Chapter 12
Natural Antifungal Agents Isolated from Argentine Plants. A Summary of Studies Developed in the Period 2000–2020

Gisela Seimandi, Estefanía Butassi, Melina Di Liberto, Estefanía Cordisco, Alan Blanc, Maximiliano Sortino, Laura Svetaz, and Marcos Derita

Abstract Fungal species are able to carry out beneficial actions on industrial processes that directly affect human being wellness. They can also be the cause of severe pathologies both in humans or food products. Fungicidal agents currently used to treat human or plant pathogens have many drawbacks after prolonged or inappropriate use, proving to be inefficient in a short term. Therefore, academics and the pharmaceutical or agrochemical industries are constantly encouraged to search for new chemical entities with antifungal action. In this sense, taking advantage of secondary plant metabolites to find out antifungal molecules could be of high interest. During the last 20 years, we have constituted a group of scientists that broach the subject related to antifungal products obtained from vegetable sources, and we have assayed hundreds of plant species and a considerable number of natural metabolites isolated from them, against the main fungal pathogens that affect humans and crops. The aim of this chapter is to update the plants that have demonstrated the best antifungal action during this period of time and the natural compounds responsible for this. In addition, new strategies like the evaluation of photoactive species and synergism, as well as comparisons with results obtained by other authors reported in the literature, will be discussed.

Keywords Antifungals · Natural products · Human pathogens · Fruit pathogens · Photoactivity · Synergism · Argentine plants

G. Seimandi
ICiAgro Litoral, Universidad Nacional del Litoral-CONICET, Esperanza, Argentina

E. Butassi · M. Di Liberto · E. Cordisco · A. Blanc · M. Sortino · L. Svetaz (✉)
Farmacognosia, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Rosario, Argentina

M. Derita (✉)
ICiAgro Litoral, Universidad Nacional del Litoral-CONICET, Esperanza, Argentina

Farmacognosia, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Rosario, Argentina

M. Rai, I. Kosalec (eds.), *Promising Antimicrobials from Natural Products*,
https://doi.org/10.1007/978-3-030-83504-0_12

Abbreviations

1-M-3-(3′,4’-DHP)-PC	1-Methyl-3-(3′,4′-dihydroxyphenyl)-propyl caffeate
1-M-3-(4’-HP)-PC	1-Methyl-3-(4′-hydroxyphenyl)-propyl caffeate
3,7-DHF	3,7-Dihydroxy flavone
3-H-7,8-DMF	3-Hydroxy-7,8-dimethoxy flavone
7-H-8-MF	7-Hydroxy-8-methoxyflavanone
7-HF	7-Hydroxy flavanone
AIDS	Acquired immune deficiency syndrome
AMB	Amphotericin B
APDT	Antimicrobial photo dynamic therapy
BBT	2,2′:5′,2″-Terthienyl (α-T); 5-(3-buten-1-ynyl)-2,2′-bithiophene
BBTOAc	5-(4-Acetoxy-1-butynyl)-2,2′-bithiophene
BBTOH	5-(4-Hydroxy-1-butynyl)-2,2′-bithiophene
CFU	Colony forming units
DCM	DiChloroMethane
DHC	2′,4´-Dihydroxychalcone
DHMC	2′,4´-Dihydroxy-3′-methoxychalcone
EtOH	Ethanolic
FCZ	Fluconazole
HTSS	High-throughput synergy screening
ITZ	Itraconazole
MeOH	Methanolic
MFC	Minimal fungicidal concentration
MIC	Minimal inhibitory concentration
PBT	5-(3-Penten-1-ynyl)-2,2′-bithiophene
PCM	Paracoccidioidomycosis
PDT	Photo dynamic therapy
PhytB	Phytolaccoside B (3-O-β-D-xylopiranosylphytol accagenin)
PhytE	Phytolaccoside E (3-O-β-D-glucopyranosyl-(1,4)-β-D-xylopiranosyl-phytolaccagenin)
PhytF	Phytolaccoside F [3-O-α-L-rhamnopyranosyl-(1,2)-β-D-glucopyranosyl-(1,2)-β-D-xylopyranosyl-phytolaccagenic acid]
PhytG	Phytolaccagenin
PSs	Photosensitizer
*Pt*AqEb	*Phytolacca tetramera* aqueous extract from berries
*Pt*AqEl	*Phytolacca tetramera* aqueous extract from leaves
*Pt*AqEr	*Phytolacca tetramera* aqueous extract from roots
*Pt*BEb	*Phytolacca tetramera* butanoic extract from berries
*Pt*BEl	*Phytolacca tetramera* butanoic extract from leaves
*Pt*BEr	*Phytolacca tetramera* butanoic extract from roots

*Pt*DEb	*Phytolacca tetramera* dichloromethane extract from berries
*Pt*DEl	*Phytolacca tetramera* dichloromethane extract from leaves
*Pt*DEr	*Phytolacca tetramera* dichloromethane extract from roots
*Pt*MEb	*Phytolacca tetramera* methanolic extract from berries
*Pt*MEl	*Phytolacca tetramera* methanolic extract from leaves
*Pt*MEr	*Phytolacca tetramera* methanolic extract from roots
ROS	Reactive oxygen species
TLC	Thin layer chromatography
UHPLC-ESI-MS	Ultra-high performance liquid chromatography-electrospray ionization mass spectrometry
UVA	Ultraviolet A radiation

1 Introduction

Fungal diseases are life-threatening to human health and cause an important burden around the world and are associated with high numbers of morbidity and mortality. Moreover, food contaminations due to different fungal infections are frequently the cause of great economic losses in horticultural businesses and economy. However, the same fungi which may exhibit great pathogenicity could also be used by the industry for different applications:

Candida albicans and *C. glabrata* are species of yeasts which cause candidiasis, a recurrent disease that is produced in humid and warmer environments of the human body such as the oral or vaginal cavity, skin folds, oropharyngeal, and bronchial secretions (Bonifácio et al. 2019). Moreover, they could cause dangerous opportunistic fungal infections on immunocompromised hosts and candidemia in adults, mainly in patients with hematological disorders (Butassi et al. 2015). On the other hand, the production of lipids (Enshaeieh et al. 2013), butyl oleate, and ethyl oleate catalyzed by *Candida* spp. (Chen et al. 2018) is used in the industry as a source for biodiesel production. Moreover, these yeasts may be harnessed for producing biosurfactants (Nwaguma et al. 2019). *Saccharomyces cerevisiae* is another yeast that commonly colonizes mucosa and can cause superficial or invasive visceral infections associated with immunosuppressed individuals (Davicino et al. 2007). However, some studies described the biocontrol capacity of *S. cereviciae* against other phytopathogenic fungi of fruits such as *Botrytis* spp. (Nally et al. 2012). Another study demonstrated that a strain of this fungus could synthesize the bioactive peptide pediocin PA-1 that showed its antibacterial activity against two Gram-negative strains such as *Shigella boydii* and *S. flexneri* (Nguyen et al. 2020). These systems have been regarded as safe because they are suitable for bioindustrial processes applied to food. *Cryptococcus* spp. cause important systemic mycosis globally, and their most common clinical manifestation is cryptococcal meningitis, principally in patients suffering from AIDS (Lima et al. 2016). But this fungal genus

produces useful enzymes like α-amylase, lipase, polygalacturonase, and xylanase which could be used for the treatment of polymer waste or wastewater (Basak and Das 2014; Thirunavukarasu et al. 2016).

Microsporum gypseum causes skin diseases in humans and animals such as the disseminated and recalcitrant tinea corporis eruption, particulary in immunocompromised patients (Singh 2011). In animals, it produces circular and patchy alopecia, scales, follicular papules, erythema, hyperpigmentation, and pruritus. On the other hand, some studies concluded that the application of keratinolytic microbes, such as fungi (including *M. gypseum*), could be useful for the treatment of keratinaceous wastes (Ghaffar et al. 2018). *Trichophyton* spp. are the most common dermatophytic fungi and the causal agents of fungal nail infections (onychomycosis), a very common disorder in industrialized nations, and it represents a risk for diabetics or patients with keratinization problems (Nenoff et al. 2013). These fungi affect the *stratum corneum* of the epidermis and the nail keratin, but they are not common in the hair roots. Like *M. gypseum*, the keratinases produced by *Trichophyton* spp. may actively degrade the chicken feather waste (Anbu et al. 2008). *Epidermophyton floccosum* constitutes the causal agent of many skin diseases and may lead to recurrent outbreaks of dermatophytosis in hospitals or health institutions due to its persistence in the environment (Svetaz et al. 2010). Frequently, it causes tinea cruris, tinea pedis, tinea corporis, and onychomycosis (Lacaz et al. 2002).

Paracoccidioides brasiliensis is the etiological agent of the disease paracoccidioidomycosis (PCM), the most important systemic mycosis in Latin America (do Prado et al. 2018). The isolates of this fungus are highly virulent, since it is capable of adapting to transient iron availability as strategies to survive and overcome stress conditions inside the host (do Amaral et al. 2019). *Aspergillus* spp. are airborne pathogenic fungi which may cause skin and respiratory infections which could be lethal in immunocompromised patients (Davicino et al. 2007). However, these fungi are able to produce lipases with high industrial potential (Contesini et al. 2010). Many pharmaceutical or agrochemical products have been obtained from them as well as aromatic compounds. Their capacity for effluent biodegradation and bioadsorption of the toxic metals Cd and Cr is well known (Ahmad et al. 2005).

Fusarium spp. cause pernicious infections on humans and crops but also offer some industrial applications. They could cause some opportunistic infections in humans, mostly in immunocompromised patients, such as keratitis and onychomycosis (Salah et al. 2015). Moreover, Torres et al. (2009) suggested that fumonisins (a type of toxins produced by this fungal genus) increase the incidence of esophageal cancer. Particularly, *F. verticillioides* cause root and stem rots in cereals that are cultivated in subtropical and temperate regions, and their mycotoxins are harmful to human and animal health causing leucoencephalomalacia in equines, pulmonary edema in porks, and immunosuppression in poultry (Sampietro et al. 2014). *F. oxysporum* cause accelerated wilting in banana (Forsyth et al. 2006) and tomato (Duyvesteijn et al. 2005), since it can penetrate the roots and colonize vascular tissues leading to the disruption of water translocation towards the shoots. On the other hand, lipase enzymes obtained from *F. oxysporum* have shown several

properties with significant industrial applications, such as an additive for detergents formulations (Prazeres et al. 2006). *Rhizopus* spp. are opportunist fungi which may cause different pathogenicity in humans (mucormycosis, an invasive fungal infection with high morbidity and mortality principally in immunocompromised patients) (Teal et al. 2016), animals, and vegetables (soft rot, a disease that produces great economic losses in fleshy fruits) (Pergomet et al. 2018). Species of this fungal genera are considered good bioremediators, as they can bioadsorb high concentrations of heavy metals such as Cd and Cr (Ahmad et al. 2005). Additionally, these fungi offer capacity to produce pectinolytic enzymes which have wide applications in fruit juice and wine industries (Anisa and Girish 2014). *Mucor* spp. principally cause chronic cutaneous and subcutaneous infections, but they can also produce rhinocerebral and sinopulmonary infections (frequently lethal), blood and intestinal infections, as well as septic arthritis (Morin-Sardin et al. 2017). Some *Mucor* species have been used for metabolites production or biotransformations, for biodiesel production and in the food industry as starters of cheese fermentations (Morin-Sardin et al. 2017).

During the last decades, most pathogens have developed resistance towards synthetic fungicides, and consequently, the search for new alternatives applied to the treatment of fungal diseases is urgently required (Di Liberto et al. 2017; Carrizo et al. 2020). Antifungals show different targets over the fungal cells and among them we could mention: cell wall (inhibition of β-glucan or chitin synthesis); cell membrane (binding to ergosterol or inhibition of its synthesis, e.g. phenols disrupt the cytoplasmic membrane and cause the cells leakage); inhibition of cell division (by cutting of microtubule polymerization); inhibition of RNA/DNA (by causing deficient RNA synthesis or inhibition of DNA transcription); and the inhibition of efflux pumps which function by transporting toxic substances out of the cell (inhibiting the efflux pumps, drug resistance may be reduced) (Alanís Garza 2005; Freiesleben and Jäger 2014).

Natural products are the best known reservoir of chemicals. Plants have developed different active principles for defense towards the fungal attack, and their content depends on different factors, mainly climatic conditions (Acosta de la luz 2003; Petenatti et al. 2008). The simple phenolic compounds, such as hydroxybenzoics, monophenols (e.g., cresol), diphenols (e.g., hydroquinones), and triphenols (e.g., gallic acid), are the more common secondary metabolites displaying fungicide properties (Lizcano González 2007; Martinez 2012). Moreover, compounds, such as phytoalexins, steroidal saponins, alkaloids, and some proteins, have also been depicted to have an important function in the defense systems of plants against pathogens (Montez-Belmont et al. 2000; Alanís Garza 2005; Lizcano González 2007). The secondary metabolites offer different actions against pathogens and they could be classified in three main groups according to their biosynthetic pathway (Lizcano González 2007; Freiesleben and Jäger 2014): (1) **phenolic compounds** such as coumarins and phytoalexins which are incorporated into the plant cell wall to increase rigidity and prevent the entry of pathogens; (2) **terpenoids** such as mono-, di-, or tri-terpenes, saponins, steroids, cardiac glycosides, and sterols which may act disrupting the cell membrane and directly eliminating the pathogenic

organism in order to restrain its invasion towards the rest of the plant; (3) **nitrogen-containing compounds** such as alkaloids and lectins which also eliminate the pathogenic organism and restrain its invasion through the attack to the cell membrane and cell wall. Other compounds such as phytoalexins, substances with low molecular weight and whose biosynthesis is induced by pathogens or herbivores have demonstrated a biostatic or biocidal effect at relatively low concentrations (Reichling 2018).

2 Summary of Argentinean Antifungal Plants Evaluated against Human Pathogens

Secondary metabolites are mainly obtained by distillation or extraction of aromatic or non-aromatic plant species, respectively. Plant extracts constitute a group of substances, with diverse chemical characteristics, extracted from different parts of plants such as roots, barks, seeds, buds, leaves, and fruits (Martinez 2012). On the other hand, essential oils are highly volatile substances (lipophilic molecules) synthesized and stored in glandular trichomes, which are capable to disrupt the fungal cell wall or membrane through a permeabilization process and also may inhibit the synthesis of fungal DNA, RNA, proteins, and polysaccharides (Martinez 2012; Karpiński 2020). Many researchers all over the world have investigated the properties and capacity of some plants against fungal pathogens. Table 12.1 summarizes the native or naturalized plants of Argentina which showed antifungal activities against different fungal species throughout the last 20 years (2000 to 2020).

