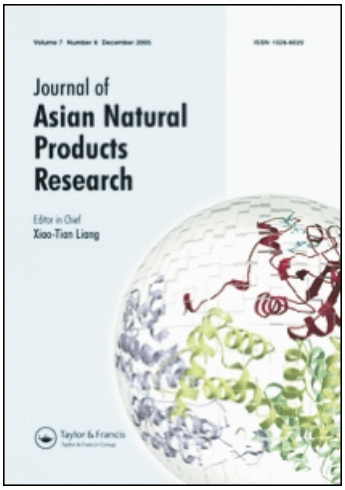

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Natural products – antifungal agents derived from plants

Tasleem Arif [a], J.D. Bhosale[a], Naresh Kumar[a], T.K. Mandal[a], R.S. Bendre[b], G.S. Lavekar[a] and Rajesh Dabur[a]*

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A new spectrum of human fungal infections is increasing due to increased cancer, AIDS, and immunocompromised patients. The increased use of antifungal agents also resulted in the development of resistance to the present drugs. It makes necessary to discover new classes of antifungal compounds to cure fungal infections. Plants are rich source of bioactive secondary metabolites of wide variety such as tannins, terpenoids, saponins, alkaloids, flavonoids, and other compounds, reported to have *in vitro* antifungal properties. Since the plant kingdom provides a useful source of lead compounds of novel structure, a wide-scale investigation of species from the tropics has been considered. Therefore, the research on natural products and compounds derived from natural products has accelerated in recent years due to their importance in drug discovery. A series of molecules with antifungal activity against different strains of fungus have been found in plants, which are of great importance to humans. These molecules may be used directly or considered as a precursor for developing better molecules. This review attempts to summarize the current status of important antifungal compounds from plants.

Keywords: antifungal; tannins; saponins; alkaloids; flavonoids; bioactive metabolites

1. Introduction

The prevalence of resistance to antifungal agents significantly increased in the past decade. Resistance to antifungal agents has important implications for morbidity, mortality, and healthcare in the community. Humans and fungi share some of the same molecular processes; therefore, there is always the risk that what is toxic to the fungal cells will be toxic to the host cells. Patients with AIDS, organ transplant patients, patients receiving chemotherapy, and diabetes patients represent current medical challenges [1]. The drugs currently available to treat fungal infections have serious drawbacks such as the development of fungal resistance and toxic side effects. The broad-spectrum drug amphotericin B was the sole drug for nearly 30 years, and it is one of the few drugs that actually kill fungal cells, but can cause significant nephrotoxicity in the patients. The imidazoles and the triazoles in late 1980s and early 1990s, respectively, were major advances which act by inhibiting processes of the fungal cell, but they have been found to result in recurrence of the infection and the development of resistance to the drug [2]. Therefore, there is need to search new,

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safer, and more potent agents to combat serious fungal infections.

There is already a rich history of research that has been carried out to verify folk medicine practices. Medicinal plants have been a source of wide variety of biologically active compounds for many centuries and used extensively as crude material or as pure compounds for treating various disease conditions. Relatively 1–10% of plants are used by humans out of the estimated 250,000–500,000 species of plants on earth [3]. The chemical diversity of natural products is complementary to the diversity found in synthetic libraries. However, natural products are sterically more complex and have greater ring system diversity because of the long evolutionary selection process. Therefore, strategies to exploit the natural sources and to develop methodologies for the preparation of natural product like libraries through the diversification of natural product mixtures by combinatorial biosynthesis and related techniques are possible. Mainstream medicine is increasingly receptive to the use of antimicrobial and other drugs derived from plants, as traditional antibiotics become ineffective [4]. A number of compounds isolated from plants such as dimethyl pyrrole, hydroxydihydrocornin-aglycones, indole derivatives, etc., are reported to have antifungal activities [5]. However, development of useful antifungal drugs from these compounds has not yet been possible. This review is an attempt to cover important antifungal compounds isolated from higher plants.

2. Major groups of antifungal compounds from plants

Plants have an almost limitless ability to synthesize aromatic substances of different functional groups, most of which are phenols or their oxygen-substituted derivatives. Maximum compounds are secondary metabolites, of which more than 13,000 have been isolated that is less than 10% of the total. In many cases, these substances serve as plant defense mechanisms against predation by microorganisms, insects, and herbivores. Some plants used for their odors (terpenoids), pigment (quinones and tannins), and flavor (terpenoid capsaicin from chili peppers) were found to be endowed with medicinal properties. Some of the herbs and spices used by humans as season food yield useful medicinal compounds.

2.1 Phenols

In recent years, a number of studies have been reported on the antifungal activity of phenolic compounds from natural sources (Figure 1). The site(s) and number of hydroxyl groups on the phenol group are thought to be related to their relative toxicity to microorganisms, with evidence that increased hydroxylation results in increased toxicity. The mechanisms thought to be responsible for phenolic toxicity to microorganisms include enzyme inhibition by the oxidized compounds, possibly through reaction with sulfhydryl groups or through more nonspecific interactions with the proteins. Another studies on mechanism of action of the diterpenic and phenolic compounds isolated from *Euphorbia* species showed

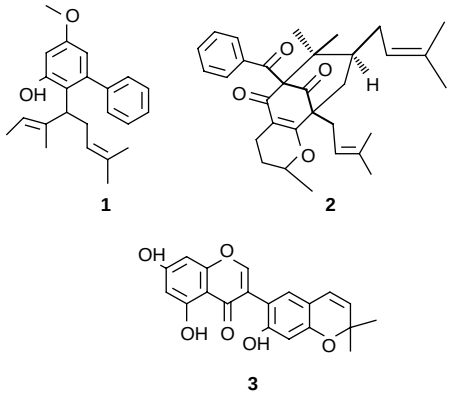


Figure 1. Structures of phenols **1–3**.

that these compounds modulate to a different extent azole antifungal resistance mediated by Pdr5p, Snq2p, and Cdr1p [6].

Tannins and salicylic acid are polyphenol compounds extracted from *Gaullher procumbens*, *Rhammus purshiand*, and *Anacardum pulsatilla* showed antifungal activity [5]. Geranylated biphenyl derivative 3-hydroxy-4-geranyl-5-methoxybiphenyl (**1**) from the green fruits of *Garcinia mangostana* has strong antifungal and a number of other biological activities [7]. A novel polyisoprenylated benzophenone (**2**) from an ethanol extract of *Cuban propolis* showed significant antimicrobial and antifungal activities against a variety of bacteria and yeasts [8]. 4-Hydroxyphenyl-6-*O*-[(3*R*)-3,4-dihydroxy-2-methylenebutanoyl]-D-glucopyranoside isolated from foliage of *Toronia toru* was the main antimicrobial component of the crude extract [9]. Some of the prenylindoles isolated from *Monodora angolensis* and *Isolona cauliflora* had antifungal and antimalarial activities [10]. Eriosemaones A–D (**3**; MIC = 20 μg/ml) are reported to have good antifungal activities [11].

