Antifungals from Indian plants: A revisit in the covid –era

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Abstract

Although most fungi are harmless to people, some of them are capable of causing infections under specific conditions. Nonetheless, it can evade the immune system via various processes, including recombination, mitosis, and expression of genes involved in oxidative stress responses that prompt chronic fungal diseases. Despite the development of health care facilities, the incidence rate of fungal diseases is still impressively high.

Moreover, The occurrence of multidrug-resistant strains(MDR) of fungus has further necessitated the need to reconsider various classes of new antifungals from natural sources. The approach based on structural modifications of phytochemicals from traditional antifungals is high on expectation for improvement of the pharmacokinetic and pharmacodynamic property of this agent, further could reverse the antibiotic resistance. This review article aims to provide an insight into antifungal agents in natural prospects. In addition, modifications to the chemical structures of traditional antifungals are known to improve antifungal activity and pharmacokinetic parameters. We hereby present a review on plants of Indian origin,along with their diverse phytochemicals viz. Alkaloids, terpenoids, flavoinds, phenolics etc for the development of novel formulations.

Considering these facts, it could be stated that phytochemicals represent a valuable source of bioactive compounds with potent antimicrobial activities.

1. Introduction

It is a well-known fact that humans co-habitat with various microorganism but an inherent innate immune system protects them from disease.

Fungi are microorganisms characterized by a substance in their cell walls called chitin. A few fungi, like many types of mushrooms, are edible. Different kinds of fungi, like aspergillus, can be extremely dangerous and lead to dangerous illnesses[1].

Various types of fungi can cause fungal diseases (see table No-1, Table no-2). Sometimes, fungi that aren't commonly found on or inside your body can colonize it and cause an infection. In different cases, fungi that are normally present on or inside your body can multiply out of control and cause an infection

Table no 1 : Classes Of Fungi [2]

Subclass	Example
Chytridiomycota	Allomyces, Blastoladiella, Coelomomyces, Physoderma, Synchytrium
Zygomycota	Amoebophilus, Mucor, Phycomyces, Rhizopus, Thamnidium
Ascomycota	Ascobolus, Aspergillus, Candida, Crinula, Neurospora, Penicillium, Pneumocystis, Saccharomyces
Basidiomycota	Agaricus, Boletes, Dacrymyces, Lycoperdon, Polyporous, Uromyces, Ustilago
Giomeromycota	Acaulospora, Entrophospora, Glomus
Microsporidia	Amblyopia, Encephalitozoon, Enterocytozoon, Nosema
Cryptomycota	Rozella

Fungal infections can be infectious. They can spread from one individual to another. In some cases, you can also catch illness-causing fungi from infected animals or contaminated soil or surfaces.[2]

A fungal infection is also called mycosis. Although most fungi are harmless to people, some of them are

capable of causing infections under specific conditions.

Fungi reproduce by releasing spores that can be gotten up by direct contact or even breathed in. That's why fungal diseases are most likely to influence your skin, nails, or lungs. Fungi can also penetrate your skin, influence your organs, and cause body-wide systemic diseases.

Fungal infections are divided into two types: primary and opportunistic. Opportunistic infections occur mainly in immunocompromised hosts, but primary infections may also occur in hosts with a healthy immune system.

A few kinds of fungi don't regularly cause infections in people but can cause illness in humans with weakened immune systems. These are called opportunistic diseases [1]. Worldwide, among some 2 million fungal species found only 600 species are known to cause diseases. The significant species that are mostly engaged with causing diseases are Cryptococcus, Candida, Trichophyton, and Aspergillus. The nature of fungal infection (see Table no -3) affecting the community can be categorised in the five following types:

1. Invasive fungal infections: cryptococcal meningitis, Candida bloodstream infection, invasive aspergillosis, Pneumocystis pneumonia
2. Chronic lung or deep tissue infection: chronic pulmonary aspergillosis
3. Allergic fungal disease: allergic bronchopulmonary aspergillosis also known as ABPA and severe asthma with fungal sensitization (SAFS).
4. Mucosal infection: oral and oesophagal candidiasis, Candida vaginitis
5. Skin, hair, and nail infection: athlete's Foot tinea capitis and onychomycosis [1] [3].

In this Covid -19 era, Indians as a community have become vulnerable to some rare life-threatening fungal infection. The reason behind this resurgence is the presence of a large no of diabetic and patients with other comorbidities.

Moreover, the widespread use of antifungals as prophylaxis used in case of life-threatening complications in patients with chemotherapy-induced neutropenia and patients on long-term immunosuppressive therapies following hematopoietic stem cell or solid-organ transplantation leads to a breakthrough of invasive mould infections aspergillosis; mucormycosis;[4].

