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A review on antifungal and antibacterial activities of some medicinal plants

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ABSTRACT

The recurrence of fungal infections that occur during allogeneic bone marrow transplantation, cancer treatment, organ transplantation, and infected wounds has necessitated the discovery of more effective and better compatible antifungal and antibacterial compounds. A very limited number of antifungal and antibacterial compounds are effective against various forms of local and systemic fungal and bacterial infections. Considering the enormous potential of herbal and fungal metabolites for the isolation and screening of new antibiotics due to various pharmaceutical applications as an alternative source remains largely unknown. Endophytes are one of the microbial communities that live inside all plants without showing any symptoms, promising to produce a variety of biologically active compounds and new metabolites that are used in medicine, agriculture, and industrial sections.

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Introduction

Natural materials derived from plants have played a significant role in drug discovery and in improving the health care system [1-4]. The World Health Organization (WHO) estimates that about 80 percent of the world's population relies on natural resources for their basic health care needs, while the remaining 20 percent of the world's population uses integrated natural resources [5]. In the 21st century, 11 percent of the 252 essential medicines considered by the WHO to be essential medicines came exclusively from flowering plants. Recently, the field of cancer and infectious diseases (fungal and bacterial diseases, etc.) are mostly dependent on natural products, and of the 175 molecules of approved anticancer drugs, about 41% are natural products or their derivatives from medicinal plants, microorganisms, and animals as values of 25%, 13%, and 3%, respectively [6-9]. In scientific literatures around the world, more than 35,000 plant species in various human cultures are used for medicinal purposes [10]. However, this number of plant species can be much higher, because the knowledge of native use of medicinal plants is mainly transmitted orally from generation to generation and remains largely undocumented. Among the 250,000 higher plant species reported, only 5 to 15% have been studied for their bioactive molecules [11]. Therefore, medicinal plants show that their primary and secondary metabolites can be used in current therapies as micro and nano formulations (Figure 1) [10, 12, 13]. For instance, crude extract of *Trillium govanianum* showed the ability to synthesize silver nanoparticles with antibacterial activity against *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Xanthomonas campestris*, as well as antifungal activity against *Paecilomyces*, *Alternaria alternata*, *Curvularia*, *Aspergillus niger*, *Candida albicans*, and *Rhizopus* [14]. Therefore, in this article, some plant species (Table 1) that are used to treat fungal and bacterial diseases are discussed.

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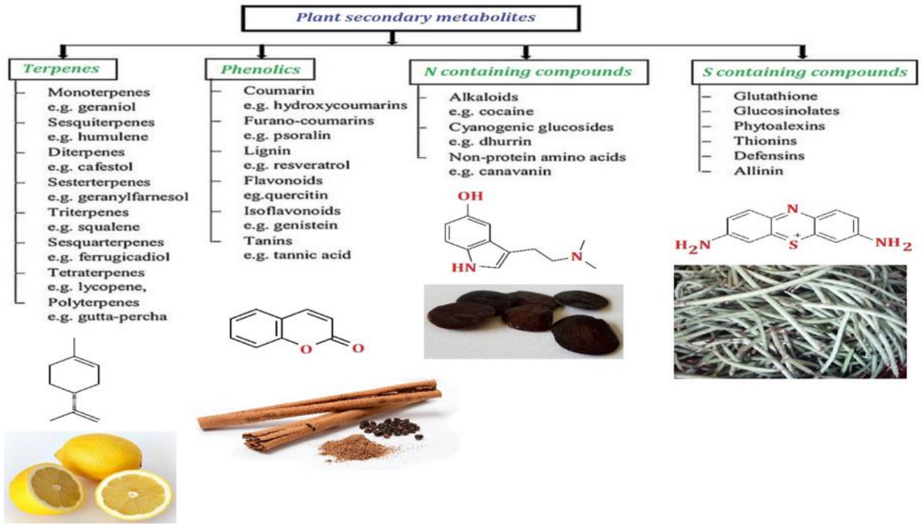

Fig. 1. Important secondary metabolites of plants with related chemical structures [10].

