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The Rising of "Modern *Actinobacteria*" Era

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Abstract: The term "Modern *Actinobacteria*" (MOD-ACTINO) was coined by a Malaysian Scientist Dr. Lee Learn-Han, who has great expertise and experience in the field of actinobacteria research. MOD-ACTINO is defined as a group of actinobacteria capable of producing compounds that can be explored for modern applications such as development of new drugs and cosmeceutics. MOD-ACTINO members consist of already identified or novel actinobacteria isolated from special environments: mangrove, desert, lake, hot spring, cave, mountain, Arctic and Antarctic regions. These actinobacteria are valuable sources for various industries which can contribute directly/indirectly towards the improvement in many aspects of our lives.

Keywords: modern; bioactive; actinobacteria; environment; bioprospecting

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INTRODUCTION

The *Actinobacteria* has a long evolutionary history for it has existed on earth around 2.7 billion years ago, anteceding the Great Oxidation event that occurred 2.3 billion years ago[1, 2]. In the *Bacteria* kingdom, ancient *Actinobacteria* is one of the major phyla associated with the early colonization of land and they play important roles in assisting Earth's ecosystems function[2]. As one of the most primitive lineages among prokaryotes, actinobacteria have extraordinary diversity of morphology and function[3,4]. This phylum consists of free-living Gram-positive bacteria with a variety of morphological features including coccus, rod, and complex fragmenting hyphal that develops into branched mycelium[3,5]. These bacteria can be found predominantly in terrestrial soil and marine ecosystems[6]. Actinobacteria have significant functions, for instances, they are important agents of global carbon and nitrogen cycles; agents of bioremediation; probiotics in humans and animals; pathogens of humans, animals and plants; producers of enzymes and clinically important metabolites[1,3,7].

Following the pioneering research led by Professor Waksman, the '52 Nobel laureate who revealed streptomycin antibiotic from *Streptomyces griseus*, actinobacteria have since become the "star" in the scientific community[8,9]. Essentially, the investigation of novel *Actinobacteria* (genera or species) and bioprospecting of active isolates have intensified around the world, often through random large-scale sampling of environment, selective isolation and subsequently bioactivity screening of isolates[6]. This resulted in the discovery and screening of over thousands of species of actinobacteria. Historically, the actinobacteria were documented as a controversial kind of microorganisms due to their diverse and unique appearances, for which, several of them resemble the appearance of fungi[10]. The taxonomy of phylum *Actinobacteria* has been revised over time and the recent roadmap has been proposed with 6 major classes in the phylum, namely: *Actinobacteria*, *Acidimicrobiia*, *Coriobacteriia*, *Nitriliruptoria*, *Rubrobacteria*, and *Thermoleophilia*. Class *Actinobacteria* is the largest among others as it consists of 15 orders: *Actinomycetales*, *Actinopolysporales*, *Bifidobacteriales*, *Catenulispo-*

rales, *Corynebacteriales*, *Glycomycetales*, *Jiangellales*, *Kineosporiales*, *Micrococcales*, *Micromonosporales*, *Propionibacteriales*, *Pseudonocardiales*, *Streptomycetales*, *Streptosporangiales*, and *Frankiales*[11,12]. The genus *Streptomyces* (order: *Streptomycetales*, family: *Streptomycetaceae*) is the most famous actinobacteria as they have been greatly studied due to their tremendous bioactive potentials[7].

THE ERA OF MODERN *Actinobacteria* (MOD-ACTINO)

Actinobacteria have been distinguished for their prolific production of antibiotics. From the 1950s to 1970s, approximately 60% of new antibiotics were predominantly isolated from streptomycetes[13]. Eventually, researchers have further exposed the presence of actinobacteria in special and extreme environments with the increasing efforts to discover new metabolites from various microbial sources. This essentially leads to a significant paradigm shift in the exploration of *Actinobacteria*, such instances include the isolation of actinobacteria from underexplored unique habitats and the investigation of their secondary metabolites with different activities other than antimicrobials (e.g. antioxidant, anticancer)[14]. Furthermore, the non-*Streptomyces* genera (e.g. *Sinomonas*, *Microbacterium*, *Nocardia*) which referred as the "rare *Actinobacteria*" have shown growing importance as valuable sources in discovery of novel bioactive secondary metabolites[15]. Malaysia Research Star Award winner, Dr. Lee Learn Han — who has great expertise and experience in the field of actinobacteria research, coined the term "Modern *Actinobacteria*" (MOD-ACTINO) to define actinobacteria with modern applications (Figure 1). In this context, the term refers to actinobacteria that synthesize natural products with new interesting bioactivities in recent years, for examples, drug leads with anti-viral (HIV), anti-protozoa (malaria), antioxidant, and neuroprotection properties as well as compounds utilized for cosmetic formulation. In addition, this term covers actinobacteria which produce approved drugs and have been subjected to drug repurposing effort. MOD-ACTINO also inclusive of known or novel actinobacteria that have been discovered from special environments.

