

**INTEGRATED REVIEW OF ANTIFUNGAL RESISTANCE: MECHANISTIC INSIGHTS,
CLINICAL CHALLENGES AND THERAPEUTICS INTERVENTION****Rajshree D. Mhaske¹, Dr. Sachin J. Dighade^{2*}**¹Assistant Professor, Department of Pharmaceutics, Institute of Pharmacy and Research, Anjangaon Bari Road, Badnera – Amravati, Maharashtra, India.²Principal, Institute of Pharmacy and Research, Anjangaon Bari Road, Badnera – Amravati, Maharashtra, India.***Corresponding Author: Dr. Sachin J. Dighade**

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DOI: <https://doi.org/10.5281/zenodo.23799705>**How to cite this Article:** Rajshree D. Mhaske¹, Dr. Sachin J. Dighade². (2026). Integrated Review Of Antifungal Resistance: Mechanistic Insights, Clinical Challenges And Therapeutics Intervention. European Journal of Pharmaceutical and Medical Research, 13(11), 76–84.

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Article Received on 01/09/2026

Article Revised on 21/10/2026

Article Published on 01/11/2026

ABSTRACT

Deeply invasive fungal infections are emerging as an increasingly substantial worldwide healthcare challenge, especially for medically compromised and individuals with weakened immune systems. The aforementioned infectious conditions are challenging to address because clinical diagnosis is often prolonged and mycotic organisms swiftly acquire resistance against commonly used drug classes such as azoles, polyenes, and echinocandins. In the present review, we explore the molecular and cellular mechanisms responsible for antifungal resistance, incorporating modifications at drug target sites, overexpression of targets, upregulation of stress-response pathways like Hsp90 and calcineurin, genomic flexibility, and drug efflux through transporters such as ABC and MFS families. We also discuss diagnostic strategies, from traditional methods to modern molecular and biomarker-based assays. Special emphasis is devoted to WHO-listed highest-priority pathogens such as *Candida auris*, and the therapeutic innovations currently being investigated to combat them. These involve next-generation antifungals (fosmanogepix, ibrexafungerp, rezafungin), naturally derived compounds, combination therapies, biologics, and nanotechnology-based delivery systems. Ultimately, strengthening patient outcomes worldwide will require integrating sophisticated diagnostic approaches with these emerging treatment to counteract existing clinical challenges.

KEYWORDS: Invasive fungal infections; Antifungal drug resistance; Efflux pumps.**1. INTRODUCTION**

Fungal infections are now a significant global public health burden, suffering nearly one billion individuals with topical infections of the skin, hair, and nails, while millions experience mucosal, invasive, and systemic fungal diseases. Major fungal pathogens, including *Candida*, *Aspergillus*, *Cryptococcus*, *Pneumocystis jirovecii*, endemic dimorphic fungi, and Mucorales, leads to morbidity and mortality worldwide. The impact of critical fungal diseases involves millions of serious cases related to chronic pulmonary aspergillosis, invasive candidiasis, cryptococcal meningitis, invasive aspergillosis, and other life-threatening infections. Delays in diagnosis and limited therapeutic options, increasing antifungal resistance.^[1]

Incidences of invasive candidiasis has increased considerably in recent decades, majorly due to extensive antibiotic exposure, conventional immunosuppressive therapies, improved detection, and increased survival among critically ill patients. Although *Candida albicans* remains a major cause of invasive candidiasis, non-*albicans Candida* species such as *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei*, and the emerging *C. auris* are more frequently recognized.^[2] In figure No.1. represent different fungal infection affect topically and invasive systemically, the top images highlight key presentations of chronic mucocutaneous candidiasis and chromoblastomycosis; alongside of first, a mucicarmine-stained cerebellar section from a patient who succumbed to AIDS-related cryptococcal meningoencephalitis; the stain vividly accentuates the abundance of mucopolysaccharide-rich yeast cells in deep pink. The

bottom section of figure shows invasively affected thoracic Computed Tomography (CT) scan displaying a prominent pulmonary aspergilloma (indicated by the black box) within a pre-existing lung cavity, alongside its

subsequent surgical resection. Notably, three adjacent cavitation sites are also present which are marked by red arrows in figure a characteristic feature consistent with chronic pulmonary aspergillosis.^[2,3]

