Chapter 7
Antibacterial and Antifungal Plant Metabolites from the Tropical Medicinal Plants

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Abstract A wide-ranging organism, such as plants, fungi, insects, marine organisms, and bacteria are the main sources of bioactive substances. Among them, medicinal plants offer harmless elusive means to improve our health conditions. Moreover, plant-derived bioactive is an inspiration for developing several therapeutic agents having extensively diverse chemo-structures and exhibit superior biological properties like antimicrobial, anticancer, and antioxidant, anti-inflammatory properties. Hence, many of them are used in therapeutic applications to treat various human ailments. Markedly, tropical countries harbor the maximum global biodiversity and constitute several vital plant species with pharmacological potential. Hence, they are being explored for bioactive compounds, and other raw materials to manufacture herbal medicines or chemo-drugs. In the present time, the emergence of microbial resistance to conventional antibiotics has become a major threat in treating microbial infections. Further, side effects caused by classical antibiotics have forced scientists to work toward exploring novel antimicrobial agents to overcome these hitches. Phytoconstituents have been shown to have prospective antimicrobial properties against both sensitive and resistant pathogenic microbes by exerting diverse mode of action. In this chapter, the potential of tropical plant species with antibacterial and antifungal activities are reviewed in detail.

Keywords Tropical medicinal flora · Natural products · Antifungal and antibacterial activities · Plant metabolites · Phytotherapies

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7.1 Introduction

Many medicinal plants contain large amounts of bioactive compounds, such as phenolic compounds, terpenoids, nitrogen compounds, vitamins, and various other secondary metabolites that are being used for various therapeutic purposes, since the dawn of mankind (Arumugam et al. 2016; Swamy et al. 2017; Kirubakari et al. 2019). The nature is a treasure of several medications, and provides assistance in the treatment of different health issues, affecting humans. Indian, Egyptian, Roman, Chinese, and Greek traditional medicines have documented the use of herbs against numerous health problems. Currently, despite the development of medicine, technological progress, and the creation of new synthetic substances with medicinal properties, the use of natural products is gradually growing, mainly in developed countries. Thus, medicinal plants are present as an alternative in health care (Pandey and Kumar 2013; Swamy et al. 2016; Mohanty et al. 2017; Anand et al. 2019). Natural products contribute immensely to the development of numerous drug molecules having several therapeutic applications (Beutler 2009). A wide-ranging organism, such as plants, fungi, insects, marine organisms, and bacteria are the main sources of natural products. Among them, medicinal plants offer harmless elusive means to improve our health conditions. Moreover, plant-derived bioactives are an inspiration for developing several therapeutic agents having extensively diverse chemo-structures and exhibit superior biological properties like antimicrobial, anticancer, antioxidant, and anti-inflammatory properties. Hence, many of them are used in therapeutic applications to treat various human ailments (Swamy et al. 2016; Kirubakari et al. 2019).

In this context, the tropical region is home to almost a third of the world's flora represented in many different biomes with exuberant biodiversity (Brooks et al. 2002; Sobrinho et al. 2014). However, even in the face of the vast biodiversity and even having great potential for study and knowledge of new perspectives on the issue of genetic resources, the environmental degradation and the intrusion of new cultural elements accompanied by the breakdown of traditional life systems threaten, in addition to a collection of empirical knowledge, the heritage invaluable genetics for future generations (Chazdon 2019). Therefore, it is essential that scientific and technological innovation provides advances in order to add value to the products of the tropical biodiversity, and we can make use of these assets ensuring the sovereignty and vanguard of our nations.

At present, microbial infections due to pathogenic microbes, in addition to their resistance to conventional antibiotics are posing a major challenge and threatening the health of humans and other animals. Globally, microbial infections cause millions of human demises, and are increasing every year (Rudramurthy et al. 2016; Khameneh et al. 2019). Bacterial and fungal infections, in general, have increased significantly at an accelerated rate. They are being considered as a wide public health problem that affects the whole world, affecting countless people. Due to this advancement, it is necessary to put aside many conventional methods of combating such diseases, which are often not having the expected effect, and to seek new

sources or methods that can significantly affect these infections (Swamy and Rudramurthy 2016; Anand et al. 2019; Kirubakari et al. 2019). Plant-derived bioactives are known to be relatively safer compared to the presently available antibiotic agents. Further, phytocompounds exert numerous tonic advantages linked with their extraordinary effectiveness. Various plant metabolites have demonstrated synergistic bioactivity when combined with antibiotic agents against several multi-drug resistant pathogenic microbes. These plant metabolites comprise phenolics, flavonoids, alkaloids, tannins, terpenoids, and many more (Arumugam et al. 2016; Mohanty et al. 2017; Shin et al. 2018; Kirubakari et al. 2019).

In view of these aspects, the discovery of new active substances from natural sources is the most priority to researchers, considering several advantages. The pharmacological potential of medicinal plants occurring in the Tropical region has attracted to develop novel antimicrobials (Calixto 2019). Further, side effects caused by classical antibiotics have forced scientists to work toward exploring novel antimicrobial agents to overcome these hitches. Phytoconstituents have shown to have prospective antimicrobial properties against both sensitive and resistant pathogenic microbes by exerting diverse mode of action. In this chapter, the potential of tropical plant species with antibacterial and antifungal activities is reviewed in detail.

7.2 Target for Antimicrobial Agents and Resistance Mechanisms

Microbial infections are affecting the lives of several thousands of populaces around the globe, and are accounted for a major cause of human deaths. Nearly 17% of total deaths in the year 2013 were because of microbial infections. Further, microbes are evolving toward resistance to existing antimicrobials, making the present way of treating pathogens less effective. In recent times, clinically pathogenic bacteria and fungi are being classified on the basis of microbial resistance to either a single or multi-drug. Majorly, microbial resistance is due to many reasons, including overdose, misuse, and continuous use of antibiotics (Swamy and Rudramurthy 2016; Rudramurthy et al. 2016; Khameneh et al. 2019). On the other hand, bacterial resistance has become an increasing health problem with great impact on the pharmaceutical industry, as many antibiotics have become resistant. More recently, different approaches are being recommended to overcome the multi-drug-resistance mechanisms by pathogenic microbes. One such endorsed approach is the combination therapy, involving two or more molecules with the weakened antibiotics (Inui et al. 2007; Kirubakari et al. 2019). These molecules can be other than antibiotic drugs having antibacterial potentials, for example, phytochemicals. Particularly, these molecules function either individually or together with antibiotic drugs to improve the antimicrobial property, and thus can be very effective against wide-ranging bacterial pathogens (Khameneh et al. 2019).

