Chapter 5
Novel Antimicrobial Compounds from Indigenous Plants and Microbes: An Imminent Resource

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Abstract Resistance of microbes towards the antibiotics has agitated the scientific community to look for authentic compounds from plants and microbes. They also make sure that these metabolites are strong enough to fight back the diseases in the long run. Traditional medicines that were used during the ancient times remain as unsung heroes until today. Only few medicines are of plant origin, and their usage is limited due to efficacy, treatment time and toxicity factors. But still, it can be overcome by the modern methods. Due to the increasing health problems all over

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the world, people are now switching over to the pharmaceutical products from plants and microbes. Considering these facts, this chapter has been framed to give a deep understanding of the current and forthcoming antimicrobial compounds from indigenous plants and microbes. It also discusses about the modern methods that are employed in the processing of antimicrobial compounds and their effects against different groups of pathogens.

Keywords Antimicrobial compounds · Phytochemicals · Techniques · Herbal medicine

5.1 Introduction

From the past decade, we have been receiving many alerts on emerging and re-emerging diseases. Though the traditional medicine obtained from plants and microbes was neglected for various reasons, now people have started to pay attention to the conventional herbal medicine. There are very many incidents where plant-derived metabolites have served as a preventive and curative drug. For instance, Nilavembu concoction was advised to consume during dengue outbreak in India. These are instant remedies to patients and have been found to be effective in preventing the disease. The side effects are not much harmful and provide remedy in the long run.

The secondary metabolites obtained from plants do not play a vital part in the plant's reproduction, growth, etc. (Fraenkel 1959). However, there are evidences that these products serve in the defence mechanism of plants (Stamp 2003). With this cue, researchers are inspecting the derivatives of herbal plants. Plants have a specialized pathway to synthesize the compounds. The study of these compounds has been elucidated with the help of various techniques, namely solvent extraction; microwave-assisted extraction; supercritical fluid extraction (SFE); solid phase micro extraction (SPME); chromatography methods such as HP-TLC, TLC, UPLC, GC-MS, LC-MS; phytochemical screening assays, nuclear magnetic resonance (NMR), Fourier-transform infrared spectroscopy (FTIR), etc.

Plant-derived compounds are comparatively safer than their chemically synthesized counterparts (Upadhyay et al. 2014; Rajeh et al. 2010). These compounds are primarily responsible for their antimicrobial activity (Savoia 2012). Phenolics and polyphenols such as flavonoids, quinones, coumarins and other types like alkaloids and terpenoids do possess the antimicrobial properties from the secondary metabolite group (Cowan 1999; Savoia 2012). The mechanisms by which plants control the microbial population are: (a) inhibition of biofilm formation, (b) inhibition of capsule production of bacteria, (c) microbial membrane disruption, (d) weakening of cell wall and metabolism and (e) by toxins production (Upadhyay et al. 2014).

Microbial-derived metabolites on the other side perpetuate their properties in the form of antibacterial, antifungal, antitumour and anticancer compounds. The major group of microbes that had a remarkable place in the pharmaceutical industry is Actinomycetes (Bérdy 1989). It was followed by fungi, bacteria and cyanobacteria, which had a notable role in metabolite production (Prasad et al. 2016, 2018).

This chapter enlightens the readers about the novel plant metabolites and microbial metabolites in the recent years. The merits and demerits of the recent extraction and analytical techniques with respect to the metabolite production are discussed in detail in Sect. 5.2.

5.2 Traditional Medicine

Traditional medicine has been a magical potion since prehistoric times for human population. It has been followed in many countries all over the world such as traditional medicine in China (Fabricant and Farnsworth 2001; Qi et al. 2013), Ayurveda and Unani in India (Parasuraman et al. 2014), Kampo in Japan (Yakubo et al. 2014), Sasang constitutional medicine in Korea (Kim and Noble 2014), traditional Aboriginal medicine in Australia (Oliver 2013), traditional medicine in Africa (Boakye et al. 2015) and Russian herbal medicine (Shikov et al. 2014). Traditional medicine has been a platform for formulating the modern pharmaceutical products. Plants which are used in traditional medicine can be derived from a single or mixed plant material and might contain a range of phytoconstituents. These components might act solely or in integration with other drugs to treat a particular disease (Parasuraman et al. 2014). The World Health Organization (WHO) recognized that traditional medicine plays a vital part in meeting the essential health maintenance requirement of the global population and emphasize definite types of the medicine (WHO 2014).

The medicinal components from both flora and fauna, despite being used in traditional medicine, have also been given much value as a primary source during the development of herbal preparations and modern medicines (Kang and Phipps 2003). Animal parts like hooves, skins, bones, feathers, tusks and their by-products such as honey, venom, wax and ambergris serve as the key constituents in the preparation of curative, protective and preventive medicine (Adeola 1992). Further, a major portion of bioactive compounds are derived from plant sources like herbs, shrubs, trees and higher plants followed by microorganisms and others (Farnsworth and Morris 1976). Figure 5.1 represents the group of antimicrobial compounds that are produced from plants.

