RESEARCH PAPER

Escalating Antimicrobial and Antifungal Resistance: Mechanistic Insights and Natural Product-Based Interventions

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ABSTRACT

Background: Antimicrobial resistance (AMR) and antifungal resistance (AFR) have emerged as significant health risks in the world, with recent (2024-2025) data on the growth in resistance of pathogens (*Acinetobacter baumannii, Candida aureus*, *Trichophyton indotineae*, etc.) causing treatment failure and mortality.

Objective: To discuss the current tendencies in AMR and AFR, clarify the molecular-based mechanisms, and assess the possibility of the natural product-based intervention as alternative or additive treatment.

Methods: The recent literature and worldwide surveillance reports were reviewed in the form of a narrative, and the selected topic included resistance epidemiology, molecular pathways (enzymatic degradation, target modification, efflux pumps, biofilms, and gene transfer), and emerging natural therapeutics such as phytochemicals and nanocarrier systems.

Results: There was great increase in the number of multidrug resistant bacterial and fungal pathogens, with last-line agent resistance. Natural products like cinnamaldehyde, eugenol and curcumin showed potential antimicrobial effects especially by a synergistic and biofilm disrupting mechanism. Greater bioavailability was increased with the help of advanced delivery systems, but clinical validation is limited.

Conclusion: AMR and AFR is an urgent world problem that needs comprehensive measures. Natural products have a good potential in adjunctive solutions, but the standardized clinical validation and regulatory frameworks are the key to successful translation of these solutions into practices.

Keywords: *antimicrobial resistance, antifungal resistance, natural alternatives, Candida auris, Trichophyton indotineae, phytochemicals, nanocarriers, efflux pump inhibition, biofilm disruption, One Health*

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1. INTRODUCTION

The World Health Organization (WHO) identified antimicrobial resistance (AMR) as one of the top ten health threats globally and estimated possible deaths of up to 10 million people each year unless measures are taken to curb it (WHO, 2019; O'Neill, 2016). Historically under-recognized but recently as acute as the urge to tackle the problem of multidrug-resistant Candida auris and Trichophyton indotineae (Lockhart et al., 2022; Singh et al., 2023), antifungal resistance (AFR) is becoming a paramount issue, too. Collectively, AMR and AFR are on the verge of reversing decades of medical innovation by making ordinary infections more and more incurable and jeopardizing vital medical processes, including surgery, chemotherapy and organ transplantation (WHO, 2019). A notable part is the period of 202425 that was particularly important to surveillance of resistance. Gram-negative bacteria, in particular, carbapenem-resistant Acinetobacter baumannii and extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae are the priority pathogens identified by the revised WHO list (WHO, 2024). Simultaneously, the overall use of fungicides in agriculture and its evolution under the influence of climate conditions has promoted the emergence of fungal resistance and led to increased levels of azole in Aspergillus fumigatus and nearly pandemic terbinafine resistance in T. indotineae (Meis & Chowdhary, 2022; WHO, 2024). Worryingly, according to a recent surveillance in the United Kingdom, the number of resistant infections is growing at 13% since 2018 and more than 35,000 deaths due to these infections occur annually despite the decreased use of antibiotics in livestock (UK Health Security Agency, 2024). Although more global effort is being made such as the 2025 WHO Tracking Antimicrobial Resistance Country Self-Assessment Survey (TrACSS), therapeutic innovation has stalled. The number of new antibiotics/antifungals joining the clinical use is low in the last decade, whereas the resistance to last-resort agents (like ceftazidime/avibactam and echinocandins) has been on the increase (WHO, 2025; CDC, 2024). These issues highlight the necessity to implement complementary measures. Natural products, such as essential oils, phytochemicals, and plant-based nanocarrier formulations are increasingly investigated as

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antimicrobials and antifungals (Usai et al., 2023; Zhang et al., 2024). By means of this review, the most recent (202425) data on AMR and AFR trends are synthesized, the molecular mechanisms of resistance are explained, the pathogens that need the most clinical attention are identified, and the natural alternatives as the possible therapeutic adjuncts are critically evaluated. This article highlights the essence of multidisciplinary approaches as a solution to the rising level of resistance by linking traditional pharmacology with new plant-based alternatives. Although several surveillance reports have described resistance prevalence, there are important missing links of the ecological drivers, potential of applying the molecular insights, and clinical validation of natural compounds (WHO, 2024; Murray et al., 2024) is missing.

2. Antimicrobial Resistance

Antimicrobial Resistance (AMR) occurs when bacteria, viruses, fungi, and parasites cease to react to antimicrobial treatment, complicating the treatment of the infection, thus endangering its further distribution, serious disease, and mortality (WHO, 2023).

Figure 1: Schematic illustration of antimicrobial action

2.1 Antifungal Resistance

Antifungal Resistance (AFR) is a form of AMR where fungi (such as *Candida*, *Aspergillus*) become resistant to antifungal medications, making fungal infections difficult or sometimes impossible to treat with standard drugs (CDC, 2025)

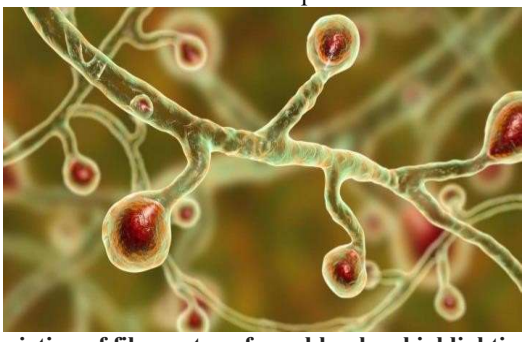

Figure 2: Microscopic depiction of filamentous fungal hyphae highlighting morphological features

2.2 Global Burden and Evolving Trends In Antimicrobial And Antifungal Resistance

The worldwide trend of antimicrobial resistance (AMR) and antifungal resistance (AFR) has become especially obvious during the recent surveillance reports, and the stage of 20242025 can be viewed as the turning point in the history of resistance dynamics. Recent data highlight the critical impact of antimicrobial abuse in combination with environmental reservoirs and adaptive evolutionary stresses on the clinical relevance of a long-standing, steady, and increasingly overwhelmingly significant increase in resistance to a wide range of high-priority bacterial and fungal pathogens.