This approach effectively restores the desired antimicrobial property (Brown 2015; Fazly Bazzaz et al. 2018; Rana et al. 2018).

Antimicrobial agents exhibit their actions through various ways, including the interfering with the biosynthesis or inhibiting bioactivities of bacterial components. The established targets for antibiotics may include (a) biosynthesis of bacterial proteins; (b) biosynthesis of bacterial cell wall; (c) damage of bacterial cell membrane; (d) interfering with bacterial DNA replication and/or repair mechanisms, and (e) suppressing metabolic pathways. Some classes of antibiotic drugs like tetracyclines, macrolides, and aminoglycosides exhibit their antibacterial properties, which particularly inhibit protein biosynthesis via targeting the ribosomal subunits (Swamy et al. 2016; Khameneh et al. 2019). A protein is generally synthesized inside the cells by several means of the molecular processes, including initiation, elongation, termination, and assembly of protein-mediated by ribosomes. Hence, bacterial pathogens can be targeted by inhibiting the actions of ribosomes and affecting protein synthesis (Walsh 2003). Further, some antibiotics can modify the permeability of the bacterial exterior cell membrane, and later disrupt the structural alterations of cell membrane, leading to a rapid bacterial death by creating osmotic imbalances. The polymyxin class of antibiotics attach to the lipid A constituent of lipopolysaccharide, and results to cause cell membrane structural modifications (McBain et al. 2003; Tenover 2006). Several classes of antibiotics inhibit cell wall synthesis. Bacterial cell wall has covalently cross-linked strands of peptide and glycan, and can be responsible for increased mechanical strength, and prevents cell lysis due to osmotic pressure. The enzymes transglycosylases and transpeptidases are responsible for forming this layer. Antibiotics such as penicillins and cephalosporins are shown to target the cell wall assembly, and exhibit bactericidal properties. Antibiotics such as vancomycin is proved to, particularly disrupting the peptidoglycan layer, and weaken the cell wall structure to result in bacterial cell death (Schneider and Sahl 2010). The DNA gyrase enzyme is accounted to perform the uncoiling and supercoiling of DNA strands, and controls DNA replication process. Thus, targeting this enzyme can be another target for antibacterial drugs/antibiotics. The antibiotics, ciprofloxacin (a fluoroquinolone), and nalidixic acid suppress the replication of DNA by attaching to DNA Gyrase enzyme bound DNA complex (Maxwell 1997). Bacteria might exhibit drug-resistance property to one or more antibiotics via different types of mechanisms. The resistance property may vary from one bacterial species to another and to different classes of antimicrobial agents. So, knowing about the resistance mechanisms exhibited by bacterial strains can be very useful in designing novel antibacterial drugs (Walsh 2003; Tenover 2006; Khameneh et al. 2016).

Noteworthy to mention here that the drug-resistance could be linked to a single or more types of mode of actions together (Fig. 7.1). Some of the major proved mechanisms of antibacterial drug-resistance by bacteria includes the destruction of the antibiotic drugs by producing damaging enzymes, modifying antibiotic drugs by secreting modifying enzymes, stimulation of efflux pumps, and changing the structure of target in the bacterial cells, so that it will have less affinity for recognizing antibacterial agents (Khameneh et al. 2016; Munita and Arias 2016; Peterson

