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**REVIEW ARTICLE**

# A Review of Antifungal Natural Products Against the Pathogenic Fungi Causing Athletes' Foot Disease

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**Abstract:** In this review, the antifungal natural agents against four common tinea pedis dermatophytes (*Epidermophyton floccosum*, *Trichophyton mentagrophytes*, *T. tonsurans* and *T. rubrum*) will be introduced in detail. These natural products are divided into 2 parts: 61 active compounds and extracts (including essential oils). The compounds were classified into 9 categories according to their chemical structures, which are coumarin, lignan, terpenoid, saponin, quinone, alkaloid, flavonoid, phenyl derivatives and others. Related pharmaceutical approach and extraction method of antifungal natural agents for tinea pedis will be discussed for future application.

**Keywords:** Tinea pedis, natural products, dermatophyte, anti-fungal, *Epidermophyton floccosum*, *Trichophyton mentagrophytes*, *T. tonsurans* and *T. rubrum*.

## 1. INTRODUCTION

Tinea pedis, namely Hong Kong foot, or athlete's foot, is a common skin tinea disease that causes various discomforts in the affected areas. It was first described by Pellizari in 1882 [1]. Tinea pedis is not a life-threatening disease, but the life quality of infected person can be impacted severely. It's worth noting that tinea pedis can be developed into serious secondary infections when immune system is suppressed or destructed by diseases or some treatments, such as AIDS and immunosuppressive drugs [2]. Generally, adults are not prone group of tinea pedis resulting from enhanced ability of defensing fungal infection of triglycerides in the sebum generated following puberty. But postmenopausal woman is easy to develop tinea pedis than other adults because of reduction of triglycerides [3].

The infected sites of tinea pedis are usually human feet. About 15%-20% of people are troubled by tinea pedis around world [4]. Tinea pedis is mainly caused by three filamentous genera of fungi such as *Microsporum*, *Trichophyton* and *Epidermophyton* [5]. According to the infection characteristics, dermatophytes are classified into three categories: anthropophilic, zoophilic and geophilic [6]. They could spread from human, animals and soil. In this review, we focused on anthropophilic category strains of dermatophytes, \which mainly infect humans with animals rarely being affected.

The treatments for tinea pedis have evolved over time. In early time, patients chose plant extract or mineral to cure tinea pedis. The first traditional Chinese medicine monograph on surgery "Liu Juanzi Gui Yi Fang", written by Gong Qingxuan about 499 AD, has described the treatment method using the mixture cream of mercury, aluminite, *Fructus cnidii* and *Coptis chinensis* [7].

In 1930s thallium acetate was used to treat tinea pedis in some countries [8], but it caused adverse effects including hepatitis and peripheral neuritis. Before and during World War II, some synthetic fatty acid compounds, such as propionic acid preparations, copper oleate, salicylanilide undecylanic acid salts and Whitfield's ointment, achieved varying degrees of therapeutic on tinea pedis [9-11].

The first breakout of anti-dermatophytic drug, griseofulvin, was first isolated from the fungus *Penicillium griseofulvum* Direck in 1939 [12]. Its antifungal activity was not known until the late 50's Gentles and Blank reported the success treatment of dermatomycoses with orally administered griseofulvin [13, 14]. The mechanism of griseofulvin is obstructing the structure of the mitotic spindle structure and restraining cell division at the metaphase stage. Griseofulvin also can inhibit the synthesis of nucleic acid and antagonizing chitin in the cell wall of fungi [4]. Griseofulvin had been antifungal agent available for the treatment of tinea pedis for many years. But the resistance and toxicities of this drug always are noteworthy problems [15].

Tolnaftate is a synthetic thiocarbamate used as an anti-dermatophytes agent since 1964 [16, 17]. Tolnaftate inhibits sterol biosynthesis at level of squalene epoxidation, which is necessary for dermatophytes growing (Fig. **1**) [18].

Ketoconazole is also a common agent for tinea pedis, which exhibits broad spectrum fungicidal effect on dermatophytes. It disturbs the synthetic pathway of ergosterol which is important for formation of cellular membrane. As a result, ketoconazole affects permeability and function of the cell membrane. Fluconazole is another commonly used antifungal drug with similar mechanism of action as ketoconazole [19].

Terbinafine is a fungicidal agent curing tinea pedis. The fungicidal mechanism of action terbinafine results from blocking the formation of ergosterol by inhibiting squalene epoxidase [20]. Fungicidal drugs like terbinafine are commonly used during treatment

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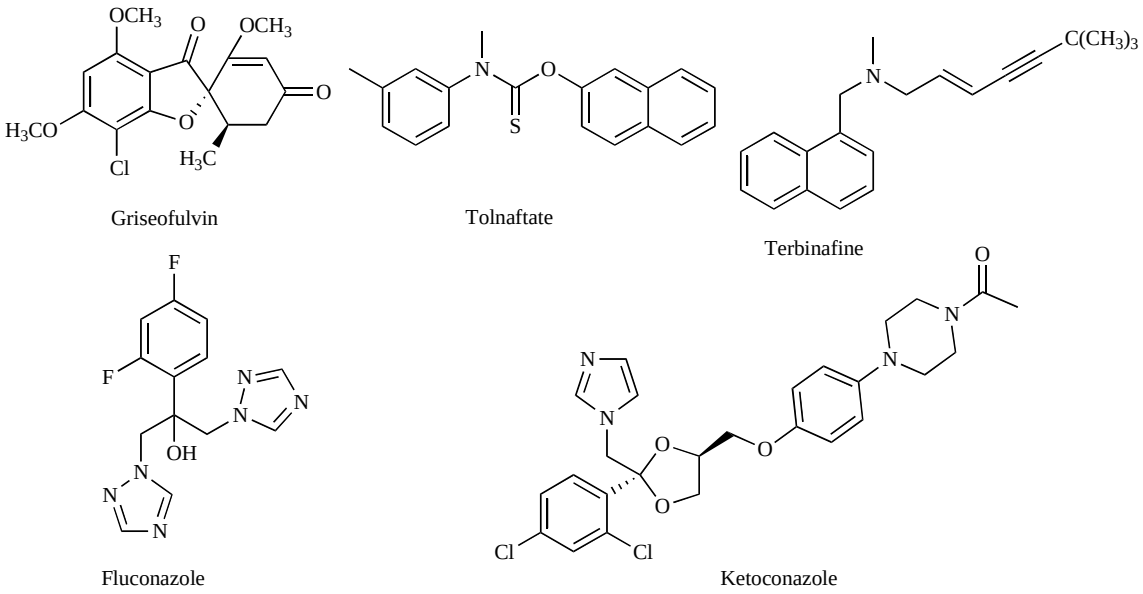



**Fig. (1).** Chemical structures of anti-dermatophytic medicines used in clinical practice.

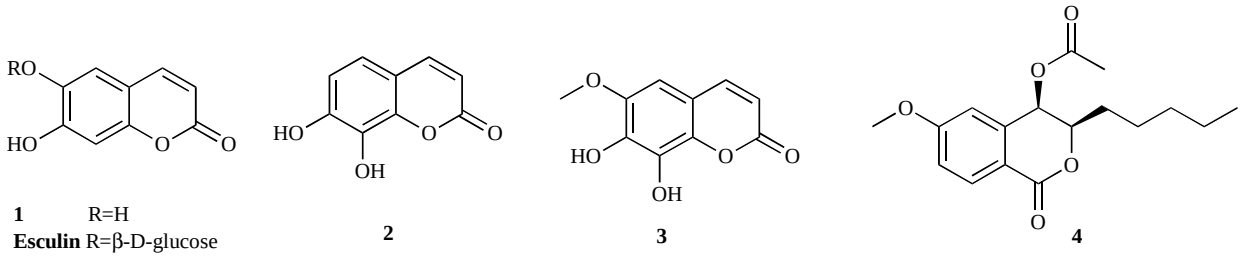



**Fig. (2).** Chemical structures of representative antifungal coumarins.

compared with fungistatic azoles (miconazole, clotrimazole and ketoconazole) due to high cure rate and short-term therapy [21].

In recent years, dermatophytes showed more and more drug-resistance [22-25]. There is an increasing need for finding new antifungal agents with low toxicity and high sensitivity. Natural compounds from plants and microorganisms are always the most important sources of antifungal agents [26]. In this review, we will report the compounds and essential oils with anti-dermatophytic activities from plants, microorganisms and animal.

## 2. NATURAL PRODUCTS WITH ANTIFUNGAL EFFECTS

In this review, active compounds, essential oils and extracts are introduced, respectively. Active compounds are classified into 9 categories according to their chemical structures including coumarin, lignan, terpenoid and sterol, saponin, quinone, alkaloid, flavonoid, phenyl derivatives and others.

### 2.1. Coumarin

Coumarin is a class of chemicals with the basic structure of C6-C3 units (2H-1-benzopyran-2-one). Generally, heterocyclic ring is oxygenated at C-7. Families *Umbelliferae*, *Rutaceae*, *Leguminosae* and *Compositae* are the most common source of coumarin [27].