India has been known to possess the rich source of medicinal plants. Around 8000 medical preparations from plants have been classified in Ayurveda. The famous Vedas have acknowledged more medicinal plants, accounting for 67 medicinal plants in Rig Veda around 5000 BC, 290 species in Atharva Veda during the 4500–2500 BC, 81 species in Yajur Veda, 1270 species in Sushrut Samhita and 1100 plant varieties in Charak Samhita for the drug preparation and its use. To our sur-

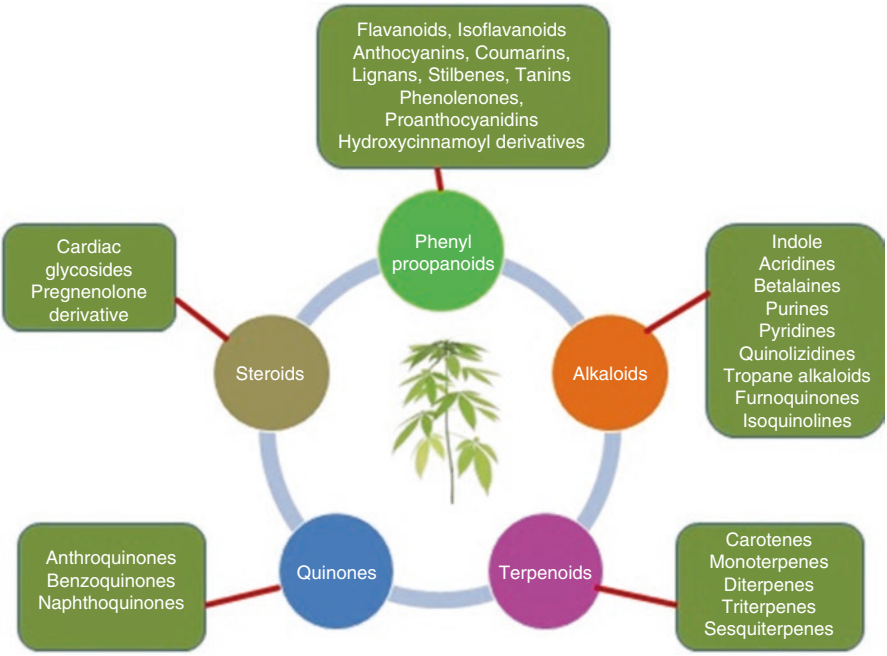

Fig. 5.1 Plant metabolite classification

prise, these plant preparations are still in use as a standard material in Ayurvedic medicine (Joy et al. 2001).

5.2.1 Technologies/Methodologies for the Compounds from Plants and Microbes

The assays and assessment techniques used to validate the antimicrobial potential of the secondary metabolites against pathogens need to be addressed in an elaborate manner. In this way, the choice of method for plants/microbes can be made, and accordingly, the precise results are obtained (Rios et al. 1988). Though the plant/microbial derived drugs are in a successful rate, their screening procedures in the past were strenuous, expensive and sluggish. This has eventually led to the increase of high-end technologies to screen and identify the metabolites. Table 5.1 discusses the recent methods in the identification of bioactive components and phytochemical analysis.

The standard antimicrobial screening methods availed currently comprise diffusion, dilution and bioautographic methods. Both diffusion and bioautographic method accomplish a qualitative analysis of the samples by revealing the presence or absence of inhibitory compounds. In contrast, dilution method defines the

Table 5.1 Merits and demerits of phytochemical analysis

Technique	Advantage	Disadvantage	References
Ultra-high-performance liquid chromatography (UHPLC)	Less time taken for analysis, minimum amount of samples and solvents used and amplified peak capacity	–	Gaudêncio and Pereira (2015)
High-performance liquid chromatography-nuclear magnetic resonance (HPLC-NMR)	Versatile separation technique providing structural information on separated compounds	(a) Needs ample concentration of the sample based on the availability of the metabolites in eluates (b) NMR spectrum's achievement time	Wolfender (2010)
Ultrafiltration high-performance liquid chromatography (HPLC)	Screens intricate combination of bioactive components	(a) Since the target protein should be analogous to the affinity (K_d) of the weakest ligand, a high sample concentration is required (b) False-positive results due to non-specific enzyme–ligand interactions (c) Not suitable for transmembrane proteins	van Breemen et al. (1997), Johnson et al. (2002)
Ultrafiltration liquid chromatography-mass spectrometry (LC-MS) with enzyme channel blocking assay (ECB)	Inhibits the possible ligands to arrive at the primary binding region	–	Song et al. (2014)
Bioaffinity chromatography	The synchronized examination of the fingerprint and biological activity allows the spotting of peaks with the preferred activity	(a) The buffer and solvent used in the analysis should be suitable for the extraction of the desired protein (b) The instrumentation is too complicated, and the reaction time between the components and the protein is minimal	Potterat and Hamburger (2013)
Ligand fishing	Chances of identification of low-affinity ligands	(a) The necessary quantity of protein for effective fishing is 50 μg (b) Possibility of retaining false positives	Vanzolini et al. (2013)
Cell membrane affinity chromatography	(a) The active compounds can be identified directly (b) The desired transmembrane protein can be subjected to immobilization	(a) One major demerit is that there is a chance of co-immobilization of numerous receptor types (b) The mobile phase is mostly aqueous, and there is a need to run the parallel control column, to check the nonexistence of non-specific interaction	Moaddel and Wainer (2009)

quantity of the compound (Valgas et al. 2007). Table 5.2 reviews the common and recent technologies in antimicrobial activity screening and evaluation methods.