Pandemic initiated use of steroids and antivirals, antimicrobials have further increased the risk for secondary infections with fungus. further risen in the no of immunocompromised patients.

In India, the prevalence of mucormycosis before Covid-era was as high as 0.14 cases per 1000 population, which is about 80 times the prevalence of mucormycosis in developed countries making India more vulnerable [5] [6].

2. Conventional antifungal treatment

The synthetic antifungal agents are categorized structurally mainly under the classes of azole, allylamine, morpholine, hydroxypyrimidine, and polyene. (see Table no-3) [8]

Therapeutic options for aspergillosis are limited, particularly so for oral formulations, with azole drugs forming the backbone of therapy [9]. Many patients that develop resistant infections fail treatment, so resistance is an important factor in the outcome of these cases [10]. Multidrug resistance and side effects of synthetic antifungals: an emerging crisis

Table no-2: Epidemiology of Fungal infections worldwide [7]

Fungal infection	**Distribution**	**Estimated life-threatening infections/year at that location***	**Mortality rates (% in infected population)***
Opportunistic invasive mycoses		More than200,000	30-95
Aspergillosis (Aspergillus furnigatus)	Worldwide	More than400,000	46-75
Candidiasis (Candida albicans)	Worldwide	More than1000,000	20-70
Cryptococcus neoformans	Worldwide	More than10,000	30-90

Mucromycosis (Pneumocystis jirovecii)	Worldwide, prevalent in Asia (China, India)	More than400,000	20-80
Endemic dimorphic mycoses			
blastomyces (dermatitidis)	Midwestern and Atlantic United States	aprrox3,000	<2-68
Coccidioidomycosis (Coccidiodes immitis)	Southwestern United States	aprrox25,000	<1-70
Histoplasmosis (Histoplasmosis capsulatum)	Midwestern United States	aprrox25,000	28-50
Paracoccidioidomycosis (paracoccidioides braselliensis)	Brazil	aprrox4,000	5-27
Penicilliosis (Penicillium mameffei)	Southheast Asia	More than8,000	2-75

Table no-3: Treatment by antifungals [11] [12]

S. No	Class	Drugs	Diseases
1	Azole antifungals	Clotrimazole, Econazole, Isoconazole, Miconazole, Ketoconazole, Itraconazole	Topical fungal infections, Candidiasis, aspergillus and candida infections, vaginal yeast infections
2	Echinocandins	Caspofungin, Micafungin	Oesophagal Candidiasis, Salvage therapy
4	Polyenes	Amphotericin B, Nystatin	Systemic mycosis, superficial mycosis
5	Phenolic cyclohexane	Griseofulvin	Dermatophytic infections
6	Synthetic pyrimidines	Flucytosine	Cryptococcosis, severe invasive aspergillosis, cryptococcal meningitis treated along with other antifungals
7	Morpholines	Amorolfine	Topical fungal infections
8	Pyridines	Buthiobate, Pyrifenox	Dermatophytic infections, Tinea conditions
9	Phthalimides	Captan	Invasive dermatophytic conditions and candida infections

The rapid increase of severe systemic infections and the spread of resistant microorganisms are indisputable facts. MDR is an unavoidable natural phenomenon, posing serious worldwide menace combat the MDR (see Table no-4). Pathogens tend to adopt various resistance mechanisms to survive unfavourable conditions. Inadequacy of available antimicrobial drugs compels the continuous development of newer drugs and novel therapies[13]. A combinational approach with new novel drug delivery systems and newer molecules from plants and their modified derivatives acting by various mechanism simultaneously can be an answer.

Moreover, these drugs possess serious side effects (see Table no-5) on the physiology viz. amphotericin B, which acts by binding to the sterol component of a cell membrane, leading to alterations in cell permeability and cell death, or fluconazole which is a highly selective

inhibitor of fungal cytochrome P450 dependent enzyme lanosterol 14-a-demethylase for fungistatic effect, and thus having numerous side effects.[17]

Table no-4: List of drug-resistant fungi based on disease in the current scenario[13]

Disease	**Genus/species of resistant Fungi**	**drug name**	**references**
Candidiasis	Candida sp.	Fluconazole and echinocandins	[14]
Cryptococcosis	Cryptococcus sp.	Fluconazole	[15]
Aspergillosis	Aspergillus sp.	Azoles	[10]
Onychomycosis	Scopulariopsis sp.	Amphotericin B, flucytosine, and azoles	[16]
mucormycosis	Rhizopus sp. or Mucor sp, Apophysomyces sp	Posaconazole	[4]

Table No-5: Side Effects Of Antifungal Drugs [12]