2.2 Flavonoids

Flavones (Figure 2(A) and (B)) are phenolic structures containing one carbonyl group and the addition of a 3-hydroxyl group yields a flavonol. Amentoflavone (**4**) from *Selaginella tamariscina* exhibited potent antifungal activity (IC_{50} value of 18.3 μg/ml) against several pathogenic fungal strains and has a very low hemolytic effect on human erythrocytes [12].

The four compounds eupomatenoid-3, eupomatenoid-5 (**5**), conocarpan (**6**), and orientin (**7**), from *Piper solmsianum* exhibited antifungal action against all the dermatophytes tested, with MIC values in the range of 2.0–60.0 μg/ml and with a potency as high as the standard antifungal drug ketoconazole [13]. A flavonoid from rhizome of *Alpinia officinarum* had strong antifungal activity against variety of pathogenic fungi and MIC was reported to up to 3.0 μg/ml [14]. Isopiscerythrone (**8**), allolicoisoflavone A (**9**), piscisoflavones A (**10**) and B (**11**) [15], and quercetin-3,7-dimethyl ether [16] from different plants were reported to be endowed with antifungal activity.

Inula viscose is currently used as a popular medicine for its therapeutic effects. Flavonoids, azulenes, sesquiterpenes, and essential oils of the plant were proved to have a significant antifungal activity against dermatophytes even at low concentrations (10 μg/ml). The high concentrations of the sesquiterpene (carboxyeudesmadiene), occurring in the leaf extracts, may explain its greater antifungal activity [17].

An isoflavan, 2-hydroxy maackiain from the root extract of *Hildegardia barteri* was observed to have antifungal activity [18]. Flavonoid derivatives, scandenone, tiliroside, quercetin-3,7-*O*-α-L-dirhamnoside (**12**), and kaempferol-3,7-*O*-α-L-dirhamnoside (**13**), were reported to have antifungal activities against *C. albicans* at 1.0 μg/ml as potent as ketoconazole [19]. The flavones hispidulin and belamcanidin from *Artemisia giraldii* were shown to inhibit the growth of the broad range of human pathogenic fungi [20]. In addition, 3-*O*-(1″,8″,14″-trimethylhexadecanyl)naringenin [21] was reported to be endowed with antifungal properties.

2.3 Coumarins

Coumarins have been reported to stimulate macrophages which could have an indirect negative effect on infections. Coumarins are phenolic substances made of fused benzene and α-pyrone rings (Figure 3). Their fame has come mainly from their antithrombotic, anti-inflammatory, and vasodilatory activities and their use to prevent recurrences of cold sores caused by HSV-1 in humans [22].

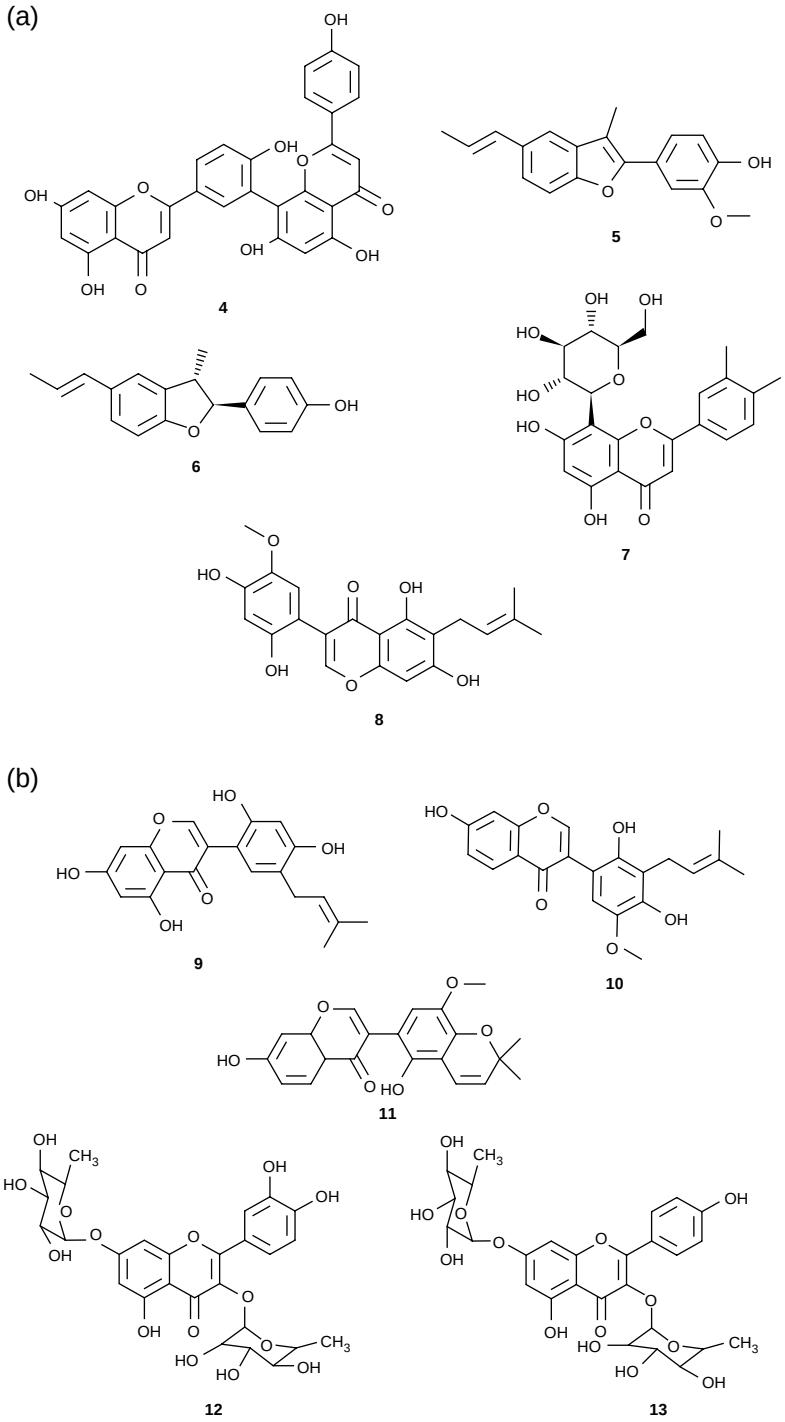


Figure 2. (a) Structures of flavonoids **4**–**8**. (b) Structures of flavonoids **9**–**13**.