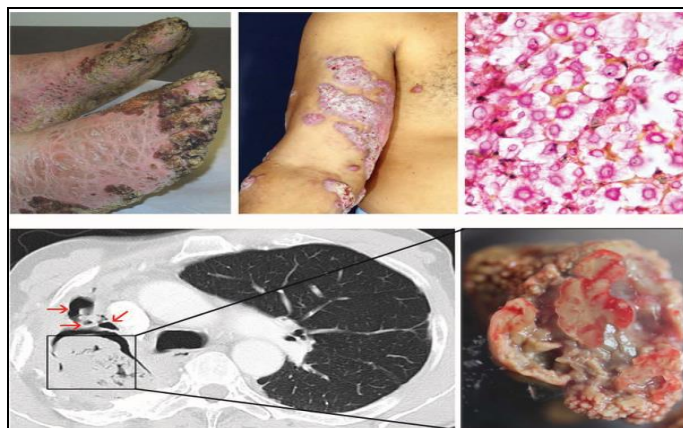


Figure No. 1: Topical and Systemic Fungal Infection.

Many of species diminished antifungal susceptibility, notably to azoles such as fluconazole, thus challenging clinical management giving rise to healthcare-associated outbreaks. Similarly, invasive aspergillosis predominantly affects immunocompromised patients,

including with prolonged neutropenia, chronic granulomatous disease, hematopoietic stem-cell transplantation, and solid-organ transplantation. Major mortality emphasizes the importance of rapid diagnosis and timely antifungal intervention.^[2]

The World Health Organization (WHO) has prioritized 19 fungal pathogens by risk level:

Critical group	High group	Medium group
<ul style="list-style-type: none"> • <i>Cryptococcus neoformans</i> • <i>Candida auris</i> • <i>Aspergillus fumigatus</i> 	<ul style="list-style-type: none"> • <i>Nakaseomyces glabrata</i> • <i>Histoplasma spp.</i> • <i>Eumycetoma causative agents</i> • <i>Mucorales</i> • <i>Fusarium spp.</i> • <i>Candida tropicalis</i> • <i>Candida parapsilosis</i> 	<ul style="list-style-type: none"> • <i>Scedosporium spp.</i> • <i>Lomentospora prolificans</i> • <i>Coccidioides spp.</i> • <i>Pichia kudriavzevii</i> • <i>Cryptococcus gattii</i> • <i>Talaromyces marneffei</i> • <i>Pneumocystis jirovecii</i> • <i>Paracoccidioides spp.</i>

Table No. 1: WHO Fungal Pathogen List.

Invasive fungal infections and prevalence of antifungal resistance have major challenges to global health, particularly among immunocompromised and other high-risk populations. Strengthening diagnostic approaches, ensuring access to appropriate antifungal therapy, and maintaining effective global surveillance are essential for improving disease management and monitoring the emergence of resistance.^[4]

1.1. Fungal Cell Wall: Structure, Function and Antifungal Target

The fungal cell wall is a flexible framework that makes mechanical endurance, maintain cellular integrity, protect cellular structure, function and which facilitates fungal viability and virulence. In contrast with mammalian

cells, fungi have a cell wall made up of polysaccharides such as β -glucans and chitin, which is not found in mammals making it therapeutically relevant target for antifungal drug development. Across most fungal species, the underlying structural organization largely formed by branched β -(1,3)-glucan, which is contributed to chitin and various other cell-wall components. These polysaccharides interact through hydrogen bonding and form fibrous microfibrils that together offers a strong, basket-like scaffold. This architecture rich fungal cells to counteract internal hydrostatic pressure and maintain their structural integrity. Consequently, enzymes involved in cell-wall synthesis and remodelling can be selectively targeted with limited direct effect on human cellular structure. A ranges of clinically used antifungal agents utilised this feature of vulnerability by altering cell-wall biosynthesis or its interconnected pathways.

