Chapter 16
Actinomycetes in Medical and Pharmaceutical Industries

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Abstract Actinomycetes are critical sources of medically important pharmaceutical metabolites. Among the identified actinomycetes, the genera *Streptomyces* has been investigated for several biomedically important antibiotics, mainly aminoglycosides, chloramphenicol, tetracycline, ivermectin, macrolides rifamycins, and other non-beta lactam antibiotics. Actinomycetes are used in the large-scale production of antibiotics; thus, they have a vast application in the biopharmaceutical industry and can be utilized in the production of antibacterial, antifungal, anti-inflammatory, and anticancer drugs. Many ecological niches remain underexplored as evidenced by the dearth of studies and reports. Therefore, it is always critical to recognize the unexplored environments or niches for obtaining novel secondary metabolites or drugs and diverse actinomycetes species. Different groups of actinobacteria produce a variety of bioactive compounds. However, extensive research has to be carried out to identify and recover new bacterial communities with a broad range of secondary metabolites. Recently, profound research work was conducted toward harnessing the rare actinomycetes diversity, and they are usually difficult to isolate. Many scientists believe that these types of rare actinobacteria have the potential to encompass distinctive bioactive compounds, which are prerequisites in the production of novel drugs.

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16.1 Introduction

Actinomycetes morphologically can be considered fungi and bacteria. However, their molecular organization is closely related to prokaryotes, indicating they belong to bacteria. They belong to the order Actinomycetales and are generally aerobic, Gram-positive, and spore-forming bacteria. A typical actinomycetes species can form 0.5–1.0 μm hyphae and appears similar to mycelium (Williams and Wellington 1982). Their cellular G + C content of DNA is greater than a 55-mole percent, and phylogenetic relationships can be determined using a 16S rRNA gene sequence. They are considered to be in the bacteria domain and considered as one of the largest taxonomic among the major 18 lineages. The name "Actinomycetes" comes from the Greek "atkis" (a ray) and "mykes" (fungus) (Pasindu 2016). They replicate by producing chains of spores and on their tips (through spores), while other filamentous species fragment into new cells. Hyphal development is charted by fragmentation and release of spores (Williams and Wellington 1982).

Actinomycetes are found in freshwater, seawater, cold and warm-blooded animals, and compost. The soil habitat is the main precursor for the availability of these species. Over 20 genera were isolated from the soil samples; a sustainable sums of several million per gram are common. Statistics in waterlogged, anaerobic soils and acidic soils are often originated to below 10^2–10^3 per grams of dry weight soil (Casida 1965; Williams et al. 1971; Hagedorn 1976). Actinomycetes are important microbe well exploited for secondary metabolites. For the past several years, a group of researchers has been involved in finding a prominent strain that can produce potential secondary metabolites. Among the main genera of actinomycetes species, a few examples are *Streptomyces*, *Actinobacteria*, *Nocardioforms*, *Actinoplanetes*, *Thermonospores*, and *Maduromycetes*. These are suprageneric, and are classified as irregular, non-sporing, Gram-negative rods (genus Actinomyces), Nocardio, from actinomycetes (genera *Nocardia* and *Rhodococcus*), and as actinomycetes with multi-ocular sporangia (genus *Dermatophilus*) (Goodfellow et al. 2012). These species are widely used in biotechnological applications for producing commercially important biomolecules.

Natural products play a pivotal role in various sectors of daily life. They are of major importance in industries, curing human disease, and pharmacological and biotechnology applications such as bacterial disease or infection and cancer (Girao et al. 2019). The natural products produced from actinobacteria include antibacterial, antitumor, anticancer, antifungal, antiviral, anti-inflammatory, immunosuppressive, and cytotoxic studies (Girao et al. 2019). Actinomycetes species have led the exploitation in the discovery of new compounds from conservative environments and reawakening of known compounds (Magad et al. 2019). The present review in

this chapter reveals the application of actinomycetes in medical and pharmacological industries.

16.1.1 Bioactivity of Actinomycetes

Among the actinomycetes species, *Streptomyces* isolates produce the most natural bioactive substances, approximately 70–80% of which are widely used in pharmaceutical and agrochemical applications (Berdy 2005; Ganachari et al. 2019; Manteca et al. 2008). Since 1955, the genus *Streptomyces* have been the most important strain used in the production of antibiotics (Watve et al. 2001). The first most crucial product produced from *Streptomyces* was antibiotics (Hwang et al. 2001). The other areas are antibacterial, antitumor, anti-parasitic, and antifungal (Kurtboke 2012; Dietera et al. 2003; Hopwood 1999). It can even be used to produce antivirals, herbicides, insecticides, and pesticides. They are used as a pharmacology substance as immune-modulators, immune-suppressive, and immune-stimulatory. In addition, they act as neurological agents and vasoactive substances (Petrosyan et al. 2003).

16.2 Production of Antibiotics

16.2.1 Tetracycline

In the 1940s, the first members of the tetracycline group were reported as chlortetracycline and oxytetracycline. These molecules were produced from *Streptomyces aureofaciens* and *Streptomyces rimosus* (Finch 1997). The structure is represented in Fig. 16.1a. In the strugecture, the functional groups are attached to the linear fused tetracyclic nucleus. The antibacterial activity was detected in 6-deoxy-6-demethyltetracycline, and it is called the minimum pharmacophore (Mitscher 1978).

16.2.1.1 Mode of Action

The antibiotic will prevent the overload of aminoacyl-tRNA with bacterial ribosome by inhibiting bacterial protein production (Chopra 1994; Schnappinger and Hillen 1996). Depending upon the susceptibility of Gram-positive or Gram-negative organisms, these molecules will transverse from one or more membrane systems to interact with their targets. The mechanism is primarily the uptake and ribosomal binding process. It has dual anti-bacterial and anti-protozoal properties, and the microbial selectively of the class as a whole (Ian and Marilyn 2001).