Figure 1. The ideas of "Modern *Actinobacteria*" (MOD-ACTINO) proposed by Dr. Lee Learn Han.

By the end of 20th century, actinobacterial natural products have been found to exert extensive biological activities comprising antibacterial (against antibiotic resistant strains), antifungal, antiparasitic, immunosuppressant, antioxidant, and anticancer agents[8,16–22], Numerous actinobacterial bioactive compounds are well-known for the treatment of plant, animal, and human diseases. For instances, kasugamycin is a marketed antifungal antibiotic produced from *Streptomyces kasugaensis* which used for the control of rice blast caused by phytopathogenic fungus *Magnaporthe oryzae*[23,24]. Moreover, several chemotherapeutic drugs such as bleomycin (from *Streptomyces verticillus*) and doxorubicin (from *Streptomyces peucetius*) that have been introduced into clinical use are of actinobacterial origin[25–27]. Another remarkable drug discovery event from genus *Streptomyces* is achieved by Professor William C. Campbell and Professor Satoshi Omura through the isolation of a new "miracle" drug avermectin from *Streptomyces avermitilis* (renamed as *Streptomyces avermectinius*)[28]. Avermectin was later being refined into the safest and most potent derivative known as ivermectin. Ivermectin is an antiparasitic drug effective against helminths, arachnids and insects. It was marketed in 1981 for veterinary use around the world and subsequently approved for human use in 1987. Ivermectin is administered for treatment of onchocerciasis and lymphatic filariasis in many parts of the world. This "miracle" drug has revolutionized the treatment of these devastating parasitic dis-

eases, thereby improving the health of millions of individuals. Resultantly, the 2015 Nobel Prize in Physiology or Medicine was awarded (with one half jointly) to Professor William C. Campbell and Professor Satoshi Omura[28,29].

Research on actinobacteria is still ongoing as they never cease to amaze us with their vast potential of bioactive secondary metabolite production. Studies conducted nowadays, towards the 21st century, have gradually revealed the immense ability of actinobacteria in producing compounds with new captivating bioactivities far more than expected. This is witnessed through findings of compounds with *in vitro* anti-human immunodeficiency virus (HIV) activity produced by actinobacteria[30–32]. One of the earliest research studies on this was reported by Chokekijchai *et al*. (1995)[33], for which a new anti-HIV polypeptide was obtained from a *Streptomyces* sp. isolated from soil sample collected in Japan. Besides, a recent study conducted by Ding *et al*. (2010)[34] had successfully isolated a novel pentacyclic indolosesquiterpene — xiamycin produced by mangrove-derived *Streptomyces* sp. GT2002/1503 which is active against HIV. Apart from anti-HIV activity, a number of actinobacteria were documented to produce compounds (e.g. borrelidin, metacycloprodigiosin, bafilomycin A_1) with promising activity against human malaria parasite (*Plasmodium falciparum*)[35–37]. Furthermore, studies also reported the production of neuroprotective substances by actinobacteria that may be potential medicines for brain ischemia and other neurodegenerative diseases such as multiple sclerosis, Parkinson's diseases, and Alzheimer's disease[38,39]. As an example, Hayakawa *et al*. (2013)[40] revealed a new neuroprotective compound isolated from *Streptomyces* sp. RAI20 - indanostatin, which is also the first reported 1,3-indanone from bacteria. The compound was found to partially protect C6 glioma cells (derived from rat neural tumors induced by N-nitrosomethylurea) against glutamate toxicity which could be useful as treatment for cerebral ischemic disorders.

Likewise, the possibility of incorporating actinobacterial bioactive metabolites in modern skin care cosmetics has further uplift the value of MOD-ACTINO. The human skin is the largest organ of our integumentary system which could face esthetic issues such as freckles, acne, and aging. Dahal *et al*. (2016)[41] proposed the addition of actinobacterial derived resources into cosmetics products for beneficial effects which could enhance the appearance of human skin such as anti-acne, anti-aging, skin whitening, and antioxidant effects. In the study, 12 strains of actinobacteria belonging to the genera *Streptomyces*, *Actinokineospora*, and *Calidifontibacter* exhibited antibacterial activity against skin pathogens *Staphylococcus epidermidis* and *Propionibacterium acnes*. The crude supernatant of these actinobacteria also demonstrated promising tyrosinase inhibition, elastase inhibition, and antioxidant activities. Another research conducted by Tan *et al*. (2019)[42] had reported the isolation of a mangrove *Streptomyces* sp. MUM273b which possessed antioxidant and UVB protective properties. Hence, actinobacterial derived resources can be added to cosmetics applications to improve skin conditions by providing skin whitening effects, acne vulgaris treatment, anti-aging effects, anti-oxidant effects, and anti-UV properties.

