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Review Report on Natural Products as Anti-Fungal Agents

Farooqui SS[1], Somia G[1]*, Faizan B[2] and Faiza A[3]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jinnah University for Women, Karachi, Pakistan

[2]Department of Chemistry, University of Karachi, Karachi, Pakistan

[3]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ziauddin University, Karachi, Pakistan

Review Article

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***Corresponding author:** Somia Gul, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jinnah University for Women, 74600, Karachi, Pakistan, Email: drsomi1983@yahoo.com

Abstract

Human fungal infections have been greatly increasing nowadays mainly, in patients of cancer, AIDS and those that are immune-compromised. Therefore, the usage of anti-fungal drugs has also been increased, resulting in resistance to the currently available drugs. The resistance to anti-fungal drugs has an inference to the health of the community. As the currently used anti-fungal drugs have limited effective activity, more drug-drug interactions, and toxicity issues, it seems essential to identify therapeutic options for fungal infections. Discovering new anti-fungal compounds from the natural products like plants could provide a significant source for new medicinal products. This review discusses the currently available natural products reported as antifungal agents, current status of those products, as well as, advancement and future perspective of natural products as anti-fungal agents.

Keywords: Antifungal; Natural Products; Plant Sources; Fungal Infections

Introduction

Nature executes miracles for us every single day, starting from providing us beautiful views, clean water, fresh air, plentiful food, medicines, regulating the weather etc. In short, nature is our sole supplier. We humans have become smarter as a species but without diverse nature and a healthy functioning natural environment, we will be lost as a tourist without a map. There is a saying by John Muirthat, One can acquire far more than he perceives in every step in with nature [1].

Nature has been a source of medicinal products, with many beneficial drugs originated from plant sources [2]. This review specifies natural products as anti-fungal agents, anti-fungal drugs, current status, advancement and future perspective of natural products as anti-fungal agents.

Natural products have shown significant importance in the development of new active molecules in the past years. It has been proven to be an excellent source of novel chemical entities [3]. From sources like plants, microorganisms, marine products, which are considered to be among the most important part of the nature, a number of small molecules with distinct chemical structure and potent bioactivities have been discovered [4]. Natural products like plants can give rise to a variety of medicinal components that can obstruct the growth of pathogens [5]. The characteristics of natural products are manifold, which has an impact on the evaluation of anti-fungal activity, such as the release of active

constituents, stability, dissolution, solubility and absorption [6]. It is believed that historically pharmaceutical companies used to avail plant extracts to produce crude therapeutic formulations, but later in the mid-20th century, with the evolution of antibiotics, drug formulations of sufficiently purified compounds have become more typical [7]. Apart from other natural sources, the plant sources have significant use like plants consists of a broad biodiversity that also includes increase chemo diversity, approximately, less than 10% of secondary metabolites of plants have been isolated [8]. These substances act as defense mechanism of plants against microorganism attack in many of the cases, and plants are the prime source of medicinal preparations like essential oils, extracts etc. They are used in the traditional medicine and also indicated in the treatment of infectious diseases [8].

Fungal Infections are caused by fungal microorganism which damages the cell membrane, which leads to loss of cellular components and eventually results in inflammation of the infected tissue [9]. Some of the molecular processes are same in humans and fungi, which make it difficult and risky to treat. The intracellular structure of fungi and human contains similar eukaryotic cells and both are heterotrophic [10]. Human fungal infections have been seen increasing nowadays mainly, in patients of cancer, AIDS and those are immunocompromised [11]. The usage of antifungal drugs has been increased and therefore, resulted in the development of resistance to the currently available drugs [12]. The resistance to anti-fungal drugs has an inference to the health of the community because fungal infections are severe infections and if the anti-fungal treatment has developed resistance or it is limited, it may be more difficult to treat. For instance, If the anti-fungal treatment has developed resistance to blood stream infections related to candida (a yeast), it can lead to disability or death [13,14].

The future perspective is the need for emerging new antifungals, the reason behind this emergence is based on several factors such as the fungal diseases mortality should be improvised [15]. There is a need of new and better fungicidal drugs that has rapid action as the current antifungal used have prolonged treatment and they are expensive too [15]. Pharmacokinetics and pharmacodynamics of the drugs should be improvised [16]. The current antifungal have toxicities related to the host, also the interaction with other drugs cannot be acceptable [16]. As there are limited classes of antifungal, so there is a need to discover new natural plant products with antifungal activity and with some other mechanism of actions [16]. These factors are essential to discover newer antifungal agents that will synergize with currently used antifungal drugs and help in achieving better fungicidal responses.