Beyond its structural role, the cell wall has an important significance in host–fungus interactions, Its surface components modulated immune surveillance, adhesion, colonization, and pathogenicity. β -glucan is a major component associated molecular pattern that can be identified by host immune receptors and elicited antifungal immune responses.

Dispite this, pathogenic fungi such as *Candida* can modify or mask to exposed β -glucan, consequently limiting immune detection and facilitating persistence within the host. Conversely, disturbances in cell-wall organization or synthesis may amplify β -glucan exposure, strengthening immune recognition and contributing to fungal elimination.

Chitin also essential for fungal viability and host interaction. Studies involving *Candida* mutants with impaired chitin production reveals that it reduced virulence in both immunocompetent and immunocompromised hosts, although these strains may preserve the ability to colonize in different organs. These observation indicates that the fungal cell wall is not simply a protective barrier but a dynamically regulated structure contributed to physiological acclimization, immune evasion, virulence, and susceptibility to antifungal intervention. Therefore, investigation of cell-wall architecture and its biosynthetic pathways play a crucial role for identifying new antifungal targets and developing strategies to overcome fungal survival and resistance.^[5,6,7,8]

1.2. Epidemiology, Diagnosis, and Clinical Management

1.2.1 Diagnosis of Fungal Infections

Precises and reliable diagnosis is pivotal for selecting relevant antifungal therapy and enhancing clinical outcomes. Established diagnostic approaches include **Direct microscopy of fungal culture, Biomarker detection, PCR-based molecular assays, Sequencing, and tissue-based identification**. Biomarkers such as galactomannan (GM), 1,3- β -D-glucan (BDG), and *Aspergillus* DNA can support the diagnosis of invasive fungal infections however, their clinical applicability may be suboptimal by variable specificity and risk of environmental or procedural contamination. Molecular techniques, such as PCR and quantitative PCR, enable pathogen discrimination but may be affected by low fungal DNA concentrations, contamination, or PCR inhibitors. Characterization of pathogen from biopsy specimens can additionally facilitate therapeutic approach, although formalin-fixed tissues may reduce the efficiency of molecular testing. Therefore, combining complementary diagnostic methods may improve the reliability of fungal identification, particularly in complex clinical samples.^[9,10,11]

1.2.2 Current Antifungal Therapy

Therapeutic approach of fungal diseases depends on the site and severity of pathogenic invasion. Topical

antifungal agents are widely employed for superficial infections, whereas invasive diseases generally require systemic therapy. At present, systemic antifungal treatment is largely based on four major drug classes: **Polyenes, Flucytosine, Azoles, and Echinocandins**. Amphotericin B has broad antifungal potency but is associated with significant toxicity, particularly nephrotoxicity; lipid-based formulations were optimised to improve its safety profile. Flucytosine is mainly used in combination therapy, particularly for cryptococcal meningitis, as its resistance can develop easily when it is used as monotherapy. Azoles act by restricting ergosterol biosynthesis and remain important agents in the treatment of several fungal infections. Echinocandins inhibit β -(1,3)-glucan synthesis and selectively interfere with fungal cell-wall formation, providing another important therapeutic option.^[12, 23]

Some agents that target fungal cell wall synthesis are Fosmanogepix represents a novel antifungal agent which targeting to **Gwt1 enzyme** in the glycosylphosphatidylinositol (GPI) biosynthesis pathway, which disrupting fungal cell wall integrity and growth while sparing human cells. It shows broad activity against yeasts and molds and has advanced into clinical trials with FDA fast-track designation for multiple invasive fungal infections.

Nikkomycin Z is a natural nucleoside that inhibits **chitin synthase**, blocking chitin formation in fungal cell walls. Since chitin is absent in mammalian cells, this mechanism offers high specificity and minimal toxicity, making it a promising antifungal candidate.^[13]

1.2.3 Limitations of Antifungal Treatment and Resistance

Even though the availability of several antifungal agents, treatment is increasingly challenging by **drug toxicity, limited therapeutic options, and the emergence of antifungal resistance**.

