ORIENTAL JOURNAL OF CHEMISTRY
An International Open Access, Peer Reviewed Research Journal
www.orientjchem.org
ISSN: 0970-020 X
CODEN: OJCHEG
2024, Vol. 40, No.(3):
Pg. 630-645

Evaluating the Impact of Antifungal Drugs on Human Health and Exploring Alternative Treatments

DEBASHREE MANDAL

Department of Chemistry, East Calcutta Girls' College, P237, Lake Town Road, Block B, Sreebhumi, Lake Town, Kolkata 700089, India.
*Corresponding author E-mail: debashree1981@gmail.com

http://dx.doi.org/10.13005/ojc/400302

(Received: April 22, 2024; Accepted: May 27, 2024)

ABSTRACT

Fungi occurred naturally like Candida yeast, in the human body. It may grow on skin, inside the digestive system and vagina. Antifungal drugs are used to kill or stop this fungal growth. According to their mode of action they are divided into azoles (inhibit ergosterol synthesis), echinocandins (damage cell walls), and polyenes (destroy fungal cells) etc. Depending on the seriousness of infection and type of infection, generally antifungal drugs are administered to a body. Oral antifungals are taken by mouth for systemic infections. Topical antifungals (creams, ointments) treat localized skin and nail infections. Intravenous (IV) administration is used for severe cases. Common side effects of antifungals are yeast infection, hepatotoxicity, ringworm, nail and skin infections etc. Serious fungal infections pose a growing threat to human health specially for vulnerable patients having significant morbidity and mortality such as AIDS patients, transplant recipients, and individuals using certain medications. Some of the existing antifungal drugs, particularly azoles, are facing increasing resistance. In order to ensure successful treatment of these drug-resistant infections, there is a critical need for the development of novel antifungal agents which is very challenging. Here about the antifungals, its classification, pros and cons of using antifungal drugs, prevention and control of antifungals are discussed in detail.

Keywords: Fungal infection, Antifungal, Classification, Impact, Resistance, Prevention.

INTRODUCTION

Fungi infections have been seen in the environment all over the world. Fungal infections pose a growing threat to immune-compromises. Antifungal drugs/antimycotics are used to kill or stop this fungal growth or multiplication. People can take it orally, apply them topically, or intravenously, but in time. Antifungal drugs aim at various types of fungi cell membrane, including dermatophytes, yeasts, and molds. The journey from early modalities to modern antifungal agents has been marked by groundbreaking discoveries and ongoing efforts to combat fungal infections. Cutaneous fungal infections, such as actinomycosis, blastomycosis, sporotrichosis, and tinea form, pose a significant threat to individuals, causing discomfort and often affecting their quality of life. In 1903, potassium iodide (KI) was used as an antifungal treatment for these infections, with varying degrees of success.[1]

Griseofulvin was invented in 1930. But the invention of the first antifungal antibiotic was reported in 1944 and from then the work of antifungal antibiotics started. Polyene antifungals, such as Nystatin, Amphotericin B, have been in use since the 1950s. In the early 1960s, Griseofulvin emerged as the first orally effective antifungal antibiotic. It was primarily used for managing dermatophytosis (fungal infections of the skin and nails). Iodinated trichlorophenol haloprogin followed as one of the first broad-spectrum antifungal agents. A significant milestone occurred in 1969 with the discovery of azole antifungal agents. These compounds revolutionized antifungal therapy. Then in the 1990s, liquid Amphotericin B, fluconazole, itraconazole, second generation triazole reported. After 2000, Voriconazole, Posaconazole, Micafungin, Anidulafungin, Isavuconazole etc. showed their activity.[2] Super bioavailable Itraconazole was introduced in 2018. Antifungal infections have become a significant concern in the pandemic period. During COVID-19, coronaviruses have increased the risk of fungal infections[3] because during treatment against these viruses, steroids and other drugs decrease the immunity of the body's defenses against fungi. Most common fungal infections[4] in pandemic periods are a) Aspergillosis: This fungal infection is increasing due to the fungus *Aspergillus*.[4a] Invasive aspergillosis is a serious fungal infection that predominantly affects individuals with weakened immune systems. In India 250,900 cases have been seen. These include patients with chronic obstructive pulmonary disease, neutropenia, those on corticosteroids, recipients of hematopoietic stem cell transplants, and individuals with severe influenza or COVID-19 pneumonia. COVID-19 patients are in a severe treatment process, they may have pulmonary Aspergillosis. Invasive aspergillosis was also associated with 2,360 deaths from AIDS in 2020. b) Invasive candidiasis: This type of infection occurs due to *Candida* species which may affect various organs. The annual incidence of candidemia in India is approximately 188,035 cases whereas invasive candidiasis, around 470,000 per year. Life threatening infections (invasive candidiasis) is generally in immuno-compromised patients (like HIV patients, cancer patients receiving chemotherapy, and patients receiving immuno-suppressive drugs). c) Mucormycosis (Black fungus): It is one of the fatal fungal infections which is now a major public health problem in India, especially those COVID-19 patients who have uncontrolled diabetes and steroid usage. The annual incidence of mucormycosis across India was approximately 195,000 cases. d) Chronic Fungal Rhinosinusitis: For these cases early diagnosis and treatment are very crucial to prevent severe illness and death. Antifungal resistance is a growing global concern, impacting millions of people worldwide. In India, a recent study reveals that fungal infections[5] have led to an increase in deaths from 2 million to approximately 3.8 million annually which constitute a significant public health challenge. 6.8% of total global deaths is due to fungal infection.[6] As many types of infection are invented day by day, new antifungal drugs are also coming to the medicine market by the hard work of our researchers, doctors worldwide are striving to address the limitations of current antifungal drugs and advance the development of more effective treatment options,[7-17] and a broader spectrum of activity to tackle drug-resistant fungal infections. The effectiveness of antifungal drugs depends on their ability to eliminate or inhibit fungal pathogens causing infection while minimizing adverse effects on the patient. Here are some factors that affect the effectiveness of antifungal drugs: 1) Spectrum of activity: Different antifungal drugs have activity against different types of fungi. The choice of drug is often based on the type of fungus involved in the infection, whether it's a yeast (like *Candida* species) or a mold (like *Aspergillus* species). 2) Drug resistance: As with other antimicrobial agents, the emergence of resistance to antifungal drugs is a growing concern in the field of medicine. The resistance can significantly reduce the effectiveness of these drugs in treating fungal infections. This is a growing problem with diseases such as invasive candidiasis, where some species of *Candida* are becoming resistant to first-line treatments like fluconazole. 3) Pharmacodynamics and Pharmacokinetics[2b]: The absorption, distribution, metabolism, and excretion of antifungal drugs can affect their effectiveness. For instance, some drugs do not penetrate the central nervous system effectively, making them less useful for treating meningitis. 4) Patient factors: The immune status of the patient is paramount such as HIV/AIDS patients, undergoing chemotherapy, transplants, may respond less effectively to antifungal therapy compared to individuals with healthy immune systems. 5) Site of infection: Certain areas of the body like the eye, nail, central nervous system etc. are more difficult to reach with antifungal drugs. The effectiveness of treatment can be limited by

poor drug penetration to these sites. 6) Toxicity and tolerability: Some antifungal drugs have significant side effects that can limit their use. For example, amphotericin B is very effective but has considerable nephrotoxic potential, which requires careful monitoring and sometimes leads to discontinuation of the treatment. 7) Combination therapy: Whether these drugs are used alone or in combination can also affect their effectiveness. Combination therapy can be employed to enhance the antifungal action or to prevent the development of resistance. Many fungal infections already have existing challenges in terms of treatability, such as potential toxicities and interactions with other underlying infections. The drug-resistant infections are leading to treatment failures, prolonged hospital stays, and the need for more expensive treatment options. In addition to the challenges posed by drug resistance, changes in species distribution can also impact treatment recommendations for fungal infections. For effective management of antifungal treatment, it is very crucial to know about the various types of fungal infections, different classes of antifungal drugs, their mechanisms of action, administration routes, and potential side effects.

Classification of the landscape of antifungals

The therapeutic index of a drug is a crucial concept in pharmacology, as it helps determine the optimal dosage range for effective treatment while minimizing the risk of toxicity. Therapeutic index high indicates a wide safety margin between the effective dose and the toxic dose, while a low therapeutic index implies a narrow window between therapeutic and harmful doses. For antifungal drugs, the therapeutic index can vary widely depending on the drug's class, spectrum of activity, and the fungal organism targeted. Four main classes[7] are described here depending on many factors. These are polyenes, azoles, allylamines and echinocandins (for invasive candidiasis). Different types of antifungal drugs with examples of various types of infections, side effects, and treatment have been discussed here.

Antifungal medications according to chemical structure[18-19]

Polyenes[1,7]: Macrocyclic polyene antifungal (Fig. 1) with hydroxylated region on the ring opposite the conjugated chemical structure makes these antifungals amphiphilic. These organic antifungal drugs destroy serious fungal infections. These have a low therapeutic index. They are effective against a broad spectrum of fungal species, but their use is limited by significant toxicities, notably nephrotoxicity (kidney damage). Some examples of polyene antifungals are a) Amphotericin B[1]: It is used for severe fungal infections (mycoses) such as invasive candidiasis, aspergillosis, mucormycosis, histoplasmosis, blastomycosis, coccidioides, and cryptococcal disease, which pose a significant burden on global healthcare systems, especially in immunocompromised individuals. Though, some amphotericin B may attack animal membrane cholesterol, growing the danger of human toxicity at therapeutic doses. Side effects are abdominal discomfort, skin reaction, jaundice, allergic reactions etc. b) Natamycin[1]: This drug is in the polyene macrolide family. It is used in human medicine. c) Nystatin[1]: It is a medication that is commonly used for the treatment of fungal infections particularly those caused by *Candida* species.

Azoles[1,7]: Most common broad spectrum azole antifungal drugs classified into imidazoles,[1] triazoles,[1] and thioazoles. Azoles contain a five-membered ring with two or three nitrogen atoms. Side effects may cause the problem of gastrointestinal (such as vomiting, abdominal pain, nausea, diarrhea, flatunence etc.), skin related such as dizziness, headache, increased liver enzymes, hair loss, fever etc. Fluconazole and Itraconazole generally have a higher therapeutic index with fewer side effects making them suitable for a longer duration of therapy. They are often used first-line due to their safety profile and broad spectrum of activity. There are three subgroups of azole antifungals.