2.1 Zuccagnia punctata*: A Treasure Used in Traditional Medicine: Validation of its Antifungal Properties and Isolation of Bioactive Compounds*

Zuccagnia punctata Cav. (Fabaceae, Caesalpinioideae) is the only representative species of this genus that is endemic of central and western arid and semi-arid regions of Argentina (Fig. 12.1). It is an aromatic shrub of 1–5 m in height which grows on hills and plains between 700–2700 m.a.s.l. It is commonly known as "jarilla macho," "jarilla de la puna," "jarilla pispito," "laca," or "pus-pus" and has a certain resemblance to the true "jarillas," a species of the genus *Larrea* (Zygophyllaceae), with which it coexists (Vattuone et al. 2013). *Z. punctata* has a long history of use in the traditional indigenous medicine of Argentina. Infusions and decoctions in water, as well as extracts prepared by maceration in ethanol of its aerial parts, have been widely used as foot antiseptic, rubefacient, antibacterial, antifungal, anti-inflammatory, antitumor, asthma, arthritis, rheumatism, among others (Ortega et al. 2000; Vattuone et al. 2013). To date, there have been numerous

Table 12.1 Native or naturalized plants of Argentina with antifungal activities against human pathogenic fungi. Part used of each species evaluated and references are also depicted

Species	Parts used (extract types)	Reported antifungal activities	References
Aquifoliaceae			
Ilex paraguariensis A.St.-Hil.	Leaves (aqueous extracts)	*Malassezia furfur* (cause catheter-related systemic infections in humans and animals, dandruff, psoriasis and foliculitis)	(Filip et al. 2010)
Amaranthaceae			
Amaranthus spinosus L.	Aerial parts (hexane and MeOH extracts)	*Fusarium* sp.	(Thembo et al. 2010)
Amaranthus viridis L.	Whole plant (lectines)	*F. oxysporum*	(Kaur et al. 2006)
Anacardiaceae			
Astronium urundeuva Engl.	Aerial parts (saline and hydroethanolic extract)	*C. albicans* and *Fusarium* sp.	(Sa et al. 2009; Bonifácio et al. 2019)
Lithraea molleoides (Vell.) Engl.	Aerial parts (MeOH extracts)	Dermatophytic strains	(Muschietti et al. 2005)
Myracrodruon urundeuva Allemão	Whole plant (EtOH extracts)	*C. albicans*, *C. neoformans* and *C. gattii*	(dos Santos Silva et al. 2020)
Schinopsis balansae Engl.	Leaves (urushiol fraction)	*F. graminearum*	(Aristimuño Ficoseco et al. 2017)
Schinus areira L.	Aerial parts (EtOH extracts)	*M. gypseum*, *T. rubrum*, *T. mentagrophytes* and *E. floccosum*	(Svetaz et al. 2010)
Schinus molle L.	Whole plant (essential oils)	*Fusarium* sp. and *P. brasiliensis*	(Sampietro et al. 2014; Prado et al. 2018)
Apiaceae			
Gymnophyton polycephalum clos	Aerial parts (essential oils)	Treating dermatophyte infections	(Lima et al. 2011)
Araucariaceae			
Araucaria araucana (Molina) K.Koch	Wood (MeOH extracts)	*T. mentagrophytes* and *Fusarium* sp.	(Céspedes et al. 2006)
Aristolochiaceae			
Aristolochia argentina Griseb.	Aerial parts (EtOH extracts)	*F. verticillioides*	(Carpinella et al. 2010)
Asteraceae			
Acanthostyles buniifolius (hook. Ex hook. & Arn.) R.M.King & H.rob.	Aerial parts (MeOH extracts)	*M. gypseum*, *T. mentagrophytes* and *T. rubrum*	(Muschietti et al. 2005)

(continued)

Table 12.1 (continued)

Species	Parts used (extract types)	Reported antifungal activities	References
Baccharis artemisioides hook. & Arn.	Aerial parts (EtOH extracts)	*F. verticillioides*	(Carpinella et al. 2010)
Baccharis boliviensis (Wedd.) Cabrera	Aerial parts (hydroalcoholic preparations)	Treating dermatophyte infections	(Carrizo et al. 2020)
Baccharis darwinii hook. & Arn.	Aerial parts (petroleum ether and MeOH extract)	*C. neoformans, M. gypseum, T. rubrum* and *T. mentagrophytes*	(Kurdelas et al. 2010)
Baccharis grisebachii Hieron.	Aerial parts (hexane and CH_2Cl_2 extracts)	*Microsporum canis*	(Feresín et al. 2001)
Baccharis inamoena Gardner	Aerial parts (essential oils)	*T. rubrum*	(Sobrinho et al. 2016)
Baccharis salicina Torr. & A.Gray	Aerial parts (EtOH extracts)	*F. verticillioides*	(Carpinella et al. 2010)
Baccharis spartioides (hook. & Arn. Ex DC.) J.Rémy	Aerial parts (essential oils)	*C. albicans*	(Demo et al. 2005)
Baccharis trimera (less.) DC.	Aerial parts and seeds (decocción; essential oils)	*Saccharomyces cerevisiae, C. albicans, Trichophyton* sp. and *Microsporum* sp.	(Davicino et al. 2007; Caneschi et al. 2015)
Chromolaena laevigata (lam.) R.M.King & H.rob.	Aerial parts (essential oils)	*T. rubrum*, *T. mentagrophytes* and *C. albicans*	(Murakami et al. 2013; Valarezo et al. 2016)
Flourensia oolepis S.F.Blake	Aerial parts (EtOH extracts)	*F. verticillioides*	(Carpinella et al. 2010)
Gaillardia megapotamica (Spreng.) baker	Aerial parts (EtOH extracts)	*F. verticillioides*	(Carpinella et al. 2010)
Gochnatia glutinosa (D.Don) D.Don ex hook. & Arn.	Aerial parts (MeOH extracts)	Dermatophytes fungi	(Postigo et al. 2012)
Heterothalamus alienus (Spreng.) Kuntze	Aerial parts and roots (EtOH extracts)	*F. verticillioides, T. rubrum* and *T. mentagrophytes*	(Pacciaroni et al. 2008; Carpinella et al. 2010)
Mikania periplocifolia hook. & Arn.	Aerial parts (EtOH extracts)	*M. gypseum*, *T. rubrum*, *T. mentagrophytes* and *E. floccosum*	(Svetaz et al. 2010)
Parastrephia quadrangularis (Meyen) Cabrera	Aerial parts (MeOH extracts)	*F. verticillioides*	(Di Ciaccio et al. 2018)
Parthenium hysterophorus L.	Leaves (MeOH, EtOH and EtOAc extracts)	*C. albicans*	(Malarkodi and Manoharan 2013)

(continued)

Table 12.1 (continued)

Species	Parts used (extract types)	Reported antifungal activities	References
Pluchea dodonaeifolia (hook. & Arn.) H.rob. & Cuatrec.	Aerial parts (two flavanones: Naringenin and pinocembrin)	*C. albicans*	(Soberón et al. 2020)
Porophyllum obscurum (Spreng.) DC.	Aerial parts (hexane extracts)	*Candida* sp. (treatment of oropharyngeal candidiasis)	(Postigo et al. 2017)
Pseudognaphalium gaudichaudianum (DC.) Anderb.	Whole plant (EtOH/MeOH extracts and decoction)	*S. cerevisiae, Sporothrix schenckii* and *Fonsecaea pedrosoi*	(Davicino et al. 2007; Gaitán et al. 2011)
Pterocaulon alopecuroides (lam.) DC.	Aerial parts (crude MeOH/CH_2Cl_2/ hexane extracts)	*S. cerevisiae, C. neoformans, M. gypseum, T. rubrum and T. mentagrophytes* (hight activity)*; C. albicans, C. tropicalis, A. flavus, A. niger* and *A. fumigatus* (moderate activity)	(Stein et al. 2005)
Pterocaulon balansae Chodat	Aerial parts (crude MeOH/CH_2Cl_2/ hexane extracts)	*C. tropicalis, S. cerevisiae, C. neoformans, M. gypseum, T. rubrum and T. mentagrophytes* (hight activity)*; C. albicans, A. flavus, A. niger* and *A. fumigatus* (moderate activity)	(Stein et al. 2005)
Pterocaulon polystachyum DC.	Aerial parts (crude MeOH/CH_2Cl_2/ hexane extracts)	*S. schenckii, M. gypseum, T. rubrum and T. mentagrophytes* (hight activity)*; C. albicans, C. tropicalis, S. cerevisiae, C. neoformans, A. flavus, A. niger* and *A. fumigatus* (moderate activity)	(Stein et al. 2005; Stopiglia et al. 2011)
Senecio grisebachii baker	Flowers (CH_2Cl_2/ EtOH and aqueous extracts)	*M. gypseum* and *T. mentagrophytes*	(Portillo et al. 2001).
Senecio nutans Sch. Bip.	Aerial parts (essential oils)	*Fusarium* sp. (moderate activity)	(Galvez et al. 2020)
Senecio subpanduratus O.Hoffm.	Aerial parts (essential oils)	*C. albicans, C. guillermondii, C. krusei* and *C. glabrata*	(Arancibia et al. 2010)
Senecio viridis Phil.	Aerial parts (essential oils)	*Fusarium* sp. (moderate activity)	(Galvez et al. 2020)
Solidago chilensis Meyen	Leaves (essential oils)	*M. gypseum, T. mentagrophytes* and *C. albicans*	(Alonso and Desmarchelier 2015)
Tagetes minuta L.	Roots (hexane and CH_2Cl_2 extracts)	Treatment of skin mycoses and *Candida* virulence	(Giacone et al. 2020)

(continued)

Table 12.1 (continued)

Species	Parts used (extract types)	Reported antifungal activities	References
Tagetes terniflora Kunth	Aerial parts (essential oils)	*Fusarium* sp. (moderate activity)	(Galvez et al. 2020)
Trichocline reptans (Wedd.) Hieron.	Aerial parts (EtOH extracts)	*F. verticillioides*	(Carpinella et al. 2010)
Vernonanthura nudiflora (less.) H.rob.	Aerial parts (EtOH extracts)	*F. verticillioides*	(Carpinella et al. 2010)
Berberidaceae			
Berberis microphylla G.Forst.	Leaves and stems (aqueous extracts)	*C. albicans* and dermatophyte fungi	(Freile et al. 2006)
Bignoniaceae			
Amphilophium cynanchoides (DC.) L.G.Lohmann	Leaves and stems (EtOAc extracts)	*A. niger*	(Apud et al. 2020)
Dolichandra cynanchoides Cham.	Leaves and stems (CH_2Cl_2 extracts)	*A. niger* and *A. carbonarius*	(Apud et al. 2020)
Tecoma stans (L.) Juss. Ex Kunth	Bark (EtOH extracts)	*F. pedrosoi*	(Gaitán et al. 2011)
Boraginaceae			
Cordia curassavica (Jacq.) Roem. & Schult.	Leaves (essential oil)	*C. albicans* and *C. krusei*	(Rodrigues et al. 2012)
Caryophyllaceae			
Stellaria media (L.) Vill.	Whole plant (EtOH extracts)	For psoriasis treatment	(Ríos et al. 2018)
Combretaceae			
Terminalia australis Cambess.	Aerial parts (EtOH extracts)	*M. gypseum*, *T. rubrum*, *T. mentagrophytes* and *E. floccosum*	(Svetaz et al. 2010)
Terminalia triflora (Griseb.) Lillo	Aerial parts (MeOH/EtOH extracts)	*M. gypseum*, *T. mentagrophytes, T. rubrum, S. schenckii* and *F. pedrosoi*	(Muschietti et al. 2005; Gaitán et al. 2011)
Commelinaceae			
Commelina diffusa Burm.f.	Aerial parts (MeOH extracts)	*Trichophyton* sp.	(Mensah et al. 2006)
Cyperaceae			
Cypertus rotundus L.	Tuber (aqueous and petroleum ether extracts)	*Aspergillu fumigatus* and *Candida tropicallis*	(Biradar et al. 2010)
Euphorbiaceae			
Croton urucurana Baill.	Blood from bark (presence of catechins)	*Trichophyton* genus	(Gurgel et al. 2005)
Sebastiania brasiliensis Spreng.	Aerial parts (MeOH extracts)	*T. rubrum*, *T. mentagrophytes, E. floccosum* and *M. canis*	(Muschietti et al. 2005)

(continued)

Table 12.1 (continued)

Species	Parts used (extract types)	Reported antifungal activities	References
Sebastiania commersoniana (Baill.) L.B.Sm. & downs	Aerial parts (MeOH extracts)	*T. rubrum*, *T. mentagrophytes*, *E. floccosum* and *M. canis*	(Muschietti et al. 2005)
Fabaceae			
Acacia caven (Molina) Molina	Aerial parts (crude extracts)	*F. oxysporum*	(Quiroga et al. 2001)
Albizia inundata (Mart.) Barneby & J.W.Grimes	Aerial parts (MeOH extracts)	*C. krusei*	(Tempone et al. 2008)
Anadenanthera colubrina var. *cebil* (Griseb.) Altschul	Whole plant (EtOH extracts)	*C. albicans*, *C. neoformans* and *C. gattii*	(dos Santos Silva et al. 2020)
Astragalus pehuenches Niederl.	Stem (EtOH extracts)	*S. schenckii* and *F. pedrosoi*	(Gaitán et al. 2011)
Dalea elegans hook. & Arn.	Aerial parts (EtOH extracts)	*F. verticillioides*	(Carpinella et al. 2010)
Geoffroea decorticans (hook. & Arn.) Burkart	Leaves and twigs (EtOH extracts)	*Aspergillus* sp.	(Quiroga et al. 2009)
Peltophorum dubium (Spreng.) Taub.	Aerial parts (MeOH extracts)	*A. flavus*	(Di Ciaccio et al. 2020)
Prosopis ruscifolia Griseb.	Aerial parts (MeOH extracts)	*Aspergillus parasiticus* and *A. flavus.*	(Gomez et al. 2019)
Pterogyne nitens Tul.	Leaves (flavonoids)	*Epidermophyton, Trichophyton, Cryptococcus*, and *Candida* species	(Lima et al. 2016)
Senna spectabilis (DC.) H.S.Irwin & Barneby	Fruits (MeOH extracts)	*F. verticillioides*	(di Ciaccio et al. 2018)
Zuccagnia punctata Cav.	Aerial parts (MeOH/EtOH extracts)	*Candida* sp., *C. neoformans*, *S. cerevisiae*, *Aspergillus* sp., *M. gypseum*, *E. floccosum, S. schenckii* and *Trichophyton* sp.	(Svetaz et al. 2010; Gaitán et al. 2011; Butassi et al. 2015)
Gentianaceae			
Gentianella multicaulis (Gillies ex Griseb.) Fabris	Aerial parts	*M. gypseum, T. mentagrophytes and T. rubrum*	(Lima et al. 2012)
Iridaceae			
Eleutherine bulbosa (mill.) Urb.	Bulbs (EtOH/ BuOH extracts)	*Trichophyton, Trichosporon, Aspergillus and Rhizopus* species	(Mohanta et al. 2014)
Lamiaceae			
Clinopodium gilliesii (Benth.) Kuntze	Aerial parts (essential oils)	Treating dermatophyte infections	(Lima et al. 2011)

(continued)

Table 12.1 (continued)

Species	Parts used (extract types)	Reported antifungal activities	References
Glechon spathulata Benth.	Aerial parts (essential oils)	*T. rubrum* and *E. floccosum*	(Venturi et al. 2015)
Hedeoma multiflora Benth.	Leaves and stems (essential oils)	*A. flavus* and *A. parasiticus*	(Fiuza et al. 2009)
Hyptis mutabilis (rich.) Briq.	Leaves (essential oils)	*Mucor* spp.	(Oliva et al. 2006)
Lepechinia floribunda (Benth.) Epling	Aerial parts (EtOH extracts)	*F. verticillioides*	(Carpinella et al. 2010)
Ocimum campechianum mill.	Leaves (essential oil)	*C. albicans* and *S. cerevisiae*	(Sacchetti et al. 2004)
Salvia cuspidata Ruiz & Pav.	Aerial parts (EtOH extracts)	*F. verticillioides*	(Carpinella et al. 2010)
Lycopodiaceae			
Lycopodiella cernua (L.) pic. Serm.	Leaves (triterpenes)	*C. albicans*	(Zhang et al. 2002)
Malvaceae			
Sida cordifolia L.	Aerial parts (acetone extracts)	*Candida* sp. and *Trichosporon inkin*	(Ahmed et al. 2018)
Myrtaceae			
Eugenia uniflora L.	Leaves (essential oil)	*P. brasiliensis*	(Costa et al. 2010)
Moraceae			
Maclura tinctoria (L.) D.Don ex Steud.	Leaves (EtOH extracts)	*C. albicans* and *C. neoformans*	(ElSohly et al. 2001)
Oxalidaceae			
Oxalis erythrorrhiza Gillies ex hook. & Arn.	Aerial parts (hexane and CH_2Cl_2 extracts)	*M. canis*	(Feresín et al. 2001)
Passifloraceae			
Passiflora caerulea L.	Leaves (MeOH extracts and nanoparticles)	*A. flavus* and dermatophytes fungi (principally *T. rubrum*)	(AL-Rubaey et al. 2019; Santhoshkumar et al. 2019)
Phytolaccaceae			
Phytolacca bogotensis Kunth	Leaves (CH_2Cl_2 extracts)	*S. schenckii*	(Gaitán et al. 2011)
Phytolacca dioica L.	Berries (hydrolysis of extracts)	*C. albicans* and *C. neoformans*	(Liberto et al. 2010)
Seguieria americana L.	Leaves (CH_2Cl_2 extracts)	*F. pedrosoi* and *S. schenckii*	(Gaitán et al. 2011)
Trichostigma octandrum (L.) H. Walter	Leaves (CH_2Cl_2 extracts)	*F. pedrosoi*	(Gaitán et al. 2011)