S. No	**Side effects**	**Drugs**
1	Non-melanoma skin cancer prolonged therapy	Voriconazole
2	Fever, Chills	Isavuconazole, Ketoconazole, Voriconazole, Flucytosine, Anidulafungin, Caspofungin
3	Rash	Flucytosine, Fluconazole, Ketoconazole, Clotrimazole, Voriconazole
4	Nausea, vomiting	Isavuconazole, Itraconazole, Flucytosine, Fluconazole, Ketoconazole, Clotrimazole, Voriconazole
5	Abdominal pain	Flucytosine, Ketoconazole, Isavuconazole, Voriconazole
6	Anaemia	Amphotericin B, Caspofungin, Flucytosine
7	Leukopenia, Thrombocytopenia	Flucytosine, Fluconazole
8	Decreased renal function	Amphotericin B, Caspofungin, Voriconazole
9	Headache	Flucytosine, Fluconazole, Ketoconazole, Isavuconazole, Voriconazole, Caspofungin
10	Dark urine, clay-coloured stools, jaundice	Anidulafungin C, Micafungin

3. Indian Plants of interest with antifungal activity

Previous ethnopharmacological studies reveal the importance of medicinal plants in health and community care. They provide a vast resource for physiologically active bioactive compounds like polysaccharides, phenolic, tannins, flavonoids, terpenoids like steroids, saponins, alkaloids etc. [12]. This high chemical diversity of natural products make them successful candidates by affecting the evolutionary pressure to create biologically active molecules. Starting with the discovery of penicillin, Some antifungals, including polyenes and echinocandins, derive directly from natural sources. Nowadays, 80% of all available clinically used

antibiotics are directly (or indirectly) derived from NPs [17].

The indian system of medicines are having a backup of more than 2000 plant spices. This review aims to give insight on researches based on plant drugs. the Table no-6 enlist the plants with reported antifungal activities.

Table No 6: Medicinal Plants of India active against different human pathogenic fungi[45]

S. No.	***Botanical name***	**Family**	**Parts used**	**Chemical classes**	**Activity**	**Ref**
1	*Xanthium strumarium L*	Asteraceae	Leaves	Essential oil	Active Against Candida Aspergillus	[30] [31]
2	*Moringa pterygosperma,*	Moringaceae	Leaves	Extracts (Aqueous, metahnol)	Candidiasis	[30] [32]
3	*Micromeria nervosa*	Labiatae	Oil Arieal parts	Phenolic compounds Extracts (Aqueous and Ethanolic)	Antifungal	[30] [33]
4	*Inula viscose*	Compositae	Oil Arieal parts Flowers	Phenolic compounds Extracts (Aqueous and Ethanolic)	Active Against Colletotrichum Ascomycetes Basidiomycetes	[30] [33]
5	*Piper aduncum*	Piperaceae	Inflorescence Leave	Terpenes, Essential oil	Dermatomycosis	[30] [34]
6	*Aniba panurensis*	Lauraceae	Whole plant	Alkaloid (Indazolidium)- novel agent	Active Against Drug resistant strain of candida	[35]
7	*Syzygium jambolanum*	Myrtaceae	Seeds Leaf fruit stem bark	Alkaloids Glycoside	Anticandidal	[30] [36]
8	*Cassia tora*	Leguminosae	Seeds	Anthraquinone	Anticandidal	[35]
9	*Mentha piperita*	Lamiaceae	Oil Arieal parts	Terpenes Essential Oil	Active Against Candida Aspergillus	[30]

						[37]
10	*Cymbopogon citratus*	Poaceae	Oil Arieal parts	Terpenes Essential Oil	Active Against Malassezia Trichophyton Dermatophytes	[30] [38]
11	*Tectona grandis*	Verbenaceae	Bark Leaves	Extract (Aqueous)	Candidiasis	[39] [32]
12	*Aquilegia vulgaris*	Ranunculaceae	Leaves Stems	Bis (benzyl)	Anticandidal	[35]
13	*Persea americana*	Lauraceae	Leaves	Chromene	Anticandidal	[35]
14	*Tithonia diversifolia*	Asteraceae	Whole plant	Saponins Polyphenols	Anticandidal	[40]
15	*Prunus yedoensis*	Rosaceae	Leaves	Diterpenes	Anticandidal	[35]
16	*Datura metel*	Solanaceae	Whole plant	Diterpenoid, Alkaloids	Anticandidal	[41]
17	*Schinus terebinthifolius*	Anacardiaceae	Stem bark	Extract	Anticandidal	[35]
18	*Alibertia macrophylla*	Rubiaceae	Leaves	Extract	Anticandidal	[35]
19	*P. regnellii*	Piperaceae	Leaves	Extract	Anticandidal	[35]
20	*Ecballium elaterium*	Cucurbitaceae	Fruit	Extract	Anticandidal	[35]
21	*Vernonanthura tweedieana*	Asteraceae	Root	Extract	Anticandidal	[39]
22	*Psidium guajava*	Myrtaceae	Leaves	Extract (methanol)	Anticandidal	[35]
23	*Achillea millefolium*	Asteraceae	Arieal parts Leaves	Flavonoids Phenolic acids	Anticandidal Antiaspergillus	[30] [33]

