Plant Products with Antifungal Activity: From Field to Biotechnology Strategies

Giovanna Simonetti, Alessio Valletta, Olga Kolesova, and Gabriella Pasqua

1 Introduction

Plant extracts have been traditionally used to treat a number of diseases due to the fact that they have various medicinal activities, such as anti-inflammatory, anti-androgenic, anti-proliferative, antifungal, antimicrobial, antioxidant, and others. Roots, stems, leafs, flowers, and fruits of medicinal plants are used in Ayurvedic medicine as well as European, Russian, and Asiatic folk medicine to treat different infections caused by bacteria, fungi, virus, parasite, as well as noninfectious metabolic disorders (Chuang et al. 2007). The compositions of plant extracts contain a plurality of pharmaceutical important biological active molecules, but only a small percentage of plants have been explored for their antifungal activity.

About 1.2 billion people worldwide are estimated to suffer from a fungal disease (Denning and Bromley 2015). There are an estimated three to six million fungal species. Of these, only very few (about 150–300) are known to cause disease in humans. Human fungal pathogens are a common underestimated cause of severe diseases associated with high morbidity and mortality. Four human fungal pathogens cause invasive infections as C*andida albicans*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, and *Histoplasma capsulatum* (Kullberg and Arendrup 2015; Kim 2016).

Skin mycoses affect more than 20–25% of the world's population (Havlickova et al. 2008), and frequently they are associated with yeasts as *Candida* and *Malassezia* and dermatophytes such as *Trichophyton* and *Microsporum* (White et al. 2014). Although these skin-related infections are not generally life-threatening, they

G. Simonetti (✉) · O. Kolesova
Department of Public Health and Infectious Diseases, "Sapienza" University of Rome, Rome, Italy
e-mail: giovanna.simonetti@uniroma1.it

A. Valletta · G. Pasqua
Department of Environmental Biology, "Sapienza" University of Rome, Rome, Italy

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Table 1 Fungal infections classified according to the site of infection

Site of infection	Fungi genus	Diseases
Superficial	*Malassezia*	Pityriasis versicolor
	Hortaea	Tinea nigra
	Trichosporon	White piedra
	Piedraia	Black piedra
Cutaneous	*Trichophyton*, *Epidermophyton*, *Microsporum*	Tinea corporis, tinea manuum, tinea pedis
	Candida	Cutaneous candidiasis
Subcutaneous	*Sporothrix*	Sporotrichosis
	Phialophora, *Fonsecaea pedrosoi*	Chromoblastomycosis
	Pseudallescheria, *Madurella*, and others	Mycetoma
	Exophiala, *Bipolaris*, *Exserohilum*, and other dematiaceous moulds	Phaeohyphomycosis
Systemic	*Candida*	Systemic candidiasis
	Histoplasma	Histoplasmosis
	Blastomyces	Blastomycosis
	Paracoccidioides	Paracoccidioidomycosis
	Cryptococcus	Cryptococcosis
	Aspergillus	Aspergillosis
	Zygomycetes	Zygomycosis
	Fusarium, *Paecilomyces*, *Trichosporon*	Hyalohyphomycosis
	Penicillium	Penicilliosis

represent a common global problem and can become chronic. Furthermore, the treatments often require long-term therapy and are not resolving in all (Pfaller 2012). Side effects and resistance are frequently due to the current antifungal agents (Table 1), such as the most widely used azole drugs (Pfaller 2012; Zavrel and White 2015).

Phytomedicine, which has been historically an important aspect of traditional medicine in non-industrialized countries, is becoming now an integral part of healthcare in these countries. Different strategies can be applied to improve the yields of bioactive metabolites in the plant and to obtain standardized extracts in chemical mode (Dias et al. 2016; Atanasov et al. 2015).

This chapter provides an overview of the published results on plant-derived natural products showing antifungal activity against human pathogens. Moreover, biotechnological approaches have been explored in order to increase the production of active extracts, in alternative to obtain extracts from plants directly collected from their natural habitat. The use of plants as source of bioactive compounds is related with the accessibility of the starting material. Cultivation of medicinal plants could be a sustainable alternative to wildcrafting, but until today, two thirds of the used plants are still collected in the wild. Moreover, some species are protected to conserve the biodiversity. The Nagoya Protocol on "access to genetic resources and

the fair and equitable sharing of benefits arising from their utilization to the Convention on Biological Diversity" needs to be respected and should become a major tool for benefit sharing as well as the conservation and sustainable use of biological diversity (Buck and Hamilton 2011).

It should be emphasized that often the amount of the extract from plant is low, depending on the developmental degree of the biosynthetic organ, and season-dependent. Moreover, the chemical composition of the extract is not only dependent on the species but also on soil composition, processing, and storage (Atanasov et al. 2015). Cultivation of medicinal plants under controlled conditions could make possible to maintain the concentration of important compounds in the plant. The aim is also to increase potency, reduce toxin levels, and increase uniformity and predictability of extracts. The trend towards niche production of high-value species for non-food markets offers great opportunities (Lubbe and Verpoorte 2011). In recent years, different strategies have been developed to produce active compounds using plant cell and organ cultures. Moreover, in vitro propagation of plants, where possible, could solve the problems concerning the loss of genetic diversity and habitat destruction. The literature reports a significant progress in the use of plant tissue cultures, called "chemical factories" of secondary metabolites (Rao and Ravishankar 2002), also offering the opportunity to optimize yield and achieve a uniform, high-quality products.

Actually biosynthetic pathways of secondary metabolites are mostly poorly understood, and relatively few genes for key enzymatic or regulatory steps have been isolated (Canter et al. 2005). The production of plant secondary metabolites by means of large-scale culture of plant cells in bioreactors is technically feasible, but unfortunately, some of the most interesting products are only in very small amounts or not all produced in plant cell cultures. Screening, selection, and medium optimization may lead to 20- to 30-fold increase in case one has producing cultures. In case of phytoalexins, elicitation will lead to high production. Metabolic engineering offers new perspectives for improving the production of compounds of interest. A promising approach to improve the production of important metabolites is to upregulate the enzymes important for the synthesis of metabolites or to increase their precursors (Verpoorte et al. 2002).

2 Human Fungal Diseases

About 1.2 billion people worldwide are estimated to suffer from a fungal disease. An estimated 1.5 to two million people die of a fungal infection each year surpassing those killed by either malaria or tuberculosis (Denning and Bromley 2015). Four human fungal pathogens that cause invasive infections are C*andida albicans*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, and *Histoplasma capsulatum* (Kim 2016). Fungal infections may be classified according to the site of infection, route of acquisition, and type of virulence. When classified according to the site of infection, fungal infections are designated as superficial, cutaneous, subcutaneous,

and systemic (Table 1). Most are infections of the skin or mucosa. Superficial mycoses are limited to the stratum corneum and include common skin diseases as well as rare infections confined to specific geographical areas or groups of patients (Brooks et al. 2013). Cutaneous infections involve the integument and its appendages, including hair and nails. Cutaneous mycoses are most commonly caused by dermatophytes, which require keratin for survival, but they can be caused by non-dermatophyte moulds or *Candida* species. Dermatophytes can be classified as anthropophilic, zoophilic, or geophilic, depending on their primary habitat (humans, animals, and soil, respectively). The clinical picture of dermatomycoses is variable due to the degree of keratin destruction by the fungus and the inflammatory response of the host. For example, anthropophilic dermatophytes cause little inflammation but can cause recurrent or chronic infections, while zoophilic and geophilic dermatophytes tend to induce acute and highly inflammatory responses. Inflammatory symptoms such as pruritus, erythema, swelling, and burning can have a significant impact on the quality of life of the affected individual (Schaller et al. 2016). The deep mycoses are uncommon infections caused by fungi, and they are divided into subcutaneous and systemic mycoses. Subcutaneous mycoses include a range of different infections characterized by infection of the subcutaneous tissues usually at the point of traumatic inoculation. While skin manifestations always occur in subcutaneous mycoses, or mycoses of implantation, as they are also known, they are only occasionally seen in systemic mycoses (Carraco-Zuber et al. 2016). Systemic mycoses involve the lungs, abdominal viscera, bones, and/or central nervous system. The most common portals of entry are the respiratory tract, gastrointestinal tract, and blood vessels Brooks et al. 2013) (Table 1).

3 Antifungal Susceptibility Methods

In vitro antifungal tests are crucial in the screening process. Diffusion method is used in many clinical microbiology laboratories for routine antimicrobial susceptibility testing. In this procedure, antimicrobial agent diffuses into the agar and inhibits growth of the test microorganism, and then the diameters of inhibition growth zones are measured. The diffusion method is not appropriate to determine the minimum inhibitory concentration (MIC), as it is impossible to quantify the amount of the extracts and its constituents diffused into the agar medium. The disc diffusion method is a qualitative test, and its results should not be used for quantitative purposes.