(continued)

Table 12.1 (continued)

Species	Parts used (extract types)	Reported antifungal activities	References
Piperaceae			
Piper sp.	Aerial parts (EtOH extracts)	*Candida* sp., *C. neoformans*, *S. cerevisiae*, *Aspergillus* sp., *M. gypseum*, *E. floccosum* and *Trichophyton* sp.	(Svetaz et al. 2010)
Poaceae			
Elionurus muticus (Spreng.) Kuntze	Aerial parts (essential oil)	*Candida* sp.	(Sabinil et al. 2006)
Polygonaceae			
Persicaria acuminata (Kunth) M.Gómez	Aerial parts (CH_2Cl_2 extracts)	Yeasts and dermatophytes fungi	(Derita et al. 2009)
Persicaria ferruginea (Wedd.) Soják	Aerial parts (MeOH and hexane extracts)	*E. floccosum* and *Neurospora crassa*	(López et al. 2011)
Persicaria hydropiperoides (Michx.) small	Whole plant (MeOH extracts)	*C. albicans*	(Braga et al. 2007)
Persicaria maculosa gray	Aerial parts (CH_2Cl_2 extracts)	*T. mentagrophytes, T. rubrum* and *M. gypseum*	(Derita and Zacchino 2011a)
Persicaria punctata (Elliott) small	Aerial parts (polygodial compound)	*C. albicans* and dermatophytes fungi	(Alves et al. 2001).
Pteridaceae			
Pityrogramma calomelanos (L.) link	Leaves (MeOH extracts)	*Curvularia lunata*	(Guerra et al. 2020)
Solanaceae			
Solanum sisymbriifolium lam.	Leaves and stems (MeOH extracts)	*C. albicans, A. niger, A. flavus, A. xylinium*	(Vaghela et al. 2009)
Ranunculaceae			
Clematis campestris A.St.-Hil.	Aerial parts (EtOH extracts)	*M. gypseum*, *T. rubrum*, *T. mentagrophytes* and *E. floccosum*	(Svetaz et al. 2010)
Rutaceae			
Zanthoxylum coco Gillies ex Hook. f. & Arn.	Aerial parts (flavonoids and lignans)	*F. verticillioides*	(Carpinella et al. 2010)
Zanthoxylum rhoifolium lam.	Leaves (volatile oil)	*A. flavus*	(da Silva et al. 2006)
Smilaceae			
Smilax campestris Griseb.	Aerial parts (EtOH extracts)	*C. krusei* and *C. gattii*	(Morais et al. 2014)

(continued)

Table 12.1 (continued)

Species	Parts used (extract types)	Reported antifungal activities	References
Solanaceae			
Cestrum parqui (lam.) L'Hér.	Leaves and flowers (EtOH/MeOH extracts and saponins)	*Fusarium solani*, *A. niger*, *M. gypseum*, *T. rubrum*, *T. mentagrophytes, E. floccosum, F. pedrosoi* and *S. schenckii*	(Svetaz et al. 2010; Gaitán et al. 2011; Ahmed et al. 2012)
Verbenaceae			
Acantholippia seriphioides (A.Gray) Moldenke	Aerial parts (essential oils)	Dermatophytes fungi	(Lima et al. 2011)
Aloysia citriodora Palau	Aerial parts (essential oils)	*C. albicans*	(Demo et al. 2005)
Aloysia gratissima (Gillies & Hook.) Tronc.	Aerial parts (essential oils)	*Fusarium* sp. (moderate activity)	(Galvez et al. 2020)
Lippia integrifolia (Griseb.) Hieron.	Aerial parts (MeOH extracts)	*M. canis* and *E. floccosum*	(Muschietti et al. 2005)
Lippia junelliana (Moldenke) Tronc.	Flowers, leaves and stems (essential oils)	*C. albicans, C. parapsilosis* and *C. krusei*	(Córdoba et al. 2019)
Winteraceae			
Drimys winteri J.R.Forst. & G.Forst.	Aerial parts (EtOH extracts)	*Candida* sp., *C. neoformans*, *S. cerevisiae*, *aspergillus* sp., *M. gypseum*, *E. floccosum* and *Trichophyton* sp.	(Svetaz et al. 2010; Butassi et al. 2015)
Zygophyllaceae			
Larrea cuneifolia Cav.	Leaves (aqueous extracts)	*C. albicans*	(Espino et al. 2019)
Larrea divaricata Cav.	Aerial parts (EtOH extracts)	*S. cerevisiae* and *C. albicans*	(Davicino et al. 2007).
Larrea nítida Cav.	Whole plant (CH_2Cl_2 extracts)	*C. albicans*	(Butassi et al. 2015)

pharmacological studies that have shown important activities that support the traditional uses of this plant (Isla et al. 2016).

Regarding its chemical composition, 13 phenolic compounds were isolated from extracts of the aerial parts of *Z. punctata*: two chalcones, 2′,4′-dihydroxy-3′-methoxychalcone (DHMC) and 2′,4′-dihydroxychalcone (DHC); five flavones, 3,5,7-trihydroxyflavone (galangin), 3,5-dihydroxy-7-methoxy flavone (izalpinin), 3,5,4′-trihydroxy-7-methoxy flavone (rhamnocitrin), 3-hydroxy-7,8-dimethoxy flavone (3-H-7,8-DMF); and 3,7-dihydroxy flavone (3,7-DHF); four flavanones, 7-hydroxy flavanone (7-HF), 5,7-dihydroxy flavanone (pinocembrin), 5-hydroxy-7-methoxy flavanone (pinostrobin), and 7-hydroxy-8-methoxyflavanone (7-H-8-MF); and two caffeic acid derivatives, 1-methyl-3-(4′-hydroxyphenyl)-propyl caffeate [1-M-3-(4'-HP)-PC] and 1-methyl-3-(3′,4′-dihydroxyphenyl)-propyl caffeate [1-M-3-(3′,4'-DHP)-PC]. Chalcones being the main components of such extracts (Ortega et al. 2000; Nuño 2015). In the essential oil of the aerial parts of *Z.*

Fig. 12.1 *Zuccagnia punctata* Cav. (Fabaceae, Caesalpinioideae). (**a**) specimens in their natural environment. (**b**) Aerial parts

punctata, 80 constituents were identified, mainly oxygenated monoterpenes. The main components were identified as linalool and (−)-5,6-dehydrocamphor (Álvarez et al. 2012).

Below we describe the results obtained from our recent studies on the antifungal activity of extracts, essential oil, and compounds obtained from *Z. punctata* against phytopathogenic and human pathogenic fungi.

The activity of the crude ethanolic extract of aerial parts of *Z. punctata* was evaluated by the agar dilution method (Zacchino et al. 1999), against strains of fungi isolated from soybean plants growing in the most important producing regions of Argentina that presented typical symptoms of disease (*Phomopsis longicolla, Alternaria alternata, Sclerotium bataticola, Fusarium equiseti, F. graminearum,* and *Colletotrichum truncatum*) (Svetaz et al. 2004). The ethanolic extract showed activity against all of the fungi tested with Minimal Inhibitory Concentration (MIC) values between 100 and 500 μg/mL. This extract was successively partitioned between *n*-hexane, chloroform, and *n*-butanol; the chloroform extract showed the lowest MIC value (62.5 μg/mL) against the most relevant pathogenic fungus on soybean seed (*P. longicolla*). Repeated bioassay-guided chromatographies of the chloroform extract led to the isolation of DHMC, DHC, 7-HF, 1-M-3-(4'-HP)-PC, and 1-M-3-(3′,4'-DHP)-PC. The chalcones DHMC and DHC showed potent antifungal activities against all fungi tested with MIC values ranging from 6.25 and 3.12 to 50 μg/mL, respectively. 7-HF and 1-M-3-(4'-HP)-PC showed very interesting activities only against *P. longicolla* (MIC = 6.25 μg/mL), while 1-M-3-(3′,4'-DHP)-PC did not show any activity up to 50 μg/mL. It is interesting to note that four of the five compounds isolated from the antifungal chloroform extract of *Z. punctata* displayed very good activities (MIC ≤6.25 μg/mL) against *P. longicolla.* Additionally, DHMC and DHC showed strong activities against *C. truncatum* (MIC = 6.25 μg/mL) (Svetaz et al. 2004). Both pathogens are the cause of the most serious soybean diseases due to their high incidence and persistence, causing reduction of seed quality and yields. *P. longicolla* is a primary agent of seed decay, a severe pathogen that affects soybean seed quality and *C. truncatum* is the causal agent of soybean anthracnose, a disease acquired mainly in the last growing step that affects stems and pods diminishing the number of seeds and their weight (Pioli et al. 2000).

Concerning to human pathogenic fungi, petroleum ether and dichloromethane extracts of fruits, aerial parts, and resinous exudate (obtained by dipping the fresh aerial parts in dichloromethane) of *Z. punctata* showed moderate antifungal activities against the yeasts *C. albicans*, *S. cerevisiae,* and *C. neoformans* (MICs: 62.5–250 μg/mL) and very strong antifungal activities against the dermatophytes *M. gypseum*, *T. rubrum,* and *T. interdigitale* (MICs: 8–16 μg/mL) thus supporting the ethnopharmacological use of this plant. Antifungal activity-directed fractionation of the most active extract led to the isolation of DHMC and DHC as the compounds responsible for the antifungal activity. DHCM displayed a selective and strong activity against dermatophytes (MIC = 8 μg/mL) and DHC showed a broader spectrum of activity inhibiting the yeasts *C. albicans*, *S. cerevisiae,* and *C. neoformans* (MICs: 16–31.2 μg/mL) and dermatophytes (MIC = 4 μg/mL). Second-order studies showed that DHC, in addition to being the most active chalcone, is fungicidal rather than fungistatic and that it would act through a different mechanism of action from that of antifungal drugs in current clinical use, so it appears to be a very promising antifungal agent (Svetaz et al. 2007).

The essential oil obtained by hydrodistillation from aerial parts of *Z. punctata* was evaluated against a panel of human opportunistic and pathogenic fungi using standardized procedures (CLSI 2017). The microbroth dilution method showed that the essential oil was not active against *C. albicans*, *C. tropicalis*, *S. cerevisiae,* or *C. neoformans* (MIC >1000 μg/mL) and possessed marginal activity against *Aspergillus niger*, *A. flavus,* and *A. fumigatus* (MIC = 1000 μg/mL). In contrast, it showed an interesting antifungal activity against dermatophytes (*M. gypseum*, *T. rubrum,* and *T. interdigitale*) with MIC values between 15.6 and 125 μg/mL, being *T. rubrum* the most susceptible species. A total of 80 constituents were identified in the oil, with linalool and (−)-5,6-dehydrocamphor being the main constituents. Both compounds were also tested against the same fungal strains. Linalool showed moderate activity against dermatophytes (MICs: 125–250 μg/mL) but was inactive against yeasts and *Aspergillus* spp. The other major component was inactive up to 250 μg/mL against all the fungi tested. The main components of the essential oil would not be responsible for its antifungal activity, but the identification of thymol and carvacrol as minor components suggests that they could contribute to this activity. The results of their antifungal evaluation undoubtedly suggest that both compounds could contribute to the activity of the essential oil since they were active against all of the evaluated fungal species (MICs: 15.6–250 μg/mL). Both compounds displayed interesting activities against dermatophytes (MICs: 15.6–31.2 μg/mL), while carvacrol also showed very good activity against *A. flavus* and *A. fumigatus* (MIC = 31.2 μg/mL) (Álvarez et al. 2012).

Fig. 12.2 *Phytolacca tetramera* Hauman (Phytolaccaceae)

2.2 Phytolacca tetramera*: Berries Extracts and Compounds with Potential Antifungal Activity*

Phytolacca tetramera Hauman (Phytolaccaceae), commonly known as "ombusillo," is an endemic species from Argentina (Fig. 12.2). It is currently considered one of the threatened plant species, being in critical danger of extinction (Delucchi et al. 2006), mainly due to anthopic causes that lead to the reduction of their habitat, such as human settlements, construction of roads, the periodic weeding of these roads, agricultural and livestock activity, industrial facilities, etc. (Hernandez et al. 2008).

Our research group has studied this plant species for several years, and the information about the chemical composition, antifungal activity, and mechanism of action allowed us to know the importance of this plant for the treatment of fungal infections, promoting thus its conservation. From our studies, an area related to research and development for the conservation *in situ* of *P. tetramera* was created (Petri et al. 2010).

After Escalante et al. (2002) studies, the antifungal activity of methanolic, dichloromethanic, butanolic, and aqueous extracts of *P. tetramera* obtained not only from berries but also from leaves and roots (*Pt*MEb, *Pt*DEb, *Pt*BEb, *Pt*AqEb, *Pt*MEl, *Pt*DEl, *Pt*BEl, *Pt*AqEl, *Pt*MEr, *Pt*DEr, *Pt*BEr, and *Pt*AqEr) was assessed with the standardized CLSI (2017) microbroth dilution method against the yeasts *C. albicans* and *C. glabrata* (Butassi et al. 2019). The use of the most recent guidelines of CLSI (2017) for yeasts assured more reproducible and more reliable results. Table 12.2 shows the results corresponding to the re-evaluation of the antifungal activity of *P. tetramera* extracts.

Results showed that *Pt*MEb, *Pt*DEb, and *Pt*BEb were moderately active against *C. albicans* and *C. glabrata*, with *Pt*DEb being the most active against the tested strains (MIC = 250 μg/ml), followed by *Pt*MEb (MICs between 500 and 1000 μg/

Table 12.2 MICs (μg/ml) of the different extracts of *P. tetramera* against *C. albicans* (*Ca*) CCC 125–2000 and *C. glabrata* (*Cg*) CCC 115–2000 determined by the microbroth dilution method recommended by CLSI (2017). ITZ = itraconazole (used as standard drug)

	*Pt*MEb	*Pt*DEb	*Pt*BEb	*Pt*AqEb	*Pt*MEl	*Pt*DEl	*Pt*BEl	*Pt*AqEl	*Pt*MEr	*Pt*DEr	*Pt*BEr	*Pt*AqEr	ITZ
Ca	1000	250	1000	i	i	i	i	i	i	i	i	i	0.50
Cg	500	250	1000	i	i	i	i	i	i	i	i	i	2.00

i: inactive (MIC>1000 μg/ml). *C. albicans* and *C. glabrata* were clinically isolates obtained from CEREMIC, Centro de Referencia en Micología, FCByF, UNR

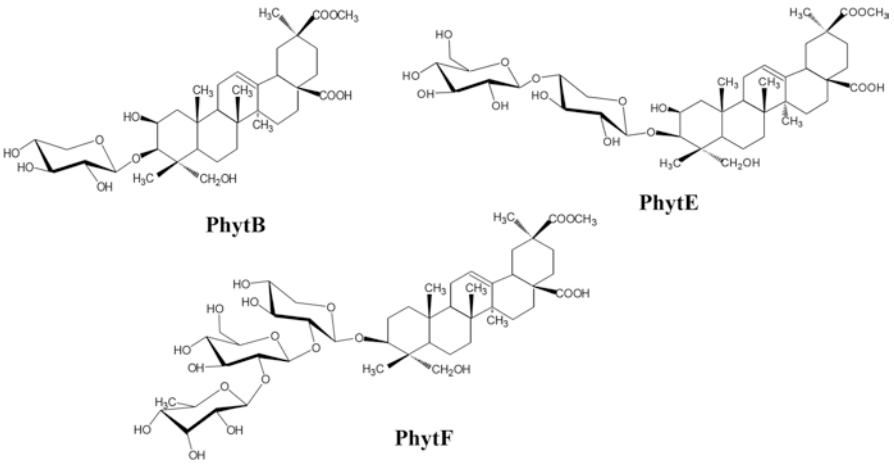


Fig. 12.3 Phytolaccoside B, phytolaccoside E and phytolaccoside F isolated from berries of *P. tetramera* butanolic extract

ml) and *Pt*BEb (MIC = 1000 μg/ml). The rest of the extracts was inactive (MIC >1000 μg/ml) (Table 12.2).