			Bark	Coumarins, Terpenoids (monoterpene,sequiterpene, diterpene, triterpenes) Sterols		
24	*Ajania fruticulosa*	Asteraceae	Fruits	Guaianolides	Anticandidal	[35]
25	*Lupinus albus*	Leguminosae	Leaf surface	Isiflavonoids	Active Against Trichophyton	[35]
26	*Chamaecyparis pisifera*	Cupressaceae	Leaves Twigs	Isoflavone	Anticandidal	[35]
27	*Justicia secunda*	Acanthaceae	Leaf Whole plant	Extract (Methanol)	Anticandidal	[30] [33]
28	*Cajanus cajan*	Fabaceae	Roots	Alkaloids Flavonoids Tannins Extracts (Methanolic)	Anticandidal	[30] [34]
29	*Curcuma longa*	Zingiberaceae	Rhizome	Oil ofTurmeric	Anticandidal	[35] [30] [33]
30	*Terminalia chebula*	Combretaceae	Fruit Bark Roots Leaves Seed	Phenolics Tannins Extract of seed (Methanol , aqueous)	Strong Antifungal Anticandidal Antimucor Antiaspergillus	[30] [42]
31	*Parapiptadenia rigida*	Fabaceae	Stem bark	Pyrrolidine amide	Anticandidal	[35]
32	*Piptadenia colubrina*	Mimosaceae	Stem bark	Saponins Tannins Lecuanthocyanidins ,Extract (alchohol and aqueos)	Dermatophytes Active against Trichophyton	[35]
33	*Mimosa tenuiflora*	Mimosaceae	Stem bark	Sesquiterpene lactone	Anticandidal	[35]
34	*Eugenia uniflora*	Myrtaceae	Leaves	Sesquiterpenes Monoterpene	Anticandidal	[35]

				hydrocarbons		
35	*Zingiber officinale*	Zingiberaceae	Rhizomes	Steroidal saponin	Anticandidal	[39] [43] [32]
36	*Ocimum gratissimum,*	Lamiaceae	Whole plant Oil of Tulsi	Terpenes (monoterpene)	Active against Candida Mucor Aspergillus Mycospora Trichophyton Pathogenic plant fungi	[30] [34]
37	*Eucalyptus globolus*	Myrtaceae	Leaves Leave Oil	Terpenes Extract (methanol)	Anticandidal (highly significant)	[30] [12]
38	*Punica granatum*	Punicaceae	Seeds	Terpenes Extract (methanol)	Anticandidal	[30] [12]
39	*Artemisia mexcana*	Asteraceae	Arieal parts Leaves Bark	Terpenes Extract (methanol	Anticandidal Fusarium Aspergillus Trichophyton Mocor	[30] [12]
40	*Bocconia arborea*	Papaveraceae	Oil Arieal parts	Terpenes, Extract (methanol) Alkaloids	Anticandidal	[30] [12]
41	Hypericum scabum	Hypericaceae	Aerial Parts Bulb Seed	Extract (Trichloromethanol, n-hexane, aqueous)	Active Against Candida Cryptococcus neoformans Rhodotorula	[30] [33]
42	*Rubia tinctorum*	Rubiaceae	Root	Anthraquinone Qninones Alizarin Triterpene	Anticandida	[44]

4. Role of Phytochemicals in antifungal activity: a mechanistic approach

Each class of synthetic antifungals has a unique mechanism of action each class though is unique: azoles inhibit the synthesis of ergosterol; polyenes attach to ergosterol; allylamine mount up squalene in the upstream of the ergosterol biosynthesis pathway; hydroxypyrimidine hampers the DNA replication, and morpholine diminishes ergosterol by inhibiting d14-sterol reductase [19].

The prime target of sensitive anti-fungal agents is the

ergosterol pathway as it is optimized to protect the fungi against mechanical and oxidative stress [18] [8].

Though the mechanisms of action of natural antifungal products and their structure-activity relationships are largely unexplained, researchers suggest that these phytoconstituents act singly or with combined mechanisms providing a wider spectrum and sensitivity in overcoming the development of drug résistance against agents. This varied and voluminous range of phytochemicals classified Based on their chemical structures into major i.e. alkaloids, sulfur-containing compounds, terpenoids, and polyphenols etc... They are advantageous because of their properties like antioxidant, antifungal, antibacterial, immunity enhancer [20].