Interestingly, there is an increasing number of studies that support the concept of using actinobacteria as probiotics in animal feed especially for aquaculture[43]. Probiotics in aquaculture are expected to confer health benefits to the host such as growth enhancement, improvement in nutrient digestion and immune response, also, to assist in prevention of bacterial infection through production of inhibitory compounds[43,44]. A few number of studies have suggested the utilization of actinobacteria as potential probiotic strains against shrimp and fish pathogenic *Vibrio* spp.[45–49]. Meanwhile, the members of *Streptomyces* and *Bacillus* are also compelling probiotic strains as they have been shown to be capable of promoting growth and increasing resistance against bacterial infections in fishes and shrimps[50–52]. Most studies recommended the genus *Streptomyces* as the most potent actinobacteria probiotic for aquaculture mainly due to their ability to produce a multitude of extracellular enzymes and antibiotics, and to form heat- and desiccation-resistant spores[44,50]. Therefore, these MOD-ACTINO will be a great asset to the biopharmaceutical, agriculture, aquaculture, and cosmetic industries.

Aside from the exploration of actinobacteria-derived compounds for development of novel drugs, research also emphasizes on the investigation of drug repurposing. Drug repurposing (drug repositioning/reprofiling/retasking) is defined as an approach to search for new applications of approved or investigational drugs that are beyond the scope of the original medical indication[53]. Previously approved actinobacteria-derived drugs such as rapamycin (sirolimus; produced by *Streptomyces hygroscopicus*) was initially known as an antifungal agent[54]. Rapamycin was approved as an immunosuppressant for the prevention of allograft rejection in 1999 due to its strong suppression of interleukin-2 (IL-2)-stimulated T cell proloferation[55]. It is a macrolide and an allosteric inhibitor of mammalian target of rapamycin (mTOR)[55,56]. The mTOR is a serine/threonine protein kinase and it is often upregulated in different types of cancers. As a result, researchers are determined to examine its anticancer potentials. Rapamycin has been verified to be a potent immunosuppressant and a promising anticancer/antitumor agent that can be used as a single agent or in drug combination[57–59]. Thus, this demonstrated one of the criteria of MOD-ACTINO where the actinobacterial compounds exhibited different bioactivities from their originally identified bioactivity.

PRESENCE OF MOD-ACTINO IN SPECIAL ENVIRONMENTS

Actinobacteria are sporulating organisms that possessed astonishing capability to generate extraordinary properties[60–62]. This is often associated with their complex morphological changes in their multicellular life cycle and their large genome size as observed particularly in streptomycetes[3,11,63]. The complexity of these organisms has enabled them to thrive in extreme and special environments[15] such as the Arctic and Antarctic regions[64,65], mountain plantations[66], glaciers[67], caves[68], deserts[69], hot springs[70], and mangroves[71–75]. These environments are special in terms of physical parameters (e.g. unusually high/low temperature,

radiation, pressure) or chemical conditions (e.g. acidic/alkaline pH, high salinity, low levels of nutrients and moisture)[76,77]. The actinobacteria evolved by developing unique defense mechanism that enables them to survive under hostile and extreme conditions. Consequently, actinobacteria from special and extreme environments may be thermotolerant, acidtolerant, alkalitolerant, psychrotolerant, halotolerant, haloalkalitolerant or xerophilous[76].

In addition, several novel genera/species have been discovered from these special environments. For instances, *Mumia flava* gen. nov., sp. nov. (family *Nocardioidaceae*)[78], *Barrientosiimonas humi* gen. nov., sp. nov. (family *Dermacoccaceae*)[79], and *Monashia flava* gen. nov., sp. nov. (family *Intrasporangiaceae*)[80] were each novel species of a new genus isolated from mangroves in Malaysia; *Actinocrinis puniceicyclus* gen. nov., sp. nov. (family *Actinospicaceae*)[81] isolated from acidic spring; and *Desertiactinospora gelatinilytica* gen. nov., sp. nov. (family *Streptosporangiaceae*) isolated from desert[82]. Besides, other novel species of rare actinobacteria were also identified such as *Microbacterium mangrovi* sp. nov.[83] and *Sinomonas humi* sp. nov.[84] from mangroves; *Rhodococcus kroppenstedtii* sp. nov.[85] and *Micromonospora acroterricola* sp. nov.[86] from desert; and *Nonomuraea monospora* sp. nov.[87] from cave soil. In fact, recent studies also uncovered many novel bioactive actinobacteria which originated from these unique niches. There are multiple novel *Streptomyces* strains recovered from mangrove environments with useful bioactivities, for examples, *Streptomyces colonosanans* sp. nov. (antioxidant and anticancer)[88], *Streptomyces monashensis* (antioxidant and anticancer)[27,89], *Streptomyces mangrovisoli* sp. nov. (antioxidant)[90], *Streptomyces pluripotens* sp. nov. (antibacterial)[91], and *Streptomyces malaysiense* sp. nov. (antioxidant and anticancer)[92]. Many compounds produced by MOD-ACTINO exhibit important properties which can be developed into new drugs/drug leads with higher efficacy in the near future.