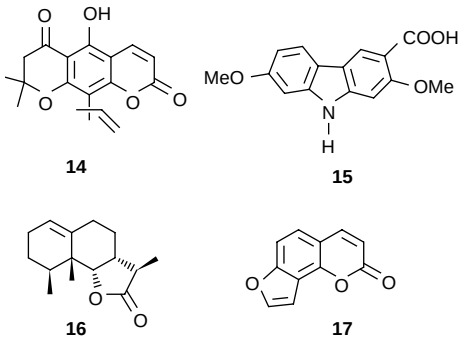


Figure 3. Structures of coumarins **14–17**.

Clausenidin (**14**), dentatin, nor-dentatin, and carbazole derivatives, and clauszoline J (**15**) isolated from *Clausena excavata* showed antimycotic activity (MIC = 50 μg/ml). *O*-Methylated clausenidin (MIC = 50 μg/ml), a synthetic coumarin, also exhibited moderate antimycotic activity [23]. A bioactive eremophilanolide (**16**), 1-tigloyloxy-8βH,10βH-eremophil-7(11)-en-8α,12-olide isolated from *Senecio poepigii* showed antifungal properties [24]. A prenylated coumarin was isolated from the dichloromethane leaf extract of *Baccharis pedunculata* and identified to be responsible for the antifungal activity against some human pathogenic fungi [25].

Angelicin (**17**), a naturally occurring furanocoumarin, showed antifungal activity LD_{50} 2.0 μg/ml. Synthetic coumarins and angelicin derivatives were also reported to be active against *C. albicans*, *C. neoformans*, *S. cerevisiae*, and *A. niger*. Simultaneously, angelicin and several potent antifungals were reported to be nontoxic [26]. An antifungal dihydrofuranocoumarin, 2′(*S*),3′(*R*)-2′-acetoxyisopropyl-3′-acetoxy-2′,3′-dihydroangelicin, was reported from the aerial parts of *Tordylium apulum* [27]. A coumarin along with two new phenolic glycosides from the stem bark of *Amburana cearensis* was found to be endowed with *in vitro* antifungal and antibacterial activities [28].

Fsafetida foetida yields prenylated coumarins exhibiting strong antifungal activity against the dermatophytes, 5,8-dihydroxyumbelliprenin being most active with MIC of 10 mM [29]. Data about the antifungal properties of coumarins are limited but many reports give reason to believe in the utility of these phytochemicals [30].

2.4 Quinones

Quinones (Figure 4) are aromatic rings with two ketone substitutions and characteristically highly reactive. They can switch between diphenol and diketone easily through oxidation and reduction reactions. These compounds, being

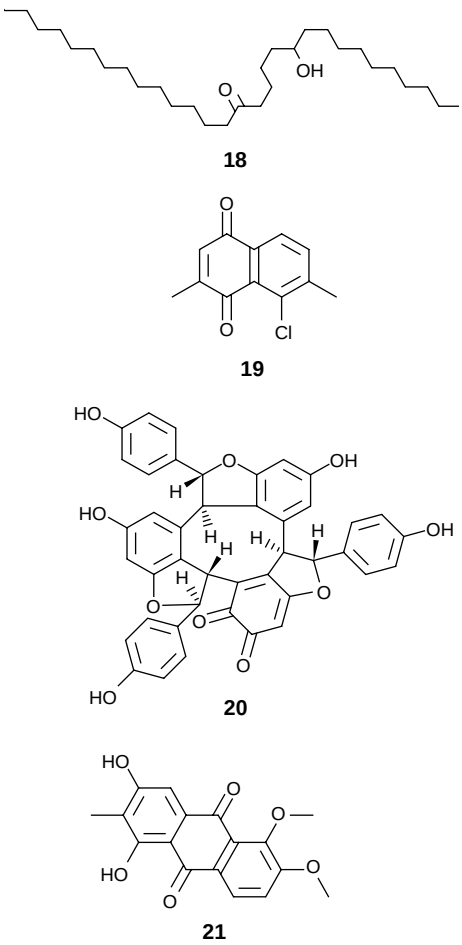


Figure 4. Structures of quinines **18–21**.

colored, are responsible for the browning reaction in cut or injured fruits and vegetables. In addition to providing a source of stable free radicals, quinones are known to complex irreversibly with nucleophilic amino acids in proteins. Therefore, the quinones inactivate the protein and impair their function. Quinones bind with surface-exposed adhesins, cell wall polypeptides, membrane-bound enzymes, and form complex which inactivate the enzymes.

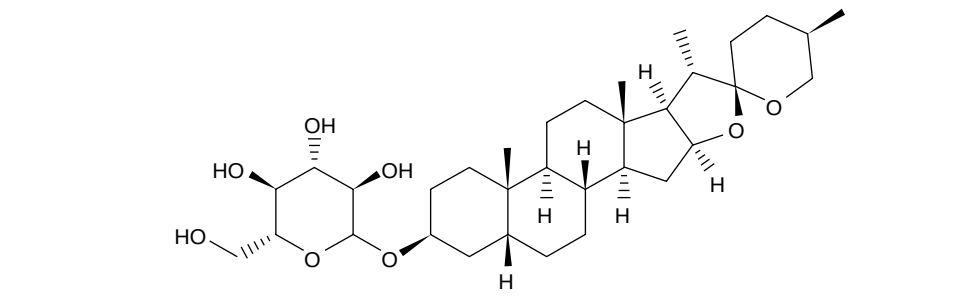
In the anthraquinone group, there are only a few reports concerning their antifungal activity. The naphthoquinones kigelinone, isopinnatal, dihydro-α-lapachone, and lapachol from *Kigelia pinnata* were reported for antifungal activity [31]. A compound, 11-hydroxy-16-hentriacontanone (**18**), isolated from *Annona squamosa* was reported for its antifungal potential [32]. A study of the antimicrobial compounds from *Moneses uniflora* resulted in the isolation of a 8-chloro-2,7-dimethyl-1,4-naphthoquinone (8-chlorochimaphilin) (**19**), together with chimaphilin and 3-hydroxychimaphilin as the antimicrobial components [33]. Hopeanolin (**20**), an unusual resveratral trimer with an *o*-quinone nucleus, from the stem bark of *Hopea exalata* demonstrated antifungal activity in the MIC value range of 0.1–22.5 μg/ml [34]. 2,6-Dimethoxy-*p*-benzoquinone (MIC = 50 μg/ml) from the heartwood of *Rhizophora apiculata* exhibited activity against fungi [35]. Example of antifungal anthraquinone from medicinal species includes a new 1,3-dihydroxy-2-methyl-5,6-dimethoxyanthraquinone (**21**) from the roots of *Prismatomeris fragrans* [36].

