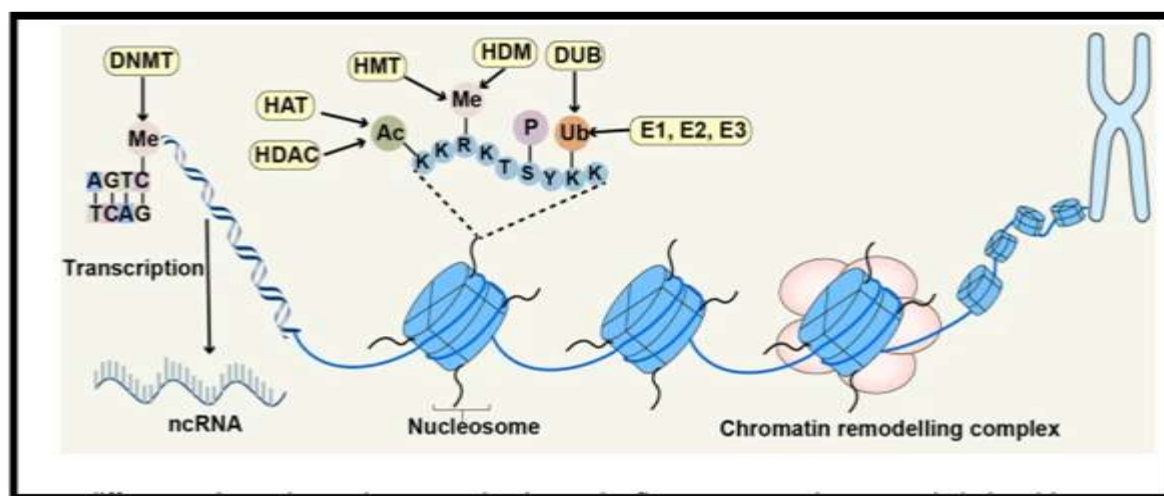

Figure 3: Four different epigenetic regulatory mechanisms. The figure presented DNA methylation, histone modification, chromatin remodelling, and ncRNAs. DNA methylation is a universal chemical modification by which methyl groups (Me) are added to the DNA molecule, usually happening on the CpG islands. Histone undergoes several different post-translational modifications, including acetyl (Ac), Me, phosphate (P) and ubiquitin (Ub). Chromatin remodelling complexes change the packaging state of chromatin by moving, sliding, disrupting, or restructuring the nucleosome. ncRNAs are participated in multiple physiological and pathological process by targeting different molecules [70]. https://www.nature.com/articles/s41392-023-01333-7

4. Using lysine deacetylases/ lysine acetyltransferases Modulators as Novel Antifungal Drugs

Pharmacological Modulation of Antifungal Resistance in Candida spp.

Few antifungals are available that can either inhibit growth of fungi or kill/destroy them [95]. The utilization of amphotericin B leads to the disruption of plasma membrane function. Biogenesis of cell wall glucans is inhibited by echinocandins. Flucytosine disturbs the synthesis of DNA. Azoles are inhibitors of the metabolism of ergosterol. Antifungal treatments are limited in their effectiveness by their toxicity, the increasing prevalence of drug resistance, and the unfavourable drug-drug interaction. However, drug that was previously considered the "gold standard", amphotericin B consistently induces significant toxicity in patients, thereby limiting its efficacy and usage. Triazoles continue to be the treatment of choice due to their moderate costs, outstanding

toxicity profiles, and ease of oral administration [96].

Nevertheless, the majority of triazoles exhibit fungistatic activities rather than fungicidal activities, which in turn facilitates the development of resistance [97]. Several non-*CS albicans Candida* (NCAC), particularly *C. glabrata*, demonstrate significant intrinsic resistance to triazoles and, in some cases, even resistance to echinocandins [98]. Nevertheless, the fungicidal echinocandins have a limited application due to their poor oral absorption and lack of efficacy against *C. neoformans* or invasive aspergillosis [99]. In addition, a recent study [98] declared the increased prevalence of echinocandins-resistant *Candida* isolates. This matter is of significant concern, particularly due to the increasing prevalence of these species in clinical isolates obtained from the bloodstream [98]. The incidence of echinocandin-resistant *C. glabrata* at some medical facilities in the United States increased dramatically from 2%–3% in 2001 to more than 13% in 2010 [100]. Furthermore, the identification of *C. glabrata* isolates that are resistant to antifungal drugs, such as azoles and echinocandins, has led to apprehension among patients infected with these strains, as there are only a few therapeutic options available.