5.2.2 Novel Metabolites from Plants

Gymnema sylvestre from family Apocynaceae has been reported to have larvicidal, anticancer, hypolipidemic, antimicrobial, antiviral and antioxidant activities. Ten percent aqueous extract of the leaves inhibited 9 out of 13 microbial strains, with a wide-spectrum activity showing inhibition zone of 14–23 mm. Among the gram-negative bacteria, *Klebsiella pneumoniae* was the most sensitive with 22.1 mm of inhibition zone, followed by *Salmonella typhimurium* with 21.2 mm and *Escherichia coli* with 19.6 mm. *Pseudomonas aeruginosa* was the most vulnerable bacterium for the plant metabolites with 23.3 mm of inhibition zone followed by *Candida albicans* with 22.6 mm of inhibition zone. The zones of inhibition of *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA) were 20 mm and 19 mm, respectively. *Staphylococcus epidermidis* and *Enterococcus faecalis* were unresponsive to the plant metabolites (Arora and Sood 2017).

Ficus species from family Moraceae have been shown to have antifungal (Hassan et al. 2006), anti-diarrhoeal (Ahmadu et al. 2007), anti-inflammatory and anti-nociceptive activities (Amos et al. 2002). In addition to possessing the common metabolites, the ethanolic extracts of leaf and stem bark of *Ficus sycomorus* and *Ficus platyphylla* showed prominent antimicrobial activity against *Trichophyton mentagrophytes*, *Staphylococcus aureus* and ciprofloxacin-resistant *Salmonella typhi* (Adeshina et al. 2009). Table 5.3 lists the antibacterial activity of the medicinal plants.

Recently, an interesting study on green tea and Korean mixed tea subjected to antibacterial and antifungal activities was done, and the results indicated that green tea possessed substantial antibacterial and antifungal activities, while the mixed tea presented less activity. It was evident that epigallocatechin gallate (EGCG) was the responsible compound for the property (Muthu et al. 2016).

Moringa oleifera is known to possess immense pharmacological properties such as antioxidant, antidiabetic, antihypertensive, antitumor, antiulcer, cholesterol-lowering agent and is used in the traditional medicine. Though most of the plant parts are potent in producing metabolites, seed coat has been analysed for antimicrobial activity. *Candida albicans* was the most sensitive microbe for the ethanolic extract. *Staphylococcus epidermidis* and *Staphylococcus aureus* were the most sensitive Gram-positive bacteria. Among Gram-negative bacteria, *Klebsiella pneumoniae* was the most sensitive (Arora and Onsare 2014). A potent bioactive compound from turmeric was found to be effective against *Helicobacter pylori.* The metabolite curcumin (diferuloylmethane) was anticipated as a promising antimicrobial compound to solve gastroduodenal diseases like peptic ulcer, gastritis, etc. The minimum inhibitory concentration (MIC) of curcumin against different strains of

H. pylori was in the range of 5–50 μg/mL (De et al. 2009). Tables 5.4 and 5.5 list the antifungal and antiviral activities of the medicinal plants, respectively.

5.3 Novel Metabolites from Microbes

5.3.1 Antibacterial Activity

Penicillium sp. is a well-renowned fungus that produces an array of secondary metabolites like antibacterial substances (Lucas Esther et al. 2007), immunosuppressants, cholesterol-lowering agents (Kwon et al. 2002), antiviral substances (Nishihara et al. 2000), antifungal substances (Nicoletti et al. 2007) and also strong

Table 5.2 Common and recent methods to evaluate the antimicrobial activity

Technique/method	Advantages	Disadvantages	References
Agar disk diffusion	Minimal cost, simple to perform, tests a wide variety of microbes and antimicrobial agents, result interpretation is very simple	No differentiation of bacteriostatic and bactericidal effects	Reller et al. (2009), Kreger et al. (1980)
Antimicrobial gradient method (Etest)	(a) Minimum inhibitory concentration (MIC) can be done (b) The antimicrobial interface among two drugs can be studied	Expensive	White et al. (1996)
Thin layer chromatography (TLC)—bioautography	(a) Simplest method to identify the antifungal compounds, especially spore forming fungi (b) Can effectively separate a complicated mixture of compounds		Dewanjee et al. (2015)
Dilution test (a) Broth macro dilution (b) Broth micro dilution	MIC is accurately measured	Laborious, manual errors, inaccuracy of the antimicrobial solutions during preparation, lot of space requirement Results are not effectively reproduced	CLSI (2012)
ATP Bioluminescence assay	(a) Less time (3–4 days) (b) Antimicrobial analysis in situ or in vivo	Rapidity	Beckers et al. (1985), Vojtek et al. (2014)
Flow cytofluorometric method	Reproduce results rapidly in short time (2–6 h)	Inaccessibility of the flow cytometry equipment	Ramani and Chaturvedi (2000)