Some medicinal plants

Asphodelus

The plant *Asphodelus Linnaeus* belongs to the family Asphodelaceae, and is native to temperate regions of Europe, the Mediterranean, Africa, the Middle East and the Indian subcontinent, and is now more widespread elsewhere. This family consists of the following three subfamilies: Asphodeloideae (including 13 genera), Hemerocallidoideae Lindley (including 19 genera) and Xanthorrhoeoideae M.W. Chase (only one sex). *Asphodelus* L. (Asphodelaceae) is a genus of 18 species and a total of 27 subspecies and varieties that are distributed along the Mediterranean basin and has traditionally been used to treat several diseases, especially inflammatory and infectious skin disorders. Medicinal use of the genus *Asphodelus* is also common in North Africa, West and South Asia [15]. There are various medicinal applications for the family of Asphodelaceae: rubbing cut glands to treat skin eczema, root ashes to treat alopecia, root are crushed for antifertility application, decoctions of leaves and stems to cure paralysis, fresh leaf juice for treatment burnt, leaf extract with honey to treat dysentery [16]. According to phytochemical studies, hydroxyanthracene derivatives, flavonoids, phenolic acids and triterpenoids were the main classes of compounds identified in the roots, leaves and seeds of this plant that with their biological activities as antimicrobial, antifungal, antiparasitic, cytotoxic, anti-inflammatory or antioxidant agents were associated [17, 18].

These are perennial, herbaceous plants with slender hairy leaves and elongated stems and spikes of white or yellow flowers. Many of them have small rhizomatous crowns and thick, fleshy roots. Different parts of the plant such as leaves, fruits, seeds, flowers and roots are used as traditional herbal medicines alone or in combination to treat various diseases [19].

In addition to medicinal uses, in the Iberian Peninsula, alcohol from fermented tubers is extracted and used as fuel, and local people in Iran, Turkey, and Egypt use the root tubers of *A. aestivus* and *A. microcarpus* to produce glue. A strong adhesive is used by shoemakers and cobblers, as well as yellow and brown dyes for wool, root tubers (the swollen roots containing nutrients and water), after being moistened and fried, are used as daily food to eliminate astringent compounds as well as young stems, leaves and roasted seeds. *A. aestivus* and *A. microcarpus* were commonly used as anti-inflammatory and antiseptic agents. In particular, *A. aestivus*, *A. fistulosus* and *A. microcarpus* are used in mucosal skin infections in various countries including Cyprus, Egypt, Libya, Palestine and Spain [15].

A. microcarpus, *A. ramosus*, and *A. tenuifolius* were generally identified as anti-inflammatory agents specifically for the treatment of psoriasis, eczema, and rheumatism. *A. ramosus* and *A. tenuifolius* are often reported as diuretics among residents of Egypt, India, Pakistan, and Turkey [20]. Phytochemical studies have shown the presence of different groups of compounds such as anthraquinones (free or in the form of glycosides), phenolic acids, flavonoids, and triterpenoids from *A. acaulis*, *A. albus*, *A. aestivus*. *A. cerasiferus*, *A. fistulosus*, *A. microcarpus*, *A. ramosus*, and *A. tenuifolius* [15].

Anthraquinone derivatives such as chrysophanol and aloe-emodin, triterpenoids and naphthalene derivatives have been reported in the roots, while the aerial parts mainly contain flavonoids such as luteolin, isovitoxin and isovortinin, phenolic acids. Fatty acids, namely myristic, palmitic, oleic, linoleic, and linolenic, were found in seeds and roots. Only *A. aestivus* and *A. microcarpus* were studied for the properties of flower essential oil [21].