Methodology

The methodology to review the natural plant products containing antifungal activity has been conducted by using computer based software, research data analysis, large enhanced sites like Alzeihviers, Pubmed, Science direct and Google Scholar [1]. It includes searches related to natural plant products containing anti-fungal activity tested against certain causative organisms. The study has been completed within a period of 2 months and the keywords that helped to search the matter includes; Plants containing anti-fungal activities, Treatment for fungal infections by natural plant products, Causes of fungal infections, Current treatment available for fungal infections, Resistance and toxicity issues with currently available anti-fungal drugs, Antifungal activity of natural plants against causative organisms, Significant features of natural plant products, Need for emergence of new anti-fungal and Specifications of plant species and its significance against fungal infections [1].

Current Available Treatments for Fungal Infections:

The current situation shows that the anti-fungal drugs have various limitations like interaction between drugs, toxicity, limited effective activity, poor pharmacokinetics (Table1) [2]. These intrinsic properties are aggravated in patients that are immunocompromised, because their immunity level cannot aid in the suppression of the infection and requires proper and prolong treatment [3]. In contrast, the natural plant products have least harmful effects on the immune system and are well tolerated by the body. The resistance of fungal infections to the currently used anti-fungal is the alarming trend, and the related issue is linked in accordance with the fact that the latest category of accredited antifungal, the echinocandins, were basically introduced fifty years ago [4]. The Food and drug administration (FDA) has also felt the requirement for latest anti-fungal by keeping Candida and Aspergillus on their record of qualifying pathogens [5]. The specifications of the currently used anti-fungal drugs are listed in Table 1.

The toxicity issues like renal toxicity, congestive heart failure, transaminase abnormalities, resistance to drugs and drug-drug interactions, exhibited by the currently available anti-fungal drugs lead to the emergence of current advancements in natural products as anti-fungal drugs in order to minimize the toxicity level and to increase its therapeutic effects [17-19].

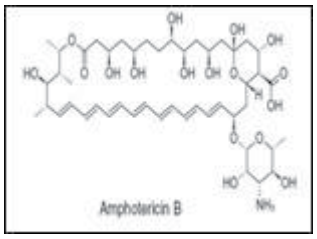
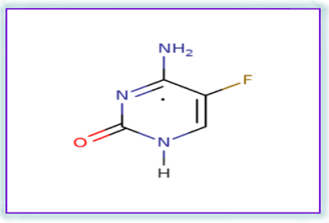
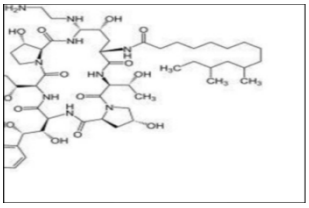
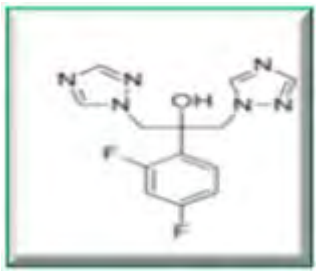
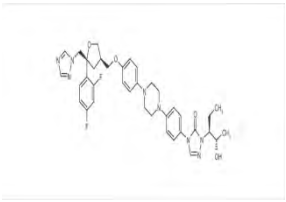
Drug	Discovery	Indication	Toxicity	Structure
AmphotericinB deoxycholate	1958	It yields effective and wide range antifungal activity [6-8].	Reactions related to infusion and substantial renal toxicity [7,9].	 Amphotericin B [6].
Flucytosine, apyrimidine analogue	1973	It is effective against Cryptococcus and Candida sp [7].	Its practice is restricted due to the issue of toxicity and resistance to drugs [7].	 Flucytosine [10]
Echinocandin drugs	2000s	It offers excellent activity against Candida p [7].	It has few drug-drug interactions [7].	 Caspofungin [7].
Azoles first-generation drugs, inclusive of fluconazole and itraconazole.	1990s	These classes of drugs provide benefits of oral administration and are effective against pathogens and yeast [10].	It has been associated with the development of congestive heart failure [10].	 Fluconazole [10]
Azolessecond-generation drugs, inclusive of voriconazole and posaconazole.	2000s	It has very broad-spectrum activity against dermatophytes, yeasts, and molds. Candida spp [10].	Produces clinically significant transaminase abnormalities inapprox. 13% of patients [10].	 Psoconazole [10].

Table 1: Specifications of Currently Used Anti-Fungal Drugs.

Current Advancements in Natural Products as Anti-Fungals

The current advancement shows that a number of plant species can be used to treat fungal infections. The specification for plant species that are active against fungal microorganisms and contains anti-fungal activity are listed in Table 2.