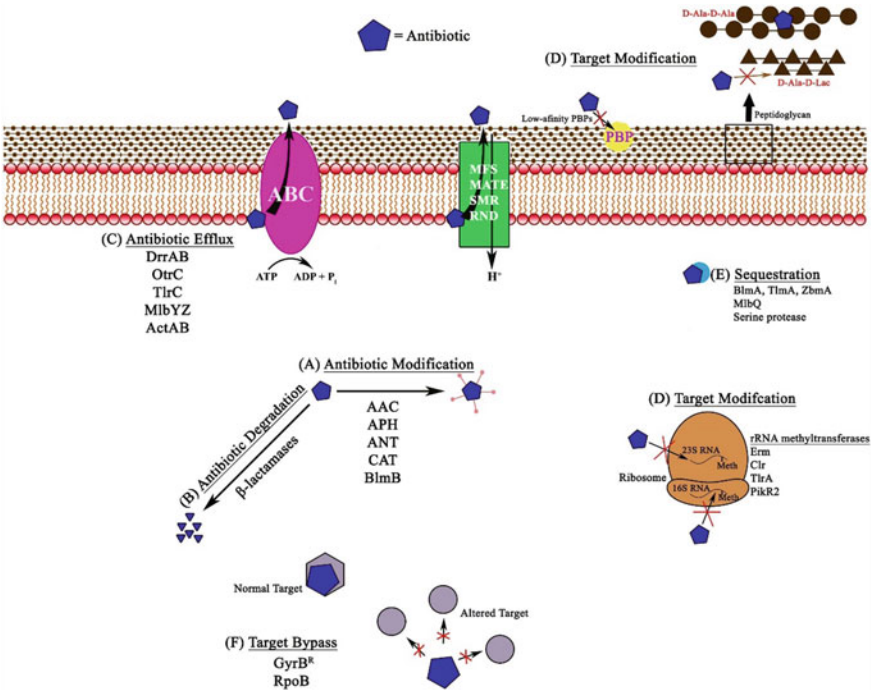

Fig. 7.1 Schematic representation of different antibiotic resistance mechanisms in bacteria, shown with examples. **A** Antibiotic modification involves the addition of acetyl, phosphate, or adenyl groups to aminoglycosides by *N*-acetyl transferases (AAC), *O*-phosphotransferases (APH), and *O*-adenyltransferases (ANT). Other examples include chloramphenicol acetyl transferases (CAT) and bleomycin *N*-acetyltransferases (BlmB). **B** Antibiotic degradation is observed with β-lactamases, which hydrolyze the antibiotic. **C** Antibiotic efflux pumps remove the antibiotic from the cell using energy from ATP hydrolysis in ABC pumps like DrrAB, OtrC, TlrC, and MlbYZ, or proton gradients in MFS, MATE, SMR, and RND family pumps. **D** Target modification includes various target alterations, such as 23S rRNA or 16S rRNA methylation, alterations in the peptidoglycan precursors (for example, in the case of glycopeptides), or synthesis of alternate low-affinity targets (PBPs) that reduce or completely block antibiotic (penicillins) from associating with the target. **E** Antibiotic sequestration involves proteins that can associate with the antibiotic and block them from reaching their targets. **F** Target bypass involves generation of additional antibiotic targets or subunits that are not susceptible to binding of the antibiotic. Meth, methylation (Adapted from Peterson and Kaur 2018)

and Kaur 2018; Khameneh et al. 2019). In general, antibacterial drugs will be more effective at definite concentrations and after it reaches to the precise site of action. Efflux pumps may function by acting as an efflux or transfer system, where antibacterial drugs are quickly pushed out of cells than the time required for drug molecule to get diffused into the bacterial cell. This condition will subsequently lead to a condition, where the intra-bacterial concentration will be much lesser as compared to the concentration required for effective actions. For instance, the cytoplasm consists of ribosomes required for proteins. When protein synthesis

inhibitors, including antibiotics are treated, they are enforced to pass through the cell membrane, and later accumulate at a higher level to inhibit protein synthesis (Levy 1992; Paulsen et al. 1996; Munita and Arias 2016; Shriram et al. 2018). A wide range of pathogenic bacterial species, including *Staphylococcus aureus*, *Acinetobacter baumannii*, *P. aeruginosa*, in addition to fungal species, *Candida albicans* show antibiotic resistance through this mechanism. Efflux pumps can eliminate the antibiotic agents from bacterial strains, for example, trimethoprim and fluoroquinolones resistance in *Pseudomonas aeruginosa*. Further, making use of efflux pump inhibitors along with antibacterial drugs could be a better option of treatment in overcoming the threatening microbial infections due to multi-drug resistant microbes (Blair et al. 2015; Munita and Arias 2016; Khameneh et al. 2019). The structural modifications of porins (protein channels) can control the diffusion of intracellular molecules, including antibiotics. Through this way, few bacterial strains prevent the antibiotics influx by altering the structure of porins, and also membrane permeability to exhibit resistance mechanism. This mechanism of antimicrobial resistance is mediated by several microbes, including gram-negative pathogenic *Pseudomonas* spp. and *Acinetobacter* spp. (De et al. 2001; Vila et al. 2007; Pages et al. 2008). Bacterial species belonging to Enterobacteriaceae can degrade the β-lactam antibiotics (cephalosporins, penicillins, and carbapenems) (Olsen et al. 2015; Blair et al. 2015). *P. aeruginosa* produces modifying enzymes that destroy or alter the structure of antibiotics, including chloramphenicol and fosfomycin (Munita and Arias 2016; Khameneh et al. 2019). In addition, a study carried out with α-Bisabolol isolated from *Matricaria chamomilla* L in single and complex form with β-Cyclodextrin as TetK and NorA efflux pump inhibitors in *Staphylococcus aureus* strains. α-Bisabolol potentiated the action of tetracycline and reduced the MIC of norfloxacin to a clinically relevant concentration. The complexed substance showed synergism; however, the effect of the isolated α-Bisabolol was superior to the complex. These results indicate α-Bisabolol is a potential substance to be used as an efflux pump inhibitor (Cruz et al. 2020).

The continued use of medicinal plants and the empirical knowledge of the communities about them has aroused interest in pharmacological research related to plants. Many botanical families are being studied with the purpose of finding biochemical substances in these plants against bacteria and fungi that are resistant to multiple drugs that are currently available in the market. The combination of traditional knowledge about medicinal plants, together with technology and science has enabled countless advances in research, aimed at the search for new alternatives in the treatment of bacterial and fungal infections. Of the native families of the tropical flora, the family Myrtaceae, Asteraceae, Piperaceae, Lauraceae, Verbenaceae, Lamiaceae, among many others stand out to be very important. These tropical plants solvent extracts, decoctions or crude extracts and essential oils have been researched extensively in relation to their bioactive potentials.

Due to the difficulty in the treatment of multi-resistant bacteria, it is notoriously necessary to find new substances that have antimicrobial actions to be used in the combat of these microorganisms. In this context, photodynamic therapy emerges as a new alternative in this scenario. *Light Emitting Diodes* (LED) has been a very

promising resource, although infrequent in clinical practice, but it has already proven to be very effective in antibacterial action (Gwynne and Gallagher 2018). It is characterized by producing an absolutely safe irradiation power, consumes little energy, extremely long-life span, good power, and low intensity. Macedo da Silva et al. (2020) reported antibiotic-modulating activities of the essential oils of *Eugenia brasiliensis* Lam and *Piper mosenii* C. DC singly or in association with blue LED (Light-emitting diode) light. They concluded that the association of aminoglycosides with the blue LED light and essential oils represents an effective modulatory potential against resistant bacteria such as multi-resistant strains of *Escherichia coli* and *Staphylococcus aureus*. *Piper aduncum* essential oil was evaluated in a modulatory experiment associated with blue LED light. The combination of volatile oil with antibiotics showed synergistic effect against S. aureus and *E. coli* which was potentiated in the presence of blue LED. The results obtained in this study showed that the essential oil obtained from *Piper aduncum* interferes with the action of antibiotics against bacteria exposed to blue LED (Barbosa et al. 2018).