2.5 Saponins

Saponins are secondary metabolites that occur in a wide range of plant species (Figure 5). They are stored in plant cells as inactive precursors but are readily converted into biologically active antibiotics by enzymes in response to pathogen attack. Saponins are glycosylated compounds widely distributed in the plant kingdom and can be divided into three major groups; a triterpenoid, a steroid, or a steroidal glycoalkaloid. Saponins appear to act by disrupting the membrane integrity of fungal cells.

Spirostanol steroidal saponins were isolated from the roots of *Smilax medica*, together with the smilagenin 3-*O*-β-D-glucopyranoside (**22**) and disporoside A exhibited antifungal activity against the human pathogenic yeasts *C. albicans*, *C. glabrata*, and *C. tropicalis* with MIC value in the range of 6.25–50 μg/ml [37]. Two new steroidal saponins isolated from the roots of *Smilax aspera* subsp. mauritanica exhibited antifungal activity against the human pathogenic yeasts, *Candida albicans*, *C. glabrata*, and *C. tropicalis* in the range of 25–50 μg/ml [38]. Phytolaccosides B (**23**) and E from *Phytolacca tetramera* showed antifungal activities against a panel of human pathogenic opportunistic fungi [39]. Tigogenin-3-*O*-β-D-xylopyranosyl-(1 → 2)-[β-D-xylopyranosyl-(1 → 3)]-β-D-glucopyranosyl-(1 → 4)-[α-L-rhamnopyranosyl-(1 → 2)]-β-D-galactopyranoside was found to have *in vivo* activity in *C. albicans* vaginal infection model. Another saponin from same plant, tigogenin-3-*O*-β-D-glucopyranosyl-(1 → 2)-[β-D-xylopyranosyl-(1 → 3)]-β-D-glucopyranosyl-(1 → 4)-β-D-galactopyranoside was found to be *in vitro* very effective against several pathogenic *Candida* species (MIC_{80} = 4.4–9.4 μg/ml) and *C. neoformans* (MIC_{80} = 10.7–18.7 μg/ml) [40].

Recently, steroidal saponins ypsilandroside B, ypsilandroside A, isoypsilandroside A, isoypsilandroside B, and isoypsilandrogaine isolated from *Ypsilandra thebetica* were reported for antimicrobial activities [41]. Eight saponins from *Tribulus terrestris* were reported, out of which two compounds showed promised antifungal activity against fluconazole-



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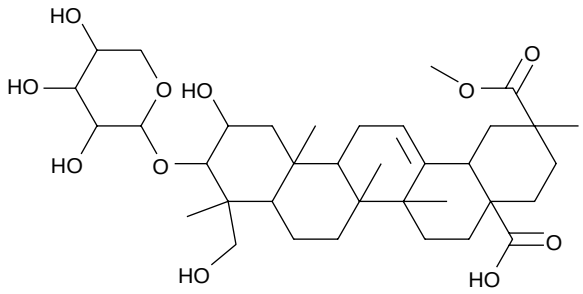

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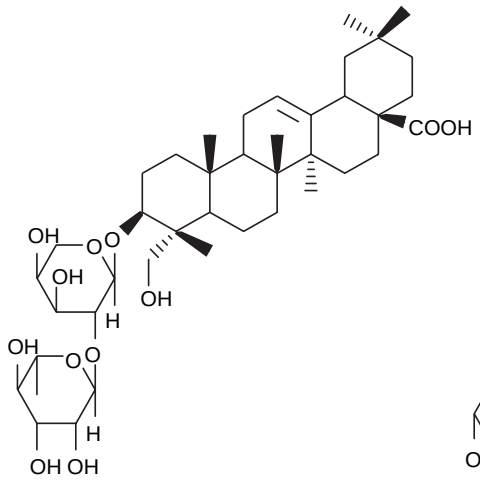

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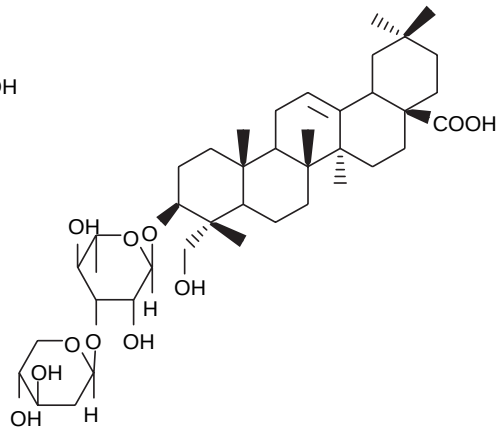

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Figure 5. Structures of saponins **22–25**.

resistant *Candida* strains ($MIC_{80} = 4.4$ μg/ml), *C. neoformans* ($MIC_{80} = 10.7$ μg/ml), and *C. krusei* ($MIC_{80} = 8.8$ μg/ml) [40]. Saponins from *Solanum chrysotrichum* showed promising activity having low MIC 12.5 μg/ml against several fungal pathogens [42]. Three spirostanol saponins designated sansevierin A, sansevistatin 1, and sansevistatin 2 and three steroidal saponins isolated from the *Sansevieria ehrenbergii* exhibited antimicrobial activity, particularly against the pathogenic fungi *C. albicans* and *C. neoformans* [43]. Kalopanaxsaponins A (**24**) and I (**25**)

showed antifungal activity against *C. albicans* and *C. neoformans* at a concentration of (MIC) 25 μg/ml [44]. Spirostanol saponin (25*R*),5α-spirostan-3β,6β-diol 3-*O*-{β-D-glucopyranosyl-(1 → 2)-*O*-[β-D-xylopyranosyl-(1 → 3)]-*O*-β-D-glucopyranosyl-(1 → 4)-β-D-galactopyranoside} from the flower of *Allium leucanthum* was reported to have antifungal activity with a MCF ranging from 6.25 to 12.5 μg/ml on the most yeast stains tested [45].

Several saponins from *A. suberi* were reported to have considerable MIC values ranging from 25 to 50 μg/ml [46]. Saponins from *Medicago sativa*, *M. murex*, *M. Arabica*, and *M. hybrida* were reported to be active against three dermatophytic fungi *Microsporum gypseum*, *T. interdigitale*, and *T. tonsurans* (MIC < 0.09 mg) [47].