2.2.1 Global Trends in Antimicrobial Resistance, 2024–25-:

The WHO's 2024 priority pathogen list underscores the critical threat posed by carbapenem-resistant *Acinetobacter baumannii*, third-generation cephalosporin-resistant Enterobacteriaceae, and multidrug-resistant *Mycobacterium tuberculosis* (WHO, 2024; *Lancet Infect Dis*, 2025). These organisms drive severe infections with high morbidity, mortality, and limited treatment options. ICU surveillance further highlights the crisis: a multicentre study in China reported high resistance rates to key agents like ceftriaxone and ciprofloxacin, eroding first-line efficacy (Li et al., 2025). MDR-TB remains a major burden in India, China, and Eastern Europe, with treatment success rarely exceeding 60% (WHO, 2023). In the UK, resistant infections have risen 13% since 2018, causing >35,000 deaths annually despite livestock antibiotic controls (UKHSA, 2024; NAO, 2025; Gregory, 2025). This disconnect illustrates the multifactorial drivers of resistance, including environmental transmission and ecological adaptation. Alarmingly, resistance is emerging even against last-line agents: ceftazidime-avibactam already shows ~6% resistance globally (Livermore et al., 2024). Such premature loss of efficacy underscores the urgent need for alternative therapeutic strategies.

2.2.2 Emerging Trends in Antifungal Resistance, 2024–25-:

Antifungal resistance is rising at an alarming pace. Candida auris has emerged as a "superfungus," showing

resistance to azoles, echinocandins, and polyenes, with invasive infections carrying 30–50% mortality and clonal hospital outbreaks that are difficult to control (Janniger & Schwartz, 2024; CDC, 2024). Equally concerning is the global spread of terbinafine-resistant Trichophyton indotineae, which has reshaped dermatophyte epidemiology. Resistance rates exceed 80–85% in isolates from India, Brazil, and Europe, forcing a shift to itraconazole despite its toxicity and drug-interaction risks (Kaushik et al., 2025). This reflects a broader trend where therapy is dictated by resistance profiles rather than clinical preference. Environmental factors also play a role. Agricultural use of azole fungicides has driven resistance in Aspergillus fumigatus, with the TR34/L98H mutation widely detected in environmental isolates from regions such as the Netherlands and India (Abdalla et al., 2024). This underscores the need to integrate environmental and agricultural practices into antifungal resistance mitigation strategies.

Table 1: Clinical Impact of Major Resistant Pathogens (2024–2025).

Pathogen	2024 Resistance (%)	2025 Resistance (%)	Clinical Impact
Acinetobacter baumannii	68%	72%	High ICU mortality and limited treatment options
Candida auris	30–40% (echinocandin resistance)	45–50% (echinocandin resistance)	Nosocomial outbreaks and high mortality
Trichophyton indotineae	80% (terbinafine resistance)	85–90%	Shift to itraconazole with increased toxicity

3. Molecular Mechanisms of Bacterial Resistance

3.1 Enzymatic Degradation of Antibiotics

One of the most prominent mechanisms of bacterial resistance involves the enzymatic inactivation of antibiotics, particularly through the production of β-lactamases and carbapenemases, including KPC, NDM, VIM, IMP, and OXA variants. These enzymes hydrolyze the β-lactam ring, rendering penicillins, cephalosporins, and carbapenems ineffective (Bush & Bradford, 2020). Recently (2024-2025), the speed at which metallo- 2 -lactamases are disseminated through plasmid-mediated transfer between Enterobacteriaceae, Pseudomonas aeruginosa, and Acinetobacter species is emphasized. Combination therapies like aztreonam avibactam have slightly reduced the impact but new resistance mechanisms like penicillin-binding protein (PBP) changes and increased efflux already impaired the effectiveness of these therapies in the long run (Livermore et al., 2024).

Clinical importance: The mechanism is that which adds to carbapenem resistance in the critical care unit, resulting in a higher mortality rate and highly limited treatment modalities, especially when in a resource-restricted setting.

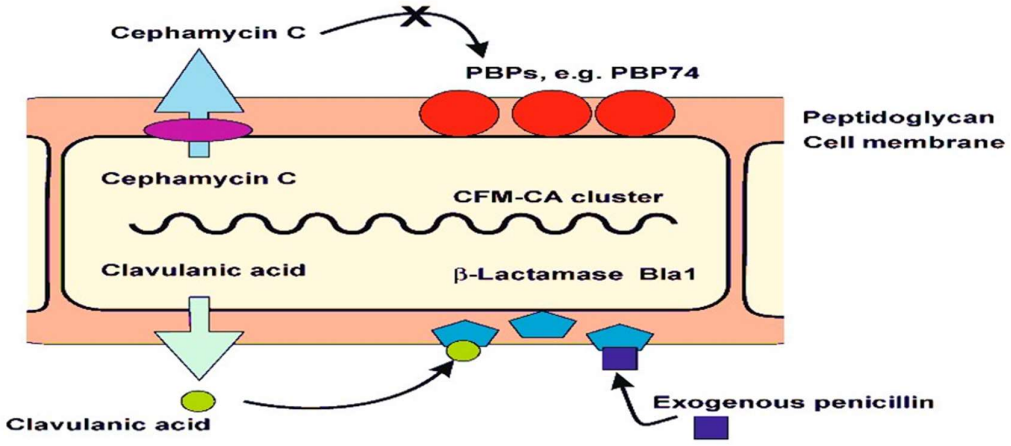

Figure 3: Mechanisms of β-lactam–degrading enzymes

3.2 Drug Target Modification

Mutations of antibiotic targets sites are another important resistance mechanism. Mutations in penicillin-binding proteins (PBP2b and PBP2x) decrease the affinity of β-lactam antibiotics in Streptococcus pneumoniae, and mutations in the rpoB gene confer resistance to rifampicin by changing the RNA polymerase 2 -subunit in Mycobacterium tuberculosis.

