Chapter

Medicinal Plants Having Antifungal Properties

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Abstract

In the past few decades, a worldwide increase in the incidence of fungal infections has been observed as well as rise in the resistance of some species of fungi to different fungicidal used in medicinal practice. Besides, fungi are the one of the most neglected pathogens as demonstrated by the fact that the amphotericin B and other sold treatments are still used as gold standard as antifungal therapy. The majority of used antifungal treatments have various drawbacks in terms of toxicity, efficacy as well as cost and their frequent use has also led to the emergence of resistant strains. Hence, there is a great demand for developing an antifungal belonging to a wide range of structural classes, selectively acting on new targets with least side effects. Natural products, either as pure phytocompounds or as standardized plant extracts, provide unlimited opportunities for new drug lads because of their having normally matchless chemical diversity. Present chapter focused on the work done in the field of antifungal activities of various plant components and novel approaches which will be the future prospective for the new drug discoveries and providing better antifungal therapy.

Keywords: antifungal, phytocompounds, fungicidal, antifungal therapy, fungal infections

1. Introduction to fungal disease

Fungal infections are one of the most deadly infections accounting in excess of 1.5 million deaths annually worldwide. The major reason that makes fungal infections more life threatening because they are been neglected by the society. Though in last 20 years there are many developments in the diagnosis and treatment of fungal disease but still majority of population are devoid of the benefits of these developments [1]. Among all the fungal diseases, infection of skin hold the 4th position and it accounts for the majority of death also [2].

Plant kingdom has always been a hub for many natural compounds with novel structure and this keep the investigators interested in doing research about many plants species till today. Results of new researchers showed that plants are enrich of many bioactive secondary metabolites such as saponins, alkaloids and terpenoids which characterized by antifungal property. Depending on that, these plants can be considered as a potent future source for anti-fungal drugs [3]. When recent scenario regarding fungal diseases and antifungal drugs are taken into consideration it

has been seen that the development of resistance of fungus towards the presently used antifungal drugs has increased [4–11]. With the challenges like morbidity and mortality there always lies difficulty in antifungal treatment for patients receiving therapy for AIDS, diabetes, chemotherapy or organ transplant as some of the molecular processes of fungus are similar to humans, so toxicity to fungal cells could affect human cells too [12]. In the last 30 years few drugs have made an impact in the treatment of fungal infection as shown in (**Table 1**), one of them is amphotericin B which is among the few fungicidal drugs present antifungal therapy has but it also showed several critical side effects (**Table 2**) [13]. In addition to this, during the period between late of 1980s and the beginning of 1990s emergence of Imidazoles and Triazoles was seen. These classes of drugs were efficient in inhibiting processes associated with fungal cells. The major drawback associated with them was relapse of infection and resistance developed by the fungus towards them [14]. Therefore, it become an oblige for the research to discover and produce a new, efficient, and safe anti-fungal treatments from new sources like plants. Therefore current chapter attempts to elaborate the current scenario about the important plants and their antifungal derivatives that can be future prospective to work on for development of more potent antifungal drugs.

There are around 2 million of fungal species found in the whole world but only 600 of them cause infection. The major species that are mostly involved in causing infection are *Cryptococcus*, *Candida, Trichophyton and Aspergillus. All the fungal infections which affects human, that are prevailing in the world can be grouped into five types.* The types are as follows:

1. *Invasive fungal infections*: examples are cryptococcal meningitis, Candida bloodstream infection, invasive aspergillosis, Pneumocystis pneumonia

2. *Chronic lung or deep tissue infection*: under this type example is chronic pulmonary aspergillosis

3. *Allergic fungal disease*: examples are allergic bronchopulmonary aspergillosis also known as ABPA and severe asthma with fungal sensitization (SAFS)

S. No	Class	Drugs	Uses
1.	Azole antifungals	Clotrimazole, Econazole, Isoconazole, Miconazole, Ketoconazole, Itraconazole	Topical fungal infections, Candidiasis, aspergillus and candida infections, vaginal yeast infections
2.	Echinocandins	Caspofungin, Micafungin	Esophageal 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

Table 1.
The synthetic drugs available in market for treatment of fungal diseases are – [15].

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.	Anemia	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-colored stools, jaundice	Anidulafungin C, Micafungin

Table 2.
Adverse side effects of different antifungals.