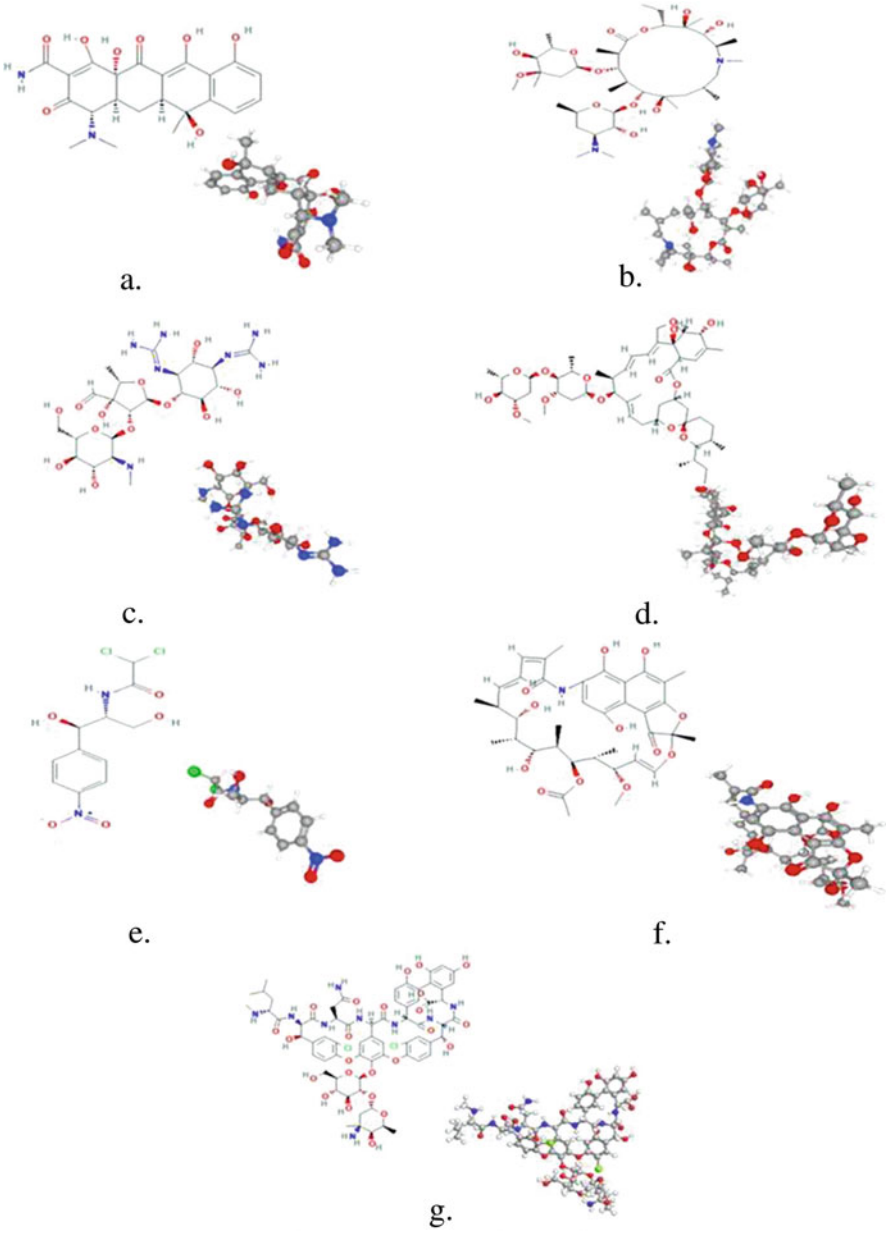

Fig. 16.1 Different types of antibiotic structures produced from the actinomycetes species. (**a**) Structure of tetracycline $C_{22}H_{24}N_2O_8$ 2D and 3D structure. (**b**) Structure of azithromycin (macrolide) $C_{38}H_{72}N_2O_{12}$ 2D and 3D structure. (**c**) Structure of streptomycin (aminoglycoside) $C_{21}H_{39}N_7O_{12}$ 2D and 3D structure. (**d**) Structure of ivermectin $C_{48}H_{74}O_{14}$ 2D and 3D structure. (**e**) Structure of chloramphenicol $C_{11}H_{12}Cl_2N_2O_2$ 2D and 3D structure. (**f**) Structure of rifamycin $C_{37}H_{47}NO_{12}$ 2D and 3D structure. (**g**) Structure of vancomycin (non-beta lactam antibiotic) $C_{66}H_{75}Cl_2N_9O_{24}$ 2D and 3D structure

16.2.1.2 Applications of Tetracycline

Pharmacokinetic Behavior and Administration in Humans

Tetracycline's mode of administration is generally carried out orally, and sometimes it is also available as parenteral products such as Rolitetracycline. The ability to use either oral or parenteral formulations of doxycycline provides the significant benefit of switching programs from intravenous to oral administration (Cunha 1999). It plays a part in the treatment of respiratory tract infections. It penetrates the sebum and is expelled in sweat, which contributes to its effectiveness in managing acne (Ian and Marilyn 2001).

Prophylactics and Human Therapy

For diseases associated with *Helicobacter pylori*, tetracycline is used as triple therapy management for gastritis and peptic ulcers (Van der Hulst et al. 1996). Due to the rapid increase in Mefloquine-resistant *P. falciparum* strains, tetracycline is used as a prophylaxis and malaria treatment (Bunnag et al. 1996; Pradines et al. 2000; Schwarz and Regev 1999). The combination of ofloxacin and minocycline is used in the treatment of leprosy (Ji et al. 1998).

Veterinary Medicine

It is used for the management of infection in cattle, sheep, swine, and poultry (Chopra et al. 1992; Gustafson and Kiser 1985). The drugs were supplemented directly in the form of feed or soluble, and can be directed in aerosols to animals. It is also used in the treatment of domestic pets (Kordick et al. 1997; Levy 1992).

