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A review of the most effective medicinal plants for dermatophytosis in traditional medicine

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Abstract

Fungi can evade the immune system via different processes, including recombination, mitosis, and expression of genes involved in oxidative stress responses. These processes can lead to chronic fungal diseases. Despite the growth of health care facilities, the incidence rate of fungal infections is still considerably high. Dermatophytes represent the main cause of cutaneous diseases. Dermatophytes attack keratinized tissues, such as nail, hair, and stratum corneum, due of their gravitation towards keratin, which leads to dermatophytosis. Medicinal plants have long been used to treat different diseases, and in the recent years, use of plant-based products to fight fungal, bacterial, and parasitic infections have attracted extensive attention. This is because the use of medicinal plants has many advantages, such as decreased costs and fewer side effects. This review article was conducted to report medicinal plants with anti-dermatophytosis properties. Seventy-six articles were retrieved from databases Google Scholar, PubMed, ScienceDirect, and Scopus. After exclusion of duplicate and irrelevant articles, 54 articles were selected. Of the remaining articles, 23 articles were screened and included in this study. According to the findings, Azadirachta indica, Capparis spinosa, Anagallisarvensis, Juglans regia, Inula viscosa, Phagnalon rupestre, Plumbago europaea, Ruscus aculeatus, Ruta chalepensis, Salvia fruticosa, Artemisia judaica, Ballota undulate, Cleome amblyocarpa, Peganum harmala, Teucrium polium, Aegle marmelos, Artemisia sieberi, Cuminum cyminum, Foeniculum vulgare, Heracleum persicum, Mentha spicata, Nigella sativa, and Rosmarinus officinalis are the most effective plants against dermatophytes which have been identified to date.

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1. Background

Fungal infections are divided into two types: primary and opportunistic. Opportunistic infections occur mainly in immunocompromised hosts, but primary infections may also occur in hosts with a healthy immune system. Besides that, fungal infections can be systemic or local [1]. Fungi can evade immune system responses via different processes, including recombination, mitosis, and expression of genes involved in oxidative stress responses, and, therefore, can cause chronic fungal diseases. Despite the expansion of health care facilities, the incidence rate of fungal infections is still very high. For example, fungal infections are the fourth leading skin diseases worldwide. In 1984, 984 million people suffered from fungal skin infections. Secondary infection, deafness, tinea, and skin lesions are some of the complications due to fungal infections [2].

Dermatophytes represent the main cause of cutaneous diseases. Dermatophytes attack keratinized tissues, such as nail, hair, and stratum corneum, causing dermatophytosis [1]. Dermatophytosis is very common and can be life-threatening for the elderly and immunocompromised people. The highest prevalence of this disease is seen in people between the ages of 20-31 years. Dermatophytes cause skin scaling, create gray loops in the skin, and cause hair loss and loosening and nail deformities [3]. Dermatophytes have three genera: Microsporum, Tricophyton, and Epidermophyton, whose reservoirs are soil, animals, and humans [4].

The cloning process of dermatophytes is associated with the release of proteolytic enzymes and spontaneous stimulation of the host inflammatory responses, and causes dermatophytosis or tinea (ringworm). Inflammatory symptoms at the infection site include redness, swelling, and alopecia. Swelling causes transmission of infection to other parts of the body that causes circular lesions. The severity of infection due to dermatophytes depends on age, surrounding temperature, humidity level, and health and social conditions [5]. Different genera of dermatophytes have many phenotypic and genotypic similarities that make their detection challenging. Colony testing, microscopic examination of morphology, genotypic tests, and in some cases, detection of nutritional requirements, temperature tolerance, and urease production are used to detect dermatophytes [6]. Some parts of the body, such as nail subdistal region and area between the fingers, are more prone to dermatophytosis because they are exposed to the fungus in the long-term and provide certain factors, such as sugar and pH, that are required for the fungus [5].