Alkaloids, the heterocyclic nitrogen molecule primarily act by Efflux pumps Inhibition (EPI) like piperine (piper longum, by inhibition of cell division like berberine (Berberis vulgaris), by the destruction of the cell wall by solasodine (Solanum khasianum) [21].

Organosulfur compounds, the Sulphur containing compounds such as allicin and ajoene from Allium sativum, dialkenyl and dialkyl sulphides, S-allyl cysteine and S-ally-mercapto cysteine, and isothiocyanates showed antimicrobial and antifungal activities by different thiol-dependent enzymatic systems. Phenethyl isothiocyanate, found within brassica vegetables might be related to factors viz. intracellular accumulation of reactive oxygen species and depolarization of mitochondrial membrane [3] [22][23].

Phenolic compounds, as bioactive molecules contain a large set viz flavone, isoflavones, flavonoids and flavonolignans, chalcones, polyphenols etc., play an important role in enhancing antibiotic or antifungal activity against resistant pathogens through various mechanisms viz. reverse inhibitors and competitive with ATP (apigenin), direct interaction with peptidoglycan inhibiting cell wall synthesis (Sophoraflavanone B), inhibitors of some enzymes like dihydrofolate, reductase, urease, sortase, and finally by inhibitory activity against DNA gyrase like in case of anthraquinones and tannins like chebulic acid [24].

Tannins also inactivate microbial adhesions and transport proteins through antibiofilm effects [25].

Quinones also exhibit antibiofilm activity by complex formation with nucleophilic amino acids leading to protein inactivation and loss of cell function. Purpurin, a natural red pigment found in madder root act by the downregulation of filamentation-associated genes and hyphal protein. [25]

Coumarins are reported to have several activities like a vasodilator, estrogenic, anticoagulant, analgesic, anti-inflammation, sedative and hypnotic, hypothermic, anti-helminthic, anticancer, antioxidant and dermal photosensitizing activity are potential subjects for multidrug therapy as well as against MDR pathogens [26]. Pterostilbene isolated from plants Pterocarpus marsupium act via ergosterol biosynthesis, oxidoreductase activity and heat shock proteins. [25]

Terpenes, the most diverse class of phytochemicals, widespread are high potential candidates as antifungal agents. Monoterpenes, like carvone, thymol, preferential impact on the structures of the membrane through increasing its fluidity and permeability, altering the topology of its proteins and making disturbances across the respiration chain, hence show synergistic activity in a combination of fluconazole [27].

Chitosan, an algal polysaccharide, derivatised with double Schiff bases showed profound antifungal activity compared with chitosan against *Fusarium oxysporum* f. sp. *Niveum* and plant pathogenic fungi[28].

5. Novel drug delivery systems and herbal formulation

Herbals as a novel delivery system are potential candidates as their side effects are minimal. Moreover, the natural compounds show a synergistic effect due to the presence of a complex mixture of molecules. Traditionally the natural components are known to be less toxic and their probability to develop resistance is mere. Many formulations like antifungal phytosomes (Zanthalene), liposomes (neem extract), nanoparticles (in candidiasis), micro and nanoemulsion (Quercus extract), microspheres (curcumin), neosomes(chitosan), transdermal delivery system (plumbagin), ethosomes(Tridax), transferomes(cholchicines), hydrogels (synthetic antifungal) are the few to name.

6. Conclusion and prospects

Natural products derived from medicinal plants with traditional or folklore medicines are promising candidates for the treatment of fungal diseases. The sighted isolates of phytochemicals showed overwhelming sensitivity against many clinical fungi. The clinical effect of antifungals was neither restricted to any particular class of phytochemical nor any particular plant family. These reviewed preclinical studies deserve the paramount attention of the pharma industry for further detailed studies to identify more clinically useful agents. In addition, mechanistic studies revealed that these natural chemicals exert their effects through multiple mechanisms, unlike synthetic standard antifungal agents.

Studies revealed that plant product with different receptor sites and mechanism of action, have less proven resistance and have better tolerability to manage the current emergence of resistance to numerous synthetic agents. The newer techniques in the drug discovery for natural product further encourages researchers to isolate and characterize phytopharmaceuticals may lead to some exceptional molecules. Moreover, the Development of novel drug with effective preliminary study including an effective site for action, safety and better clinical profile is today the requirement of immunocompromised subjects, as well as MDR crisis covid era for better lifecare.

References

[1] Asghar Sepahvand et al, Hossein Eliasy, and Mehdi Mohammadi, "A review of the most effective medicinal plants for dermatophytosis in traditional medicine | Biomedical Research and Therapy." http://www.bmrat.org/index.php/BMRAT/article/view/450 (accessed Jun. 11, 2021).