HARNESSING THE POTENTIALS OF MOD-ACTINO AND CONCLUSIONS

With the growing importance of actinobacteria in various fields, the advancement in molecular biology especially in this post-genomic era can assist us to reach a higher level of understanding of these organisms by studying their genome. The availability of next generation sequencing (NGS) technologies and the -omics methods (metagenomics, metaproteomics) have greatly assisted in overcoming the issue on detection of unculturable bacteria as well as contributed to the research on actinobacteria biosynthetic gene clusters and their secondary metabolites production[93]. Lately, there is an increase in the number of new genome sequences of actinobacteria which have been made available to the public. Majority of them were resulted from projects aimed to understand the connection of secondary metabolites productions or to evaluate new actinobacterial natural products to their biosynthetic pathways via genome mining[94]. In particular, the bioactive actinobacteria strains have been subjected to whole genome sequencing to further appreciate their biological importance in bioactive metabolites or enzyme production[95–104]. It is anticipated that the accessibility to large sets of actinobacterial genome sequences will provide us a more thorough understanding of actinobacteria phylogeny and facilitate in the identification of medically useful new natural products[105]. Members of MOD-ACTINO are valuable sources for various industries which can contribute directly/indirectly towards the improvement in many aspects of our lives. MOD-ACTINO will be the "key" microorganisms to further improve human health and wellbeing in the modern society.

Authors Contributions

The research and manuscript writing were performed by JW-FL, VL and L-HL. LT-HT, H-LS and B-HG provided vital guidance of the research and proof of the writing. The research project was founded by JW-FL and L-HL.

Conflict of Interest

The authors declare that there is no conflict of interest in this work.

Reference

1. Lewin, GR, Carlos, C, Chevrette, MG, *et al.* Evolution and ecology of *Actinobacteria* and their bioenergy applications. Annu Rev Microbiol 2016; 70: 235–254.
2. Battistuzzi, FU, Feijao, A, and Hedges, SB. A genomic timescale of prokaryote evolution: insights into the origin of methanogenesis, phototrophy, and the colonization of land. BMC Evol Biol 2004; 4(1): 44.
3. Chandra, G and Chater, KF. Developmental biology of *Streptomyces* from the perspective of 100 actinobacterial genome sequences. FEMS Microbiol Rev 2014; 38(3): 345–379.
4. Law, JW-F, Tan, K-X, Wong, SH, *et al.* Taxonomic and characterization methods of *Streptomyces*: A review. Prog Microbes Mol Biol 2018; 1(1): a0000009.
5. Miyadoh, S, *Atlas of Actinomycetes*. 1997, Japan: The Society for Actinomycetes, Japan.
6. Kurtböke, D. *Ecology and habitat distribution of actinobacteria*. In: *Biology and Biotechnology of Actinobacteria*. J Wink, F Mohammadipanah, and J Hamedi, Cham: Springer; 2017: 123–149.
7. Lee, L-H, Chan, K-G, Stach, J, *et al.* The search for biological active agent (s) from actinobacteria. Front Microbiol 2018; 9: 824.
8. Arul Jose, P and Jebakumar, SRD. Non-streptomycete actinomycetes nourish the current microbial antibiotic drug discovery. Front Microbiol 2013; 4: 240.
9. Comroe Jr, JH. Pay dirt: The story of streptomycin: Part I. From Waksman to Waksman. Am Rev Respir Dis 1978; 117(4): 773–781.
10. Ser, H-L, Tan, LT-H, Law, JW-F, *et al.* Focused review: Cytotoxic and antioxidant potentials of mangrove-derived *Streptomyces*. Front Microbiol 2017; 8: 2065.
11. Law, JW-F, Pusparajah, P, Ab Mutalib, N-S, *et al.* A review on mangrove actinobacterial diversity: The roles of *Streptomyces* and novel species discovery. Prog Microbes Mol Biol 2019; 1(1): a0000024.
12. Ludwig, W, Euzzéby, J, Schumann, P, *et al.* Road map of the phylum Actinobacteria. In: Bergey's Manual® of Systematic Bacteriology *V*.M Goodfellow, *et al.*, New York: Springer; 2012: 1–28.
13. Bérdy, J. Thoughts and facts about antibiotics: Where we are now and where we are heading. J Antibiot 2012; 65(8): 385.
14. Ser, H-L, Yin, W-F, Chan, K-G, *et al.* Antioxidant and cytotoxic potentials of *Streptomyces gilvigriseus* MUSC 26^{T} isolated from mangrove soil in Malaysia. Prog Microbes Mol Biol 2018; 1(1): a0000002.
15. Li, F, Liu, S, Lu, Q, *et al.* Studies on antibacterial activity and diversity of cultivable *Actinobacteria* isolated from mangrove soil in Futian and Maoweihai of China. Evid Based Complement Alternat Med 2019; 2019: 3476567.
16. Kino, T, Hatanaka, H, Miyata, S, *et al.* FK-506, a novel immunosuppressant isolated from a *Streptomyces*. J Antibiot 1987; 40(9): 1256-1265.
17. Kemung, HM, Tan, LT-H, Khan, TM, *et al. Streptomyces* as a prominent resource of future anti-MRSA drugs. Front Microbiol 2018; 9: 2221.
18. Kemung, HM, Tan, LT-H, Chan, K-G, *et al.* Investigating the antioxidant potential of *Streptomyces* sp. MUSC 11 from mangrove