Dilution methods are the most appropriate ones for the determination of MIC values, since they offer the possibility to estimate the concentration of the tested antimicrobial agent in the agar (agar dilution) or broth medium (macrodilution or microdilution). Dilution methods may be used to quantitatively measure the in vitro antimicrobial activity against fungi. MIC value recorded is defined as the lowest concentration of the assayed antimicrobial agent that inhibits the visible growth of the microorganism tested, and it is usually expressed in μg/mL or mg/L. The most

recognized standards are provided by the CLSI and the European Committee on Antimicrobial Susceptibility Testing (EUCAST). The dilution assays give the most reliable results and are capable of determining the MIC and MBC of a particular sample (Balouiri et al. 2016).

*3.1 Anti-*Candida *Plant Products*

Candida species are opportunistic fungal pathogens. These fungi belong to the normal microbiota of an individual's mucosal oral cavity, gastrointestinal tract, and vagina, but in particular, conditions such as immunocompromised patients and diabetes hemodialysed patients can cause cutaneous and systemic mycoses. *Candida* may spread in different parts of the body and cause a wide range of diseases such as meningitis, endocarditis, pyelonephritis, renal papillary necrosis, multiple parenchymal abscesses, endophthalmitis, septic arthritis and osteomyelitis, peritonitis, and pneumonia (Hope et al. 2012). Moreover, the use of devices including catheters and prolonged hospitalization increase the prevalence of invasive candidiasis. Catheter-related microbial biofilms are associated with 90% of *Candida* infections and considered as the major cause of morbidity and mortality among hospitalized patients (DiDone et al. 2011). The difficulty to eradicate *Candida* infections is owing to its unique switch between yeast and hyphae forms and more likely to biofilm formations that render resistance to antifungal therapy. Biofilms provide a safe haven for *Candida*, facilitate drug resistance, and act as sources for chronic infections (Donlan 2001). Systemic candidiasis is caused by different species of *Candida*. The most common causative agents of candidiasis are *C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, and *C. tropicalis*. In recent years, *C. dubliniensis*, *C. guilliermondii*, *C. kefyr*, *C. lusitaniae*, *C. pelliculosa*, and *C. zeylanoides* have been detected with increasing frequency (Kauffmann and Mandell 2010; El-Atawi et al. 2017). Azoles (fluconazole, itraconazole, voriconazole, and ketoconazole), echinocandins (micafungin, caspofungin), and amphotericin B are used to treat *Candida* human infections (Arendrup and Patterson 2017). Azole antifungal agents are most useful in the therapy for mucosal infections related to *Candida*. However, after a previous treatment with azole antifungal agent, the patient could show a microbiological resistance (Arendrup and Patterson 2017). Drugs currently on the market have been developed by studying the few known targets for fungal cells, such as the particular composition of the cell membrane and the related enzymes. Ergosterol, nucleic acids, and glucan are the most studied molecular targets to destroy *Candida* species, being considered the basis of the development of new antifungal drugs. Since the availability of these drugs is limited, resistances developed by the fungal cells represent an important problem to be managed. Although amphotericin B is the most well-known agent in terms of efficacy in serious *Candida* infections, it has the greatest potential toxicity. At the same time, fluconazole is less toxic but also has some side effects such as nausea, headache, and others (Table 2) (Grohskopf and Vincent 1996). The specific type of medication and length of treatment will depend

Table 2 Side effects of antifungal agents

Chemical group	Drugs	Side effects
Macrolides	Amphotericin B	Hypokalaemia, hypomagnesaemia, renal injury, nausea, vomiting, abdominal pain, rash, headache, hepatic necrosis (Laniado-Laborín and Cabrales-Vargas 2009)
Pyrimidine	Flucytosine	Hepatotoxicity, bone marrow depression, nausea, vomiting, and diarrhoea (Vermes et al. 2000)
Azole	Ketoconazole Fluconazole Itraconazole Voriconazole	Dizziness, drowsiness, insomnia, impaired consciousness, vision, hallucinations, paraesthesia, tremor, convulsions, flatulence, nausea, vomiting, diarrhoea, constipation, thrombophlebitis, chills, fever, aches, nausea/vomiting, hypotension, nephrotoxicity, hypokalaemia hypomagnesaemia, suppression erythro-thrombopoiesis (Verweij et al. 2009)
Echinocandins	Caspofungin Micafungin	Phlebitis and the histamine-like reaction marked by rash, urticaria, flushing, bronchospasm, hypotension and facial swelling, arrhythmias, and cardiac failure (Koch et al. 2015)

on many factors, including the age and health of the infected person, the location and severity of the infection, and the specific species of *Candida* causing the infection (Pappase et al. 2015).

Recent studies have shown that some plant extracts have anti-*Candida* activity like some antifungal synthetic drugs (Martins et al. 2015a; Soliman et al. 2017). Several of these showed promising minimum inhibitory concentration (MIC) such as peppermint (0.08 μg/mL), *Thymus villosus* (0.64 μg/mL), eucalyptus (0.05 μg/mL), lemongrass oil (0.06 μg/mL), *Cinnamomum zeylanicum* (0.01 μg/mL), ginger grass oil (0.08 μg/mL), and coriander (0.2 μg/mL) (Soliman et al. 2017).

Among them, the essential oils and extracts rich in different phenol compounds are being tested in the search of new antifungals with fewer side effects. Although the mechanisms of action are not yet completely clear, it has been speculated that plant products could represent a viable alternative to the antifungal drugs; however, up to date, none of these plant products is marketed for anti-*Candida* therapy (Güllüce et al. 2003; Raut and Karuppayil 2014).

Essential oils are complex volatile compounds whose composition varies depending on factors such as the climate, the age of the plant, and even the organ from which they are extracted. In the case of *Agastache rugosa,* the composition of the oil extracted from the flower is different from the one extracted from the leaf, and this means different antifungal activity (Shin and Kang 2003).

Curcumin is a particular polyphenol, which shows a marked activity against *Candida*. The study of curcumin against 14 strains of *Candida* including 4 ATCC strains and 10 clinical isolates showed that curcumin is a potent antifungal compound against *Candida* species with MIC values range from 250 to 2000 μg/mL (Neelofar et al. 2011). In another study, anti-*Candida* activity of curcumin was demonstrated against 38 different strains of *Candida* including some fluconazole-resistant strains and clinical isolates of *C. albicans*, *C. glabrata*, *C. krusei*, *C. tropicalis*, and

C. guilliermondii. The MIC_{90} values for sensitive and resistant strains were 250–650 and 250–500 μg/mL, respectively (Khan et al. 2012; Zorofchian Moghadamtousi et al. 2014).

The investigation of curcumin mediation for photodynamic therapy can reduce the biofilm biomass of *C. albicans*, *C. glabrata*, and *C. tropicalis*. The results demonstrated that association of four LED fluences for light excitation with 40 μM concentration of curcumin inhibited up to 85% metabolic activity of the tested *Candida* species. Photodynamic effect considerably decreased *C. albicans* viability in either planktonic or biofilm cultures probably through increasing the uptake of curcumin by cells (Dovigo et al. 2011).

Phenolic compounds are widely found in plant foods (fruits, cereal grains, legumes, and vegetables) and beverages (tea, coffee, fruits juices, and cocoa). The most common phenolic compounds are phenolic acids (cinnamic and benzoic acids), flavonoids, proanthocyanidins, coumarins, stilbenes, lignans, and lignins. The anti-*Candida* mechanisms of phenolic compounds reported in the literature include inactivation of enzyme production (Teodoro et al. 2015) and anti-biofilm activity (Evensen and Braun 2009).

Resistant *Candida* species to the current antifungal drugs have been observed; thus, alternative therapy based on plant extracts rich in phenolic compounds should be considered (Martins et al. 2015b).

Rangkadilok et al. (2012) demonstrated that *Dimocarpus longan* Lour. (longan) seed exhibited antifungal activity against *Candida* species. In contrast, longan pulp and whole fruit did not demonstrate any inhibitory effects. Ellagic acid showed the most potent antifungal activity followed by corilagin and gallic acid, respectively. Ellagic acid inhibited *C. parapsilosis* more effectively than *C. krusei* and also some *C. albicans* clinical strains. Baidam cultivar possessed higher antifungal activity (MIC = 500–4000 μg/ml) as it contained higher contents of ellagic acid and gallic acid (MIC = 1000–8000 μg/ml).

Mahmoudabadi et al (2007) studied the anti-*Candida* activity against 14 isolates of *C. albicans*, *C. parapsilosis*, *C. tropicalis*, and *C. glabrata* was of aqueous and alcoholic extracts of *Zataria multiflora*. Aqueous extract showed no remarkable activity against *Candida* species. Conversely, MIC of the methanolic and ethanolic extracts was 70.7 and 127 mg/L, respectively. The biological activity of *Zataria multiflora* was mainly associated with its main chemical components, including thymol, rosmarinic acid, flavonoids, and carvacrol.

Brighenti et al. (2017) screened 60 plant extracts from Brazilian Pantanal biome for *C. albicans* anti-biofilm activity. Effects on biofilm inhibition and disruption and cytotoxicity were also evaluated. The most active extract was chemically characterized. *Buchenavia tomentosa* ethanolic extract showed noticeable antifungal activity and was selected for biofilm experiments. Subinhibitory concentration of extract inhibited fungal adhesion. Maximum killing reached 90% of *C. albicans* cells in suspension and 65% of cells in biofilms. The active extract was noncytotoxic. Chemical characterization showed the presence of phenols. Ellagic and gallic acids showed activity on *C. albicans*.