Oral antifungal medicines are potent in nature but come with significant limitations. They are costly and can cause serious side effects, including organ toxicity and frequent drug interactions. Griseofulvin trigger liver damage, headaches, nausea, vomiting, and sensitivity to sunlight, while Ketoconazole cause liver problems along with issues such as impotence, anaemia, and abdominal pain. Another limitation is that many oral antifungals dissolve poorly in water, which reduces drug absorption in the body and complicates the development of effective formulations. Topical antifungal treatments are generally safer and more affordable, but they are not without problems. They can irritate the skin, causing redness, burning, or stinging at the site of application. In nail infections, topical agents perform poorly because they cannot penetrate the nail bed effectively. Their success also depends on applying the right amount, and even then, they struggle to pass through the skin's protective

outer layer, the stratum corneum, which limits their bioavailability.^[26]

Resistance mechanisms differ as per the drug class and fungal species. Azole resistance may emerge through alterations in **ERG11**, increased production of the target enzyme, or enhanced activity of fungal efflux pumps that minimized intracellular drug concentrations. Echinocandin resistance, particularly in *Candida glabrata*, is frequently associated with mutations in **FKS**

genes, which encode components of the β -(1,3)-glucan synthase complex. Polyene resistance is infrequently observed but may occur through changes affecting membrane sterol composition. These cellular adaptation responsible for treatment ineffectiveness and promote persistent or recurrent infections. Consequently, improved diagnostic methods, suitable antifungal treatment, resistance surveillance, and development of novel therapeutic strategies play a key role for effective long-term management of fungal infections.^[12]

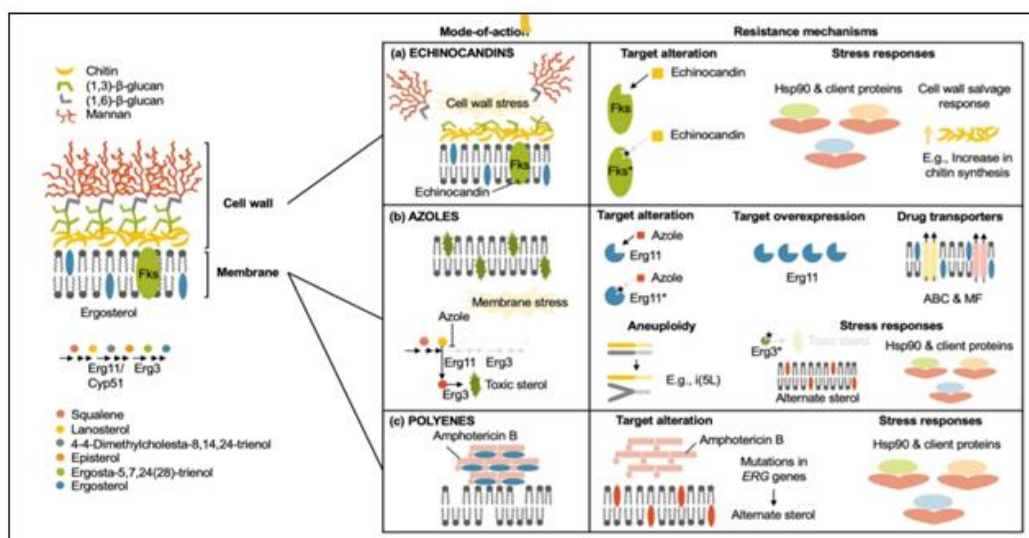


Figure No. 2: Antifungal Mode-of-Action and Mechanisms of Resistance.