By bioassay-guided fractionation (Escalante et al. 2002), three monodesmosidic triterpenoid saponins were isolated from *Pt*BEb: phytolaccoside B (3-O-β-D-xylopiranosylphytolaccagenin) (PhytB), phytolaccoside E (3-O-β-D-glucopyranosyl-(1,4)-β-D-xylopiranosyl-phytolaccagenin) (PhytE), and phytolaccoside F [3-O-α-L-rhamnopyranosyl-(1,2)-β-D-glucopyranosyl-(1,2)-β-D-xylopyranosyl-phytolaccagenic acid] (PhytF) (Fig. 12.3). The three saponins belong to the olean-type triterpenoid saponins, possessing 28,30 dicarboxylic groups and an olefinic double bond on C-12. PhytB and PhytE, but not PhytF, showed antifungal activities against a panel of human pathogenic opportunistic fungi. PhytB was the most active compound and showed the broadest spectrum of action (MICs between 25 and 125 μg/ml) (Escalante et al. 2002).

The chemical composition of *P. tetramera* extracts obtained from berries, leaves, and roots was studied using Thin Layer Chromatography (TLC). These studies allowed the detection of PhytB, PhytE, and phytolaccagenin (PhytG) in all the extracts except in aqueous ones (Butassi et al. 2019) (Fig. 12.4).

According to this chemical analysis, the antifungal activity of PhytB, PhytE, and PhytG was evaluated against *C. albicans* and *C. glabrata*. PhytB and PhytG were active against both pathogens with MIC = 62.5 μg/ml. In contrast, PhytE did not show activity (MIC >250 μg/ml) (Butassi et al. 2019). Based on these results, PhytB and PhytG were selected as active markers (EMA 2010) and were quantified in all the extracts using UHPLC-ESI-MS (Table 12.3) (Butassi et al. 2019). The most potent extract of *P. tetramera* (*Pt*DEb) showed the highest amount of active markers, followed by *Pt*MEb and *Pt*BEb. The extracts from leaves and roots contained a low level of both PhytB and PhytG. Therefore, it could be stated that these two compounds contribute strongly to the antifungal activity of the active extracts.

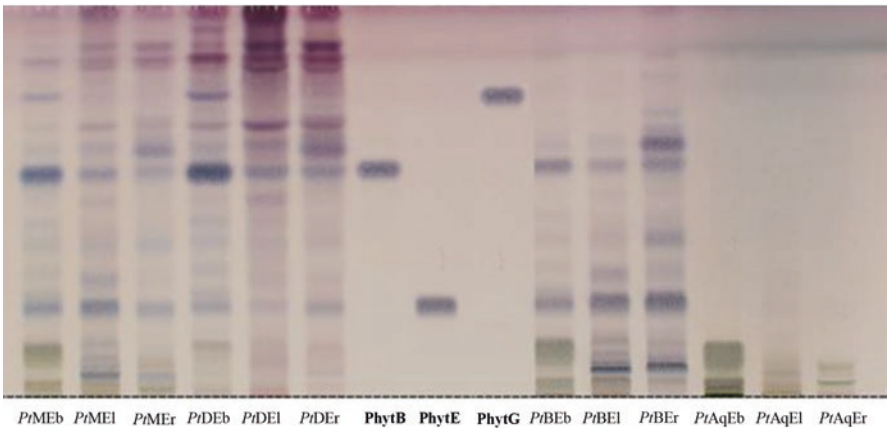


Fig. 12.4 Chemical profile of different extract types obtained from *P. tetramera* berries, using PhytB, PhytE, and PhytG as markers

Table 12.3 Content (mg of compound/g plant material) of active markers PhytB and PhytG in *P. tetramera* extracts analyzed by UHPLC-ESI-MS. Values are the mean ± standard deviation ($n = 3$). Nd: not detected

	Extracts	PhytB (mg/g)	PhytG (mg/g)
Berries	*Pt*MEb	66.12 ± 0.33	24.92 ± 0.09
	*Pt*DEb	155.24 ± 5.27	121.48 ± 1.36
	*Pt*BEb	36.27 ± 0.30	0.68 ± 0.03
Leaves	*Pt*MEl	2.11 ± 0.28	0.01 ± 0.005
	*Pt*DEl	0.61 ± 0.11	0.06 ± 0.0002
	*Pt*BEl	3.13 ± 0.66	Nd
Roots	*Pt*MEr	0.09 ± 0.01	0.004 ± 0.0003
	*Pt*DEr	0.56 ± 0.10	0.017 ± 0.005
	*Pt*BEr	0.55 ± 0.21	Nd

Additionally, the mechanism of action of the active markers PhytB and Phyt G and the most active extract *Pt*DEb was studied. For that, morphological studies (using scanning electron, phase contrast, and fluorescence microscopies) which target the fungal cell wall [cellular sorbitol assay and enzymatic (1,3)-β-D-glucan synthase (GS) and chitin synthase 1 (ChS) assays] and studies which target the fungal cell membrane (ergosterol-binding assay) were carried out. Table 12.4 summarizes the results obtained.

Table 12.4 Mechanism of action studies of the active markers PhytB and PhytG and the most active extract *Pt*DEb

	Mechanism of antifungal action	References
PhytB	Produces shortening of *Neurospora crassa* hyphae and highly branched bulbous hyphal tips	(Escalante et al. 2008)
	Modifies the normal morphology of the yeast *S. cerevisiae* producing aggregates and swollen cells	(Escalante et al. 2008)
	Produces an increase of chitin synthase 1 activity. A high deposit of chitin would lead ultimately to the arrest of cell growth	(Escalante et al. 2008)
PhytG	Binds to ergosterol and disrupts the fungal plasma membrane causing cell wall damage and cell death	(Butassi et al. 2019)
*Pt*DEb	Modifies the normal morphology of the yeast *Schizosaccharomyces pombe* producing smaller, wrinkled, brighter, deformed, and swollen cells. The wrinkled and brighter appearance of *S. pombe* cells indicates a phenotype of dead cells, which was more abundant during the process of cell separation	(Butassi et al. 2019)
	Modifies the normal morphology of the yeast *C. albicans* producing swollen or elongated and refringent cells, which suggest sick or dead cells due to an altered plasma membrane. Produces an enrichment of chained cells, indicating a defect in the final process of cell separation	(Butassi et al. 2019)
	Binds to ergosterol and disrupts the fungal plasma membrane causing cell wall damage and cell death	(Butassi et al. 2019)

2.3 *The Genus* Polygonum*: An Update for its Antifungal Effects and Influence of Chemotaxonomy*

Polygonum constitutes one of the plant genera most used by Argentinian traditional medicine to treat fungal conditions. This genus comprises about 250 species that have a wide geographical distribution, from Polar Regions to the tropics of all continents. Formerly, it was divided into five sections: *Echinocaulon*, *Amblygonum*, *Persicaria*, *Tiniaria* and *Polygonum* but nowadays, due to its botanical and phytochemical complexity, species are classified into two true genera: *Polygonum* and *Persicaria*. According to the plant list (www.plantlist.org) most of them have been regrouped with accepted names, but their synonyms are still used (Álvarez et al. 2020). In Argentina, about 20 species belonging to both genera grow throughout the country, but the most active in terms of their antifungal properties is *Persicaria acuminata* syn. *Polygonum acuminatum* and *Persicaria maculosa* syn. *Polygonum persicaria* (Fig. 12.5) (Derita and Zacchino 2011a).

From the bio-guided fractionation of *P. acuminata* aerial parts, five sesquiterpenes with drimane skeleton were isolated: drimenol, isopolygodial, confertifoline, polygodial, and 1-*β*- (p-methoxycinnamoyl) polygodial. Among them, the most active was polygodial, inhibiting the growth of *C. albicans*, *C. neoformans,* and the dermatophytes *M. gypseum*, *T. rubrum,* and *T. mentagrophytes* with MICs between 3.9 and 62.5 μg/mL and MFCs between 7.8 and 125 μg/mL, being fungicide as well as a strong inhibitor of fungal growth (Derita et al. 2013).

Fig. 12.5 *Persicaria acuminata* (**a**) and *P. maculosa* (**b**)

The bioguided fractionation of *P. maculosa*, in addition to the sesquiterpenes mentioned above, allowed the isolation of the flavanone pinostrobin and the chalcones flavokawin B and cardamonin. The latter compounds were active against *C. albicans*, *C. neoformans,* and the dermatophytes *M. gypseum*, *T. rubrum,* and *T. mentagrophytes* displaying MICs between 15.6 and 500 μg/mL. Unlike *P. acuminata*, the antifungal activity of *P. maculosa* was due not only to polygodial and isopolygodial but also to flavonoids, which added an interesting chemotaxonomical data (Derita and Zacchino 2011b).

Flavonoids have played an important role in the systematics of *Polygonum* species being proposed as chemotaxonomic markers of the genus. However, as stated before, the finding of polygodial within the *Persicaria* section promoted a sesquiterpene (not a flavonoid) to be proposed as a chemotaxonomic marker for the *Persicaria* section. Consequently, with the aim of finding compounds that could be suggested as new chemical markers for the delimitation of *Persicaria* section of the genus, a comparative study about the presence and quantification of sesquiterpenes and flavonoids in six species belonging to the section was carried out. It was found that *P. hydropiperoides*, *P. lapathifolia,* and *P. ferruginea*, which were the three species that did not contain polygodial, showed the presence of the three flavonoids. In turn, *P. punctata* and *P. acuminata* contained the four sesquiterpenes but no flavonoids. Surprisingly, *P. persicaria* was the only species belonging to this section that presented both types of compounds (Derita and Zacchino 2011b). All these findings contributed to the regrouping of these species into the current *Polygonum* and *Persicaria* genera (Álvarez et al. 2021).

3 Photoactivity: An Underexplored Property for Detection of Antifungal Plants

Antimicrobial photodynamic therapy (APDT) is increasingly being recognized as an alternative clinical treatment for fungal infections. Their advantages include a broad spectrum of activities (viruses, protozoa, Gram-positive and Gram-negative bacteria and fungi), the possibility of eliminating microorganisms independently of their antimicrobial resistance pattern, low probability of adverse side effects and low cost (Donnelly et al. 2008). In addition, APDT is highly selective (Dai et al. 2012), resistance has not been described (Wainwright et al. 2017), it has been implicated in changes in the expression of virulence determinants factors and showed efficacy against biofilms (Kato et al. 2013). PDT involves the administration of a non-toxic photosensitizer (PSs) and harmless visible light of the correct wavelength to generate reactive oxygen species (ROS), which can oxidatively damage surrounding biomolecules, such as lipids, proteins, and nucleic acids, thus killing pathogenic microorganisms (Liang et al. 2016; Pinto et al. 2018). ROS are produced by the reaction of the excited PSs and oxygen (O_2) through type I reactions, that involve electron-transfer reactions that generate hydroxyl radical ($OH^{\bullet}$), hydrogen peroxide (H_2O_2), and superoxide radical ($O_2^{\bullet -}$) and type II reactions that involve energy transference to produce singlet oxygen $^1O_2$ (Maisch et al. 2007).

PSs are present in certain plants as a chemical defense mechanism developed to protect themselves from the action of microbes and herbivorous attack. This action is triggered when these secondary metabolites are excited to higher energy levels by absorbing solar or artificial radiation at a particular wavelength range (Mamone et al. 2014). Siewert and Stuppner (2019) described 10 classes of natural PSs: thiophenes, furanocoumarins, polyacetylenes, curcumins, xanthenoids, alkaloids, anthraquinones and perylenequinones, phenalenones, and porphyrins. Thiophenes is one of the larger groups with more than 150 natural biologically active compounds with absorbance maximum for photobiological effects between 314–350 nm (Postigo et al. 2017; Siewert and Stuppner 2019), present in plants of the family Asteraceae including the genus *Porophyllum*, *Tagetes,* and *Flaveria* widely distributed in Argentina (Downum and Towers 1983; Ibrahim et al. 2016). *Porophyllum* comprises 25 species, six of them inhabit the Argentinean central-western region, they are annual or perennial plants with secretory cavities in oil-bearing leaves and bracts which emanate a strong foul odor (Johnson 1964; Loockerman et al. 2003). *Tagetes* includes approximately 56 species that have been used as a source of essential oil for flavoring in the food industries, and their flowers, which are rich in orange–yellow carotenoids, are used as food coloring (Vasudevan et al. 1997). *Flaveria* comprises 21 species widely distributed in America, only *F. bidentis* and *F. haumanii* occur in Argentina (de los A. Páez et al. 2019).

Below we describe the photodynamic antifungal activity of different extracts obtained from six species belonging to the genus *Porophyllum*, *Tagetes,* and *Flaveria* which were evaluated against *C. albicans.* The experiments were carried on following the guidelines of CLSI (2017) document that assures confident and reproducible

Table 12.5 Minimal Fungicide Concentrations (MFC expressed in μg/mL) against *C. albicans* (light/darkness)

Species *Voucher specimen*	Parts used	Extract type			
		Hex	DCM	EA	Met
Flaveria bidentis (L.) Kuntze (Del Vitto & Petenatti #9491, UNSL)	Whole plant	**0.24 / NA**	**0.98 / NA**	NA / NA	NA / NA
Porophyllum lanceolatum DC. (Del Vitto & Petenatti #9478, UNSL)	Whole plant	**500 / NA**	**125 / NA**	NA / NA	NA / NA
Porophyllum obscurum (Spreng.) DC (Del Vitto & Petenatti # 9436, UNSL)	Whole plant	**0.98 / NA**	**7.81 / NA**	NA / NA	NA / NA
Porophyllum ruderale (Jacq.) Cass (Del Vitto & Petenatti #9539, UNSL)	Whole plant	**62.50 / NA**	**31.25 / NA**	NA / NA	NA / NA
Tagetes minuta L. (Del Vitto and Petenatti #9230, UNSL)	Stems	**3.91 / NA**	**31.25 / NA**	NA / NA	NA / NA
	Leaves	**7.81 / NA**	**7.81 / NA**	NA / NA	NA / NA
	Flowers	**31.25 / NA**	**31.25 / NA**	NA / NA	NA / NA
	Roots	**1.95 / NA**	**0.49 / NA**	**62.5 / NA**	NA / NA
Tagetes patula L. (Del Vitto & Petenatti #9239, UNSL)	Aerial parts	**250 / NA**	**500 / NA**	NA / NA	NA / NA
	Roots	**1.95 / NA**	**15.63 / NA**	NA / NA	NA / NA

Hex: Hexane; DCM: dichloromethane; EA: ethyl acetate; Met: methanol. NA: not active (MFC >1000 μg/mL). In bold, photoactive extracts

results. Microplates were submitted to irradiation (light) or kept in darkness. In light experiments, UVA irradiations were performed with a homemade UVA light array composed of a set of three lamps (Alic, Buenos Aires, Argentina), emitting at 315–400 nm (100 W). Microplates were aligned perpendicular to the samples that illuminate uniformly the entire area of the microplate, placed at a distance to 12 cm from the light source and irradiated for 60 min. In darkness experiments, assays were carried out in the same conditions but microplates were wrapped with aluminum foil to avoid exposure to light. Table 12.5 shows the Minimal Fungicide Concentrations (MFC expressed in μg/mL) against *C. albicans* under light/darkness conditions.