Dermatophytes can induce increased immediate, delayed, or mediated cell susceptibility. In infected people with a normal immune system, response to increased susceptibility is induced within 30 days and is spontaneously recovered after 50 days. Dermatophyte distribution is different across the world [5]. In the past half-century, *Tricophyton rubrum* has been the most common dermatophyte, and in poor developing countries, *Mycosis* is endemic and affects a large number of children. *Epidermophyton floccosum* was common during two decades, i.e. 1980-1990, and among the isolated dermatophytes, is the leading dermatophyte in Iran with 31.4% prevalence [7,8]. In eastern and southern Europe, low quality of life has caused increased infection with animal-friendly dermatophytes. As well, urbanism, contacts, and travels have led to increased prevalence of *T. rubrum* [9].

Medicinal plants have long been used to treat different diseases in developed and developing countries [10–13]. In recent years, medicinal plants have also attracted much attention because their uses have had many benefits, such as decreased expenses and fewer side effects [14–17]. Use of plant-based products to fight fungal, bacterial, and parasitic infections has also been considered as an effective approach [7,8]. Moreover, certain measures can be taken to produce drugs by identifying the active compounds of the plants [18,19]. The antifungal effects of some plants, such as ginger, *Narcissus tazetta*, *Myrtus communis*, dill, cilantro, garlic, onions, henna, oak, black beans and thyme, on fungal infections have already been demonstrated. Flavonoids, alkaloids, tannins, citronellol , geraniol, thymoquinone, and phenolic compounds are some of the antifungal or other microbial active compounds found in these plants [20,21]. This review article was conducted to report medicinal plants with anti-dermatophytosis properties.

2. Materials and Methods

We searched the keywords "Medicinal plants", "Traditional medicine" with the keyword "Dermatophytosis" in the *Google Scholar*, *PubMed*, *Science Direct*, and *Scopus* databases.

After the first search, seventy-six articles were found to be relevant.

After exclusion of duplicates and irrelevant articles by checking article topics, 54 articles were selected. After reviewing abstracts of the remaining articles, 23 articles were included in this study.

3. Results

Fungal diseases are known as mycoses, according to the National Institute of Allergies and Infectious Diseases. Mycoses can affect various parts of the body, including body hair, lungs, nervous system, nails, and skin. The most common types of fungal infections are tinea infections and fungal infections of hair, skin or nails; these include athlete's foot, jock itch, candida, and vaginal yeast infections. Fungal skin infections usually involve itching, skin discoloration, and changes in skin texture in the affected area.

Certain herbs are known as fungicides, or agents that destroy fungi and their spores. Since fungal infections are often tenacious and difficult to eliminate, several different medicines may be necessary to provide therapeutic relief. On the other hand, the routine fungicides like azoles have several side effects.

According to findings of the study herein, *Azadirachta indica*, *Capparis spinosa*, *Anagallisavensis*, *Juglans regia*, *Inula viscosa*, *Phagnalon rupestre*, *Plumbago europaea*, *Ruscus aculeatus*, *Ruta chalepensis*, *Salvia fruticosa*, *Artemisia judaica*, *Ballota undulate*, *Cleome amblyocarpa*, *Peganum harmala*, *Teucrium polium*, *Aegle marmelos*, *Artemisia sieberi*, *Cuminum cyminum*, *Foeniculum vulgare*, *Heracleum persicum*, *Mentha spicata*, *Nigella sativa*, and *Rosmarinus officinalis* are the most effective plants on dermatophytes that have been identified to date. Various form of extracts and essences of these plants were found to have growth inhibition or killing effect on dermatophytosis agents and their pathogenicity. Most of the plants belong to family Lamiaceae. All the plants have very good effects against dermatophytosis agents in either minimum inhibitory concentration test (MIC) or in minimum fungicidal concentration test (MFC), and other tests. Even some clinical dermatophytosis isolates show drug resistance from these plants. **Table 1** shows further information about the botanical names, studied doses, and effects of these plants.

4. Discussion

According to the findings of the present study, *A. indica*, *C. spinosa*, A . *avensis*, *J. regia*, *I. viscosa*, *P. rupestre*, *P. europaea*, *R. aculeatus*, *R. chalepensis*, *S. fruticosa*, *A. judaica*, *B. undulate*, *C. amblyocarpa*, *P. harmala*, *T. polium*, *A. marmelos*, *A. sieberi*, *C. cyminum*, *F. vulgare*, *H. persicum*, *M. spicata*, *N. sativa*, and *R. officinalis* are the most effective plants on dermatophytes that have been identified to date.