Mechanisms Compared to other pathogens Fungal pathogens have analogous mechanisms with mutations in ERG11(sterol 14a-demethylase) and SQLE (squalene epoxidase) demonstrating a convergent evolutionary approach in which organisms evolve adaptations to pharmacological effects by modifying drug-binding sites.

Clinical impact: The result of these changes is treatment failure during first-line treatments and is one of the reasons why extensively drug-resistant

tuberculosis (XDR-TB) has arisen, making it difficult to control the disease on the global scale.

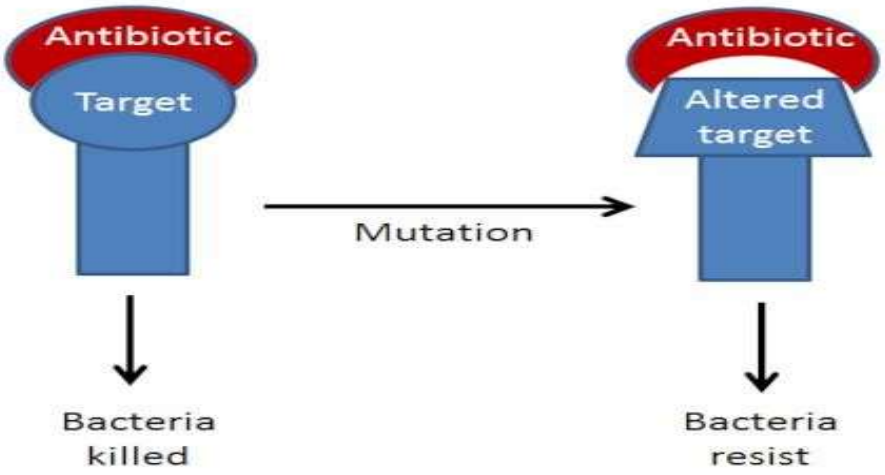

Figure 4: Mechanisms involving modification of drug targets that reduce antimicrobial effectiveness

3.3 Enhanced Drug Efflux Systems (Active Antibiotic Expulsion)

Multidrug efflux systems, such as AcrAB -TolC in Escherichia coli and MexAB -OprM in Pseudomonas aeruginosa, are essential contributors to the mechanisms of antibiotic resistance through active exportation of a broad spectrum of antimicrobial agents. These tri-partite protein complexes cross the inner membrane, periplasm and outer membrane, and thus create a continuous channel that releases the toxic compounds directly to the outside environment. The expression of these efflux systems is highly regulated by chromosomal control genes; marA and ramA. Persistent overexpression of efflux pumps caused by mutations or upregulation of these transcriptional regulators reduces the accumulation of drugs into the cell and the development of multidrug-resistant (MDR) phenotype.

Recent Advances (2024–2025):

The latest advances emphasize the use of artificial intelligence (AI)-based computational methods in the identification of possible efflux pump inhibitors. The models make use of structural information of efflux complexes like AcrAB TolC and MexAB OprM to screen huge collections of chemical libraries and to predict high-affinity inhibitory compounds. Clinical translation is a significant issue even despite the positive in silico and experimental results. No efflux pump inhibitor is currently approved to be used therapeutically, indicating efficacy, toxicity, and pharmacokinetics limitations (Blair et al., 2015; arXiv, 2025).

Clinical Significance:

Efflux pumps overexpression leads to a significant decrease in the intracellular concentration of antibiotics, therapeutic failure, chronic infections, and transmission of multidrug-resistant bacterial strains.

3.4 Horizontal Gene Transfer (HGT)

Horizontal gene transfer (HGT) occurs when genes are transferred vertically within a species and horizontally across a species lineage, thereby influencing the species' evolutionary potential. Horizontal gene transfer (HGT) is when genes are passed on vertically within a species and horizontal across a species lineage, thus affecting the evolutionary possibilities of the species.

Horizontal gene transfer is one of the most significant pathways of resistance transfer, which allows spreading resistance determinants on a large scale and between bacterial species. The mcr-1 (causing colistin resistance) and carbapenemase-coding genes (bla-NDM, bla-KPC) are also often present on plasmids and transposons, which contributes to their spread to all countries (Liu et al., 2016). The latest information provided by WHO shows that mcr-1 has been found in more than 60 countries, with the highest prevalence in the Asia-Pacific area and the growing number of countries where it is detected in Europe.

Critical perspective: The ability of plasmids to transfer multiple resistance genes at the same time (e.g., *bla*-NDM combined with *mcr-1*) circumvents the pan-resistant bacteria, which essentially renders second-line lines of therapy.

Clinical significance: This process is the basis of the worldwide resistance dissemination and is a significant barrier to be contained irrespective of the health care environment of high transmission.