7.3 Tropical Plants with Relevant Antibacterial Activities

Due to increased bacterial resistance to multiple drugs, antimicrobials arise to concern and the search for new alternatives therapeutic plants, with medicinal plants representing an important source to obtain these medicines. The antimicrobial activity of extracts and oils essential of medicinal plants has been proven in several studies conducted in countries that have a diversified flora (Lautié et al. 2020). In South America, with a wide variety of medicinal plants, research showing that these may be sources of antimicrobial substances has been frequently reported in recent years (Spézia et al. 2020). According to Michelin et al. (2005), plant antibiotics have a chemical structure that differs from that of antibiotics derived from microorganisms, and may regulate the intermediate metabolism of pathogens, activating or by blocking reactions and enzymatic synthesis or even changing the structure of membranes. However, since the advent of antibiotics, the use of plant derivatives as antimicrobials has been little explored (Cowan, 1999).

The acquisition of resistance to antimicrobials is a phenomenon genetic, related to alteration of genes contained in micro-organisms, which codify different biochemical mechanisms that impede the action of drugs, These mechanisms of action can be interference with cell wall synthesis; inhibiting protein synthesis; interfering with nucleic acid synthesis; decreasing permeability to the antimicrobial agent; and destructing the structure of the cell membrane (Tenover 2006). Bacterial resistance can arise by acquisition of mutations or by acquisition of genetic material from other bacteria. Genes encoding proteins involved in resistance mechanisms can be located on the chromosome or on extra-chromosomal elements, such as plasmids and transposons, which move easily from one strain to another, from one species to another, or even from one genus to another (Sultan et al. 2017). Despite the

availability of new antibiotics, bacterial resistance occurs at an increasingly rapid rate in the different Gram positive and Gram and represents a major therapeutic challenge (Hayes et al. 2020). In recent decades the focus given to the control of bacterial infections, may have contributed to the emergence of bacteria multi-drug resistant, mainly methicillin-resistant Staphylococcus, Penicillin, and erythromycin-resistant *Pneumumococcus*, *Enterococcus* resistant to vancomycin and also *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* resistant to β-lactams and carbapenens (Ventola 2015).

Considering the increase of multi-resistant bacteria due to the use of antimicrobial agents, The World Health Organization (WHO) has recognized the importance of the potential therapeutic power of plants, and that the associated use of medicinal plants and/or their by-products with antimicrobial drugs can inhibit or intensify the therapeutic effect of conventional medicines. In this context, we can observe some advancements with the products from some species (Table 7.1), which are already used in the medical clinical routine as antibacterial herbal medicines.

7.4 Synergisms of Phytochemicals and Conventional Antimicrobial Drugs

Research into natural products with modulating properties has been widely disseminated. Many of these plant products have considerable synergistic effects, positively altering the effect of antibiotics and providing an important alternative to combat increased microbial resistance. The synergistic effects that are usually obtained by associating natural products with antibiotics are related to the increase in the influx of the drug, which alters the permeability of the cell membrane, favoring the penetration of antibiotics and potentiating their effect. Thus, studies on the association of natural products and synthetic drugs are still promising in an attempt to discover new chemical classes with antibiotic potential (Cheesman et al. 2017; Khameneh et al. 2019).

Increasing microbial resistance to existing drugs is a problem that is a serious health issue, and therefore there is a pressing need to look for new classes of antibacterial substances, especially from natural sources. A therapeutic alternative for the treatment of micro-organisms resistant to antibiotics is the use of plant extracts. There are many advantages in using antimicrobial compounds from medicinal plants, as fewer side effects, better patient tolerance, more economical, better acceptance due to long history of use, and being renewable because it is available in nature (Parekh and Chanda 2007). Unlike synthetic drugs, antimicrobials of plant origin are not associated with side effects and have a large therapeutic potential for many infectious diseases (Chanda et al. 2010; Habbal et al. 2011). Numerous studies have proven the antimicrobial activity in vitro plant. However, the problem of drug resistance continues to grow. Thus, the need of the moment is

Table 7.1 Some of the plant products with antimicrobial activity

Common name	Scientific name	Compound	Active against	Dosage form
Aloés	*Aloe vera* (L.) *Burm.f*	Alloin	Bacteria	Capsule 60 mg
Barberry	*Berberis vulgaris*	Berberine	Bacteria, protozoa	Soft gel 1000 mg
Black pepper	*Piper nigrum*	Piperine	Fungi, lactobacillus, micrococcus	
Calêndula	*Calendula officinalis*	Triterpenoids	Bacteria, fungi	Tinture
Canela da índia	*Cinnamomum zeylanicum*	Eugenol	Bacteria, fungi,	extracts 250 mg and 500 mg
Burdock	*Arctium lappa*	Tannins	Bacteria, fungi, viruses	Capsule 475 mg
Caraway	*Carum carvi*	Carvone, Limonene	Bacteria, fungi, viruses	Capsule 1000 mg
Cascara sagrada	*Rhamnus purshiana*	Tannins	Bacteria, fungi, viruses	Capsule 425, 450 mg
Chamomile	*Matricaria chamomilla*	Anthemicacid	M. tuberculosis, S. typhimurium, S. aureus	
Clove	*Syzygium aromaticum*	Eugenol	General	Capsule 500 mg
Cranberry	*Vaccinium spp.*	Fructose	Bacteria	Capsule 500 mg
Croton	*Crotonspp*L	proanthocyanidinsand/ oralkaloids	General	Teaandpills
Erva de Carpinteiro (mil folhas)	*Achillea millefolium* L	Lactones	Bacteria	extracts
Eucalyptus	*Eucalyptus globulus*	Tannin	Bacteria, viruses	Inhalerand tablet
Garlic	*Alliumsativum*	Allicin, ajoene	General	Tablet
Ginger	*Zingiber officinale*	Gingerol	Bacteria	Capsule 100 mg
Goldenseal	*Hydrastis canadensis*	Berberine, hydrastine	Bacteria, Giardiaduodenale	Solution, 500 mg per dosage
Green tea	*Camelliasinensis*	Catechin	General	
Grumixama	*Eugenia brasiliensis*	Tannin	General	An infusion of 10 g of leaves or bark in 300 ml water
Licorice	*Glycyrrhiza glabra*	Glabrol	S. aureus, M. tuberculosis	Capsule 450 mg
Mentha	*Mentha L*	Menthol	General	Infusionandtinture