Therefore, the efficacy of antifungal treatment is compromised by the escalating prevalence of systemic fungal infections, the emergence of drug resistance, and the scarcity of antifungal drugs. The urgency of the development of innovative and novel antifungal agents is further under comprehension [98].

Innovative therapeutics for non-infectious diseases have been developed by employing regulators of KATs/KDACs. Due to protein acetylation, a process that is associated with a variety of neurological diseases and malignancies [85]. Therefore, Currently, there are a multitude of KDAC inhibitors in clinical use or in the process of being developed as chemotherapy [84]. The efficacy of the fungal KDAC inhibitor MGCD290 was demonstrated in the presence of fluconazole and echinocandins efficacy in the treatment of drug-resistant *Candida* species and filamentous fungi [101]. The most well-known inhibitor of KDAC is Trichostatin A (TSA), which increases the susceptibility of *Candida* species to azoles [102]. TSA's inhibitory effect on ergosterol synthesis or the incorporation of the SET3C KDAC complex are potential explanations for the observed synergy. The reason for this is that TSA functions as a regulator of Set3, which in turn regulates the protein kinase A (PKA) signalling pathway through *Efg1* [103].

Histone Deacetylase Inhibitors

Monotherapy with Histone Deacetylase Inhibitors (KDACIs) has a minimal impact on the overall survival of *Candida* species, both in vitro and in vivo [104]. However, the genetic data indicates that the treatment of *Candida* spp. with KDACI can have the potential to disrupt chromatin structure, alter stress response pathways, and impair phenotypic plasticity. Therefore, the yeast's ability to tolerate and/or respond to anti-fungal drugs may be impaired. In conjunction with conventional antifungals, the synergistic anti-*Candida* effect of KDACIs is consistently underscored in an increasing number of studies [105].

The cyclopentylidene-(4-(4-chlorophenyl) thiazol-2-yl) hydrazine CPTH2, a lysine acetyl-transferase (KAT) inhibitor, has been found to exhibit fungistatic actions in vitro against Candida species from the CTG-clade [106]. The exact fungal molecular target of this compound is still unknown. On the other hand, genetic data indicates that it does not have a specific effect on Gcn5p. It is remarkable that CPTH2 is more effective against caspofungin-resistant

Candida isolates. It is important to note that CPTH2 is more effective against caspofungin-resistant *Candida* isolates, which suggests not only a mechanistic connection between echinocandin resistance and the CPTH2 target, but also its potential therapeutic benefits in the treatment of fungal infections [107].

Shih *et al*. [108] demonstrated that chitosan, which is a by-product of chitin deacetylation, possess therapeutic value for *Candida* infections due to its exceptional biocompatibility, biodegradability, and low toxicity. Chitosan significantly reduced the expression of *ADA2* and several *ADA2*-mediated cell wall-related genes (*ALS2, PGA45,* and *ACE2*), as well as efflux transporter genes (*MDR1* and *CDR1).* In addition, chitosan inhibited *GCN5,* which encodes a catalytic subunit of the SAGA complex. *ADA2Δ* cells and *GCN5Δ* cells exhibited phenotypes that were comparable in response to chitosan and other cell surface-disrupting agents.

In fungi, there are three major categories of fungal KDAC proteins: classes I, II, and III. Several *Candida* species that have been sequenced contain over ten unique genes that are classified under these categories. The KDACIs are pan-inhibitors that target a variety of KDAC classes. However, they can also be isoform selective, which enables them to distinguish between proteins of the same class. Additionally, they are class-selective and target a particular class. Most of these small molecules have been researched and developed to target human KDAC proteins with the intention of treating cancer throughout history [109]. In contrast, the KDAC protein family exhibits substantial sequence conservation between humans and yeast. Consequently, numerous KDAC inhibitors that are unique to humans can also be effective in fungal cells [110].

