MEDWIN PUBLISHERS
Committed to Create Value for Researchers

Open Access Journal of Microbiology & Biotechnology
ISSN: 2576-7771

Actinotherapy: Highlights on the Pharmaceutical Potentials of Actinomycetes

Elkhateeb WA*, Elnahas MO and Daba GM

Chemistry of Natural and Microbial Products Department, Pharmaceutical Industries Division, National Research Centre, Egypt

***Corresponding author:** Waill A Elkhateeb, Chemistry of Natural and Microbial Products Department, Pharmaceutical Industries Division, National Research Centre, Dokki, Giza, 12622, Egypt, Tel: +201013241936; Fax: +20233370931; Email: waillahmed@yahoo.com

Review Article
Volume 6 Issue 2
Received Date: April 12, 2021
Published Date: April 27, 2021
DOI: 10.23880/oajmb-16000194

Abstract

Endophytes are microorganisms that are associated with the plant tissues without having any harmful effect on the host plant. Various medicinal plants are valuable sources of endophytic actinobacteria that exhibit high economic impact. The endophytic microbes can synthesis a wide range of novel compounds that found great applications in agricultural, pharmaceutical, as well as other industries. It is noteworthy to focus the current research on valuable applications of these microbial populations that could help in solving many problems related to the environment, agriculture, and health. Moreover, the characterization of different endophytic actinobacteria that are associated with valuable medicinal plants may help understanding plant-endophyte interactions. The current review discusses the diversity of endophytic actinobacteria rich in therapeutic agents that have been known for their medicinal applications.

Keywords: Endophytic Actinomycetes; Streptomycetes; Pharmaceutical Potentials; Biological Activities

Introduction

Actinomycetes are Gram-positive bacteria with high G + C content. They are an important component of microbial diversity and are being recovered from a range of habitats and unusual environments [1]. GC content is a crude measure of the relatedness of microorganisms, but it is still useful for differentiating large phylogenetic divisions. They exhibit a wide range of life cycles, which are unique amongst prokaryotes. Actinomycetes are unicellular like bacteria, but they produce a mycelium which is non-septate (coenocytic) and more slender, like true bacteria they do not have distinct cell-wall and their cell wall is without chitin and cellulose (commonly found in the cell wall of fungi). On culture media unlike slimy distinct colonies of true bacteria which grow quickly, actinomycetes colonies grow slowly, show powdery consistency and stick firmly to the agar surface. They produce hyphae and conidia/sporangia-like fungi. Certain actinomycetes whose hyphae undergo segmentation resemble bacteria, both morphologically and physiologically [2]. Actinomycetes are sensitive to acidity / low PH (optimum PH range 6.5 to 8.0). Actinomycetes are heterotrophic, aerobic, and mesophilic (25-30°C) organisms and some species are commonly present in compost and manures are thermophilic growing at 55-65°C temperature (Thermoatinomycetes, Streptomyces) [3,4].

The Actinomycetes get their name from the fact that some of them form branching filaments that look kind of like the branching hyphae (collectively referred to as a mycelium) formed by fungi. To lessen confusion, Actinomycetes are now commonly referred to as Actinobacteria [5]. Actinobacteria are neat because they tend to produce cool secondary metabolites, many of which have been successfully isolated and turned into useful drugs and other organic chemicals. In particular, an appreciable number of Actinobacteria produce antibiotics, which they use to compete with fungi and other bacteria for resources [6]. Actinomycetes are considered as a unique group of microorganism which locus between the true bacteria and the true fungi. Actinomycetes are the prokaryotic microorganisms that belong to the phylum Actinobacteria and possess mycelia like fungus and form spores. They are Gram-positive, spore-forming bacteria characterized by the formation of aerial and substrate mycelia [7].