Punica granatum is a plant with worldwide application in folk medicine. Polyphenols extracted from pomegranate fruit were active against phytopathogenic fungi. The extract of *P. granatum* showed good results as a topical antifungal agent for the treatment of candidosis associated with denture stomatitis (Bassiri-Jahromi et al. 2017; Vasconcelos et al. 2003).

The tannin punicalagin is the major component of pomegranate fruit peel. This substance was isolated not only from *Punica granatum* but also was described from *Terminalia mollis* and *Terminalia brachystemma*, as having antifungal activity against *C. albicans*, *C. krusei*, and *C. parapsilosis* (Liu et al. 2009).

Alcoholic and water hot extracts of the *Punica granatum (pomegranate*) peels as well as the dried powder were prepared. The antifungal activity of the extracts containing gallotannic acid was evaluated by means of the agar-well diffusion assay. The extract exhibited potent activity against *C. albicans* and *C. tropicalis* (Shaokat et al. 2017).

In vitro antifungal activity of acetonic extracts of *Punica granatum* L., *Quercus suber* L., and *Vicia faba* L. against seven pathogen fungi and the in vivo antifungal activity against *C. albicans* have been studied. The phytochemical screening was also carried out and showed that the extracts contained mainly proanthocyanidins. Other polyphenols were also present but in low quantity. The acetone extract of *V. faba* L. showed in vitro activity, and it was the most active for treating candidiasis in mice (Akroum 2017).

The antifungal activity of extracts from 10 different plants, commonly used in folk medicine, was evaluated against 19 *Candida* strains, including *C. albicans*, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis* species. Although the majority of the extracts had no antimicrobial effect, *Juglans regia* extract was very effective, exerting an inhibitory effect against all the tested *Candida* strains, while *Eucalyptus globulus* was effective against 17 of them. *Pterospartum tridentatum* and *Rubus ulmifolius* presented similar antifungal effects, being effective against six *Candida* strains. The diameter of halo ranged, respectively, between 9–14 mm and 9–21 mm to the mentioned plant extracts. Both extracts showed similar MIC_{50} values for *C. albicans* strains, while *C. parapsilosis* and *C. glabrata* were more sensible to *E. globulus*. Otherwise, all the *C. tropicalis* strains were more sensible to *J. regia* (Martins et al. 2015b).

Recently, it has been demonstrated that extracts by *Vitis vinifera* seeds obtained from mature grapes, rich in polymeric flavan-3-ols, exhibit good antifungal activity against *Candida* species suggesting their use in mucocutaneous fungal infections (Pasqua and Simonetti 2016; Simonetti et al. 2014, 2017b). Moreover, it has been demonstrated a significant inhibition of *Candida albicans*, in an experimental murine model of vaginal candidiasis, using grape seed extract (GSE) with high content of polymeric flavan-3-ols (Simonetti et al. 2014). The antifungal activity of unripe grape extracts from agro-industrial wastes has been evaluated against several strains of *Candida* spp. All the extracts tested showed antifungal activity. The geometric mean MIC ranged from 53.58 to 214.31 μg/ml for *Candida* spp. (Simonetti et al. 2017a). It is important to highlight that grapeseed extracts (GSE), recognized safe by the Food and Drug Administration, are used as food additives and in cosmetics.

The high tolerability of plant products is another important aspect, unlike synthetic drugs that often have adverse effects on humans and animals, such as the nephrotoxicity of amphotericin B (Table 2).

3.2 Anti-dermatophytes Plant Products

Dermatophytes are a group of pathogenic fungi and the major cause of dermatophytosis infections of the human skin, hair, and nail. Cutaneous and subcutaneous mycoses caused by dermatophytes fungi affect keratinized structures of the body.

Dermatomycosis, depending on the primary localization of the damage (epidermis, nails, or hair), is divided into epidermomycoses, onychomycosis, and trichomycosis. The most frequently involved dermatophyte genera of humans and other animals are *Trichophyton*, *Epidermophyton*, and *Microsporum*. They have some common biological properties. The most common anthropophilic dermatophytes are *Trichophyton rubrum*, *Trichophyton tonsurans*, *Trichophyton violaceum*, and *Epidermophyton floccosum*; anthropozoophilic are *Trichophyton mentagrophytes*, *Microsporum canis*, and *Microsporum ferrugineum*; and geophysical are *Microsporum gypseum* and *Trichophyton ajelloi*. Dermatophytes even if they are not responsible for systemic mycoses are the etiologic agents of the most common human mycoses. Dermatophytes as pathogens have the ability to survive in the environment of the macroorganism, and they can introduce hyphae into intercellular spaces, facilitated by the production of enzymes that lyse keratin, collagen, and elastin. Moreover, it has been shown that the low immunogenicity of dermatophytes such as *T. rubrum* can be associated with the production of lipophilic toxin that inhibits cellular immunity and the proliferation of keratinocytes (Vorzheva and Chernyak 2004).

Nowadays, the fungal infections of the human skin, hair, and nail are treated by the oral or topical antifungal agents such as fluconazole, triazoles, and terbinafine which have a high spectrum of activity against dermatophytes. Despite the fact that many antifungal agents are available, their side effects (Table 2) and interactions with drugs, as well as the presence of resistant organisms, have created the need for safer and more effective treatment. In addition, treatment of dermatophytosis is usually expensive and should be applied for a long time.

Some extracts are active against dermatophyte fungi. Simonetti et al. (2017a, b) demonstrated that *Vitis vinifera* seed extracts obtained from different tables and wine cultivars have antidermatophytic activity against collection of strains of *T. mentagrophytes*, *M. gypseum*, and *M. canis*. Geometric minimal inhibitory concentration ranged from 20 to 97 μg/ml. The activity of the extracts was lower than terbinafine but comparable with that of fluconazole.

The antifungal activity of unripe grape extracts from agro-industrial wastes has been demonstrated against several strains of dermatophytes. All the extracts tested showed antifungal activity. The geometric mean MIC ranged from 43.54 to 133.02 μg/mL for dermatophytes. The highest negative significant correlation has

been found between MICs and caffeoyl derivatives ($r = -0.962$, $p < 0.01$) (Simonetti et al. 2017a, b).

Endo et al. (2015) demonstrated the antifungal activity of *Rosmarinus officinalis* and *Tetradenia riparia* hydroalcoholic extracts against dermatophytes. According to the fluorescence microscopy and scanning electron microscopy results, *Rosmarinus officinalis* and *Tetradenia riparia* hydroalcoholic extracts cause inhibition of hyphal growth and irregular growth pattern. The MIC values range from 62.5 to 250 μg/mL (Morais et al. 2017). The dragon's blood from *Croton urucurana*, used by indigenous cultures of the Amazon River for the treatment of infected wounds, has shown to have antifungal activity. The results showed that dragon's blood MIC against *T. rubrum*, *T. mentagrophytes*, *M. canis*, and *E. floccosum* was 2.5 mg/ml and against *T. tonsurans* was 1.25 mg/ml (Gurgel et al. 2005).

Rodrigues et al. (2012) showed that the extract from aerial parts of *Pothomorphe umbellata*, a native Brazilian plant, is active against dermatophytes, in particular, against *T. rubrum*.

T. rubrum is one of the most common species of human dermatophytes which causes tinea pedis, nail infection, tinea cruris, and tinea corporis. MIC value of the ethanol extract of *Pothomorphe umbellata* was 156.25 μg/mL, while the methanol extract shows MIC value of 78.13 μg/mL. The antifungal activity of *Pothomorphe umbellata* could be due to the presence of ß-sitosterol, stigmasterol, and campesterol. In essential oil were identified several compounds as spathulenol, β-caryophyllene, caryophyllene oxide, germacrene D, bicyclogermacrene, b-elemene, b-pinene, a-cadinol, d-cadinene, a-copaene, and limonene.

*3.3 Anti-*Malassezia *Plant Products*

Malassezia spp. are normally present in the normal biota of a healthy human skin. Usually *Malassezia* spp. cause only chronic recurrent superficial mycoses without any life threat. In individuals with immunosuppression as well as endocrinopathies, chronic dermatoses and bacteria infections *Malassezia* could cause skin infections like dandruff, pityriasis versicolor, seborrhoeic dermatitis, and folliculitis. According to the recent studies, *Malassezia* spp. play a role in the pathogenesis of atopic dermatitis and psoriasis, especially in cases involving the scalp (Velegraki et al. 2015). The *Malassezia* genus includes 14 species: *M. furfur*, *M. pachydermatis*, *M. sympodialis*, *M. globosa*, *M. obtusa*, *M. restricta*, *M. slooffiae*, *M. equina*, *M. dermatis*, *M. japonica*, *M. nana*, *M. capre*, *M. yamatoensis*, and *M. cuniculi*; however, only 9 of them could infect humans (Cabanes et al. 2011). A number of different methods have already been proposed for the treatment of *Malassezia* skin mycoses, but they have many disadvantages, in particular, long-time course duration, insufficient therapeutic efficacy, and tolerance resistance to antifungal therapy. Nowadays, *Malassezia* systemic infections require prompt identification of the pathogenic agent and treatment with liposomal amphotericin B, itraconazole, or fluconazole. Fungi of the genus *Malassezia*, due to their cultural characteristics, have

extraordinary resistance to environmental factors and natural and synthetic antimycotic agents of systemic and topical application, which is why it is possible to explain the existing problems in the treatment of patients (Velegraki et al. 2015; Bragutsa 2007).