No significant differences were observed in the number of yeasts Colony Forming Units (CFU/mL) in the growth controls between darkness and light experiments, suggesting that the action of UVA irradiation did not reduce *C. albicans* viability. None of the evaluated extracts, at a concentration up to 1000 μg/mL, showed antifungal activity in experiments performed without irradiation. All hexane and DCM

extracts were considered photoactive, because they showed antifungal activity against *C. albicans* only under UVA irradiation. Most ethyl acetate and methanolic extracts did not exhibit antifungal photosensitive activity at concentrations up to 1000 μg/mL. The observed higher activity of the apolar extracts, compared with the more polar extracts, could be attributed to the presence of apolar thiophenic compounds previously reported for the studies on related species (Gil et al. 2002; Postigo et al. 2017; Ibrahim et al. 2018; Giacone et al. 2020). The main photoactive components of these extracts were identified as 2,2′:5′,2″-terthienyl (α-T); 5-(3-buten-1-ynyl)-2,2′-bithiophene (BBT); 5-(4-acetoxy-1-butynyl)-2,2′-bithiophene (BBTOAc); 5-(4-hydroxy-1-butynyl)-2,2′-bithiophene (BBTOH); and 5-(3-penten-1-ynyl)-2,2′-bithiophene (PBT). When different parts of the plant were studied, the highest activity was obtained in root extracts, that is, the organ where thiophenes accumulate (Marotti et al. 2010).

4 Probing Synergistic Effects to Increase Antifungal Activity in Plants

Combination therapy has emerged as an effective strategy for antifungal treatment to fight against microbial resistance (Hemaiswarya et al. 2008). In fact, the high incidence rates of *Candida* infections are supposed to be closely related with their recalcitrant resistance to conventional antifungals and their capacity for biofilm formation (Zavrel and White 2015). Synergism, defined as a phenomenon in which the combined action of two agents is more effective than the action of a single agent, has been the main focus for combinatory therapy as it greatly reduces the effective dosages of them required to treat an infection (Yang et al. 2017). Combinations of drugs with different targets prevents the development of drug resistance, may improve the interaction with its target and can reduce toxicity, since lower concentrations of both agents can be used (Ayaz et al. 2019). Research of new antimicrobials boost the use of bioactive compounds and extracts from plants, either alone, combined, or together with antibiotics (Ríos and Recio 2005) that can potentiate the activity of antimicrobials by targeting different sites in the microbial cell (multitarget effect), by improving their solubility or bioavailability (pharmacokinetic or physicochemical effects) or by targeting the resistance mechanism (Wagner and Ulrich-Merzenich 2009).

In recent years, there has been an increased interest in using herbs along with conventional drugs rather than using them in place of drugs that raises concerns about studying herb–drug interactions (Spitzer et al. 2017). Here we detail the results of our research on the antifungal activity of plant extracts of the Argentine flora alone and in combination with currently used antifungal drugs (Cordisco et al. 2019). The antifungal activity of 253 plant extracts used in traditional Argentine medicine (obtained from 153 species of plants, belonging to 120 genera and 56 families) was evaluated alone and in combination with the antifungal drugs amphotericin B (AMB), fluconazole (FCZ), and itraconazole (ITZ), against *C. albicans*.

MICs alone and in combination were determined with the broth microdilution technique following the guidelines of CLSI (2017) and using a modification of the High-Throughput Synergy Screening (HTSS) test, respectively (Zhang et al. 2007). Only 27 extracts tested alone showed activity (MICs between 31.25–1000 μg/mL), which represents 10.67% of the total evaluated. For this reason, we decided to re-explore all extracts through combination trials with antifungal drugs, hoping to detect those with enhanced activity and thus take full advantage of nature's chemodiversity and find new structures with antifungal activity.

First, we analyzed the importance of ethnopharmacological uses in the selection of extracts by investigating whether the probability of detecting plant extracts which enhance the activity of antifungal compounds is higher when obtained from species with reports of ethnopharmacological uses related to fungal infections. To achieve this, the plant extracts were classified into three groups according to whether they have reports of ethnopharmacological uses related to fungal infections (Group I = 37 species), if they are not reputed as antifungal but belong to a genus which has species with ethnopharmacological use related to antifungal activity (Group II = 11 species) and without any ethnopharmacological use related to fungal infections (Group III = 46 species). The results obtained from the combinations between the commercial antifungals and the extracts of the different group of plants showed that 7/37 (18.92%), 1/11 (9.09%), and 1/46 (2.17%) plant species of Groups I–III, respectively, enhanced the activity of AMB (Fig. 12.6a); 7/37 (18.92%), 1/11 (9.09%), and 4/46 (8.69%) plant species of Groups I–III respectively, enhanced the activity of FCZ (Fig. 12.6b) and 10/37 (27.03%), 2/11 (18.18%), and 7/46 (15.22%) plant species of Groups I–III, respectively, enhanced the activity of ITZ (Fig. 12.6c). These results indicated that when extracts came from plants with ethnopharmacological use related to fungal pathologies, there were more possibilities of finding extracts that enhance the activity of commercial antifungal drugs, suggesting that the ethnopharmacological approach is useful in designing extract–antifungal combinations with enhanced activity. Regarding the antifungal drug, the activity of azoles, especially ITZ, has been improved to a greater extent with respect to AMB (Cordisco et al. 2019).

Additionally, we evaluated whether the probability of detecting plant extracts which enhance the activity of antifungal compounds is greater when they have antifungal activities alone (MIC $\leq$1000 μg/mL) than when they do not possess it (MIC >1000 μg/mL). Our results indicated that there is a greater probability of finding an enhancement in the activity of commercial drugs when the combination is performed with extracts that have shown activity alone as compared to those previously inactive extracts. It is important to note that 42 extracts behaved as enhancers in combination with at least one of the antifungal agents evaluated and that among these, a total of 27 extracts had not shown activity alone. These extracts would have been considered inactive and discarded for further studies according to the classic strategy, however, by using this new paradigm, they remain potential candidates in the search for new antifungals (Cordisco et al. 2019).

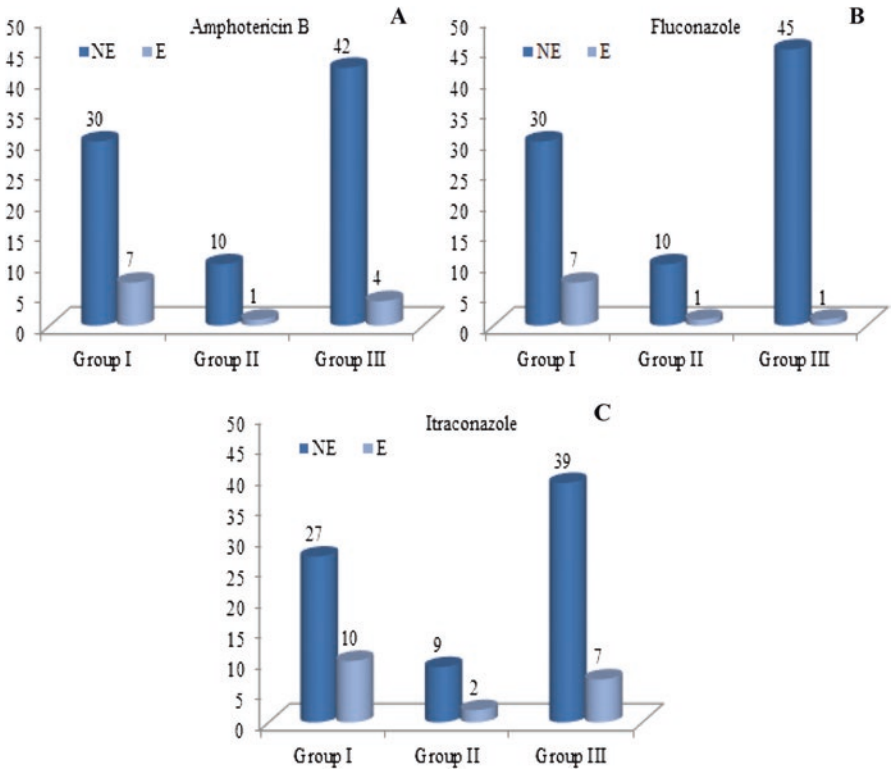


Fig. 12.6 Number of species from Groups I, II, and III which showed no enhancement (NE) and enhancement (E) of the activity of (**a**) amphotericin B; (**b**) fluconazole and (**c**) itraconazole

5 An Extension of Plant Antifungal Properties toward the Control of Phytopathogenic Fungi on Fruits

Phytopathogenic fungi cause pre- and post-harvest diseases in vegetable, cereal, and fruit crops and are responsible for considerable world agriculture economic losses. The most common species of phytopathogenic fungi that cause the deterioration of fruits, leaves, stems, and ground organs (roots, tubers, corms, etc.) belong to the genera *Alternaria*, *Botrytis*, *Diplodia*, *Monilinia*, *Penicillium*, *Colletotrichum*, *Phomopsis*, *Fusarium*, *Rhizopus,* and *Mucor* (Juárez-Becerra et al. 2010).

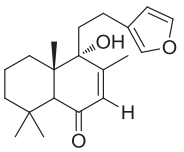
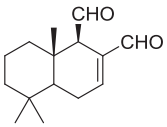
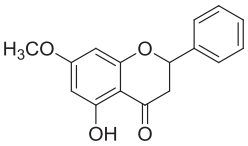
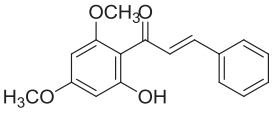
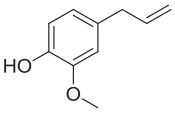
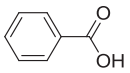
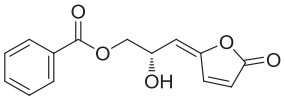
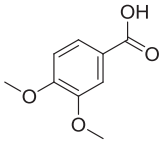
Plant extracts and their isolated active compounds have been tested for their efficacy in the control of a wide range of phytopathogenic fungi (Jiménez-Reyes et al. 2019). In this sense, an *in vitro* study revealed the antifungal activity of 18 Argentinean plants species against four phytopathogenic fungi that greatly affect the post-harvest stage of commercially important fruits, including *Penicillium digitatum*, *Botrytis cinerea*, *Monilinia fructicola,* and *Rhizopus stolonifer*. All the species studied were at least active against one fungus of the panel, while three of them (*Solidago chilensis* Meyen, *Drimys winteri* J.R.Forst, and *Polygonum stelligerum*

Cham.) displayed high antifungal properties inhibiting the growth of the selected pathogens. The antifungal activity of these plants was attributed to the presence of solidagenone in *S. chilensis*, polygodial in *D. winteri* and pinostrobin, and flavokawin B in *P. stelligerum* (Di Liberto et al. 2019). All these compounds have been identified as antimicrobial compounds (Muñoz-Concha et al. 2007; Derita and Zacchino 2011a; Ramirez et al. 2013; Carrasco et al. 2017) with the exception of solidagenone, which has been recently evaluated for its antiproliferative potential (Gomes et al. 2018). In a similar study, 17 Chinese medicinal plants were determined against eight species of plant pathogenic fungi, including *Rhizoctonia cerealis*, *F. graminearum*, *Gaeumannomyces graminis*, *F. oxysporum*, *Valsa mali*, *Colletotrichum gloeosporioides*, *F. oxysporum* sp. *Cucumebrium,* and *Colletotrichum lagenarium*. The results showed that the ethanol extracts of *Syzygium aromaticum* (L.) Merr. Et Perry (Myrtaceae) has the highest antifungal effect over the tested pathogens, isolating 2-methoxy-4-(2-propenyl) phenol (eugenol) as the active compound (Yang et al. 2019). Moreover, the antifungal activity of hexane, dichloromethane, and methanol extracts of 45 Thai plants were *in vitro* screened against plant phytopathogenic fungi (*Alternaria porri*, *C. gloeosporioides*, *F. oxysporum,* and *Phytophthora parasitica*). Seven extracts strongly inhibited the mycelial growth of the fungi. The plant extract with highest antifungal activity was *Melodorum fruticosum* Lour. (Annonaceae). Two of the eight isolated compounds (benzoic acid and melodorinol) exhibited strong activity against mycelial growth of *P. parasitica* (Mongkol et al. 2016). Extracts from the chilean plants *Ephedra breana* Phil. (Ephedraceae) and *Nolana sedifolia* Poepp. (Solanaceae) have revealed antifungal activity against *B. cinerea* (Vio-Michaelis et al. 2012). The bioactive compounds of these plants were veratric, *p*-hidroxybenzoic, and caffeic acids in *E. breana*, and *p*-coumaric and ferulic acids in *N. sedifolia*. All these compounds have been identified as antimicrobials (Fu et al. 2010). These examples, regarding the antifungal potential of plant products, are listed in Table 12.6.

On the other hand, essential oils have gained popularity in the agricultural sector due to their great antifungal activity and mycotoxin inhibition. They are ecological, biodegradable, and safe to human health (Dwivedy et al. 2016; Stegmayer et al. 2020). Their volatility makes them suitable as fumigants in protected environments and for post-harvest diseases of horticultural crops (Shukla 2018). The antimicrobial activity of essential oils is attributed mainly due to the bioactivity of the major compound or the overall synergistic effect of all major and minor compounds (Mishra et al. 2013). Although their modes of action are still unclear, they are known to decline the biosynthesis of ergosterol and disrupt the cell membrane.

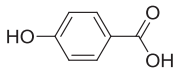
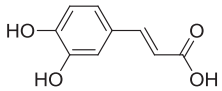
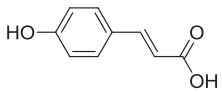
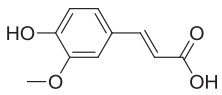
Essential oils from *Illicium verum* Hook.f (Schisandraceae) and its main component *trans*-anethole showed potent antifungal activity against several phytopathogenic fungi and could be developed as natural fungicides for disease control in fruit and vegetable preservation (Huang et al. 2010). Essential oils from the Lamiaceae plants peppermint (*Mentha piperita* L.) and sweet basil (*Ocimum basilicum* L.) proved to be effective fumigants against the two post-harvest phytopathogens *M. fructicola* and *R. stolonifer* in stored peach (*Prunus persica*) (Ziedan and Farrag 2008). A number of essential oils based on food preservatives are commercially

Table 12.6 Natural products isolated from plants which proved to be potent against different phytopathogenic fungi

Structure	Compound	Source	Controlled plant pathogen	Reference
	Solidagenone	*S. chilensis*	*P. digitatum*; *B. cinerea*; *M. fructicola*; *R. stolonifer*	(Di Liberto et al. 2019)
	Polygodial	*D. winteri*	*P. digitatum*; *B. cinerea*; *M. fructicola*; *R. stolonifer*	(Di Liberto et al. 2019)
	Pinostrobin	*P. stelligerum*	*P. digitatum*; *B. cinerea*; *M. fructicola*; *R. stolonifer*	(Di Liberto et al. 2019)
	Flavokawin B	*P. stelligerum*	*P. digitatum*; *B. cinerea*; *M. fructicola*; *R. stolonifer*	(Di Liberto et al. 2019)
	Eugenol	*S. aromaticum*	*R. cerealis*, *F. graminearum*, *G. graminis*, *F. oxysporum* f. sp. *vasinfectum*, *V. mali*, *C. gloeosporioids*, *F. oxysporum* sp. *cucumebrium*, *C. lagenarium*	(Yang et al. 2019)
	Benzoic acid	*M. fruticosum*	*P. parasitica*	(Mongkol et al. 2016)
	Melodorinol	*M. fruticosum*	*P. parasitica*	(Mongkol et al. 2016)
	Veratric acid	*E. breana*	*B. cinerea*	(Vio-Michaelis et al. 2012)

(continued)

Table 12.6 (continued)

Structure	Compound	Source	Controlled plant pathogen	Reference
	*p*-Hydroxybenzoic acid	*E. breana*	*B. cinerea*	(Vio-Michaelis et al. 2012)
	Caffeic acid	*E. breana*	*B. cinerea*	(Vio-Michaelis et al. 2012)
	*p*-Coumaric acid	*N. sedifolia*	*B. cinerea*	(Vio-Michaelis et al. 2012)
	Ferulic acid	*N. sedifolia*	*B. cinerea*	(Vio-Michaelis et al. 2012)

used and listed in "Generally Recognized as Safe" category by the Food and Drug Administration (FDA) and Environment Protection Agency (EPA) in the United States (Burt 2004), but only a few commercial biopesticides containing essential oils or artificial mixtures of terpene constituents are available. Cinnamite and Valero (from Mycotech Corporation) are commercialized as aphicide/fungicide being based on cinnamaldehyde and cinnamon oil, respectively. SPoran (a fungicide based on rosemary oil), from EcoSMART Technologies, is another example of biopesticide commercially available.