The greatest variety of antibiotics is produced by Actinomycetes among all microbes. More than 50% of the known natural antibiotics are produced by Actinomycetes [8]. Actinomycetes are omnipresent nature's pharmacists which provide us with a plethora of novel bioactive compounds to be explored. It is through interdisciplinary collaborations and innovative ideas that we will continue to unlock their potential. Actinomycetes are the largest group among the 18 major categories in the classification of bacteria, have different morphological, cultural, biochemical, and physiological characters. About 75% of the drug compounds derived from natural sources is known to be obtained from this large group of Gram-positive soil bacteria [9,10]. Actinomycetes are potential producers of many enzymes, enzyme inhibitors, growth-promoting substances, and antibiotics [11].

The genus *Streptomyces* is a particularly fruitful source of these compounds, many which have been developed as antifungals, antibiotics (Antibacterials), and chemotherapeutic (anticancer) drugs. Actinomycetes, mainly *Streptomyces* species, produce tetracyclines, aminoglycosides (streptomycin and its relatives), macrolides (erythromycin and its relatives), chloramphenicol, ivermectin, rifamycins, and most other clinically useful antibiotics that are not beta-lactams [12,13]. Actinomycetes are the most predominantly used in antibiotic production technology. Nearly all plant species serve as a source for endophytes and are accepted as a promising source of novel medicinal compounds. Using microorganism 23,000 active secondary metabolites were produced, in that 10,000 were isolated from actinomycetes. *Streptomyces* species produce 7,600 bioactive compounds. Depending upon the source of isolation the biological function of actinomycetes varies [14-16]. Singh and Dubey, [17], have isolated and identified novel endophytic strain *Streptomyces californicus* ADR1 from the plant *Datura metel*. Secondary metabolites produced by *Streptomyces californicus* ADR1 were characterized for their antibacterial, anti-biofilm, and antioxidant properties.

Endophytic Actinomycetes

Endophytes are microbes that inhabit such biotopes, namely, higher plants, which are why they are currently considered to be a pool of novel secondary metabolites offering the potential for applications in medicine, agriculture, and industry. These microbial resources will be of interest to mankind providing sustainable and environment-friendly solutions. Recently, endophytic actinomycetes are being progressively explored for new therapeutic molecules which may effectively address the current human health issues in the areas of infectious diseases [18,19]. Recently many studies reported that several bio-pharmacological compounds were isolated from endophytes actinomycetes with activities such as antiviral, anti-inflammatory, antimicrobial, and antitumor activities and antioxidant activities [20-22].

Endophytic actinomycetes, which reside within the plant tissues such as roots, stem, and leaves, are reported to have several beneficial effects on the host plants, such as, inhibition of pathogens, increase in the availability of nutrients like nitrogen and phosphorus, increasing plant growth, etc. Besides these roles, they are also known to produce secondary metabolites of varied therapeutic significance [23]. The beneficial interactions of endophytic actinomycetes with plants are being considered an important area of research. These endophytic actinomycetes are an attractive source of novel bioactive compounds having pharmaceutical and agricultural importance [24]. *Enterococcus faecium* (vancomycin resistant) and *Staphylococcus aureus* (methicillin resistant) are considered as high-priority pathogens for which new antibiotics are required the most urgently. Infections involving such pathogens are often associated with biofilms, which are responsible for a multi-fold increase in drug resistance of the pathogens, therefore, it is highly wanted new antibiotics possess anti-biofilm activities [17,25]. So there is an urgent need to explore novel organisms like endophytic actinomycetes excrete novel metabolites for therapeutic applications [18,26].

Pharmaceutical Potentials of Actinomycetes

Actinomycetes produce different types of new secondary metabolites; many of these metabolites possess biological activities and have the potential to be developed as therapeutic agents. Endophytic actinomycetes and marine actinomycetes are the underexploited sources for the discovery of novel secondary metabolites [27,28]. Actinomycetes are pharmaceutically relevant microorganisms holding great potential in the treatment of a wide range of diseases. Bioactive compounds isolated from Endophytic and marine actinomycetes have shown promising bioactivities as an antibiotic, antifungal, cytotoxic, neurotoxic, antimitotic, antiviral, anticancer, and antineoplastic agent [29].