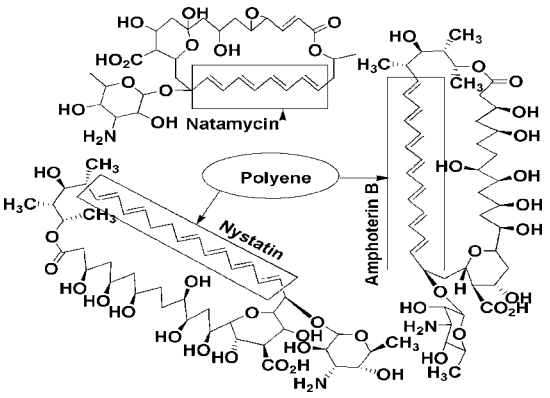

Fig. 1. Chemical Structure of Polyene

Imidazoles[7d]: All imidazole antifungals have a 1,3-diazole imidazole ring with two nitrogen

atoms (Fig. 2). The infections under the imidazole antifungal drugs are treated are: 1) Clotrimazole[7b]: This topical agent is to treat skin, oral, candidiasis, and vaginal yeast infections. 2) Oxiconazole[7c]: This is cream applied to various skin related problems. 3) Miconazole[7c]: This imidazole antifungal is used for vaginal candidiasis and oropharyngeal candidiasis. The common side effects are symptoms like burning, itching, skin/vagina irritation, stomach pain, fever etc. 4) Butoconazole[7c]: It is a cream suppository used to treat vulvovaginitis.

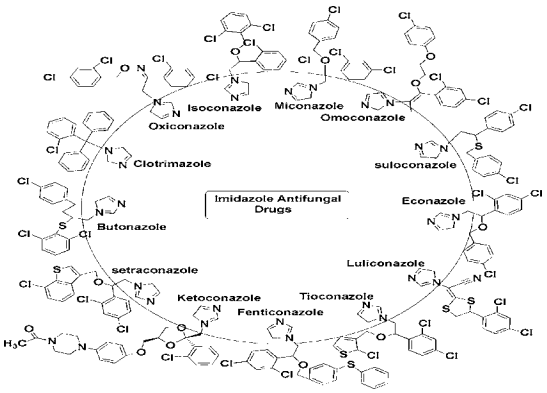

Fig. 2. Chemical Structure of Imidazole antifungal drugs

Isoconazole: It used in the treatment of foot and vaginal infections. 6) Sulconazole: It is a topical antifungal medication that is used to treat various fungal infections of the skin including tinea corporis, tinea pedis and tinea cruris. 7) Tioconazole: This is a cream medication used to treat various fungal infections such as tinea corporis (ringworm), tinea pedis, tinea cruris and cutaneous candidiasis. Burning, itching, redness, skin rash and swelling symptoms arise as side effects. 8) Econazole: This is topical cream which is used for skin. It may cause burning, itching, redness, and skin rash. 9) Ketoconazole: It is a medication that is commonly used in the treatment of fungal infections on the skin and scalp. It is available in cream or shampoos, typically at concentration of ~2%. 10) Luliconazole: This medication is used to treat skin infections such as Jock itch, Athlete's foot, Ringworm etc. The side effects show application site irritation, itching, and skin exfoliation. 11) Omoconazole: It is used for treating cutaneous candidiasis, dermatophytosis, pityriasis versicolor etc. in the form of creams or ointments. 12) Sertaconazole: This medication is marketed as Ertaczo, primarily used to treat skin infections. 13) Fenticonazole[20]: It is also sold under the brand name Ertaczo. It is used to treat vaginal infections like burning, itching, and discharge etc. caused by various types of fungi. 14) Zinoconazole[21]: This cream is used to treat cutaneous candidiasis, dermatophytosis, and pityriasis versicolor. ii) Triazoles[7e]: These drugs can be administered both by intravenously and orally. This drug contains a five membered ring with three nitrogen atoms (Fig. 3). Some examples of triazoles are 1) Fluconazole[22]: It is a widely used medication that has proven effective for the infection of esophageal, oropharyngeal, peritoneal, urinary tract, vaginal candidiasis, candidemia, candida pneumonia, coccidioidomycosis, histoplasmosis/ blastomycosis and cryptococcal meningitis (in AIDS patients) etc. Yeast infections caused by the *Candida* species pose a significant risk to cancer patients undergoing chemotherapy or radiation therapy. 2) Itraconazole: It is used for the treatment of aspergillosis, blastomycosis, histoplasmosis, candidiasis, coccidioidomycosis, sporotrichosis, allergic bronchopulmonary aspergillosis and onychomycosis (toenail or fingernail) etc. 3) Terconazole: This cream or suppository used to treat vulvovaginitis. It shows some common side effects such as headache, rash, itching, burning, missed menstrual periods etc. 4) Voriconazole: It is used for invasive aspergillosis, mucosal or invasive *candida* infections. The adverse effects of this medication can range from hypokalemia and visual disturbance to transient vision change, particularly in patients on long term therapy. 5) Posaconazole: It is needed for invasive fungal infections which pose a significant threat to individuals with compromised immune systems or underlying systems. 6) Isavuconazole: It is marketed as Cresemba, needed for invasive fungal infections. It is also used as an alternative therapy for salvage treatment of mucormycosis[23]. 7) Albaconazole (UR-9825): It shows potential activity for broad-spectrum against fungal infections. The drug works by blocking several CYP450 liver enzymes and antiprotozoal agents[24-25]. 8) Efinaconazole: This topical medicine is obtained as Jublia, a topical medicine used for the fungal nail infections (onychomycosis) which affects the nails, particularly toenails. 9) Epoxiconazole: Though this fungicide is used to protect crops from various fungal pathogens by inhibitting the metabolism of fungi cells. 10) Propiconazole: It is known as demethylation

inhibiting fungicide which is used to protect crops in agricultural fields. 11) Ravuconazole: It has similar activity to Voriconazole, but as it did not demonstrate significant advantages over existing voriconazole drugs. 12) Isavuconazole: This medication is marketed as Cresemba which acts against invasive fungal infections. It acts as an alternative therapy such as mucormycosis or invasive aspergillosis. iii) Thiazoles[26-27]: All thiazole antifungals have a 1,3-diazole imidazole ring with nitrogen and sulphur atoms (Fig. 4). The examples are 1) Dasatinib: This medication is marketed as Sprycel and acts against chronic myelogenous leukemia and acute lymphoblastic leukemia. This tablet acts as blockers of specific proteins on cancer cells to encourage their growth which helps shrink the cancer or prevent further growth. Some common side effects of this medication may include fatigue, diarrhea, nausea, muscle pain, headache and fluid retention. 2) Epithiolone B: Epothilone B is a natural product that belongs to the class of polyketide macro lactones. It is produced by the bacteria Sorangium cellulosum and exhibits potent anticancer activity. The synthesis of Epothilone B, a 16-membered polyketide macro lactone with a methyl thiazole group with alternative sulphur and nitrogen atom connected to the macrocycle by an olefinic bond, has been achieved through various methods. It inhibits microtubule function. 3) Tiazofurin: This anticancer agent is an antineoplastic drug that acts as an inhibitor of the enzyme IMP dehydrogenase. It also has antiviral activities. 4) Abafungin[28]: This medication shows broad-spectrum, commonly used for the treatment of dermatomycoses.

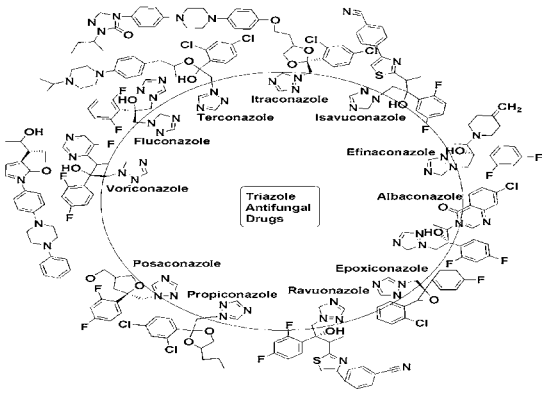

Fig. 3. Chemical Structure of triazole antifungal drugs

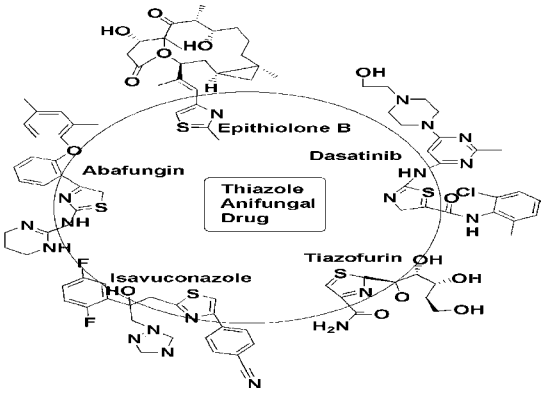

Fig. 4. Chemical Structure of thiazole antifungal drugs

Echinocandins[7]: These narrow spectrum drugs are used for the treatment of resistant *Candida* species. Some examples of echinocandins are 1) Anidulafungin: Eraxis and Ecalta is the trade name of Anidulafungin. 2) Caspofungin[8]: This medication is marketed as *Cancida*. It has a favourable therapeutic index with limited toxicity and is effective against a variety of *Candida* species and *Aspergillus*. 3) Micafungin: This medication is marketed as Mycamine which acts against invasive fungal infections.

Allylamines[7c]: Allylamines are effective against dermatophytosis (e.g. tinea capitis, tinea pedis etc.). 1)Terbinafine[8]: It is used to treat dermatophytosis (especially onychomycosis) infections and has a high therapeutic index. The common adverse effects are headache, diarrhea, stomach pain, severe liver damage etc. 2) Naftifine: It is marketed as Exoderil or Naftin and acts against the treatment of athlete's foot, jock itch, topical fungal infections etc.

Benzylamines[7c,29]: It is used for the treatment of dermatophyte infections, like athlete's foot and jock itch. e.g. Butenafine.