1.3. Molecular Mechanisms of Antifungal Drug Resistance

Antifungal resistance is a multifactorial process which is presented diagrammatically in figure No. 2 illustrates the mechanisms of action of major antifungal drug classes—echinocandins, azoles, and polyenes—and the corresponding fungal resistance mechanisms. It highlights resistance through target alteration, target overexpression, aneuploidy, drug efflux transporters, stress responses, and cell-wall/sterol adaptation.^[14]

1.3.1 Alteration and Overexpression of Drug Targets

Targets site alteration represents the major mechanisms underlying antifungal resistance. Mutations in target-encoding genes may modify drug-binding site and reduce drug affinity, which leads to decreasing effectiveness. Resistance may also emerge when the target is overproduced, allowing fungal cells to maintain sufficient target activity despite of drug exposure. target modification and over expression highlight how even small genetic changes can significantly influence antifungal treatment outcomes.^[15]

1.3.2 Metabolic Adaptation and Stress-Response Pathways

Vulnerability to fungicidal drug exerts significant burden on pathogenic cells, which activating defensive cascades. Heat shock protein 90 (**Hsp90**), a biomolecular proteostasis implicated within a stabilizing key signalling proteins, this factor serve as a role in fungal acclimation

and recalcitrance. Similarly, the **Target of Rapamycin (TOR) pathway** remodels proliferation of metabolic activity as well as intracellular adaptation towards external stimuli. Modulation of these pathways has therefore been investigated as a strategy to restore antifungal activity. For example, Beauvericin has been reported to enhance azole activity by interfering with TOR signaling and drug efflux. These findings suggest that targeting fungal stress-adaptation mechanisms could complement conventional antifungal therapy.^[15,16]

1.3.3 Genetic Plasticity, Aneuploidy, and Chromosomal Changes

Fungus-derived genetic material exhibit markedly responsive along with rapid genetic and chromosomal changes under drug pressure. **Aneuploidy**, involving abnormal chromosome numbers, can transiently or persistently influence the gene expression of resistance-associated genes. modifications in genome copy number, including polyploidy that is increased chromosome sets, whole-genome duplication, multiple chromosome sets, may further promote heterogeneity and facilitate adaptive change. Accordingly, genomic adaptability offers fungal species with a rapid means of adapting to antifungal stress as well as, has the potential to the development and persistence of resistance.^[15,17]

1.3.4 Alteration of Ergosterol and Membrane Composition

Modifications within the ergosterol biosynthetic pathway become significantly influential in **azole resistance**. Azoles inhibit lanosterol 14 α -demethylase, encoded by **ERG11** in yeasts and **CYP51A** in many molds, consequently leading to disrupting ergosterol synthesis and fungal cellular membrane structural integrity. Mutations or increased expression of these targets can reduce drug susceptibility. In *Candida albicans*, a wide range of ERG11 gene mutations contribute to impaired azole responsiveness, indicating, significant involvement associated with target modification in resistance development.^[12]

1.3.5 Reduced Drug Uptake and Drug Sequestration

Concentration of an antifungal drug within the fungal cell (**Drug Influx**) is influenced not only on its cellular target but also on how efficiently it is taken up and remains within the fungal cell. Impaired drug uptake has the potential to decrease the amount of the antifungal agent accessing its intracellular target, although the transport mechanisms contributing to this phenomenon remain partially characterized. **Drug efflux**, conversely, is a well-established mechanism. Drug efflux transporters, actively expel antifungal agents from fungal cells which is responsible for reducing intracellular drug concentrations.^[12]

1.4. Efflux Pump-Mediated Antifungal Resistance

Two major transporter families are involved in efflux pump-mediated antifungal resistance: **ATP-binding cassette (ABC) transporters** and **major facilitator superfamily (MFS) transporters**. Despite the fact that both systems carry out drug extrusion, both mechanisms differ with respect to their energy requirements. ABC transporters harness energy derived from ATP hydrolysis, whereas MFS transporters utilize the proton electrochemical gradient across the plasma membrane.^[18,19,26]

1.4.1 ABC and MFS Transporters in Antifungal Drug Resistance^[18,24]

MFS transporters constitute extensively widespread membrane proteins that carry a diverse range of compounds. In fungal species, drug-associated MFS transporters are commonly categorized into Drug:H⁺ Antiporter 1, Drug:H⁺ Antiporter 2 (**DHA1** and **DHA2**) families based on their transmembrane organization. DHA1 transporters usually exhibit 12 membrane-spanning segments, whereas DHA2 transporter proteins comprise 14. Upregulated expression of MFS transporters, specifically **Mdr1p**, has been linked to fluconazole resistance in experimentally derived resistant mutants and clinical fungal isolates.