Overall, many of the sulfuric compounds, phenolic compounds, flavonoids, tannins, and anthocyanins in the plants cause antifungal effects. Here, in this review article, we touched on the active compounds of the reported plants according to phytochemical investigations. Eugenol is the main antifungal compound of *O. sanctum* [45]. Tetranortriterpenoid has been demonstrated to be main antifungal compound present in *A. indica*, while some other compounds, such as 6-deacetylnimbin, azadiradione, nimbin, salannin and epoxyazadiradione, are considered main active compounds of *A. indica* with antifungal activity [46]. Moreover, rutin, tocopherols, carotenoids, and vitamin C have been confirmed to be the antimicrobial and antifungal compounds of *C. spinosa*. Glycosidic saponin is the antifungal active compound of *A. arvensis* [47].

A study on *C. amblyocarpa* demonstrated that this plant contained a number of valuable fatty acids, such as stearic acid, oleic acid, and linoleic acid. In addition, *C. amblyocarpa* contained some other compounds, including vitamin C, gallic acid, gallotannins and iridoid, that have many properties, namely antifungal [48]. In *A. judaica*, certain antifungal active compounds

Table 1. The botanical name,studied dose, and effect of medicinal plants effective on dermatophytosis

Row	Botanical name	Family	Therapeutic effects
1	Ocimum sanctum Linn.	Lamiaceae	The results of testing MIC* and MFC** demonstrated that 200 microg/ml of *O. sanctum* leaf extract had antifungal effects against clinical isolates of dermatophytes [22].
2	*Azadirachta indica*	Meliaceae	Studies on MIC and MFC of *A. indica* demonstrated that 15 microg/ml of this plant's seed extract exerted significant effects on elimination and prevention of the growth of different dermatophytes [23].
3	*Capparis spinosa*	Capparidaceae	Studies on MIC and MFC indicated that 15 microg/ml of *C. spinosa* exerted full inhibitory effects on the growth of *Microsporumcanis* and *Tricophytonviolaceum* as well as great inhibitory effect on *Tricophytonmentagrophytes* [24].
4	*Anagallis arvensis*	Primulaceae	According to experiments conducted on MIC and MFC of hydroalcoholic *A. arvensis* extract, 15 microg/ml of this extract caused full inhibition of *T. violaceum* growth, and inhibited the growth of *M. canis* and *T. mentagrophytes* to a great extent [25].
5	*Juglans regia*	Juglandaceae	Three and 5 microg/ml of *J. regia*, according to agar dilution, led to full inhibition of the growth of *M. canis* and *T. violaceum*. Moreover, 0.6 microg/ml of *J. regia* caused 97.6% inhibition of *T. mentagrophytes* growth [26] .
6	*Inula viscosa*	Compositae	According to agar dilution, 18.5 and 20 microg/ml of aqueous *I. viscosa* extract exerted great inhibitory effects on *T. violaceum*, *M. canis*, and *T. mentagrophytes*, respectively, and caused inhibition of *T. violaceum* growth [27].
7	*Phagnalon rupestre*	Compositae	P. rupestre is from family Asteraceae. According to drop vapor diffusion, the active compounds of this plant at 128-132 mg/ml can exert potent (around 90%) inhibitory effects on dermatophytes [27] .
8	*Plumbago europaea*	Plumbaginaceae	Study of *P. europaea* antifungal effects indicated that this plant exerted 87%, 88.4%, and 100% inhibitory effects at 20, 19, and 15 microg/ml concentrations on *M. canis*, *T. mentagrophytes*, and *T. violaceum*, respectively [28] .
9	*Ruscus aculeatus*	Liliaceae	Study on *R. aculeatus* indicated that its extract caused inhibition of three genera of dermatophytes with 83.6%, 86.3%, and 100% inhibition of *M. canis*, *T. mentagrophytes*, and *T. violaceum* at MIC of 35, 29, and 15 microg/ml, respectively [29] .
10	*Ruta chalepensis*	Rutaceae	*R. chalepensis* can exert inhibitory effects on both bacteria and fungi. *R. chalepensis* essential oil at 512 microg/ml caused 90-100% inhibition of *M. canis* growth [30] .
11	*Salvia fruticosa*	Labiatae	*. fruticosa* essential oil exerted moderate antifungal effects on *Tricophyton rubrum* according to disk diffusion method [31] .
12	*Artemisia judaica*	Asteraceae	The MIC of *A. judaica* essential oil was derived 0.64 microg/ml for *Epidermophyton floccosum*,*T. rubrum*, *M. canis*, *Microsporiumgypseum*, *Tricophyton verrucosum*, and *T. mentagrophytes* [32].