Mercer *et al*. [28] investigated a prodrug approach to promote the delivery of coumarin at the site of infection. This new approach was proved by a comparison of antifungal activity between coumarin (esculetin) **(1)** and coumarin glycoside (esculin) (Fig. **2**). The antifungal activity of esculetin (MIC = 89.07-178.14 μg/mL) against *T. tonsurans*, *T. rubrum* and *T. mentagrophytes* was notably better than esculin. In addition, two additional coumarins, daphnetin **(2)** (MIC = 22.27-89.07 μg/mL) and fraxetin **(3)** (MIC = 26.02-104.09 μg/mL), were tested in this experiment, and they even showed better activity than esculetin. The antifungal activity difference revealed that a coumarin converting to its glycoside would cause reduced/no the antifungal activity of coumarin, and the position of hydroxyl groups on the benzene ring would affect the activity of a coumarin.

By spectrometric methods and phytochemical approaches, a dihydroisocoumarin was isolated from *Xyris pterygoblephara* [29]. The antifungal activity of (*3R*,*4R*)-(-)-6-methoxy-3,4-dihydro-3-n-pentil-4-acethoxy-1H-2-benzopyran-1-one **(4)** was evaluated using the agar diffusion and microdilution methods. And the result of this compound against *E. floccosum*, *T. mentagrophytes* and *T. rubrum* presented similar inhibition zone to amphotericin B (the positive control).

### 2.2. Lignan

The basic structure of lignan is oxidative dimerization of two phenylpropanoid units [30].

Two lignans, magnolol **(5)** and honokiol **(6)** were isolated from the barks of *Magnolia obovata* (Fig. **3**) [31]. Both of them showed significant antifungal activity against *E. floccosum* and *T. mentagrophytes*. The MIC of honokiol was 25μg/mL against *E. floccosum* and *T. mentagrophytes*, while the MIC of positive control (itraconazole and clotrimazole) was in the range of 0.03-4.88 μg/mL. Honokiol had higher antifungal activity (MIC = 25 μg/mL) against

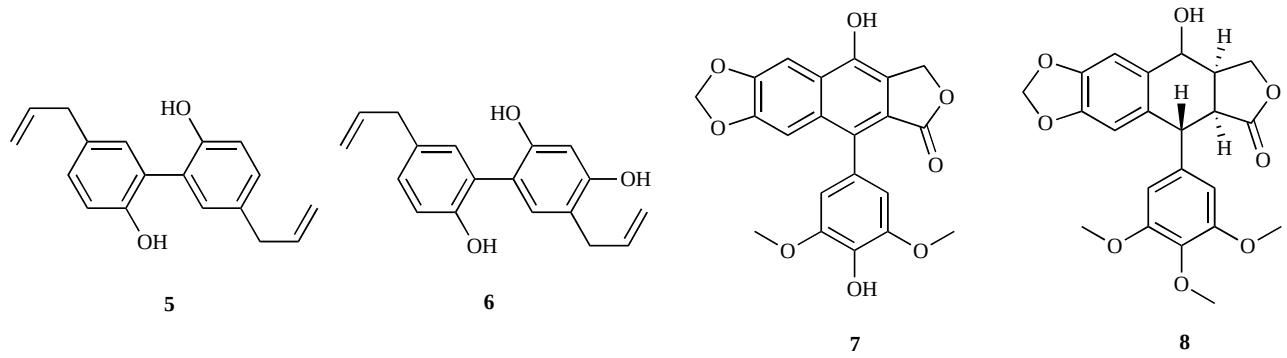



**Fig. (3).** Chemical structures of representative antifungal lignans.

*T. mentagrophytes* than magnolol, which indicated that the position of hydroxyl group on aromatic ring influenced its antifungal effect.

Attaurrahman *et al*. [32] evaluated the bioactivity and chemical structure of two lignans, 4'-*O*-demethyldehydropodophyllotoxin **(7)** and picropodophyllone **(8)**, from the leaves of *Podophyllum hexandrum*. The growth inhibition for *E. floccosum* caused by two lignans was measured at the concentration 2.5 mg/mL using the agar diffusion method.

### 2.3. Terpenoid and Sterol

This review will introduce 3 sterols and 19 terpenoids, including 2 monoterpenoids, 9 sesquiterpenoids and 8 triterpenoids. Terpenoid contributes over 40,000 metabolites of plants, which is the largest class of plant metabolites. The majority of them are the combination of 1−6 isoprene units [33].

From the *Ageratina pichinchensis* var. *bustamenta* (a kind of folk medicine in Mexico), taraxerol **(9)**, and (+)-β-eudesmol **(10)** were obtained using n-hexane extraction (Fig. **4**) [34]. Taraxerol was an antifungal triterpenoid with MIC at 12.5μg/mL against *T. mentagrophytes* and *T. rubrum*, while (+)-β-eudesmol with MIC of 25μg/mL presented weaker antifungal effect than taraxerol. It is noted that after transformation of the double bond in (+)-β-eudesmol to an epoxide function in compound 4α,15-epoxyeudesm-11-ol **(11)** (MIC = 50 μg/mL) and oxidation of the compound to its corresponding ketone 11-hydroxy-15-noreudesm-4-one **(12)** (MIC > 100 μg/mL), the two derivatives showed much weaker antifungal effect than (+)-β-eudesmol, indicating that the double bond is an important functional group for the antifungal activity of (+)-β-eudesmol.

Two sesquiterpene dialdehydes, polygodial **(13)**, isopolygodial drimenol **(14)**, and a related alcohol (drimenol) **(15)** were found in the dichloromethane extracts of the leaves of *Polygonum acuminatum* Kunth (Persicaria section). Polygodial exhibited strong antifungal activity against *T. rubrum* and *T. mentagrophytes* with an MIC value of 7.8 μg/mL, while isopolygodial showed weaker effect (MIC = 62.5 μg/mL) on the dermatophytes. This result demonstrated that the aldehyde function at C-9β makes polygodial more active than isopolygodial [35-36]. Drimenol and the semisynthetic isodrimenol **(16)** also presented weaker activity (MIC = 62.5-250 μg/mL) than polygodial, which further indicated that an aldehyde functional group at C-9β plays an important role in the antifungal activity. However, Derita *et al*. [37] gave a different result of MIC values of polygodial and isodrimenol. In this test, the MICs of these four compounds were 62.5μg/mL, and the MFCs (minimum fungicidal concentration) of them were 125μg/mL.

The sesquiterpene alcohol (*α*-bisabolol) **(17)** was derived from the essential oils of several plants, such as *Chamomilla* sp., *Chrysothamnus nauseosus*, and *Arnica longifolia*, *Aster esperius* [38]. The antifungal effects against *E. floccosum*, *T. mentagrophytes*, *T. rubrum and T. tonsurans* of α-bisabolol were evaluated, and the compound showed approximately 70% inhibition against *T. mentagrophytes*, *T. tonsurans* and 30% inhibition against *T. rubrum* and *E. floccosum* at the concentration of 200 μg/mL.

Five applanoxidic acids **(18-22)** and three sterols **(23-25)** were isolated from *Ganoderma Applanatum* and *G. austral* [39]. Only the applanoxidic acids **(18)** showed moderate antifungal effect against *T. mentagrophytes* with an MIC value of 0.5 mg/mL, and other 7 compounds **(19-25)** only showed weak antifungal activity (MIC > 1.0 mg/mL).

Artemisinin isolated from *Artemisia annua* is a well-known antimalarial drug from China. *A. annua* is originated from china. From this plant, artemisinic acid was isolated **(26)**. Goswami *et al*. [40] found that artemisinic acid presented antifungal activity against *E. floccosum*. But the MIC of artemisinic acid was not determined.

One remarkable antifungal triterpenoid (oleanolic acid) **(27)** was derived from *Syzygium aromaticum* (Cloves) [41]. Oleanolic acid even exhibited higher antifungal activity against *T. tonsurans* with an MIC value of $1.25\times10^{-3}$ μg/mL which was more active than the positive control fluoconazole. This study revealed that oleanolic acid is a potential antifungal natural agent and needs further investigation. Habila et al. also evaluated the antifungal effect of 3β-acetoxy-oleanolic acid **(28)**, which was a derivative modified with an acetyl group on the C-3 position of oleanolic acid. 3β-acetoxy-oleanolic acid showed stronger antifungal effect (MIC = $0.63\times10^{-3}$ μg/mL) on *T. tonsurans* than oleanolic acid, which indicates that the acetyl group on the C-3 position may improve the antifungal activity.

The epoxy terpenoid, clemateol **(29)**, obtained from the essential oil from *Calea clematidea* exhibited weak antifungal effect against *E. floccosum*, *T. rubrum* and *T. mentagrophytes* with MICs in the range from 1.52 to 6.06 mg/mL [42]. And after basic hydrolysis, the compound **(30)** showed better antifungal effect than clemateol.