6 Conclusions

Throughout this chapter, we highlighted the most relevant results obtained during the last 20 years in our laboratory, which is internationally recognized for its quality on antifungal studies. The main human and plant fungal pathogens as well as the properties of fungi that are exploited in different industries were deeply discussed. An extensive list of Argentine plants belonging to different botanic families which have been described in the literature as antifungals was exhaustively detailed, taking into account its parts used, the fungi type against they were active, and the research group that generated the information.

The results obtained up to date give support to the ethnopharmacological use of *Z. punctata*, *P. acuminata, P. maculosa,* and *P. tetramera* as the most important species used as antiseptic and antifungal in the traditional medicine of Argentina, indicating the potential of their extracts, essential oils, and metabolites isolated from them for the control of a wide range of fungi affecting both crops and humans.

In view of the lack of new classes of drugs or different molecular targets against the most threatening yeast *C. albicans*, photodynamic therapy emerged as an

alternative approach to treat fungal infections. Plants containing phototoxic compounds were discovered in various botanic families, and several researchers have demonstrated that herbal extracts could be used in antimicrobial treatments, including antifungal. Aligned with this, the re-exploration of inactive extracts, by combining them with commercial antifungal agents, allowed to obtain synergistic mixtures, offering new possibilities for antifungal formulations. A greater probability of finding an enhancement in the activity of commercial drugs was observed when the combination was performed with extracts that had shown activity alone compared to the previously inactive extracts. Notably, 42 extracts behaved as enhancers in combination with at least one of the antifungal agents evaluated and 27 of them had not shown activity alone. These extracts would have been considered inactive and discarded for further studies according to the classic strategy, however, by using this new paradigm, they remain potential candidate in the search for new antifungals.

Acknowledgments Authors gratefully acknowledge Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT) and Universidad Nacional de Rosario (UNR) for financial support (PIP N° 2015-0524, PICT N° 2015-2259, PICT N° 2016-1833 and BIO571-UNR). GS, EB, MDL, EC, and AB are also thankful to CONICET for their doctoral fellowships.

References

de la Luz LA (2003) Principios agroclimáticos básicos para la producción de plantas medicinales. Rev Cubana Plant Med 1:1–10

Ahmad I, Zafar S, Ahmad F (2005) Heavy metal biosorption potential of *aspergillus* and *Rhizopus* sp. isolated from wastewater treated soil. J Appl Sci Environ Mgt 9(1):123–126

Ahmed DB, Chaieb I, Salah KB, Boukamcha H, Jannet HB, Mighri Z, Daami-Remadi M (2012) Antibacterial and antifungal activities of *Cestrum parqui* saponins: possible interaction with membrane sterols. Int Res J Plant Sci 3(1):001–007

Ahmed H, Juraimi AS, Swamy MK, Ahmad-Hamdani MS, Omar D, Rafii MY, Sinniah UR, Akhtar MS (2018) Botany, chemistry, and pharmaceutical significance of *Sida cordifolia*: A traditional medicinal plant. In: Akhtar MS, Swamy MK (eds) Anticancer plants: properties and application. Springer, Singapore, pp 517–537

Al-Rubaey NKF, Abbas FM, Hameed IH (2019) Antibacterial and anti-fungal activity of Methanolic extract of *Passiflora* caerulea. Indian J Public Health Res Dev 10(1):930–935

Alanís Garza BA (2005) Rastreo de la actividad antifúngica de plantas del noreste de México, contra los principales agentes causales de micosis pulmonar en la región. In: pH thesis. Universidad Autónoma de Nuevo, León

Alonso J, Desmarchelier C (2015) Plantas medicinales autóctonas de la Argentina: bases científicas para su aplicación en atención primaria de la salud, 1st edn. Corpus Libros Médicos y Científicos, Buenos Aires, Argentina

Álvarez NH, Fernandez LN, Seimandi GM, Stegmayer MI, Ruiz VE, Derita MG (2021) Antifungal activity validation of wild plants used in argentine Ethnomedicine. In: Rai M, Bhattarai S, Feitosa C (eds) Ethnopharmacology of wild plants. CRC Press/Taylor & Francis Group, U.S.A., pp 111–128. in press

Álvarez SL, Cortadi A, Juárez MA, Petenatti E, Tomi F, Casanova J, van Baren CM, Zacchino S, Vila R (2012) (−)-5,6-Dehydrocamphor from the antifungal essential oil of *Zuccagnia punctata*. Phytochem Lett 5:194–199

Alves TMDA, Ribeiro FL, Kloos H, Zani CL (2001) Polygodial, the fungitoxic component from the Brazilian medicinal plant *Polygonum punctatum*. Mem Inst Oswaldo Cruz 96(6):831–833

Anbu P, Hilda A, Sur HW, Hur BK, Jayanthi S (2008) Extracellular keratinase from *Trichophyton* sp. HA-2 isolated from feather dumping soil. Int Biodeterior Biodegradation 62(3):287–292

Anisa SK, Girish K (2014) Pectinolytic activity of *Rhizopus* sp. and *Trichoderma viride*. J Pure Appl Microbiol 4(2):28–31

Apud GR, Aredes-Fernández PA, Kritsanida M, Grougnet R, Sampietro DA (2020) Antifungal activity of Bignoniaceae plants on *aspergillus carbonarius* and *aspergillus Niger*. Nat Prod Res 34(18):2656–2659

Arancibia L, Naspi C, Pucci G, María ARCE (2010) Aromatic plants from Patagonia: chemical composition and antimicrobial activity of the essential oil of *Senecio mustersii* and *S. subpanduratus*. Bol Latinoam Caribe Plantas Med Aromat 9(2):123–126

Aristimuño Ficoseco ME, Sequin CJ, Aceñolaza PG, Vattuone MA, Catalán CAN, Sampietro DA (2017) Antifungal metabolites from *Schinopsis balansae* Engl (Anacardiaceae): isolation, identification and evidences of their mode of action on *fusarium graminearum* Schwabe. Nat Prod Res 31(12):1450–1453

Ayaz M, Ullah F, Sadiq A, Ullah F, Ovais M, Ahmed J, Devkota HP (2019) Synergistic interactions of phytochemicals with antimicrobial agents: potential strategy to counteract drug resistance. Chem Biol Interact 308:294–303

Basak G, Das N (2014) Characterization of sophorolipid biosurfactant produced by *Cryptococcus* sp. VITGBN2 and its application on Zn (II) removal from electroplating wastewater. J Environ Biol 35(6):1087–1094

Biradar SS, Wadkar GH, Rasal VP, Kane SR (2010) Anti-fungal screening of tubers of *Cyperus rotundus* Linn. Res J Pharmacogn Phytochem 2(4):317–318

Bonifácio B, Vila T, Fantacini Masiero I, Bento da Silva P, Da Silva IC, Lopes de Oliveira É, dos Santos Ramos MA, Perez de Souza L, Vilegas W, Rogério Pavan F, Chorilli M, Lopez-Ribot JL, Bauab TM (2019) Antifungal activity of a Hydroethanolic extract from *Astronium urundeuva* leaves against *Candida albicans* and *Candida glabrata*. Front Microbiol 10:1–12

Braga FG, Bouzada MLM, Fabri RL, Matos MDO, Moreira FO, Scio E, Coimbra ES (2007) Antileishmanial and antifungal activity of plants used in traditional medicine in Brazil. J Ethnopharmacol 111(2):396–402

Burt S (2004) Essential oils: their antibacterial properties and potential applications in foods-a review. Int J Food Microbiol 94(3):223–253

Butassi E, Svetaz LA, Ivancovich JJ, Feresin GE, Tapia A, Zacchino SA (2015) Synergistic mutual potentiation of antifungal activity of *Zuccagnia punctata* Cav. And *Larrea nitida* Cav. Extracts in clinical isolates of *Candida albicans* and *Candida glabrata*. Phytomedicine 22(6):666–678

Butassi E, Svetaz LA, Zhou S, Wolfender JL, Cortes JCG, Ribas JC, Diaz C, Perez del Palacio J, Vicente F, Zacchino SA (2019) The antifungal activity and mechanisms of action of quantified extracts from berries, leaves and roots of *Phytolacca tetramera*. Phytomedicine 60:152884

Caneschi CA, Martins FJ, Larrudé DG, Romani EC, Brandão MAF, Raposo NRB (2015) In vitro antifungal activity of *Baccharis trimera* less (DC) essential oil against dermatophytes. Trop J Pharm Res 14(11):2083–2089

Carpinella MC, Ruiz G, Palacios SM (2010) Screening of native plants of Central Argentina for antifungal activity. Allelopathy J 25(2):423–431

Carrasco H, Robles-Kelly C, Rubio J, Olea AF, Martínez R, Silva-Moreno E (2017) Antifungal effect of polygodial on *Botrytis cinerea*, a fungal pathogen affecting table grapes. Int J Mol Sci 18(11):2251

Carrizo SL, Zampini IC, Sayago JE, Simirgiotis MJ, Bórquez J, Cuello AS, Isla MI (2020) Antifungal activity of phytotherapeutic preparation of *Baccharis* species from argentine Puna against clinically relevant fungi. J Ethnopharmacol 251:112553

Céspedes CL, Avila JG, Garcıa AM, Becerra J, Flores C, Aqueveque P, Bittner M, Hoeneisenm M, Martínez M, Silva M (2006) Antifungal and antibacterial activities of *Araucaria araucana* (Mol.) K. Koch heartwood lignans. Z. Naturforsch. C. 61(1–2):35–43

Chen C, Cai D, Qin P, Chen B, Wang Z, Tan T (2018) Bio-plasticizer production by hybrid acetone-butanol-ethanol fermentation with full cell catalysis of *Candida* sp. 99–125. Bioresour Technol 257:217–222

CLSI (Clinical and Laboratory Standards Institute) (2017) Reference method for broth dilution antifungal susceptibility testing of yeasts. Approved standard-document M-27, 4th edn. Wayne, Pennsylvania, USA

Contesini FJ, Lopes DB, Macedo GA, da Graça Nascimento M, de Oliveira Carvalho P (2010) Aspergillus sp. lipase: potential biocatalyst for industrial use. J Mol Catal B Enzym 67(3–4):163–171

Cordisco E, Sortino M, Svetaz L (2019) Antifungal activity of traditional medicinal plants from Argentina: effect of their combination with antifungal drugs. Curr Tradit Med 5(1):75–95

Córdoba S, Vivot W, Szusz W, Albo G (2019) Antifungal activity of essential oils against *Candida* species isolated from clinical samples. Mycopathologia 184:615–623

Costa DP, Alves Filho EG, Silva LM, Santos SC, Passos XS, Silva MRR, Seraphin JC, Ferri PH (2010) Influence of fruit biotypes on the chemical composition and antifungal activity of the essential oils of *Eugenia uniflora* leaves. J Braz Chem Soc 21(5):851–858

da Silva SL, Figueredo PM, Yano T (2006) Antibacterial and antifungal activities of volatile oils from *Zanthoxylum rhoifolium*. Leaves Pharm Biol 44(9):657–659

Dai T, Fuchs BB, Coleman JJ, Prates RA, Astrakas C, St Denis TG, Ribeiro MS, Mylonakis E, Hamblin MR, Tegos G (2012) Concepts and principles of photodynamic therapy as an alternative antifungal discovery platform. Front Microbiol 3:120

Davicino R, Mattar MA, Casali YA, Correa SG, Pettenati EM, Micalizzi B (2007) Actividad antifúngica de extractos de plantas usadas en medicina popular en Argentina. Rev Peru Biol 14(2):247–252

De Los Páez AV, Albornoz PL, Lizarraga E, Sobrero MT, Chaila S (2019) Anatomía foliar y caulinar, y caracterización fitoquímica foliar de Flaveria bidentis y F. haumanii (Asteraceae) de Santiago del Estero, Argentina. Act. Bot. Mex:126

Delucchi G (2006) Las especies vegetales amenazadas de la Provincia de Buenos Aires: Una actualización. Aprona Bol Cient 39:19–31

Demo M, Oliva MDL, López ML, Zunino MP, Zygadlo JA (2005) Antimicrobial activity of essential oils obtained from aromatic plants of Argentina. Pharm Biol 43(2):129–134

Derita MG, Leiva ML, Zacchino SA (2009) Influence of plant part, season of collection and content of the main active constituent, on the antifungal properties of *Polygonum acuminatum* Kunth. J Ethnopharmacol 124(3):377–383

Derita M, Montenegro I, Garibotto F, Enriz R, Cuellar Fritis M, Zacchino S (2013) Structural requirements for the antifungal activities of natural drimane sesquiterpenes and analogues, supported by conformational and electronic studies. Molecules 18(2):2029–2051

Derita M, Zacchino S (2011a) Validation of the ethnopharmacological use of *Polygonum persicaria* for its antifungal properties. Nat Prod Comm 6(7):931–933

Derita M, Zacchino S (2011b) Chemotaxonomic importance of sesquiterpenes and flavonoids in Argentinian species of *Polygonum* genus. J Ess Oil Res 23:11–14

Di Ciaccio LS, Catalano AV, López PG, Rojas D, Cristos D, Fortunato RH, Salvat AE (2020) In vitro antifungal activity of *Peltophorum dubium* (Spreng.) Taub. Extracts against *aspergillus flavus*. Plants 9(4):438

di Ciaccio LS, Fortunato RH, Salvat AE (2018) Antifungal activity of species of the genus *Senna* (Caesalpinoideae, Leguminosae) from northern Argentina against *fusarium verticillioides*. Rev Investig Agropecu 44(1):111–120

Di Ciaccio LS, Spotorno VG, Córdoba Estévez MM, Rios DJL, Fortunato RH, Salvat AE (2018) Antifungal activity of *Parastrephia quadrangularis* (Meyen) Cabrera extracts against *fusarium verticillioides*. Lett Appl Microbiol 66(3):244–251

Di Liberto MGD, Stegmayer MI, Svetaz LA, Derita MG (2019) Evaluation of Argentinean medicinal plants and isolation of their bioactive compounds as an alternative for the control of postharvest fruits phytopathogenic fungi. Rev Bras Farmacogn 29(5):686–688

Di Liberto M, Svetaz L, Castelli MV, Rai M, Derita M (2017) Role of essential oils for the cure of human pathogenic fungal infections. In: Rai M, Zacchino S, Derita M (eds) Essential oils and nanotechnology for treatment of microbial diseases. CRC Press/Taylor & Francis Group, U.S.A, pp 127–142

do Amaral CC, Fernandes GF, Rodrigues AM, Burger E, de Camargo ZP (2019) Proteomic analysis of *Paracoccidioides brasiliensis* complex isolates: correlation of the levels of differentially expressed proteins with in vivo virulence. PLoS One 14(7):e0218013

do Prado AC, Garces HG, Bagagli E, Rall VLM, Furlanetto A, Fernandes Junior A, Furtado FB (2018) Schinus molle essential oil as a potential source of bioactive compounds: antifungal and antibacterial properties. J Appl Microbiol 126(2):516–522