(continued)

Table 7.1 (continued)

Common name	Scientific name	Compound	Active against	Dosage form
Oak	*Quercus rubra*	Tannins		Capsule 500, 650 mg
	Allium cepa	Quercetin		
Onion	*Allium cepa*	Allicin	Bacteria, Candida	
Oregon grape	*Mahonia aquifolia*	Berberine	Plasmodium	Capsule 500 mg
Pata de Vaca	*Bauhinia L*	Ellagicacid	Bacteria	Infusion/decoction: 2–3 cups of tea a day, preferably after the meals
Romã	*Punica granatumLinn*	peletierina, isopeletierina, methylpeletierina	Fungi—Candida	Infusion, decoction
Salvia	*V. curassavica*	α-Humuleno	Bacteria Fungi	Tinture
Senna St. John's wort	*Hypericum perforatum*	Hypericin, others	General	Table 450 mg
Thyme	*Thymusvulgaris*	Caffeicacid	Viruses, bacteria, fungi	Capsule 450 mg
Turmeric	*Curcuma longa*	Curcumin, Turmericoil	Bacteria, protozoa	

Adapted from Khameneh et al. 2019

to develop useful or new antimicrobial agents' ways to treat the resistant microorganism (Negi and Dave 2010). In that case, a new form of therapy would be the use of the combination of synergistic antimicrobial therapy between antimicrobial agents known and bioactive plant extracts. The combination therapy between plant extracts and antibiotics can expand the antimicrobial spectrum, prevent the emergence of mutant resistance, and minimize toxicity. Sometimes the use of a single antibiotic does not produce the inhibitory effects desired effectiveness, but a combination of drugs often has an effect synergistic that surpasses your individual performance. The synergistic effect can be due to the formation of the right complex that becomes more effective in inhibiting a particular species of microorganism, either by inhibition of the synthesis of the cell or causing its lysis or death (Chanda and Rakholiya 2011). Thus, the most economically viable combination of natural products associated with available antibiotics shows as an alternative, since the synergistic effect between the two can provide an increased antibacterial activity against sensitive and resistant microorganisms. Therefore, the potentiated effect of these associations can serve as a new infection treatment strategy, enabling drug use antimicrobial when it alone is not effective on certain bacterial strains. The association of extracts from various plants with ampicillin, chloramphenicol, and tetracycline against sensitive bacteria (*S. aureus, Salmonella*

choleraesuis, P. aeruginosa, Bacillus subtilis, Proteus spp) and resistant bacteria isolated from hospital environment (*K. pneumoniae, Shigella spp, Proteus spp, P. aeruginosa, Enterobacter aerogenes, E. coli and S. aureus*) showed that in some cases it occurred synergism enabling already ineffective antibiotics to act on these bacteria (Liu et al. 2017).

7.5 Antibiotic Resistance—Combination Therapy (Antibiotic + Phytochemical/Plant Extract)

It is estimated that the herbal medicine market moves up to US$ 300 billion around the world and the traditional pharmaceutical market is growing at an annual rate of 3% to 4% worldwide, while that of herbal medicines rises from 6 to 7% (Calixto 2019). On the other hand, the World Health Organization (WHO) recognizes the importance of the therapeutic potential of plants, but does warnings about improper use and preparation, and recommends caution if they consider the lack of knowledge about possible side effects with a joint administration of prescribed drugs. In any case, what occurs in most societies today is a complementarity between allopathy and the use of medicinal plants. In recent years and in most developing countries, people have resorted to self-medication, which has often led to increased microbial resistance to the drug. However, the trend in drug discovery is gradually returning to natural products because of the constant development of microbial resistance to synthetic drugs. The large-scale use of antibiotic therapy in recent decades is largely a result of the aging process, which influences the increase of infections associated with chronic age-related diseases such as metabolic, cardiovascular, and neoplastic diseases. These conditions are often associated with oxidative stress and act directly on the global pharmaceutical burden. Resistance to antimicrobials represents a growing challenge for modern science. Especially in a hospital environment, the use of powerful, broad-spectrum antibiotics, inadequate or sub-therapeutic treatment, as well as the lack or deficiency of preventive measures contribute to the development of resistance to these drugs. To this end, strategies that prolong the effectiveness of currently available antibiotics, encourage their rational use and reduce or avoid the spread of multi-drug-resistant microorganisms (MDRs) are sought. Understanding the mechanisms of antibiotic resistance is a fundamental step toward the discovery of effective therapeutic measures (Rice 2018; Yelin and Kishony 2018).

Extracts from *Piper* species have been reported to be effective against Gram-positive and Gram-negative bacteria and could be a potential lead to the discovery of new antimicrobial drugs (Mgbeahuruike et al. 2017; Salehi et al. 2019). Antimicrobial photodynamic therapy has grown considerably in recent decades as an effective and inexpensive alternative. *Piper aduncum* is popularly known as monkey pepper with antibacterial activity. This study aimed to evaluate the antibacterial and modulatory activity of *Piper aduncum* essential oil (EOPad)

associated with blue LED light, which was exposed to the LED for 20 min. The Germacrene A was identified as the main component. The OEPad presented MIC $\geq$ 1024 μg/mL against S. aureus and E. coli. The combination of EOPad with antibiotics showed synergistic effect against S. aureus and *E. coli* which was potentiated in the presence of blue LED. The results obtained in this study showed that the essential oil obtained from *Piper aduncum* interferes with the action of antibiotics against bacteria exposed to blue LED (Barbosa et al. 2018).