ABC transporters, conversely represent ATP-dependent transport systems. The transporter's structure comprises a pair of transmembrane domains (TMDs), which mediate substrate recognition and transport, as well as

two **Nucleotide-Binding Domains (NBDs)** facilitating ATP binding and hydrolysis.

Fungal ABC transporters can be majorly categorised into **Pleiotropic Drug Resistance (PDR)**, **Multidrug Resistance (MDR)**, and **Multidrug Resistance-Associated Protein (MRP)** families. Among these, PDR transporters have gained substantial attention because their respective overexpression is frequently correlated with azole resistance. Their potential to detect structurally diverse compounds facilitates, fungal cells to acquire multidrug-resistant phenotypes.

At the molecular level, ABC-mediated efflux comprises a synchronized transport mechanism. The drug interacts with the transporter, followed by ATP binding to the nucleotide-binding domains. ATP-induced conformational rearrangements modify the orientation of the transporter and facilitate drug release outside the cell. Subsequent ATP hydrolysis resets the transporter for another cycle. The overall consequence is a reduction in intracellular drug accumulation and consequently, reduced antifungal activity.

1.4.2 Efflux Pumps as a Fungal Stress-Response Mechanism

A key significant aspect arising through latest investigations indicates that efflux-mediated resistance not be considered independently from the wider-ranging fungal stress-response network. Antifungal administration has the potential to the early stages induce **transient adaptive responses**, which help fungal cells survive drug-induced stress. Persistent drug exposure may subsequently promote the emergence of durable genetic alterations that sustain antifungal resistance. Prolonged resistance may involve **genetic alterations in drug targets, upregulated efflux-pump expression, modifications in transcriptional regulators, chromosomal rearrangements and aneuploidy**. In contrast, transient acclimation encompasses signal-transduction pathways that rapidly modulate cellular processes upon exposure to antifungal stress.

A number of evolutionarily conserved signaling pathways contribute to this adaptive response, including the Mitogen-Activated Protein Kinase (**MAPK**), **cyclic AMP-protein kinase A signaling pathway (cAMP-PKA)**, **calcineurin signaling pathway**, and **Hsp90-associated pathways**. Among these, calcineurin is prominently important in regulating cellular equilibrium in the presence of membrane-related, salt-induced, alkaline-pH, and antifungal stresses. Induction of calcineurin signaling facilitates downstream transcriptional responses.

Hsp90, a molecular chaperone, additionally promotes to antifungal tolerance by means of maintaining the stability of several stress-response proteins, including calcineurin. The association between Hsp90-calcineurin interaction highlights the manner in which fungal stress

adaptation can potentially protect cells against antifungal treatment and create a window to develop for stable resistance mechanisms.^[18,20]

1.4.3 Regulation and Experimental Analysis of Efflux Pumps

Efflux activity has the potential to promote phenotypes features apart from drug extrusion, comprising **biofilm-associated resistance, protection against oxidative stress, adaptation to hostile environments, and potentially altered virulence.**

Experimental investigation concerning efflux pumps generally combines **gene-expression analysis, genetic manipulation, transporter-function assays, intracellular drug accumulation studies, and susceptibility testing.** These strategies discriminate whether resistance is predominantly related to heightened drug efflux, altered drug targets, or multiple mechanisms operating concurrently.^[18]

1.4.4 Therapeutic Implications of Efflux Pump Inhibition

Since elevated drug extrusion limits intracellular antifungal exposure, efflux pumps constitute promising therapeutic intervention. **Efflux pump inhibitors (EPIs)** are being studied as adjunctive agents which may augment intracellular drug accumulation and restore antifungal activity. Another strategy includes co-administering conventional antifungal drugs with compounds that interfere with transporter regulation or stress-response pathways.