Table 5.3 Antibacterial secondary metabolites from medicinal plants

Medicinal plants	Endophyte/ actinomycetes	Organism/ species	Secondary metabolite	References
Acrostichum aureum	Endophyte	*Penicillium* sp.	Cyclo(Pro-Thr)	Cui et al. (2008)
Acrostichum aureum	Endophyte	*Penicillium* sp.	Cyclo (Pro-Tyr)	Cui et al. (2008)
Alpinia oxyphylla	Actinomycetes	*Streptomyces* sp.	2,6-dimethoxy terephthalic acid	Zhou et al. (2014)
Bruguiera gymnorrhiza	Endophyte	*Streptomyces* sp. HKI0576	Divergolides	Ding et al. (2011a, b)
Cynodon dactylon	Endophyte	*Aspergillus fumigatus* CY018	Asperfumoid	Wang et al. (2008)
Garcinia dulcis (Roxb.) Kurz.	Endophyte	*Phomopsis* sp. PSU-D15	Phomoenamide	Rukachaisirikul et al. (2008)
Garcinia dulcis (Roxb.) Kurz.	Endophyte	*Phomopsis* sp. PSU-D15	Phomonitroester	Rukachaisirikul et al. (2008)
Ginkgo biloba L	Endophyte	*Xylaria*	7-amino-4-methylcoumarin	Liu et al. (2008)
Kandelia candel	Endophyte	*Streptomyces* sp. HKI0595	Xiamycin B	Ding et al. (2011a, b)
Kandelia candel	Endophyte	*Streptomyces* sp. HKI0595	Indosespene	Ding et al. (2011a, b)
Kandelia candel	Endophyte	*Streptomyces* sp. HKI0595	Sespenine	Ding et al. (2011a, b)
Porteresia coarctata (Roxb.)	Endophyte	*Penicillium chrysogenum,* (MTCC 5108)	3,1″-didehydro-3[2″(3″,3″-dimethylprop-2-enyl)-3″-indolylmethylene]-6-methyl pipera-zine-2,5-dione	Devi et al. (2012)
Zea mays	Endophyte	*Acremonium zeae*	Pyrrocidines A–B	Wicklow and Poling (2009)

mycotoxins (Frisvad Jens and Samson Robert 2004). A group of scientists from Brazil has reported three metabolites from *Penicillium* sp. Among the three compounds, methyl 6-acetyl-4-methoxy-5,7,8-trihydroxynaphthalene-2-carboxylate worked as a wonder substance having a broad spectrum of antimicrobial activity against *Candida albicans* with a minimum inhibitory concentration of 32 μg/mL and *Bacillus cereus* and *Listeria monocytogenes* with MIC of 64 μg/mL (Petit et al. 2009). Another novel compound extracted from *Penicillium* sp. is 7-methoxy2,2-dimethyl-4-octa-4′,6′-dienyl-2*H*-napthalene-1-one which exhibited antimicrobial activity against *K. pneumoniae,* gram-negative bacteria and MRSA, *S. aureus*, *S. epidermidis,* Gram-positive bacteria. This study has also proven results in cytotoxicity and mutagenicity assay, revealing the suitability of the compound for further use (Kaur et al. 2015).

Table 5.4 Antifungal secondary metabolite from medicinal plants

Medicinal plants	Endophyte/ actinomycetes	Organism/species	Secondary metabolite	References
Alpinia galanga a (*L.*)	Endophyte	*Streptomyces* sp. LJK109	3-Methylcarbazole	Taechowisan et al. (2012)
Alpinia galanga a (*L.*)	Endophyte	*Streptomyces* sp. LJK109	1-Methoxy-3-methylcarbazole	Taechowisan et al. (2012)
Alpinia oxyphylla	Actinomycetes	*Streptomyces* sp.	2,6-Dimethoxy terephthalic acid	Zhou et al. (2014)
Catunaregam tomentosa	Endophyte	*Curvularia geniculata*	Curvularides A–E	Chomcheon et al. (2010)
Emblica officinalis Gaertn	Actinomycetes	*Streptomyces griseofuscus*	Indole acetic acid (IAA), siderophores	Gangwar et al. (2014)
Emblica officinalis Gaertn	Actinomycetes	*Streptomyces cinereus*	(IAA), siderophores	Gangwar et al. (2014)
Emblica officinalis Gaertn	Actinomycetes	*Streptomyces flavus*	Indole acetic acid (IAA)	Gangwar et al. (2014)
Ginkgo biloba	Endophyte	*Chaetomium globosum* No. 04	Chaetoglobosin A, G, D, R	Zhang et al. (2013)
Gloriosa superba	Endophyte	*Aspergillus* sp.	KL-4	Budhiraja et al. (2013)
Melia azedarach	Endophyte	*Aspergillus fumigatus* LN-4	12β-Hydroxy-13α-methoxyverruculogen TR-2	Li et al. (2012)
Melia azedarach	Endophyte	*Aspergillus fumigatus* LN-4	3-Hydroxyfumiquinazoline A	Li et al. (2012)
Phyllanthus niruri	Actinomycetes	*Actinomadura* sp.	Volatile organic compounds (VOCs)	Priya (2012)
Xinglong Chinese tree	Endophyte	*Pestalotiopsis adusta*	Pestalachloride A	Li et al. (2008)