### 2.4. Saponin

Saponin is based on the skeletons of triterpene or steroid precursors with glycosyl residues attached. Traditionally, saponins are classified into two categories: triterpene and steroid glycosides, according to the carbon skeleton. The sources of saponins are vari-

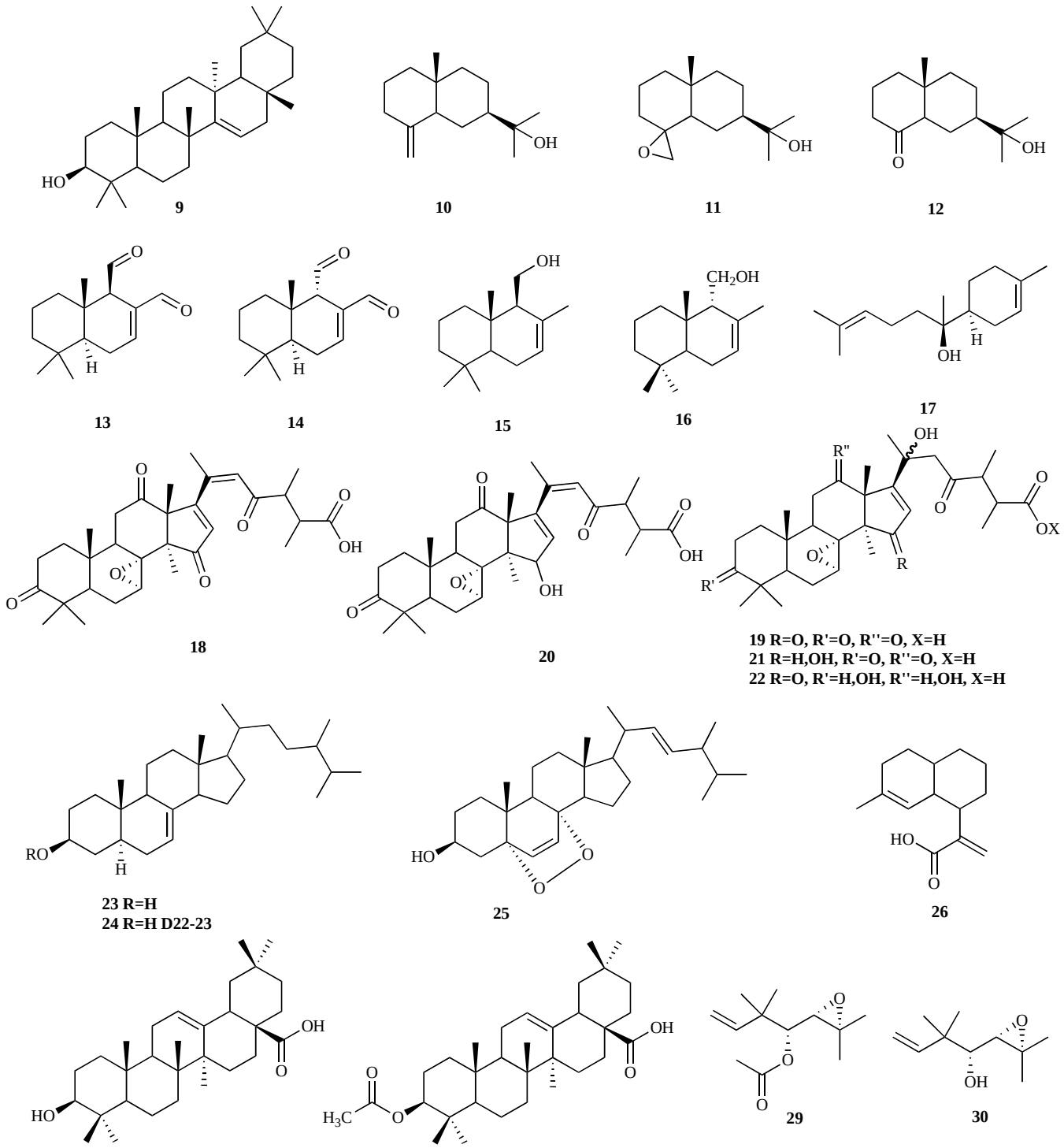



**Fig. (4).** Chemical structures of representative antifungal terpenoids and sterols.

ous and extensive. More and more attentions have been attracted by saponins due to their remarkable biological activities [43].

A mixture of two steroid saponins **(31-32)** obtained from the underground portion of *Allium ursinum* L. was active against *T. mentagrophytes* at the concentration of 400 μg/mL. Sobolewska *et al*. (Fig. **5**) [44] pointed that this weak inhibitory effect on fungi resulted from relatively long sugar chain. The analogue of (*25R*)-spirost-5-en-3b-ol tetrasaccharide with shorter sugar chain presented stronger inhibitory effect on *Candida* [45].

Saponin-rich extracts of *Medicago sativa* L. contained 6 triterpene saponins (4 medicagenic acid saponins, 1 hederagenin saponins and 1 soyasapogenol saponins) [2]. The extracts of *M. sativa* roots and *M. sativa* aerial parts, along with one of the 3-*O*-β-D-glucopyranoside medicagenates **(33)** all inhibited *T. tonsurans* with a MIC value of <0.0625 mg/mL, which were regarded as potent antifungal agents. Other three bidesmosidic glycosides of medicagenic acid, (3-*O*-β-D-glucopyranosyl, 28-*O*-β-D-glucopyranoside medicagenate **(34)**, 3-*O*-[-β-D-glucopyranosyl],28-*O*-[β-D-xylopyra-