4. *Mucosal infection*: oral and esophageal candidiasis, Candida vaginitis are examples of this group.

5. *Skin, hair and nail infection*: examples of this kind of infections are athlete's foot tinea capitis and onychomycosis [16].

2. Plants having antifungal activity

The epidemiological data suggest that the incidence and prevalence of serious mycoses continues to be a public health problem. The increased use of antifungal agents has resulted in the development of resistance to these drugs. The spread of multidrug-resistant strains of fungus and the reduced number of drugs available make it necessary to discover new classes of antifungals from natural products

S. No.	Botanical name	Family	Parts used	Chemical classes	Microorganism tested
1.	*Eugenia uniflora*	Myrtaceae	Leaves	Sesquiterpenes, Monoterpene, hydrocarbons	*C. albicans, C. dubliniensis, C. glabrata, C. krusei* [17]
2.	*Psidium guajava*	Myrtaceae	Leaves	Methanolic extract	*C. albicans, C. dubliniensis, C. glabrata, C. krusei* [17]
3.	*Curcuma longa*	Zingiberaceae	Rhizome	Turmeric oil	*C. albicans, C. dubliniensis, C. glabrata, C. krusei* [17]
4.	*Piptadenia colubrina*	Mimosaceae	Stem bark	—	*C. albicans, C. dubliniensis, C. glabrata* [17]
5.	*Schinus terebinthifolius*	Anacardiaceae	Stem bark	Extract	*C. albicans, C. dubliniensis* [17]

S. No.	Botanical name	Family	Parts used	Chemical classes	Microorganism tested
6.	*Persea americana*	Lauraceae	Leaves	Chromene	*C. albicans C. dubliniensis C. glabrata, C. krusei* [17]
7.	*Parapiptadenia rigida*	Fabaceae	Stem bark	Pyrrolidine amide	*C. albicans* [17]
8.	*Ajania fruticulosa*	Asteraceae	Fruits	Guaianolides	*Candida albicans, C. glabrata A. fumigatus* [17]
9.	*Alibertia macrophylla*	Rubiaceae	Leaves	Extract	*Cladosporium sphaerospermum; C. cladosporioides; A. niger; Colletotrichum gloeosporioides* [17]
10.	*Aniba panurensis*	Lauraceae	Whole plant	—	*C. albicans* [17]
11.	*Aquilegia vulgaris*	Ranunculaceae	Leaves and stems	Bis (benzyl)	*A. niger* [17]
12.	*Mimosa tenuiflora*	Mimosaceae	Stem bark	Sesquiterpene lactone	*C. albicans, C. dubliniensis, C. glabrata, C. krusei* [17]
13.	*P. regnellii*	Piperaceae	Leaves	Extract	*Trichophyton rubrum, Trichophyton mentagrophytes, Microsporum canis* [18]
14.	*Rubia tinctorum*	Rubiaceae	Root	Triterpene	*A. niger, Alternaria alternaria, P. verrucosum, Mucor mucedo* [19]
15.	*Tithonia diversifolia*	Asteraceae	Whole plant	Contained saponins, Polyphenols	*Microbotryum violaceum, Chlorella fusca* [20]
16.	*Vernonanthura tweedieana*	Asteraceae	Root	Extracts	*T. mentagrophytes* [21]
17.	*Zingiber officinale*	Zingiberaceae	Rhizomes	Steroidal saponin	*P. oryzae* [22]
18.	*Datura metel*	Solanaceae	Whole plant	Diterpenoid, Alkaloids	*C. albicans, C. tropicalis* [23]
19.	*Lupinus albus*	Leguminosae	Leaf surface	—	*T. mentagrophytes* [24]
20.	*Ecballium elaterium*	Cucurbitaceae	Fruit	Extract	*Boitylis cinerea* [25]
21.	*Cassia tora*	Leguminosae	Seeds	Anthraquinone	*Botrytis cinerea, Erysiphe graminis, Phytophthora infestans, Puccinia recondita, Pyricularia grisea* [26]
22.	*Chamaecyparis pisifera*	Cupressaceae	Leaves and Twigs	Isoflavone	*P. oryzae* [27]
23.	*Prunus yedoensis*	Rosaceae	Leaves	Diterpenes	*C. herbarum* [28]

Table 3.
List of plants having antifungal activity against pathogenic fungi.

including medicinal plants. Medicinal plants have also been reported in traditional systems of medicine for the treatment of both human and animal mycoses, and are considered to be a valuable source for the discovery of new antifungal drugs. Many books have also reported and recorded the use of medicinal plants in the traditional system of medicine. Therefore, we have focused here mainly on the antifungal plants and their use against pathogenic fungi. The antifungal activity associated plants are illustrated in (**Table 3**).