Antimicrobial Activity

Several diseases that develop by various plant pathogens are found to be suppressed by actinomycetes. Also, these actinomycetes were effective against various soil-borne pathogens that could infect plants. Among these pathogens are *Aphanidermatum* sp., *Colletotrichum orbiculare*, *Fusarium oxysporum*, *Plectosporium tabacinum*, *Phythium* sp., *Rhizoctonia solani* and *Verticillium da*hlia, etc. *Azadirachta indica*, *Emblica officinalis*, *Murraya koenigii*, *Rauwolfia serpentine*, *Terminalia chebula* are examples of medicinal plants. About 76 endophytic actinomycetes were isolated from the leaves, stems, and roots of these plants. Of which 21 endophytic actinomycetes exhibit antimicrobial activity against some pathogen. Moreover, *Microbispora rosea* (EAAG89) isolate showed maximum antimicrobial activity against *Pseudomonas syringae* and *Staphylococcus aureus*. A broad-spectrum antimicrobial activity was exerted by many Streptomycetes sp., against various bacteria and fungi such as *Escherichia coli*, *Pseudomonas aeruginosa, Aspergillus Niger*, and *Fusarium oxysporum* [30].

Another study showed that 34 actinomycetes were also isolated from some medicinal herbs such as *Abrus precatorius* L., *Aloe vera* L. Burm.F, *Asparagus racemoses* Willd, *Catharanthus roseus* L.G.Don.Burm and *Plumbago zeylanica* L. Thirteen isolates out of 34 showed antimicrobial activities against both Gram-positive and Gram-negative bacteria [31]. It was also reported that 131 endophytic actinomycetes strains were isolated from roots of banana. Of which, 99 were *Streptomyces* species, 28 were Streptoverticillium, 2 were Streptosporangium, however, the remaining 2 strains were not determined. The studies showed that healthy banana plantlets develop resistance against *Fusarium wilt* through the antimicrobial effect of the endophytic actinomycetes named '*Streptomyces grise rubiginous'* [32]. Additionally, the endophytic actinobacteria played an important role in treating multidrug-resistant human pathogens where the endophytic strains act as a valuable source of novel antimicrobial compounds [33,34]. *Nocardiopsis* sp., GRG1 KT235640), is an endophytic actinobacterium that was isolated from brown algae. This species showed antibacterial activity against some urinary tract pathogens [35]. Moreover, *Micrococcus yunnanensis* strain rsk5, isolated from the medicinal plant named *Catharanthus roseus*, showed a broad spectrum of antibacterial activity against *Staphylococcus aureus* as well as other pathogens such as *Bacillus megaterium*, *Bacillus subtilis, Escherichia coli*, *Enterococcus faecalis, Pseudomonas aeruginosa*, and *Proteus vulgaris* [34].

Antidiabetic Activity

Some endophytic actinobacteria also showed antidiabetic activity due to the production of alpha-glucosidase inhibitors. Some strains were isolated from medicinal plants such as *Caesalpinia sappans*, *Curcuma aeruginosa,* and *Tinospora crispa*, which exhibited promising antidiabetic properties. These strains produce compounds that can retard the glucose release from the dietary complex carbohydrates as well as delay the glucose absorption. Endophytic actinomycete BWA65 was reported to produce these inhibitors which an antidiabetic activity that doubled its host plant (*Tinospora crispa*). Moreover, it was reported that the tissue cultured plants in which endophytes were devoted showed very low capacity to produce the inhibitor compounds [36]. Thus, indicating that the production of alpha-glucosidase inhibitors by this plant is greatly correlated to the presence of endophytic actinobacteria [36]. Also, a previous study reported the production of alpha-amylase inhibitors from endophytic actinobacteria *Streptomyces longisporoflavus* and *Streptomyces* sp. that were isolated from an antidiabetic medicinal plants *Leucas ciliata* and *Rauwolfia densiflora*. The alpha-amylase inhibitors exerted an antidiabetic activity like that of alpha-glucosidase inhibitors. The actinobacteria extracts did not exhibit insulin-releasing capacity, however, the extracts were found to improve the ability of insulin to pass glucose into muscles [12].