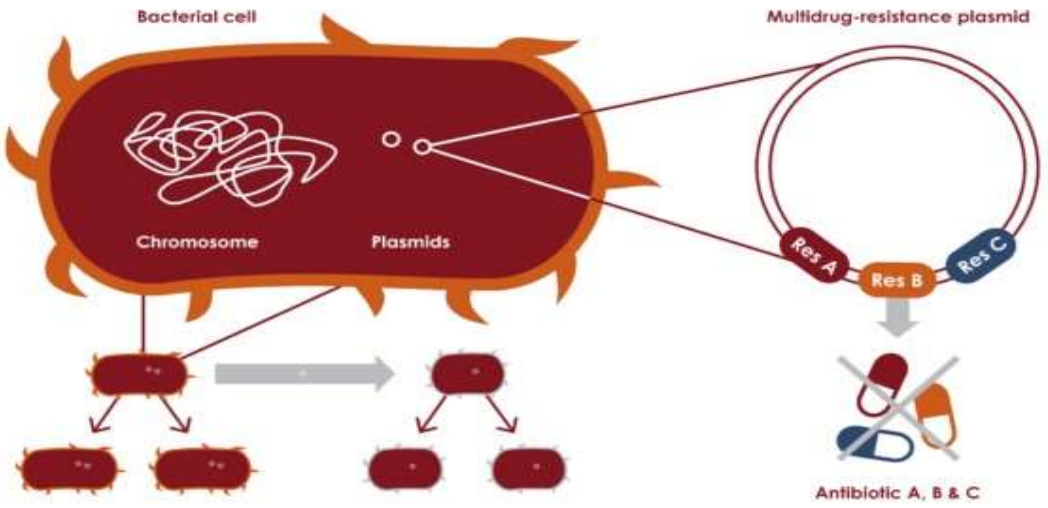

Figure 5: Mechanisms involved in the mobilization of plasmids

4. Molecular Mechanisms of Fungal Resistance

4.1 Ergosterol Biosynthesis Mutations

Y132F, Y257N and V165A replacements on the ERG11 gene are a primary mechanism of azole resistance in Candida. The mutations cause changes in the structure of sterol 14 alpha-demethylase, which decreases the affinity of azole binding and allows the ergosterol production to proceed (Cowen et al., 2024). Recent structural studies have shown that the mutations alter the geometry of the azole-binding pocket to enable drug dissociation and functional resistance. In C. auris, a combination of several ERG11 mutations can be present which can further increase the level of resistance.

Clinical significance: The mechanism is associated with extensive azole resistance in invasive candidiasis and frequently leads to cross-resistance of a large range of azole agents.

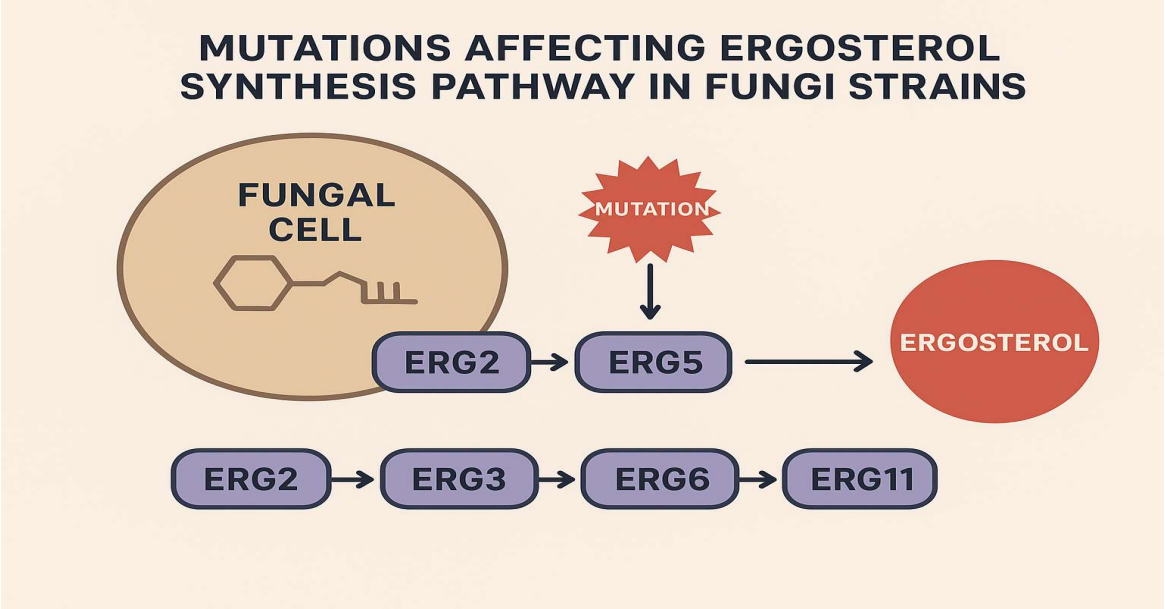

Figure 6: Mutations affecting ergosterol synthesis pathways in fungi

4.2 Squalene Epoxidase (SQLE) Mutations

Mutations in the SQLE gene (L393S, F397Y, Q408R, F415S and H440Y) were found to be the major contributors of terbinafine resistance in *Trichophyton indotineae*. These mutations inhibit the proper binding of terbinafine to squalene epoxidase and inhibit its activity to block the process of ergosterol biosynthesis (Foschi et al., 2025; CDC, 2025). The combined high rate of these mutations in South Asia and the rapid international spread of the mutations signifies a major change in the epidemiology of dermatophyte infections.

Clinical significance: The general ineffectiveness of terbinafine has led to the adoption of itraconazole that is also less predictable and more toxic.