* Minimum inhibitoryconcentration; ** minimum fungicidal concentration

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Row	Botanical name	Family	Therapeutic effects
13	*Ballota Undulate*	Lamiaceae	*B . undulate* can exert inhibitory effect on *T. rubrum* with 50 mg/dL of ethanol solvent and ethyl acetate, chloroform, and N-hexane solvents ([33] .
14	*Cleome amblyocarpa*	Cleomaceae	*C. amblyocarpa* can exert inhibitory effect on *T. rubrum* with over 150 mg/dL of ethanol, ethyl acetate, and chloroform solvents as well as with 125 mg/dl of N-hexane solvent [34] .
15	*Peganum harmala*	Zygophyllaceae	*P . harmala* can exert inhibitory effect on *T. rubrum* with 3.3 mg/dL of ethanol solvent, 3 mg/dl of ethyl acetate, 3.2±0.4 mg/dl of chloroform solvent, and 3.0±0.0 mg/dl of N-hexane solvent [35] .
16	*Teucrium polium*	Lamiacea	*T. polium* extract exerted 89.6% and 100% inhibitory effect on *T. rubrum* and *M. canis*, respectively, at 45 microg/ml concentration according to well diffusion, microdilution, and poisoned food technique [36] .
17	*Aegle marmelos*	Rutaceae	The MIC test of *A. marmelos* essential oil indicated that 500 microg/ml of this essential oil exerted inhibitory effect on dermatophytes [37] .
18	Artemisia sieberi	Asteraceae	The effect of *A. sieberi* essential oil on *T. rubrum*, *T. verrucosum*, *Tricophyton schoenleinii*, *T. mentagrophytes*, *M. canis*, and *M. gypseum* was investigated by adding 4 microL of the essential oil to disk; *A. sieberi* essential oil exerted the most potent inhibitory effect on *T. rubrum* and the lowest inhibitory effect on *M. gypseum*. *A. sieberi* essential oil MIC for these fungi was investigated and the fungi's growth was found to be inhibited fully at 1-8 microg/ml of this essential oil depending on the type of the studied fungus [38] .
19	*Cuminum cyminum*		After 7-day treatment of the culture medium with different doses of *C. cyminum* essential oil, *T. rubrum* was eliminated by all doses, and *M. gypseum* growth was inhibited by 85% by the lowest dose and completely by other doses of the essential oil [39] .
20	*Foeniculum vulgare*	Apiaceae	The inhibitory effect of *F. vulgare* essential oil on the growth of *T. rubrum* and *T. mentagrophytes* mycelia was investigated. *F. vulgare* essential oil at 0.2, 0.4, and 0.5 microg/ml exerted antifungal effects [40].
21	Heracleum persicum	Apiaceae	The antifungal effect of *H. persicum* on *T. mentagrophytes*, *T. rubrum*, *E. floccosum*, *M. gypseum*, and *Microsporumkenisbe* was investigated by MIC and MFC. This plant at 0.25-4 exerted inhibitory effects on these dermatophytes [41].

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Row	Botanical name	Family	Therapeutic effects
22	*Mentha spicata*	Lamiaceae	The antifungal effect of *M. spicata* essential oil on *T. rubrum* and *M. gypseum* was investigated by disk diffusion method and found to be potent. *M. spicata* essential oil up to 16 and 36 ml inhibited the growth of *T. rubrum* and *M. gypseum*, respectively [42].
23	*Nigella sativa*	Ranunculaceae	The effects of *N. sativa* essential oil, methanolic extract, and aqueous extract on *T. mentagrophytes*, *M. canis*, and *M. gypseum* were investigated by disk diffusion method. The essential oil was found to have the most potent effect [43].
24	*Rosmarinus officinalis*	Lamiaceae	The antifungal effect of *R. officinalis* on *M. canis* isolates was investigated by MIC and MFC that were derived 2.5 and 7.5 microg/ml, respectively, at which the fungi were fully inhibited. Besides that, four of seven cats treated with different combinations of plant-based extracts all of which contained *R. officinalis* were fully recovered. Three of the four recovered cats had negative culture and one had positive culture [44].