Larvicidal and Antimalarial Activity

The larvicidal activity of various *Streptomyces* sp. isolated from *Artemisia herba*-alba, *Balotta undulate, Echinops spinosus*, and *Mentha longifolia* was reported El-Shatoury S, et al. [37]. This studied showed the cytotoxic effect of some endophytic actinobacteria against larvae of *Artemia salina*. Moreover, the actinobacteria from *Artemisia* and *Echinops* showed a mortality rate that reached up to 100 % death after 12 h of treatment. Two endophytes named *Streptomyces albovinaceus* and *S. badius* were isolated from plants belonging to the family *Asteraceae* were also reported to exhibit larvicidal effect against the first and fourth instar stages of *Culex quinquefasciatus* (mosquito larvae) [21].

A study reported by Castillo, et al. [38], showed that munumbicins type D was considerably active against the parasite *Plasmodium falciparum* that causes malaria, with IC_{50} of 4.5 ng ml^{-1}. This study also reported that antimalarial activity of each of the munumbicins against *P. falciparum* was very promising with IC_{50} of 175,130, 6.5, and 4.5 ng ml^{-1} in munumbicin A–D, respectively. A special interest was directed toward munumbicins C and D due to their low IC_{50} values. And it was observed that munumbicins B, C, and D (in a concentration of 80 μg ml^{-1}) did not result in any obvious lysis to human red blood cells. Thus, the authors suggested that the employment of these compounds as antimalarial drugs due to their effectiveness with reduced toxicity [38,39].

Cytotoxicity

Some bioactive compounds with anticancer activity were isolated from endophytic actinobacteria of medicinal plants. Kakadumicin A from endophytic streptomycete (NRRL 30566) inhibited the human breast cancer cell line BT20 where IC_{50} was 4.5 ng ml^{-1} [40]. Also, human cancer cell lines OVCAR-3, SF539, NCI-H522, and LOX-IMVI were reported to be inhibited by pterocidin extracted from *Streptomyces hygroscopicus* TP-A0451 that was isolated from *Pteridium aquilinum* plant [41]. Moreover, the cytotoxic activity of naphtomycin A obtained from *Streptomyces* sp. CS isolated from *Maytenus hookeri* towards A549 and P388 and human cells were detected and it showed promising antitumor activity with IC_{50} 3.17 and 0.07 mM, respectively [42-44]. The results of another study also examined the cytotoxic activity of 6-alkalysalicilic acids, salaceyins A and B derived from *Streptomyces laceyi* MS53 against SKBR3 human breast cancer cell line. I t was found that these compounds inhibit the cancer cells and the IC_{50} values were 3.0 and 5.5 mg ml^{-1} [45]. Also, an anticancerous drug named paclitaxel was obtained from endophytic actinomycete *Kitasatospora* sp. that was isolated from *Taxus baccata*. Another antitumor compound brartemicin was extracted from the actinomycete *Nonomuraea* sp. that was isolated from *Artemisia vulgaris*. Brartemicin is a trehalose-derived metabolite that was able to inhibit the invasion of murine colon carcinoma 26-L5 cells with an IC_{50} value of 0.39 μM [46].

Taechowisan, et al. [47], examined the effect of 4-phenylcoumarins obtained from *Streptomyces aureofaciens* on human lung cancer cell lines and observed that 5,7-dimethoxy-4-phenylcoumarin inhibited the cell proliferation more actively comparing to 5,7-dimethoxy-4-p-methoxylphenylcoumarin. Moreover, it was reported that 5, 7-dimethoxy-4-phenylcoumarin could result in delaying or preventing the formation of metastases, that is besides the low cytotoxicity to normal cells. Taken together, this compound might be recommended as chemo-preventatives and also might be combined with other antitumor treatments [47].

Antioxidant and Antiinflammatory Activities

The phenolic compounds are well known as natural antioxidants that could protect the cells from the harmful effects of free radicals by scavenging them. *Streptomyces* sp. isolated from *Alpinia oxyphylla* are endophytic actinobacteria that produce two compounds which are 2, 6-dimethoxy terephthalic acid and yangjinhualine A. these compounds exerted antioxidant activity [48,49]. About 66.6 % of the total endophytic actinobacteria that have been isolated from various medicinal plant isolates showed their ability to produce effective antioxidant compounds [21]. Another, bioactive compounds that showed antiinflammatory effect were also produced by some endophytic actinomycetes.