Simonetti et al. (2017a, b) demonstrated anti-*Malassezia* activities of *Vitis vinifera* seed extracts obtained from different tables and wine cultivars. Geometric minimal inhibitory concentration ranged from 32 to 161 μg/mL for *M. furfur*. The MIC for *M. furfur* was inversely correlated with the amount of the polymeric fraction ($r = -0.7228$) and only weakly was correlated to the content of flavan-3-ol monomers.

Shams-Ghahfarokhi et al. (2006) studied the antifungal activity of aqueous extracts obtained from *Allium cepa* and *Allium sativum* against *M. furfur*. *Allium cepa* and *Allium sativum* are used in the folk medicine of many countries due to their antifungal, antiprotozoal, antihelminthic, antiviral, disinfectant, and antitumor properties as well as in the treatment of gastric and hepatic disorders, diabetes mellitus, hypertension, hypercholesterolaemia, and immunodeficiency syndromes. The results of Shams-Ghahfarokhi indicate that *Allium cepa* and *Allium sativum* extracts were active against *M. furfur* with MIC values ranging from 0.08 to 0.16 mg/ml.

Filip R. et al. (2010) have evaluated the effect of the aqueous extract of *Ilex paraguariensis* on the growth of *M. furfur*. *Ilex paraguariensis* is a plant that typically grows in north-eastern area of Argentina, Southern Brazil, and Eastern Paraguay. The results demonstrated that the aqueous extract of *Ilex paraguariensis* possesses inhibitory activity against *M. furfur* (MIC = 1000 μg/ml). Probably the presence of chlorogenic acid, caffeic acid, theobromine, and rutin in the extract provides observed anti-*Malassezia* activity.

Onlom et al. (2014) investigated antifungal activities of the extracts obtained from the roots of *Asparagus racemosus* Willd against *M. furfur* and *M. globosa*. *Asparagus racemosus* Willd or shatavari (Asparagaceae family) is an important medicinal plant in Ayurvedic medicine due to various activities including phytoestrogenic, antibacterial, anti-candidal, antidiarrhoeal, antioxidant, immunostimulant, anti-dyspepsic, and antitussive effects. It has been shown that defatted ethanolic extract from the roots of *Asparagus racemosus* has anti-*Malassezia* activity against both *M. furfur* and *M. globosa* with MIC value 25 mg/mL.

*3.4 Anti-*Aspergillus *Plant Products*

Aspergillus spp. infections have grown in importance in the last years. The *Aspergillus* genus consists of about 40 pathogenic species. *Aspergillus fumigatus*, along with *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus* are the main pathogens of aspergillosis (Kulko 2012). *A. fumigatus* is an opportunistic pathogen that usually affects cavities that have formed in the lungs from preexisting lung diseases. In the lungs, *A. fumigatus* forms tangled mass of fungus fibres and blood clots. The fungus mass gradually enlarges, destroying lung tissue in the process, but usually does not spread to other areas. *A. niger* is a causative agent causing

invasive aspergillosis. Invasive aspergillosis in immunocompromised host is a major infectious disease leading to reduce the survival rate of world population. Until recent years, the only drugs available to treat aspergillosis were amphotericin B and itraconazole, the latter in oral and intravenous formulations. Recently, voriconazole, posaconazole, and caspofungin have also been approved for the treatment of aspergillosis. Infections caused by *A. terreus* resistant to amphotericin B, are treated with triazoles, voriconazole, and echinocandin. Although resistance to antifungal drugs is not as great a concern as resistance to antibacterial agents, there has been an increase in the number of reported cases of both primary and secondary resistance in human mycoses (Denning et al. 1997). Therefore, the resistance of the fungus to the drug or an inadequate concentration of the antifungal drug at the site of infection might contribute to the high mortality rate seen for these infections (Hedayati et al. 2007).

Bansod and Rai (2008) tested oils extracted from 15 medicinal plants that were screened for their activity against *A. fumigatus* and *A. niger*. The results showed that *Cymbopogon martini*, *Eucalyptus globulus*, and *Cinnamomum zylenicum* oils to control (miconazole nitrate) have antifungal activity. The oils of *Mentha spicata*, *Azadirachta indica*, *Eugenia caryophyllata*, *Withania somnifera*, and *Zingiber officinale* exhibited moderate activity. The *Cuminum cyminum*, *Allium sativum*, *Ocimum sanctum*, *Trachyspermum copticum*, *Foeniculum vulgare*, and *Elettaria cardamomum* oils demonstrated comparatively low activity against *A. niger* and *A. fumigatus* as compared to control. Mixed oils showed maximum activity as compared to standard. Arunkumar and Muthuselvam (2009) reported the activity of *Aloe vera* extracts against *A. flavus* and *A. niger*. The higher antifungal activity was observed with acetonic extract (15 ± 0.73 nm and 8 ± 0.37 nm).

3.5 *Anti-*Cryptococcus *Plant Products*

Cryptococcosis is an important systemic mycosis and the third most prevalent disease in human immunodeficiency virus HIV-positive individuals. About 8% of the patients with AIDS and HIV-infected have cryptococcosis. Fungi of the *Cryptococcus* genus are causative agents of cryptococcosis. Very often the disease affects people with depressed immune systems. Commonly this disease affects the central nervous system and, in some cases, less often, the lungs, mucous membranes, and skin. Cryptococcosis occurs by the inhalation of infectious cells and is considered a primary pulmonary infection, which may lead to a disseminated infection. The disseminated infection could affect the central nervous system, causing meningitis, encephalitis, or meningoencephalitis. Among all the fungi of the genus *Cryptococcus*, which includes a large number of species, only *C. neoformans* (in Europe and North America) and *C. gattii* (tropical and subtropical zones) are considered to be pathogenic in humans. *C. neoformans* has a spherical, round, or oval shape and an average cell size of 8–40 μm. The main antifungal agents for cryptococcosis treatment are amphotericin B, flucytosine, and oral triazole antifungal drugs, such as fluconazole and itraconazole (Gullo et al. 2013). However, the use of flucytosine in patients with AIDS has been controversial due to its toxicity.

Despite the existing methods of treatment, the main lines of modern clinical trials include a comparative analysis of the efficacy and safety of antimycotic drugs for various infectious agents, as well as the search for the most optimal systemic drugs (Piraccini and Gianni 2013).

Considerable interest of the scientific community has been attracted to plant-based fungicides, because plants have their own protection against fungal pathogens through the ability to produce antifungal compounds in order to be protected from biotic attack, which may be necessary for resistance to fungal infections (Gurgel et al. 2005).

Valente et al. (2013) showed that *Oenanthe crocata* L. essential oil have activity against *C. neoformans*. The oil was predominantly composed of monoterpene hydrocarbons (85.8%), being the main compounds trans-b-ocimene (31.3%), sabinene (29.0%), and cis-b-ocimene (12.3%). The oil was particularly active against dermatophytes and *C. neoformans*, with MIC values ranging from 0.08 to 0.16 μg/mL.

Rangkadilok and collaborators (2012) showed that longan (*Dimocarpus longan* Lour.) seed extract has antifungal activity against *C. neoformans*. This natural plant contains polyphenolic compounds which exhibit several pharmacological properties. Extract of longan fruit contained high levels of polyphenolic compounds such as corilagin, gallic acid, and ellagic acid. Longan seed extract exhibited antifungal activity against *C. neoformans* with MIC of 4000 μg/ml.

Ranganathan and Balajee (2000) demonstrated that extracts of *Cassia alata* and *Ocimum sanctum* have anti-*Cryptococcus* activity. The ethanolic extract of *O. sanctum* did not show any activity against all the strains up to a concentration of 1000 μg/mL. The MIC of ethanolic extract of *C. alata* ranged from 500 to 1000 μg/ml, and the extract showed fungicidal activity at 1000 μg/ml at acidic pH. Decreased activity at neutral pH and least activity at pH 8 were recorded for the extract. The combination of extract of *O. sanctum* and *C. alata* inhibited growth of the organism at a concentration ranging from 62.5 to 125 mg/ml. The combination of the extracts showed fungicidal activity at 125 μg/ml. It is known that the leaves of *C. alata* contain anthraquinones, flavonoids, quinones, and sterols which could be a reason of the effect of the extract combination on *C. neoformans* (Table 3).