soil in Malaysia. Prog Drug Discov Biomed Sci 2019; 2(1).
19. Kemung, HM, Tan, LT-H, Chan, K-G, *et al.* Antioxidant activities of *Streptomyces* sp. strain MUSC 14 from mangrove forest soil in Malaysia. Biomed Res Int 2020; 2020: 6402607
20. Tan, LT-H, Chan, C-K, Chan, K-G, *et al. Streptomyces* sp. MUM256: a Source for apoptosis inducing and cell cycle-arresting bioactive compounds against colon cancer cells. Cancers (Basel) 2019; 11(11): 1742.
21. Tan, LT-H, Chan, K-G, Chan, CK, *et al.* Antioxidative potential of a *Streptomyces* sp. MUM292 isolated from mangrove soil. Biomed Res Int 2018; 2018: 4823126.
22. Azman, A-S, Othman, I, Fang, C-M, *et al.* Antibacterial, anticancer and neuroprotective activities of rare *Actinobacteria* from mangrove forest soils. Indian J Microbiol 2017; 57(2): 177–187.
23. Law, JW-F, Ser, H-L, Khan, TM, *et al.* The potential of *Streptomyces* as biocontrol agents against the rice blast fungus, *Magnaporthe oryzae* (*Pyricularia oryzae*). Front Microbiol 2017; 8: 3.
24. Umezawa, H, Okami, Y, Hashimoto, T, *et al.* A new antibiotic, kasugamycin. J Antibiot Ser A 1965; 18: 101–103.
25. Evans, WE, Yee, GC, Crom, WR, *et al.* Clinical pharmacology of bleomycin and cisplatin. Head Neck Surg 1981; 4(2): 98–110.
26. Takemura, G and Fujiwara, H. Doxorubicin-induced cardiomyopathy: From the cardiotoxic mechanisms to management. Prog Cardiovasc Dis 2007; 49(5): 330–352.
27. Law, JW-F, Ser, H-L, Ab Mutalib, N-S, *et al. Streptomyces monashensis* sp. nov., a novel mangrove soil actinobacterium from East Malaysia with antioxidative potential. Sci Rep 2019; 9(1): 3056.
28. Omura, S. Ivermectin: 25 years and still going strong. Int J Antimicrob Agents 2008; 31(2): 91–98.
29. Van Voorhis, WC, van Huijsduijnen, RH, and Wells, TN. Profile of William C. Campbell, Satoshi Ōmura, and Youyou Tu, 2015 Nobel Laureates in Physiology or Medicine. Proc Natl Acad Sci 2015; 112(52): 15773–15776.
30. Takeuchi, H, Asai, N, Tanabe, K, *et al.* EM2487, a novel anti-HIV-1 antibiotic, produced by *Streptomyces* sp. Mer-2487. J Antibiot 1999; 52(11): 971–982.
31. Matsuzaki, K, Ogino, T, Sunazuka, T, *et al.* Chloropeptins, new anti-HIV antibiotics inhibiting gp120-CD4 binding from *Streptomyces* sp. J Antibiot 1997; 50(1): 66–69.
32. Nakashima, H, Ichiyama, K, Inazawa, K, *et al.* FR901724, a novel anti-human immunodeficiency virus (HIV) peptide produced by *Streptomyces*, shows synergistic antiviral activities with HIV protease inhibitor and 2', 3'-dideoxynucleosides. Biol Pharm Bull 1996; 19(3): 405–412.
33. Chokekijchai, S, Kojima, E, Anderson, S, *et al.* NP-06: a novel anti-human immunodeficiency virus polypeptide produced by a *Streptomyces* species. Antimicrob Agents Chemother 1995; 39(10): 2345–2347.
34. Ding, L, Münch, J, Goerls, H, *et al.* Xiamycin, a pentacyclic indolosesquiterpene with selective anti-HIV activity from a bacterial mangrove endophyte. Bioorg Med Chem Lett 2010; 20(22): 6685–6687.
35. Isaka, M, Jaturapat, A, Kramyu, J, *et al.* Potent in vitro antimalarial activity of metacycloprodigiosin isolated from *Streptomyces spectabilis* BCC 4785. Antimicrob Agents Chemother 2002; 46(4): 1112–1113.
36. Na, M, Meujo, DA, Kevin, D, *et al.* A new antimalarial polyether from a marine *Streptomyces* sp. H668. Tetrahedron Lett 2008; 49(44): 6282–6285.
37. Otoguro, K, Ui, H, Ishiyama, A, *et al.* In vitro and in vivo antimalarial activities of a non-glycosidic 18-membered macrolide antibiotic, borrelidin, against drug-resistant strains of *Plasmodia*. J Antibiot 2003; 56(8): 727–729.
38. Hayakawa, Y, Yamazaki, Y, Kurita, M, *et al.* Flaviogeranin, a new neuroprotective compound from *Streptomyces* sp. J Antibiot 2010; 63(7): 379–380.