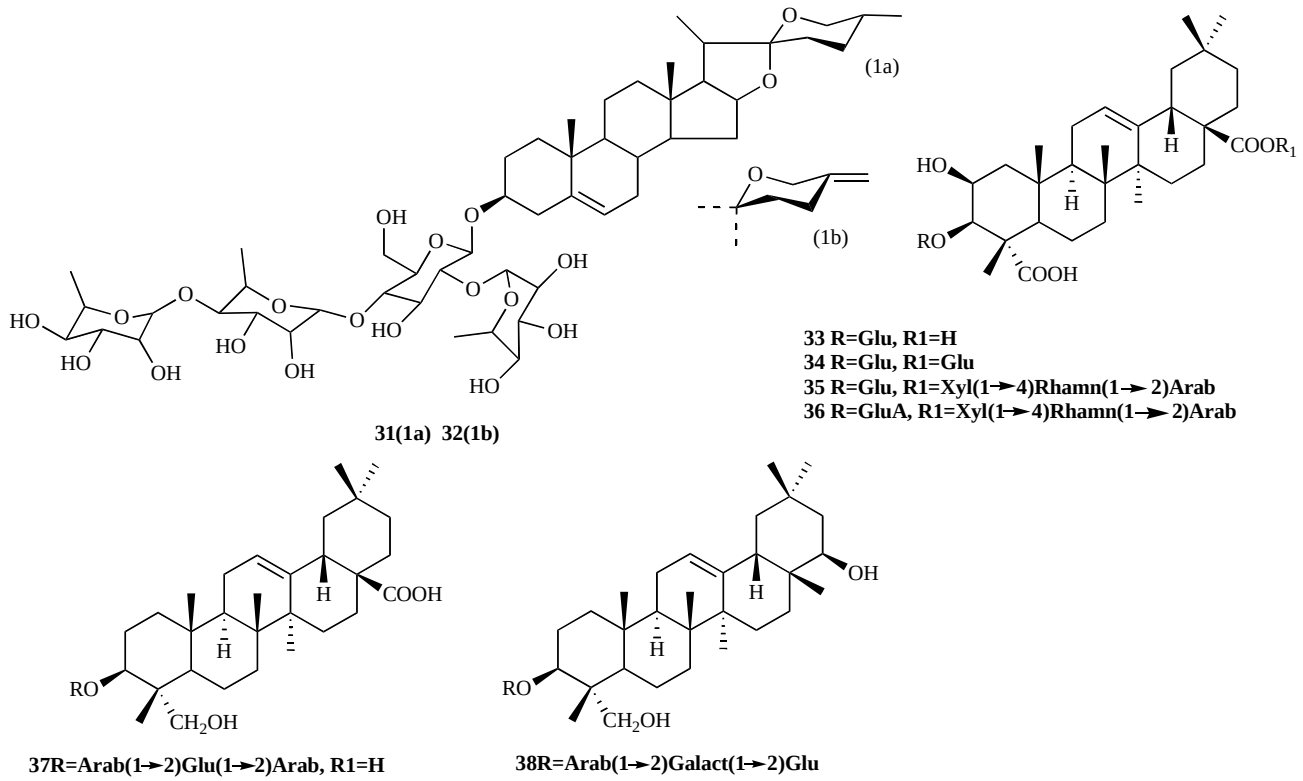



**Fig. (5).** Chemical structures of representative antifungal saponins.

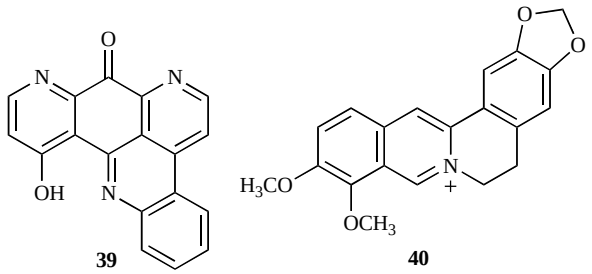



**Fig. (6).** Chemical structures of representative antifungal alkaloids.

nosyl(1→4)-α-L-rhamnopyranosyl(1→2)-α-L-arabinopyranoside] medicagenate **(35)** and 3-*O*-[β-D-glucuronopyranosyl],28-*O*-[β-D-xylopyranosyl (1→4)-α-L-rhamnopyranosyl (1→2)-α-L-arabinopyranoside] medicagenate **(36)** with MICs of 0.25mg/mL were found to have weaker antifungal activity than 3-*O*-β–D-glucopyranoside medicagenate which is a monodesmosidic compound. The difference of the antimycotic activity indicated that these monodesmosidic compounds appeared to be more active than the bisdesmosidic compounds. Since the parent aglycone is different, 3-*O*-[α-L-arabinopyranosyl(1→2)-β-D-glucopyranosyl(1→2)-α-L-arabinopyranoside] hederagenin (**37**) and 3-*O*-[α-L-rhamnopyranosyl(1→2)-β-D-galactopyranosyl(1→2)-β-D-glucopyranoside) soyasapogenol B (**38**) were not effective (MIC > 1.0mg/mL) as the medicagenic acid saponins.

## 2.5. Alkaloid

Alkaloid is a group of natural compounds containing nitrogen atoms.

The polycyclic alkaloid, meridine **(39)**, was purified from the sponge *Corticium* sp. (Fig. **6**) [46]. Meridine strongly inhibited *T. mentagrophytes* (MIC = 6.2 μg/mL) and *E. floccosum* (MIC = 1.6 μg/mL). The mechanism of action of this agent had shown the inhibition of nucleic acid biosynthesis.

A common natural alkaloid, berberine **(40)**, was also tested in a susceptibility test of *E. floccosum*, *T. mentagrophytes* and *T. rubrum*. Finally, berberin isolated from *Berberis heterophylla* showed a significant effect on these three fungi with MIC in range of 12.5~25 μg/mL [47].

## 2.6. Flavonoid

Flavonoid is a class of polyphenolic substances. Generally, the basic skeleton of flavonoid is formed by two phenyl rings and a heterocyclic ring [48]. It presented various biological activities.

Fisetin **(41)** obtained from the xylem sap of *Hymenaea courbaril* L (jatoba), which was investigated in *in vitro* activity against *T. tonsurans T. rubrum* and *T. mentagrophytes* (Fig. **7**) [5]. Fisetin exhibited significant antifungal activity against *T. rubrum* (MIC = 32 μg/mL) and *T. mentagrophytes* (MIC = 64μg/mL) and moderate effect against *T. tonsurans* with an MIC value of 128 μg/mL. Also, fisetin presented higher activity and lower cytotoxicity than the fresh xylem sap.

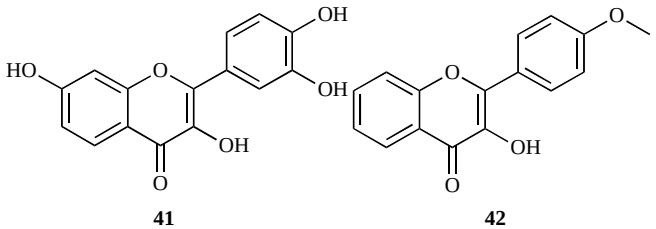


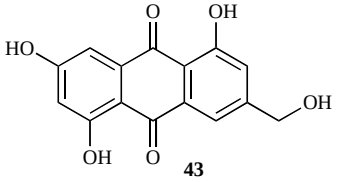

**Fig. (7).** Chemical structures of representative antifungal flavonoids.

4'-Methoxy flavone (**42**) was obtained from the seeds of *Psoralea corylifolia* [49]. It showed different degrees of antifungal

activity against *T. rubrum* (MIC = 62.5 μg/mL), *T. mentagrophytes* (MIC = 62.5 μg/mL) and *E. floccosum* (MIC = 125 μg/mL) by the disc diffusion method on a Sabouraud dextrose agar.

### 2.7. Quinone

An anthraquinone from the *Streptomyces* sp. isolate ERI-26 (bacteria) was investigated for its antimycotic activity against *E. floccosum*, *T. mentagrophytes* and *T. rubrum* for the first time [50]. The compound 1, 5, 7-trihydroxy-3-hydroxy methyl anthraquinone **(43)** showed a considerable antifungal effects against *E. floccosum* and *T. rubrum* with an MIC value of 62.5μg/mL, but presented a moderate effect against *T. mentagrophytes* with an MIC value of 250μg/mL (Fig. **8**).




**43**

**Fig. (8).** Chemical structure of representative antifungal quinone.

### 2.8. Phenyl Derivatives

Espeletone **(44)** was obtained from the *n*-hexane extracts of *Eupatorium aschenborniana* (Fig. **9**). Espeletone possessed moderate antifungal activity against *T. mentagrophytes* and *T. rubrum* [51].

A chromene, namely encecalin **(45)**, was purified from the *n*-hexane extract of *Ageratina pichinchensis* var. bustamenta, which is a Mexican folk medicine [34]. Encecalin exhibited a significant antifungal activity against *T. rubrum* (MIC = 6.2 μg/mL) and *T. mentagrophytes* (MIC = 12.5 μg/mL).

Through a bioassay-guided isolation from *Eupatorium aschenborniana*, an analogical chromene, encecalinol **(46)**, exhibited similar activity with encecalin except slightly weaker antifungal activity against *T. rubrum* than encecalin (MIC = 12.5 μg/mL). Also two new benzofurane compounds were isolated from this plant, namely 5-acetyl-3β-angeloyloxy-2β-(1-hydroxyisopropyl)-6-methoxy-2,3-dihydrobenzofurane **(47)** and 5-acetyl-3β-angeloyloxy-2β-(1-hydroxyisopropyl)-2,3-dihydrobenzofurane **(48)** [51]. The later benzofurane compound (MIC = 50 μg/mL) showed higher inhibitory effect than the first benzofurane compound (MIC in the range of 100-200 μg/mL). Comparing the activity of these four compounds, it is can be inferred that the chromene is more active than the benzofuranes against *T. rubrum* and *T. mentagrophytes*.

Oh *et al*. [52] investigated the antifungal activities and chemical structure of a novel bromophenol isolated from the red alga *Odonthalia corymbifera*. The *in vitro* antifungal activity against *T. mentagrophytes* and *T. rubrum* of the natural bromophenol, 4-(2-aminoethyl)-2,6-dibromophenol **(49)**, was moderate (MIC > 100 μg/mL), while their synthesized derivatives **(50-54)** presented higher antifungal activity (MIC in the range of 1.56-50 μg/mL), especially 2,3-dibromo-4,5-dihydroxybenzylmethyl ether **(51)** (MIC = 12.5 μg/mL) and 2,2',3,3'-tetrabromo-4,4',5,5'-tetrahydroxydiphenylmethane **(52)** (MIC = 1.56 μg/mL). These results indicated that the diphenolic backbone and the presence of one or more bromines on the phenol ring could affect antifungal activity.

Two phenolic compounds, 4-*O*-β-D-(6-*O*-gentisoylglucopyranosyl) vanillic acid **(55)** and 2-*O*-β-D-(6-ogentisoylglucopyranosyl) gentisic acid **(56)**, were first obtained from the fern *Stenoloma chusanum* (L.) Ching (Fig. **7**) [53]. *S. chusanum* is a folk medicine originated from China. Only vanillic acid could effectively inhibit *T. rubrum*, *T. mentagrophytes* and *E. floccosum* with