4 Production of Antimicrobials Through Plant Tissue Cultures

As discussed above, plants are a vast and still largely unexplored source of antimicrobial secondary metabolites. Different methods can be adopted to obtain antimicrobial compounds of plant origin, and each one has its own advantages and disadvantages.

Since the ancient times, plant bioactive compounds have been obtained through direct extraction from wild plants. It should be noted that specialists are required for the harvesting of wild plants intended for human use, since many plants morphologically similar to the species of interest may have a different phytochemical profile corresponding to different biological activities and may contain toxic metabolites,

Table 3 Antifungal activity of extracts obtained from plants collected directly from their natural habitat

Plant family	Species name (plant common name)	Natural habitat	Main active constituents	Part of plant	Fungal species	Antifungal activity	Reference
Annonaceae	*Annona squamosa* (sugar-apples)	South and Central America, Africa, India, Southeast Asia, Australia	Alkaloids, Glycosides Flavonoids, Tannins Phenols Saponins	leaves		MIC (µg/ml)	Kalidindi et al. (2015)
					Alternaria alternata	800	
					Candida albicans	600	
					Fusarium solani	600	
					Microsporum canis	400	
					Aspergillus niger	400	
Apiaceae	*Oenanthe crocata* (water dropworts)	Mediterranean region	Terpenes	Aerial parts		MIC (µg/ml)	Valente et al. (2013)
					Candida albicans	0.64–1.25	
					Candida guilliermondii	0.64	
					Candida krusei	1.25	
					Candida parapsilosis	1.25	
					Candida tropicalis	1.25	
					Cryptococcus neoformans	0.16	
					Epidermophyton floccosum	0.08	
					Microsporum canis	0.08	
					Microsporum gypseum	0.08	
					Trichophyton mentagrophytes	0.16	
					Trichophyton mentagrophytes	0.16	
					Trichophyton rubrum	0.08	
					Trichophyton verrucosum	0.64–1.25	
					Aspergillus flavus	2.5	
					Aspergillus fumigatus	1.25	
					Aspergillus niger	1.25	

Apocynaceae	*Alstonia macrophylla* (hard alstonia)	Far East	Alkaloids	Leaves		MIC (μg/ml)	Chattopadhyay et al. (2001)
					Trichophyton mentagrophytes	64,000	
					Trichophyton rubrum	32,000	
					Microsporum gypseum	128,000	
Asclepiadaceae	*Cryptolepis buchanani* (kareballi)	India	Tannins Alkaloid Saponins Flavonoids	Leaves		Inhibition zone (mm)	Verweij et al. (2009)
					Chrysosporium keratinophilum	12	
					Trichophyton rubrum	14	
					Chrysosporium indicum	11	
Asteraceae	*Tridax procumbens* (coatbuttons)	Central America	Carboxylic acid Ethyl esters	Aerial parts		Inhibition zone (mm)	Policegoudra et al. (2014)
					Trichophyton mentagrophytes	7	
					Trichophyton rubrum	4	
					Trichosporon beigelii	2	
					Candida albicans	2	
	Baccharis trinervis (cambara-rebentao, casadinha preta, assapeixe-fino)	South America	Monoterpenes	Aerial parts		MIC (μg/ml)	Sobrinho et al. (2016)
					Trichophyton rubrum	150–310	
Ebenaceae	*Diospyros virginiana L.* (American persimmon)	Southeastern of the United States, China	Vitamins Carotenoids Carotenes	Fruits		MIC (μg/ml)	Ciric et al. (2014)
					Aspergillus fumigatus	5	
					Aspergillus versicolor	40	
					Aspergillus ochraceus	10	
					Aspergillus niger	40	
					Penicillium verrucosum	10	
					Penicillium ochrochloron	40	
					Penicillium funiculosum	10	
					Trichoderma viride	40	

(continued)

Table 3 (continued)

Plant family	Species name (plant common name)	Natural habitat	Main active constituents	Part of plant	Fungal species	Antifungal activity	Reference
Euphorbiaceae	*Croton urucurana Baill.* (red sap dragon's Dimocarpus blood)	South America	Flavans	Resin		MIC (μg/ml)	Gurgel et al. (2005)
					Trichophyton rubrum	2500	
					Trichophyton mentagrophytes	2500	
					Trichophyton tonsurans	1250	
					Microsporum canis	2500	
					Epidermophyton floccosum	2500	
Hypericaceae	*Hypericum perforatum* (St. John's wort)	Temperate regions	Xanthones	Roots		MIC (μg/ml)	Tocci et al. (2013b)
					Candia albicans	663.98	
					Candida parapsilosis	1024	
					Candida glabrata	1024	
					Candida tropicalis	406.37	
					Candida krusei	256	
					Cryptococcus neoformans	53.81	
					Trichophyton mentagrophytes	181	
					Microsporum gypseum	362.04	
Juglandaceae	*Argemone mexicana* (Mexican poppy)	India, Mexico, Nigeria	Terpenes	Stem and leaves		Inhibition zone (mm)	More and Kharat (2016)
					Mucor indicus	30	
					Aspergillus flavus	23	
					Aspergillus niger	21	
					Penicillium notatum	20	
Lamiaceae	*Zataria multiflora* (Zataria)	Middle East	Terpenes	Essential oils		MIC (ml/ml)	Mahboubi et al. (2017)
					Trichophyton rubrum	0.125	
					Trichophyton mentagrophytes	0.03	
					Microsporum canis	0.03	
					Microsporum gypseum	0.125	
					Trichophyton schoenleinii	0.06	

	Rosmarinus officinalis (Rosemary)	Africa, Iberian Peninsula	Flavonoids	Leaves		MIC (μg/ml)	Morais et al. (2017)
					Trichophyton rubrum	250	
					Trichophyton mentagrophytes	6.5	
					Microsporum gypseum	125	
	Tetradenia riparia (misty plume bush, ginger bush, iboza)	Southern Africa	Flavonoids	Leaves		MIC (μg/ml)	Morais et al. (2017)
					Trichophyton rubrum	62.5	
					Trichophyton mentagrophytes	125	
					Microsporum gypseum	62.5	
	Lavandula stoechas (lavender)	Iberian Peninsula, Italy	Monoterpenes	Essential oils from aerial parts		MIC (ml/ml)	Zuzarte et al. (2013)
					Candida albicans	2.5	
					Candida tropicalis	2.5	
					Candida krusei	2.5	
					Candida guilliermondii	1.25	
					Candida parapsilosis	2.5	
					Cryptococcus neoformans	0.64	
					Epidermophyton floccosum	0.32	
					Microsporum canis	0.64	
					Microsporum gypseum	0.64	
					Trichophyton mentagrophytes	0.64	
					Trichophyton mentagrophytes	0.64	
					Trichophyton rubrum	0.64	
					Trichophyton verrucosum	0.64	
					Aspergillus fumigatus	1.25	
					Aspergillus flavus	5	
					Aspergillus niger	2.5	

(continued)

Table 3 (continued)

Plant family	Species name (plant common name)	Natural habitat	Main active constituents	Part of plant	Fungal species	Antifungal activity	Reference
	Thymus herba-barona (Caraway thyme)	Mediterranean Region	Phenols Monoterpenoid phenols	Essential oils from aerial parts		MIC (ml/ml)	Zuzarte et al. (2013)
					Candida albicans	0.16	
					Candida tropicalis	0.16	
					Candida krusei	0.16	
					Candida guilliermondii	0.16	
					Candida parapsilosis	0.16	
					Cryptococcus neoformans	0.16	
					Epidermophyton floccosum	0.16	
					Microsporum canis	0.16	
					Microsporum gypseum	0.16	
					Trichophyton mentagrophytes	0.16	
					Trichophyton mentagrophytes	0.16	
					Trichophyton rubrum	0.16	
					Trichophyton verrucosum	0.16	
					Aspergillus fumigatus	0.16	
					Aspergillus flavus	0.32	
					Aspergillus niger	0.32	
Lamiaceae	*Zataria multiflora* (Avishan shirazi)	Southwestern Asia	Thymol Phenolic acids Monoterpenoid phenols	Aerial parts		MIC (µg/ml)	Mahmoudabadi et al. (2007)
					Candida albicans	125,000	
					Candida glabrata	126,000	
					Candida parapsilosis	125,000	
					Candida tropicalis	131,000	
					Candida albicans	76,000	
					Candida glabrata	66,000	
					Candida parapsilosis	64,000	
					Candida tropicalis	76,000	