Other antifungal drugs: 1) Morpholine derivative: e.g. Amorolfine. It is used to treat topical dermatophytosis. But itching, irritation, redness etc. commonly has side effects. 2) Heterocyclic Benzofuran derivative: Griseofulvin acts against dermatophytosis that affects the skin, hair, nails particularly keratin. Side effects are hepatotoxicity, carcinogenicity, teratogenicity, confusion, headaches, urticaria and severe skin reactions. 3) Fluorinated Pyrimidine derivative (Antimetabolite)[1,30]: This narrow spectrum drug is

used to treat *Candida* or *Cryptococcus* species containing infection. Side effects of this drug are bone marrow suppression with pancytopenia. e.g. Flucytosine. 4) Pyridone derivatives: e.g. Ciclopirox[7c] which is a medication commonly used for the treatment of various skin conditions such as Tinea versicolor, dermatophytosis etc. However, like any antifungal drugs, this medication also comes with its own set of potential effects such as skin irritation, redness, itching, and burning at the application site. 5) Peptide-nucleoside[31-32]: It acts against fungal pathogens and has minimal toxicity to the mammalian cell as well as reduces resistance. e.g. Nikkomycin Z[8,33]. 6) Tetrahydrofuran derivatives[34-35]: It is used in agriculture as biosepticide. e.g. Sordarins, azasordarins etc. 7) Thiocarbamate antifungal[36-39]: Tolnaflate cream is the best example which acts against skin infection. It may cause skin irritation. 8) Quinoline antifungal[40-43]: e.g. clioquinol[44]. It interferes with fungal cell membranes by inhibiting enzymes involved in the synthesis of cell wall polysaccharides. 9) Chalcone based antifungal derivatives[45-47]: These derivatives are used against fungal infections, e.g. Metochalcone, Sofalcone. Like Ketoconazole, it has similar antifungal activity. 10) Aurones[48-49]: Some species are effective against *Aspergillus fumigatus*, *Aspergillus niger*, *Trichoderma viride*, and *Penicillium chrysogenum*. 11) *Carbol fuchsin* (*Castellani's paint*)[50]: This topical antiseptic is a mixture of phenol and basic fuchsin. It is used for skin related problems, staining bacteria, and fungal infections. 12) Coal tar: It is a mixture of approximately 10,000 chemicals including phenols, polycyclic aromatic hydrocarbons (PAHs) and heterocyclic compounds. It is used in medicated shampoo, soaps, ointments as it has antifungal activities to treat dandruff, seborrheic dermatitis, psoriasis (skin related fungal infection) etc. 13) Copper(II) sulfate ($CuSO_4.5H_2O$)[51]: Copper sulfate shows antifungal activities against yeasts and fungi, including *Aspergillus*, *Candida*, and *Cryptococcus* species. 14) Copper iodide[52a] nano structured material: Recenly this nanostructed material[52b] has gotten attention in research due to its potential antifungal activities. They are effective against pathogenic stains. 15) Crystal violet–a triarylmethane dye[53]: It has antifungal, antibacterial, and anthelmintic properties and is used as a topical antiseptic. 16) Chlorhexidine[54]: This is a topical antibacterial and antifungal which is used in dental and gum care as an antiseptic to prevent oral candidiasis. 17) Chlorophetanol: This topical antifungal agent belongs to the organic phenol ether family. 18) Iodoquinol[55-58]: This topical agent is used for dermatitis and other fungal infections. e.g. Diiodohydroxyquinoline. 19) Miltefosine[59]: This phospholipid is of alkyl phosphocholine family. 20) Orotomide (F901318)[8,60-63]: It is also known as Olorofim. It is administered both orally and intravenously to prevent various molds including Aspergillus fumigatus, Coccidioidomycosis etc. 21) Piroctone olamine (Octopirox)[64-65]: It is used to prevent dermatological therapy like seborrheic dermatitis, candidiasis etc. 22) Potassium iodide (KI)[66-70]: It is an important antifungal drug enlisted in World Health Organization (WHO) approved essential drug list because it kills fungi directly. It is used to treat both cutaneous and lymphocutaneous sporotrichosis. 23) Potassium permanganate ($KMnO_4$)[71]: It (0.1% solution) is used for Athlete's foot infection. 24) Selenium disulfide (SeS_2): This topical agent is mainly used in lotion and cream for preventing skin related antifungal infection such as Seborrheic dermatitis, Tinea Versicolor. The side effects of this shampoo arise more than ketoconazole shampoo. 25) Sodium thiosulfate ($Na_2S_2O_3$): This topical antifungal is used with combination of salicylic acid for skin related problem like tinea versicolor. 26) Sulfur (S)[72-74]: It has antifungal properties as well as antibacterial and keratolytic activity. It is commonly used for skin related problems like seborrheic dermatitis, pityriasis versicolor etc. It is also used as a fungicide in agriculture to prevent fungus. 27) Triacetin[75]: Research is ongoing in this path because it inhibits fungal growth and prevents infections. It is used in cosmetics. 28) Undecylenic acid: It is used as an active ingredient in topical antifungal treatments to prevent and eliminate topical fungal infections. 29) Zinc pyrithione[76-77]: It is a coordination complex of zinc. It is used for seborrheic dermatitis, antibacterial properties, psoriasis, eczema etc. 30) Ciclopirox[78]: This topical antifungal drug acts against tinea corporis, tinea pedis, and tinea cruris, tinea versicolor. 31) Benzoic acid[79]: It serves as an antifungal agent in Whitfield's ointment which acts against tinea corporis and tinea pedis.

According to Mechanism of medications work[80-81]

These are classified as: a) Inhibitor of fungal cytochrome P450: e.g. Azoles, Miconazole, Fluconazole. Fungal cytochrome P450 enzymes play a crucial role in the synthesis of ergosterol, a key component of fungal cell membranes. By inhibiting

lanosterol 14-alpha-demethylase, antifungal medications can disrupt the biosynthesis of ergosterol which lead to cell membrane dysfunction and ultimately vanish the fungal cell wall. Side effects: Anaphylaxis, nausea, gastrointestinal disturbance, phototoxicity, cardiomyopathy, hepatotoxicity, cytochrome P450 inhibition, Local burning sensation, pruritus etc. b) Inhibitior of 17-hydroxylase/17, 20-lyase: e.g. Ketoconazole c) Inhibitor of ergosterol binding: e.g. Polyenes (Amphotericine B, Nystatin, Pimaricin). It targets the cell wall or membrane and knots to ergosterol (fungal cell membrane). Pores are formed on the fungal membrane and then kill fungal cells by disrupting electrolyte balance which makes the fungal cell prone to cell lysis to cell death. Side effects: Amphotericin B may cause Nephrotoxicity, hepatotoxicity, fever, hypokalemia, hypomagnesemia whereas Nystatin may cause Gastrointestinal symptoms, Contact dermatitis, Stevens-Johnson syndrome. d) Inhibitor of squalene monooxygenase: Allylamines (Terbinafine), Benzylamines, Thiocarbamate. Allylamines produce ergosterol by inhibiting fungal squalene epoxidase. Side effects: Headache, Hepatotoxicity, Dysgeusia, Gastrointestinal upset, Rash, photosensitivity etc. e) 1,3-β-Glucan synthase inhibitor[80c]: e.g. Echinocandins prevent the formation of the fungal 1,3-β-glucan synthase, which produces 1,3-β-glucan, a main constituent of fungal cell walls. Medically it is used for both invasive aspergillosis and candidiasis. It targets the cell wall or membrane. Side effects: Hepatic toxicity etc. f) Inhibitor of Pyridine analogue/ thymidylate synthase: e.g. Flycytosine, Griseofulvin etc. It is an antimetabolite compound absorbed into a fungal receptor through cytosine permease and turned into 5-fluorouracil with the help of fungal cytosine deaminase. It disrupts microtubule function. Side effects: Gastrointestinal disturbance, anemia, Bone marrow suppression etc. g) Inhibitor of mitosis: e.g. Griseofulvin which fixes to keratin precursor cells and accumulates in nails, hair, any keratin-rich tissues. Then it inhibits fungal cells from disruption to produce more cells (mitosis). h) Inhibitor of aminoacyl tRNA synthetase: e.g. Tavaborole. It targets the intracell. i) Inhibitor of protein synthesis: e.g. Zinc Pyrithione. It acts in transporting fungal cellular membrane, which prevents protein synthesis, and thus, reduces ATP synthesis. Therefore, protein damage occurs due to this metabolic change. j) Inhibitor of DNA/RNA/protein synthesis: e.g. Ciclopirox (Pyridone derivatives), flucytosine (pyrimidine derivative). This topical medicine interferes DNA/ RNA/ protein synthesis. Side effects: Hepatic toxicity, Rash, Ventricular tachycardia etc. f) Inhibitor of fungal germination: e.g. Potassium Iodide.

According to type of fungal infections[2,82]

The name of the fugals disease and the responsible fungus is very important to identify first, that we know from the fungal nomenclature.[83] The wide range of fungal infections are covered by a) Skin Infections: Mycosis refers to fungal infections, which can manifest in various forms such as i) Tinea pedis ii) Tinea cruris iii) Tinea corporis iv) Tinea Versicolor and v) Seborrheic dermatitis b) Onychomycosis/Nail Infections c) Mucosal/Esophageal candidiasis/Oral Thrush d) Serious systemic infections: More severe cases affect internal organs (e.g. Aspergillosis, Meningitis), Pneumocystis pneumonia, ocular histoplasmosis syndrome, Vaginal infection, Coccidioidomycosis, Blastomycosis, Cryptococcus gattii infection, Mucormycosis,[5] Paracoccidioidomycosis, and Talaromycosis. The symptoms of various fungal infections are given in Table 1.