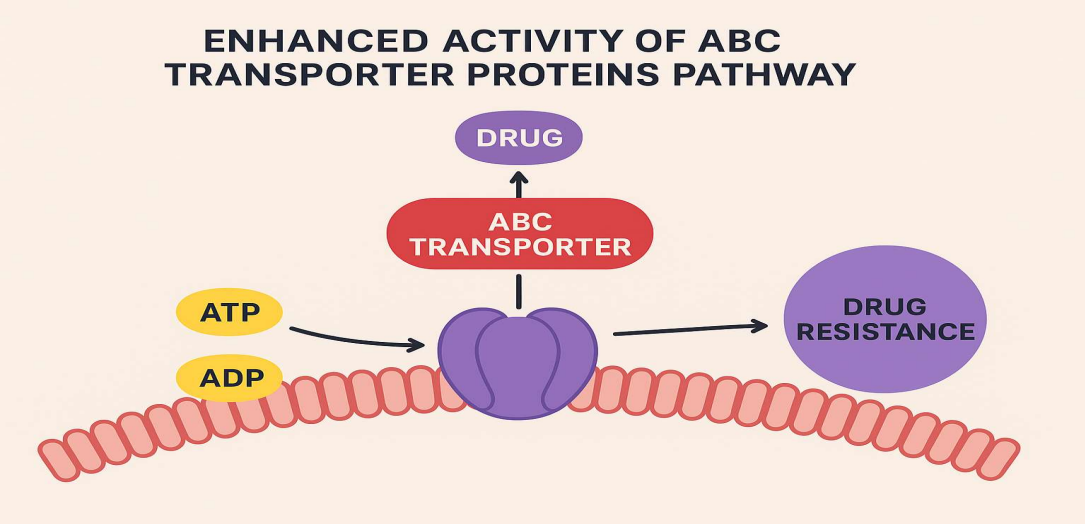

Figure 7: Mechanisms underlying enhanced activity of ABC transporter proteins

Epidemiological impact: The global spread of T. indotineae is an important change in the epidemiology of dermatophytes, in the past mainly dominated by T. rubrum and T. mentagrophytes. T. indotineae has a high transmissibility and intrinsic fitness, which means it will eventually be the most widespread dermatophyte worldwide.

Clinical implications: Terbinafine failure has become common in the treatment of dermatophytes; it must be replaced by itraconazole that has higher toxicity (hepatotoxicity, drug interactions) and worse clinical outcomes, especially in the more severe cases.

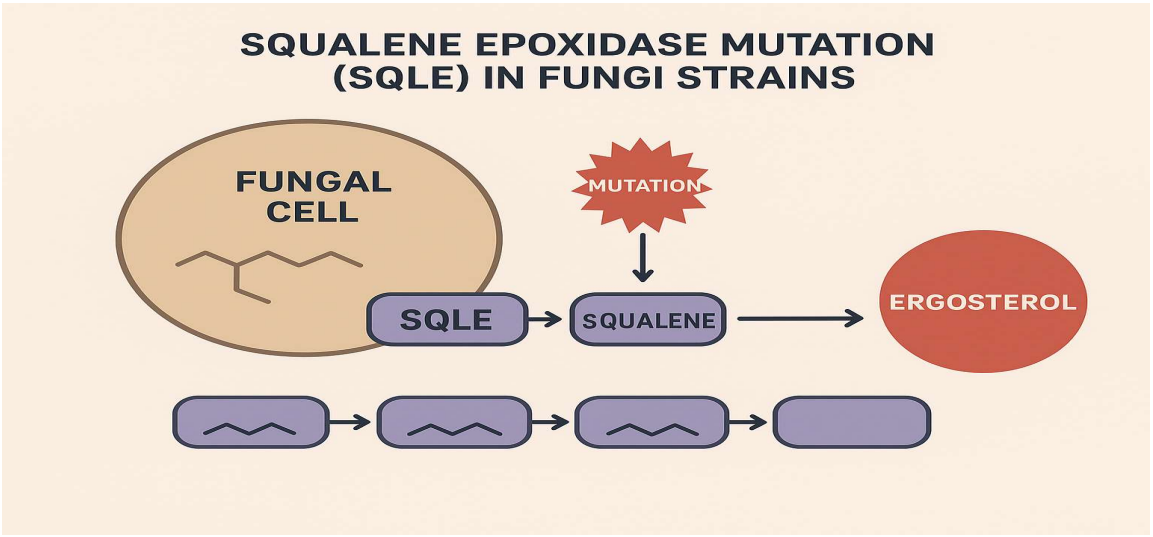

Figure 8: Mechanisms of Squalene Epoxidase Mutation (SQLE)

4.3 Efflux Transporter Upregulation

Candida auris and Candida albicans are fungal pathogens that are resistant to overexpression of efflux transporters, including CDR1, CDR2 (ATP-binding cassabe transporters) and MDR1 (major facilitator superfamily). The expulsion of antifungal agents is active in these transporters, and it decreases the intracellular concentrations of drugs and plays a role in multidrug resistance. Transcriptional regulators that regulate these transporters, including TAC1, are constitutively overexpressed via mutations. **Mechanistic parallel:** This is a resistance strategy closely oriented to the bacterial efflux systems, and diably reflects the nature of evolutionary convergence among the separate groups of microbial life. **Clinical significance:** Efflux-based resistance is one of the primary factors of long-term hospital epidemiology and decreased efficacy towards antifungals.