	Salvia amplexicaulis (salvia)	Southeastern Europe	Phenolic acids Flavonoids (including flavones and flavonols) Polyphenol	Aerial parts, including stems Leaves, Inflorescences		MIC (μg/ml)	Alimpic et al. (2017)
					Candida krusei	64,000	
					Candida albicans	32,000	
					Candida parapsilosis	16,000	
					Aspergillus glaucus	8000	
					Trichophyton mentagrophytes	16,000	
Liliaceae	*Aloe vera*	South-west Arabian Peninsula	Tannins Saponins Flavonols	Leaves		Inhibition zone (mm)	Arunkumar and Muthuselvam (2009)
					Aspergillus flavus	11–15	
					Aspergillus niger	10–8	
	Allium ascalonicum (shallot, onion)	Worldwide	Flavonols Saponins	Bulbs		Inhibition zone (mm)	Mahmoudabadi and Nasery (2009)
					Microsporum gypseum	11	
					Trichophyton mentagrophytes	10.7	
					Trichophyton mentagrophytes	16	
					Epidermophyton floccosum	15.3	
					Epidermophyton floccosum	17.6	
Meliaceae	*Azadirachta indica* (neem)	Indian subcontinent	Flavonols Phytosterols	Leaves Seeds		MIC (μg/ml)	Mahmoud et al. (2011)
					Trichophyton rubrum	31	
					Trichophyton mentagrophytes	31	
					Microsporum nanum	31	
Moringaceae	*Moringa oleifera* (moringa, drumstick tree, horseradish tree)	Far East	Alkanes	Seed		MIC (μg/ml)	Chuang et al. (2007)
					Trichophyton rubrum	2500	
					Trichophyton mentagrophytes	2500	
					Epidermophyton floccosum	2500	
					Microsporum canis	2500	

(continued)

Table 3 (continued)

Plant family	Species name (plant common name)	Natural habitat	Main active constituents	Part of plant	Fungal species	Antifungal activity	Reference
Myrtaceae	*Eucalyptus camaldulensis* (river red gum)	Iran	Saponin Glycosides Tannins Phenols	Leaves		MIC (µg/ml)	Falahati et al. (2005)
					Microsporum canis	1600	
					Microsporum gypseum	1600	
					Trichophyton rubrum	1600	
					Trichophyton schoenleinii	400	
					Trichophyton mentagrophytes	400	
					Epidermophyton floccosum	400	
	Eucalyptus citriodora (lemon-scented gum, blue-spotted gum, lemon eucalyptus)	Australia	Terpenoids	Leaves		MIC (µg/ml)	Tolba et al. (2015)
					Microsporum canis	0.6	
					Microsporum gypseum	5	
					Trichophyton mentagrophytes	1.25	
					Trichophyton rubrum	0.6	
	Eucalyptus microcorys (tallowwood)	Australia	Phenolic acid Rutin	Leaves		MIC (µg/ml)	Bhuyan et al. (2017)
					Geotrichum candidum	4.88	
					Aspergillus brasiliensis	2.44	
					Candida albicans	1250	
Oxalidaceae	*Psidium guajava* (yellow lemon guava guava *L*)	Central America, South America	Carboxylic acid Terpenes Aromatic dicarboxylic acid Polyphenols	Leaves		MIC (µg/ml)	Morais-Braga et al. (2016)
					Trichophyton mentagrophytes	2670	
					Trichophyton rubrum	2670	
					Trichophyton tonsurans	16,000	

Piperaceae	*Piper regnellii* (piper)	Tropical and subtropical regions of the world	Neolignans conocarpan, eupomatenoid-3, eupomatenoid	Leaves		MIC (μg/ml)	Koroishi et al. (2008)
					Trichophyton mentagrophytes	250	
					Microsporum canis	250	
					Trichophyton rubrum	62.5	
					Microsporum gypseum	62.5	
	Dimocarpus longan (longan, lumyai)	Southern Asia	Carboxylic acids	Leaves		MIC (μg/ml)	Rangkadilok et al. (2012)
					Cryptococcus neoformans	500	
	Pothomorphe umbellatum (pariparoba)	Amazonian region	Phytosterols	Aerial parts		MIC (μg/ml)	Rodrigues et al. (2012)
					Trichophyton rubrum	1250	
Polypodiaceae	*Drynaria quercifolia* (Oakleaf fern)	India, Southeast Asia, Australia	Terpenes Phytosterols Flavonols	Leaves		Inhibition zone (mm)	Nejad and Deokule (2009)
					Trichophyton mentagrophytes	25	
Rutaceae	*Aegle marmelos* (Bengal quince, golden apple)	Indian subcontinent	Alkaloids Tannins Phlobotannins Flavans	Essential oil		MIC (μg/ml)	Balakumar et al. (2011)
					Trichophyton mentagrophytes	400	
					Trichophyton rubrum	400	
					Microsporum canis	400	
					Microsporum gypseum	400	
Sapindaceae	*Matayba guianensis* (Camboata de pombo)	South America	Phytosterols	Root bark		MIC (μg/ml)	Assis et al. (2014)
					Candida albicans	1.95	
					Candida parapsilosis	0.97	
					Trichophyton mentagrophytes	15.62	
					Trichophyton rubrum	31.25	
Vitaceae	*Vitis vinifera* (grapevine)	Mediterranean region	Flavan-3-ols	Seeds		MIC (μg/ml)	Simonetti et al. (2014), Simonetti et al. (2017a, b)
					Candida albicans	5.7–20.2	
					Candida species	1–32	
					dermatophytes	20–97	
					Malassezia furfur	32–161	

widely spread in the plant kingdom (Kinghorn 2010). Furthermore, since the natural resources are limited, they may be depleted at a rate faster than they regenerate. Due to the overexploitation, a number of plants producing bioactive metabolites have become endangered species (Chen et al. 2016).

The plant cultivation using conventional agricultural methods represents a possible alternative to the exploitation of wild plant resources. However, this approach is not always feasible or economically viable. Some species are distributed in certain areas and are difficult to cultivate outside of their local ecosystems (Mander e Liu 2010). Several woody plants are slow-growing, and their cultivation could be therefore economically disadvantageous. Finally, field-growing plants may be damaged by unpredictable adverse environmental conditions or pathogen attacks.

In both field-grown and wild-collected plants, the quality and quantity of metabolite production are often fluctuating and heterogeneous, depending on environmental conditions (Gerth et al. 2006). The synthesis of secondary metabolites often occurs in a particular stage of life cycle, or it is confined to specific organs, tissues, or cells.

The main alternatives to direct extraction from plants are the chemical synthesis and the biotechnological production.

Only in the last century, a restricted number of active ingredients were replaced by synthetic or semi-synthetic compounds, whose molecular structure has been often inspired by that of natural compounds. Well-known examples are salicylic acid and its derivative acetylsalicylic acid (Lichterman 2004). Several methods have recently been developed for the total synthesis of resveratrol (Nicolaou et al. 2010; Snyder et al. 2011; Klotter and Studer 2014), a stilbene compound whose antiviral activity has been demonstrated against several human and animal viruses, including influenza A virus (Palamara et al. 2005), Epstein-Barr virus (De Leo et al. 2012), herpes simplex virus (Docherty et al. 1999), respiratory syncytial virus (Zang et al. 2011), varicella zoster virus (Docherty et al. 2006), African swine fever virus (Galindo et al. 2011), and HIV-1 (Clouser et al. 2012). However, it must be said that the chemical synthesis, although of high scientific value, at present is rarely adopted for the large-scale production of bioactive plant metabolites, due to low yields that make it often economically unsuitable. One limiting factor for chemical synthesis of many secondary metabolites is their large size and the presence of multiple chiral centres (Wilson and Roberts 2012).

As regards the biotechnological production of natural antimicrobial compounds, in recent decades, great interest has been given to plant tissue cultures, a collection of techniques in which plant cells, tissues, organs, or whole plantlets are cultivated on synthetic media, in aseptic environment, under controlled physico-chemical conditions. In vitro plant cultures could be used as “bio-factories” for the production of high-value secondary metabolites (Wilson and Roberts 2012).

Different types of in vitro plant cultures can be distinguished based on the degree of differentiation. The lowest degree of differentiation is exhibited by cell cultures. These are initiated from surface sterilized explants (i.e. isolated plant tissues), which are inoculated on jellified media, containing growth regulators, and nutrients (Hall 2000). In appropriate growing conditions, some cells of the explant proliferate,

forming disorganized masses of dedifferentiated cells called "calli", which can be grown indefinitely in a periodically renewed jellified culture media or transferred to liquid media to create suspension cultures (Wilson and Roberts 2012).

A higher degree of differentiation is observed in organ cultures. The regeneration of plant organs (organogenesis) can be induced by subjecting the explants or cultured cells to specific hormone combinations. The regeneration of roots (rhizogenesis) or shoots (caulogenesis) can proceed either directly or indirectly. The direct mode involves the development of organs directly from the differentiated tissues of explants in contrast to the indirect mode, where an intervening step of callus formation precedes regeneration (Pulianmackal et al. 2014).

An interesting biotechnological system for the production of high-value secondary metabolites is represented by the hairy root cultures, which are obtained through the infection of plant cells with *Agrobacterium rhizogenes*. Hairy root cultures are characterized by a high grow rate in hormone-free culture media and by a high degree of genetic and metabolic stability. These genetically transformed roots can produce levels of secondary metabolites comparable to that of intact plants (Srivastava and Srivastava 2007).