All species were sent to biological activity tests with documented ethnomedical data, indicating a general or partial correlation with their traditional application as antimicrobial, antifungal, antiparasitic, cytotoxic, anti-inflammatory, or antioxidant agents [22]. Part of the plant (root gland) is mainly reported to contain anthraquinone derivatives, triterpenoids, and naphthalene derivatives, while the aerial parts (leaves) are mainly present with the presence of flavonoids, phenolic acids and a small amount of anthraquinone [23]. According to previous phytochemical studies, 1,8-dihydroxyanthraquinone ($C_{14}H_8O_4$) derivatives (e.g., aloe-emodin and chrysophanol) were the most commonly reported anthraquinones of *A. aestivus*, *A. luteus*, and *A. microcarpus* extracts that may be responsible for the activity. Antimicrobial /fungal agents have been reported. Phytosterols (such as fucosterol, B-sitosterol, and stigmasterol) and B-amyrin were the most common triterpenoids found in the roots and seeds of this plant. According to the literature, beta-amyrin has antibacterial/antifungal properties that complement the reported biological activity of *A. tenuifolius* [23].

Trillium

Trillium is a genus of the family Melanthiaceae with ~50 flowering plant species [24]. Saponins are steroidal glycosides or triterpenes that are widely distributed in plants and have hemolytic properties and toxic effects. Steroid saponins are less common and are more commonly found in monocotyledonous plants than in widely distributed triterpenoid saponins and are also found in dicotyledonous plants [25]. The basal skeleton of steroidal sapogenins (27 °C) may be a 6-ring or 5-ring spirochete, while triterpenoid sapogenins (30 °C) may be structurally different, often from five or rarely four units. In general, in the C-3 moiety of glycone, the glycone (sugar) contains one to several monosaccharide binding units. Connected sugar chains may consist of one to three chains, straight, branched, or both. The presence of different substituents in sapogenins as well as the composition, binding, and number of sugar moieties indicate the structural diversity of saponins [26]. Similarly, the structural complexity of saponins is due to their diverse physicochemical, pharmacological, and biological properties, as well as their commercial relevance for promising molecules with numerous applications in the food, cosmetic, pharmaceutical, and health fields [27]. In fact, saponins have been extensively studied to develop new natural remedies and to prove the effectiveness of traditional herbal remedies. Raw saponin-containing drugs, which have less irritating effects following oral administration, are commonly used as expectorants and antitussives. It is worth noting that many saponins have anti-inflammatory, analgesic, antipyretic, anti-allergic and anti-cancer properties [28].

Steroids are a group of cholesterol-derived secondary metabolites that exhibit a variety of chemical structures and biological functions. Almost all steroid molecules have a perhydroxyl base structure of cyclopentenophenanthrene. Differences in skeletal structure and joining different groups lead to different classes of steroids. Steroids have many medicinal uses, and research is ongoing to find these metabolites as potential lead compounds in drug design and discovery [29]. For example, ecdysteroids are polyhydroxy steroids produced by certain plants, including plants belonging to the genus *Trillium*. Herbs such as *Tinospora cordifolia* (Guduchi) contain steroids and have significant medicinal properties and are used as anabolic, anti-diabetic, analgesic, anti-inflammatory, and anti-parasitic activities in the field of medicine and treatment [30]. The secondary metabolites isolated from the genus *Trillium* belong mainly to the chemical class of saponins and steroidal steroids, including steroids, although flavonoids and trihydroxy fatty acids have also been reported. Isolated compounds showed significant potential when tested in various in vitro and in vivo. To date, among the steroid saponins tested, both spirostanol and furostanol saponins, as well as many others, have shown associated cytotoxicity against various cancer cell lines, a small number of which have shown high potential against fungal strains tested. While some of them have antioxidant and COX-2 inhibitory activity [31].

Table 1. Some medicinal plants with therapeutic properties.