Animal Growth Promoters

To improve the growth and feed translation proficiency of the animals, antibiotics are used in the foods both therapeutically and sub-therapeutically. Generally, low concentrations are auxiliary in the feed to promote the growth of the animals such as young chickens, for example, using chlortetracycline and oxytetracycline (Levy et al. 1999).

Other Uses

It is used to control the infection of aquacultures such as catfish, lobster, and salmon. Furthermore, it is used in treating fruit trees and other plants infected by *Erwiniaamulovara* and mycoplasma infection. It can even be used in seeds infected by the strain *Xanthomonascampestis* and foulbrood disease found in honeybees infected either by *Bacillus larvae* or *Streptococcus pluton* (Levy 1992).

16.3 Aminoglycoside

Aminoglycosides were first reported in 1944 produced from *Streptomyces griseus,* for example as Streptomycin. Others include Neomycin (*S. fradiae*), Kanamycin (*S. kanamyceticus*), Gentamicin (*M. purpurea*), Netilmicin (*Sisomicin*), Tobramycin (*S. tenebrarius*), and amikacin (resultant from kanamycin) (Kevin et al. 2016). The structure of aminoglycoside antibiotic, for example, streptomycin, is represented in Fig. 16.1b. It consists of glycoside linkages to a dibasic aminocyclitol, called 2-deoxystreptamin. It is also connected with residues of amino sugars (Mingeot-Leclercq et al. 1999). From the identity of the animocyclitol moiety, the drug has been categorized into four sub-classes as follows: (a) no deoxystreptamine (for example, carrying a streptidine ring called streptomycin); (b) a mono-substituted deoxystreptamine ring (for example, aparmycin); (c) a 4,5-di-substituted deoxystreptamine ring (for example, neomycin and ribostamycin); or (d) a 4,6-di substituted deoxystreptamine ring (for example, amikacin, gentamycin, tobramycin, and plazomicin) (Magnet and Blanchard 2005).

16.3.1 Mode of Action

Generally, aminoglycosides antibiotics are attracted to and bind the A site on the 16S ribosomal RNA of the 30S ribosome and inhibit the protein synthesis (Wachino and Arakawa 2012). It carries adverse specificity for different areas on the A site and alters its structure. Because of this interface, the antibiotic endorses mistranslation by prompting codon misreading on the aminoacyl transfer RNA delivery. Being prone to errors in protein production leads to the incorrect amassing in the polypeptide chain leading to cell membrane damage (Kotra et al. 2000; Mingeot-Leclercq et al. 1999; Davis et al. 1986; Ramirez and Tolmasky 2010). Some aminoglycoside groups can interact with protein synthesis by hindering elongation or directly inhibiting the origination process (Davis 1987; Wachino and Arakawa 2012; Ramirez and Tolmasky 2010).

16.3.2 Applications of Aminoglycosides

- For treatment, both empirical and definitive therapies for a broad range of these antibiotics are used in a single form of agent and in combination with other antibiotics (Avent et al. 2011; Jackson et al. 2013).
- In high-risk patients, or when the causative pathogen is resistant to commonly used agents for severe sepsis and nosocomial infections, these antibiotics are used in synergy with a beta-lactam for the empirical treatments (American Thoracic Society; Infectious Diseases Society of America 2005; Dellinger et al. 2013).
- A patient who suffers from the MDR strain of carbapenem-resistant *Enterobacteriaceae* (CRE) will be given the option of aminoglycoside antibiotic therapy.
- Combination therapies are used in treating multi-drug resistant tuberculosis (MDR-TB) and non-tuberculosis (NTM) infection. Aminoglycoside possesses potent bactericidal activity against *M. tuberculosis* (Ho et al. 1997).
- The antibiotic therapy is used for patients with fibro cavity, severe nodular/bronchiectasis, or macrolide-resistant lung disease caused by a strain known as *M. avium* complex infection with antibiotics such as amikacin and streptomycin (Griffith et al. 2007). It is also used in treating certain zoonotic infection such as plague and tularemia.

16.4 Macrolides Antibiotic (Azithromycin)

16.4.1 Azithromycin

Macrocyclic is an exciting molecule that possesses high specificity for treating different class of diseases. Macrocyclic drugs are primarily used to cure of infectious diseases (Dubravko and Roberto 2016). Azithromycin is derived from erythromycin, consisting of 14 membered macrolides, erythromycin A, isolated from the *Streptomyces erythreus* (*Saccharo-polysporaerythraea*), and has been used in humans since 1952. Azithromycin (9-dexo-9a-aza-9a-methyl-9a-homoerythromycin) results architecturally from erythromycin A by substituting the 9a carbonyl in the aglycone ring with a methyl-substituted nitrogen in addition to expansion of the ring to 15 members (Bright et al. 1988). The change in the structure blocks the internal response to form the hemiketal, resulting in acid hydrolysis of the ester bond to the neutral cladinose sugar as the main breakdown pathway (Fiese and Steffen 1990). The structure is represented in Fig. 16.1c.

16.4.1.1 Mode of Action

The antibacterial effects caused by azithromycin, such as erythromycin, mainly affect the ability to attach to the 50S ribosomal subunit of an organism by impeding bacterial protein synthesis (Retsema et al. 1987). Macrolides generally inhibit the RNA-dependent protein synthesis by the reverse binding process depending on the domain of the bacterial ribosome (Sturgill and Rapp 1992; Hansen et al. 1999).

16.4.1.2 Application

Upper Respiratory Tract Infections

Azithromycin is commonly used for the treatment of pharyngitis, otitis media, and sinusitis, which are frequently caused by bacteria (Jerry et al. 2011).

Lower Respiratory Tract Infections

Azithromycin has proved to be effective in the treatment of acute bronchitis, acute exacerbation of chronic bronchitis (ACEB), and community-acquired pneumonia, which are generally categorized as respiratory infections (Langtry and Brogden 1997).

Sexually Transmitted Diseases

Azithromycin has shown to be efficacious against *C. trachomatis,* which causes uncomplicated urethritis or cervicitis infection (Lau and Qureshi 2002). It is also recommended to cure genital ulcer diseases triggered by *H. ducreyi* (*chancroid*) (Workowski and Berman 2010). It can be used for the treatment of uncomplicated gonorrhea (Handsfield et al. 1994).