Another study showed the free radical-scavenging capacity of the crude extract of *Streptomyces* sp. BO-07: an endophyte in *Boesenbergia rotunda* (L.) Mansf A. through the decoloration of the ethanolic solution of DPPH. Two compounds had shown antioxidant activity with Scavenging capacity SC_{50} values of 85.84 and 88.26 μg/ml, respectively. L-ascorbic acid was employed as a positive control, with SC_{50} value of 50.25 μg/ml [47]. Interestingly, *Streptomyces aureofaciens* was observed to produce 5,7-dimethyloxy-4-p-methoxylphenylcoumarin and 5, 7-dimethoxy-4-phenylcoumarin, these are two compounds are potent antiinflammatory agents [50].

Enzyme Production

Among the different genera of actinomycetes, *Streptomyces* sp. is known to produce various enzymes. Enzymes play important roles in different industries since enzymes increase the required reaction rates compared to the actual chemical reaction. Enzyme production 23 endophytic actinomycetes isolates from the tomato plant was examined. The isolated actinomycetes were tested to hydrolyze different substrates as well as evaluating the enzymatic index (EI) for different enzymes such as catalase, amylase, cellulose esterase, catalase, caseinase, gelatinase and pectinase, and lipase. They showed that lipases activity showed the highest EI. However, the cellulose hydrolysis showed the lowest EI value [16]. *Streptomyces gulbargensis* DAS 131 is an alkali-thermotolerant strain that is newly isolated. This strain is employed to produce an extracellular amylase that has a wide range of industrial applications including distilling, textile, brewing, and food industries [51]. Many *Streptomyces* sp. are well known as producers of cellulase. Among these species are *Streptomyces rutgersensis*, *S. drozdowiczii*, *S. lividans* and *S. longispororuber*. The produced cellulase found great applications in biorefineries, textiles, brewing, wine, animal feedstocks industries as well as pretreatment of industrial wastes [51]. Additionally, *Streptomyces* sp. isolated from Coringa mangrove forest also produce cellulase [52]. Mangrove forest is an ecosystem that is enriched with large quantities of organic matter. About 30–50% of the organic matters in mangrove leaves are leachable, water-soluble compounds, such as tannins and sugars, and the remaining part consists of plant structural polymers which are mainly lignocelluloses [53,54]. The cellulase enzymes produced by the microorganisms that degrade cellulose have gained great importance due to the diversity of their application.

Conclusion

There is an extensive need to find new therapeutic compounds, mainly anti-infective compounds due to the increase in the resistance development in many pathogens to the known antibiotics. Thus, the isolation of promising endophytic actinobacteria that exert antimicrobial properties has gained great importance from many researchers in different fields. The identification of the diverse endophytic actinobacteria populations that are associated with medicinal plants helps to understand the plant-endophyte interactions as well as the evolution of mutualism. The endophytic actinobacteria gained a lot of attention due to its ability to produce wide biologically active compounds that exert different activities such as antimicrobial, antidiabetic, anticancer, antimalarial, etc. So, it is crucial to develop different methods to understand the genetic control that is responsible for the synthesis of secondary metabolites. It is also required to study the mechanisms that help these endophytes to interact with their host plants. Finally, it is necessary to comprehend the biochemistry and physiology of endophytic actinobacteria as well as secondary metabolite production capacity and their defensive role inside the host plants.