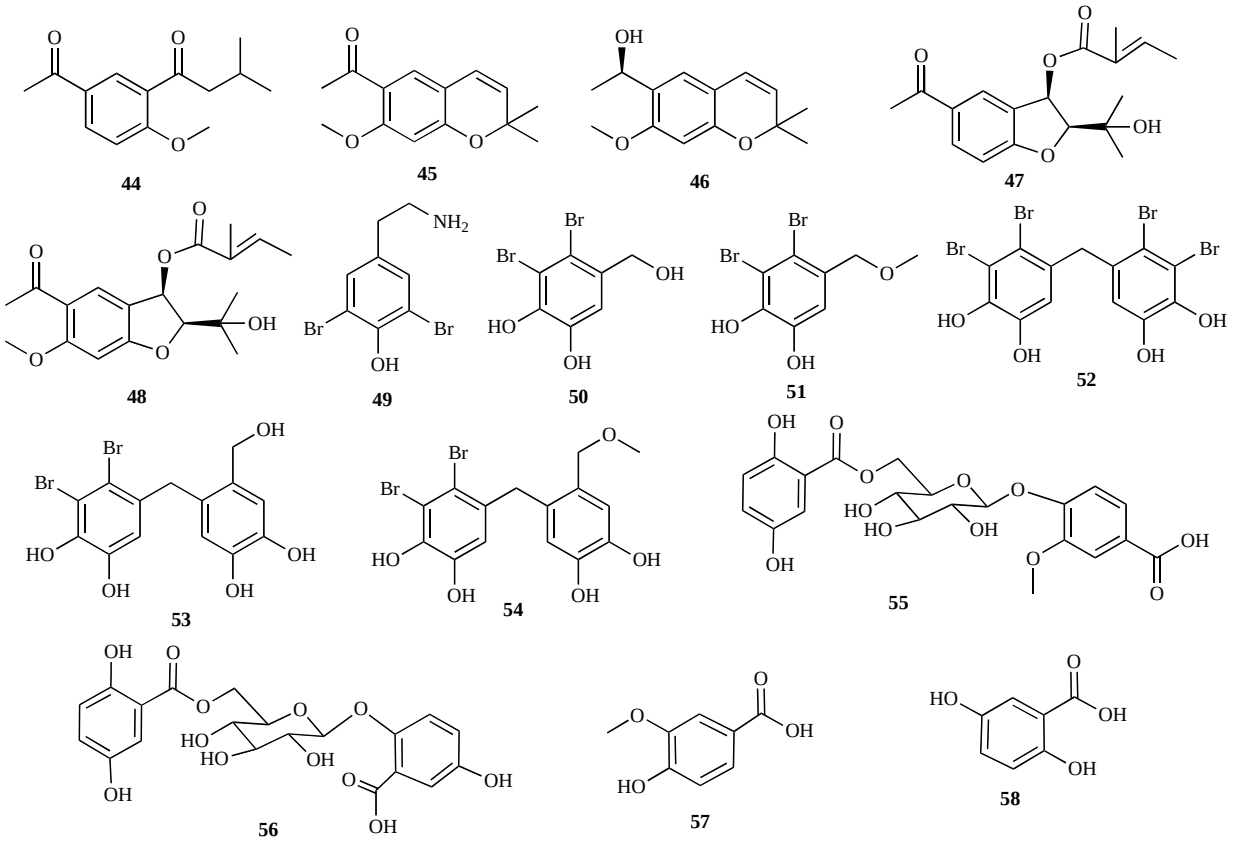



**Fig. (9).** Chemical structures of representative antifungal phenyl derivatives.

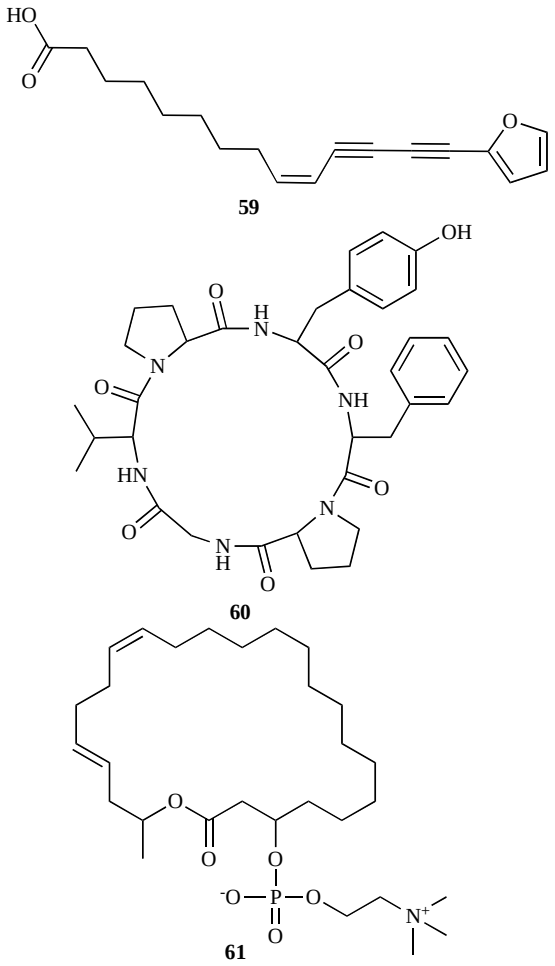



**Fig. (10).** Chemical structures of representative antifungal other compounds.

MIC in the range of 50-100 μg/mL, while gentisic acid showed no effect on these fungi. After hydroxylation of these two compounds, vanillic acid **(57)** showed higher inhibitory effect (MIC = 25 μg/mL) against *E. floccosum* than its glycosides and gentisic acid **(58)** showed significant antifungal effects against *T. rubrum*, *T. mentagrophytes* and *E. floccosum* with an MIC value in the range of 50-100 μg/mL. The result demonstrated that simple phenolic compounds were found to have higher fungitoxic activity than their corresponding glycosides.

### 2.9. Others

Identification and characterization of a diyne-furan fatty acid EV-086 **(59)** were reported from a plant in the literature (Fig. **10**). Diyne-furan fatty acid EV-086 was found from a plant cell culture of *Anarrhinum bellidifolium*. The antifungal activity against *T. mentagrophytes* and *T. rubrum* of this fatty acid was evaluated [54]. Diyne-furan fatty acid EV-086 showed considerably strong activity (MIC = 4 ng/mL). The result indicated that diyne-furan fatty acid EV-086 was a valid antimycotic target for *T. rubrum* and *T. mentagrophytes*.

A proline-rich cyclopeptide was isolated from the roots of *Gypsophila Arabica* [55]. The compound, gypsin B7 **(60)**, exhibited significant antifungal activity against *T. rubrum* with an MIC value of 6.25μg/mL, which showed the same effect as the positive control griseofulvin. The researchers also indicated that gypsin B7 can be synthesized.

Isolation of the chloroform-methanol (1:1) extract of *Eupenicillium shearii* IFM54447 (fungi) yielded a new 24-membered macrolide named eushearilide **(61)**, which showed inhibitory activity against *T. tonsurans*, *T. mentagrophytes* and *T. rubrum* using the agar diffusion method. Hosoe *et al*. [56] found that eushearilide contained a choline phosphate ester moiety and non-conjugated diene according to the complete analysis of the IR, NMR, UV and MS spectral data.

A phenazine-like compound was isolated from the methanol extract of a bacteria source, *Pseudomonas chlororaphis* isolate S105. Dermatophytes such as *E. floccosum*, *T. mentagrophytes*, *T. rubrum and T. tonsurans* can be restrained by 88.5%, 73.6%, 97.9% and 87.1%, respectively [57]. The *P. chlororaphis* culture supernatant had higher inhibition against all the tinea pedis dermatophytes than the phenazine-like compound.

### 2.10. Extracts and Essential Oils

Plant extracts especially essential oils occupied a huge part of natural antifungal agents against tinea pedis. There are two unique advantages of essential oils: firstly, they have high safety for the use in patients; secondly, they present low risk for fungi to develop resistance to the essential oils [58]. The activity of an essential oil can be reasonably attributed to the major or most dominant compounds, and the interaction of these compounds in the essential oils [59]. Most of the essential oils contain various monoterpenes and phenolic compounds, which are often responsible for the antimycotic effect on fungi that causes tinea pedis. The MICs of most of the essential oils generally show higher activity than the positive control.

Khosarvi *et al*. investigated anti-dermatophytic properties of nine plant essential oils, including those from Nigella sativa, Rosmarinus officinalis, Heracleum persicum, Foeniculum vulgare, Menta spicata, Artemisia sieberi, Cuminum cyminum, Ziziphora clinopodioides and Zataria multiflora. All the essential oils showed activities against E. floccosum (No. 19), T. rubrum (No. 29) and T. mentagrophytes (No. 32) with MICs in the range of 0.25-4 mg/mL and with MFC in the range of 0.5-8 mg/mL. The most significant activity was observed with A. sieberi [60].

The antimycotic activities of the bergamot natural essence and its distilled extracts and furocoumarin-free extracts on dermatophytes such as E. floccosum, T. rubrum, T. tonsurans and T. mentagrophytes were studied. MICs against all the strains (v/v) were evaluated for the furocoumarin-free extract (0.08% to 1.25%), distilled extract (0.02% to 1.25%) and natural essence (0.156% to 2.5%) [25].

The essential oil of Otanthus maritimus (L.) Hoffmanns. & Link showed significant antifungal activity against several dermatophyte strains including E. floccosum FF9, T. mentagrophytes FF7 and T. rubrum CECT 2794. Their MIC (v/v) values were determined as 0.16 μL/mL and the MLCs (minimal lethal concentration) were ranging from 0.32 to 0.64 μL/mL. O. maritimus oil contains 40.4-57.2% chrysanthenone, 12.2-15.5% filifolone, 10.1-12.2% cischrysantenyl acetate and 6.7-7.2% α-pinene. Likewise, the essential oil showed no cytotoxicity in this study [61].