The antimicrobial potential of leaf of *Piper caldense* essential oil was investigated, and its potential was investigated. The minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC) was determined. Besides the essential oil was also tested as a modulator for several antibiotics, and its effect on the morphology of *Candida albicans* (CA) strains was also investigated. The essential oil modulated the activity of fluconazole against CA URM 4387 strain, which was demonstrated by the lower IC_{50} obtained, 2.7 μg/mL, whereas fluconazole itself presented an IC50 of 7.76 μg/ml. No modulating effect was observed in the MFC bioassays. The effect on fungal morphology was observed for both CA INCQS 40,006 and URM 4387 strains. The results demonstrated that the oil has potential as an adjuvant in antimicrobial formulations (Bezerra et al. 2020).

A study was carried out with essential oil from the fresh leaves of *Hyptis martiusii* to investigate the modulating activity in association with different antibiotics against the bacteria *Staphylococcus aureus, Escherichia coli,* and *Pseudomonas aeruginosa*, and to evaluate the cytotoxic activity of the species. The research has shown that the essential oil of *Hyptis martiusii Benth* (OEHM) leaves presents synergism only in association with gentamicin antibiotics and imipenem against the bacteria *Pseudomonas aeruginosa* and *Escherichia coli*. However, it presents antagonism in association with amikacin, gentamicin, and imipenem against the three bacteria studied. Apart from ciprofloxacin, no relevant results were demonstrated. In relation to the cytotoxic activity, the mean lethal concentration (lc50) exposed a value of 263.12 μg/ml. The results reveled that *H. martiusii* presents synergistic cytotoxic activity against the evaluated bacteria (Figueiredo et al. 2018).

A study carried out by Ferreira et al. (2019) identified the chemical composition of the *Senna spectabilis* species, and they analyzed the antimicrobial potential in vitro and its modulating effect on antibiotic activity. The antibiotics used in the experiment were aminoglycosides (amikacin and gentamicin), lincosamides (clindamycin), cephalosporins (cephalexin), and azithromycin. The *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa,* and *Salmonella enterica* strains were used in this approach. The results have shown that the antimicrobial action of the extract of *S. spectabilis* is only regular; however, in modulation, the extract in combination with the tested antibiotics showed a synergistic effect against most of the tested bacteria, potentiating the effect of the antibiotics used.

Ferreira and Costa evaluated the antimicrobial activity of ethanolic extracts of *Banisteriopsis anisandra* (Malpighiaceae) and drug interactions with drugs widely used in the field of oral health. They obtained the leaf extract and performed serial dilutions, which were tested against *Candida albicans* (ATCC 10,231),

Streptococcus mutans (ATCC 25,175), *Streptococcus salivarius* (ATCC 7073), and *Staphylococcus aureus* (ATCC 6538). As positive control, antibiotics ampicillin (10 μg/ml), amoxicillin (10 μg/ml), and penicillin (30 μg/ml) were used for bacterial strains; and the antifungal ketoconazole (2 mg/ml), for yeast. There was a positive drug interaction of the extracts with antibiotics and ketoconazole in concentrations of 1: 2 for the extract. The extract of *B. anisandra* has an antimicrobial potential and drug interaction with drugs related to oral health. Studies on the pharmacological properties of the species in question are rare and the results are the first reports on its antimicrobial activity in association with antibiotics and antifungals.

The positive results found not only in these reported studies, but also in countless other studies, with different species increasingly show the importance of the search for new metabolites that can help and reinforce drugs that no longer play the role of eliminating pathogenic microorganisms.

7.6 Essential Oils with Antimicrobial Activity from Tropical Medicinal Plants

In nature, EOs play an important role in providing plant protection against pathogenic bacteria, viruses, and fungi and preventing the attack by insect pests. In addition, EOs can attract or repel insects when present in pollen and seeds. To protect chemical compounds' ecological equilibrium, the use of EOs in pharmaceutical, food, bactericidal, and fungicidal is becoming more prevalent in recent times (Swamy et al. 2016). EOs yielding medicinal and aromatic plants are normally native to warm countries, where they represent an important traditional pharmacopeia.

Apiaceae, Lamiaceae, Myrtaceae, Poaceae, and Rutaceae families are of particular importance for medicinal applications. For example, some of the EOs, like anise, caraway, black caraway, clove, oregano, cumin, coriander, sage, basil, dill, lemon balm, peppermint, thyme, and tea oils, already have widespread medicinal applications. Some of the essential oil containing plant families, like Liliaceae, Fabaceae, Pinaceae, Piperaceae, Cupressaceae, Asteraceae and Hypericaceae, also exhibit a considerable medicinal potential.

The Apocynaceae family is considered to be dicotyledonous characterized usually by the presence of latex, consisting of about 155 genus and 2000 species, with distribution in Tropical and Subtropical regions (Lorenzi 1998). This family can be considered one of the most important plant sources of chemical constituents with therapeutic utility in modern medicine. The most important genres in this family are *Alstonia, Aspidosperma, Vinca, Tabernaemontana, Mandevilla, Hancornia, Nerium, Strophantus, Catharanthus, Allamanda, Thevetia, Wrightia, Plumeria, Himatanthus* and *Rauvolfia*. The Apocynaceae family is chemically characterized by structures alkaloids mainly monoterpenic. Several indolic alkaloids have already been isolated

from this family, especially from the Aspidosperma and Geissospermum genus (Ekalu et al. 2019). In addition to representatives with numerous medicinal properties, the family Apocynaceae is an important source of economic resources. Rubber is derived from the latex of several species, markedly inferior in quality to that of the extracted from *Hevea brasiliensis* (Willd. ex A. Juss.) Müll. Arg. the rubber tree. At African countries and indigenous peoples of South America, toxic species are used to poison arrows in animal hunting and fishing. Other species provide excellent quality wood for the manufacture of furniture such as case of the genus Aspidosperma, whose most common representative is *A. peroba Allemão* ex Saldanha, known as "peroba-rosa" (Baratto et al. 2010).