Donnelly RF, McCarron PA, Tunney MM (2008) Antifungal photodynamic therapy. Microbiol Res 163(1):1–12

dos Santos Silva F, Landell MF, Paulino GVB, Coutinho HDM, Albuquerque UP (2020) Antifungal activity of selected plant extracts based on an ethnodirected study. Acta Bot Bras 34(2):442–448

Downum KR, Towers GHN (1983) Analysis of thiophenes in the Tageteae (Asteraceae) by HPLC. J Nat Prod 46(1):98–103

Duyvesteijn RG, Van Wijk R, Boer Y, Rep M, Cornelissen BJ, Haring MA (2005) Frp1 is a *fusarium oxysporum* F-box protein required for pathogenicity on tomato. Mol Microbiol 57(4):1051–1063

Dwivedy AK, Kumar M, Upadhyay N, Prakash B, Dubey NK (2016) Plant essential oils against food borne fungi and mycotoxins. Curr Opin Food Sci 11:16–21

ElSohly HN, Joshi AS, Nimrod AC, Walker LA, Clark AM (2001) Antifungal chalcones from *Maclura tinctoria*. Planta Med 67(1):87–89

EMA (European Medicines Agency) (2010) Guidelines on Declaration of Herbal Substances and Herbal Preparations in Herbal Medicinal Products/Traditional Herbal Medicinal Products. EMA/HMPC/CHMP/CVMP/287539/2005 Rev 1. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003272.pdf. (Accessed 27.09.2020)

Enshaeieh M, Abdoli A, Nahvi I (2013) Medium optimization for biotechnological production of single cell oil using *Yarrowia lipolytica* M7 and *Candida* sp. J Cell Molecular Research 5(1):17–23

Escalante A, Gattuso M, Pérez P, Zacchino S (2008) Evidence for the mechanism of action of the antifungal phytolaccoside B isolated from *Phytolacca tetramera* Hauman. J Nat Prod 71:1720–1725

Escalante A, Santecchia C, López S, Gattuso M, Gutiérrez Ravelo A, Delle Monache F, Zacchino S (2002) Isolation of antifungal saponins from *Phytolacca tetramera*, an Argentinean species in critic risk. J Ethnopharmacol 82(1):29–34

Espino M, Solari M, de los Ángeles Fernández M, Boiteux J, Gómez MR, Silva MF (2019) NADES-mediated folk plant extracts as novel antifungal agents against *Candida albicans*. J Pharm Biomed Anal 167:15–20

Feresín G, Alejandro T, Silvia NL, Susana AZ (2001) Antimicrobial activity of plants used in traditional medicine of San Juan province, argentine J. Ethnopharmacol 78(1):103–107

Filip R, Davicino R, Anesini C (2010) Antifungal activity of the aqueous extract of *Ilex paraguariensis* against *Malassezia furfur*. Phytother Res 24:715–719

Fiuza TDS, de Sabóia-Morais SMT, de Paula JR, Tresvenzol LM, Pimenta FC (2009) Antimicrobial activity of the crude ethanol extract from *Hyptidendron canum* leaves. Pharm Biol 47(7):640–644

Forsyth LM, Smith LJ, Aitken EA (2006) Identification and characterization of non-pathogenic *fusarium oxysporum* capable of increasing and decreasing fusarium wilt severity. Mycol Res 110(8):929–935

Freiesleben S, Jäger A (2014) Correlation between plant secondary metabolites and their antifungal mechanisms–a review. Medicinal Aromat Plan Theory 3(2):1–6

Freile M, Giannini F, Sortino M, Zamora M, Juárez A, Zacchino S, Enriz D (2006) Antifungal activity of aqueous extracts and of berberine isolated from *Berberis heterophylla*. Acta Farm Bonaer 25(1):83–88

Fu J, Cheng K, Zhang ZM, Fang RQ, Zhu HL (2010) Synthesis, structure and structure–activity relationship analysis of caffeic acid amides as potential antimicrobials. Eur J Med Chem 45(6):2638–2643

Gaitán I, Paz AM, Zacchino SA, Tamayo G, Giménez A, Pinzón R, Cáceres A, Gupta MP (2011) Subcutaneous antifungal screening of Latin American plant extracts against *Sporothrix schenckii* and *Fonsecaea pedrosoi*. Pharm Biol 49(9):907–919

Galvez CE, Jimenez CM, Gomez ADLA, Lizarraga EF, Sampietro DA (2020) Chemical composition and antifungal activity of essential oils from *Senecio nutans*, *Senecio viridis, Tagetes terniflora* and *Aloysia gratissima* against toxigenic *Aspergillus* and *Fusarium* species. Nat Prod Res 34(10):1442–1445

Ghaffar I, Imtiaz A, Hussain A, Javid A, Jabeen F, Akmal M, Qazi JI (2018) Microbial production and industrial applications of keratinases: an overview. Int Microbiol 21(4):163–174

Giacone L, Cordisco E, Garrido MC, Petenatti E, Sortino M (2020) Photodynamic activity of *Tagetes minuta* extracts against superficial fungal infections. Med Mycol 58(6):797–809

Gil A, Ghersa CM, Perelman S (2002) Root thiophenes in *Tagetes minuta* L. accessions from Argentina: genetic and environmental contribution to changes in concentration and composition. Biochem. Syst. Ecol 30(1):1–13

Gomes D, Zanchet B, Locateli G, Benvenutti R, Dalla Vechia C, Schönell A, Diel K, Zilli G, Miorando D, Ernetti J, Oliveira B, Zanotelli P, Santos M, Barisson A, Banzato T, Ruiz A, Carvalho J, Cechinel Filho V, García P, San Feliciano A, Roman Junior W (2018) Antiproliferative potential of solidagenone isolatedof *Solidago chilensis*. Rev Bras Farmacogn 28:703–709

Gomez AA, Terán Baptista ZP, Mandova T, Barouti A, Kritsanida M, Grougnet R et al (2019) Antifungal and antimycotoxigenic metabolites from native plants of Northwest Argentina: isolation, identification and potential for control of *aspergillus* species. Nat Prod Res 1-4

Guerra F, Ansari AA, Kurup R, Subramanian G (2020) Antifungal activity of *Senna alata*, *Senna bicapsularis* and *Pityrogramma calomelanos*. J Complement Altern Medical Res 10(3):11–21

Gurgel LA, Sidrim JJC, Martins DT, Cechinel F, Rao V, V.S. (2005) In vitro antifungal activity of dragon's blood from *croton urucurana* against dermatophytes. J Ethnopharmacol 97(2):409–412

Hemaiswarya S, Kruthiventi AK, Doble M (2008) Synergism between natural products and antibiotics against infectious diseases. Phytomedicine 15(8):639–652

Hernández M, Rodríguez A, Gallo D, Fernández D (2008) *Phytolacca tetramera* Hauman, una especie amenazada de la Provincia de Buenos Aires. In: Resumen Jornada "Seminario Técnico en la Reserva de Biosfera Parque Costero del Sur como herramienta del conocimiento científico". Buenos Aires, Municipalidad de Magdalena

Huang Y, Zhao J, Zhou L, Wang J, Gong Y, Chen X, Guo Z, Wang Q, Jiang W (2010) Antifungal activity of the essential oil of *Illicium verum* fruit and its main component trans-anethole. Molecules 15(11):7558–7569

Ibrahim SRM, Abdallah HM, El-Halawany AM, Esmat A, Mohamed GA (2018) Thiotagetin B and tagetannins A and B, new acetylenic thiophene and digalloyl glucose derivatives from *Tagetes minuta* and evaluation of their in vitro antioxidative and anti-inflammatory activity. Fitoterapia 125:78–88

Ibrahim SRM, Abdallah HM, El-Halawany AM, Mohamed GA (2016) Naturally occurring thiophenes: isolation, purification, structural elucidation, and evaluation of bioactivities. Phytochem Rev 15:197–220

Isla MI, Moreno MA, Nuño G, Rodriguez F, Carabajal A, Alberto MR, Zampini IC (2016) Zuccagnia punctata: a review of its traditional uses, phytochemistry, pharmacology and toxicology. Nat Prod Commun 11(11):1749–1755

Jiménez-Reyes MF, Carrasco H, Olea AF, Silva-Moreno E (2019) Natural compounds: a sustainable alternative to the phytopathogens control. J Chil Chem Soc 64(2):4459–4465

Johnson RR (1964) Monograph of the plant genus *Porophyllum* (Compositae, Helenieae). University of Kansas

Juárez-Becerra GP, Sosa-Morales ME, López-Malo A (2010) Hongos fitopatógenos de alta importancia económica: descripción y métodos de control. Temas Selectos de Ingeniería de Alimentos 4(2):14–23

Karpiński TM (2020) Essential oils of Lamiaceae Family plants as antifungals. Biomol Ther 10(1):103

Kato IT, Prates RA, Sabino CP, Fuchs BB, Tegos GP, Mylonakis E, Hamblin MR, Ribeiro MS (2013) Antimicrobial photodynamic inactivation inhibits *Candida albicans* virulence factors and reduces in vivo pathogenicity. Antimicrob Agents Chemother 57(1):445–451

Kaur N, Dhuna V, Kamboj SS, Agrewala JN, Singh J (2006) A novel antiproliferative and antifungal lectin from *Amaranthus viridis* Linn seeds. Protein Pept Lett 13(9):897–905

Kurdelas RR, Lima B, Tapia A, Egly Feresin G, Gonzalez Sierra M, Rodríguez MV, Zacchino S, Enriz RD, Freile ML (2010) Antifungal activity of extracts and prenylated coumarins isolated from *Baccharis darwinii* Hook & Arn. (Asteraceae). Molecules 15(7):4898–4907

Lacaz CDS, Porto E, Martins JEC, Heins-Vaccari EM, Takahashi de Melo N (2002) Tratado de micologia médica. Rev Inst Med Trop S Paulo 44(5):297–298

Liang YI, Lu L, Chen Y, Lin Y (2016) Photodynamic therapy as an antifungal treatment. Exp Ther Med 12:23–27

Liberto MD, Svetaz L, Furlán RL, Zacchino SA, Delporte C, Novoa MA, Asencio M, Cassels BK (2010) Antifungal activity of saponin-rich extracts of *Phytolacca dioica* and of the sapogenins obtained through hydrolysis. Nat Prod Commun 5(7):1013–1018

Lima B, López S, Luna L, Agüero MB, Aragón L, Tapia A, Zacchino S, López ML, Zygadio J, Feresin GE (2011) Essential oils of medicinal plants from the Central Andes of Argentina: chemical composition, and antifungal, antibacterial, and insect-repellent activities. Chem Biodivers 8(5):924–936

Lima CS, Polaquini CR, dos Santos MB, Gullo FP, Leite FS, Scorzoni L, da Silva Bolzani V, Mendez-Giannini MJ, Fusco-Almeida AM, Alvez Rezende A, Regasini LO (2016) Anti-*Candida* and anti-*Cryptococcus* evaluation of 15 non-alkaloidal compounds from *Pterogyne nitens*. Asian Pac J Trop Biomed 6(10):841–845

Lima B, Sánchez M, Luna L, Agüero MB, Zacchino S, Filippa E, Palermo JA, Tapia A, Feresin GE (2012) Antimicrobial and antioxidant activities of *Gentianella multicaulis* collected on the Andean slopes of San Juan Province. Argentina Z Naturforsch C 67(1–2):29–38

Lizcano González MC (2007) Evaluación de la actividad antifúngica del extracto de tomillo (*Thymus vulgaris*) contra *Botrys cinerea*. Pontificia Universidad Javeriana, Bogotá, Fusarium oxysporum y Sclerotinia sclerotiorum. pH Tesis

Loockerman DJ, Turner BL, Jansen RK (2003) Phylogenetic relationships within the Tageteae (Asteraceae) based on nuclear ribosomal ITS and chloroplast ndhF gene sequences. Syst Bot 28(1):191–207

López SN, Furlan RLE, Zacchino SA (2011) Detection of antifungal compounds in *Polygonum ferrugineum* Wedd. Extracts by bioassay-guided fractionation. Some evidences of their mode of action. J Ethnopharmacol 138(2):633–636

Maisch T, Baier J, Franz B, Maier M, Landthaler M, Szeimies RM, Baumler W (2007) The role of singlet oxygen and oxygen concentration in photodynamic inactivation of bacteria. Proc Natl Acad Sci 104(17):7223–7228

Malarkodi E, Manoharan A (2013) Antifungal activity of *Parthenium hysterophorus* L. J Chem Pharm Res 5(1):137–139

Mamone L, Di Venosa G, Gándara L, Sáenz D, Vallecorsa P, Schickinger S, Rossetti MV, Batlle A, Buzzola F, Casas A (2014) Photodynamic inactivation of gram-positive bacteria employing natural resources. J Photochem Photobiol B Biol 133:80–89

Marotti I, Marotti M, Piccaglia R, Nastri A, Grandi S, Dinelli G (2010) Thiophene occurrence in different *Tagetes* species: agricultural biomasses as sources of biocidal substances. J Sci Food Agric 90:1210–1217

Martinez JA (2012) Natural fungicides obtained from plants. INTECH Open Access Publisher

Mensah AY, Houghton PJ, Dickson RA, Fleischer TC, Heinrich M, Bremner P (2006) In vitro evaluation of effects of two Ghanaian plants relevant to wound healing. Phytother Res 20(11):941–944

Mishra PK, Singh P, Prakash B, Kedia A, Dubey NK, Chanotiya CS (2013) Assessing essential oil components as plant-based preservatives against fungi that deteriorate herbal raw materials. Int Biodeterior Biodegradation 80:16–21

Mohanta YK, Laxmipriya P, Panda SK (2014) Antifungal activity of *Eleutherine bulbosa* bulb against mycelial fungus. Int J Agric Technol 10(5):1165–1171

Mongkol R, Piapukiew J, Chavasiri W (2016) Chemical constituents from *Melodorum fruticosum* Lour. Flowers against plant pathogenic fungi. Agric Nat Resour 50(4):270–275

Montez-Belmont RM, Cruz VC, Martínez GM, García GS, Licona RG, Domínguez SZ, Bravo-Luna L, Bermúdez-Torres K, Flores-Moctezuma HE, Caravajal-Moreno MC (2000) Propiedades antifúngicas en plantas superiores. Análisis retrospectivo de investigaciones. Rev Mex Fitopatol 18(2):125–131

Morais M, Amaral Pinto M, Araújo S, Fonseca Castro A, Duarte Almeida J, Rosa L, Rosa C, Johann S, Rodríguez dos Santos Lima, L. (2014) Antioxidant and antifungal activities of *Smilax campestris* Griseb. (Smilacaceae). Nat Prod Res 28(16):1275–1279

Morin-Sardin S, Nodet P, Coton E, Jany JL (2017) Mucor: a Janus-faced fungal genus with human health impact and industrial applications. Fungal Biol Rev 31(1):12–32

Muñoz-Concha D, Vogel H, Yunes R, Razmilic I, Bresciani L, Malheiros A (2007) Presence of polygodial and drimenol in *Drimys* populations from Chile. Biochem Sys Ecol 35(7):434–438

Murakami C, Lago JH, Perazzo FF, Ferreira KS, Lima ME, Moreno PR, Young MC (2013) Chemical composition and antimicrobial activity of essential oils from *Chromolaena laevigata* during flowering and fruiting stages. Chem Biodivers 10(4):621–627

Muschietti L, Derita M, Sülsen V, de Dios Muñoz J, Ferraro G, Zacchino S, Martino V (2005) In vitro antifungal assay of traditional argentine medicinal plants. J Ethnopharmacol 102(2):233–238

Nally MC, Pesce VM, Maturano YP, Muñoz CJ, Combina M, Toro ME, Castellanos de Figueroa LI, Vazquez F (2012) Biocontrol of *Botrytis cinerea* in table grapes by non-pathogenic indigenous *Saccharomyces cerevisiae* yeasts isolated from viticultural environments in Argentina. Postharvest Biol Technol 64(1):40–48