Genetic strategies directed toward efflux-pump genes or their regulatory proteins have contributed significant evidence for elucidating their involvement to resistance. However, advancing these observations into therapeutic applications continues to be difficult because an effective inhibitor needs to preferentially modulate with fungal transporters without producing undesirable toxicity or pharmacokinetic alterations within the host.^[12]

1.5. Strategies to Combat Antifungal Resistance

1.5.1 Natural Compounds as Antifungal Agents^[21,28]

The therapeutic potential of natural bioactive compounds in addressing antifungal-resistant is currently being investigated, including the alkaloid compound berberine and solenopsin, the phenolic compounds curcumin, eugenol, and resveratrol, and other bioactive agents such as Nikkomycin Z. These compounds may mediate their fungicidal effects via disrupting the fungal cell membrane, preventing biofilm formation, inducing oxidative stress, inhibiting chitin synthesis, and interfering with fungal morphological changes. Natural bioactive compounds may additionally modulate efflux-pump activity, thereby facilitating greater intracellular drug accumulation. Their combination together with currently used antifungal agents may contribute to synergistic activity and potentially improve treatment

outcomes in infections associated with drug-resistant *Candida auris*.

Agents such as Apigenin, Pinorelinol, PapyriflavonolA, Hibicuslide C act on fungal membranes, while Methyl chavicol and Linalool, Cinnamaldehyde and Eugenol, Curcumin, Tomatidine, Magnolol interfere with ergosterol biosynthesis or cause membrane damage. Some agents combine multiple mechanisms, such as Dill seed essential oil and diterpenes which disrupt membranes and mitochondria. Mitochondria-targeting compounds include Silibinin, Berberine, Shikonin, Baicalin and Medioresinol all of which induce ROS accumulation and apoptosis. Finally, several natural products show strong antifibrom activity, including Carvacrol, Thymol, Cinnamaldehyde, 6-Shogaol, Warburganal, Polygodial, Betulinic acid, Riccardin D, Scopoletin, Escin, Tea polyphenols, Coriandrum sativum oil, Baccharis halimifolia extracts, Saponins, Proanthocyanidins, Baicalein, and Licochalcone A. Together, these agents highlight the diverse ways natural products can weaken fungal defenses and serve as promising leads for antifungal therapy.

1.5.2 Novel Synthetic Antifungal Compounds^[22]

Another potential strategy for combating antifungal resistance comprises the advancement of next-generation synthetic antifungal agents. Drugs such as Isavuconazole, Rezafungin, Ibrexafungerp, Fosmanogepix, Olorofim, and Opelconazole have been designed to target distinct fungal pathways compared with those of conventional antifungal therapies. By inhibiting β -1,3-D-glucan synthesis, Rezafungin and Ibrexafungerp interfere with fungal cell-wall formation. The development of therapeutic agents with distinct mechanisms of action may contribute to counteract resistance associated with existing antifungal targets and broaden treatment alternatives for drug-resistant fungal infections.

1.5.3 Biological Antifungals^[21]

Biological interventions constitute an alternative prospective approach to managing drug-resistant fungal infections. Principal approaches involve the use of monoclonal antibodies, vaccines, and antifungal peptides. Monoclonal antibodies can specifically identify fungal components and stimulate host immune responses, while vaccines are designed to elicit protective immune responses against fungal pathogens. Antifungal peptides, including C14R, LL-37, NFAP2, and histatin-5, can produce their effects through mechanisms such as membrane disruption, generation of oxidative stress, mitochondrial impairment, and triggering fungal cell death.

1.5.4 Nanotechnology-Based Antifungal Strategies^[21,29]

The application of nanotechnological approaches provides an opportunity for improving antifungal drug delivery and therapeutic efficacy. Diverse nanomaterials,

such as silver nanoparticles, zinc oxide nanoparticles, chitosan-based systems, and other polymeric and lipid-based formulations, have been explored for antifungal applications. These nanocarriers may promote the delivery of antifungal agents to fungal cells and strengthen activity against drug-resistant organisms. However, numerous nanotechnology-driven strategies remain at the preclinical stage, and further research is needed to establish their safety and clinical efficacy.