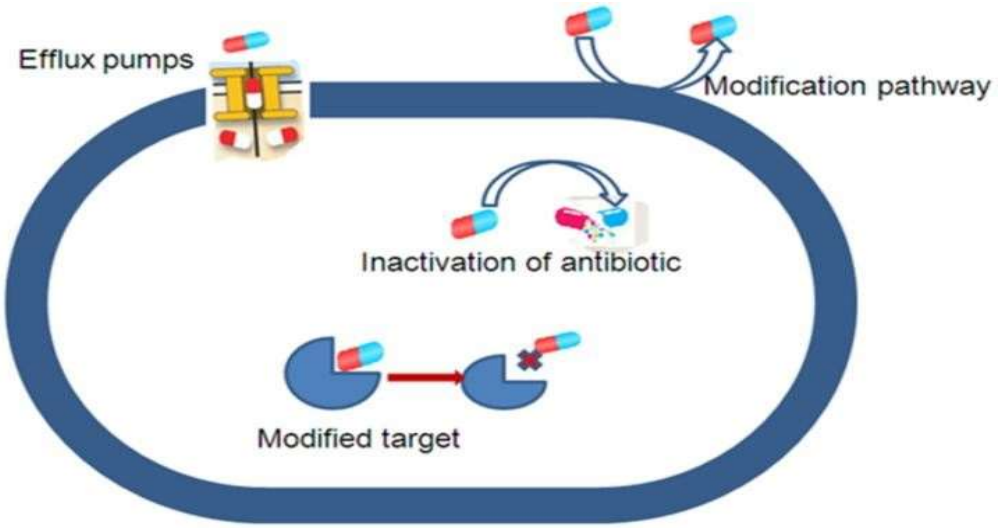

Figure 9: Mechanisms of Multidrug efflux transporters

4.4 Biofilm Formation

Candida albicans, C. auris, and Aspergillus fumigatus develop protective biofilm-forming microbes that consist of polysaccharides, proteins, and lipids that diminish the penetration of drugs and enhance horizontal gene transfer between microbes (Rajendran et al., 2021). Biofilms may increase the antifungal susceptibility by 10-1000-fold of planktonic cells. **Distinct characteristic to fungi:** although bacteria are also capable of forming biofilms, fungal biofilms have special architectural organizations such as hypha networks in A. fumigatus and dense clusters of yeasts in Candida albicans, which give rise to heterogeneous micro-environment and drug penetration and resistance phenotypes. **Clinical importance:** Biofilms are responsible of chronic, recurring infections that are resistant to first line antifungals; they are known to be extremely troublesome in infections related to indwelling medical equipment (e.g., central venous catheters colonized by C. auris).

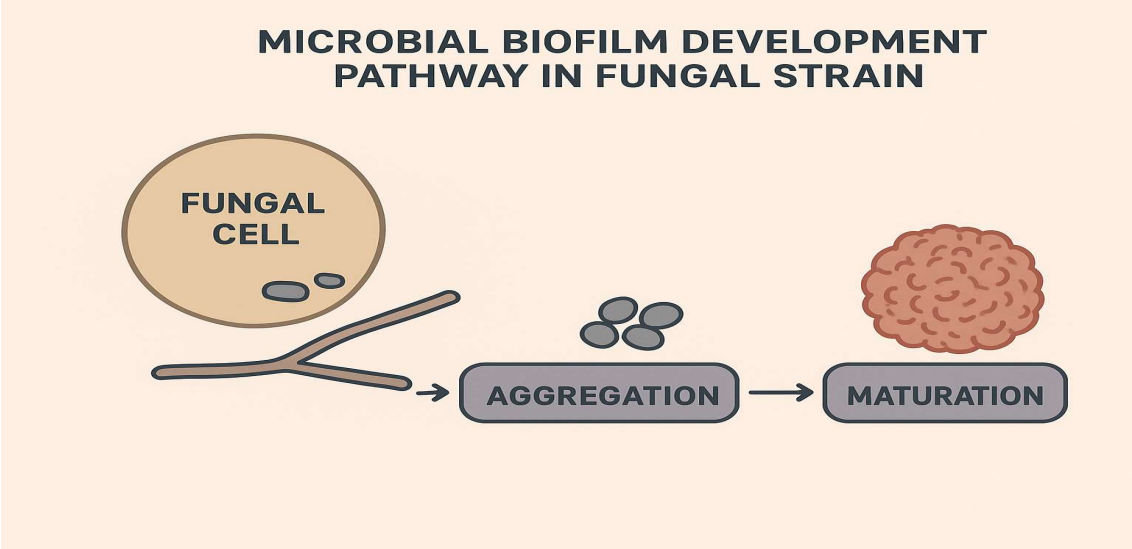

Figure 10: Mechanisms of Microbial biofilm development

5. Comparative Analysis Of Bacterial And Fungal Resistance Mechanisms

The overall analysis of bacterial and fungal mechanisms of resistance shows both the basic similarities and the most important differences that have direct implications in the development of the therapeutics. Although the development of both microbial groups is imposed by the action of selective drugs, differences in their structure and metabolism predetermine different resistance mechanisms. Nevertheless, this overlap of some strategies, in particular, efflux-mediated resistance and target modification, points to the possible paths into cross-kingdom therapeutic interventions.

Notably, bacterial resistance is usually described as a high level of spread, which is due to the mobile genetic elements, i.e., plasmids, and transposons, that facilitate the horizontal transfer of genes between species. Conversely, the fungal resistance is more likely to depend on the chromosomal mutations, transcriptional regulation and the biofilm-related adaptation. In spite of

these variations, the two systems exhibit impressive evolutionary plasticity and can therefore rapidly adapt to pharmacological stress.

Table 2. Comparative Resistance Pathways: Bacteria vs. Fungi

Mechanism Type	Bacterial Example	Fungal Example	Shared Principle	Key Difference
Enzymatic Inactivation	Carbapenemases (NDM, KPC, VIM, IMP)	ERG11/SQLE mutations	Drug target/metabolite sequestration	Bacteria degrade drugs; fungi alter biosynthetic targets
Target Modification	PBPs (*S. pneumoniae*), rpoB (*M. tuberculosis*)	ERG11/SQLE mutations (*Candida*, *Trichophyton*)	Altered drug binding affinity	Bacteria modify protein–drug interface; fungi alter membrane-integrated enzyme structure
Efflux Transporters	AcrAB–TolC (*E. coli*), MexAB–OprM (*Pseudomonas*)	CDR1/CDR2/MDR1 (*Candida*)	Active drug extrusion	Both employ pump families (RND/ABC), but bacterial pumps export more diverse substrate classes
Gene Transfer & Adaptation	Plasmids, transposons (*mcr-1*, *bla*-NDM)	Biofilm-mediated HGT, chromosomal duplication	Rapid resistance dissemination	Bacteria utilize mobile elements; fungi rely on chromosomal events and biofilm cooperation
Phenotypic Heterogeneity	Heteroresistance in *S. aureus*	Biofilm-mediated phenotypic variation	Population-level resistance diversity	Bacterial heteroresistance is reversible; fungal biofilm-mediated resistance is more stable

In the comparison, it is apparent that even though bacteria and fungi employ different structural pathways, they employ similar survival strategies; that is, reduce drug interaction, increase efflux and adjustment at the population level.