The therapeutic potential of the *Himatanthus drasticus* (Mart.) Plumel, Apocynaceae was assayed. This specie presents triterpene-rich fraction which the anti-inflammatory activity is mediated by NF-alpha, iNOS, COX-2 and NF-kB (Almeida et al. 2017). The essential oil of *Mikania cordifolia* and its major constituent limonene was investigated alone or associated against *Pseudomonas aeruginosa, Escherichia coli,* and *Staphylococcus aureus*. The antibiotic-modulating activity was determined in combination with conventional antibacterial drugs. The results demonstrated no relevant antibacterial activity; however, a modulatory effect was observed against *P. aeruginosa*, presenting synergistic effects when associated with gentamicin and norfloxacin. In addition, the oil reduced the MIC of norfloxacin against *E. coli* as well as reduced the MIC of gentamicin against *S. aureus*. The best effect of limonene was obtained against S. aureus. It is possible to conclude that the *Mikania cordifolia* essential oil and the isolated compound limonene modulate the action of antibiotics against MDR bacteria (Araújo et al. 2020). The essential oil bacterial pathogens action is associate to capacity to destabilize the cellular machinery, leading to breakdown of membrane wall, disrupting many cellular activities including energy production and membrane transport. The lipidic components of essential oils induce membrane rupture leading to leakage of cellular components and loss of ions (Fig. 7.2) (Swamy et al. 2016; Tariq et al. 2019; Basavegowda et al. 2020).

7.7 Plant-Derived Natural Products with Antifungal Activity

The resistance of microorganisms to therapeutic agents currently used has caused economic and social impact. Fungal resistance has been somewhat neglected when compared to the great repercussion that bacterial resistance has reached. One is strictly related to the other, since the intensive use of antibacterial antibiotic therapy reduces competitiveness in human biota and favors the growth of yeasts of *Candida spp*. which in due course change from diners to pathogens. In addition, other factors contribute to increased resistance, such as the significant increase in the number of immunosuppressed patients and the prolonged use of surgical devices, considered resistance drives.

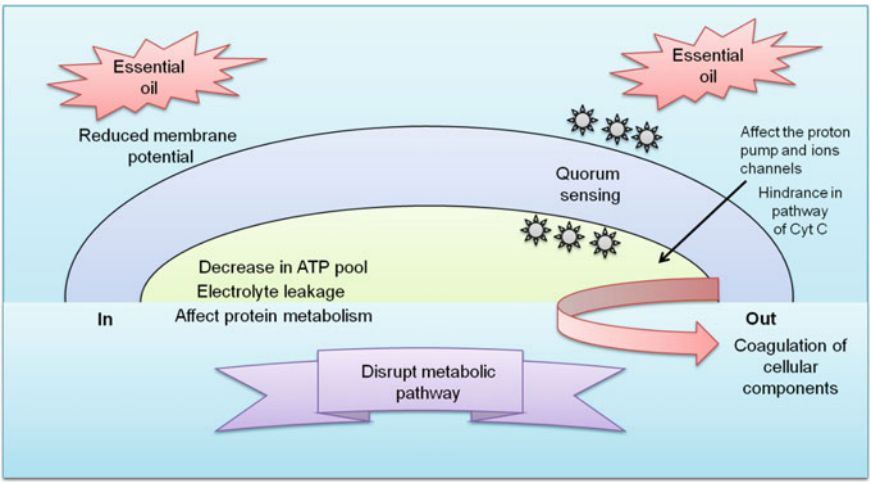

Fig. 7.2 Antimicrobial mechanisms of essential oils on microbes (Adapted from Swamy et al. 2016)

Infections caused by *Candida spp*. have shown a high level of incidence, where *Candida albicans* and *Candida tropicalis* stand out, with notoriety for the former, as agents capable of causing invasion. Their virulence factors provide adaptability, since they allow the fulfillment of important criteria for survival, such as having tolerance to high temperatures and invasive potential, promoting lysis and absorption of human tissues and resisting immunological defenses. The current context requires searches for bioactive substances with antifungal potential. New therapeutic agents may be contained in plants and consequently, their extracts and essential oils may serve as subsidies for in-depth studies and research that contemplate and target the formulation of new drugs. Research has been conducted to promote the combination of commercial drugs, for which resistance phenomena have already been verified, with natural products in the form of extracts, fractions, essential oils or isolated constituents, in an attempt to circumvent the resistance of *Candida spp*.

Recently, a medicinal plant *Mesosphaerum suaveolens* aqueous extracts of leaves (AELMs) and aerial parts (AEAPMs) was evaluated against strains of the genus *Candida*. The modulatory effect was observed with the drug fluconazole. The AELMs have shown good results since modulated fluconazole activity decreased fluconazole's IC50 from 7.8 μg/mL to an IC50 of 4.7 μg/mL (CA LM 77 strain) and from 28.8 μg/mL to 18.26 μg/mL (CA INCQS 40,006 strain) for the *C. albicans* strains. For the *C. tropicalis* LM 23 strain, the AEPMs obtained an IC50 of 25 μg/mL and the AELMs an IC50 of 359.9 μg/mL. The AEAPMs as well as the AELMs presented clinically relevant activities for *C. tropicalis* strains (Costa et al. 2020).

A modulatory effect of *Psidium guajava* L., (known as goiaba) an important medicinal plant found in tropical regions, was assayed against *Candida albicans*, *Candida tropicalis* and *Candida krusei* in association with fluconazole. The synergistic effect varied from 925.56 to 1.57 μg/mL. The flavonoid and tannic fractions, rich in phenolic compounds, potentiated the action of Fluconazole, reducing its concentration and impeding morphological transition, one of the virulence factors of the genus (Bezerra et al. 2018).

7.8 Fungal Resistance and Modulatory Potential of Extracts, Fractions and Essential Oil from Tropical Medicinal Species

The involvement of fungal infections in humans has gained prominence in recent years, and among the most common fungi infections, those of the genus Candida stand out, being among the species causing opportunistic infections. This is justified by the fact that they are very well adapted to the human body, being able to colonize it without producing signs of disease under conditions of physiological normality. However, they can become pathogenic in immunosuppressed patients, generating infections that are difficult to diagnose and are associated with high mortality and morbidity. As for clinical manifestations, we can divide them into cutaneous, systemic, and allergic. The treatment of these pathologies is performed with synthetic drugs with systemic action such as amphotericin B, fluconazole, itraconazole, voriconazole and echinocandins, azoles being the most used, due to their low cost and low toxicity.