References

1. Nalini MS, Prakash HS (2017) Diversity and bioprospecting of actinomycete endophytes from the medicinal plants. Lett Appl Microbiol 64(4): 261-270.
2. Oskay M (2009) Comparison of Streptomyces diversity between agricultural and non-agricultural soils by using various culture media. Scientific Research and Essay 4(10): 997-1005.
3. Ceylan Ö, Ökmen G, Uğur A (2008) Isolation of soil Streptomyces as source antibiotics active against antibiotic-resistant bacteria. EurAsian J BioSci 2: 73-82.
4. Manjula C, Rajaguru P, Muthuselvam M (2009) Screening for antibiotic sensitivity of free and immobilized actinomycetes isolated from India. Adv Biol Res 3(3-4): 84-88.
5. Chater KF (2006) Streptomyces inside-out: a new perspective on the bacteria that provide us with antibiotics. Philos Trans R Soc Lond B Biol Sci 361(1469): 761-768.
6. Law JW, Tan KX, Wong SH, Ab Mutalib NS, Lee LH (2018) Taxonomic and characterization methods of Streptomyces: a review. Progress In Microbes & Molecular Biology 1(1): 1-10.
7. Chaudhary HS, Soni B, Shrivastava AR, Shrivastava S (2013) Diversity and Versatility of Actinomycetes and its Role in Antibiotic Production. J Appl Pharma Sci 3(8): S83-S94.
8. Passari AK, Mishra VK, Saikia R, Gupta VK, Singh BP (2015) Isolation, abundance and phylogenetic affiliation of endophytic actinomycetes associated with medicinal plants and screening for their in vitro antimicrobial biosynthetic potential. Front Microbiol 6: 273.
9. Yoo JC, Han JM, Nam S, Ko O, Choi CH, et al. (2002) Characterization and cytotoxic activities of nonadecanoic acid produced by *Streptomyces scabiei* subsp. chosunensis M0137 (KCTC 9927). J Microbiol 40(4): 331-334.
10. Weber T, Welzel K, Pelzer S, Vente A, Wohlleben W (2003) Exploiting the genetic potential of polyketide producing *Streptomycetes*. J Biotechnol 106(2-3): 221-232.
11. Ventura M, Canchaya C, Tauch A, Chandra G, Fitzgerald GF, et al. (2007) Genomics of Actinobacteria: Tracing the evolutionary history of an ancient phylum. Microbiol Mol Biol Rev 71(3): 495-548.
12. Akshatha VJ, Nalini MS, D'Souza C, Prakash HS (2014) Streptomycete endophytes from anti-diabetic medicinal plants of the Western Ghats inhibit alphaamylase and promote glucose uptake. Lett Appl Microbiol 58(5): 433-439.
13. Akshatha JV, Prakash HS, Nalini MS (2016) Actinomycete endophytes from the ethnomedicinal plants of southern India: antioxidant activity and characterization studies. J Biol Active Prod Nat 6(2): 166-172.
14. Alam MT, Merlo ME, Takano E and Breitling R (2010) Genome based phylogenetic analysis of Streptomyces and its relatives. Mol Phylogenet Evol 54(3): 763-772.
15. Jasmine DJ, Agastian P (2013) In vitro antioxidant activity and in vivo alpha glucosidase activity of endophytic actinomycetes isolated from *Catharanthus roseus* (l.) G. Don. Journal of pharmacy Research 6(6): 674-678.
16. Segaran G, Sundar RD, Settu S, Shankar S, Sathiavelu M (2017) A review on endophytic actinomycetes and their applications. J Chem Pharm Res 9(10): 152-158.
17. Singh R, Dubey AK (2020) Isolation and characterization of a new endophytic actinobacterium *Streptomyces californicus* strain ADR1 as a promising source of anti-bacterial, anti-biofilm and antioxidant metabolites. Microorganisms 8(6): 929.

18. Singh R, Dubey AK (2015) Endophytic actinomycetes as emerging source for therapeutic compounds. Indo Global J Pharm Sci 5(2): 106-116.

19. Saini P, Gangwar M, Kalia A, Singh N, Narang D (2016) Isolation of endophytic actinomycetes from *Syzygium cumini* and their antimicrobial activity against human pathogens. Journal of Applied and Natural Science 8(1): 416-422.

20. Tanvir R, Sajid I, Hasnain S (2013) Screening of endophytic Streptomycetes isolated from *Parthenium hysterophorus* L. against nosocomial pathogens. Pak J Pharm Sci 26(2): 277-283.