According to Administration[81]

Here are some key points about antifungal administration with varying degree of severity: a) Ocular: Used when the fungal infection affects the eye. Natamycin is an example of an ocular antifungal. b) Intrathecal: Administered when there's a central nervous system infection that other systemic options cannot effectively treat (e.g. amphotericin B). c) Vaginal: Used for fungal infections in the vaginal region (e.g. intravaginal clotrimazole for candida vulvovaginitis). d) Topical antifungal drugs: Applied directly to the skin for localized fungal infections (e.g. topical terbinafine for tinea pedis). Azole drugs are available in topical form such as creams, ointments, gels, shampoos, powders and lozenges. Nystatin is available only in cream form. Ciclopirox, quinolines, Potassium, Zinc Pyrithione etc. are used for topical fungal infections. e) Oral: Taken orally if the antifungal has good bioavailability (e.g. ketoconazole for coccidioidomycosis). Nystatin (Polyene drug), Griseofulvin etc. are given orally. f) Intravenous: Administered intravenously to rapidly reach the bloodstream (e.g. amphotericin B for coccidioidomycosis, flucytosine caspofungin, anidulafungin, and micafungin). g) Vaginal suppositories: These soft tablets are inserted into the vagina for localised treatment.

Table 1: Symptoms and related antifungal medications of various fungal infections[82b]

Infection	Symptoms	Antifungal drugs
Body Ringworm or topical fungal infection or Dermatophytosis or Tinea corporis[80c]	Red, scaly, itchy patches on skin, scalp, feet, or anywhere else and it spreads with scratching.	Topical: Ketoconazole, Clotrimazole, Miconazole, Terbinafine. Oral: Itraconazole, Fluconazole, Terbinafine.
Athlete's foot or Tinea pedis[80c]	Itching, stinging, or burning sensations between the toes or on the soles of the feet. Blisters or ulcers on the feet that may itch. Cracked, flaking, or peeling skin on the feet particularly toes.	Topical: Terbinafine, Clotrimazole, Miconazole, Tolnaftate, Butenafine. Oral: Itraconazole, Fluconazole, Terbinafine.
Jock itch[82b] or Tinea cruris[82b]	Itching, red scaly patches, abnormally dark or light spot appears after infection clears.	Topical: Ketoconazole, Clotrimazole, Miconazole, Terbinafine. Oral: Itraconazole, Fluconazole.
Tinea versicolor[82b]	Oval red patches of skin discoloration, typically on the trunk and shoulders. Mild itching.	Topical: Ketoconazole, Clotrimazole, SeS2, Terbinafine, Ciclopirox. Oral: Itraconazole, Fluconazole, Ketoconazole.
Onychomycosis[82e]	Discoloured and brittle nails, nail thickness specially seen in the toenails.	Terbinafine
Vaginal yeast infection[80c]	itching, redness, and swelling in the vaginal area.	Amphotericin B, Nystatin, Clotrimazole, Miconazole
Mucosal/Esophageal candidiasis[80c]	White lesions appear in the mouth that can also be red and painful. It may be seen in the throat. Chest pain, vomiting.	Fluconazole, Itraconazole, Caspofungin, Micafungin, Anidulafungin (intravenous).
Seborrheic dermatitis[52b]	Flaky white to yellowish scales on oily areas such as the scalp, forehead, eyebrows, eyelids, the sides of the nose, behind the ears, and the chest. Soreness or itching on the affected area.	Topical: Ketoconazole, SeS_2, Ciclopirox, coal tar, Zinc Pyrithione, Calcineurin inhibitors such as pimecrolimus cream or tacrolimus ointment for inflammation
Oral Thrush[82d]	Creamy white lesions, sometimes redness on the tongue, inner cheeks, roof of the mouth, gums, and tonsils.	Nystatin, Clotrimazole, Miconazole, Fluconazole.
Aspergillosis[8]	Lung infections	Amphotericin B, Itraconazole, Fluorocytosin
Pneumocystis pneumonia[82b]	Lung infections	Trimethoprim, Sulphamethoazole, Pentamidine, Ecothionate
Candidemia[80c]	Blood infection	Fluconazole, Amphotericin B, Anidulafungin, Caspofungin, Micagungin, Voriconazole
Candidiasis[26b,80c] or yeast infection	Vaginal (burning, itching, redness, swelling), skin (small itchy red bumps on skin folds), heart or skull (bloodstream of the membrane) infection.	Butoconazole, Nystatin, Clotrimazole, Miconazole, Fluconazole.
Meningitis[82b]	Sudden high fever, severe headache, vomiting, nausea, photophobia.	Amphotericin B, Fluconazole, Voriconazole
Rhinosinusitis[82]	Sinus infection.	
Ocular histoplasmosis[82b]	Distorted vision, blind spots, decreased vision.	Amphotericin B, Itraconazole, Ketoconazole
Blastomycosis[1]	Cough, fever, chest pain, joint pain, night sweat, weight loss, fatigueness, ulcers.	Amphotericin B, Itraconazole, Ketoconazole
Cryptococcus gattii[8,82]	Pulmonary infection, meningitis (central nervous system), ulcers.	Amphotericin B, Fluconazole
Mucormycosis[5]	Sinus, lungs, skin, gastrointestinal infection.	Amphotericin B
Paracoccidioidomycosis[82b]	lungs, skin ulcers, mucous membranes, lymph nodes, and internal organ's infection.	Itraconazole, Ketoconazole
Talaromycosis[82c]	Fever, weight loss, anaemia, fatigue, skin lesions, cough, lymphadenopathy, Hepatosplenomegaly.	Amphotericin B, Itraconazole, Voriconazole
Coccidioidomycosis[82b] or Valley fever	Cough, fever, headache, joint pain, rash on body	Amphotericin B, Fluorocytosin, Itraconazole, Fluconazole,
Sporotrichosis[82b]	Firm painless nodules at the hands/arms which turn to ulceration.	Amphotericin B, Itraconazole, KI
Pseudallescheriasis[82b]	Fever, cough, shortness of breath, chest pain, joint pain, headache, skin lesions.	Amphotericin B, Miconazole

Impact and resistance of antifungal drugs[84-85]

The impact of antifungal drugs on human health is substantial, as they are crucial for treating various fungal infections. The effectiveness, spectrum of activity, therapeutic index, resistance mechanisms,[86] and modes of use vary between antifungal drugs. Antifungal resistance arises when antifungal drugs no longer treat fungal infection. The reasons for resistance are i) Improper use: Proper management and judicious use of antifungal drugs are essential for effective treatment. ii) Antibiotic use: Skipping doses of drugs or stopping treatment prematurely or receiving insufficient doses can make fungi better at resisting the medications. But in general, resistance grows if antifungal is taken over a long period or for incomplete doses. Antibiotics during therapy may also disrupt the balance of helpful bacteria in the digestive tract. This can lead to rapid growth of the yeast candida infection which needs prolonged antifungal therapy. iii) Fungicide exposure: Antifungal resistance also arises due to fungicide exposure. People working closely with crops treated by fungicides may be more susceptible to antifungal-resistant infections. iv) Natural resistance: Fungi themselves develop resistance inherently to antifungal drugs. v) Spontaneous resistance: Some fungi may stop responding to previously effective drugs without a known reason. vi) Transmitted resistance: Infectious drug resistant fungi can transmit from person to person. vii) Limited treatment options: Significantly antifungal resistance restricts available treatment options. Thus, drug resistance is a challenge to human wellbeing as it is a global public health concern. Furthermore, the use of antifungal drugs is not without risk; there can be adverse effects on human health, such as drug-drug interactions that may decrease the drugs' efficacy or affect the patient's health.[87] Antifungal drug resistance mechanisms differ among fungal species and drug classes but can generally be categorized into several major types: a) Alterations in drug target: The fungal cell can alter the target site of the drug, reducing drug binding affinity and efficacy. This is seen in resistance to azoles, where mutations in the target enzyme lanosterol 14-α-demethylase can occur. b) Drug efflux: Fungi may increase the expression of efflux pumps, which actively transport the antifungal drug out of the cell, reducing drug accumulation to sub-lethal levels. This mechanism is also commonly associated with azole resistance. c) Biofilm formation: Fungi can form biofilms, which are structured communities of cells. Biofilms act as a physical barrier to drug penetration and may also exhibit altered phenotypes with increased resistance to antifungal agents. d) Enzymatic degradation: Some fungi can produce enzymes that degrade or modify antifungal drugs, rendering them ineffective. e) Overexpression of target: The target of the antifungal drug may be overproduced by the fungal cell, meaning that more of the drug is needed to exert an effective antifungal action. f) Alternative pathway utilization: The fungus can bypass a metabolic pathway inhibited by an antifungal drug by using an alternative pathway that does not require the drug's target enzyme or pathway component. Understanding and combating these resistance mechanisms are critical to maintaining the effectiveness of current antifungal medications and for the development of new drugs that can overcome resistance.

Prevention and control: Prevention is the key to any infection. The therapeutic index is a critical consideration when prescribing antifungal drugs, especially in populations with existing comorbidities or those who are particularly vulnerable, such as the immunocompromised. Providers must weigh the efficacy of an antifungal agent against the possible side effects and drug interactions to optimize patient care. If anyone suspects a fungal infection or has any concerns, seek immediate professional advice to reduce our risk.

Prevention: To prevent fungal infection[88] people have to maintain their hygiene at their home. i) Maintain Good Hygiene: a) Keep skin dry: Fungi prefer to grow in moisture. After showers or sweating, thoroughly we should dry off by changing clothes or by wiping especially in skin folds and areas. b) Change clothes regularly: Clean dry clothes help prevent fungal spores from accumulating. c) Wear breathable fabrics: Always we have to choose for cotton or moisture-wicking materials to allow air circulation. d) Wash: By washing our hands and feet with soap and water, we can reduce the intensity of fungal infection. ii) Foot Care: a) Dry feet: It's time to pay attention to spaces between toes. b) Choose proper footwear: We always prefer cheap footwear and do not look at our footwear. But we have to wear breathable shoes and change socks daily. c) Avoid walking barefoot in public areas: We should not work barefoot in parks, especially in gyms, pools, and communal showers. iii) Nail Hygiene: a) Trim nails regularly: Fungi prefer to grow under growing nails.

So, we have to try keeping them short and clean every week with our own clippers and files. b) Avoid nail trauma: We must prevent injuries that can lead to nail infections. iv) Oral Health: a) Maintain oral hygiene: Brush and floss regularly is one of the most essential for oral hygiene. b) Limit sugar intake: High sugar levels can contribute to oral thrush (a fungal infection). v) Immunity: It is one of the reasons for fungal infections. vi) Obesity: Obesity can lead to fungal infections. So, we should be aware of moisture under skin folds. vii) Stress: Stress can reduce our immunity which may lead to fungal growth. viii) Hormone: Hormonal changes in the female genital tract can lead to vaginal infections. ix) Diagnosis of fungal infections symptom[89]: As early as possible the fungal infection is diagnosed; a person should get a quick recovery.