Helicobacter pylori Infections

Azithromycin has shown promise for treatment of *H. pylori* associated peptic ulcer disease, by decreasing ulcer recurrence and promoting healing (Jerry et al. 2011).

Other Diseases

It has shown good effectiveness in avoiding and handling the spread of *Mycobacterium aviumintracellulare* (MAC) disease in patients with human immunodeficiency virus (HIV) (Jerry et al. 2011).

16.5 Ivermectin

Ivermectin is a derivative of a broad spectrum of anti-parasitic macrocyclic lactones called ivermectins. It is isolated and extracted from the species *Streptomyces avermitilis*. Ivermectin (Mk-0933, 22,23-dihydro derivatives of avermectin B1) has arrangements similar to macrolide antibiotics (Sunita et al. 2012). It comprises a blend of two homologous compounds, 22,23-dihydro avermectin B_{1a} (>80%) and 22,23-dihydro avermectins B_{1b} (>20%), as shown in Fig. 16.1d (Campbell 1992).

16.5.1 Mode of Action

Ivermectin brings high-affinity efficacy binding to glutamate-gated chloride ion channels in invertebrate muscle and nerve cells of the microfilaria. This process causes a surge in the absorptivity of the cell membrane to chloride ions and leads to hyperpolarization of the cell, which are important for paralysis and death of the parasite. It is also alleged that it acts as an antagonist of the neurotransmitter gamma-aminobutyric acid (GABA), thereby distracting GABA mediated central nervous system (CNS) neuro synaptic transmission (DRUGBANK Online n.d.).

16.5.2 Application

16.5.2.1 Onchocerciasis (African River Blindness)

Onchocerciasis is used against *Onchocerca volvulus*, characterized by subcutaneous nodules (*onchocercomas*), hard, thickened skin (lichenification), and disseminated prurigo on the trunk and extremities (Okulicz et al. 2004). It is extensively used in humans to control endemic *oncohocerciasis* (De Sol et al. 1990).

16.5.2.2 Filariasis

Filariasis is an infection by filarial worms (*Filariabancrofti, Wuchereriamalayi*) that are key vectors for mosquitoes (*Culex, Anopheles, Aedes, and Manonia*), and it is

cured with oral ivermectin in patients; it disappears, but the efficacy of the antibiotic depends on how often it is administered (Ottesen et al. 1990; Bockarie et al. 1998).

16.5.2.3 *Lymphatic filariasis*

It is a potential therapeutic to control *Bancroftianfilariasis* with or without combination with diethylcarbamazine (Bockarie et al. 1998).

16.5.2.4 Cutaneous Larva Migrans

The disease is mainly caused by *Ancylostomabraziliense*, and it generally occurs because of the cutaneous penetration of hookworm larvae from animals and is treated with a single oral dose of ivermectin (Caumes et al. 1992).

16.5.2.5 Cutaneous Larva Currens

This cutaneous manifestation is associated with *Strongyloidiasis* (Stonglyloidesstercoralis) and treated with ivermectin; patients usually recover within 3 months (Tarlow et al. 2002).

16.5.2.6 Demodicosis

Demodex flliculorum is commonly found on human skin, and it causes demodicosis. It is especially prevalent in immune-suppressed patients, and leads to demodicosis affecting the face, which is challenging to treat. This can be effectively treated with ivermectin; another example is papulopustular rosacea-like facial demodicosis cured by ivermectin and 5% permethrin (Dourmishev et al. 2005).

16.5.2.7 Myiasis

In humans, infection is passed on by fly larvae carrying *Cochilomyia hominivorax,* and the disease is treated with 1% propylene glycol and ivermectin (Victoria et al. 1999). Cutaneous myiasis is caused by *H. lineatum,* and it is cured by ivermectin antibiotic, leading to the impulsive passage of the maggots (Dourmishev et al. 2005).

16.5.2.8 Loiasis

The horsefly (Chyrsobs) is a vector for Loa loa. Clinical manifestation includes a transient prurigo nodularis-like bulge (Calabar distension) on the upper extremities.

Ivermectin has shown excellent results in the treatment of loiasis (Kombila et al. 1998).

16.5.2.9 Gnathostomiasis

Gnathostomiasis is also known as larva migrans profundus and infects humans through the nematode (roundworm) *Gnathostoma spinigerum* and *Gnathostoma hispidum*. Ivermectin has shown effective treatment of gnathostomiasis (Chappuis et al. 2001; Nontasut et al. 2000).

16.5.2.10 Crusted Scabies and Immune-Compromised Patients

Single doses of ivermectin or frequent doses or in union with keratolytic agents or topical scabicidal agents are used in the management of crusted scabies (Del Giudice et al. 1996). It is especially challenging to treat patients with HIV infection; ivermectin has been noted to bring relief in scabies-infected and HIV-infected patients (Meinking et al. 1995).

16.6 Chloramphenicol

Chloramphenicol was introduced in 1949 as the first broad-spectrum antibiotic, and it quickly gained acceptance. The synthesis process is easy, inexpensive, and does not have any significant toxicity, and it can be administered orally or parenterally (Henry et al. 1981). Chloramphenicol can be extracted through a synthetic process and isolated from soil and compost bacteria known as the genera *Streptomyces venzuelae*. This antibiotic can be used in treating meningitides caused by *Heamophilus influenza, Streptococcus pneumonia*, and *Neisseria meningitides* because of its bactericidal action alongside these organisms, and the facility to achieve great concentration in the cerebrospinal fluid (Howard 2004). The structure constitutes a nitrobenzene ring bonded with non-ionic chlorine. It consists of two unusual components, one-nitro ($–NO_2$) group and a dichloroacetyl ($–COCHCl_2$) group. The molecule possesses two asymmetric carbon atoms (shown in Fig. 16.1e). As an outcome, four optical isomers of chloramphenicol are possible. Out of these isomers, only the D(−) thero isomer carries a high efficacy active site for an antibiotic.