Table 5.5 Antiviral secondary metabolites from medicinal plants

Medicinal plants	Endophyte/ actinomycetes	Organism/species	Secondary metabolite	References
Acer truncatum Bunge	Endophyte	*Paraconiothyrium brasiliense*	Brasilamides A–D	Liu et al. (2010)
Aegiceras corniculatum	Endophyte	*Emericella* sp.	Merimidine A	Zhang et al. (2011)
Aegiceras corniculatum	Endophyte	*Emericella* sp.	Emerimidine B	Zhang et al. (2011)
Aegiceras corniculatum	Endophyte	*Emericella* sp.	Emeriphenolicin A–F	Zhang et al. (2011)
Bruguiera gymnorrhiza	Endophyte	*Streptomyces* sp.	Xiamycin A	Ding et al. (2011a, b)
Xylocarpus granatum	Endophyte	*Jishengella endophytica*	Perlolyrine, 1-hydroxy-β-carboline	Wang et al. (2014)

Two metabolites elucidated as 4-Chromanone, 6-hydroxy-2-methyl-(5CI) and Modiolide A were isolated from a unique endophytic fungus *Periconia siamensis* extracted from leaves of *Thysanoleana latifolia.* These compounds were found to be effective against *Listeria monocytogenes*, MRSA, *Bacillus cereus* and *Pseudomonas aeruginosa* (Bhilabutra et al. 2007). Table 5.6 provides the list of bacterial metabolites from various microbes.

The lactic acid bacterial cultures were treated against *Mycobacterium avium* subsp. *Paratuberculosis* to test for the production of bacteriocin (Kralik et al. 2018). Recently, volatile organic compounds with antimicrobial activity were extracted from the bacterium *Bacillus amyloliquefaciens* strain S13. These compounds were found to be effective against *Saccharomyces cerevisiae, Agrobacterium tumefaciens* and *Bacillus subtilis* (Sonia Hamiche et al. 2019).

Bacillus subtilis isolated from soil sample served as a potent biological agent by controlling the fatal phytopathogens, namely *Botrytis cinerea*, *Monilia linhartiana*, *Alternaria solani*, *Rhizoctonia* sp. and *Phytophthora cryptogea*. This paves the way to control several plant diseases. The same bacterium also showed antibacterial activity against two pathogens *Pseudomonas syringae* and *Xanthomonas campestris* (Todorova and Kozhuharova 2010). There is more impending work from the researchers in this field, and the microbial-derived drugs should be used wisely by the human population.

5.3.2 Antifungal Activity

Very few antifungal drugs are successful in the market, owing to their poor efficacy and other reasons like azole resistance (Carledge et al. 1997). However, there are recent enhancements involving polyene lipid formulation with less toxicity and

Table 5.6 Bacterial secondary metabolites with antimicrobial activity

Isolated organism	Source of organism	Identified secondary metabolite	Antimicrobial activity against	Inhibition concentrationIC 50 valuesMg mL^{-1}	References
Streptomyces sp.	Marine water	Fijimycins A–C, etamycin A	Methicillin-resistant *Staphylococcus aureus*	4–16	Peng et al. (2011)
Streptomyces sp.	Marine water	Heronamycin A	*Bacillus subtilis*	14 and 18	Raju et al. (2012)
Halobacillus litoralis YS3106	Marine water	Halolitoralin A, B and C	*Candida albicans*	20, 30 and 30	Yang et al. (2002)
			Trichophyton rubrum	25, 35 and 40	
Pseudomonas sp.	Marine water	1-acetyl-beta-carboline	Methicillin-resistant *Staphylococcus aureus*	32–128	Lee et al. (2013)
Streptomyces sp. Merv8102	Marine water	Essramycin	*Staphylococcus aureus, Escherichia coli, Micrococcus luteus* and *Pseudomonas aeruginosa*	1.0–8.0	El-Gendy et al. (2008)
Bacillus sp. 091D194	Marine water	Macrolactin W	*Bacillus subtilis, Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa*	64	Mondol et al. (2011)
Pseudomonas sp.	Algae: *Diginea* sp.	Cyclic tetrapeptides	*Bacillus subtilis, Vibrio anguillarum*	No activity	Rungprom et al. (2008)
Rhodococcuserythropolis and*Pseudomonas* sp.	Petrosia ficiformis	Nil	*Staphylococcus aureus*	Minimal inhibition zone was observed	Chelossi et al. (2004)
Enterobacter sp.	*Dysidea granulose*	Crude extracts	*Salmonella typhi, Escherichia coli* and *Klebsiella pneumonia*	Minimal inhibition about 5	Gopi et al. (2012)

(continued)

Table 5.6 (continued)