Types of KDACs as epigenetic modulators

Class I and Class II KDAC inhibitors (Hos2- and Rpd3-like proteins)

Trichostatin A (TSA) was one of the first KDACIs to be investigated for treatment of fungal infections. TSA is derived from the metabolites of *Streptomyces hygroscopicus*. a fungistatic agent that is prescribed to specifically target *Aspergillus niger* and *Trichophyton* species [111]. Over a decade later, it was discovered that TSA had the capacity to inhibit mammalian histone deacetylases. As a result, more research was conducted on TSA in conjunction with the development of subsequent KDACI drugs to investigate its potential as a treatment for inflammation and cancer [112]. TSA, or trichostatin, is a chemical compound that prevents the activity of a diverse array of enzymes known as KDACs, or lysine deacetylases. The primary focus is placed on Class I and II KDACs, which are dependent on zinc for their functionality.

In *C. albicans*, the Y-H conversion is stimulated, and phenotypic plasticity is significantly impacted by TSA treatment [113]. Additionally, *C. albicans* fluconazole trailing is diminished by more than 200 times in the presence of TSA [84]. As a result, the efficacy of azoles can be improved by either eliminating or inhibiting the growth of drug-resistant cells. Additionally, the presence of TSA can impede the development of azoles resistance in *C. albicans.* Moreover, the suppression of trailing growth in *C. albicans, C. parapsilosis,* and *C. tropicalis* was facilitated by the synergistic effects of TSA and itraconazole [114], implying that the application of antifungals in conjunction with KDAC inhibition may be a viable therapeutic approach for NCAC infections [115, 116].

Another categorization of Class I/II KDACI refers to molecules that incorporate uracil, with suberoylanilide hydroxamic acid (SAHA) being the most

prominent example. SAHA is commercially known as vorinostat [117, 118]. The activity of four uracil-based hydroxamic acid KDACIs, in combination with SAHA, was examined on both *C. albicans* and *C. parapsilosis* in 2007 [119]. In contrast to TSA, these KDACIs and fluconazole exhibited limited synergism, except for a *C. albicans* isolate that exhibited reduced susceptibility to fluconazole in the presence of two of the KDACIs. Nevertheless, experimental trials demonstrated that the two uracil-based KDACIs could effectively prevent the development of fluconazole resistance in *C. albicans*. This evidence suggests that histone acetylation was employed in the initial adaptation of *C. albicans* to antifungal drugs [120].

Sirtuin KDAC Inhibition in Candida species

Specifically, acetyl groups from lysine residues are removed by a group of enzymes known as Class III KDACs, which are known as sirtuins. the proteins Sir2p, Hst1p, Hst2p, Hst3p, and Hst4p are present in most *Candida* species. Nicotinamide adenine dinucleotide (NAD^+) is essential for the deacetylation process to be executed by sirtuins. Consequently, nicotinamide (NAM) effectively inhibits their enzymatic activity by acting as a non-competitive inhibitor [121]. Wurtele *et al*. [122] presented evidence that *C. albicans* and *C. krusei* are adversely affected by a concentration of 50 mM NAM. Additionally, at elevated concentrations. Effectively, it impairs the growth of *C. parapsilosis* and *C. glabrata*. NAM's adverse effects are the consequence of the inhibition of *Ca_Hst3p* and the elevation of Histone H3K56 [123] Additionally, it was determined that the application of NAM to living organisms significantly decreased *C. albicans* burden in the kidneys of infected rodents [124]. Components of the sirtuin family include Hst enzymes. The HDAC complex Set3 is comprised of Hst1, while Hst3 is involved in the nucleosome assembly process. Utilizing the HAT Rtt109, Hst3 dynamically modulates the level of lysine 56 acetylation on histone H3 [125].

According to a recent study, NAM and fluconazole exhibit synergistic antifungal effects against both *C. albicans* and *NCAC* species, including *C. glabrata*, which is inherently resistant to azoles, as well as fluconazole-resistant *C. albicans* isolates [126]. The findings of this study further substantiated the findings of previous in vivo studies, which demonstrated that the administration of NAM to mice infected with *C. albicans* leads to improved survival and reduced kidney injury. The severity of these effects is associated with the dosage [126]. Furthermore, NAM inhibits the biofilm development of *C. albicans* and initiates a transition from white to opaque, which is contingent upon the activity of the H3K56 acetyl-transferase *RTT109* [127].