Therapeutically, such an overlap implies that broad-spectrum solutions such as the efflux pumps or biofilms could be targeted. Nevertheless, some novel mechanisms, like enzymatic drug degradation in bacteria, or modification of ergosterol biosynthesis in fungi, need organism-specific conditions.

6. Therapeutic Implications of Resistance Mechanisms

Antimicrobial and antifungal resistance has clinical outcomes that go beyond treatment failure, and it impacts drug choice, treatment effects and health care burden. The mechanistic nature of resistance is thus critical towards informing rational-therapeutic interventions and designing new-generation interventions.

Table 3: Therapeutic Implications of Resistant Microbes

Microbe Type	Resistance Mechanism	Example	Therapeutic Implication
Bacteria	β-lactamase production	*E. coli, Klebsiella*	Carbapenem failure
	Efflux pump (AcrAB-ToIC)	*E. coli*	Efflux pump inhibitors under trial
	Plasmid-mediated *mcr-1* gene	*Enterobacteriaceae*	Colistin resistance
Fungi	*ERG11* mutation	*Candida albicans*	Azole resistance
	SQLE mutation	*T.indotineae*	Terbinafine resistance
	ABC transporter upregulation	*C.auris*	Multidrug resistance
	Biofilm formation	*C. albicans*	Drug penetration barrier

7. Critical Appraisal: Gaps, Challenges, And Future Directions

Recent surveillance results (2024-2025) show a progressive and quick increase in antimicrobial resistance (AMR) and antifungal resistance (AFR). Even though the mechanistic understanding and surveillance growth are further improved, it remains that there are multiple vulnerabilities that restrict successful global response measures, which require timely and synchronized measures (WHO, 2024a; Murray et al., 2024).

7.1 Surveillance and Epidemiological Gaps

Geographic imbalance:

The concentration of surveillance persists globally, with high-income areas of the world, including North America and Western Europe, having a disproportionate concentration compared with the low- and middle-income nations, which frequently must bear the weight of the resistance. Whereas the WHO GLASS program incorporates the information about more than 100 countries, the situation with the sub-Saharan African,

Southeast Asian, and Central American areas is insufficient, which may hide the new hot spots of resistance (GLASS, 2025).

Limited mechanistic insight:
The existing surveillance measures focus mainly on prevalence data as opposed to mechanistic or ecological determinants. It is noteworthy that the resistance rates are still increasing, even when antimicrobial use in agriculture is decreased, which indicates that the environmental reservoirs, global mobility, and climate-based adaptation are important factors. A combination of genomic sequencing and ecology with phenotypic data is crucial in predictive surveillance (UKHSA, 2024; Cookson, 2025).

7.2 Translational Gaps: From Mechanism to Therapy

Mechanisms without translation:
Even though the main resistance mechanisms, including ERG11 mutations, plasmid-mediated mcr-1, and efflux pumps overexpression, are well-known, their implementation into diagnostic or treatment measures is still low.
Despite a long history of research and development, efflux pump inhibitors have not been obtained clinical approval because of toxicity and pharmacokinetic shortcomings. Equally, innovation in antifungals falls behind antibacterial innovation with only a handful of new classes of drugs developed in the last 20 years, and new resistance even to echinocandins.
Resistance to advanced therapies:
The development of resistance to the last-line agents, such as ceftazidime-avibactam and echinocandin, questions the sustainability of the combination therapy in the long term. This is a trend that indicates that there is an increasing selection pressure, and multi-target resistance mechanisms are evolving (Livermore et al., 2024).

7.3 Natural Products: Promise Versus Clinical Reality

Although natural compounds show an excellent in vitro antimicrobial synergy, e.g., cinnamaldehyde with MRSA and eugenol with fluconazole, their clinical implementation is minimal. The most important challenges are the variation in the phytochemical composition, non-standardized dosing, the absence of pharmacokinetic measurements, and shortage of randomized clinical trials (Suresh et al., 2024).
Moreover, weak bioavailability of resveratrol and curcumin compounds limit systemic activity. Even though nanocarrier and phytosomal formulations are promising in preclinical models, they were not clinically validated yet. The fact that they are still ambiguous in regulations also makes it harder to incorporate them in mainstream therapeutics.

7.4 Climate Change and Ecological Drivers

The role of environmental and climatic factors as determinants of resistance evolution is becoming increasingly recognized. Increased world temperatures and ecological changes are dependent on the development of resistant and thermotolerant fungal pathogens. An example is Trichophyton indotineae that is more able to survive in warmer temperatures, and Candida auris that does not have any temperature tolerance, which allows it to endure in the context of a clinical setting.
At the same time, there is extensive agricultural application of azole fungicides which have also led to the rise of resistant strains of Aspergillus fumigatus. The high interrelations between the environmental and clinical resistance indicates the necessity of combined stewardship across sectors.

7.5 One Health Integration Imperative

AMR and AFR are natural One Health problems, both of which are interconnected systems of human, animal, and environmental. Nevertheless, the modern surveillance systems are still disjointed. The clinical, veterinary and environmental data are usually gathered separately which restricts the overall understanding. Moreover, the agricultural activities, especially the use of fungicides are not often in tandem with the policies of clinical stewardship. There is no prediction capacity due to absence of environmental factors like climate, soil microbiota and ecological dynamics in resistance models.