Plant genera	Species	Major metabolites	Region	Traditional and new applications	Ref.
Asphodelus	*A. acaulis, A. albus, A. aestivus. A. cerasiferus, A. fistulosus, A. microcarpus, A. ramosus, A. tenuifolius*	Hydroxyanthracene derivatives, flavonoids, phenolic acids and triterpenoids	Europe, the Mediterranean, Africa, the Middle East and the Indian subcontinent	Rubbing cut glands to treat skin eczema, root ashes to treat alopecia, root are crushed for antifertility application,	[15-18]
Trillium	*T. tschonoskii T. erectum T. govanianum T.kamtschaticum T. grandiflorum*	Spirostane and furostane aglycones and steroids and saponins	North America, temperate areas of Asia, and western north America	Raw saponin-containing drugs, which have less irritating effects following oral administration, are commonly used as expectorants and antitussives.	[26-28]
Cereus	*C. hildmannianus* C. *uruguayanus, C. repandus, C. peruvianus, C. jamacaru, C. bicolor*	Alcohol dehydrogenase, malate dehydro-genase, isocitrate dehydrogenase, sorbitol dehydrogenase, esterases, acid phosphatases and peroxidases	France, Spain, Andorra, South Africa, Kenya, India, Vietnam and Taiwan, Australia, Portugal, Italia and Sweden	The use of the *C. hildmannianus* cladodes extracts in folk medicine for weight loss, reducing cholesterol and low-density lipoprotein (LDL) levels, as a diuretic, against pulmonary disorders, rheumatism, and as a cardiotonic, and as a topical treatment for wounds. Cladodes of *C. hildmannianus* are used for the treatment of lithiasis.	[32, 33]
Euclea	*E. natalensis*	Betulin 1, lupeol 2, shinanolone 13, 20 (29) -lupene-3 beta-isoferulate 14, octahydroeuclein 15, and B-sitosterol 16	South Africa	The roots of this plant have commercial potential as remedies for chest ailments, toothache, bronchitis, pleurisy, asthma, headache, and urinary tract infections	[22, 34-36]

In addition, the biological activity of steroidal saponins depends mainly on the aglycone moieties (steroidal sapogenins) as well as the number and structure of monosaccharide units in their sugar chains. A slight structural variation confirms significant differences in their antifungal and cytotoxic properties, for example, spirostanol saponins show higher antifungal potential compared to their furostanol-like saponins. Therefore, it should be noted that more detailed studies on the structure-activity relationship and molecular and biochemical goals of steroid saponins are needed to discover the therapeutic potential of this important class of natural products as clues to the discovery of a new drug [37].

To date, more than 40 steroidal saponins containing spirostane or spirostan ($C_{27}H_{44}O_2$) and furostane aglycones have been isolated from Trillium. Their structure was determined using spectroscopic techniques, including fast-atom bombardment mass spectrometry and extensive two-dimensional nuclear magnetic resonance (NMR) experiments (COSY, TOCSY, NOESY, HSQC, and HMBC). Available data show that Trillium plants are a rich source of steroids and saponins and have therapeutic potential in the management of cancers, fungal infections, inflammatory and painful disorders. It is noteworthy; more comprehensive studies to screen new sources of phytochemicals are needed to develop promising effective herbal medicine in the treatment of degenerative and chronic infectious diseases. Finally, the most promising Trillium secondary metabolites must be studied in humans in well-designed randomized clinical trials to reach the highest level of clinical evidence [38].

Cereus

In 1625, *Cereus peruvianus* was reported by *Tabernaemontanus* as a tall, columnar, branching plant and was fully described by Linnaeus in 1768. Currently in the classification, *C. peruvianus* (L .) Mill. Synonymous with *C. hildmannianus* (K.) Schum., Is considered an accepted name. It is considered one of the most promising species for medicinal and nutritional purposes [32]. The chemical composition of *C. hildmannianus* necrotic clades is dependent on yeasts and bacteria that use plants as hosts and produce volatile compounds that are important to Drosophila sp. In addition to the expression of genes involved in signaling processes, stimulus-response and reproduction, as an ecological interaction, as well as a difference in the size of morphological structures, in Drosophila sp. used to identify species. In the roots of *C. hildmannianus*, two nematode species were identified: *Meloidogyne arenaria* and *M. enterolobii* [33].