16.6.1 Mode of Action

Generally, mRNA's mechanism will bind to the ribosomes and form peptide bonds and inhibit protein synthesis. It will bind reversibly to the 50s subunit of the 70s ribosome, which prevents the attachment of an amino acid to the end of the aminoacyl-RNA (its binding region); hence, it inhibits the activity of the peptidyl transferase enzyme (Howard 2004).

16.6.2 Application

16.6.2.1 *H. influenzae*

Chloramphenicol antibiotic is the choice drug for dealing with severe infection caused by the ampicillin-resistant *H. influenzae* (McGowan et al. 1976). A combination of chloramphenicol and ampicillin was used in therapy for pediatric patients with meningitis caused by *H. influenzae* (American Academy of Pediatrics, Committee on Infectious Disease 1976).

Typhoid and Enteric

Chloramphenicol antibiotics are the prime drug to treat typhoid and enteric (Robertson et al. 1968; The choice of antimicrobial drugs 1978; Gleckman 1975) caused by the bacterium *Salmonella enterica* subsp. *Enterica serovar typhi* growing in the intestines and blood.

Brain Abscess

Some organisms, especially *B. fragilis,* are able to penetrate the blood–brain barrier and spread their toxicity, leading to a brain abscess. Chloramphenicol is the choice of drug for treatment (The choice of antimicrobial drugs 1978; Heineman and Braude 1963; Brewer et al. 1975; Finegold et al. 1975; Unsigned editorial 1978).

Rickettsial Infection

Anaplasmosis, ehrlichisois, and Q fever are types of infection mainly caused by bacteria and have the ability to grow inside cells of another organism. Most of these types of infections are spread through ticks, mites, fleas, or lice. Chloramphenicol or tetracycline can be used as treatment against rickettsia infections (Vianna and Hinman 1960; Peterson 1960; Haynes et al. 1970; Rose et al. 1950).

16.7 Rifamycins

The antibiotic rifamycins were discovered in 1957 and are commonly produced from the fermentation process by *Streptomyces mediteeranei* species (Sensi et al. 1960). The antibiotic for treatment belongs to a family known as Ansamycin antibiotics (Rinehart and Shields 1976; Wehrli 1977). It is so named because it has a basket-like molecular structural design encompassing an aromatic moiety linked at non-adjacent positions by an aliphatic chain (Prelog and Oppolzer 1973). It consists of a heterocyclic structure encompassing a naphthoquinone core spanned by an aliphatic Ansa chain. The napthoquinoic chromophore substance emits rifampicin as a red-orange crystalline color. It consists of four critical hydroxyl groups bound to the Ansa bridge and naphthol rings, which form hydrogen bonds with amino acid residues on the protein. It inhibits the activity of bacterial RNA polymerase (Campbell et al. 2001). Rifampicin 3-(4-methyl-1-piperazinyl)-iminomethyl is derived from the rifamycin SV precursor antibiotic (Bennett 2015), as shown in Fig. 16.1f.

16.7.1 Mode of Action

Rifamycins and other forms of this group of antibiotics have antibacterial activity by inhibiting RNA synthesis. The antibiotic will form strong bonds with the DNA-dependent RNA polymerase of prokaryotes and interfere with the RNA synthesis initially, which takes interfaces between the naphthalene rings and the aromatic moiety in the polymerase. RNA polymerase consists of zinc atoms that allow an obligatory phenolic–OH group to join the naphthalene ring (Keer 2013).

16.7.2 Applications

16.7.2.1 *M. tuberculosis*

Rifamycin has a bactericidal activity for both Gram-positive and Gram-negative bacteria. It is broadly used in infection triggered by *Mycobacterium* sp. (especially *M. tuberculosis*). It can be used in combination with another bactericidal agent to overcome the antibiotic drug resistance scenario.

16.7.2.2 *E. coli* and *C. difficile*

Rifamycin showed inhibition activity of the pathogenic strains of *E. coli* (enterohaemorrhagic, enterotoxigenic ETEC, enteropathogenic, and enteroaggregative EAEC strains). The *Clostridium difficile* strain has been treated with rifamycin SV (Farrell et al. 2011).

16.7.2.3 Other Infections

Rifamycin is commonly used to eliminate the infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA) through synergetic antibiotics. It is also used in osteomyelitis and prosthetic joint infections (Perlroth et al. 2008). This drug can be used against *Neisseria meningitidis* (meningococcal) infections and as a substitute treatment for toxicities that occurred through tick-borne pathogens such as *Borrelia burgdorferi* and *Anaplasma phagocytophilum* (Wormser et al. 2006; Thomas et al. 2009).

16.8 Vancomycin

Vancomycin is a tricyclic glycopeptide antibiotic, initially reported by the scientist of Eli Lily company in 1956. A new actinomycete species was discovered, known as *Streptomyces orientalis* (now *Nocardisorientalis*), isolated from the soil samples at Borneo (Jerome 1987). Another strain used in the production of vancomycin was reported in 1958, which is *Amycolatopsis orientalis,* and has been introduced in clinical practice (Rossolini et al. 2014). Vancomycin is prescribed to combat severe infection caused by Gram-positive pathogens and for the organisms that are resistant to the added antimicrobial agents. Vancomycin is recommended for patients allergic to penicillin and cephalosporin antibiotics (Gupta et al. 2011; Hicks and Hernandez 2011). It consists of a glycosylated hexapeptide chain connected with unusual amino acids. Vancomycin is rigid due its aromatic rings, which are halogenated and cross-linked with aryl ether bonds. It carriers a seven-member peptide chain with two sugar moieties, vancosamine and glucose. The vancomycin chemical structure is shown in Fig. 16.1g.