1.5.5 Combination Antifungal Therapy^[25]

The employment of combination therapy, encompassing an antifungal drug together with an additional therapeutic compound, represents an additional strategy for addressing antifungal-resistant. Reported combinations include Anidulafungin with Manogepix or 5-fluorocytosine, Amphotericin B with Rolapitant or intravenous immunoglobulin, and azole antifungals in combination with other therapeutic agents. Combination therapy involves combining two or more antifungal agents or pairing an antifungal drug with another therapeutic compound to target multiple fungal pathways simultaneously and enhance antifungal activity. However, their effectiveness depends on factors such as fungal species, drug concentration, drug interactions, and the underlying resistance mechanism.

1.5.6 Photodynamic-Based Therapy^[30]

Photodynamic antifungal therapy (PDT) employs photosensitizer activated by specific light to generate reactive species that damage fungal cells. Methylene blue combined with red light is one example. PDT can rapidly kill fungi and may be effective against resistant strains, but its application is limited by poor tissue penetration, reduced activity against biofilms, oxygen dependence, phototoxicity, and the potential need for repeated treatment. Further research is required for clinical application.

2. Summery and Clinical Finding

Expanding prevalence of fungal infections and increasing challenges of antifungal resistance highlight the need for strengthened disease monitoring, timely diagnosis, and effective management. In several regions, fungal infections are challenging to detect because of restricted access to fungal diagnostic services, limited-sensitivity to conventional methods, and the high expense of modern diagnostic tests and therapeutic drug monitoring. prolonged or inaccurate diagnosis increase the risk of inappropriate treatment and may promote to antifungal resistance. Upgrading diagnostic facilities, antifungal susceptibility testing, and global surveillance can help in the early identification of infections and facilitate better clinical management. molecular diagnostic methods and antigen-based tests, such as PCR and antigen detection assays, offer rapid and more reliable diagnosis, especially in vulnerable patients.

Optimizing antifungal therapies is challenging because have common cellular characteristics with host cells,

making it difficult to get therapeutic targets that are both effective and well tolerated. However, emerging antifungal drugs such as ibrexafungerp, fosmanogepix, and olorofim, along with combination therapy, immunotherapy, biologics, vaccines, natural bioactive compounds, nanotechnology-based approaches, and photodynamic therapy, offer promising approaches for addressing resistant infections. These approaches may contribute to counteract clinically relevant resistance mechanisms, including drug efflux, target modifications, and biofilm formation. collectively, stronger control measures of fungal infections will necessitate early and cost-effective diagnosis, appropriate use of antifungal drugs, effective global surveillance, and ongoing development of new treatment strategies. Together, these efforts can help to reduce treatment failure and improve patient outcomes.

3. CONCLUSION

Fungal infections continue to be a major global health concern, especially in vulnerable and immunocompromised groups. In this review, we emphasized how crucial the fungal cell wall and membrane are to host interaction, pathogenicity, survival, and antifungal susceptibility. Efflux pump overexpression, target modifications, stress-response pathways, genomic adaptations are some of the interrelated mechanisms that give rise to antifungal resistance. These results highlight resistance as a diverse, dynamic process rather than a singular genetic event. Better diagnostics, standardized supervision, efficient antifungal governance, and the creation of targeted therapies are all essential to fulfill this challenge. Recent researches should to concentrate on enhancing comprehension of resistance mechanisms, exploring reliable biomarkers, and incorporating novel approaches in clinical settings.

4. ACKNOWLEDGEMENT

The author gratefully acknowledges the Institute of Pharmacy and Research, Badnera-Amravati, Maharashtra, India, for its institutional support. The author further acknowledges the valuable contributions of researchers whose published work provided important insights into antifungal resistance mechanisms, efflux-mediated resistance, *Candida auris*, and emerging antifungal strategies.

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