[2] Microbiology. New York: Tata McGraw-Hill, 2003.

[3] G. S. Kobayashi, "Disease Mechanisms of Fungi," in Medical Microbiology, 4th ed., S. Baron, Ed. Galveston (TX): University of Texas Medical Branch at Galveston, 1996. Accessed: Jun. 11, 2021. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK8103/

[4] F. Lamoth, S. J. Chung, L. Damonti, and B. D. Alexander, "Changing Epidemiology of Invasive Mold Infections in Patients Receiving Azole Prophylaxis," Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am., vol. 64, no. 11, pp. 1619–1621, Jun. 2017, DOI: 10.1093/CID/cix130.

[5] A. Skiada, I. Pavleas, and M. Drogari-Apiranthitou, "Epidemiology and Diagnosis of Mucormycosis: An Update," J. Fungi, vol. 6, no. 4, p. 265, Nov. 2020, doi: 10.3390/jof6040265.

[6] C. J et al., "Saksenaea erythrospora, an emerging mucoralean fungus causing severe necrotizing skin and soft tissue infections - a study from a tertiary care hospital in north India," Infect. Dis. Lond. Engl., vol. 49, no. 3, Mar. 2017, doi: 10.1080/23744235.2016.1239027.

[7] G. D. Brown, D. W. Denning, N. A. R. Gow, S. M. Levitz, M. G. Netea, and T. C. White, "Hidden Killers: Human Fungal Infections," Sci. Transl. Med., vol. 4, no. 165, pp. 165rv13-165rv13, Dec. 2012, doi: 10.1126/scitranslmed.3004404.

[8] M. K. Kathiravan et al., "The biology and chemistry of antifungal agents: a review," Bioorg. Med. Chem., vol. 20, no. 19, pp. 5678–5698, 2012.

[9] T. J. Walsh et al., "Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America," Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am., vol. 46, no. 3, pp. 327–360, Feb. 2008, doi: 10.1086/525258.

[10] S. J. Howard and M. C. Arendrup, "Acquired antifungal drug resistance in Aspergillus fumigatus: epidemiology and detection," Med. Mycol., vol. 49, no. S1, pp. S90–S95, Apr. 2011, doi: 10.3109/13693786.2010.508469.

[11] Revankar SJ., Merck Manual professional version. Wayne State University School of Medicine, 2018.

[12] G. Murtaza, M. Mukhtar, A. Sarfraz, and G. Murtaza, "A Review: Antifungal Potentials of Medicinal Plants," J. Bioresour. Manag., vol. 2, Jun. 2015, doi: 10.35691/JBM.5102.0018.

[13] J. Tanwar, S. Das, Z. Fatima, and S. Hameed, "Multidrug Resistance: An Emerging Crisis," Interdiscip. Perspect. Infect. Dis., vol. 2014, pp. 1–7, 2014, doi: 10.1155/2014/541340.

[14] J. Loeffler and D. A. Stevens, "Antifungal Drug Resistance," Clin. Infect. Dis., vol. 36, no. Supplement_1, pp. S31–S41, Jan. 2003, doi: 10.1086/344658.

[15] L. Rodero et al., "G484S Amino Acid Substitution in Lanosterol 14-α Demethylase (ERG11) Is Related to Fluconazole Resistance in a Recurrent Cryptococcus neoformans Clinical Isolate," Antimicrob. Agents Chemother., vol. 47, no. 11, pp. 3653–3656, Nov. 2003, doi: 10.1128/AAC.47.11.3653-3656.2003.

[16] M. Cuenca-Estrella, A. Gomez-Lopez, E. Mellado, M. J. Buitrago, A. Monzón, and J. L. Rodriguez-Tudela, "Scopulariopsis brevicaulis, a Fungal Pathogen Resistant to Broad-Spectrum Antifungal Agents," Antimicrob. Agents Chemother., vol. 47, no. 7, pp. 2339–2341, Jul. 2003, doi: 10.1128/AAC.47.7.2339-2341.2003.

[17] H. Khan et al., "Plant bioactive molecules bearing glycosides as lead compounds for the treatment of fungal infection: A review," Biomed. Pharmacother., vol. 93, pp. 498–509, Sep. 2017, doi: 10.1016/j.biopha.2017.06.077.

[18] S. W. Wong-Deyrup et al., "Plant-derived isoquinoline alkaloids that target ergosterol biosynthesis discovered by using a novel antifungal screening tool," Biomed. Pharmacother., vol. 137, p. 111348, May 2021, doi: 10.1016/j.biopha.2021.111348.