16.8.1 Mode of Action

Vancomycin can act upon the invading bacterial pathogens by directly inhibiting the cell wall synthesis, and more precisely, it will inhibit the peptidoglycan biosynthesis (Hicks and Hernandez 2011). In Gram-positive bacterium, this element is also considerable, which forms massive and insoluble layers on the outer membrane, totaling up to 40 layers comprising multiple skeletons of amino sugars *N*-acetyl-glucosamine and *N*-acetyl muramic (Chambers 2010). The latter encloses lateral short peptide filtrates with cross-links, which are a type of high glassy resistant polymeric chain (Chambers 2010). The drug constrains this polymerization or the transglycosylase reaction once it binds with high affinity to the C-terminal D-alanyl D-alanine residues of lipid-linked cell wall precursors and bridges the linkage to the glycopeptide polymer (Hicks and Hernandez 2011). As an outcome, it hinders the

cross-links of peptides from binding to tetrapeptide side chains; namely, it averts its linkage to the growing tip of the peptidoglycan (Chambers 2010).

16.8.2 Application

16.8.2.1 *Staphylococcus aureus*

Vancomycin is the most effective drug for treating severe penicillin-resistant staphylococcal infections, including pneumonia, osteomyelitis, endocarditis, sepsis, and wound infections (Geraci et al. 1956, 1985). It is an efficient drug for the treatment of MRSA (Craven et al. 1983; Thompson et al. 1982).

16.8.2.2 *Staphylococcus epidermidis*

The increased prevalence of *S. epidermidis*as nosocomial infections, and particularly patients suffering from granulocytopenia (MacCulloch 1981; Wade et al. 1982) and *S. epidermidis,* is most frequently associated with catheter infection (Tchekmedyian et al. 1986; Schoenbaum et al. 1975). Vancomycin can be used as therapy.

16.8.2.3 Non-enterococcal Streptococci

In patients infected with streptococcal and allergic to the beta-lactam antibiotic, vancomycin acts as an effective agent against these infections. It also has a synergistic effect with aminoglycoside treated *S. viridans* or *S. bovis,* which causes endocarditis on native valves (Geraci and Wilson 1981).

16.8.2.4 Enterococcus

The antibiotic vancomycin is generally used to treat penicillin-allergic patients. Its role is very significant in controlling enterococcal infections, together with endocarditis (Hande et al. 1976).

16.8.2.5 Diphtheroid

Vancomycin can be used as an empiric therapy against JK-diphtheroids. This strain has a crucial role in controlling the main pathogen in the immunocompromised host (Schoch and Cunha 1986). *C. diphtheria* is collectively known as diphtheroids (Hande et al. 1976).

16.8.2.6 *Pseudomembranous colitis*

PMC or antibiotic-associated *C. difficile* colitis is an ailment described by profuse watery diarrhea, including abdominal pain, blood stool, and fever. Vancomycin is effective in treating PMC and *C. difficile* colitis (Silva et al. 1981).

16.8.2.7 Antibacterial Activity

An agent or substance that hinders bacterial growth or destroys bacteria is known as antibacterial activity. Many antibacterial products were produced from actinomycetes species and are widely used in the present status. A bonactin compound extracted from *Streptomyces* sp. BD21–2 showed biological function over Gram-positive and Gram-negative organisms (Schumacher et al. 2003). A novel class of a gucyclinone antibiotic was extracted from the *Streptomyces griseus NTK* 97 strain, known as frigocyclinone (Fig. 16.2). The drug consists of the moiety terramycin to which a c-glycoside linkage is attached with amino-de-oxysugar ossamine. It has exhibited bactericidal tendency for Gram-positive bacteria (Bruntner et al. 2005). Benzooxzle antibiotics such as carboxamyci produced from *Streptomyces* sp. NTK 937 showed inhibition action for Gram-positive bacteria (Hohmann et al. 2009). An

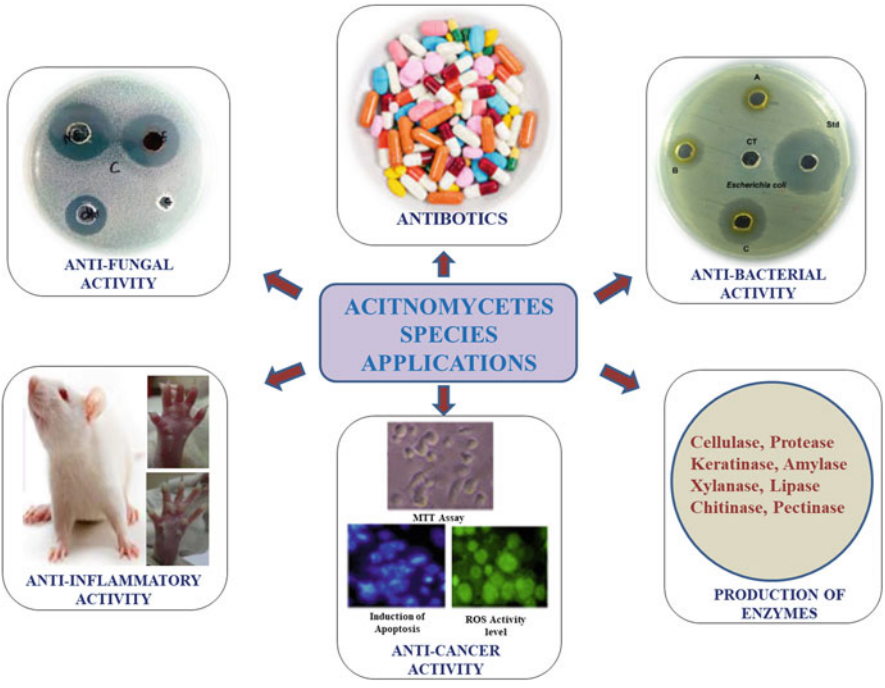

Fig. 16.2 Application of the products produced from actinomycetes species

antibiotic known as bis-anthraquinone extracted from *Streptomyces* sp. showed biotic activities against VRE, MSSA, and TRSA, respectively (Socha et al. 2006), as shown in Tables 16.1 and 16.2.