Isolated organism	Source of organism	Identified secondary metabolite	Antimicrobial activity against	Inhibition concentrationIC 50 valuesMg mL^{-1}	References
Pseudoalteromonasflavipulchra	*Montipora aequituberculata*	Nil	15 strainsof methicillin-resistant *Staphylococcus aureus*	Minimal inhibition zone was observed	Chen et al. (2010)
Flavobacteria, α- and γ-*Proteobacteria* and*actinobacteria*	Unidentified	Nil	*Escherichia coli, Bacillus subtilis, Staphylococcus lentus, Candida glabrata*	Minimal inhibition zone was observed for 3 days	Heindl et al. (2010)
PseudoalteromonasPhenolica O-BC30	Marine water	2, 2′,3-Tribromophenyl-4,4′-dicarboxylic acid	Methicillin-resistant *Staphylococcus aureus*	1–4	Isnansetyo and Kamei (2009)
Brevibacilluslaterosporus PNG276	Marine water	Tauramamide as its methyland ethyl esters	*Enterococcus* sp.	0.1	Desjardine et al. (2007)
Streptomyces strain	Marine water	Marinopyrroles A and B	Methicillin-resistant *Staphylococcus aureus*	0.61 and 1.1	Hughes et al. (2008)
Streptomyces sp. BCC45,596	Marine water	Urdamycinone E,urdamycinone G anddehydroxyaquayamycin	*Mycobacterium tuberculosis*	3.13–12.50	Supong et al. (2012)
Rapidithrix sp.	Marine water	Ariakemicins A and B	*Brevibacterium* sp.	83	Oku et al. (2008)
			Staphylococcus aureus	0.46	
			Bacillus subtilis	83	
			Cytophaga marinoflava	>700	
			Pseudovibrio sp.	>700	
			Enterococcus sp.	>700	
			Pseudomonas aeruginosa	>700	
			Candida albicans	>700	

Isolated organism	Source of organism	Identified secondary metabolite	Antimicrobial activity against	Inhibition concentrationIC 50 valuesMg mL^{-1}	References
Fischerella sp.	Marine water	Ambiguine H isonitrile and Ambiguine I isonitrile	*Candida albicans*	6.25 and 0.39	Smitka et al. (1992)
			Staphylococcus albus	0.625 and 0.078	
			Saccharomyces cerevisiae	1.25 and 0.312	
			Bacillus subtilis	5 and 0.312	
			Escherichia coli	10 and 2.5	
Fischerella ambigua	Marine water	Ambiguine K and M isonitriles	*Mycobacterium tuberculosis*	6.6 and 7.5	Mo et al. (2009)
Micrococcus sp.,*Vibrio* sp., and *Pseudoalteromonas* and *Bacillus* sp.	Sponge: *Aplysina aerophoba*and *Aplysina cavernicola*	Nil	Gram-positive bacteria, Methicillin-resistant *Staphylococcus aureus*, gram-negative bacteria, *Staphylococcus epidermidis*	Minimal inhibition zone was determined	Hentschel et al. (2001)

novel triazoles possessing a wide range of action against many fungal isolates (Granier 2000). The drug target is presumably on the fungal cell wall, which comprises three major constituents: chitin, glucan and mannoproteins. Hence, the drug's action is determined by the nature of the fungal cell wall composition. There are also natural fungal inhibitors isolated from microbes which are covered in detail in the subsequent sections.

A potent strain named *Lactococcus lactis* LI4 strain isolated from dairy foods was found to prevent the growth of *Candida albicans* DMST 5239. Surprisingly, the activity of the culture was persistent in pH 2.0–4.0 (Lertcanawanichakul 2011). It was reported that by combining both natural and engineered lactococci strains, a group of compounds termed alkyl ketones were produced, and they were responsible for the antifungal activity against yeast genera *Candida* and *Rhodotorula* and *Aspergillus* and *Fusarium* (Stoyanova et al. 2006, 2010). Few reports have suggested that these strains can be efficiently used in the preservation of vegetables and fruits from fungal contamination (Trias et al. 2008).

In 2007, Gai et al. studied antifungal compounds in the ethanolic extracts of *Fusarium* sp. Based on the identification studies of the bioactive compound, it was interpreted as Fusarielin E (Gai et al. 2007). In a recent study, two glycolipids isolated from *Bacillus licheniformis* exhibited antifungal activities against *Rhizoctonia solani*, *Colletotrichum acutatum*, *Aspergillus niger*, *Candida albicans* and *Botrytis cinerea*. They were identified as leodoglucomide and leodoglycolipid (Tareq et al. 2015).

Haliangicin, a beta-methoxyacrylate antibiotic, exhibited effective inhibition of growth against *Pythium ultimum*, *B. cinerea* and *Saprolegnia parasitica* (Fudou et al. 2001a, b). *Bacillus laterosporus* isolated from Papua produced Basiliskamides A and B and showed potent antifungal action against *Aspergillus fumigatus* and *Candida albicans* (Barsby et al. 2002).

A novel compound named Saadamycin isolated from *Streptomyces* sp. exhibited antifungal action against *A. fumigatus, T. mentagrophytes, A. niger, F. oxysporum, Epidermophyton floccosum, Microsporum gypseum* and *C. albicans* (El-Gendy and El-Bondkly 2010). A novel hexapeptide, Sclerotide B, derived from marine-based *Aspergillus sclerotiorum* PT06-1 possessed antifungal action against *Candida albicans* (Zheng et al. 2009). The same organism from an anonymous source exhibited antimycotic activity against *A. flavus* (Bao et al. 2010). Two sesquiterpene type compounds isolated from *Penicillium bilaiae* MA-267 showed antifungal activity against phytopathogenic fungi such as *Colletotrichum gloeosporioides*, *Gaeumannomyces graminis*, *F. graminearum* and *Alternaria brassicae* (Meng et al. 2014). Peniciadametizine A isolated from *Penicillium adametzioides* AS-53, presented selective antimycotic activity against the phytopathogenic fungus *A. brassicae* (Liu et al. 2015). Table 5.7 shows the list of fungal secondary metabolites.