Patra et al. found that the essential oil of Foeniculum vulgare exhibited the significant activity against nail-infective fungi, E. floccosum, T. mentagrophytes, T. rubrum and T. tonsurans at the concentrations of 0.2, 0.6, 0.5 and 0.4 μL/mL, respectively. After

48 months of storage under the temperature of up to 80°C, there was no decrease of antifungal effects. Additionally, there were no toxic effects on the cells of mammalian skin exhibited by the essential oil of up to 5% concentration. The oil also exhibited a broad mycocidal spectrum, restraining the hyphal growth of other infective fungi [62].

Zeng et al. also investigated the antifungal effects fennel oil (Foeniculum vulgare L.), and further studied the mechanism of the oil against 3 fungal strains. The results revealed that the oil had strong antifungal activities against T. Tonsurans, T. mentagrophytes and T. rubrum, which exhibited better antifungal effect than the common antifungal drug amphotericin B and fluconazole. The antifungal mechanism of the fennel essential oil was also investigated by transmission electron microscopy experiments and flow cytometry. The results showed that the inhibition effect was caused by damage of the intracellular organelles and plasma membrane. The mitochondrial enzyme activities (succinate dehydrogenase, malate dehydrogenase and ATPase) could be inhibited by fennel essential oil [58].

Oil of Melaleuca alternifolia, namely tea-tree oil exhibited antifungal activity against 58 strains of the clinical isolated fungi. Currently, tea-tree oil is a frequently-used antimicrobial agent in medical treatment. In this study, 8 strains of T. rubrum, 9 strains of T. mentagrophytes, 2 strains of E. floccosum and 10 strains of T. tonsurans exhibited high susceptibility to tea-tree oil [63].

There are 16 strains of antagonistic bacteria isolated form the soil samples of Iran, which were identified as the genera Bacillus, Pseudomonas, Acinetobacter and Streptomyces using 16S rRNA sequence analysis. The inhibitory effect of these bacteria was evaluated aiming at dermatophytes. They showed activities against dermatophytes of two genera Epidermophyton (E. floccosum) and Trichophyton (T. mentagrophytes, T. rubrum, T. tonsurans) by using visual plate agar assay method. Among them, a strain of Pseudomonas chlororaphis isolate S105 was the strongest antagonistic bacterium with growth inhibition from 66.6 % to 99.8% to the dermatophytes in this study [57].

The antifungal activities of Juniperus turbinata and J. communis ssp. alpina, J.oxycedrus essential oils were determined. The composition of the oils was determined by GC and GC/MS analysis. The tested dermatophyte strains (E. floccosum, T. mentagrophytes and T. rubrum) were inhibited by all the essential oils. The oil extracted from the leaves of J. oxycedrus ssp. oxycedrus showed strongest activity, with the MIC and MFC values of 0.08–0.16 μL/mL. And it is shown that 5.5% α-pinene and 5.7% δ-3-carene exist in this oil [64].

The Ocimum gratissimum L. collected from Togo prepared using steam-distilled. The essential oil composition was identified by GC and GC/MS technique, and result shows that 31.24% Thymol, 15.57 % p-cymene, 12.34% γ-terpinene were the major components of the essential oil. The in vitro antifungals assay for O. gratissimum oil was conducted in this study. The assay was recorded with the MICs in the range of 80-150 μL/L on the dermatophytes (E. floccosum, T. mentagrophytes and T. rubrum). Likewise, the MFC (minimum fungicidal concentration) against dermatophytes varied from 300 μL/L to 350 μL/L [65].

Goncalves et al. investigated the essential oils of Seseli montanum subsp. peixotoanum (Samp.) M. Lainz and S. tortuosum L. from Portugal. They found the oils have antifungal activity against E. floccosum, T. mentagrophytes and T. rubrum with the MICs and MLCs range from 0.64 to 2.5 μL/mL [66].

The chemical composition essential oil of Daucus carota subsp. halophilus was studied using GC and GC-MS analysis. Two samples of Daucus carota were collected during the period of flowering umbels (sample 1) and ripe umbel (sample 2). The antifungal activity of D. carota oils were tested on E. floccosum, T. mentagrophytes and T. rubrum, and sample 1 exhibited better antifungal effect than sample 2. They reported that the high content of elemicin in sample 1 can enhance the antifungal activity of the oil, and there was no cytotoxic effect shown at the concentrations ranging from 0.16 to 0.64 μL/mL for about 24h testing period [67].

The essential oil of Vitex agnus-castus L. grown in Italy was studied for its antifungal activity against the dermatophyte strains (E. floccosum, T. mentagrophytes and T. rubrum,) and its chemical composition. Antifungal effect of the leaf essential oil was the strongest, with the MIC values of 0.64 μL/mL for T. rubrum and E. floccosum and 1.25 μL/mL for T. mentagrophytes. GC/MS result showed that 1,8-cineole, sabinene, α-terpinyl acetate, α-pinene, (E)-β-farnesene, (E)-caryophyllene, manool, bicyclogermacrene and spathulenol are the main components in the extracts of all plant organs [68].

The inhibitory effect of essential oils from Syzygium aromaticum L. Merr. Et Perry and Leptospermum petersonii Bailey on the dermatophytes E. floccosum (KCCM 11667), T. rubrum (KCCM 60443) and T. mentagrophytes (KCTC 6077) were evaluated by the agar diffusion method. S. aromaticum oil presented over 80% inhibition against the tested fungal strains at a concentration of 0.2 mg/mL. Clove oil shows strong inhibitory effect on the hyphal growth of T. mentagrophytes and T. rubrum at a concentration of 0.2 mg/mL. Eugenol was the strongest antifungal component in the clove oil against T. mentagrophytes. Morphological changes (disruption to the expansion of the endoplasmic reticulum and destruction to the cellular wall and membrane) in the hyphae of T. mentagrophytes were observed using transmission electron microscopy after administration with 0.11 mg/mL eugenol. All of the dermatophytes tested except T. rubrum were sensitive to L. petersonii oil with more than 90% inhibition at a concentration of 0.2 mg/mL. And geranial was reported to be the most potent antifungal component of L. petersonii oil [69].

Marongiu et al. found that the main components of Smyrnium olusatrum L. essential oils from Portugal and Italy were different. But Portuguese and Italian essential oils both contain α-pinene (31.9% vs. 1.2%) and β-phellandrene (67.3% vs. 42.7%). The oils presented antifungal activity against E. floccosum, T. mentagrophytes and T. rubrum with an MIC value of 0.32 μL/mL [70].

The essential oils extracted from the leaves and flowers of Calea clematidea Bakeristillati were collected, and their chemical composition was identified by GC and GC/MS. The antifungal effects of the oils were evaluated in this study. A new natural epoxy terpenoid, clemateol, exists in the essential oil of the leaves, while thymol methyl ether is the main constituent in the essential oil of the flowers (80 %). The oil of the leaves exhibited moderate antifungal effect on E. floccosum, T. tonsurans, T. menthagrophytes var i nterdigitale and T. rubrum [42].

The essential oils of Baccharis semiserrata and B. uncinella from Southern Brazil were studied for their antifungal activity. Baccharis uncinella oil actively inhibited T. mentagrophytes. Both the leaf and twig essential oils from B. semiserrata showed inhibitory effect against E. floccosum and T. mentagrophytes. It was found that T. rubrum could be inhibited by semiserrata leaf essential oil [71].

Seseli containing numerous species played an important role in folk medicine since ancient times. It is shown that E. floccosum and T. mentagrophytes were inhibited by the essential oil of Seseli annuum wild-growing in Serbia with the MICs of 25 and 12.5 μL/mL, respectively [72].

Apium graveolens L. (wild celery) often serves as seasoning in people's diets. Marongiu et al. investigated the antifungal activities of the volatile fractions of A. graveolens from Italy and Portugal, respectively. The oil from Italy had high content of neophytadiene and present stronger antifungal activity than the oil from Portugal against E. floccosum, T. mentagrophytes and T. rubrum with the MIC values of 0.04–0.64 μL/mL [73].

The main components of Macleaya cordata (Willd) R. Br, a traditional herb against malignant sore and skin disease, were alkaloids. Macleaya cordata alkaloids had significant effect on these five kinds of skin fungi. The antifungal activity against five strains of five skin fungus of M. cordata alkaloids was determined. The MIC of T. rubrum and E. floccosum were 1.6 mg/mL, The MIC against T. mentagrophytes was 0.8 mg/mL [74].

Purified phlorotannin obtained from three brown seaweeds, Fucus spiralis Linnaeus, Cystoseira usneoides (Linnaeus) M. Roberts and Cystoseira nodicaulis (Withering) M. Roberts presented antifungal activity against E. floccosum, T. mentagrophytes and T. rubrum with the MIC values of 3.9-31.3mg/mL. The antifungal mechanism of the purified phlorotannins was investigated. Ergosterol composition of fungal cell membrane was affected by the phlorotannin extracts from C. usneoides and C. nodicaulis. The levels of chitin of cell wall composition of the dermatophytes were reduced by the phlorotannin extracts of F. spiralis [75].