21. Tanvir R, Sajid I, Hasnain S (2014) Biotechnological potential of endophytic actinomycetes associated with Asteraceae plants: isolation, biodiversity and bioactivities. Biotechnology Lett 36(4): 767-773.

22. Sharma K, Beniwal A, Kumar R, Thakur K, Sharma R (2015) Secondary metabolites derived from actinomycetes: iron modulation and their therapeutic potential. The Natural Products Journal 5(2): 72-81.

23. Kumar U, Singh A, SivaKumar T (2011) Isolation and screening of endophytic actinomycetes from different parts of Emblica officinalis. Ann Biol Res 2(4): 423-434.

24. Prashith-Kekuda TR (2016) Isolation, characterization and antimicrobial potential of endophytic actinomycetes. Int J Curr Microbiol Appl Sci 5(7): 100-116.

25. Ch'ng JH, Chong K, Lam LN, Wong JJ, Kline KA (2019) Biofilm-associated infection by enterococci. Nat Rev Microbiol 17(2): 82-94.

26. Kuncharoen N, Fukasawa W, Mori M, Shiomi K, Tanasupawat S (2019) Diversity and antimicrobial activity of endophytic actinomycetes isolated from plant roots in Thailand. Microbiology 88(4): 479-488.

27. Dilip CV, Mulaje SS, Mohalkar RY (2013) A review on actinomycetes and their biotechnological application. International Journal of pharmaceutical sciences and Research 4(5): 1730-1742.

28. Gong B, Chen S, Lan W, Huang Y, Zhu X (2018) Antibacterial and antitumor potential of actinomycetes isolated from mangrove soil in the Maowei Sea of the southern coast of China. Iran J Pharm Res 17(4): 1339-1346.

29. Newman DJ, Cragg MG (2007) Natural products as sources of new drugs over the last 25 years. J Nat Prod 70(3): 461-477.

30. Gohain A, Gogoi A, Debnath R, Yadav A, Singh BP, et al. (2015) Antimicrobial biosynthetic potential and genetic diversity of endophytic actinomycetes associated with medicinal plants. FEMS Microbiology Lett 362(19): 158.

31. Chandrakar S, Gupta AK (2017) Antibiotic potential of endophytic actinomycetes of medicinal herbs against human pathogenic bacteria. Proceedings of the National Academy of Sciences, India Section B: Biological Sciences 87: 905-915.

32. Cao L, Qiu Z, You J, Tan H, Zhou S (2005) Isolation and characterization of endophytic streptomycete antagonists of *Fusarium* wilt pathogen from surface-sterilized banana roots. FEMS microbiology Lett 247(2): 147-152.

33. Kumar RR, Jadeja VJ (2016) Isolation of actinomycetes: A complete approach. Int J Curr Microbiol App Sci 5(5): 606-618.

34. Rajivgandhi G, Vijayan R, Kannan M, Santhanakrishnan M, Manoharan N (2016) Molecular characterization and antibacterial effect of endophytic actinomycetes Nocardiopsis sp. GRG1 (KT235640) from brown algae against MDR strains of uropathogens. Bioactive Materials 1(2): 140-150.

35. Taechowisan T, Chaisaeng S, Phutdhawong WS (2017) Antibacterial, antioxidant and anticancer activities of biphenyls from *Streptomyces* sp. BO-07: an endophyte in Boesenbergia rotunda (L.) Mansf A. Food and Agricultural Immunology 28(6): 1330-1346.

36. El-Shatoury S, Abdulla H, El-Karaaly O, El-Kazzaz W, Dewedar A (2006) Plants in the World Heritage Site of Saint Katherine, Egypt. International Journal of Botany 2: 307-312.

37. Castillo UF, Strobel GA, Ford EJ, Hess WM, Porter H, et al. (2002) Munumbicins, wide-spectrum antibiotics produced by Streptomyces NRRL 30562, endophytic on Kennedia nigriscansaa. Microbiology 148(pt 9): 2675-2685.

38. Tanvir R, Sajid I, Hasnain S (2014) Larvicidal potential of Asteraceae family endophytic actinomycetes against Culex quinquefasciatus mosquito larvae. Nat Prod Res 28(22): 2048-2052.