[19] S. Dupont, G. Lemetais, T. Ferreira, P. Cayot, P. Gervais, and L. Beney, "Ergosterol biosynthesis: a fungal pathway for life on land?," Evol. Int. J. Org. Evol., vol. 66, no. 9, pp. 2961–2968, 2012.

[20] B. Khameneh, M. Iranshahy, V. Soheili, and B. S. Fazly Bazzaz, "Review on plant antimicrobials: a mechanistic viewpoint," Antimicrob. Resist. Infect. Control, vol. 8, no. 1, p. 118, Dec. 2019, doi: 10.1186/s13756-019-0559-6.

[21] B. Khameneh, M. Iranshahy, M. Ghandadi, D. Ghoochi Atashbeyk, B. S. Fazly Bazzaz, and M. Iranshahi, "Investigation of the antibacterial activity and efflux pump inhibitory effect of co-loaded piperine and gentamicin nanoliposomes in methicillin-resistant Staphylococcus aureus," Drug Dev. Ind. Pharm., vol. 41, no. 6, pp. 989–994, Jun. 2015, doi: 10.3109/03639045.2014.920025.

[22] S. Yoshida, S. Kasuga, N. Hayashi, T. Ushiroguchi, H. Matsuura, and S. Nakagawa, "Antifungal activity of ajoene derived from garlic," Appl. Environ. Microbiol., vol. 53, no. 3, pp. 615–617, Mar. 1987, doi: 10.1128/aem.53.3.615-617.1987.

[23] B. Calmes et al., "Glucosinolate-derived isothiocyanates impact mitochondrial function in fungal cells and elicit an oxidative stress response necessary for growth recovery," Front. Plant Sci., vol. 06, Jun. 2015, doi: 10.3389/fpls.2015.00414.

[24] H. Gradišar, P. Pristovšek, A. Plaper, and R. Jerala, "Green Tea Catechins Inhibit Bacterial DNA Gyrase by Interaction with Its ATP Binding Site," J. Med. Chem., vol. 50, no. 2, pp. 264–271, Jan. 2007, doi: 10.1021/jm060817o.

[25] M. S. Ahmad Khan, M. M. Altaf, and M. Sajid, "Insights of Phyto-Compounds as Antipathogenic Agents," in New Look to Phytomedicine, Elsevier, 2019, pp. 367–389. doi: 10.1016/B978-0-12-814619-4.00014-8.

[26] Y. K. Al-Majedy, A. A. H. Kadhum, A. A. Al-Amiery, and A. B. Mohamad, "Coumarins: The Antimicrobial agents," Syst. Rev. Pharm., vol. 8, no. 1, pp. 62–70, Apr. 2017, doi: 10.5530/srp.2017.1.11.

[27] A. Sharifzadeh, A. R. Khosravi, H. Shokri, and H. Shirzadi, "Potential effect of 2-isopropyl-5-methylphenol (thymol) alone and in combination with fluconazole against clinical isolates of Candida albicans, C. glabrata and C.

krusei," J. Mycol. Médicale, vol. 28, no. 2, pp. 294–299, Jun. 2018, doi: 10.1016/j.mycmed.2018.04.002.

[28] L. Wei et al., "Antifungal activity of double Schiff bases of chitosan derivatives bearing active halogeno-benzenes," Int. J. Biol. Macromol., vol. 179, pp. 292–298, 2021.

[29] K. KAUSHIK and S. AGARWAL, "The ROLE OF HERBAL ANTIFUNGAL AGENTS FOR THE MANAGEMENT OF FUNGAL DISEASES: A SYSTEMATIC REVIEW," Asian J. Pharm. Clin. Res., pp. 34–40, May 2019, doi: 10.22159/ajpcr.2019.v12i7.33831.

[30] V. Navarro, Ma. L. Villarreal, G. Rojas, and X. Lozoya, "Antimicrobial evaluation of some plants used in Mexican traditional medicine for the treatment of infectious diseases," J. Ethnopharmacol., vol. 53, no. 3, pp. 143–147, Sep. 1996, doi: 10.1016/0378-8741(96)01429-8.

[31] D. I. Ribeiro et al., "Determination of antifungal activity of essential oils of Curcuma longa L. (Zingiberaceae) and Achillea millefolium (Asteraceae) grown in the Northwest Paraná.," Arq. Ciênc. Saúde UNIPAR, vol. 14, no. 2, pp. 103–109, 2010.

[32] D. Srinivasan, S. Nathan, T. Suresh, and P. Lakshmana Perumalsamy, "Antimicrobial activity of certain Indian medicinal plants used in folkloric medicine," J. Ethnopharmacol., vol. 74, no. 3, pp. 217–220, Mar. 2001, doi: 10.1016/S0378-8741(00)00345-7.