3. Phytochemicals and their antifungal activity

Plants and their biologically active chemical constituents, sometimes called secondary metabolites or bioactives, present numerous opportunities for the improvement of livestock production by inclusion in the diet. Several papers and reviews have been published on the occurrence of antifungal compounds in plant. However, literature and systematic reviews on the natural products as an alternative to antifungal drugs are still scanty. The distribution of antifungal compounds can be defined either on the basis of their taxonomic distribution or on the basis of their chemical classes. **Table 4** shows the antifungal natural products belonging to

S. No	Plants	Plant part	Phytochemicals
1	*Aegle marmelos*	Leaves	Essential oils
2	*Alpinia galangal*	Seeds	Diterpenes
3	*Ananas comosus*	Leaves	Protein
4	*Blumea balsamifera*	Leaves	Flavonoid luteolin
5	*Camptotheca acuminate*	Leaves	Flavonoid
6	*Capsicum frutescens*	Whole plant	Triterpene saponin
7	*Cassia tora*	Whole plant	Emodin, physcion and rhein
8	*Datura metel*	Whole plant	Alkaloid
9	*Euonymus europaeus*	Leaves	Protein
10	*Haloxylon salicornium*	Aerial part	Alkaloid
11	*Juniperus communis*	Leaves	Essential oil
12	*Khaya ivorensis*	Stem bark	Triterpenes
13	*Lycium chinense*	Root bark	Phenolic compounds
14	*Musa acuminate*	Banana	Protein
15	*Ocimum gratissimum*	Bark	Essential oil
16	*Pinus pinaster*	Leaves	Pinosylvin
17	*Polygonum punctatum*	Whole plant	Sesquiterpene
18	*Smilax medica*	Root	Saponins
19	*Solanum tuberosum*	Tubers	Protein
20	*Thymus vulgaris*	Whole plant	Essential oil
21	*Trachyspermum ammi*	Leaves, flowers	Essential oil
22	*Trigonella graecum*	Whole plants	Peptides
23	*Zingiber officinalis*	Rhizome	Protein

Table 4.
List of plant components having antifungal property [29].

all major classes of secondary metabolites such as phenolics, alkaloids, terpenoids, saponins, flavonoids, proteins, and peptides, etc.

4. Novel approaches for antifungal plant components and their extracts

Novel drug delivery system has shown tremendous potential to deliver herbal drugs in the form of microcapsules, implants, nanoparticles micro particles sustained release tablets or extended release forms. Many herbal drugs using novel drug delivery system has made a mark in the market and few of them are in the developmental stage in the laboratory [30].

Active herbal components such as curcumin, digoxin, atropine, bromelain can be promising prospects for treatment of conditions like cancer or inflammation [31].

The popularity experienced by novel drug delivery system is due to its ability to deliver the herbal drugs in a better way providing enhanced therapeutic efficacy with lower toxicity [32]. In addition to this it also counteract the limitations of lower absorption and lack of specificity experienced by the available formulation of drugs. Advantages of novel drug delivery system over the presently available drug therapy is that it is specific, has rapid onset of action with faster absorption due to enhanced surface area and lastly nanoparticles provides better penetration in Blood Brain Barrier (BBB) [33].

For any herbal drugs to show expected therapeutic efficacy optimum amount of active constituent must reach the target tissues. Herbal drugs are prone to be degraded by first pass metabolism of by the pH difference of GIT. Various novel drug delivery systems such as nanoparticles, nanoemulsions, phytosomes, transferosomes and liposomes by passes all the hurdles of acidic pH as well as first pass metabolism to carry optimum amount of drugs to target tissues. Being smaller in size nano carriers also provides rapid onset of actions [34].

For delivery of drug by using novel drug delivery system, herbal drugs present themselves as potential candidate because of following reasons:

- The side effects that are seen with other drugs are absent with natural compounds.
- Natural compounds shows synergistic effect when they contain multifunctional molecules.
- Natural compounds have traditional backing for their action and safety potential whereas modern medicines are more toxic even if they are experimentally proven for their action [35].