2.6 Xanthones

Xanthones are a restricted group of plant polyphenols, biosynthetically related to the flavonoids. These are planar-six carbon molecules in a conjugated ring system consisting of a backbone molecule and various chemical groups attached to it. Xanthone backbone consists of two benzene rings attached through a carbonyl group and oxygen not allowing free rotation about the carbon—carbon bonds. The unique backbone along with type and position of the attached chemical groups defines specific properties of xanthones. Xanthones possess numerous bioactive capability including antifungal properties (Figure 6).

Caledonixanthone E (**26**) isolated from the stem bark of *Calophyllum caledonicum* was reported for strong antifungal activity ($MIC_{80} = 8$ μg/ml) [48]. Isoprenylated xanthones, toxyloxanthone C (**27**), and wighteone (**28**) showed antifungal activity against *C. albicans* with MIC values of 25 and 12.5 μg/ml, respectively [49]. The dichloromethane extract of *Securidaca longepedunculata* yielded 1,7-dihydroxy-4-methoxyxanthone (**29**) which exhibited antibacterial activity against *Staphylococcus aureus* and antifungal activity against *A. niger*, *A. fumigatus*, and a *Penicillum* species [50].

1,3,6-Trihydroxy-2,5-dimethoxyxanthone (**30**) isolated from the aerial part of *Monnina obtusifolia* was reported to have antifungal potential [51]. Seven xanthanolides from *Xanthium macrocarpum* were reported to be effective against *C. albicans*, *C. glabrata*, and *A. fumigatus* [52]. Two new 2-hydroxy-3-methylbut-3-enyl-substituted xanthones, (±)-caledol and (±)-dicaledol, were isolated from a dichloromethane extract of the leaves of *Calophyllum caledonicum* and have been reported for antifungal activity against *A. fumigatus* [53]. Xanthones from the green fruits of *Garcinia mangostana* were reported to have strong antifungal activities [54]. *Cudrania fruticosa* yielded an isoprenylated xanthone, cudrafrutixanthone which showed antifungal activity against *C. albicans* [55]. Xanthone analogues bearing the basic chain of butenafine were reported for significant activity against *C. neoformans* (1.5 μg/ml) [56].

2.7 Alkaloids

Heterocyclic nitrogen compounds are called alkaloids (Figure 7). The first medically useful example of an alkaloid was morphine, isolated in 1805 from the opium poppy *Papaver somniferum* [57].

Recently, an alkaloid, 2-(3,4-dimethyl-2,5-dihydro-1H-pyrrol-2-yl)-1-methylethyl pentanoate (**31**), has been isolated from the plant *Datura metel* and showed *in vitro* as well as *in vivo* activities against *Aspergillus* and *Candida* species [58]. Another alkaloid, 6,8-didec-(1*Z*)-enyl-5,7-dimethyl-2,3-dihydro-1H-indolizinium (**32**) from *Aniba panurensis* demonstrated the activity against drug-resistant strains of *C. albicans* [59]. Bromo-8-*n*-hexylberberine, a derivative of berberine, was reported to be 32 times more active against