Senna alata Linn is an ornamental shrub. It is widely used in folk medicine of Nigeria for the treatment of several skin infectious diseases. The ethanol extracts of S. alata L. leaves exhibited marked antifungal effects on T. mentagrophytes and E. florrcosum. The biochemical analysis indicated the presence of carbohydrates, saponins, tannins, anthracionones and alkaloids from the extract [76].

Barlian et al. investigated the antifungal activity of green sea turtle (Chelonia mydas) eggshell extract. This result showed that 8% w/v green turtle eggshell extract has inhibitory activity against T. mentagrophytes, as also proven by Scanning Electron Microscopy results [77].

The methanol extract of the leaves of Anogeissus accuminata showed activity against T. mentagrophytes (MTCC8476) and T. Rubrum (MTAA8477) (MTCC8469). The investigators assumed that tannin and flavonoids were the bioactive constituents [78].

Ibrahim et al. studied the antifungal activity of 26 natural commercial essential oils against T. rubrum, E. floccosum and T. mentagrophytes. The oils of Prunus armeniaca, Olea europaea, Mentha piperita and Prunus dulcis var. amara were the strongest antifungal agents. The mixture of these four essential oils was the most potent antifungal agent followed by the mixture of two-oil combined extracts and the weakest was pure extracted oils [79].

The water extract of the yellow roots (Arcangelisia flava Merr) was active against T. rubrum [80].

The ethanol extracts of the leaves and seeds of Moringa oleifera Lam showed antifungal activities against E. floccosum, T. rubrum and T. mentagrophytes with the MICs value of 0.625-2.5mg/mL [81].

Shin and Lim determined the antifungal effects of the essential oils extracted from several plants. The essential oils obtained from Pelargonium graveolens, Eukalyptus golbulus, Thymus vulgaris, Cymbopogon citratus exhibited antifungal activity against T. tonsurans, T. mentagrophytes and T. rubrum with the MICs ranging from 0.125 to 1 mg/mL [82].

The essential oils from the dried flowers and leaves of Myrtus communis showed activity against E. floccosum, M. canis and T. rubrum. Monoterpene derivatives are the main compounds of the oils: linalool (2.7 and 14.8%), linalyl acetate (0.5 and 9.5%), 1,8-cineole (21.9 and 13.3%), and α-pinene (50.8 and 33.6%) [83].

The volatile oil of Stenachaenium megapotamicum and the main constituent thymol showed antifungal activity, especially presenting selectivity against the filamentous fungi, such as E. floccosum and T. rubrum. Furthermore, the nanoemulsion containing volatile oil of S. megapotamicum showed significantly reduction of MIC and MFC compared with the activity of thymol and the pure oil [84].

Lippia alba (Miller) N.E. Brown is an plant with aromatic flavor and has been commonly used in Brazilian traditional medicine. L. alba oil showed antifungal activity with MICs of 39 and 156 mg/mL against T. rubrum and E. floccosum, respectively. Also the essential oil contained high content of linalool, which affected the virulence factors of dermatophytes by inhibiting the activity of proteases and keratinases [85].

The ethanol extracts of the marine macroalgae, Digenea simplex (Wulfen) Agardh (MAC51231), Rhodophyta Hypnea musciformis (Wulfen) Lamouroux (MAC51234), Sargassum vulgare Agardh (MAC51236), Padina gymnospora (Kutzing) (Sonder, MAC51235), Phaeophyta member Dictyota dichotoma (Hudson) Lamouroux (MAC51230) and Ulva lactuca Linnaeus (MAC51238) (Chlorophyta) showed inhibition against fungi growth. Likewise, the methanol extract of H. musciformis inhibited the growth of T. rubrum, T. tonsurans and T. mentagrophytes with MIC value in the range of 0.031-4.0 μg/mL [86].

Kuiate et al. found that the extract from the leaves of Cupressus lusitanica Mill. in Cameroom had antifungal properties against T. tonsurans and T. rubrum. The highest anti-dermatophytic activities of the extract fraction showed an MIC value at 125 μg/mL [87].

The species from Sapindaceae family are frequently used in traditional medicine of many places in the world. The fruit extract of Sapindus emarginatus showed significant antifungal potential with the MICs at 15.6 mg/mL against dermatophyte T. rubrum, at 62.5 mg/mL against E. floccosum [88].

The essential oils of rosemary (Rosmarinus officinalis L.) and sage (Salvia officinalis) showed activity against Epidermophyton floccosum, Trichophyton mentagrophytes, T. tonsurans and T. rubrum [89].

The essential oils of Callistemon lanceolatus and Cuminum cyminum showed 100% toxicity against T. tonsurans. The activity was sustained at the higher temperature, increased inoculum density and long storage period [90].

The essential oil fraction of Angelica dahurica Bentham et Hooker f. and the main compound α-pinene exhibited marked inhibiting activities against Trichophyton species (T. rubrum, T. mentagrophytes and T. tonsurans) with the MICs between 0.12 mg/mL and 0.25 mg/mL [91].

Henna (Lawsonia inermis) leaf can generate an orange-red dye which is widely used for decorating hands and nails. Gozubuyuk et al. found that the henna paste showed the potent antifungal activity against T. rubrum, T. mentagrophytes and T. tonsurans (20 to 50 mm inhibition zone) [92].

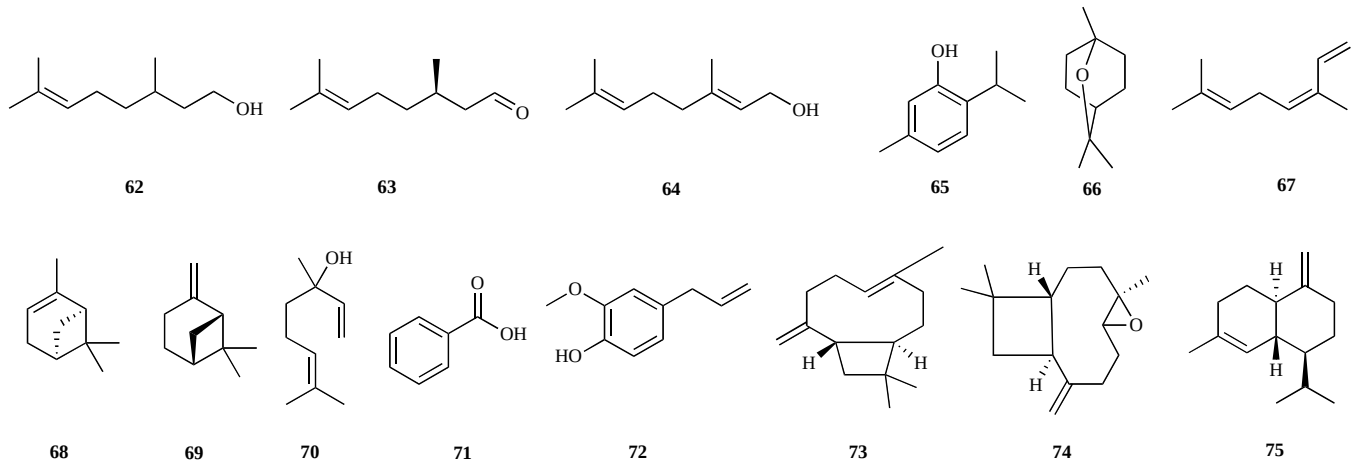



**Fig. (11).** Structures of main constituents in essential oils.

Metschnikowiaceae may show natural, strain-dependent antifungal properties, and thus acts as natural pesticides in the field of agriculture. Also the strain of Metschnikowia IHEM 25107 presented inhibitory effect on T. rubrum, T. mentagrophytes and T. tonsurans [93].

Growth inhibition of Matricatia recutita flower oil against the dermatophytes using serial two-fold concentrations in the range from 2.5 to 80 mg/mL. The result revealed that the inhibition of T. mentagrophytes is in the range 11.40 to 96.65%, while 27.79 to 100% for T. rubrum and 45.73 to 100% for T. tonsurans [94].

The following 14 compounds are found as the major constituents in various essential oils extracted from plants (Fig. **11**).

Citonellol **(62)** and citonellal **(63)** have similar structures, and they differ by citonellol owning a hydroxy group but citonellal having an aldehyde group at the same carbon. These two monoterpenoids were found in the essential oils of two plants, respectively. Shin *et al*. [82] reported that there was 17.2% of citonellal in the essential oil of the leaves of *Pelargonium graveolens*, which showed antifungal activity against *T. rubrum*, *T. mentagrophytes* and *T. tonsurans* with MIC values at 0.5mg/mL. On the other hand, the essential oil of *Leptospermum petersonii* Bailey containing 21% of citonellal presented a good inhibition activity against *E. floccosum*, *T. mentagrophytes* and *T. rubrum* at the concentration of 0.2 mg/mL [69]. Interestingly, both essential oils of *P. graveolens* oil and *L. petersonii* contained the monoterpenoid geranial at the concentration of 5.89% [82] and 28% [69], respectively. Geranial **(64)**, a citronellol analog containing an extra double bond, showed higher antifungal activity than citonellol and citonellall. However, the antifungal effect of the two essential oils was better than the monomers they contained.