8. Harnessing Natural Products To Combat Antimicrobial And Antifungal Resistance

As traditional drug development has plateaued, natural compounds have become an interesting adjunct or replacement of antimicrobial treatment. The latest studies point to essential oils, phytochemicals, and sophisticated delivery methods as a possible solution to drug resistance (Usai et al., 2023; Khameneh et al., 2024).

8.1 Essential Oils and Herbal Extracts

Plant essential oils show broad-spectrum antimicrobial and antifungal action in a completely different mechanism to conventional medicines. Their lipophilic properties allow them to interact with cell membranes of microbes causing them to become permeable, rupture and release intracellular constituents and result in cell death.
The property of disruption of microbial biofilms as well as inhibition of bacterial and fungal growth has been widely researched in Neem (Azadirachta indica) (Pavithra et al., 2024). Likewise, the main active ingredient of cinnamon oil, cinnamaldehyde, has a strong activity against Staphylococcus aureus due to its ability to increase the membrane permeability and promote intracellular concentration of antibiotics (Usai et al., 2023).
Several other essential oils such as peppermint and lavender have also proved effective in Candida albicans and methicillin resistant Staphylococcus aureus (MRSA) by destabilizing the membranes and causing oxidative stress (Khamaneh et al., 2024).
Analytical knowledge: In contrast to single-target antibiotics, the essential oils do not address only one

cellular component at a time; thus, lowering potential development of resistance and increasing their potential in combination therapy.

8.2 Phytochemicals with Synergistic Effects

The resistance mechanisms of bioactive phytochemicals are regulated instead of killed, which restores the antimicrobial activity. Cinnamaldehyde can increase the effect of vancomycin on MRSA and eugenol can resensitize fluconazole-resistant Candida to ergosterol pathways and efflux systems (Usai et al., 2023; Chouhan et al., 2024). Quorum sensing is also inhibited by polyphenols like curcumin and catechins, as well as is virulence-reducing (Suresh et al., 2024). Translational value Phytochemicals are good adjuvants that enhance the action of drugs and reduce the chances of resistance.

Table 4: Overview of bioactive plant-derived molecules, their mechanisms of action, and emerging therapeutic applications.

Compound	Target Pathogen	Mechanism of Action	Limitation	Future Potential
Neem	MRSA, Candida	Biofilm disruption	Purity varies	Nanocarrier creams (Sharma et al., 2024)
Cinnamaldehyde	MRSA, S. aureus	Synergizes with antibiotics	Few trials	Phytosomal Formulations
Eugenol	Candida albicans	Restores fluconazole action	Not standardized dosing	Clinical trial validation

8.3 Advanced Delivery Strategies: Nanocarriers And Phytosomal Systems

Natural compounds face major limitations due to poor bioavailability, but advanced delivery systems such as **phytosomes** and **nanoparticles** have significantly improved their therapeutic potential. Phytosomes, formed by complexing plant extracts with phospholipids, enhance absorption and tissue targeting, with phytosomal curcumin showing **20–30× higher bioavailability** and synergistic effects when combined with antibiotics. Nanoparticle systems, including liposomes and solid lipid nanoparticles, further boost efficacy by penetrating biofilms, prolonging retention at infection sites, and protecting bioactives from degradation; herbal nanoparticles (neem, peppermint, lavender) and liposomal eugenol have demonstrated superior antimicrobial and antifungal activity with reduced toxicity. Mechanistically, these systems provide **enhanced biofilm penetration, sustained release, increased cellular uptake, and lower host toxicity**, collectively overcoming the shortcomings of natural compounds and positioning them as promising candidates for clinical application. **Critical Considerations And Limitations**

Although natural alternatives have therapeutic potential, they have critical limitations such as phytochemical variation, non-standardized dosing, and are not approved by the regulators. Also, large-scale randomized clinical trials are limited, which hampers their clinical implementation (Suresh et al., 2024). Thus, natural products must remain put as complementary measures which need to be thoroughly validated before they can be incorporated into mainstream therapy. Priorities should in the future be to carry out properly designed clinical trials (Chouhan et al., 2024), apply standardized extraction procedures (Khamaneh et al., 2024), and possess a well-defined regulatory framework regarding nanocarrier based formulations (Rajeshkumar et al., 2024).

9. Conclusion

The problem of antimicrobial and antifungal resistance has reached a critical point of inflection, the recent (2024-2025) data show that the resistance in high-priority pathogens is on the increase: Acinetobacter baumannii, Candida auris, and Trichophyton indotineae (WHO, 2024b; CDC, 2024). Although there is a growing mechanistic knowledge, starting with the evolution of 2-lactamase through to the mutation of the ergosterol pathway, innovation has not yet emerged in the field of treatment, and even the latest agents are becoming resistant (Livermore et al., 2024; Cowen et al., 2024). A promising adjunctive strategy includes using natural alternatives, such as essential oils, polyphenols, and nanometer which involves disruption and modulation of the virulence of biofilms and drug synergy (Usai et al., 2023; Rajeshkumar et al., 2024). Nevertheless, they are limited in their clinical translation due to a lack of validation, regulatory and scaling difficulties (Suresh et al., 2024; Khameneh et al., 2024). New priorities will involve the implementation of the One Health surveillance system, the further development of genomic and AI-powered forecasting systems, revitalization of antimicrobial pipes, and strictly clinical testing of phytochemical-based treatments (WHO, 2025; Murray et al., 2024; Steenwyk et al., 2025). The post-antibiotic age can be unavoidable unless the world acts in unison. Nevertheless, this path can be changed through innovation, stewardship, and the incorporation of the natural product science knowledge into the contemporary therapeutics.

10. Conflict of Interest

None

11. References

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