4.1 Novel carrier systems used to treat different fungal infections

The major benefit provided by novel drug delivery system is to elicit better therapeutic response with minimum doses. Types of carriers used for herbal drug delivery and synthetic drugs are as follows:

4.1.1 Phytosomes

The name came from two words “Phyto” and “some” which means plant and cell-like respectively. Phytosomes contains lipid soluble complex of phospholipids and phyto-constituents. Some literatures also referred Phytosomes as ribosome [36]. Green tea phytosomes, *Ginkgo biloba* phytosomes, Centella phytosomes,

Meriva phytosome, Zanthalene phytosomes, Sericoside phytosomes are some examples of phytosomes which are recently developed and characterized for different ailments. Among all of them Zanthalene phytosomes are prepared especially for the treatment of fungal disease.

Advantages of Phytosomes

- Phytosomes are not degraded by bacteria or digestive secretion of guts.
- It has better stability because of the formation of bonds chemically connecting phytoconstituents and phosphatidylcholine molecules.
- Phytosomes delivers herbal drug to the respective target tissues [37].
- It shows greater therapeutic benefit due to better absorption of lipid insoluble polar phytoconstituents in turn shows better bioavailability [38].

4.1.2 Liposomes

Liposomes contain microscopic vesicles made up of lipid bilayer arranged in concentric fashion and the separation is filled with aqueous medium. Lipophilic substances are inserted into the lipid bilayer whereas aqueous compartment traps hydrophilic substance. Liposomes show better bioavailability, stability and enhanced pharmacokinetic property [39]. There are various herbal and synthetic liposomes are prepared for the effective treatment of different skin diseases. In 2017, a herbal liposomal gel containing ketoconazole and neem extract was developed for the effective treatment of seborrheic dermatitis against *Aspergillus niger* and *Candida albicans*. The results indicated that developed liposomal gel have great potential and showed synergetic effect for the treatment.

Advantages of liposomes

- Liposome formulation is better options for producing sustained release formulations as it enhances drug solubility.
- It is easy to load phytoconstituents of any chemical nature whether it is hydrophilic, amphiphilic or lipophilic [40].

4.1.3 Nanoparticles

This carrier system has particle size within the range between 1 and 100 nm. The particles which are of nano size are made up of polymer of synthetic or semisynthetic origin. Nanoparticles are microencapsulated to protect them from any kind of losses. Nanoparticles were made to encounter the problem of solubility and toxicity associated with triptolide [41].

Advantages of herbal nanoparticle delivery system:

- Nanoparticles having smaller size shows better dissolution in turn enhances solubility of dosage form and it also delivers drug with specificity thereby enhancing the efficacy [42].

4.1.4 Microemulsions and nanoemulsion

These are emulsions of O/W type and the particle size of the particulate is of micron. In this drug delivery system inner phase stores the drugs and because of its

contact with tissue directly drug release is slow. As per few reports oil of Pterodon emarginatus are considered to have property to enhance anti-inflammatory activity [43]. Formulation, development and evaluation of microemulsion gel of hydroalcoholic extract of *Quercus infectoria* in the treatment of different skin ailments was successfully prepared. Tannins which are prime constituent of galls can be effectively treat different skin conditions.

4.1.5 Microsphere

This drug delivery system have matrix and the drug is dispersed in a polymer which are present inside this matrix. Particle size that can be used is in between 1 and 300 μm. The release of drug is dependent on the dissolution and degradation rate of the said matrix. Release of drug occurs according to first order kinetic. For example, development and evaluation of floating microspheres of curcumin prepared by emulsion solvent diffusion method for treatment of onychomycosis. The result shows improved absorption kinetics of curcumin.

Advantages of microsphere formulations

- The major advantage of this kind of formulation is that it taken orally or parentally and their site of release can also be targeted [44].

4.1.6 Niosomes

Niosomes are similar as liposomes bjt are far more stable than liposomes. Niosomes are made up of surfactant like dialkyl polyglycerol which is noninonic in nature and are able encapsulate variety of drugs. Niosomes are more economical than liposomes [32]. Chitosan niosomal gel, miconazole niosomes are prepared as an effective nanocarrier against both dermatophytes and yeasts.