[33] M. S. Ali-Shtayeh, R. M.-R. Yaghmour, Y. R. Faidi, K. Salem, and M. A. Al-Nuri, "Antimicrobial activity of 20 plants used in folkloric medicine in the Palestinian area," J. Ethnopharmacol., vol. 60, no. 3, pp. 265–271, Apr. 1998, doi: 10.1016/S0378-8741(97)00153-0.

[34] "(PDF) Antileishmanial and antifungal activity of plants used in traditional medicine in Brazil | Fernanda Braga - Academia.edu." https://www.academia.edu/11094347/Antileishmanial_and_antifungal_activity_of_plants_used_in_traditional_medicine_in_Brazil (accessed Jun. 10, 2021).

[35] Programa de Pós graduação em Ciências Farmacêuticas, Universidade Federal do Rio Grande do Norte, Brazil. et al., "Antifungal activity of medicinal plants from Northeastern Brazil," J. Med. Plants Res., vol. 7, no. 40, pp. 3008–3013, Oct. 2013, doi: 10.5897/JMPR2013.5035.

[36] M. Chandrasekaran and V. Venkatesalu, "Antibacterial and antifungal activity of Syzygium jambolanum seeds," J. Ethnopharmacol., vol. 91, no. 1, pp. 105–108, Mar. 2004, doi: 10.1016/j.jep.2003.12.012.

[37] M. J. Saharkhiz, M. Motamedi, K. Zomorodian, K. Pakshir, R. Miri, and K. Hemyari, "Chemical Composition, Antifungal and Antibiofilm Activities of the Essential Oil of Mentha piperita L.," ISRN Pharm., vol. 2012, p. e718645, Dec. 2012, doi: 10.5402/2012/718645.

[38] E. S. Carmo, F. de O. Pereira, N. M. Cavalcante, C. W. Gayoso, and E. de O. Lima, "Treatment of pityriasis versicolor with topical application of essential oil of Cymbopogon citratus (DC) Stapf - therapeutic pilot study," An. Bras. Dermatol., vol. 88, no. 3, pp. 381–385, Jun. 2013, doi: 10.1590/abd1806-4841.20131800.

[39] K. Endo, E. Kanno, and Y. Oshima, "Structures of antifungal diarylheptenones, gingerenones A, B, C and isogingerenone B, isolated from the rhizomes of Zingiber officinale," Phytochemistry, vol. 29, no. 3, pp. 797–799, Jan. 1990, doi: 10.1016/0031-9422(90)80021-8.

[40] A. Portillo, R. Vila, B. Freixa, T. Adzet, and S. Cañigueral, "Antifungal activity of Paraguayan plants used in traditional medicine," J. Ethnopharmacol., vol. 76, no. 1, pp. 93–98, Jun. 2001, doi: 10.1016/S0378-8741(01)00214-8.

[41] J. L. Ingham, S. Tahara, and J. B. Harborne, "Fungitoxic Isoflavones from Lupinus albus and other Lupinus Species," Z. Für Naturforschung C, vol. 38, no. 3–4, pp. 194–200, Apr. 1983, doi: 10.1515/znc-1983-3-407.

[42] A. Vonshak, O. Barazani, P. Sathiyamoorthy, R. Shalev, D. Vardy, and A. Golan-Goldhirsh, "Screening South Indian medicinal plants for antifungal activity against cutaneous pathogens," Phytother. Res., vol. 17, no. 9, pp. 1123–1125, Nov. 2003, doi: 10.1002/ptr.1399.

[43] R. Dabur, A. K. Chhillar, V. Yadav, P. K. Kamal, J. Gupta, and G. L. Sharma, "In vitro antifungal activity of 2-(3,4-dimethyl-2,5-dihydro-1H-pyrrol-2-yl)-1-methylethyl pentanoate, a dihydropyrrole derivative," J. Med. Microbiol., vol. 54, no. 6, pp. 549–552, Jun. 2005, doi: 10.1099/jmm.0.45968-0.

[44] M. Y. Bouberte, K. Krohn, H. Hussain, E. Dongo, B. Schulz, and Q. Hu, "Tithoniamarin and tithoniamide: a structurally unique isocoumarin dimer and a new ceramide from Tithonia diversifolia," Nat. Prod. Res., vol. 20, no. 9, pp. 842–849, Jul. 2006, doi: 10.1080/14786410500462892.

[45] G. Murtaza, M. Mukhtar, and A. Sarfraz, "A Review: Antifungal Potentials of MedicinalPlants," J. Bioresour. Manag., vol. 2, no. 2, p. 4, Jun. 2015, doi: 10.35691/JBM.5102.0018.