Control: The following preventive measures we can take to control fungal infection. i) Diet and Immune System Support: a) Balanced diet: A healthy diet supports overall immunity. b) Stay hydrated: Proper hydration may help to maintain skin health. ii) Avoid Overuse of Antibiotics: Antibiotics can disrupt the balance of natural flora, making a person more susceptible to fungal infections. iii) Awareness: Always one should take antifungal drugs according to the prescription of a certified doctor to understand the risks and importance of completing a full course of treatment. iv) Infection control: Proper hygiene and infection prevention practices can reduce transmission. v) Monitoring and emerging strategies: Any survey helps to identify emerging resistance patterns and inform treatment. Researchers are exploring new antifungal targets and novel approaches. Potential areas of interest are a) New drug targets: Identifying unique fungal vulnerabilities. b) Combination therapies: Enhancing efficacy while minimizing toxicity. c) Host-targeted therapies: Boosting the immune response against fungi.[8,20] vi) Home Remedies or alternative methods: To remove fungal infections the following home remedy may be used a) Yoghurt and Probiotics[90]: Yoghurt and other probiotics have gain attention for their potential in preventing fungal infections due to their abundance in good bacteria. b) Apple Cider Vinegar[91]: It can inhibit the growth of *Candida*, but the dose should be maintained otherwise it may create toxic effects on our body. d) Tea Tree Oil[92]: It can inhibit the growth of candida. It can successfully treat yeast infection in humans. It is used for the nail fungus prevention or any topical fungal infection. e) Coconut Oil[93]: Research has shown that coconut oil may be effective against *Candida albicans*, a common fungus responsible for yeast infections. f) Turmeric[94-95]: Curcumin, derived from turmeric, exhibits several health benefits such as antioxidant, anti-inflammatory, antibacterial, antifungal, and antiviral properties. g) Aloe Vera[96]: It may inhibit the growth of many types of fungi, including those causing ringworm, yeast infections, and nail infections. h) Garlic[97-99]: Garlic contains a compound called allicin which inhibit or kill many fungal pathogens, including *Candida albicans* and prevent skin infections like ringworm or athlete's foot. i) Oregano Oil: It contains two potent antimicrobial agents: carvacrol and thymol which is useful for treating *Candida albicans* overgrowth. j) Neem Leaves[100-101]: neem leaves have been studied for their impact on human pathogens such as *Aspergillus*, *Candida albicans*, and *Microsporum gypseum*. k) Vitamin C[102-103]: Vitamin C, also known as Ascorbic acid, is an essential nutrient that plays a crucial role in maintaining our overall health and boosting the immune system. It has been seen to inhibit the growth of this common yeast responsible for fungal infections. l) Baking Soda[104]: Sodium Bicarbonate is known as baking soda. It is used to treat as safe organic fungicide for the treatment of various fungal diseases. When sprayed on plants, baking soda disrupts the ion balance of fungal cells, causing them to collapse. m) Hydrogen Peroxide: It acts as an antifungal agent due to its ability to kill fungus. H_2O_2 acts against tinea pedis. n) Ginger[105-106]: Ginger is a common spice in our kitchen with proven antifungal abilities against many common fungal pathogens. o) Honey[107]: *Candida* associated infections are a common problem, and the treatment options are often limited. However, research suggests that honey may have beneficial effects in combating and managing these infections especially topical mucous membrane and skin infections. p) Grapefruit Seed Extract[108]: It is derived from the seeds of grapefruit, has gained attention for its potential healing properties such as various types of candida infections, vaginal yeast infection, Athlete's Foot and nail fungus. q) Powdered Licorice[109-110]: Licorice root contains several bioactive compounds, including glycyrrhizin, which contribute to its antifungal properties like it acts against *Candida albicans*. r) Lemongrass oil[111]: This essential oil contains a bioactive component citra which has strong

antimicrobial efficacy against pathogenic bacteria and fungi. If the home remedies do not work, then patients should visit a doctor because medical advice and precautions play a crucial role in maintaining our health and well-being.

Challenges and future prospects

Conventional existing therapies have limitations such as toxicity, drug interactions, and the risk of resistance. So, we have to reduce these limitations. For minimising the limitations following steps are taken: a) The rise in fungal infections requires continued research. Researchers are already working on novel antifungal molecules. b) Balancing efficacy, safety, and resistance prevention remains critical and challenging for us till now. c) Ongoing recent clinical trials improve the treatment option. d)The antifungal allergy arises due to medications which is still now a challenge for us to decrease.[112] e) Collaborative efforts are essential to combat fungal threats.[7,113] f) Antifungal stewardship programs[114-115] are crucial for optimal treatment. In this program coordinated interventions aimed at monitoring which leads to the appropriate use of antifungal agents. In terms of alternatives to antifungal drugs, research into immunogenetics looks to understand tissue-specific mechanisms of antifungal defence, which could help manage life-threatening fungal infections.[116] Moreover, there's potential in natural antimicrobial compounds like fermented papaya leaf that have demonstrated antibacterial effects and might offer a safer route for treatment.[87] Mycoremediation is a further area of interest where certain edible fungi like Lentinula edodes have been shown to absorb and eliminate environmental pollutants, such as antifungal drugs, which proposes an eco-friendly strategy for antibiotic elimination.[117] This approach not only holds environmental benefits but also opens up a new avenue for potentially safer alternative treatments. Maintaining a balance between effective antifungal treatment, mitigating resistance and side effects involves continued research and development of both medical and alternative therapies.

CONCLUSION

The impact of antifungal drugs in combating fungal infections is significant. But the evolution of antifungal resistance remains a growing global health concern. Antifungal drugs have revolutionized the treatment of fungal infections, proving effective options for both superficial and systemic cases. As research in antifungal drugs continues to advance, there is a growing need for the development of new drugs that are more effective. Additionally, the proper use of antifungal agents, in combination with preventative measures and infection control practices, is crucial in minimizing the burden of fungal infections on global health. As antifungals are essential for treating fungal infections, vigilance is very crucial. Overall, the ongoing efforts to enhance antifungal therapies are vital in addressing the challenges posed by fungal infections and improving patient outcomes.

ACKNOWLEDGEMENT

DM thanks East Calcutta Girls' College, Lake Town, Kolkata. She would like to acknowledge Wikipedia and National Library of Medicine from where she had collected some information about antifungals.

Conflict of interest

DM declares that there is no conflict of interest.

REFERENCES

1. Malayeri, F. A.; Rezaei, A. A.; Raiesi, O., *J. Bas. Res. Med. Sci.*, **2018**, *5*(2), 48–55. doi: 10.29252/jbrms.5.2.48.
2. (a) Gupte, M.; Kulkarni, P.; Ganguli, B. N., *Appl. Microbiol. Biotechnol.*, **2002**, *58*, 46–57. doi:10.1007/s002530100822. (b) Carmo, A.; Rocha, M.; Pereirinha, P.; Tomé, R.; Costa, E. *Antibiotics.*, **2023**, *12*(5), 884-909.doi:10.3390/antibiotics 12050884.
3. Shah, K.; Deshpande, M.; Shah, P., *Front. Fungal. Biol.*, **2024**, *5*, 1339911–1339916. doi: 10.3389/ffunb.2024.1339911.
4. (a) Madan, P.; Ganta, K.; Cherukumudi, A., *Heart Vessels and Trasplantation.*, **2024**, *8*(1), 1-8. doi: 10.24969/hvt.2023.432. (b) Seyedjavadi, S. S.; Bagheri, P.; Nasiri, M. J.; Razzaghi-Abyaneh, M.; Goudarzi, M., *Front. Microbiol.*, **2022**, *13*, 888452–888464. doi: 10.3389/fmicb.2022.888452.
5. Shamithra, L.; Sigera, M.; Denning, D. W., *Open Forum Infectious Diseases.*, **2024**, *11*(1), ofad704–ofad712.doi:org/10.1093/ofid/ofad704.