4.2 Transdermal drug delivery system

In this system of drug delivery, patches encapsulating drugs are prepared and are placed on the skin. Through the skin drug enters into the blood vessels. This system is beneficial when the required effect of oral therapy was not found to be up to the mark. Patches of antismoking and anti-motion sickness are available in market [45].

Advantages of transdermal drug delivery

- The transdermal delivery system has advantages such as it provides enhanced bioavailability and provides a better alternative of dosage form for unconscious or vomiting patients [46].

4.2.1 Ethosomes

Ethosomes are composed of phospholipids and ethanol and are in the form of sac. Ethanol present in ethosomes acts as permeability enhancer. Ethosomes are found in the form of cream and gel for better patient compliance [47]. Now a days, Transethosomes and Nanoethosomes used most widely which are the advanced type of ethosomes having edge activator in it. These advanced novel carrier system is much better than conventional novel carriers like transferosomes and liposomes [48]. Clotrimazole, Itraconazole, Miconazole are synthetic drugs which are prepared and evaluated successfully for the treatment of

dermatophytosis or ringworm. *Tridax procumbens* and *Galinsoga parvifolia* are two herbs used into ethosomal gel against Trichophyton species.

Advantages of Ethosome

- Ethosomes can entrap all type of drugs and have better skin permeability [46].

4.2.2 Transferosomes

Transferosomes contains phospholipids sac which behaves as carrier for delivery of drug through the skin. As Transferosomes are flexible in nature they cross the skin through the intracellular space found within the skin. Transferosomes of Colchicines shows lesser side effect than its oral form [49].

Advantages of Transferosomes:

- Transferosomes being flexible can pass through narrow openings of skin.
- It shows high efficiency of entrapment which may increase up to 90% in case of lipophilic drug [50].

4.2.2.1 Complexation

The problem associated with herbal drug formulation is their solubility. To counter this solubility problem, complex formation is done which gives particulates with well-defined stoichiometry. Few commonly used complexing agents are EDTA and cyclodextrin [51].

Drugs/Plant components	**Novel carriers**	**Indication**	**Microorganism tested**
Essential oil (*Bidens tripartite*)	Microemulsion gel	Candidiasis	*Candida albicans*
Curcumin	Phytosome	Onychomycosis	Yeast sp.
Clotrimazole, Econazole nitrate, Fluconazole	Micelles	Superficial fungal infection	*Trichophyton* sp.
Miconazole	Solid lipid nanoparticles and nanostructured lipid carriers	Candidiasis	*Candida albicans*
Fluconazole, Ketoconazole, Itraconazole, Voriconazole, Econazole	Microemulsion	*Tinea corporis, Tinea circinata, Tinea pedis*	*Candida albicans*
Amphotericin B	Microemulsion	Invasive fungal infection	*Trichophyton rubrum*
Griseofulvin	Microemulsion gel	Dermatophytosis	*Trichophyton* sp.
Terbinafine Hcl	Niosomes	Fungal infection	*Aspergillus niger*
Griseofulvin, Amphotericin B	Transferosomes	Dermatophytosis	*Trichophyton rubrum*
Clotrimazole, Econazole	Ethosomes	Localized skin fungal infection	*Candida* sp.

Table 5.
List of some novel carriers for antifungal plant components and synthetic drugs [55].

4.2.2.2 Hydrogels

The hydrogel are three dimensional structures with cross linking of polymers. As name suggest hydrogels are hydrophilic in nature. Hydrogels can be designed into different forms according to the needs. The form can be of slabs, films and nanoparticle coating [52]. Hydrogels have the potential to bind both herbal as well as synthetic drug, this ability can be treated as avenue for further research [53]. There are many marketed formulation of novel drug delivery available in the market [46, 54] Here are list of some novel carriers used with their plant components or synthetic drugs combinations for different fungal infections (**Table 5**).

5. Conclusion

The last 20 years has shown an increase in number of fungal infection. Currently used drugs in treatment of fungal infection are having many side effects, and development of resistance is very common against these drugs. Plants have been considered as traditional source of antifungal medicines for past many years. Plant bioactive with antifungal activity can be considered as an option for development of new and improved alternative formulations in antifungal therapy. Development of improved formulations with plant phytcompounds is the need of the hour for efficient treatment of fungal diseases. Further research on this field can provide us with increased number of options in treatment of fungal diseases that will give the patients with a better quality of life.

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