39. Ser, H-L, Tan, LT-H, Palanisamy, UD, *et al. Streptomyces antioxidans* sp. nov., a novel mangrove soil actinobacterium with antioxidative and neuroprotective potentials. Front Microbiol 2016; 7: 899.
40. Hayakawa, Y, Kobayashi, T, and Izawa, M. Indanostatin, a new neuroprotective compound from *Streptomyces* sp. J Antibiot 2013; 66(12): 731–733.
41. Dahal, RH, Shim, DS, and Kim, J. Development of actinobacterial resources for functional cosmetics. J Cosmet Dermatol 2017; 16(2): 243–252.
42. Tan, LTH, Mahendra, CK, Yow, YY, *et al. Streptomyces* sp. MUM273b: A mangrove-derived potential source for antioxidant and UVB radiation protectants. MicrobiologyOpen 2019: e859.
43. Tan, LT-H, Chan, K-G, Lee, L-H, *et al. Streptomyces* bacteria as potential probiotics in aquaculture. Front Microbiol 2016; 7: 79.
44. Das, S, Ward, LR, and Burke, C. Prospects of using marine actinobacteria as probiotics in aquaculture. Appl Microbiol Biotechnol 2008; 81(3): 419–429.
45. You, J, Cao, L, Liu, G, *et al.* Isolation and characterization of actinomycetes antagonistic to pathogenic *Vibrio* spp. from nearshore marine sediments. World J Microbiol Biotechnol 2005; 21(5): 679–682.
46. Gozari, M, Mortazavi, M, Bahador, N, *et al.* Isolation and screening of antibacterial and enzyme producing marine actinobacteria to approach probiotics against some pathogenic vibrios in shrimp *Litopenaeus vannamei*. Iran J Fish Sci 2016; 15(1): 630–644.
47. Kamarudheen, N, George, CS, Pathak, S, *et al.* Antagonistic activity of marine *Streptomyces* sp. on fish pathogenic *Vibrio* species isolated from aquatic environment. Research J Pharm Tech 2015; 8(11): 1529–1533.
48. Bernal, MG, Campa-Córdova, ÁI, Saucedo, PE, *et al.* Isolation and in vitro selection of actinomycetes strains as potential probiotics for aquaculture. Vet World 2015; 8(2): 170–176.
49. Tan, LT-H, Lee, L-H, and Goh, B-H. The bioprospecting of anti-*Vibrio Streptomyces* species: prevalence and applications. Prog Microbes Mol Biol 2019; 2(1): a0000034.
50. Bernal, MG, Marrero, RM, Campa-Córdova, ÁI, *et al.* Probiotic effect of *Streptomyces* strains alone or in combination with *Bacillus* and *Lactobacillus* in juveniles of the white shrimp *Litopenaeus vannamei*. Aquac Int 2017; 25(2): 927–939.
51. Dharmaraj, S and Dhevendaran, K. Evaluation of *Streptomyces* as a probiotic feed for the growth of ornamental fish *Xiphophorus helleri*. Food Technol Biotechnol 2010; 48(4): 497–504.
52. Meidong, R, Doolgindachbaporn, S, Jamjan, W, *et al.* A novel probiotic *Bacillus siamensis* B44v isolated from Thai pickled vegetables (Phakdong) for potential use as a feed supplement in aquaculture. J Gen Appl Microbiol 2017; 63(4): 246–253.
53. Pushpakom, S, Iorio, F, Eyers, PA, *et al.* Drug repurposing: Progress, challenges and recommendations. Nat Rev Drug Discov 2019; 18(1): 41–58.
54. Sehgal, S, Baker, H, and Vezina, C. Rapamycin (AY-22, 989), a new antifungal antibiotic. J Antibiot 1975; 28(10): 727–732.
55. Benjamin, D, Colombi, M, Moroni, C, *et al.* Rapamycin passes the torch: a new generation of mTOR inhibitors. Nat Rev Drug Discov 2011; 10(11): 868–880.
56. Klawitter, J, Nashan, B, and Christians, U. Everolimus and sirolimus in transplantation-related but different. Expert Opin Drug Saf 2015; 14(7): 1055–1070.
57. Åleskog, A, Norberg, M, Nygren, P, *et al.* Rapamycin shows anticancer activity in primary chronic lymphocytic leukemia cells in vitro, as single agent and in drug combination. Leuk Lymphoma 2008; 49(12): 2333–2343.
58. Chen, B, Xu, X, Luo, J, *et al.* Rapamycin enhances the anti-cancer effect of dasatinib by suppressing Src/PI3K/mTOR pathway in NSCLC cells. PLoS One 2015; 10(6): e0129663.
59. Guo, S, Lin, CM, Xu, Z, *et al.* Co-delivery of cisplatin and rapamycin for enhanced anticancer therapy through synergistic effects and microenvironment modulation. ACS nano 2014; 8(5): 4996–5009.