Set3C histone deacetylase (HDAC) inhibitors

In *S. cerevisiae,* Set3 is a 7-subunit complex (Set3C) that is NAD+-dependent and an HDAC. In *C. albicans*, this complex comprises HDAC and non-HDAC proteins. Set3C is a complex in the yeast *S. cerevisiae* that consists of seven subunits. Both HDAC proteins and non-HDAC proteins are included in this complex. The complex produced by Set3 in *C. albicans* is also comparable [128]. *Set3, Hos2, Snt1,* and *Sif2* are the four proteins that constitute the core complex of Set3C. Each of these proteins is essential for the formation of *Set3C. Hos4, Hst1*, and *Cpr1* are the peripheral proteins of Set3C, in contrast, enzymatic function of histone deacetylase (HDAC) is demonstrated by Set3, Hos2, and Hst1. Additionally, the The plant homeodomain (PHD) finger domain of Set3 preferentially binds to methylated H3K4

and accelerates the recruitment of the Set3C complex to chromatin in *S. cerevisiae* [129]. In addition, this complex is conserved in *C. albicans*, where it is crucial for morphogenesis.

5. Functional Roles of HDACs in *Candida* species

HDACs and Yeast-to-Hyphae Transition

Candida albicans is found in a diverse array of morphological forms. A yeast phase that is ovoid in shape is typically observed on mucosal and cutaneous surfaces, where it is well-tolerated by the immune system. The potential for invasiveness of hyphal forms is enhanced by their extended tube-like extension. Although both forms contribute to disseminated infections, the ability to transition between them in a reversible manner has been directly correlated with virulence. Recent reviews have examined a variety of pathways that regulate the transition from yeast to hyphae [130].

Multiple histone deacetylases (HDACs) have been associated with the functional role of the transition from yeast to hyphae in fungi. At first, it was found that *HDA1* is essential for the regulation of a specific chromatin state that is essential for the growth and preservation of hyphae [131]. Hyphae growth is not promoted by *C. albicans* isolates that are mutant of *HDA1* gene. Consequently, the *Nrg1* repressor's binding is disrupted by the chromatin state that is induced by the recruitment of *HDA1* by the transcription factor Brg1. Consequently, Nrg1 is unable to bind to the promoter regions of genes that are specific to hyphae, thereby inhibiting their expression [132].

HDACs and Biofilm Formation

Candida albicans can produce biofilms, which are intricate structures that consist of a diverse array of microorganisms, such as yeast and hyphal forms. The biofilms have been contained within a matrix [14]. They are frequently visible on medical devices that have been surgically implanted in the body, such as intravascular catheters or prostheses in addition to the surfaces of mucosal membranes [133]. Biofilms facilitate the establishment of additional infection sites by dissemination of yeast cells into the circulation in haematogenous disseminated candidiasis. Additionally, the extracellular matrix's interference with drug diffusion is a substantial source of antifungal resistance [134, 135].

It has been established that Set3C HDACs are essential for the development of biofilms [128]. Therefore, the removal of the *SET3* and *HOS2* genes results in a reduction in the formation and dimensions of biofilms [136]. *NRG1, BRG1, TEC1, NDT80,* and *ROB1* are five of the six biofilm master regulators that have specific associations with the Set3C complex. Set3C transiently inhibits the activity of Nrg1, which is implicated in the regulation of cell proliferation, particularly during filamentation [137].

HDACs and virulence

The pathogenicity of all three families of HDACs has been significantly influenced by the KDACs. These families include zinc-dependent (classical) HDACs (e.g., class 1, class 2, HOS3-like HDACs in fungi, and class 4 found in other Eukaryotes), nicotinamide adenine dinucleotide (NAD+)-dependent SIR-like HDACs (Sirtuins), and HD2-like enzymes (found exclusively in plants). The survival rates of wild-type and mutant strains following systemic injection have been the subject of numerous *in vivo* experiments that have been conducted to investigate the role of HDACs in *C.* albicans virulence [113].