39. Castillo U, Harper JK, Strobel GA, Sears J, Alesi K, et al. (2003) Kakadumycins, novel antibiotics from Streptomyces sp. NRRL 30566, an endophyte of Grevillea pteridifolia. FEMS Microbiology Lett 224(2): 183-190.

40. Igarashi Y, Miura S-S, Fujita T, Furumai T (2006)

Pterocidin, a cytotoxic compound from the endophytic Streptomyces hygroscopicus. J Antibiot (Tokyo) 59(3): 193-195.

41. Lu C, Shen Y (2003) A new macrolide antibiotic with antitumor activity produced by *Streptomyces* sp. CS, a commensal microbe of Maytenus hookeri. J Antibiot (Tokyo) 56(4): 415-418.

42. Lu C, Shen Y (2007) A novel ansamycin, naphthomycin K from *Streptomyces* sp. J Antibiot (Tokyo) 60(10): 649-653.

43. Elkhateeb WA, Mohamed MA, Fayad W, Emam M, Nafady IM, et al. (2020) Molecular Identification, Metabolites profiling, Anti-breast cancer, Anti-colorectal cancer, and antioxidant potentials of *Streptomyces zaomyceticus* AA1 isolated from a remote bat cave in Egypt. Research Journal of Pharmacy and Technology 13(7): 3072-3080.

44. Kim N, Shin JC, Kim W, Hwang BY, Kim BS, et al. (2006) Cytotoxic 6-alkylsalicylic acids from the endophytic Streptomyces laceyi. J Antibiot (Tokyo) 59(12): 797-800.

45. Igarashi Y, Mogi T, Yanase S, Miyanaga S, Fujita T, et al. (2009) Brartemicin, an inhibitor of tumor cell invasion from the actinomycete *Nonomuraea* sp. J Nat Prod 72(5): 980-982.

46. Taechowisan T, Lu C, Shen Y, Lumyong S (2007) Antitumor activity of 4-arylcoumarins from endophytic *Streptomyces aureofaciens* CMUAc130. J Cancer Res Ther 39(2): 86-91.

47. Zhou H, Yang Y, Peng T, Li W, Zhao L, et al. (2014) Metabolites of Streptomyces sp., an endophytic actinomycete from *Alpinia oxyphylla*. Nat Prod Res 28(4): 265-267.

48. Zhou H, Yang Y, Zhang J, Peng T, Zhao L, et al. (2013) Alkaloids from an endophytic *Streptomyces* sp. YIM66017. Nat Prod Commun 8(10): 1393-1396.

49. Taechowisan T, Wanbanjob A, Tuntiwachwuttikul P, Taylor WC (2006) Identification of Streptomyces sp. Tc022, an endophyte in Alpinia galanga, and the isolation of actinomycin D. Annals of Microbiology 56: 113-117.

50. Janaki T (2017) Enzymes from actinomycetes-Review. Int J Chemtech Res 10(3): 326-332.

51. Behera B, Sethi B, Mishra R, Dutta S, Thatoi H (2017) Microbial cellulases–Diversity & biotechnology with reference to mangrove environment: A review. Journal of Genetic Engineering and Biotechnology 15(1): 197-210.

52. Cundell AM, Brown MS, Stanford R, Mitchell R (1979) Microbial degradation of Rhizophora mangle leaves immersed in the sea. Estuarine and Coastal Marine Science 9(3): 281-286.

53. Pujiyanto S, Lestari Y, Suwanto A, Budiarti S, Darusman LK (2012) Alpha-glucosidase inhibitor activity and characterization of endophytic actinomycetes isolated from some Indonesian diabetic medicinal plants. Int J Pharm Sci 4(1): 327-333.

54. Castillo UF, Strobel GA, Mullenberg K, Condron MM, Teplow DB, et al. (2006) Munumbicins E-4 and E-5: novel broad-spectrum antibiotics from Streptomyces NRRL 3052. FEMS Microbiol Lett 255(2): 296-300.