5.3.3 *Antiviral Activity*

At present, there are many well reputable microbial-driven secondary metabolites used for antiviral activity. Among the Actinomycetes, *Streptomyces roseus* played a promising role in producing leupeptin, a serine and cysteine protease (Aoyagi et al. 1969). This enzyme has proven to impede the glycoprotein-mediated admittance of *Marburg virus* (Gnirss et al. 2012). Similarly, protease inhibitors like Antipain and Elastatinal were utilized to hinder poliovirus protease (George A. Belov 2004). An interesting analogue of sialic acid, siastatin B, extracted from *Streptomyces verticillus* showed anti-influenza activity and in vitro propagation (Yoshio Nishimura et al. 1993).

There is an increasing need to focus on drugs for Hepatitis B virus (HBV) since the number of individuals who are infected with HBV is on steep escalation. The existing approved antiviral drugs comprise immunomodulators and nucleotide analogues that help to interfere in the disease advancement. Nevertheless, these drugs have their limitations such as side effects, limited efficacy and development of drug-resistant varieties. In contrast to the phytochemicals, there are very few microbial metabolites to act against HBV (Zhang and Wang 2014; Wu 2016).

To treat influenza virus, the following synthetic antiviral drugs have been approved: (a) amantadine (b) ribavirin (c) favipiravir (d) rimantadine (e) peramivir (f) and laninamivir octanoate (g) oseltamivir and (h) zanamivir. The drugs from natural products are currently under research, and the targets of these drugs are neuraminidase and haemagglutinin. Stachyflin, a novel compound isolated from *Stachybotrys sp.* RF-7260 provides conformational changes in haemagglutinin, thus preventing the fusion of host cells with virus (Nakatani et al. 2002; Minagawa et al. 2002).

The antiviral drugs that are derived from natural products exhibited a mild anti-HIV activity: disorazol, tubulysin and stigmatellin. Two myxobacterial strains named *Polyangium* sp. and *Myxococcus stipitatus* produced compounds such as thiangazole, phenalamide A1 and phenoxan with anti-HIV activity (Martinez et al. 2013). Myriocin and NA255, potent serine palmitoyl transferase inhibitors, were isolated from *Myriococcum albomyces* and *Fusarium incarnatum* and known to prevent the propagation of HBV, HCV and influenza virus (Kluepfel et al. 1972; Sakamoto et al. 2005; Tafesse et al. 2013).

5.4 Challenge to Antimicrobial Resistance

Antimicrobial resistance has turned up as a growing threat to the human health. It is affecting both the developing and developed nations, and its needs to be addressed immediately to save several lives. In the past 10 years, increasing awareness over this issue has been observed, and this is the right time that we use this occasion to obviate the disaster projected on health.

Table 5.7 Fungal secondary metabolites with antimicrobial activity

Isolated organism	Source of organism	Identified secondary metabolite	Antimicrobial activity test against	Inhibition concentrationIC 50 valuesMg mL^{-1}	References
Aspergillus protuberusSP1	Marine water	*n*-Butanol fraction	*Pneumococcus mirabilis, Escherichia coli, Klebsiella pneumoniae* and *Bacillus subtilis*	Minimal inhibition zone was observed	Mathan et al. (2011)
Zopfiella latipes	Marine water	Zopfiellamides A and B	*Arthrobacter citreus, Arthrobacter citreus, Bacillus brevis, Bacillus subtilis, Corynebacterium insidiosum, Micrococcus luteus, Bacillus licheniformis, Mycobacterium phlei, Streptomyces* sp.	2 and 10 for Zopfiellamides A	Daferner et al. (2002)
Daldinia eschscholzii	*Gracilaria*sp.	Helicascolisides A, B and C	*Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, Staphylococcus aureus, Cytophaga marinoflava*	No antibacterial activity	Tarman et al. (2012)
Eurotiumherbariorum	*Enteromorpha prolifera*	Cristatumin E	*Enterobacter aerogenes, Enterococcus* sp.	44	Li et al. (2013)
ZZF36	Algae: *Sargassum*sp.	5-Hydroxy-de-*O*-methylasiodiplodin, 6-Oxo-de-methyllasiodiplodin,Lasiodiplodin,de-*O*-Methyllasiodipodin, (E)-9-Etheno-lasiodiplodin	*Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Salmonella enteritidis, Candida albicans, Fusarium oxysporum*	6.25–100	Yang et al. (2006)
*Penicilliumchrysogenum*QEN-24S,	Algae: *Laurencia*sp.	Penicisteroid A	*Aspergillus niger, Alternaria brassicae*	Minimal inhibition zone was observed	Gao et al. (2011)
Cryptopsoriopsis spp.	Sponge (*Clidemiahirta*)	2-Butyryl-3-hydroxyphenoxy)-6-hydroxyphenyl)-3-hydroxybut-2-en-1-one, 1-(2,6-Dihydroxyphenyl) pentan-1-one and (Z)-1-(2)	*Pseudomonas fluoroscens*	6, 8–30	Zilla et al. (2013)
Eurotium cristatumKUFC7356	Sponge: *Suberites domuncula*	Eurocristatine	*Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Candida albicans, Trichophyton rubrum*	Nil effects to fungi and bacteria	Gomes et al. (2012)