Species	Family	Plant Parts	Use
Azadirachta indica.A. Juss.	Meliaceae	Leaf	It is used to treat Eczema [11,12]
Cassiatora.L.	Caesalpinoideae	Aerial Parts	It is indicated in the treatment of ring worm, itches, eczema [12].
Neriumindicum.Mill.	Apocynaceae	Leaf	The paste of its leaves are used to treat ring worm [11,12].
Ocimum sanctum.L.	Labiatae	Leaf	The fresh leaves of this plant are bruised and used to apply externally for treating ring worm [12].
Byrsonima Crassifolia	Malpighiaceae	Stem Bark	Dermatophytes can be treated by the decoction of its bark. The tincture of the bark is indicated in case of gram negative and gram positive bacteria [13,14].
Cassia Grandis	Leguminosae	Leaves	A preparation from this plant can be topically applied as an ointment for infections like dermatomucosal and also in ringworm [13]
Cassia Occidentalis	Leguminosae	Leaves	It is indicated in the treatment of ringworm, It is applied topically as an ointment, which is made from its leaves [15].
Diphysa robinioides	Leguminosae	Bark, Leaves	Utilized in traditional medicine for the treatment of ring worm and infections like dermatomucosal infection [13].
Gliricidia sepium	Leguminosae	Root, Bark	It is effective against ringworm and exanthematic infections. It can be consumed orally or can be applied topically [13].
Malpighia glabra L.	Malpighiaceae	Leaves	The leaves and fruits of this plant is used to inhibit the dermatophytes [13].
Rhizophora mangle L	Rhizophoraceae	Bark	Its tincture, that is made from the bark are effective against *C.albicans, C.krusei and C.parapsilosis,* along with minimum inhibitory concentration (MIC) of 40mg per ml [16]. The decoction of its bark has minor activity against *M.canis, M. gypseumand T. mentagrophytes*, along with minimum inhibitory concentration(MIC)of 600mg per ml and contains fungistatic activity [13,16].

Table2: Specification of Plant Species and their Uses.

The specifications of plants that exhibit anti-fungal activity against specific causative organisms are listed in Table 3.

Plant	Part of Plant Used	Anti-Fungal Activity against Different Fungi
Azadirachta indica. A. Juss.	Leaves	Active against *Pestalotiopsis theae, Colletotrichum camelliae, Curvularia eragrostridis,* and *Botryodiplodia theobrome* [11,20].
Ocimum sanctum. L.	Aerial Parts	Active against *Pestalotiopsis theae, Colletotrichum camelliae, Curvularia eragrostridis.* , and *Botryodiplodia theobrome* [12].
Nerium indicum. Mill.	Leaves	Active against *Pestalotiopsis theae, Colletotrichum camelliae, Curvularia eragrostridis,* and *Botryodiplodia theobrome* [11].
Cassia tora.L	Leaves	Active against *Pestalotiopsis theae, Colletotrichum camelliae, Curvularia eragrostridis,* and *Botryodiplodia theobrome* [12].
Byrsonima crassifolia	Stem Bark	Active against *C. albicans, C. krusei, C. parapsilosis* and *C. stellatoidea* [14]
Cassia grandis	Leaves	Active against *E. ji'occosum, M. gypseum, Trichophyton mentagrophytes* and *T. rubrum* [17].
Cassia Occidentalis	Leaves	Active against *E. jlocossum, M. gypseum, T. mentagrophytes* and *T. rubrum* [17].
Diphysa robinioides	Leaves	Active against *E. jloccosum, T. mentagrophytes* and *T. rubrum* [16].
Gliricidia sepium	Leaves	active against *M. canis* and *T. mentagrophytes* [11].
Malpighia glabra L.	Leaves, Fruit	Active against Epidermophyron floccosum Microsporum canis Trichophyton rubrum [16].
Rhizophora mangle L.	Bark	Active against *C. albicans, C. krusei* and *C. parapsilosis* and has little activity against *M. canis, M. gypseum* and *T. mentagrophytes* [16]

Table 3: Specifications of Plants Exhibiting Anti-Fungal Activity against Specific Fungus.

The mechanisms of action of some of the plants that exhibit antifungal activity are listed below in Table 4.

Plants	Mechanism of Action
Azadirachta indica. A. Juss.	It works through inhibitory effect on potentiality of breakdown of the cell wall [19].
Cassiatora.L.	They bind to free proteins or to the glycoprotein on the cuticle of the parasite and as a result cause death [18].
Ocimum sanctum.L	The mode of action of Ocimum sanctum has not yet been altogether researched [18]. The chemical constituent examines have distinguished the ocimumosides and cerebrosides dynamic in the antistress impacts [18]. A portion of its immunomodulatory impacts include γ-aminobutyric acid pathways [18].
Cassia grandis	The mechanism is correlated with the antioxidant effect and with the inhibition of α-glycosidase [21,22].

Table 4: Mechanism of Action of Some Specific Plants Exhibiting Anti-Fungal Activity.

Conclusion

It is concluded by this review report that there are many plant species that contains the activity against fungal microorganisms, and as there is no such discovery conducted to overcome the issues related to currently available anti-fungal treatment therefore, Natural products as an antifungals can be used as an cost effective medicines for the treatment of fungal infections and also in case of drug-drug interaction, toxicity, resistance to fungal infections, natural products can be used as an alternative therapy to treat such conditions.

Conflict of Interest

The authors declare no conflict of interest.

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