Thymol **(65)** was found to be the main constituent in the essential oil of six plants, which are *Thymus vulgaris*, the leaves and flowers of *Stenachaenium megapotamicum*, *Nigella sativa*, the aerial parts of *Ocimum gratissimum* L., *Zataria multiflor* and *Ziziphora clinopodioides* [60,65,82,84]. Thymol exhibited moderate antifungal activity against *T. rubrum*, *T. mentagrophytes* and *T. tonsurans* with MIC values at 0.5 mg/mL [82], and against *E. floccosum* with an MIC value of 50 μL/L [65]. Among these six essential oils, the volatile oil of *S. megapotamicum* presented the strongest antifungal activity against *T. rubrum* and *E. floccosum* [84].

1, 8-Cineole **(66)** was also found as a major component in the essential oils of seven plants, which are the leaves of *Eukalyptus golbulus*, *Vitex agnus-castus* L, the leaves of *Myrtus communis* L, *Melaleuca alternifolia* (tea-tree oil), and the aerial parts of *Myrtus nivellei* Batt. & Trab., *Cuminum cyminum* and *Rosmarinus officinalis* [63, 68, 82, 83, 89, 90]. While 1, 8-cineole showed moderate antifungal activity against *T. tonsurans*, *T. mentagrophytes* and *T. rubrum*, the essential oil of *E. golbulus* exhibited better antifungal effect than the pure 1, 8-cineole [82]. The essential oils of *M. alternifolia*, *C. cyminum* and *R. officinalis* all showed a good antifungal effects according to the results from the in vitro antifungal screening test [60, 63].

The essential oils extracted from the aerial parts of *Seseli annuum* and *S. tortuosum* L. both contained Z-β-ocimene **(67)**, a monoterpenoid, presented good antifungal activity against *E. floccosum*, *T. mentagrophytes* and *T. rubrum*. The *S. tortuosum* oil and the *S. annuum* oil showed similar antifungal activity with the MIC and MFC at 0.64 μL/mL against *E. floccosum* [66, 72]. However, the *S. tortuosum* essential oil caused cytotoxic properties to human cells at the concentrations above 0.64 μL/mL.

The *S. tortuosum* oil and the essential oil obtained from *Seseli montanum* subsp. Peixotoanum both contained two other monoterpenoids, α-pinene **(68)** and β-pinene **(69)** as the major constituents. α-Pinene showed good antifungal activity against *T. mentagrophytes*, *T. rubrum* and *E. floccosum*, while the antifungal effect of β-pinene was weak [66]. The results also demonstrated that the *S. tortuosum* oil had better effects against *T. rubrum*, *T. mentagrophytes* and *E. floccosum* than the *S. montanum* oil.

α-Pinene was also identified in the essential oil of *Stachys scardica* (Griseb.) Hayek by GC and GC–MS [95]. It is observed that the *St. scardica* oil showed better effect against *T. mentagrophytes* and *E. floccosum* than α-pinene. α-Pinene was also the main component of the antifungal essential oils or extracts from 10 plants: *Cuminum cyminum*, *Rosmarinus officinalis*, *Baccharis uncinella* D.C., leaf of *B. semiserrata* D.C., *B. semiserrata* D.C. twig, *Vitex agnus-castus* L., a fraction of the hexanic leaf extract of *Cupressus lusitanica*, the seeds of *Fennel vulgare* and the roots of *Angelica dahurica* Bentham et Hooker f [58, 60, 68, 71, 87, 91], which indicates that α-pinene may be an important compound responsible for the antifungal activity in plant kingdom.

Another significant antifungal monoterpenoid, linalool (**70**), was found in the essential oil of *Stachys recta* L. [95]. Linalool is also a common constituent in the antifungal essential oils of some other plants. There were five plants that were reported to contain linalool as a major constituent. These plants are the leaves of *Lippia alba* (Miller) N.E. Brown, the leaves of *Myrtus communis* L, *Cumi-*

*num cyminum*, *Rosmarinus officinalis* and *Citrus bergamia* [25, 60, 83, 85, 89].

Benzoic acid **(71)** is the active substance in the essential oil of the leaves of *Cymbopogon citratus*. Benzoic acid exhibited moderate antifungal effect against *T. rubrum*, *T. mentagrophytes* and *T. tonsurans* with MIC values at 0.25 mg/mL [82]. But the *C. citratus* oil displayed more effective activity than benzoic acid, indicating that there may be other effective antifungal agents existing in the *C. citratus* oil.

Park *et al*. [67] reported that a simple phenylpropanoid, eugenol **(72)**, was the main constituent in the antifungal essential oil extracted from *Syzygium aromaticum* L. Merr. Et Perry. By the microdilution and agar diffusion methods, the fungus *T. mentagrophytes* was completely inhibited by eugenol at the concentration of 0.2 mg/mL.

Skaltsa *et al*. identified two sesquiterpenes, namely β-caryophyllene **(73)** and β-caryophyllene oxide **(74)** from the essential oil of *Stachys germanica* L. ssp. *Heldreichii* (Boiss.) Hayek and *Stachys euboica* Rech. [95]. The two sesquiterpenes both inhibited *T. mentagrophytes* and *E. floccosum* in this experiment with MIC values in the range from 0.06-0.1 mg/mL. β-Caryophyllene was also found in four other antifungal essential oils: the leaves of *Baccharis semiserrata* D.C., the twigs of *Baccharis semiserrata* D.C., *Baccharis uncinella* D.C. and *Vitex agnus-castus* L. [68, 71, 95]. Skaltsa et al. also reported that a significant antifungal sesquiterpene (cadinene) **(75)** existed in the essential oils from *Stachys scardica* (Griseb.) Hayek and *Stachys euboica* Rech [95].

## 3. FUTURE PROSPECTS

Natural products are the most important sources of new drugs [96]. As mentioned in this review, many active compounds, essential oils and plant extracts with antifungal activity against tinea pedis dermatophytes are discovered from plants, animal and microorganisms. Essential oils usually used as antifungal agents in many folk medicines [63, 68, 71, 72]. Although essential oils exhibit excellent safety, their instability and volatility still need to be considered. It is important to note that some studies used pharmaceutics methods to enhance antifungal effect and reduce drug toxic reaction. Danielli *et al*. [84] mentioned that using nanoparticulate systems as carriers to deliver antifungal agents could stabilize and decrease volatility of essential oils by a suitable surfactant, along with enhancing the antifungal effect through the ability to carry substances passing through the cell membrane. Improving the stability and reducing volatility will extend the retention time of the essential oil on the affected site of tinea pedis and decrease skin irritability caused by the slow release of drug. There are a lot of other studies, which prove that nanoemulsion is a good dosage form for external formula of essential oil [97, 98]. Therefore, the nanoemulsion is a potential pharmaceutical research direction to develop essential oils for the treatment of tinea pedis, and further study is needed for practical application.

As commented earlier, there are a lot of volatile extracts (essential oils) and volatile compounds (monoterpene and sesquiterpene) showing the antifungal activity, so the extraction technique need to be designed in order to reduce the loss of the active substances during extraction. Extraction technique using carbon dioxide of supercritical state (SFE) is a good choice for the extraction of volatile antifungal agents from natural sources. Lower temperature, low water content and omitting of the step of separating the extractant are three main advantages of SFE. SFE can also realize a purer extraction of substance due to its selectivity [47]. This potential method is a good choice for the extraction of volatile agents for tinea pedis.

Mercer *et al*. [28] investigated that using prodrug approach to deliver the active compounds against tinea pedis dermatophytes could reduce the irritant side effects caused by solvents required by topical application, improve ADME properties and increase selectivity for the intended target. In this study, an active antifungal coumarin was modified into an inactive water-soluble coumarin glycoside, and the antifungal effect could be activated by β–glucosidase activity when the agent was applied on the site of infected skin. This method can also be used for the preparation of antifungal compounds with similar properties and chemical structure.

In general, a good-quality antifungal natural agent not only need to show high antimycotic efficacy and low toxicity, but also has to consider the problem of expiration. Normally, cell cytotoxicity assays and in vitro susceptibility testing is needed during an investigation of an antifungal agent. However, what has to be considered is when the fungitoxicity agent will expire, which will provide a significant reference for the practical application.

## CONCLUSION

The collected literatures presented abundant information about natural products against four common tinea pedis dermatophytes (*T. rubrum*, *T.mentagrophytes*, *T. tonsurans* and *E. floccosum*), which can provide a valuable reference for the related research of natural antifungal drugs in the future.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interests.

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