were identified, including camphor, piperitone, and ethyl cinnamate [49], while 3-hydroxy-(5-beta)-androst-2-en-17-one, 4-(1,1-dimethyl)-1,2-benzenediol, and desoxy-dihydro-isostevilo were reported to be the active compounds of *B. undulate* [16]. Limonene, 2,4-di-tetr-butyl, and p-cymene were the most important antifungal compounds of *T. polium* [14]. Moreover, 2-isopropenyl-4-methyl-1-oxa-cyclopenta[b]anthracene-5,10-dione, imperatorin, plumbagin, and b-sitosterol glucoside are some of the main antifungal compounds of *A. marmelos* [15].

Furthermore, alkaloids, flavonoids, glycosides, and tannins are the main antifungal compounds of *P. harmala* [50]. Investigations have demonstrated that the main active antifungal compounds present in *J. regia* are naphthoquinones and flavonoids [51]. Carvacrol and thymol are the most important active compounds of *P. rupestre* [52]. Azoles and flavonoids, especially sesquiterpenes, are the most important antifungal compounds of *I. viscosa* [53]. Carvacrol and thymol are the active compounds of *S. fruticosa* [8], and 2-nonanone and 2-undecanone are the active compounds of *R. chalepensis* [54]. The active compounds of *P. europaea* are plumbagin, 1-octane-ly3-acetate, limonene, and nonanal [55]. Certain active compounds, such as vitexin, rutin, isoquercitrine, nicotiflorin, and schaftoside, are present in *R. aculeatus* [56].

Thymoquinone with antifungal activity has been shown to be one of the important active compounds of *N. sativa* [57], while spearmint oil and (S)-(-)-carvone are the active compounds of *M. spicata* [58]. Additional studies have demonstrated that cuminaldehyde and pinenes were among the active compounds of *C. cyminum* [59]. In *F. vulgare*, certain compounds, like (*E*)-anethole and fenchone, had antifungal properties [60], in *A. sieberi*, α-thujone and β-thujone were found to be antifungal active compounds [61], and in *H. persicum*, hexyl butyrate and p-cymene were the important antifungal compounds [62]. Meanwhile, the active compounds of *R. officinalis* were 1.8-cineole and α-pinene [63]. As can be seen, most of the effective components of these plants are from phenolic compounds, which besides having antifungal activities have mostly antioxidant properties [64–69]. Antioxidants are beneficial compounds which are effective against a wide variety of diseases [70–75]. Hence, each individual plant, other than for treating fungal infections, might be used for other diseases, such as gastrointestinal, cardiovascular and/or immunological disorders [76–81]. These group of plants also may have antidotal activity [82].

Due to a high prevalence of dermatophytosis and high speed of acquiring this disease around the world, especially in low-income regions and developing countries, it is necessary to investigate these drugs as well as pharmaceutical and antifungal agents with anti-dermatophytes

effects. Indeed, there are life-threatening side effects due to these chemical drugs. The findings of this study may have many implications, such as in the development of new drugs or in paving the way to conduct additional studies, particularly related to mechanism.

5. **Conclusion**

Common medications used to treat fungal infections, especially those with systemic use, have many proven side effects. There is also drug resistance in many fungal species to commonly used drugs, and this resistance has grown mostly in recent years. Medicinal plants are valuable sources of effective antifungal and therapeutic agents which can be useful in the treatment of various diseases, including fungal infections. These plants have a broad use in traditional medicine and complementary medicine, in the unprocessed form, and in modern medicine, either in processed or purified active substance form. Further research studies are required for developing new drugs from these valuable sources.

6. Open Access

7. List of abbreviations

MIC: Minimum inhibitory concentration; **microg/mL**: Microgram per milliliter

8. Ethics approval and consent to participate

Not to be applied

9. Competing interests

The authors declare that they have no conflicts of interest.

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11. Authors' contributions

All of the authors have participated in manuscript preparation, Manuscript review, Design, Literature search, Manuscript editing. All authors read and approved the final version of manuscript.

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