60. Miller, AZ, Gonzalez-Pimentel, JL, Laiz, L, *et al.*, *Actinobacteria* isolated from subterranean and cultural heritage: implications for biotechnology, in EGU General Assembly Conference Abstracts. 2019. p. 9604.
61. Ser, H-L, Zainal, N, Palanisamy, UD, *et al. Streptomyces gilvigriseus* sp. nov., a novel actinobacterium isolated from mangrove forest soil. Antonie Van Leeuwenhoek 2015; 107(6): 1369–1378.
62. Ser, H-L, Law, JW-F, Chaiyakunapruk, N, *et al.* Fermentation conditions that affect clavulanic acid production in *Streptomyces clavuligerus*: A systematic review. Front Microbiol 2016; 7: 522.
63. Law, JW-F, Chan, K-G, He, Y-W, *et al.* Diversity of *Streptomyces* spp. from mangrove forest of Sarawak (Malaysia) and screening of their antioxidant and cytotoxic activities. Sci Rep 2019; 9(1): 1–15.
64. Augustine, N, Kerkar, S, and Thomas, S. Arctic actinomycetes as potential inhibitors of *Vibrio cholerae* biofilm. Curr Microbiol 2012; 64(4): 338–342.
65. Lee, L-H, Cheah, Y-K, Sidik, SM, *et al.* Molecular characterization of Antarctic actinobacteria and screening for antimicrobial metabolite production. World J Microbiol Biotechnol 2012; 28(5): 2125–2137.
66. George, M, Anjumol, A, George, G, *et al.* Distribution and bioactive potential of soil actinomycetes from different ecological habitats. Afr J Microbiol Res 2012; 6(10): 2265–2271.
67. Zhang, B, Wu, X, Zhang, G, *et al.* The diversity and biogeography of the communities of *Actinobacteria* in the forelands of glaciers at a continental scale. Environ Res Lett 2016; 11(5): 054012.
68. Niyomvong, N, Pathom-Aree, W, Thamchaipenet, A, *et al.* Actinomycetes from tropical limestone caves. Chiang Mai J Sci 2012; 39(3): 373–388.
69. Okoro, CK, Brown, R, Jones, AL, *et al.* Diversity of culturable actinomycetes in hyper-arid soils of the Atacama Desert, Chile. Antonie Van Leeuwenhoek 2009; 95(2): 121–133.
70. Duan, Y-Y, Ming, H, Dong, L, *et al. Streptomyces calidiresistens* sp. nov., isolated from a hot spring sediment. Antonie Van Leeuwenhoek 2014; 106(2): 189–196.
71. Tan, LT-H, Chan, K-G, Khan, TM, *et al. Streptomyces* sp. MUM212 as a source of antioxidants with radical scavenging and metal chelating properties. Front Pharmacol 2017; 8: 276.
72. Tan, LT-H, Ser, H-L, Yin, W-F, *et al.* Investigation of antioxidative and anticancer potentials of *Streptomyces* sp. MUM256 isolated from Malaysia mangrove soil. Front Microbiol 2015; 6: 1316.
73. Tan, LT-H, Chan, K-G, Pusparajah, P, *et al.* Mangrove derived *Streptomyces* sp. MUM265 as a potential source of antioxidant and anticolon-cancer agents. BMC Microbiol 2019; 19(1): 38.
74. Azman, A-S, Othman, I, S Velu, S, *et al.* Mangrove rare actinobacteria: taxonomy, natural compound, and discovery of bioactivity. Front Microbiol 2015; 6: 856.
75. Zainal, N, Ser, H-L, Yin, W-F, *et al. Streptomyces humi* sp. nov., an actinobacterium isolated from soil of a mangrove forest. Antonie Van Leeuwenhoek 2016; 109(3): 467–474.
76. Mohammadipanah, F and Wink, J. Actinobacteria from arid and desert habitats: Diversity and biological activity. Front Microbiol 2016; 6: 1541.
77. Shivlata, L and Tulasi, S. Thermophilic and alkaliphilic *Actinobacteria*: Biology and potential applications. Front Microbiol 2015; 6: 1014.
78. Lee, L-H, Zainal, N, Azman, A-S, *et al. Mumia flava* gen. nov., sp. nov., an actinobacterium of the family *Nocardioidaceae*. Int J Syst Evol Microbiol 2014; 64(5): 1461–1467.
79. Lee, L-H, Cheah, Y-K, Sidik, SM, *et al. Barrientosiimonas humi* gen. nov., sp. nov., an actinobacterium of the family *Dermacoccaceae*. Int J Syst Evol Microbiol 2013; 63(1): 241–248.
80. Azman, A-S, Zainal, N, Ab Mutalib, N-S, *et al. Monashia flava* gen. nov.,