The main limitation of root cultures, both transformed and untransformed, is that they indefinitely maintain an anatomical primary structure. This represents a problem when the metabolites of interest are biosynthesized predominantly or exclusively in the root in secondary structure. An example is the biosynthesis of essential oils in *Angelica archangelica* L. (Apiaceae), which occurs specifically in secondary secretory ducts formed by vascular cambium activity and located in the secondary phloem (Pasqua et al. 2003). To the best of our knowledge, no strategies have been developed to induce the transition from the primary to the secondary structure in in vitro cultured roots. The highest degree of differentiation is exhibited by the in vitro plantlet cultures, which can be obtained either by rooting of cultured shoots or by in vitro seed germination.

4.1 Production of Antimicrobials Through Plant Cell Cultures

Callus cultures and suspension cultures of several species had been exploited for the biotechnological production of secondary metabolites with antimicrobial activity.

One of the most studied plant species is grapevine (*Vitis vinifera* L., Vitaceae), which produces a broad spectrum of polyphenols with proven antimicrobial activities, including stilbenes and flavan-3-ols (Mulinacci et al. 2008; Santamaria et al. 2011).

Stilbenes are a small family of polyphenols biosynthesized through the phenylpropanoid pathway, found in a number of unrelated plant species, including grapevine, sorghum (*Sorghum bicolor* L. Moench), peanut (*Arachis hypogaea* L.), bilberries (*Vaccinium myrtillus* L.), and several conifer species (*Pinus* spp. and *Picea* spp.) (Chong et al. 2009). It has been demonstrated that stilbenes play a role in plant chemical defence against microorganisms (Jeandet et al. 2002; Ahuja et al. 2012);

thus, it should not be surprising that some of them exhibit remarkable antimicrobial activity against phytopathogenic bacteria and fungi (Morales et al. 2000; Chong et al. 2009). Pinosylvin and its 3-O-methyl ether, which are naturally accumulated by conifers, showed a strong antifungal activity against *Coriolus versicolor* and *Gloeophyllum trabeum*, two wood-destroying fungi (Schultz et al. 1992). Resveratrol and its glucoside piceid exogenously applied to apples inhibited *Venturia inaequalis*, the causal agent of apple scab, reducing spore germination and inhibiting the penetration through cuticular membranes (Schulze et al. 2005). Resveratrol inhibited conidial germination of *Botrytis cinerea*, the grey mould agent on grapes (Adrian et al. 1997), and reduced the germination of sporangia of *Plasmopara viticola*, the downy mildew agent (Pezet et al. 2004). Methylated resveratrol derivatives, such as pterostilbene, showed a much higher antifungal activity than resveratrol (Pezet et al. 2004). In in vitro tests, also the resveratrol oligomers viniferins exhibited a significantly higher antifungal activity than resveratrol (Pezet et al. 2004). It has been hypothesized that the lower antifungal activity of resveratrol is related to its higher hydrophilicity that limits diffusion across biological membranes (Pezet and Pont 1995).

As discussed above, in addition to being active against phytopathogenic microorganisms, stilbenes exhibited interesting potential as active ingredients against animal and human viral pathogens (Abba et al. 2015). Stilbene antimicrobial activity has also been demonstrated against some human pathogenic bacteria (Chan 2002; Taylor et al. 2014), protozoa (Kedzierski et al. 2007), and fungi (Chan 2002). Most of the published studies are focused on resveratrol (Paulo et al. 2001); however, in recent years, resveratrol derivatives, both natural (Sakagami et al. 2007; Basri et al. 2014) and synthetic or semi-synthetic (Chalal et al. 2014), are being studied to evaluate their antimicrobial properties.

Several studies have demonstrated that grapevine cell cultures are able to biosynthesize stilbenes and that stilbene production can be greatly increased by the use of elicitors (Waffo-Teguo et al. 2001; Decendit et al. 2002; Larronde et al. 2005; Tassoni et al. 2005; Belhadj et al. 2008; Ferri et al. 2009; Santamaria et al. 2010, 2011, 2012; Belchí-Navarro et al. 2012). The term “elicitor” refers to physical or chemical factors capable of triggering an array of plant defence responses, including phytoalexin neosynthesis (Namdeo 2007; Naik and Al–Khayri 2016).

A number of chemical elicitors have been tested that enhance stilbene production in grapevine cell cultures. Among these, the most effective proved to be jasonates, signal molecules that mediate defence responses against herbivores and pathogens, in addition to alleviating abiotic stresses, including UV stress, salt stress, osmotic stress, heat stress, cold stress, heavy metal stress, and ozone stress (Dar et al. 2015). Both jasmonic acid and its methyl ester methyl jasmonate proved effective in enhancing stilbene biosynthesis in cell cultures of *V. vinifera* cvs. Red Globe and Michele Palieri (Santamaria et al. 2010) (max total stilbene production 647 and 1220 μmol kg^{-1} FW, respectively, with methyl jasmonate) and cv. *Italia* (Santamaria et al. 2011) (max total stilbenes 1.023 mg g^{-1} DW by with jasmonic acid).

Another elicitor frequently used to increase the productivity of cell cultures is chitosan, a polysaccharide derived from the partial deacetylation of chitin, the main

structural component of the fungal cell wall and of the arthropod exoskeleton. On cell cultures of *V. vinifera* cv. *Italia*, chitosan showed a treasurable effect on stilbene biosynthesis (Santamaria et al. 2011); otherwise, it is shown to be an effective elicitor on cell cultures of *V. vinifera* cv. Barbera (Ferri et al. 2011). This is an example of how significantly stress responses can vary between different grapevine cultivars.

Few studies are available regarding the effect of physical elicitors on stilbene biosynthesis in grapevine cell cultures. In a recent paper, it has been compared the effect of methyl jasmonate (chemical elicitor) and low-energy ultrasounds (physical elicitor) on the production of viniferins in cell cultures of *V. vinifera* cv. Alphonse Lavallée (Santamaria et al. 2012). It has been observed that ultrasounds have an effect compared to methyl jasmonate and that the two elicitors, when used in combination, have a synergistic effect in enhancing δ-viniferin biosynthesis (1.43 mg g^{-1} DW). Another study compared the impact of methyl jasmonate, salicylic acid, and ultraviolet C radiation on stilbene production in cell cultures of *V. vinifera* L. cv. Cabernet Sauvignon (Xi et al. 2015). Once again, the best results were obtained by combining chemical elicitors (methyl jasmonate or salicylic acid) with physical elicitor (ultraviolet C radiation) (1.6–2 mg g^{-1} DW).

Another extensively studied species is *Hypericum perforatum* L. (St. John's wort, Hypericaceae), a medicinal plant used since ancient times for its numerous curative properties. Many studies are available regarding the antimicrobial activity of extracts obtained from *H. perforatum* plant (Reichling et al. 2001; Avato et al. 2004; Saddiqe et al. 2010; Naeem et al. 2010; Süntar et al. 2016). Only recently, the research has focused on extracts from *H. perforatum* cell cultures. These extracts are rich in xanthones, a class of non-flavonoid polyphenols whose antimicrobial activity has been reported in numerous studies (Suksamrarn et al. 2003; Pinheiro et al. 2003; Laphookhieo et al. 2006; Ahmad 2016).

Tocci and collaborators (2010) observed that cell suspensions of *H. perforatum* are able to produce different xanthones and that the total xanthone content increased in response to elicitation with chitosan, from 0.13 to about 0.56 mg g^{-1} DW. In control cells, only paxanthone was detected, while in treated cells, the emergence of 1,3,6,7- and 1,3,5,6-tetrahydroxyxanthone, cadensin G, and 1,7-dihydroxyxanthone was observed.

Conceição et al. (2006) investigated the impact of different elicitors on the production of xanthones and flavonoids in St. John's wort cultured cells. In the cells elicited with lyophilized powder of the phytopathogenic fungus *Colletotrichum gloeosporioides*, a significant increase in both the quantity and diversity of xanthones was observed, while flavonoids became undetectable. A further increase in xanthone concentration and diversity was registered in response to priming with methyl jasmonate prior to fungal elicitation. Conversely, the treatment with methyl jasmonate alone caused a decrease in xanthone content and induced the biosynthesis of a new class of flavonoids, the flavones. This finding points to the possibility of selectively increasing the production of different compounds by choosing the most appropriate elicitor/s.

Franklin et al. (2009) observed that after cocultivation of St. John's wort cell cultures with *Agrobacterium tumefaciens*, the flavonoid profile remained unaltered, while xanthone profile significantly changed with a 12-fold increase in total xanthone content and with the neosynthesis of several xanthones not detected in control cells (i.e. 1,3,6,7-tetrahydroxy-8-prenyl xanthone, 1,3,6,7-tetrahydroxy-2-prenylxanthone, 1,3,7-trihydroxy-6-methoxy-8-prenylxanthone, paxanthone). The massive presence of xanthones (over 4 mg g^{-1} DW) was related to the high antibacterial activity of the extracts obtained from cells cocultured with *A. tumefaciens*.

Other examples on the exploitation of plant cell cultures for the production of antimicrobials are reported in Table 4.

4.2 Production of Antimicrobials Through Plant Organ Cultures

Many secondary metabolites are biosynthesized and/or accumulated in specific organs, tissues, and cell types (Valletta et al. 2010); therefore, they should be produced at low levels or not produced at all in in vitro cultures of undifferentiated cells. By means of appropriate hormonal treatments and exploiting the totipotency of plant cells, it is possible to regenerate in vitro plant organs, thus obtaining root or shoot cultures (Murthy et al. 2014).