The availability of antifungal agents for the treatment of systemic infections is somewhat reduced, becoming a problem with multi-drug resistant yeasts. In addition, one of the stalemates today is resistance to antifungals and difficulties in effective treatment. As a way to ease this resistance and difficulty in treatment, medicinal plants are strongly used by the population for the treatment of infections, and this fact has aroused interest from several research centers for the study of this activity, with the aim of isolating new molecules with antimicrobial activity.

Natural plant products have been evaluated not only for their direct antimicrobial activity, but as a modification agent of resistance to antifungals, which can be a synergistic or antagonistic effect. Thus, the associated use of medicinal plants or their derived compounds may interfere, inhibiting or intensifying the therapeutic effect of conventional antimicrobials. In this context, the synergistic effect of *Piper mikanianum* essential oil species rich in safrole was investigated against *Candida* strains. An interesting result was observed where the oil was combined with gentamicin against the multi-drug resistant *E. coli strain* and also associated with fluconazole against fungal strains. The oil presented a fungistatic effect. The *P. mikanianum* essential oil has shown an inhibitory effect of one of the main virulence factors of the Candida genus, morphological transition, which has been

previously shown to be responsible for causing invasive infections in human tissues (Carneiro et al. 2020). The mechanism can be associate with membrane potential across cell wall and disrupt ATP assembly, leading to cell wall damage. Essential oils can also disintegrate mitochondrial membrane interfering with the electron transport system (ETS) pathway (Tariq et al. 2019). Several species of Asteraceae are producers of essential oil of commercial importance. The genus *Baccharis* is represented by more than 500 species, distributed predominantly in South America. In Brazil, 120 species are described, distributed in greater concentration in the South Region of the country (Giuliano 2001). This genus produces many secondary metabolites, and in general, the compounds that stand out the most are flavonoids and terpenoids, especially monoterpenes, sesquiterpenes, diterpenes and triterpenes (Trombin-Souza et al. 2017).

Recent studies have shown the biological activities of the *Baccharis* genus, such as antioxidant (Zuccolotto et al. 2019), antiparasitic (Budel et al. 2018), cytotoxic activity (Fukuda et al. 2006), as well as acts in inflammatory processes (Florão et al.2012). A study carried out with *Baccharis reticulata* demonstrated an antibiotic-modulating activity against both Gram-positive and Gram-negative bacteria. The best result was observed with the volatile oil in association with norfloxacin and gentamicin against the multiresistant strain of *S. aureus*. In addition, the oil exhibited a synergistic effect for Gram-positive and Gram-negative bacteria (Freitas et al. 2020). Evidence of in vitro synergism with MDR strains provides a higher probability of successful in vivo therapy. Thus, these associations can be useful in selecting the most promising combinations of antimicrobials for practical therapy of severe bacterial infections.

Licania rigida Benth (known as "oiticica"), belongs to the *Chrisobalanaceae* family and it is distributed in tropical and subtropical regions. A study was carried out with leaf ethanolic extract to evaluate the virulence factor associated with the ability to form biofilms on biotic and abiotic surfaces in association with fluconazole since its action on biofilms is described. The study demonstrated that biofilms formed by *Candida sp*. isolated in acrylic resin discs reduced biofilm formation. It is associated with the reduction of hydrophobicity mechanisms of the cell surface, which reduce the aggregative potential and the formation of the biofilm (Freitas et al. 2019).

These outcomes of the use of medicinal plants by different populations, a fact that passes through generations, have highlighted species that present active principles of recognized clinical relevance, which in some cases have been transformed into modern medicines. Successful therapeutic evidence observed from the daily life of traditional or local communities has inspired pharmacological research, and this forms the basis of the ethnobiological approach, which is guided by popular practices and knowledge, consolidated through time, culture and history of several people, contributing to the discovery of agents with therapeutic potential or even a new drug, more specifically.

7.9 Conclusions and Future Prospects

The valorization of biological and cultural diversity, as well as the knowledge acquired by several traditional practices, becomes a necessary tool to know and classify the use of natural resources. In this context, empirical knowledge not only has great relevance in the discovery of new medicinal plants, suppliers of bioactive chemical substances originated mainly from the secondary cellular metabolism of the plant, but also are focused on the planning of actions related to the sustainability of natural resources managed. It is known that in tropical regions some social groups have vast traditional knowledge about the different forms of exploitation and management of natural resources, mainly about plant species. Several ethnic groups have created mechanisms and strategies for disease treatment and prevention. The accumulation of knowledge and practices form empirical medical systems often based on the use of natural plant resources.

The study of these mechanisms provides ethnopharmacology with a supposed efficacy of plants that are selected depending on the concept of disease and health by these groups, and this identification also helps in the improvement of other approaches that use medicinal plants as the object of study. Obtaining new alternatives for the development of new products of natural origin, it can be characterized as a new chemically defined compound with determined pharmacological activity (pharmacotherapeutic) or a simple traditional preparation from parts of a medicinal species (phytotherapeutic) that has evaluated its efficacy.

The discovery of compounds with biological activity may be more effective from active extracts of perennial plants. This is because these plants invest effectively in lifelong chemical defenses and have higher levels of compounds. One of the main advantages of using natural products in the search for new drugs, compared to synthetic compounds, is the high probability of biological activity. Secondary metabolites are synthesized and optimized through the evolution of specific biological interactions between the producer and the environment. In this sense, the chemical diversity of these substances becomes unequalled.

Thus, it is fundamental to understand how medicinal plants behave in the environment, how these resources are used and how this information can contribute to sustainable use strategies. From this conception of traditional knowledge, it is possible to design strategies that lead to alternatives that respect the need for conservation, together with the traditions of the people who use these resources and the scientific knowledge, being able to provide information for a better time of collection and a better period in which it produces high yields of essential substances for medicinal treatment and subsequent pharmacological uses.

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