Upon injection with the *RPD31* deletion, rodents exhibited reduced virulence and filamentation defects. The hyphae-inducing conditions observed in animal models are consistent with this

result. At the same time, the set3 mutant exhibited a hyperfilamentous phenotype *in vitro* [138]. Mouse kidneys confirmed this phenotype in vivo; however, it was unexpectedly linked to diminished virulence [139]. This reduced virulence may be linked to the transcription regulation mediated by Set3C, which entails the transient downregulation of *EFG1* and *NRG1* and the induction of *BRG1* and *TEC1* [124]. *C. albicans'* pathogenesis has been shown to be reliant on the class 1 KDAC Rpd31, which is one of the two Rpd3 paralogs, in a mouse invasive infection model [140]. Currently, there is no research particularly investigating the disease-causing properties of additional *Candida* KDACs. However, there is indirect evidence suggesting that *Hos2* may also have significant impacts. Upon the removal of Hos2 from Set 3, a significant reduction in pathogenicity was observed (Figure 4) [141]. Set3 and *Hos2* are composed of the same complex and exhibit similar characteristics in numerous respect [142].

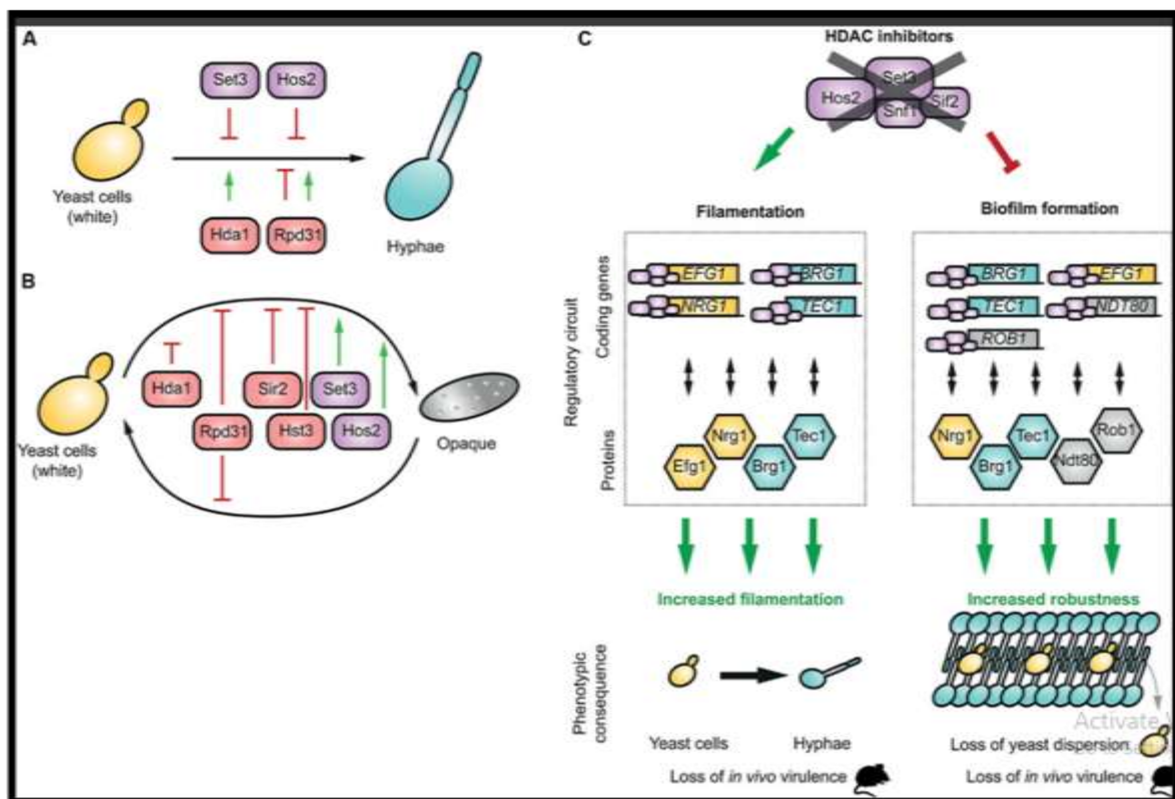

Figure 4: Different HDACs' phenotypic effects during filamentation (A) and the transition from white to opaque (B), (C) During filamentation and the formation of biofilms, HDACs regulate the expression of critical transcription factors in regulatory circuits, which in turn regulate the gene expression program. A hyperfilamentation phenotype and a loss of virulence *in vivo* are the results of HDAC inhibition, which deregulates the transcription regulatory circuit. Similarly, biofilms become more resilient upon treatment with HDAC inhibitors, but their virulence and yeast dispersion are reduced *in vivo* [141]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4974301/

6. Chemical Epigenetic Modifiers and Their effect on different fungi:

Chemical epigenetic modifiers refer to naturally occurring or artificially created tiny molecules that specifically target enzymes involved in epigenetic processes (Table 2) [143]. This targeting results in modifications to the epigenetic patterns of organisms [144]. A significant number of these chemicals function by obstructing the enzymatic machinery that is crucial for the transfer of methyl, acetyl, and alkyl groups to DNA or histones [145]. DNMT, HDAC, and proteasome inhibitors respectively target DNA, heterochromatin, and the proteasome [146].