16.8.2.8 Antifungal Activity

A substance or agent that acts to inhibit or kill fungi is known as having antifungal activity. Numerous antibiotics have been isolated from different microorganisms and showed effective fungicidal activity against pathogenic fungi. Among *Streptomyces* species, the strain *Streptomyces* sp. DA11 isolated from marine samples can produce the enzyme chitinase and has fungicidal activity against *Aspergillus niger* and *Candida albicans* (Han et al. 2009). The chitinase enzyme has wide application in the biomedical field because it shows biocompatible quality and fungicidal activity. It is also used in wound healing, cartilage tissue engineering, drug delivery, and nerve generation (Shi et al. 2006; Yan et al. 2006). Candihexin is a compound produced from *Streptomyces viridoflavus* showing antifungal activity (Martin and McDaniel 1974). Similarly, another compound nanomycin, produced from the *Streptomyces rosa,* had antifungal activity (Omura et al. 1974).

16.8.2.9 Anti-inflammatory Activity

Anti-inflammatory drugs can be used for the treatment of symptoms like swelling and redness. Inflammation means consumed flames, and nowadays, it represents a type of soreness somewhere on your body that is red, feels hot, and swells up. Cyclomarin, a type of new cyclic heptapeptide compound extracted from *Streptomyces* sp., exhibited anti-inflammatory activity in both in vivo and in vitro assays (Renner et al. 1999). A strain called *Streptomyces* sp. CNB-091, isolated from the jellyfish *Cassiopeia xamachana*, produced bicyclic depsipeptides known as salinamides A and B; these metabolites showed anti-inflammatory activity (Moore et al. 1999). A bioactive compound extracted from the *streptomyces* sp. VITPSA strain from marine samples has shown 70% hemolysis, indicating it has a moderate anti-inflammatory activity (Pooja et al. 2017), as shown in Table 16.1.

16.8.2.10 Anticancer Activity

Cancer is a major problem affecting human wellbeing. Among the different kinds of cancer, breast cancer ranks second in universal and causes the highest mortality in women (Ravikumar et al. 2010). Chinikomycin is a compound extracted from *Streptomyces* sp. and has shown anti-tumor efficacy toward human cancer cell lines (Li et al. 2005). The *Streptomyces aueroverticillatus* NPS001583 strain was isolated from marine sediments, and it produces a 22 membered macrocyclic lactam known as *Aureoverticillactam.* It has shown anti-tumor activity for human colorectal

Table 16.1 Natural products derived from actinomycetes and their antimicrobial therapeutic

Source of organism	Natural product (NP) of derivative	Chemical class	Drug name	Application	References
Non-marine sources					
Saccharopolyspora erythraea	Erythromycin (NP-derivative)	Macrolide	Telithromycin	Antibacterial for both Gram-positive and Gram-negative	Butler et al. (2017)
Streptomyces cattelya	Thienamycin (NP-derivative)	Carbapenem	Biapenem	Antibacterial for both Gram-positive and Gram-negative	Butler et al. (2017)
Streptomyces cattelya	Thienamycin (NP-derivative)	Carbapenem	Ertapenem	Antibacterial for Gram-positive and Gram-negative	Butler et al. (2017)
Streptomyces roseosporus	Natural product	Lipopeptide	Daptomycin	Antibacterial for Gram-positive	Butler et al. (2017)
Stretomyces sp.	Thienamycin (NP-derivative)	Carbapenem	Doripenen	Antibacterial for both Gram-positive and Gram-negative	Butler et al. (2017)
Streptomyces aureofaciens	Tetracycline (NP-derivative)	Tetracycline	Tigecycline	Antibacterial for both Gram-positive and Gram-negative	Butler et al. (2017)
Stretomyces sp.	Thienamycin (NP-derivative)	Carbapenem	Tebipenem pivoxil	Antibacterial for Gram-positive	Butler et al. (2017)
Amycolatopis orientalis	Vancomycin (NP-derivative)	Glycopeptide	Tealvacin	Antibacterial for Gram-positive	Butler et al. (2017)
Dactylosporangium aurantiacum	Natural product	Tiacumicin	Fidaxomicin	Antibacterial for Gram-positive	Butler et al. (2017)
Nonomuria sp.	Teicoplanin (NP-derivative)	Glycopeptide	Dalbavancin	Antibacterial for Gram-positive	Butler et al. (2017)
Amylcolastopsis orientalis	Chloroeremomycin (NP-derivative)	Glycopeptide	Oritavancin	Antibacterial for Gram-positive	Butler et al. (2017)
Actinomycete Strain	NP-derivative	Penicillanic acid sulfone derivative and β-lactamase inhibitor	Tazobactam	Antibacterial for Gram-negative	Butler et al. (2017)

Marine sources					
Salinispora tropica	Natural product	Beta-lactone-gamma	Salinosporamide A (Marizomib)	Multiple cancer	Feling et al. (2003)
Salinispora sp.	Natural product	Lactam	Arenamides A and B	Inflammation	Asolkar et al. (2009)
Streptomyces sp.	Natural product	Polyketide	Anthracimycin	Anthrax	Jnag et al. (2013)

Table 16.2 Sreening of actinomycetes strains by physicochemical to discover new compound up to March 2018