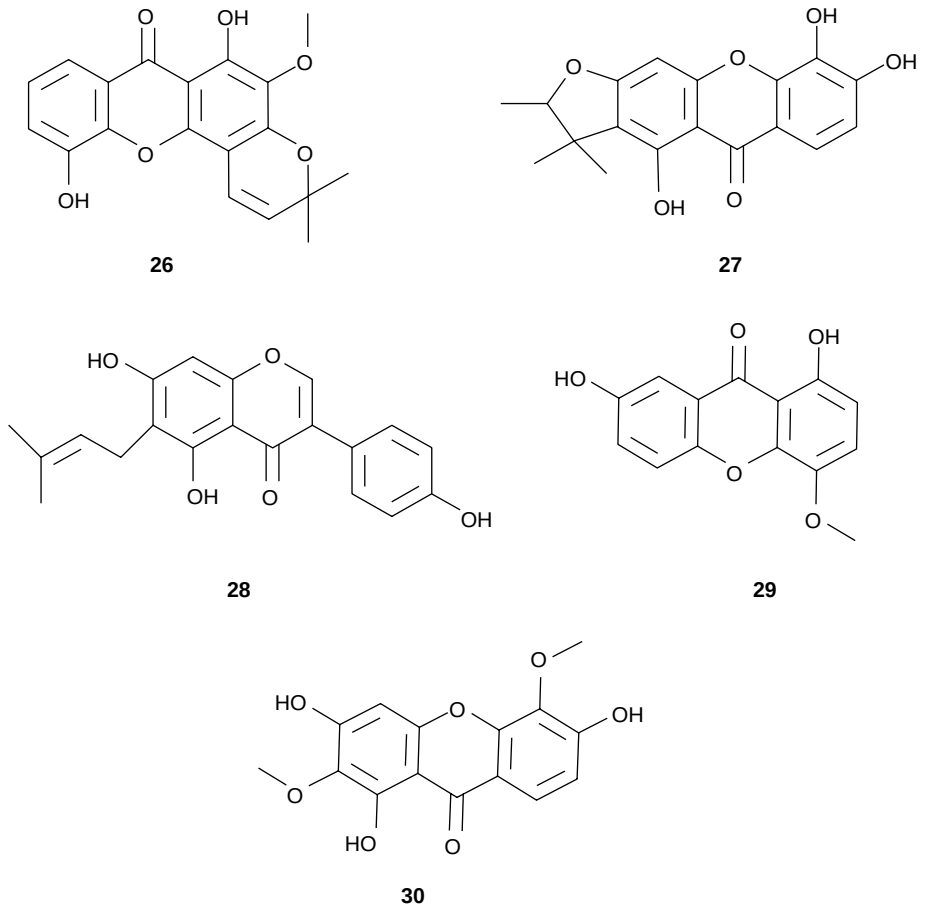


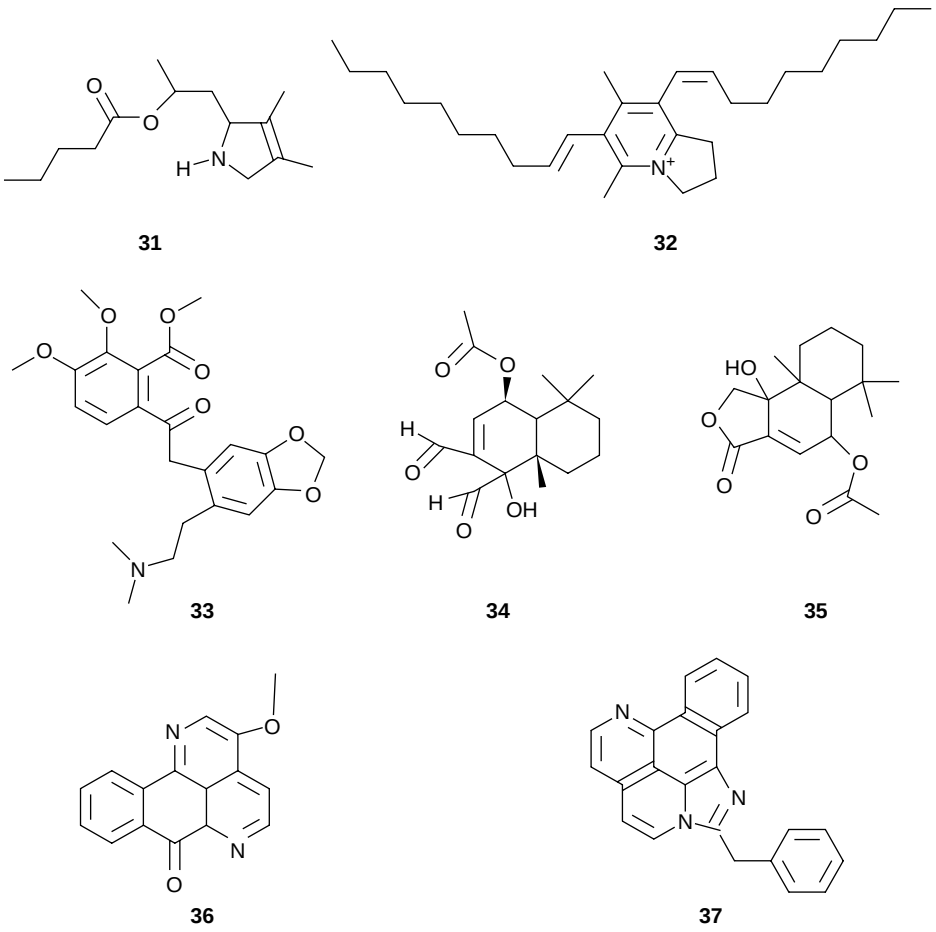
Figure 6. Structures of xanthones **26–30**.

C. albicans in comparison to the clinically used berberine [60].

The alkaloids *N*-methylhydrasteine hydroxylactam (**33**) and 1-methoxyberberine chloride from *Corydalis longipes* showed high efficacy individually [61]. Frangulanine, a cyclic peptide alkaloid, and waltherione A, a quinolinone alkaloid from leaves of *Melochia odorata*, were reported to exhibit antifungal activities against a broad spectrum of pathogenic fungi [62].

Cinnamodial (**34**) and cinnamosmolide (**35**) from *Pleodendron costaricense* showed a high activity against *C. albicans* azole-resistant strain D10 and *Wangiella dermatitides* having MIC 23.4 μg/ml [63]. The indole alkaloid venenatine from *Alstonia venenata* exhibited antifungal activity against all the 10 tested fungi, exhibiting germination levels below 10% [64]. 3-Methoxysampangine (**36**) from *Cleistopholis patens* exhibited significant antifungal activity (MIC = 3.12 μg/ml) against *C. albicans*, *A. fumigatus*, and *C. neoformans* [65]. Isoquinoline alkaloids from *Fumaria* and *Corydalis* species growing in Turkey had significant antifungal activity at 8.0 μg/ml concentration [66].

Antofine [67] from *Ficus septica*, sampangine (Figure 1) from the stem



31 **32** **33** **34** **35** **36** **37**

Figure 7. Structures of alkaloids **31–37**.

bark of *Cananga odorata*, [68] cycleanine, cocsoline, and *N*-desmethylcycleanine from *Albertisia villosa* [69] are the other antifungal alkaloids reported from higher plants.

2.8 Lectins and polypeptides

Peptides, which are inhibitory to microorganisms, were first reported in 1942 [70]. They are often positively charged and contain disulfide bonds. Their mechanism of action may be the formation of ion channels in the microbial membrane [71] or competitive inhibition of adhesion of microbial proteins to host polysaccharide receptors [72].

A lectin and a polypeptide isolated from the roots of *Astragalus mongholicus* exerted antifungal activity towards various fungi [73]. An antifungal peptide was reported from fresh fruiting bodies of the mushroom *Agrocybe cylindracea* [74]. Fabaceae species, *Trigonella foenum-graecum*, yielded defensins, small cysteine rich peptides, which exhibited antifungal activity against the broad host range fungi [75]. A novel antifungal peptide, cucurmoschin, isolated from the seeds of the black pumpkin inhibited mycelial growth in the fungi [76]. A peptide designated cicerarin from the seeds of the green chickpea *Cicer arietinum* showed antifungal activity. The antifungal activity was

preserved after exposure to 100°C for 15 min [77]. An antifungal peptide designated angularin isolated from the adzuki bean exhibited antifungal activity against a variety of fungal species [78]. Two antifungal peptides, designated α- and β-basrubrins, respectively, were reported from the seeds of the *Basella rubra* [79].

An antifungal protein, AFP-J purified from potato tubers *Solanum tuberosum,* strongly inhibited yeast fungal strains, including *C. albicans*, *Trichosporon beigelii*, and *S. cerevisiae* [80]. Antifungal peptides and proteins from plant species also included two chitin-binding proteins from spindle tree *Evonymus europaeus* [81], a thaumatin-like protein from *Musa acuminate* [82] and a protein from ginger rhizomes *Zingiber officinalis* (Zingiberaceae) [83].

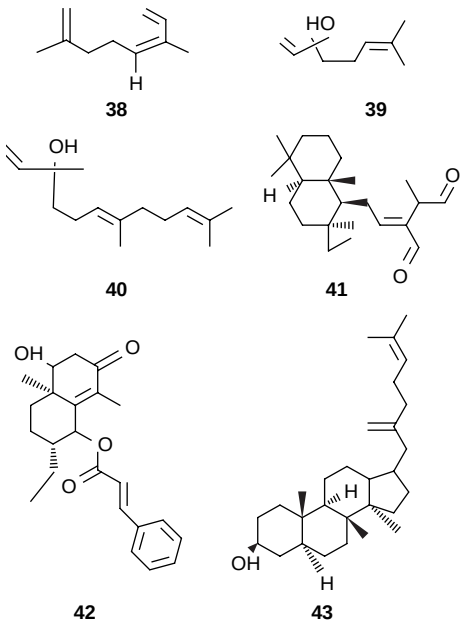


Figure 8. Structures of terpenoids **38–43**.