6. Fighting the rising tide of antifungal resistance: a global challenge by F2G nature, biopharma dealmakers (Biopharm Deal) ISSN 2730-6283 (online) ISSN 2730-6275 (print), **2023**, B24–25. www.nature.com/biopharmdeal
7. (a) Roy, M.; Karhana, S.; Shamsuzzaman, M.; Khan, M. A., *Braz. J. Microbiol.*, **2023**, *54*, 1695–1716.doi: org/10.1007/s42770-023-00999-z. (b) Khatter, N. J.; Khan, M. A. B. Clotrimazole. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; **2024**. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560643/ (c) Phillips, R. M.; Rosen, T. 37-Topical antifungal agents, Editor(s): Wolverton, S. E. Comprehensive Dermatologic Drug Therapy (Third Edition), Saunders, W. B. **2013**, 460-472.e5, ISBN 9781437720037. doi: org/10.1016/B978-1-4377-2003-7.00037-6. (d) Alghamdi, S. S.; Suliman, R. S.; Almutairi, K.; Kahtani, K.; Aljatli, D., *Drug Des. Devel. Ther.*, **2021**, *15*, 3289-3312. P doi:10.2147/DDDT.S307113 (e) Peyton, L. R.; Gallagher, S.; Hashemzadeh, M., *Drugs Today (Barc).,* **2015**, *51*(12), 705-718. doi: 10.1358/dot.2015.51.12.2421058.
8. Bouz, G.; Doležal, M., *Pharmaceuticals.*, **2021**, *14*, 1312–1332. doi: org/10.3390/ph14121312.
9. Kim, J. H.; Cheng, L. W.; Land, K. M., *Pharmaceuticals.*, **2022**, *15*, 787–793. doi: org/10.3390/ph15070787.
10. Prescott, T. A. K.; Hill, R.; Mas-Claret, E.; Gaya, E.; Burns, E., *Biomolecules.*, **2023**, *13*, 986–1010. doi: org/10.3390/biom13060986.
11. Puumala, E.; Fallah, S.; Robbins, N.; Cowen, L. E., *Clin. Microbiol. Rev.*, **2024**, *37*, e00142–23. doi: org/10.1128/cmr.00142-23.
12. Puumala, E.; Lee, Y.; Robbins, N.; Cowen, L., *Chem. Rev.*, **2021**, *121*(6), 3390–3411. doi: 10.1021/acs.chemrev.0c00199.
13. Burns, A. R.; Baker, R. J.; Kitner, M.; Knox, J.; Cooke, B.; Volpatti, J. R.; Vaidya, A. S.; Puumala, E.; Palmeira, B. M.; Redman, E. M.; Snider, J.; Marwah, S.; Chung, S. W.; MacDonald, M. H.; Tiefenbach, J.; Hu, C.; Xiao, Q.; Finney, C. A. M.; Krause, H. M.; MacParland, S. A.; Stagljar, I.; Gilleard, J. S.; Cowen, L. E.; Meyer, S. L. F.; Cutler, S. R.; Dowling, J. J.; Lautens, M.; Zasada, I.; Roy, P. *J. Nature.*, **2023**, *618*, 102–109. doi: org/10.1038/s41586-023-06105-5.
14. Hossain, S.; Robbins, N.; Cowen, L. E., *Genetics.*, **2022**, *222*(4), iyac152–iyac162. doi: org/10.1093/genetics/iyac152.
15. Caplan, T.; Lorente-Macías, Á.; Stogios, P. J.; Evdokimova, E.; Hyde, S.; Wellington, M. A.; Liston, S.; Iyer, K. R.; Puumala, E.; Shekhar-Guturja, T.; Robbins, N.; Savchenko, A.; Krysan, D. J.; Whitesell, L.; Zuercher, W. J.; Cowen, L. E., *Cell Chem. Bio.*, **2020**, *27*, 269–282. doi: org/10.1016/j.chembiol2019.12.008.
16. Puumala, E.; Zaslaver, O.; Chen, A.; Duncan, D.; Fogal, M.; Shapiro, R. S.; Mazhab-Jafari, M. T.; Whitesell, L.; Montenegro-Burke, J. R.; Robbins, N.; Cowen, L. E., *mBio.*, **2022**, *13*, e02730-22. doi: org/10.1128/mbio.02730-22.
17. Kim, S. H.; Steere, L.; Zhang, Y-K.; McGregor, C.; Hahne, C.; Zhou, Y.; Liu, C.; Cai, Y.; Zhou, H.; Chen, X.; Puumala, E.; Duncan, D.; Wright, G. D.; Liu, C. T.; Whitesell, L.; Cowen, L. E., *ACS Chem. Biol.*, **2022**, *17*(6), 1343–1350. doi: org/10.1021/acschembio.2c00257.
18. (a) Mandal, D., *Orient. J. Chem.*, **2024**, *40*(2), 342-354. doi: org/10.13005/ojc/400204. (b) Carmo, A.; Rocha, M.; Pereirinha, P.; Tomé, R.; Costa, E., *Antibiotic.*, **2023**, *12*, 884–909. doi: org/10.3390/antibiotics12050884.
19. Jartarkar, S. R.; Patil, A.; Goldust, Y.; Cockerell, C. J.; Schwartz, R. A.; Grabbe, S.; Goldust, M., *J. Fungi.*, **2022**, *8*, 39–53. doi: org/10.3390/jof8010039.
20. Veraldi, S.; Milani, R., *Drugs.*, **2008**, *68*, 2183–2194. doi: org/10.2165/00003495-200868150-00007.
21. Fares, M.; Said, M. A.; Alsherbiny, M. A.; Eladwy, R. A.; Almahli, H.; Abdel-Aziz, M. M.; Ghabbour, H. A.; Eldehna, W. M.; Abdel-Aziz, H. A., *Molecules.*, **2016**, *21*, 114-130; doi: 10.3390/molecules21010114.
22. Menzel, L. P.; Chowdhury, H. M.; Masso-Silva, J. A.; Ruddick, W.; Falkovsky, K.; Vorona, R.; Malsbary, A.; Cherabuddi, K.; Ryan, L. K.; DiFranco, K. M.; Brice, D. C.; Costanzo, M. J.; Weaver, D.; Freeman, K. B.; Scott, R. W.; Diamond, G., *Sci. Rep.*, **2017**, *7*, 4353-4362. doi: org/10.1038/s41598-017-04462-6.
23. Ellsworth, M.; Ostrosky-Zeichner, L., *J. Fungi.*, **2020**, *6*(4), 324–333. doi:10.3390/jof6040324.
24. Dietz, A. J.; Barnard, J. C.; van Rossem, K., *Clin. Pharmacol. Drug Dev.*, **2014**, *3*(1), 25–33. doi: 10.1002/cpdd.72.

25. Van Rossem, K.; Lowe, J. A., *Clin. Pharmacol.*, **2013**, *5*, 23–31. doi: 10.2147/CPAA.S39600.
26. (a) Chhabria, M. T.; Patel, S.; Modi, P.; Brahmkshatriya, P. S., *Curr. Top. Med. Chem.*, **2016**, *16*(26), 2841–2862. doi: 10.2174/1568026616666160506130731. (b) Biernasiuk, A.; Berecka-Rycerz, A.; Gumieniczek, A.; Malm, M.; Ł czkowski, K. Z.; Szymańska, J.; Malm, A., *Appl. Microbiol. Biotechnol.*, **2021**, *105*(16-17), 6355-6367. doi: 10.1007/s00253-021-11477-7. (c) Niu, Z-X.; Wang, Y-T.; Zhang, S-N.; Li, Y.; Chen, X-B.; Wang, S-Q.; Liu, H-M., *Eur. J. Med. Chem.*, **2023**, *250*, 115172. doi: org/10.1016/j.ejmech.2023.115172.
27. (a) Rouf, A.; Tanyeli, C., *Eur. J. Med. Chem.,* **2015**, *97*, 911-927, doi: org/10.1016/j.ejmech., 2014.10.058. (b) Babu, K. A.; Singhvi, I.; Ravindra, N.; Bhandareh, R. R.; Shaik, A. Design, synthesis and biological screening of 2,4-dichlorothiazole-5-carboxaldehyde-derived chalcones as potential antitubercular and antiproliferative agents., **2020** by MDPI in 6th International Electronic Conference on Medicinal Chemistry session. doi: org/10.3390/ECMC2020-07377.
28. Borelli, C.; Schaller, M.; Niewerth, M.; Nocker, K.; Baasner, B.; Berg, D.; Tiemann, R.; Tietjen, K.; Fugmann, B.; Lang-Fugmann, S.; Korting, H. C., *Chemotherapy.*, **2008**, *54*(4), 245–259. doi: 10.1159/000142334.
29. Halat, D. H.; Younes, S.; Mourad, N.; Rahal, M., *Membranes.*, **2022**, *12*, 1171–1189. doi: org/10.3390/membranes12121171.
30. Hossain, C. M.; Ryan, L. K.; Gera, M.; Choudhuri, S.; Lyle, N.; Ali, K. A.; Diamond, G., *Encyclopedia.*, **2022**, *2*, 1722–1737.doi: org/10.3390/encyclopedia2040118.
31. de Ullivarri, M. F.; Arbulu, S.; Garcia-Gutierrez, E.; Cotter, P. D., *Front. Cell Infect. Microbiol.*, **2020**, *17*(10), 105-126. doi: 10.3389/fcimb.2020.00105.
32. Matejuk, A.; Leng, Q.; Begum, M. D.; Woodle, M. C.; Scaria, P.; Chou, S-T.; Mixson, A., *J. Drugs Future.*, **2010**, *35*(3), 197–231. doi: 10.1358/dof.2010.035.03.1452077.
33. Dini, I.; De Biasi, M-G.; Mancusi, A., *Antibiotics.*, **2022**, *11*, 1483-1504. doi: org/10.3390/antibiotics11111483.
34. Xu, K.; Li, X. Q.; Zhao, D. L.; Zhang, P., *Front. Microbiol.*, **2021**, *12*, 689527–689543. doi: 10.3389/fmicb.2021.689527.
35. Dadashpour, S.; Ghobadi, E.; Emami, S., *Med. Chem. Res.*, **2022**, *31*, 833–850. doi: org/10.1007/s00044-022-02901-2.
36. Aziz, D.; Mohamed, S.; Tayel, S.; Makhlouf, A., *Drug Deliv.*, **2022**, *29*(1), 2162-2176. doi: 10.1080/10717544.2022.2094499.
37. Mazu, T. K.; Bricker, B. A.; Flores-Rozas, H.; Ablordeppey, S. Y., *Mini Rev. Med. Chem.*, **2016**, *16*(7), 555–578. doi: 10.2174/1389557516666160118112103.
38. Thind, T. S.; Hollomon, D. W., *Pest Manag. Sci.*, **2018**, *74*(7), 1547–1551. doi: 10.1002/ps.4844.
39. Kezutyte, T.; Kornysova, O.; Maruska, A.; Briedis, V., *Acta. Pol. Pharm.-Drug Res.,* **2010**, *67*(4), 327–334.
40. Senerovic, L.; Opsenica, D.; Moric, I.; Aleksic, I.; Spasiń, M.; Vasiljevic, B., *Adv. Exp. Med. Biol.-Advances in Microbiology, Infectious Diseases and Public Health.*, **2020**, *14*, 37–69. doi: org/10.1007/5584_2019_428.
41. Musiol, R.; Jampilek, J.; Buchta, V.; Silva, L.; Niedbala, H.; Podeszwa, B.; Palka, A.; Majerz-Maniecka, K.; Oleksyn, B.; Polanski., *J. Bioorganic & Medicinal Chemistry.*, **2006**, *14*(10), 3592–3598. doi: org/10.1016/j.bmc.2006.01.016.
42. Yang, G-Z.; Zhu, J-K.; Yin, X-D.; Yan, Y-F.; Wang, Y-L.; Shang, X-F.; Liu, Y-Q.; Zhao, Z-M.; Peng, J-W.; Liu, H., *J. Agric. Food Chem.*, **2019**, *67*(41), 11340–11353. doi: org/10.1021/acs.jafc.9b04224.
43. Zhang, B., *Arch. Pharm.*, **2019**, *352*(5), e1800382. doi: 10.1002/ardp.201800382.
44. Senerovic, L.; Opsenica, D.; Moric, I.; Aleksic, I.; Spasiń, M.; Vasiljevic, B., *Infectious Diseases and Public Health.*, **2020**, *14*, 37–69. doi: org/10.1007/5584_2019_428.
45. Dhaliwal, J. S.; Moshawih, S.; Goh, K. W.; Loy, M. J.; Hossain, M. S.; Hermansyah, A.; Kotra, V.; Kifli, N.; Goh, H. P.; Dhaliwal, S. K. S.; Yassin, H.; Ming, L. C., *Molecules.*, **2022**, *27*, 7062–7085. doi:org/10.3390/molecules27207062.
46. Elkanzi, N. A. A.; Hrichi, H.; Alolayan, R. A.; Derafa, W.; Zahou, F. M.; Bakr, R. B., *ACS Omega.*, **2022**, *7*(32), 27769–27786. doi: org/10.1021/acsomega.2c01779.
47. Gupta, D.; Jain, D. K., *J. Adv. Pharm. Technol. Res.*, **2015**, *6*(3), 114-117. doi: 10.4103/2231-4040.161507.