5-azactytidine (5-AZA) is utilized as a methyl transferase inhibitor. The interaction between 5-AZA and the methyltransferase that is responsible for DNA hypomethylation induces chromatin restructuring [147]. The utilization of AZA is employed to produce a novel secondary metabolite in Penicillium citreonigrum. By incorporating an epigenetic agent, such as AZA, into a culture medium that contains nutrient broth, cornmeal, oatmeal, rice, and vermiculite, the production of metabolites such as sclerotiorin, sclerotiorimine, ochrephilone, dechloroisochromophilone III, dechloroisochromophilone IV, atlantinone A, and atlantinone B is produced.

Three novel eremophilane-type sesquiterpenes (dihydrobipolaroxin B, C, and D) and a novel dihydrobipolaroxin analog have been produced by the marine fungus (SCIOW2 strain) through the addition of 5-AZA and suberoylanilide hydroxamic acid (SAHA) to the *Aspergillus* spp. medium. A 2–10-fold increase in the production of phenolic compounds, some of which exhibited cytotoxicity against liver carcinoma cells, was observed in the culture medium of Penicillium brevicompactum in response to the addition of nicotinamide or sodium butyrate (NaBut) [148].

When SAHA was introduced to the cultures of *Aspergillus westerdijkiae* at a concentration of 100 µM, it induced the synthesis of the polyketide penicillic acid [82]. Numerous biological activities, including antibacterial, antifungal, antiviral, anticancer, and herbicidal effects, have been identified in penicillic acid. This serves to illustrate the potential of epigenetic modification to improve the efficacy of penicillic acid fermentation [149].

Upon exposure to VPA at 500 µM, *Aspergillus fumigatus GA-L7*, an endophytic fungus isolated from *Grewia asiatica L.,* produced fumiquinazoline C. The substantial overexpression of all genes involved in the biosynthesis of fumiquinazoline C significantly reduced the overall enhancement of fumiquinazoline C production by approximately tenfold [150].

The production of pseurotin A, patulin, and cytochalasin E in the cultures of *Aspergillus clavatus* was significantly increased by TSA at a concentration of 0.5 µM [151]. The histone deacetylase gene rpdA was induced in *Aspergillus nidulans* by TSA at a concentration of 1 µM. Unfortunately, there was no additional research conducted on the topic of fungal secondary metabolism [152].