Nenoff P, Krüger C, Ginter-Hanselmayer G, Tietz HJ (2013) Mycology–an update. Part 1: dermatomycoses: causative agents, epidemiology and pathogenesis. J Dtsch Dermatol Ges 12(3):188–210

Nguyen TPA, Nguyen TTM, Nguyen NH, Nguyen TN, Dang TTP (2020) Application of yeast surface display system in expression of recombinant pediocin PA-1 in *Saccharomyces cerevisiae*. Folia Microbiol 2020

Nuño G (2015) Aislamiento y caracterización de biomoléculas producidas por especies vegetales que crecen en ecosistemas semiáridos. pH Tesis. Universidad Nacional de, Tucumán

Nwaguma IV, Chikere CB, Okpokwasili GC (2019) Effect of cultural conditions on biosurfactant production by *Candida* sp. isolated from the sap of *Elaeis guineensis*. Biotechnol J Int 23(3):1–14

Oliva MM, Demo MS, López AG, López ML, Zygadlo JA (2006) Antimicrobial activity and composition of *Hyptis mutabilis* essential oil. Int J Geogr Inf Syst 11(4):57–63

Ortega CA, María AOM, Gianello JC (2000) Chemical components and biological activity of *Bidens subalternans*, B. aurea (Astereaceae) and *Zuccagnia puntacta* (Fabaceae). Molecules 5(3):465–470

Pacciaroni ADV, de los Angeles Gette M, Derita M, Ariza-Espinar L, Gil RR, Zacchino SA, Silva GL (2008) Antifungal activity of *Heterothalamus alienus* metabolites. Phytother Res 22(4):524–528

Pergomet J, Di Liberto M, Derita M, Bracca A, Kaufman T (2018) Activity of the pterophyllins 2 and 4 against postharvest fruit pathogenic fungi. Comparison with a synthetic analog and related intermediates Fitoterapia 125:98–105

Petenatti E, Gette M, Derita M, Petenatti M, Solís C, Zuljan F, Del Vitto L.A. Zacchino, S. (2008) Importance of the ethnomedical information for the detection of antifungal properties in plant extracts from the argentine flora. South American medicinal plants as potential source of bioactive compounds. Transworld Research Network, Kerala, pp 15–38

Petri I, Gallo D, Ollier F (2010) First protected area in the partido de Magdalena for the preservation of ombusillo (*Phytolacca tetramera* Hauman), in situ. Agreement between the Department of Transportation of the province of Buenos Aires and the Faculty of Agricultural Sciences and Forestry of the National University of La Plata. Argentina Rev Colomb Biotecnol 12(2):259–261

Pinto AP, Rosseti IB, Carvalho ML, da Silva BGM, Alberto-Silva C, Costa MS (2018) Photodynamic antimicrobial chemotherapy (PACT), using toluidine blue O inhibits the viability of biofilm produced by *Candida albicans* at different stages of development. Photodiagn Photodyn Ther 21:182–189

Pioli RN, Benavídez R, Morandi EN, Bodrero M (2000) Epidemiological study of diseases associated to soybean carpels and seeds, in Santa Fe, Argentina. Fitopatología 35(2):111–118

Portillo A, Vila R, Freixa B, Adzet T, Cañigueral S (2001) Antifungal activity of Paraguayan plants used in traditional medicine. J Ethnopharmacol 76(1):93–98

Postigo A, Funes M, Petenatti E, Bottai H, Pacciaroni A, Sortino M (2017) Antifungal photosensitive activity of *Porophyllum obscurum* (Spreng.) DC.: correlation of the chemical composition of the hexane extract with the bioactivity. Photodiagnosis Photodyn Ther 20:263–272

Postigo A, Svetaz LA, Derita MG, Gette MA, Petenatti M, Del Vitto L, Petenatti E, Zacchino S (2012) Discovery of antifungal plants in Argentinean San Luis Province: ethnomedical information or random selection? Revista Eletrônica de Farmácia 9(1):22–22

Prazeres JND, Cruz JAB, Pastore GM (2006) Characterization of alkaline lipase from *fusarium oxysporum* and the effect of different surfactants and detergents on the enzyme activity. Braz J Microbiol 37(4):505–509

Quiroga EN, Sampietro DA, Sgariglia MA, Soberón JR, Vattuone MA (2009) Antimycotic activity of 5′-prenylisoflavanones of the plant *Geoffroea decorticans*, against *aspergillus* species. Int J Food Microbiol 132(1):42–46

Quiroga EN, Sampietro AR, Vattuone MA (2001) Screening antifungal activities of selected medicinal plants. J Ethnopharmacol 74(1):89–96

Ramirez J, Cartuche L, Morocho V, Aguilar S, Malagon O (2013) Antifungal activity of raw extract and flavanons isolated from *Piper ecuadorense* from Ecuador. Rev Bras Farmacogn 23(2):370–373

Reichling J (2018) Plant-microbe interactions and secondary metabolites with antibacterial, antifungal and antiviral properties. Annu Plant Rev 39:214–347

Ríos JL, Recio MC (2005) Medicinal plants and antimicrobial activity. J Ethnopharmacol 100(1–2):80–84

Ríos JL, Schinella GR, Andújar I (2018) Antipsoriatic medicinal plants, from traditional use to clinic. In: Martinez JL, Muñoz-Acevedo A, Rai M (eds) Ethnobotany: local knowledge and traditions. CRC Press, Taylor and Francis Group, pp 158–186

Rodrigues FF, Oliveira LG, Rodrigues FF, Saraiva ME, Almeida SC, Cabral ME, Campos AR, Costa JGM (2012) Chemical composition, antibacterial and antifungal activities of essential oil from *Cordia verbenacea* DC leaves. Pharm Res 4(3):161–165

Sa RA, Argolo AC, Napoleao TH, Gomes FS, Santos ND, Melo CM, Albuquerque AC, Xavier HS, Coelho LCB, Bieber LW, Paiva PM (2009) Antioxidant, *fusarium* growth inhibition and *Nasutitermes corniger* repellent activities of secondary metabolites from *Myracrodruon urundeuva* heartwood. Int Biodeterior Biodegradation 63(4):470–477

Sabinil LI, Gabrielli PC, Torres CV, Escobar FM, Cacciabue M, Rovera M, Kolb N (2006) Study of the cytotoxic and antifungal activity of the essential oil of *Elyonurus muticus* against *Candida* spp. Strain Mol Med Chem 11(2):31–33

Sacchetti G, Medici A, Maietti S, Radice M, Muzzoli M, Manfredini S, Braccioli E, Bruni R (2004) Composition and functional properties of the essential oil of Amazonian basil, *Ocimum*

micranthum Willd., Labiatae in comparison with commercial essential oils. J Agric Food Chem 52(11):3486–3491

Salah H, Al-Hatmi AM, Theelen B, Abukamar M, Hashim S, van Diepeningen AD, Lass-Florl C, Boekhout T, Almaslamani M, Taj-Aldeen SJ (2015) Phylogenetic diversity of human pathogenic *fusarium* and emergence of uncommon virulent species. J Infect 71(6):658–666

Sampietro DA, Belizan MME, Baptista ZPT, Vattuone MA, Catalán CA (2014) Essential oils from Schinus species of Northwest Argentina: composition and antifungal activity. Nat Prod Commun 9(7):1019–1022

Santhoshkumar J, Sowmya B, Kumar SV, Rajeshkumar S (2019) Toxicology evaluation and antidermatophytic activity of silver nanoparticles synthesized using leaf extract of *Passiflora caerulea*. S Afr J Chem Eng 29:17–23

Shukla AC (2018) Essential oils as green pesticides for postharvest disease management. Acta Hortic 1210:199–206

Siewert B, Stuppner H (2019) The photoactivity of natural products–An overlooked potential of phytomedicines? Phytomedicine 60:152985

Singh CJ (2011) Extracellular protease expression in *Microsporum gypseum* complex, its regulation and keratinolytic potential. Mycoses 54(4):e183–e188

Soberón JR, Sgariglia MA, Torrez JAC, Aguilar FA, Pero EJ, Sampietro DA, de Luco JF, Labadie GR (2020) Antifungal activity and toxicity studies of flavanones isolated from *Tessaria dodoneifolia* aerial parts. Heliyon 6(10):e05174

Sobrinho ACN, de Souza EB, Rocha MFG, Albuquerque MRJ, Bandeira PN, dos Santos HS, de Paula Cavalacante CS, Souza Oliveira S, Rodrigues Aragão P, de Morais, S.M. dos Santos Fontenelle, R.O. (2016) Chemical composition, antioxidant, antifungal and hemolytic activities of essential oil from *Baccharis trinervis* (lam.) Pers. (Asteraceae). Ind. Crops Prod 84:108–115

Spitzer M, Robbins N, Wright GD (2017) Combinatorial strategies for combating invasive fungal infections. Virulence 8(2):169–185

Stegmayer MI, Fernandez LN, Olivella L, Gutierrez HF, Favaro MA, Derita MG (2020) Aceites esenciales provenientes de plantas nativas para el control de hongos fitopatógenos que afectan a frutales. Revista FAVE 20. in press

Stein AC, Sortino M, Avancini C, Zacchino S, von Poser G (2005) Ethnoveterinary medicine in the search for antimicrobial agents: antifungal activity of some species of *Pterocaulon* (Asteraceae). J Ethnopharmacol 99(2):211–214

Stopiglia CDO, da Rocha Vianna D, de Carvalho Meirelles G, Teixeira H, Von Poser GL, Scroferneker ML (2011) Antifungal activity of *Pterocaulon* species (Asteraceae) against *Sporothrix schenckii*. J Mycolm Méd 21(3):169–172

Svetaz L, Agüero MB, Alvarez S, Luna L, Feresin G, Derita M, Tapia A, Zacchino S (2007) Antifungal activity of chalcones from *Zuccagnia punctata* Cav. Acting against clinically important fungi and studies of mechanism of action. Planta Med 73:1074–1080

Svetaz L, Tapia A, López S, Furlán R, Petenatti E, Pioli R, Schmeda-Hirschmann G, Zacchino S (2004) Antifungal chalcones and new caffeic acid esters from *Zuccagnia punctata* acting against soybean infecting fungi. J Agric Food Chem 52(11):3297–3300

Svetaz L, Zuljan F, Derita M, Petenatti E, Tamayo G, Cáceres A, Filho VC, Giménez A, Pinzón R, Zacchino S, Gupta M (2010) Value of the ethnomedical information for the discovery of plants with antifungal properties. A survey among seven Latin American countries. J Ethnopharmacol 127(1):137–158

Teal LJ, Schultz KM, Weber DJ, Gergen MF, Miller MB, DiBiase LM, Sickbert-Bennett E, Rutala WA (2016) Invasive cutaneous *Rhizopus* infections in an immunocompromised patient population associated with hospital laundry carts. Infect Control Hosp Epidemiol 37(10):1251–1253

Tempone AG, Sartorelli P, Teixeira D, Prado FO, Calixto IA, Lorenzi H, Melhem MS (2008) Brazilian flora extracts as source of novel antileishmanial and antifungal compounds. Mem Inst Oswaldo Cruz 103(5):443–449

Thembo KM, Vismer HF, Nyazema NZ, Gelderblom WCA, Katerere DR (2010) Antifungal activity of four weedy plant extracts against selected mycotoxigenic fungi. J Appl Microbiol 109(4):1479–1486

Thirunavukarasu K, Purushothaman S, Sridevi J, Aarthy M, Gowthaman MK, Nakajima-Kambe T, Kamini NR (2016) Degradation of poly (butylene succinate) and poly (butylene succinate-co-butylene adipate) by a lipase from yeast *Cryptococcus* sp. grown on agro-industrial residues. Int. Biodeterior. Biodegradation 110:99–107

Torres AM, Ramirez ML, Chulze SN (2009) *Fusarium* and fumonisins in maize in South America. In: Rai M, Varma A (eds) Mycotoxins in food, Feed and Bioweapons. Springer, Berlin, Heidelberg, pp 179–200

Vaghela J, Rana M, Savalia V, Sheth NR (2009) Evaluation of antifungal activity of methanolic extract of leaves and stems of *Solanum sisymbriifolium* LAM. Pharmacologyonline 3:1–5

Valarezo E, Arias A, Cartuche L, Meneses M, Ojeda-Riascos S, Morocho V (2016) Biological activity and chemical composition of the essential oil from *Chromolaena laevigata* (lam.) RM King & H. rob. (Asteraceae) from Loja, Ecuador. J Essent Oil-Bear Plan Theory 19(2):384–390

Vasudevan P, Kashyap S, Sharma S (1997) Tagetes: a multipurpose plant. Bioresour Technol 62(1–2):29–35

Vattuone MA, Soberón JR, Sgariglia MA, Quiroga EN, Sampietro DA (2013) *Zuccagnia punctata* Cav.: Phytochemistry, traditional uses and pharmacology. In: Céspedes CL, Sampietro DA, Seigler DS, Rai M (eds) Natural antioxidants and biocides from wild medicinal plants. CABI, pp 178–186

Venturi CR, Danielli LJ, Klein F, Apel MA, Montanha JA, Bordignon SA, Roehe PM, Fuentefria AM, Henriques AT (2015) Chemical analysis and in vitro antiviral and antifungal activities of essential oils from *Glechon spathulata* and *Glechon marifolia*. Pharm Biol 53(5):682–688

Vio-Michaelis S, Apablaza-Hidalgo G, Gómez M, Peña-Vera R, Montenegro G (2012) Antifungal activity of three Chilean plant extracts on *Botrytis cinerea*. Bot Sci 90(2):179–183

Wagner H, Ulrich-Merzenich G (2009) Synergy research: approaching a new generation of phytopharmaceuticals. Phytomedicine 16(2–3):97–110

Wainwright M, Maisch T, Nonell S, Plaetzer K, Almeida A, Tegos GP, Hamblin MR (2017) Photoantimicrobials-are we afraid of the light? Lancet Infect Dis 17(2):49–55

Yang CJ, Gao Y, Du KY, Luo XY (2019) Screening of 17 Chinese medicine plants against phytopathogenic fungi and active component in *Syzygium aromaticum*. J Plant Dis Prot 127:237–244

Yang SK, Yusoff K, Mai CW, Lim WM, Yap WS, Lim SH, Lai KS (2017) Additivity vs synergism: investigation of the additive interaction of cinnamon bark oil and meropenem in combinatory therapy. Molecules 22(11):1733

Zacchino SA, López SN, Pezzenati G, Furlán RL, Santecchia CB, Muñoz L, Giannini FA, Rodríguez AM, Enriz RD (1999) In vitro evaluation of antifungal properties of phenylpropanoids and related compounds acting against dermatophytes. J Nat Prod 62(10):1353–1357

Zavrel M, White TC (2015) Medically important fungi respond to azole drugs: an update. Future Microbiol 10(8):1355–1373

Zhang Z, ElSohly HN, Jacob MR, Pasco DS, Walker LA, Clark AM (2002) Natural products inhibiting *Candida albicans* secreted aspartic proteases from *Lycopodium cernuum*. J Nat Prod 65(7):979–985

Zhang L, Yan K, Zhang Y, Huang R, Bian JM, Zheng C, Sun H, Chen Z, Sun N, An R, Min F, Zhao W, Zhuo Y, You J, Song Y, Yu Z, Liu Z, Yang K, Gao H, Dai H, Zhang X, Wang J, Fu C, Pei G, Liu J, Zhang S, Goodfellow M, Jiang Y, Kuai J, Zhou G, Chen X (2007) High-throughput synergy screening identifies microbial metabolites as combination agents for the treatment of fungal infections. Proc Natl Acad Sci 104(11):4606–4611

Ziedan EHE, Farrag ESH (2008) Fumigation of peach fruits with essential oils to control postharvest decay. Res J Agric Biol Sci 4(5):512–519