48. Popova, A. V.; Bondarenko, S. P.; Frasinyuk, M. S., *Chem. Heterocycl. Comp.*, **2019**, *55*, 285–299.doi:org/10.1007/s10593-019-02457-x.
49. Mazziotti, I.; Petrarolo, G.; Motta, C. L., *Molecules.*, **2021**, *27*(1), 2–20. doi: 10.3390/molecules27010002.
50. Agnihotri, G.; Gandhi, S.; Lio, P. A., *Drugs Ther. Perspect.*, **2019**, *35*, 491–499.doi: org/10.1007/s40267-019-00665-1.
51. Zhang, M.; An, Q.; Wang, Y.; Ye, S.; Zhu, X., *J. Fungi.*, **2024**, *10*(3), 213–221. doi: 10.3390/jof10030213.
52. (a) Martínez-Montelongo, J. H.; Medina-Ramírez, I. E.; Romo-Lozano, Y.; González-Gutiérrez, A.; Macías-Díaz, J. E., *J. Fungi.,* **2021**, *7*, 158–180.doi:org/10.3390/jof7020158. (b) Rai, M.; Ingle, A. P.; Pandit, R.; Paralikar, P.; Gupta, I.; Anasane, N.; Dolenc-Voljń M. Chapter 11 - Nanotechnology for the Treatment of Fungal Infections on Human Skin, Editor(s): Kon, K.; Rai, M. In Clinical Microbiology: Diagnosis, Treatments and Prophylaxis of Infections, The Microbiology of Skin, Soft Tissue, Bone and Joint Infections, Academic Press., **2017**, *2*, 169-184. doi: org/10.1016/B978-0-12-811079-9.00019-7.
53. Maley, A. M.; Arbiser, J. L., *Exp. Dermatol.*, **2013**, *22*(12), 775–780.doi:10.1111/exd. 12257.
54. Alvendal, C.; Mohanty, S.; Bohm-Starke, N.; Brauner, A., *PLOS One.*, **2020**, *15*, 1-14. doi: org/10.1371/journal.pone.0238428.
55. Wall, G.; Herrera, N.; Lopez-Ribot, J. L., *J. Fungi.*, **2019**, *5*, 92-108.doi:org/10.3390/jof5040092.
56. Rollin-Pinheiro, R.; Borba-Santos, L. P.; da Silva Xisto, M. I. D.; de Castro-Almeida, Y.; Rochetti, V. P.; Rozental, S.; Barreto-Bergter, E., *J. Fungi.,* **2021**, *7*, 803–819. doi: org/10.3390/jof7100803.
57. Bidaud, A. L.; Schwarz, P.; Herbreteau, G.; Dannaoui, E., *J. Fungi.,* **2021**, *7*(2), 113–128. doi: 10.3390/jof7020113.
58. Armengol, E. S.; Harmanci, M.; Laffleur, F., *Microbio. Res.*, **2021**, *252*, 126867–126878. doi: org/10.1016/j.micres.2021.126867.
59. Nosratabadi, M.; Akhtari, J.; Faeli, L.; Haghani, I.; Aghili, S. R.; Shokohi, T.; Hedayati, M. T.; Zarrinfar, H.; Mohammadi, R.; Najafzadeh, M. J.; Khodavaisy, S.; Al-Harrasi, A.; Javan-Nikkhah, M.; Kachuei, R.; Salimi, M.; Fattahi, M.; Badali, H.; Al Hatmi, A. M. S.; Abastabr, M., *J. Fungi.,* **2022**, *8*(7), 709-717. doi:10.3390/jof8070709.
60. Georgacopoulos, O.; Nunnally, N. S.; Ransom, E. M.; Law, D.; Birch, M.; Lockhart, S. R.; Berkow, E. L., *J. Fungi.,* **2021**, *7*(5), 378–386. doi: 10.3390/jof7050378.
61. Wiederhold, N. P., *J. Fungi.,* **2020**, *6*(3), 122–132. doi: 10.3390/jof6030122.
62. Hope, W. W.; McEntee, L.; Livermore, J.; Whalley, S.; Johnson, A.; Farrington, N.; Kolamunnage-Dona, R.; Schwartz, J.; Kennedy, A.; Law, D.; Birch, M.; Rex, J. H., *mBio.,* **2017**, *8*(4), e01157–17. doi: 10.1128/mBio.01157-17.
63. Wiederhold, N. P.; Najvar, L. K.; Jaramillo, R.; Olivo, M.; Birch, M.; Law, D.; Rex, J. H.; Catano, G.; Patterson, T. F., *Antimicrob. Agents Chemother.*, **2018**, *62*(9), e00999–18. doi: 10.1128/AAC.00999-18.
64. Balato, A.; Caiazzo, G.; Caprio, R. D.; Scala, E.; Fabbrocini, G.; Granger, C., *Dermatol. Ther. (Heidelb).,* **2020**, *10*(1), 87–98. doi: 10.1007/s13555-019-00339-w.
65. do Couto, F. M. M.; do Nascimento, S. C.; Júnior, S. F. P.; da Silva, V. K. A.; Leal, A. F. G.; Neves, R. P., *Springer Plus.*, **2016**, *5*(1), 468–472.doi: org/10.1186/s40064-016-2130-8.
66. Kashef, N.; Hamblin, M. R., *Methods Mol. Biol.*, **2022**, *2451*, 621–630. doi: 10.1007/978-1-0716-2099-1_33.
67. Costa, R. O.; Macedo, P. M.; Carvalhal, A.; Bernardes-Engemann, A. R., *An Bras Dermatol.*, **2013**, *88*(3), 396–402. doi: 10.1590/abd1806-4841.20132377.
68. Huang, L.; Szewczyk, G.; Sarna, T.; Hamblin, M., *ACS Infect Dis.*, **2017**, *3*(4), 320–328. doi: org/10.1021/acsinfecdis.7b00004.
69. Reddy, G.K.K.; Padmavathi, A.R.; Nancharaiah, Y.V., *Current Research in Microbial Sciences.*, **2022**, *3*, 100137–100143. doi: org/10.1016/j.crmicr.2022.100137.
70. Maiti, P. K.; Das, S.; Ghosh, T.; Dey, R., *Annals of Medical and Health Sciences Research.*, **2013**, *3*, 397–401. doi: 10.4103/2141-9248.117956.
71. Da, X.; Nishiyama, Y.; Tie, D.; Hein, K. Z.; Yamamoto, O.; Morita, E., *Sci. Rep.*, **2019**, *9*, 1683-1694. doi: org/10.1038/s41598-019-38916-w.