Source of organism	Producing microorganisms	Name of the compound	Application	References
[a]KML, Irumamycin producing strain, [b]36 years	*Streptomyces sulbflavus* subsp. *Irumaenis AM-3603*	Bisoxazolomycin	Antibacterial	Koomsiri et al. (2017)
[a]KML, Streptomycin producing strain, [b]43 years	*Streptomyces griseus OS-3601*	Iminimycin A and B	Antibacterial	Nakashima et al. (2016a, b)
[a]KML, Nanomycin producing strain, [b]36 years	*Streptomyces rosa* subsp. *Notoensis OS-3966*	Nanomycin F–H	Inhibitor of epithelial–mesenchymal transition induced cells	Nakashima et al. (2015a, 2017)
Roots of Capsicum frutescents in Thailand	*Actinoallomu rus fulvus MK 10-036*	Actinoallolide A–E	Antitrypanosomal	Inahashi et al. (2015)
Roots of mondo grass in Saitama Pref, Japan	*A.fulvus K09-0307*	Actinoallolide A–E	Antitrypanosomal	Inahashi et al. (2015)
Roots of fern in Hamura city, Tokyo, Japan	*Allostreptomyces* sp. *K12-0794*	Hamuramicin A and B	Antibacterial	Suga et al. (2018)
Roots of orchid in Iriomote Island, Japan	*Streptosporangium oxazolinicym K07-0460* ^{T}	Sproxazomicin A–C	Antitrypanosomal	Inahashi et al. (2011a, b)
Roots of orchid in Iriomote Island, Japan	*Polymorphospora rubra K07-0510*	Trehangelin A–C	Anti-lipid peroxidation	Nakashima et al. (2013), Inahashi et al. (2016)
Roots of orchid in Iriomote Island, Japan	*Polymorphospora rubra K07-0510*	Trehangelin A–C	Enhanced production of collagen	Nakashima et al. (2013), Inahashi et al. (2016)
Sediment from mangrove forest in Iriomote Island, Japan	*Lechevalieria aerocolonigenes K10-0216*	Mangromicin A–I	Antitrypanosomal	Nakashima et al. (2014a, b, 2015b)
Sediment from mangrove forest in Iriomote island, Japan	*Lechevalieria aerocolonigenes K10-0216*	Mangromicin A–I	Antioxidative	Nakashima et al. (2014a, b, 2015b)
Sediment from mangrove forest in Iriomote Island, Japan	*Lechevalieria aerocolonigenes K10-0216*	K10-0216 KA and KB	Inhibitory effect on the lipid accumulation	Nakashima et al. (2015c)
Sediment from mangrove forest	*Lechevalieria aerocolonigenes K10-0216*	Pyrizomicin A and B	Antimicrobial	Kimura et al. (2018a)

(continued)

Table 16.2 (continued)

Source of organism	Producing microorganisms	Name of the compound	Application	References
in Iriomote Island, Japan				
Sea sediment, Namako Pond in Kagoshima Pre, Japan	*Mumia* sp. *YSP-2-79*	Mumiamicin	Antibacterial	Kimura et al. (2018b)
Sea sediment, Namako Pond in Kagoshima Pre, Japan	*Mumia* sp. *YSP-2-79*	Mumiamicin	Antioxidative	Kimura et al. (2018b)
Soil, Kangawa a Pref, Japan	*Actinomadura* sp. *K13-0306*	Sagamilactam	Cytotoxicity	Kimura et al. (2016)
Soil, Kangawa a Pref, Japan	*Actinomadura* sp. *K13-0306*	Sagamilactam	Antitrypanosomal	Kimura et al. (2016)
Soil, Okinawa a Pref, Japan	*Amycolatopsis* sp. *K16-0194*	Dipyrimicin A and B	Antibacterial	Izuta et al. (2018)

[a]*KML* Kitasato Microbial Library
[b]Length of preservation by Lyophilization**; No. 1–3,** Compounds from the KML**; No. 4–13,** Compounds from fresh isolates **(No. 4–7, Roots of plants; No. 8–10, Sediment of mangrove forest; No. 11, Marine sediment; Nos. 12 and 13, Soil)**

adenocarcinoma HT-29, Jurkat leukemia, and mouse melanoma B16F10 cell lines (Mitchell et al. 2004). *Streptomyces chinaensis* AUBN1/7 produced the polyketide structural compound called 1-hydroxyl-1-norresistomycin from marine samples and has shown antitumor activity (Gorajana et al. 2005). A butenolides structure compound extracted from the species *Streptoverticillium luteoverticillantum* 11,014 has shown antitumor activity (Li et al. 2006) (Table 16.1).

16.8.2.11 Antitrypanosomal Activity

The first antitrypanosomal drug was discovered in 1922 by scientist Paul Ehrlich. He discovered two drugs known as suramin and pentamidine. These two are highly effective against cerebral stages of African trypanosomiasis, of both *T. brucei gambiense* and *T. brycei rhodesiense* type (Stefan and Walter 2008). The source, organism, and its application are shown in Table 16.2.

16.8.2.12 Industrially Important Enzyme Production from Actinomycetes

Actinomycetes secrete the enzyme called amylases from cells to indicate its extracellular digestion activity is ready, for example, alpha-amylase. Starch degrading

amylolytic enzymes have wide applications in the food industry, fermentation, textile and paper industries, and other biotechnological applications (Pandey et al. 2000). Another important enzyme, lipase, is also produced from actinomycetes species. These enzymes are extensively used in detergent industries, foodstuff, oleochemical diagnostic settings, and pharmaceuticals (Schmid and Verger 1998). L-Asparagine produced from *S. albidoflavus, S. griseus, S. Karnatakensis,* and *Nocardia* sp. has therapeutic use in managing human cancers, especially acute lymphoblastic leukemia (Gallagher et al. 1989; Verma et al. 2007).

16.8.2.13 Other Applications

- Ecological importance: They are used as degraders of toxic materials and in bioremediation.
- Volatile organic compounds: Actinomycetes are used in the production of geosmin.
- Extracellular peroxidase activity: Actinomycetes species produce the extracellular components that can be used to prepare diagnostic kits.
- Agro active compounds: They are used in the production of fungicides such as kasugamycin and polyoxin B and D.
- Plant growth-promoting agents: They are widely used in producing bio-control agents and plant growth-promoting products for controlling *Fusarium* and *Verticillium wilts* as a seed coating and hormone-like auxins, gibberellins, and cytokinins, respectively.

16.9 Conclusion

Actinomycetes species have been known for the past 50 years as the prolific manufacturer of novel bioactive compounds widely used in different applications. Hence, these actinomycetes can be explored further to produce different bioactive compounds that would significantly improve health conditions among the population and develop humankind's socio-economic status.

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