2.9 Terpenoids and essential oils

A large number of studies have been carried out in recent years on the antifungal activity of terpenoids of natural origin (Figure 8). These reports concern mainly sesquiterpenes and sesquiterpene lactones. The fragrance of plants is carried in essential oil fraction. These oils are secondary metabolites that are highly enriched in compounds based on an isoprene structure. They are called terpenes, their general chemical formula is $C_{10}H_{16}$, and they occur as diterpenes, triterpenes, and tetraterpenes (C_{20}, C_{30}, and C_{40}), as well as hemiterpenes (C_5) and sesquiterpenes (C_{15}). The mechanism of action of terpenes is not fully understood but is speculated to involve membrane disruption by the lipophilic nature. In contrast, it was found that increasing the hydrophilicity of kaurene diterpenoids by addition of a methyl group, drastically reduced their antimicrobial activity.

A number of terpenes or terpenoids are reported to be active against fungi [84]. Monoterpenoids are generally considered to be involved in the self-defense mechanism against plant pathogens. Structural modification of the monoterpenoids has resulted in improvement of biological activity [85]. In 1977, it was reported that 60% of essential oil derivatives examined to date were inhibitory to fungi while 30% inhibited bacteria [86]. The major components of oils, i.e. cineole, geranial, carvacrol, thymol, *p*-cymene, and 1,8-cineole, are reported for antifungal activity. The antifungal activities of the essential oil from *Agastache rugosa* and its main component, estragole, combined with ketoconazole, were reported to have significant synergistic effects [87]. The essential oil from the leaves of *Litsea cubeba* has α-*cis*-ocimene (**38**), 3,7-dimethyl-1,6-octadien-3-ol (**39**), and *n*-transnerolidol (**40**) had manifest antifungal activities with MIC between 0.03 and 0.4 μl/ml for utilized pathogenic fungi and 1.0–2.0 μl/ml for moulds [88]. An antimicrobial diterpene 8,17-epoxy-labd-12-ene-15,16-dial (**41**) from *Alpinia galanga* synergistically enhanced the antifungal activity of quercetin and chalcone against *C. albicans* [89].

The *Vernonanthura tweedieana* afforded one antifungal active sesquiterpene, 6-cinnamoyloxy-1-hydroxyeudesm-4-en-3-one (**42**) [90], having same MIC and MFC values (4.0 μg/ml) against *T. mentagrophytes*.

The roots of *Delphinium denudatum* yield 8-acetylheterophyllisine, panicutine, and 3-hydroxy-2-methyl-4H-pyran-4-one which have shown antifungal activity against a number of human pathogenic fungi [91]. Triterpenoid glycosides obtained from *Solidago virgaurea* and *Bellis perennis* inhibit the growth of human-pathogenic yeasts (*Candida* and *Cryptococcus* species) [92]. The oil from leaves of *J. oxycedrus* ssp. oxycedrus was reported with MIC and MLC values ranging from 0.08 to 0.16 μl/ml and from 0.08 to 0.32 μl/ml, respectively [93]. The sesquiterpene lactones costunolide and dehydrocostunolide showed noticeable IC_{50} values. Other antifungal sesquiterpene lactones from the Asteraceae family including those isolated from *Ajania fruticulosa* were inhibitory to the growth of *C. albicans* with MIC values in the range of 20–40 μg/ml [94].

A fruit pulp extract of *Detarium microcarpum* endowed with four new clerodane diterpenes showed antifungal activity [95]. The diterpenoids 16α-hydroxy-cleroda-3,13(14)-*Z*-diene-15,16-olide and 16-oxo-cleroda-3,13(14)-*E*-diene-15-oic acid isolated from the hexane extract of the seeds of *Polyalthia longifolia* demonstrated significant antifungal activity [96]. Oleanane triterpenoid, triterpenetetrol isolated from the chloroform extract of the aerial parts of *Leontodon filii* were reported to have antifungal properties [97]. Limonene, carvone, dihydrocarvone, dillapiole, and dillapional from *Anethum sowa* revealed antifungal activity at a concentration of 1:100 to 1:250. A derivative of dillapiole, isodilapiole tribromide found to be more active [98]. Most of the species of *Oscimu*m showed *in vitro* antifungal activities against a broad range of fungi as well as bacteria. An Indian chemotype *Ocimum gratissimum*, with a high level of ethyl cinnamate, presents, *in vitro*, an interesting spectrum of antifungal properties. It was observed that chloroformic fraction inhibited 23 isolates (92%) of *C. neoformans* at a concentration of 62.5 μg/ml and eugenol inhibited four isolates (16%) at a concentration of 0.9 μg/ml. This screening may be the basis for the study of *O. gratissimum* as a possible antifungal agent [99].

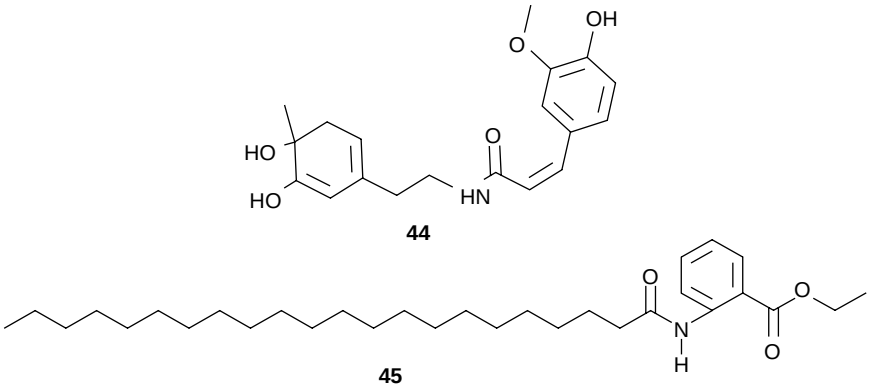
Two antifungal triterpenoid glycosides, hyalodendrosides A and B, were isolated from *Hyalodendron* sp. [100]. The essential oil and the methanolic leaf extracts of *Teucrium sauvagei* inhibited the *in vitro* growth of seven dermatophytes, whereas the essential oil showed average inhibition against only three dermatophytes [101]. *Euphorbia segetalis* yielded tetracyclic triterpenes, lupenone, 3β-acetoxy-cycloart-25-en-24-one glutinol, dammaranodienol (**43**), cycloartenol acetate, and 24-methylenecycloartanol acetate exhibited the *in vitro* antifungal activities [102].

Santolinylol and pinitol of *Artemisia giraldii* were shown to inhibit the growth of the broad range of human pathogenic fungi [103]. (*Z*,*Z*)-2-hydroxy-4-oxohenicosa-12,15-dien-1-yl acetate [104], 2-hydroxy-13-methylpodocarpa-8,11,13-trien-3-one, hugorosenone [3β-hydroxyrosa-1(10),15-dien-2-one], 18-hydroxyhugorosenone, and 18-hydroxy-3-deoxyhugorosenone [105] from higher plant exhibited good antifungal activities.