72. Sadek, M. E.; Shabana, Y. M.; Sayed-Ahmed, K.; Tabl, A. H. A., *J. Fungi.*, **2022**, *8*(4), 412–426. doi: 10.3390/jof8040412.
73. Amich, J. *J. Fungi.*, **2022**, *8*(3), 295–301. doi: 10.3390/jof8030295.
74. Gupta, A. K.; Nicol, K. *J. Drugs Dermatol.*, **2004**, *3*(4), 427-431.
75. Ivanov, M.; iri, A.; Stojkovi, D., *Int. J. Mol. Sci.*, **2022**, *23*(5), 2756–2781. doi:10.3390/ijms23052756.
76. Reeder, N. L.; Xu, J.; Youngquist, R. S.; Schwartz, J. R.; Rust, R. C.; Saunders, C. W., *Br. J. Dermatol.*, **2011**, *2*, 9-12.doi: 10.1111/j.1365-2133.2011.10571.x. PMID: 21919897.
77. Mangion, S. E.; Holmes, A. M.; Roberts, M. S., *Int. J. Mol. Sci.*, **2021**, *22*(18), 9730–9759. doi: 10.3390/ijms22189730.
78. Sonthalia, S.; Agrawal, M.; Sehgal, V. N., *Indian Dermatol Online J.*, **2019**, *10*(4), 481–485. doi: 10.4103/idoj.IDOJ_29_19.
79. Krebs, H. A.; Wiggins, D.; Stubbs, M.; Sols, A.; Bedoya, F., *Biochem. J.*, **1983**, *214*(3), 657–663. doi: 10.1042/bj2140657.
80. (a) Maurya, I. K.; Semwal, R. B.; Semwal, D. K. Chapter 4-Combination therapy against human infections caused by Candida species. Editor(s): Wani, M. Y.; Ahmad, A. Combination Therapy Against Multidrug Resistance., Academic Press., **2020**, 81-94. ISBN 9780128205761.doi:org/10.1016/B978-0-12-820576-1.00004-7. (b) Shukla, P. K.; Singh, P.; Yadav, R. K.; Pandey, S.; Bhunia, S. S. Past, Present, and Future of Antifungal Drug Development. In: Saxena, A. (eds) Communicable Diseases of the Developing World., *Topics in Medicinal Chemistry.*, **2016**, *29*, 125-167. Springer, Cham. doi: org/10.1007/7355_2016_4. (c) Niego, A. G. T.; Lambert, C.; Mortimer, P.; Thongklang, N.; Rapior, S.; Grosse, M.; Schrey, H.; Charria Girón, E.; Walker, A.; Hyde, K. D.; Stadler, M., *Fungal Diversity.*, **2023**, *121*, 95-137. doi: org/10.1007/s13225-023-00520-9.
81. Prasad, R.; Shah, A. H.; Rawal, M. K. Chapter 4: Mechanism of Action and Drug Resistance in Advances in Experimental Medicine and Biology., **2016**, 327–349. doi: 10.1007/978-3-319-25304-6_1.
82. (a) Reddy, G. K. K.; Padmavathi, A. R.; Nancharaiah, Y. V., *Curr. Res. Microb. Sci.*, **2022**, *3*, 100137–100143. doi: org/10.1016/j.crmicr. **2022**. 100137. (b) McKeny, P. T.; Nessel, T. A.; Zito, P. M. Antifungal Antibiotics. [Updated 2023 Mar 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; Available from: https://www.ncbi.nlm.nih.gov/books/NBK538168/ (c) Sheng, L.; Shen, Q.; Zhou, J., *J. Med. Mycol.*, **2021**, *31*(1), 101108. doi: org/10.1016/j.mycmed.2020.101108. (d) Quindós, G.; Gil-Alonso, S.; Marcos-Arias, C.; Sevillano, E.; Mateo, E.; Jauregizar, N.; Eraso, E., *Med. Oral. Patol. Oral. Cir. Bucal.*, **2019**, *24*(2), e172-e180. doi: 10.4317/medoral.22978. (e) Kreijkamp-Kaspers, S.; Hawke, K.; Guo, L.; Kerin, G.; Bell-Syer, S. E. M.; Magin, P.; Bell-Syer, S. V.; van Driel, M. L., *Cochrane Database Syst. Rev.*, **2017**, *7*(7), CD010031-CD010040.doi: 10.1002/14651858.CD010031.pub2
83. Denning, D. W., *Open Forum Infectious Diseases.*, **2023**, *10*(8), of ad395–ofad409. doi:org/10.1093/ofid/ofad395.
84. Bhattacharya, S.; Sae-Tia, S.; Fries, B. C., *Antibiotics.*, **2020**, *9*, 312–330. doi: 10.3390/antibiotics9060312
85. Maurya, I. K.; Semwal, R. B.; Semwal, D. K., *Combination Therapy Against Multidrug Resistance.*, **2020**, 81-94. Chapter 4-Combination therapy against human infections caused by Candida species.
86. Revie, N. M.; Iyer, K. R.; Robbins, N.; Cowen, L. E., *Curr. Opin. Microbiol.*, **2018**, *45*, 70–76. doi: 10.1016/j.mib.2018.02.005.
87. Danial, A. M.; Koh, S. P.; Abdullah, R.; Azali, A., *Food Research.*, **2020**, *4*(6), 112–117. doi: org/10.26656/fr.2017.4(S6).011.
88. Gangneux, J-P.; Godet, C.; Denning, D. W., *Allergy.*, **2022**, *77*, 3182–3184.doi: org/10.1111/all.15436.
89. Baker, J.; Denning, D. W., *British Medical Bulletin.*, **2023**, *147*(1), 62–78.doi: org/10.1093/bmb/ldad011.
90. Wu, Y.; Hu, S.; Wu, C.; Gu, F.; Yang, Y., *Front. Cell Infect. Microbiol.*, **2022**, *11*, 793419–793424. doi: 10.3389/fcimb.2021.793419.
91. Ousaaid, D.; Laaroussi, H.; Bakour, M.; Ennaji, H.; Lyoussi, B.; El, I., *Arabi. Int. J. Microbiol.*, **2021**, 2021, 6087671-608676. doi: 10.1155/2021/6087671.

92. Wróblewska, M.; Szymańska, E.; Winnicka, K., *Int. J. Mol. Sci.*, **2021**, *22*(21), 11326-11347. doi: 10.3390/ijms222111326.
93. Wankhede, R.; Wagh, A.; Sanap, G., *J. Emerg. Techno. Innov. Res.*, **2023**, *10*(12), d83-d93.
94. Adamczak, A.; Ożarowski, M.; Karpiński, T. M., *Pharmaceuticals.*, **2020**, *13*(7), 153-164. doi: 10.3390/ph13070153.
95. Moghadamtousi, S. Z.; Kadir, H. A.; Hassandarvish, P.; Tajik, H.; Abubakar, S.; Zandi, K., *Biomed. Res. Int.*, **2014**, 2014, 186864-186875. doi: 10.1155/2014/186864.
96. Hafeez, M.; Malik, D.; Ali, Q., *Biological and Clin. Sci. Res., J.*, **2020**, *1*, 1-8. doi: 10.54112/bcsrj.v2020i1.4.
97. Tesfaye, A. Scientific World Journal., **2021**, 2021, 8817288-881794.doi:10.1155/2021/ 8817288.
98. Khounganian, R. M.; Alwakeel, A.; Albadah, A.; Nakshabandi, A.; Alharbi, S.; Almslam, A. S., *Cureus.*, **2023**, *15*(5), e38637-e38643. doi: 10.7759/cureus.38637.
99. El-Saber Batiha, G.; Magdy Beshbishy, A.; Wasef, L. G.; Elewa, Y. H. A.; Al-Sagan, A. A.; Abd El-Hack, M. E.; Taha, A. E.; Abd-Elhakim, Y. M.; Devkota, H. P., *Nutrients.*, **2020**, *12*(3), 872-892. doi: 10.3390/nu12030872.
100. Mahmoud, D. A.; Hassanein, N. M.; Youssef, K. A.; Zeid, M. A. A., *Braz. J. Microbiol.*, **2011**, *42*(3), 1007-1016. doi: 10.1590/S1517-83822011000300021.
101. Alzohairy, M. A., *Evid Based Complement Alternat. Med.*, **2016**, 2016, 7382506-738517. doi: 10.1155/2016/7382506.
102. Mousavi, S.; Bereswill, S.; Heimesaat, M. M., *Eur. J. Microbiol. Immunol.*, **2019**, *9*(3), 73-79. doi: 10.1556/1886.2019.00016.
103. Meir, Z.; Osherov, N., *J. Fungi.*, **2018**, *4*(2), 72-85. doi: 10.3390/jof4020072.
104. Letscher-Bru, V.; Obszynski, C. M.; Samsoen, M.; Sabou, M.; Waller, J.; Candolfi, E., *Mycopathologia.*, **2013**, *175*(1-2), 153-8. doi: 10.1007/s11046-012-9583-2.
105. Kalhoro, M. T.; Zhang, H.; Kalhoro, G. M.; Wang, F.; Chen, T.; Faqir, Y.; Nabi, F., *Sci Rep.*, **2022**, *12*, 2191-2200. doi: org/10.1038/s41598-022-06321-5.
106. Rahmani, A. H.; Shabrmi, F. M.; Aly, S. M., *Int. J. Physiol. Pathophysiol. Pharmacol.*, **2014**, *6*(2), 125-136.
107. Fernandes, L.; Ribeiro, H.; Oliveira, A.; Silva, A. S.; Freitas, A.; Henriques, M.; Rodrigues, M. E., *J. Tradit. Complement. Med.*, **2020**, *11*(2), 130-136. doi: 10.1016/j.jtcme.2020.02.007.
108. Tsutsumi-Arai, C.; Takakusaki, K.; Arai, Y.; Terada-Ito, C.; Takebe, Y.; Imamura, T.; Ide, S.; Tatehara, S.; Tokuyama-Toda, R.; Wakabayashi, N.; Satomura, K., *PLoS One.*, **2019**, *14*(5), e0217496-e0217508. doi: 10.1371/journal.pone.0217496.
109. Hasan, M. K.; Ara, I.; Mondal, M. S. A.; Kabir, Y., *Heliyon.*, **2021**, *7*(6), e07240-e07249. doi: 10.1016/j.heliyon.2021.e07240.
110. Authier, H.; Bardot, V.; Berthomier, L.; Bertrand, B.; Blondeau, C.; Holowacz, S.; Coste, A., *Microbiol Spectr.*, **2022**, *10*(2), e02355-21. doi: 10.1128/spectrum.02355-21.
111. Gao, S.; Liu, G.; Li, J.; Chen, J.; Li, L.; Li, Z.; Zhang, X.; Zhang, S.; Thorne, R. F.; Zhang, S., *Front. Cell Infect. Microbiol.*, **2020**, *10*, 603858-603871. doi:10.3389/fcimb.2020.603858.
112. Denning, D. W.; Pfavayi, L. T., *Allergology Int.*, **2023**, *72*(4), 493-506. doi: org/10.1016/j.alit.2023.07.003.
113. Vitiello, A.; Ferrara, F.; Boccellino, M.; Ponzo, A.; Cimmino, C.; Comberiati, E.; Zovi, A., *Biomedicines.*, **2023**, *11*, 1063-1075.doi: org/10.3390/biomedicines11041063.
114. Majumdar, A.; Shah, M. R.; Park, J. J.; Narayanan, N.; Kaye, K. S.; Bhatt, P. J.; Clemente, S.; Sabbatucci, M., *Antibiotics.*, **2023**, *12*(3), 592-606.doi:10.3390/antibiotics12030592.
115. Vergidis, P.; Stevens, R. W.; Agrawal, S. G., *Curr. Fungal Infect. Rep.*, **2023**, *17*, 108–118. doi: org/10.1007/s12281-023-00465-1.
116. Chaput, A.; Peng, T.; Sun, L.; Lack, J. B.; Bays, D. J.; Stewart, E. R.; Waldman, S. E.; Powell, D. A.; Donovan, F. M.; Desai, J. V.; Pouladi, N.; Priel, D. A. L.; Yamanaka, D.; Rosenzweig, S. D.; Niemela, J. E.; Stoddard, J.; Freeman, A. F.; Zerbe, C. S.; Kuhns, D. B.; Lussier, Y. A.; Olivier, K. N.; Boucher, R. C.; Hickman, H. D.; Frelinger, J.; Fierer, J.; Shubitz, L. F.; Leto, T. L.; Thompson III, G. R.; Galgiani, J. N.; Lionakis, M. S.; Holland S. M., *JCI Insight.*, **2022**, *7*(22), e159491-e159506. doi: org/10.1172/jci.insight.159491.
117. Akhtar, N.; Amin-ul Mannan, M., *Biotechnology Reports.*, **2020**, *26*, e00452-e00461.doi:org/10.1016/j.btre.2020.e00452.