Among organ cultures, root cultures are the most investigated because of their potential in the biotechnological production of antimicrobials. The plant root resides in an environment where potentially pathogen microorganisms are massively present. On the other end, the root maintains important mutualistic relationships with edaphic microorganisms, such as mycorrhizal fungi and nitrogen-fixing bacteria. For these reasons, many secondary metabolites involved in plant-microorganism relationships, both antagonistic and mutualistic, exhibit root-specific biosynthesis and accumulation (Pasqua et al. 2005).

For example, xanthone accumulation and biosynthesis in *H. perforatum* are root-specific (Tocci et al. 2017). In the root of the plant, these polyphenols are accumulated at relatively low levels, not suitable for large-scale production (Valletta et al. 2016). Recently, it has been demonstrated that *H. perforatum* in vitro regenerated roots are able to constitutively produce xanthones at higher levels (about 4–5 mg g^{-1} DW) than the root of the plant (Tocci et al. 2011, 2012, 2013a, b; Valletta et al. 2016). Among different elicitors, chitosan resulted the most effective, capable of causing a fivefold increase in xanthone production. A similar increase was obtained by treating the root cultures with acetic acid at low concentration (Valletta et al. 2016).

Methanol extracts obtained from *H. perforatum* elicited roots were tested on several human pathogenic fungi, including *Candida* spp. and *C. neoformans*, and dermatophytes (Tocci et al. 2011, 2012, 2013a, b; Zubrická et al. 2015).

Simonetti et al. (2016), in collaboration with the German biotechnology company ROOTec, started experiments on preindustrial scale-up from the laboratory

Table 4 Examples of antimicrobial metabolites of plant origin produced by different types of in vitro cultures

Types of culture	Plant species (family)	Metabolite/s	Genera of fungi	Reference
Cell cultures	*Rauvolfia tetraphylla* L. (Apocynaceae) *Physalis minima* L. (Solanaceae)		*Aspergillus* *Aspergillus* *Fusarium* *Penicillium*	Shariff et al. (2006)
	Origanum acutidens (Hand.-Mazz.) Ietsw. (Lamiaceae)	Essential oils	*Candida* *Aspergillus* *Fusarium* *Microsporum* *Moniliania* *Mortieraula* *Penicillium Rhizopus* *Rhizoctonia* *Trichophyton*	Sökmen et al. (2004)
	Ephedra strobilacea (Ephedraceae) *Ephedra procera* C.A.Mey. (Ephedraceae) *Ephedra pachyclada* Boiss. (Ephedraceae)	Ephedrine Pseudoephedrine Norpseudoephedrine Other alkaloids	*Aspergillus* *Candida*	Parsaeimehr et al. (2010)
Untransformed root cultures	*Hypericum perforatum* L. (Hypericaceae)	Xanthones	*Candida* spp. *Cryptococcus neoformans* Dermatophytes	Tocci et al. (2011, 2012, 2013a, b)
			Malassezia furfur	Simonetti et al. (2016)
Hairy root cultures	*Ocimum basilicum* L. (Lamiaceae)	Rosmarinic acid	*Aspergillus niger*	Bais et al. (2002); Ahmad et al. (2016)
	Lithospermum erythrorhizon Siebold & Zucc. (Boraginaceae)	Shikonin derivatives	*Rhizoctonia, Nectria*	Brigham et al. (1999)
In vitro propagated plantlets	*Stevia rebaudiana* Bertoni (Asteraceae)	Not specified	*Sclerotonia* *Curvularia* *Alternaria* *Aspergillus* *Microsporum Rhizopus*	Debnath (2007)

scale to a larger scale of *H. perforatum* root cultures. In the mist bioreactor used in this study, roots are cultivated in modules included in a plastic bag. Each module is a net on which roots can grow through. At a certain frequency, culture medium is sprayed from the top of the system and collected from the bag to saturate the atmosphere. Thanks to a series of pumps, the culture is collected and sprayed again. The methanol extracts containing xanthones, obtained from the roots cultivated in bioreactor, showed an interesting activity against planktonic cells and biofilm of *M. furfur*. The minimal inhibitory concentration was 16 μg mL^{-1}, while the inhibition percentage of biofilm formation, at a concentration of 16 μg mL^{-1}, ranged from 14% to 39% (Simonetti et al. 2016).

Recently, hairy root cultures of *H. perforatum* had been obtained (Vinterhalter et al. 2006; Bertoli et al. 2008; Koperdáková et al. 2009; Tusevski et al. 2013a), and thorough analyses had been carried out to determine their polyphenolic profile (Tusevski et al. 2013a, b; Tusevski and Simic 2013); however, to the best of our knowledge, no data on the antimicrobial activity of *H. perforatum* hairy root extracts are available.

Rosmarinic acid is an ester of caffeic acid and 3,4-dihydroxyphenyllactic acid, commonly found in species belonging to families Boraginaceae and Lamiaceae (subfamily Nepetoideae) (Petersen and Simmonds 2003). Several studies indicated that rosmarinic acid and its derivatives possess antiviral and antibacterial activities (Petersen and Simmonds 2003; Swarup et al. 2007; Bulgakov et al. 2012; Abedini et al. 2013).

Basil (*Ocimum basilicum* L.) untransformed roots produce rosmarinic acid at low levels (< 0.1% g fresh weight basis) (Bais et al. 2002). Basil hairy root cultures showed three-fold increases in growth and rosmarinic acid production; in addition, in response to elicitation with cell wall extract of the fungus *Phytophthora cinnamomi*, the production was enhanced about 2.7-fold compared with the untreated control roots (Bais et al. 2002).

4.3 Production of Antimicrobials Through Plantlets Propagated In Vitro

At present, the in vitro plant propagation is a technique mainly exploited for the multiplication of species of agronomic interest and as ex situ conservation strategy. Few examples regarding the production of antimicrobials from in vitro cultured plantlets are available in the literature.

Stevia rebaudiana Bertoni (Asteraceae) is an endemic herbaceous plant indigenous to the mountains between Paraguay and Brazil. *S. rebaudiana* is currently used all over the world for the production of low-calorie sweeteners. Areal parts of *S. rebaudiana* contain diterpene glucosides, viz. stevioside and rebaudioside with a sweet taste, which are not metabolizable by the human body. The biggest part of the sweet glycosides consists of the stevioside molecule (Brandle et al. 1998). The sweetener stevioside (Nepovim and Vanek 1998) extracted from the plants is 300 times sweeter than sugar.

Debnath (2007) has developed a procedure for in vitro propagation *Stevia rebaudiana*, starting from nodal segments with axillary buds. Chloroform and methanol extract of leaves collected from in vitro propagated plants had been tested for their antimicrobial activity against several medically important bacteria (*Escherichia coli*, *Bacillus subtilis*, *Streptococcus mutans*, *Staphylococcus aureus*) and fungi (*Sclerotinia minor*, *Curvularia lunata*, *Alternaria alternata*, *A. niger*, *M. gypseum*, *Rhizopus* sp.). The methanolic extract was the most effective against all fungi and bacteria tested, followed by chloroform extract, while aqueous extract proved to be undefective. These results clearly indicate that the solvent, playing a crucial role in the solubilization of antimicrobial molecules, also affects the antimicrobial activity.

5 Conclusions

Currently, opportunistic fungal infections are considered a serious problem regarding public health. Due to the increasing incidence of drug-resistant fungi, the research of new antifungal agents is required. In the present review, the antifungal activity of natural extracts from different plants and plant matrices has been evaluated and compared. Several plant natural products have been tested against fungal human pathogens. Despite good antifungal activity of plant products, only few have been tested in vivo. Many of these extracts are "generally recognized as safe" (GRAS). Due to the complexity of the natural matrices, the use of advanced analytical techniques, such as mass spectrometry, nuclear magnetic resonance, and high-performance liquid chromatography, is necessary nowadays for the early detection and identification of new compounds in crude plant extracts. The search for new antifungal compounds of plant origin could significantly contribute to the development of emerging countries, which are particularly rich in natural resources. The production of phytochemicals with antifungal activity is also possible using biotechnology strategies. The use of this technology could bring a series of practical and ecological advantages for a sustainable production, avoiding the risk of extinction of some plant species.

It is desirable that in the near future, the research will intensify its efforts to discover new plant-based antifungals, focusing mainly on the intertropical flora, which today is the least investigated, although it has a very high biodiversity. It should also be stressed that the hot-humid climate promotes the development of fungi and therefore the plant's defences against fungal infections, including antifungal molecules. Great efforts must also be made to identify the main biologically active compounds contained in plant extracts, in order to obtain standardized products. An interesting field of study will concern the combined effects of different plant extracts, due to synergistic, additive, and antagonistic interactions between different bioactive molecules.

Finally, it is desirable that in the near future, the regulation on the use of bioactive plant extracts will be uniformed in order to promote their use and diffusion.

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