Table (2): Commonly used chemical epigenetic modifiers in fungi

Modifier	Mechanism of Action	Species	Target site	References
5-Azacytidine	Inhibition of DNA methyl transferase	*Aspergillus* spp. *Candida* spp.	DNA	[153]
5-Aza-2′ -deoxycytidine	Inhibition of DNA methyl transferase	*Candida* spp	Heterochromatin	[154]
Trichostatin A	Inhibition of HDAC of classes I and II	*Aspergillus clavatus*		[155]
Suberoylanilide hydroxamic acid	Inhibition of HDAC of classes I and II	*Candida* spp		[156]
Suberoylbishydroxamic acid	Inhibition of HDAC of classes I and II	*Aspergillus* spp		[157]
Sodium butyrate	Inhibition of HDAC of classes I and II	*Aspergillus fumigatus GA-L7*	Heterochromatin	[151]
Sodium valproate	Inhibition of HDAC of classes I and II	*Aspergillus* spp.	Heterochromatin	[158]

Conclusions

Worldwide, the incidence and geographical dispersal of fungal diseases are both increasing because of a variety of factors. These factors include a growing proportion of immunocompromised patients, the emergence of fungal strains that exhibit greater resistance to antifungal drugs, global climate warming, the increase in international travel and commerce, inadequate diagnostic and laboratory capabilities, and the lack of consciousness and scientific investigation and advancement. In addition, the availability of life-saving antifungal drugs may be limited, especially in low- and middle-income countries, due to There is a lack of coordination in health policy, which results in inadequate access to appropriate antifungal agents. A variety of epigenetic pathways have been reported to modulate or mitigate drug resistance in a variety of fungi. However, limited research has been conducted on the molecular, genetic, and epigenetic pathways that contribute to the development of drug resistance in fungi. Gaining a comprehensive understanding of the involvement of epigenetic mechanisms for reducing/controlling of resistance to antifungal drugs could help in the development of targeted treatments and interventions to effectively manage these drug-resistant strains.

Conflict of Interests

The authors have declared that they have no potential conflicts of interest.

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الملخص العربى

دور الآليات اللاجينية في تعديل مقاومة الفطريات للمضادات الفطرية

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إن صحة سكان العالم مهددة بشكل خطير وكبير بسبب مقاومة مضادات الميكروبات ونتيجة لهذا، يخصص المجتمع العلمي قدراً كبيراً من الموارد والجهود لمواجهة هذا التحدي. وعلى النقيض من ذلك، تركز غالبية هذه المساعي على المضادات الحيوية، ولا تحظى الأبحاث المتعلقة بمقاومة مضادات الفطريات بالقدر الكافي من التمثيل. تكتسب مسببات الأمراض الفطرية مقاومة الأدوية من خلال مجموعة متنوعة من الآليات. ويمكن تيسير العلاجات المضادة للفطريات المبتكرة وتعزيز فعالية مضادات الفطريات الموجودة من خلال الفهم الشامل للآليات التي تكتسب بها العدوى الفطرية مقاومة الأدوية. إن بنية الكروماتين وتنظيم التعبير الجيني من المكونات الأساسية لتكيف الأنواع الفطرية مع الإجهاد المضاد للفطريات، وهو ما يشير إلى نهج علاجي محتمل لمقاومة مضادات الفطريات. وهذا يشير إلى أن تطوير استراتيجيات تركز على هذه الآليات قد يكون نهجاً قابلاً للتطبيق للسيطرة على مقاومة مضادات الفطريات. لتنظيم مجموعة متنوعة من مكونات البيولوجيا الفطرية، فإن المسارات فوق الجينية لا غنى عنها في علم الفطريات الطبية. تعتمد عملية التطوير والقدرة على تعديل وتكييف الخصائص الفيزيائية ومقاومة مضادات الفطريات المستخدمة لعلاج الالتهابات الفطرية بشكل حاسم على هذه الأساليب. إن عملية التطوير والقدرة على تعديل وتكييف الخصائص الفيزيائية ومقاومة مضادات الفطريات المستخدمة لعلاج الالتهابات الفطرية تعتمد بشكل حاسم على هذه الأساليب. إن أحد المخاوف المهمة هو زيادة المقاومة للخيارات العلاجية المحدودة المتاحة لعلاج الالتهابات الفطرية ، مثل أسيتلة الهيستون ومثيلتها، وإعادة تشكيل الكروماتين من خلال الهيتروكروماتين، والتي تمنع آليات مقاومة الأدوية السائدة . تهدف هذه الدراسة الى مراجعة أهمية المسارات اللاجينية في التوسط في مقاومة الأدوية في الفطريات بالإضافة إلى آليات مقاومة الأدوية المضادة للفطريات.