Euclea

Euclea natalensis, is related to the family Ebenaceae (the order of Ericales) with distribution in Somalia and Ethiopia countries [39]. A group of researchers confirmed the antifungal activity of betulin 1, lupeol 2, shinanolone 13, 20 (29) -lupene-3 beta-isoferulate 14, octahydroeuclein 15, and B-sitosterol 16 isolated from the bark of *E. natalensis* root in some studies. The results of these experiments were as follows: Ingredients: *Aspergillus niger*, *Cladosporium cladosporioides* and *Phytophthora* spp. *Aspergillus niger* was significantly inhibited by shinanolone 13, 20 (29) -lupene-3 B-isoferulate 14 and B-sitosterol 16 at 0.01 mg/mL. Of all the compounds tested, only octahydroeuclein 15 was significantly effective against Phytophthora species (At 0.1 *mg/mL*).

The compounds octahydroeuclein 15 and B-sitosterol 16 significantly inhibited the growth of *Cladosporium cladosporioides* at 0 mg/mL [39].None of the isolated compounds showed significant activity against *Aspergillus flavus* at 0.01 mg/mL. Van Vuuren and Naidoo evaluated the antifungal activity of aqueous extracts and a mixture of methanol and dichloromethane (1: 1) of *E. natalensis* leaf extract against *Candida albicans*, a pathogen associated with genital candidiasis or thrush [40].Aqueous extracts and mixtures of methanol and dichloromethane showed significant activities with MIC values of 0.5 mg/mL and 3.0 mg/mL against *C. albicans*, respectively [34]. *Euclea natalensis* is an important and widely used herbal medicine in tropical Africa. This species is widely used for human diseases such as abdominal pain, the antidote for snake bites, diabetes, diarrhea, malaria, roundworms, stomach problems, toothaches, and sexually transmitted diseases. Recent research on *E. natalensis* has focused mainly on the antimicrobial properties of the crude extracts of this species, naphthoquinone, and the five-ring terpenoid compounds isolated from this species [35]. Studies have shown that naphthoquinone and five-ring terpenoid compounds isolated from *E. natalensis* such as shinanolone 13 have antibacterial effects, shinanolone 13, 20 (29) -lupene-3B-isoferulate 14, octahydroeuclein 15 and B-sitosterol 16, octahydroeuclein-6- (40) isodiospyrin 3, neodiospyrin 10, diospyrin 11, 7-methyljuglone 12 and shinanolone 13 showed the effects of diospyrin 11, 7-methyljuglone 12 antifungal effects. The compound 7-methyljuglone 12 appears to be the most effective antimicrobial among all compounds isolated from *E. natalensis* to date [41]. Any research on *E. natalensis* must establish its ethnopsychological application with phytochemistry and its medicinal effects to fully realize the ethnic medicinal potential of the species and evaluate related pharmacological activities. Based on current data, ethnocentric drug applications and documented pharmacological effects of the species indicate that there are insufficient systematic data on phytochemistry and

pharmacological effects for most ethnographic applications of the species [42].
There is still a need for research on phytochemicals, bioactive compounds and other medicinal substances and minerals that can be used to explain the widespread use of *E. natalensis* as an herbal medicine in tropical Africa. Future studies should also focus on the mechanism of biological activity and the structure-function relationships of bioactive components of species. Similarly, animal studies and clinical studies are largely nonexistent and should be performed to determine the potential of this plant for use in human medicine [36].

Conclusions

Due to the various side effects of the antibiotics including nausea, pain, abdominal, skin rashes, vomiting and headache, and emerging of drug-resistance in microbial pathogens, research about medicinal compounds including primary and secondary metabolites have led to finding effective therapeutic compounds without major side effects. In this manner, this review has tried to address progress and challenges of antifungal and antibacterial effects of major plant species. According to this review, more studies are needed to optimize herbal compounds in bioavailable doses appropriate for physiological conditions.

Study Highlights

- There are various metabolites of plants with antifungal and antibacterial activities.
- Secondary metabolites of plants may be the suitable alternatives to reduce side effects of conventional antibiotics.
- More comprehensive investigations are needed to optimize these metabolites in physiological conditions.
- Both micro and nano formulations should be considered in future studies.

Abbreviations

NMR: Nuclear magnetic resonance
WHO: World Health Organization

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with animals or human participants performed by any of the authors.

Authors' contribution

All authors: conceptualization, preparing the first drafting, and revising the manuscript.

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