2.10 Other compounds

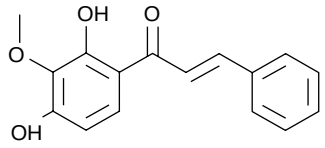
Many phytochemicals not mentioned above have been found to exert antifungal properties. This review has attempted to focus on reports of chemicals, which are found in multiple instances to be active. There are reports of phytochemicals having antifungal properties associated with several different classes not covered above (Figure 9).

N-*trans*-feruloyl-4-methyldopamine (**44**) recently isolated from *Achranthes ferruginea* was reported to be active against a broad range (LC_{50} at 16.21 and 11.70 μg/ml) of fungi [106]. Leaves of *Piper aduncum* accumulate the antifungal chromenes, methyl 2,2-dimethyl-2H-1-chromene-6-carboxylate, and methyl 2,2-dimethyl-8-(3′-methyl-2′-butenyl)-2H-1-chromene-6-carboxylate [107]. 2′,4′-Dihydroxy-3′-methoxychalcone (**46**) and 2′,4′-dihydroxychalcone (**47**) in the dichloromethane extracts of *Zuccagnia punetata* showed moderate antifungal activities against the yeasts *C. albicans*, *S. cerevisiae*, and *C. neoformans* having MIC values of 62.5–250 μg/ml and very strong antifungal activities against the dermatophytes *M. gypseum*, *T. rubrum*, and *T. mentagrophytes* with MIC values in the range of 8–16 μg/ml [108]. *Ravensara anisata* afforded two new α-pyrones showing antifungal activity against the *C. albicans* [109]. Ethyl *N*-docosanoylanthranilate (**45**) from *Gentiana tibetica* inhibited the growth of the human pathogenic fungi *C. albicans* and *A. flavus* [110]. Leaves of *Heteromorpha trifoliata* furnished the antifungal compounds falcarindiol and sarisan [111]. *Piper cubeba* afforded the compounds (8*R*,8′*R*,9′*S*)-5-methoxyclusin, (−)-clusin, (−)-yatein, ethoxyclusin, and (−)-dihydroclusin showed very potent and selective inhibitory activity with IC_{50} values ranging



44

45



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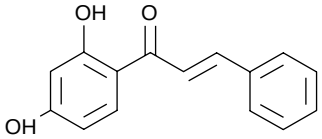

47

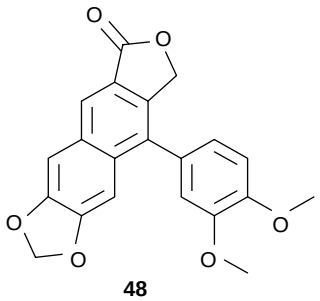

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Figure 9. Structures of other compounds **44–48**.

from 0.44 to 1.0 μM which is identical to that of the positive control, ketoconazole (IC_{50} 0.72 μM) [112].

Lupinus angustifolius yielded glucuronopyranoside and rhamnopyranoside showing moderate antifungal activity against *C. albicans* with MIC values of 25 μg/ml [113]. Other reported antifungal compounds include benzofuran derivatives [114], justicidin B (**48**) (MIC ≥ 1–12 μg/ml) [115], dendrazawayne A and B, polyacetylene amides (MIC = 5–10 μg/ml) [116], and methyldambullin [117]. Methyl populnoate, populnoic acid, and stigmast-5-en-3-*O*-β-(D-glucopyranoside) isolated from *Austroplenckia populnea*, showed antifungal activity against *C. glabrata* and *C. albicans* having IC_{50} values in the range of 5.5–0.7 μg/ml [118]. Seven species of Combretaceae family yielded 25 compounds, which were reported for reasonable to very good antifungal activity with a MIC as low as 40 μg/ml [119]. Neolignans from leaves of *Piper regnellii* showed strong activity against the dermatophyte fungi with MIC values of 15.62–62.5 μg/ml, respectively [120].

3. Conclusion

Phytomedicines are a major component of traditional system of healing in developing countries, which have been an integral part of their history and culture. Besides widespread use of botanicals as medicinal products in developing countries, such products are becoming part of the integrative healthcare system of industrialized nations, known as complementary and alternative system of medicines.

Existing costly therapy is not affordable well for the millions of individuals particularly in the developing world. Plant extracts are the cheap and easily available source to poor people. Plants are great source of thousands of new useful phytochemicals of great diversity, which have inhibitory effects on all types of microorganisms *in vitro*. Till date more than 600 plants have been reported for their antifungal properties, however, a few of them were explored for the active components. The current pharmaceutical armory of antifungal is a clear cause for satisfaction, not from gloom. However, we still do not have agents that fulfill every one of the criteria that a physician would set as desiderata for antifungal drugs. They need to be active against those fungi causing infections which we cannot yet depend on eradicating. They need to be formulated for both oral and parenteral administrations, they need to be extremely safe and as cheap as possible. The search for new antifungal agents therefore must go on.

Identification of new chemotypes for drug development remains an urgent need in antifungal therapeutics. Simultaneously, a number of antifungal compounds reported till date is tested for their *in vitro* activities and not for *in vivo* activities. *In vivo* and *in vitro* activities of a compound may be different and a very small number of plants' extracts or components have been studied for their *in vivo* activity. Therefore, these should be subjected to animal and human studies to determine their effectiveness in whole-organism systems. Also *in vitro* testing and method of extraction should be standardized so that the search could be more systematic.

The current set of clinically available antifungal agents includes three classes of natural products and four classes of synthetic chemicals. We therefore cannot abandon interest in biodiversity as a source of natural antifungal products. Furthermore, the inactive plant extracts may be subjected to chemical diversification of their components to increase the activity. The transformation of chemical groups in natural products into rare chemical groups is possible which is rarely produced by secondary metabolism. Therefore, biosynthesis machinery can be complemented to

produce a whole range of new semisynthetic compounds in one step which may become an alternative source of compounds to feed the discovery process for new interesting compounds.

The study of alternative mechanisms of infection prevention and treatment is essential. Plant products furthermore may be structurally modified to increase their *in vivo* activity. For example, isodilapiole tribromide, a derivative of dillapiole was found to more active. Another example includes echnicandin-type peptide FR901379, chemical modification of which lead towards more active FK463 compound. Therefore, attention towards the plant-derived principles, their chemical modification and chemotherapeutic potential is needed.

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