Isolated organism	Source of organism	Identified secondary metabolite	Antimicrobial activity test against	Inhibition concentrationIC 50 valuesMg mL^{-1}	References
Aspergillusochraceus MP2	Unidentified marine sponge	α-Campholene aldehydeand Lucenin-2	*Klebsiella pneumonia, Staphylococcus aureus, Pseudomonas aeruginosa*	Minimal inhibition zone was observed	Meenupriya and Thangaraj (2011)
Aspergillus versicolorLCJ-5-4	Coral: *Cladiella* sp.	Versicoloritides andtetraorcinol	*Staphylococcus aureus, Enterobacter aerogenes, Escherichia coli, Bacillus subtilis, Candida albicans, Pseudomonas aeruginosa*	Minimal inhibition zone was observed >150	Zhuang et al. (2011)
Zygosporium sp.*KNC52*	Hard coral	Sulfoalkylresorcinol	*Mycobacterium tuberculosis, Mycobacterium avium, Mycobacterium bovis,Pseudomonas aeruginosa,* methicillin-resistant *Staphylococcus aureus*	166, 50 and 12.5	Kanoh et al. (2008)
Aspergillus carneusKMM 4638	Marine water	Carneamides A–C,carnequinazolines A–Cand carnemycin A, B	*Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Bacillus cereus, Candida albicans*	No effects	Zhuravleva et al. (2012)
Aspergillus carbonariusWZ-4-11	Marine water	Naphtho-γ-pyrones	*Mycobacterium tuberculosis*	43, 21.5	Zhang et al. (2008)

As per the meeting held on 21 September 2016 to combat the antimicrobial resistance, the UN General Assembly has decided to organize a global effort with certain plans. Peter Thomson, president of the UN General Assembly, informed the representatives that the entire world should join hands to fight against this deadly factor with the integrative approaches. Besides endorsing WHO's current antimicrobial resistance plan and 2030 Agenda for Sustainable Development, the chapter represents a pledge by each member country (Muoio and Adalja 2016):

(a) To organize and manage investment into novel therapeutic technologies, research and investigation.
(b) To develop multisectoral programmes and strategies concentrated on antimicrobial resistance.
(c) To raise alertness of antimicrobial resistance to inculcate positive activities from the general public.
(d) To demand the launch of an ad hoc interagency coordination group in consultation with WHO, the Food and Agricultural Organization.

Though antibiotics are treated as a lifesaver globally, the CDC has reported that around 50% of the antibiotics that are prescribed for the patients are actually not desirable (CDC report 2013). The overuse of antibiotics commonly comes from recommending these medications to cure nonbacterial ailments for which they are inadequate. For instance, in USA, more than 60 million cases/year of viral flu are suggested antibiotics (CDC-About Antimicrobial resistance n.d.). In USA, every year, the number of people acquiring antibiotic-resistant bacterial infection is around two million, and 23,000 people die because of the chronic infection. On the other hand, over usage of these drugs might pose yeast infection in intestine, certain allergic reactions and diarrhoea (Bartlett 2002). On the contrary, no or late antibiotic treatment in case of bacterial infections is quite normal (Houck et al. 2004). This may decrease the risk of antibiotic-resistant bacteria but might pose a serious threat to life, leading to mortality (Little 2005; Spiro et al. 2006).

5.5 Future of Natural Medicine

Both microbes and medicinal herbs will endure to play a better part in pharmaceutical industry since only 0.001% of microbes and half a million plants are explored in world till date. Scientists will come up with astonishing metabolites to treat the life-threatening diseases in the near future (Singh 2015). Herbal medicine is extensively used across the globe in a constant way. This has led to the trend in replacing the synthetic drugs with the conventional medicine. However, plants/microbes are prone to contamination or infection, making their recovery and usage a critical issue. Hence, they should be subjected to a set of tests before the extraction process to ensure the safety and efficacy of the drug (Clark 1996; Firenzuoli and Gori, 2007).

One of the challenges that is imposed on herbal therapy is the extensive use of the whole plants leading to the threat of extinction. Habitat destruction, increasing

population and wildlife resource exploitation are the serious problems that are associated with this therapy (Bentley 2010). However, they can be solved by wise usage, proper plantation and harvest of the medicinal plants.

5.6 Conclusion

There is no doubt that both plants and microbes had made the entire globe to accept the fact that secondary metabolites derived from them turn to be a lifesaver. This is well correlated with the recent improvements in the research field. The development of new medicines and advanced approaches towards the disease diagnosis will surely combat the threatening antibiotic resistance. On the other hand, personalized medicine is also gaining more attention. Henceforth, both microbial and plant products will serve the pharmaceutical needs of the human population in a safe way.

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