sp. nov., an actinobacterium of the family *Intrasporangiaceae*. Int J Syst Evol Microbiol 2016; 66(2): 554–561.
81. Kim, J-J, Marjerrison, CE, Shartau, SLC, *et al. Actinocrinis puniceicyclus* gen. nov., sp. nov., an actinobacterium isolated from an acidic spring. Int J Syst Evol Microbiol 2017; 67(3): 602–609.
82. Saygin, H, Ay, H, Guven, K, *et al. Desertiactinospora gelatinilytica* gen. nov., sp. nov., a new member of the family *Streptosporangiaceae* isolated from the Karakum Desert. Antonie Van Leeuwenhoek 2019; 112(3): 409–423.
83. Lee, L-H, Azman, A-S, Zainal, N, *et al. Microbacterium mangrovi* sp. nov., an amylolytic actinobacterium isolated from mangrove forest soil. Int J Syst Evol Microbiol 2014; 64(10): 3513–3519.
84. Lee, L-H, Azman, A-S, Zainal, N, *et al. Sinomonas humi* sp. nov., an amylolytic actinobacterium isolated from mangrove forest soil. Int J Syst Evol Microbiol 2015; 65(3): 996–1002.
85. Mayilraj, S, Krishnamurthi, S, Saha, P, *et al. Rhodococcus kroppenstedtii* sp. nov., a novel actinobacterium isolated from a cold desert of the Himalayas, India. Int J Syst Evol Microbiol 2006; 56(5): 979–982.
86. Carro, L, Golinska, P, Nouioui, I, *et al. Micromonospora acroterricola* sp. nov., a novel actinobacterium isolated from a high altitude Atacama Desert soil. Int J Syst Evol Microbiol 2019; 69(11): 3426–3436.
87. Nakaew, N, Sungthong, R, Yokota, A, *et al. Nonomuraea monospora* sp. nov., an actinomycete isolated from cave soil in Thailand, and emended description of the genus *Nonomuraea*. Int J Syst Evol Microbiol 2012; 62(12): 3007–3012.
88. Law, JW-F, Ser, H-L, Duangjai, A, *et al. Streptomyces colonosanans* sp. nov., a novel actinobacterium isolated from Malaysia mangrove soil exhibiting antioxidative activity and cytotoxic potential against human colon cancer cell lines. Front Microbiol 2017; 8: 877.
89. Ser, H-L, Law, JW-F, Tan, W-S, *et al.* Genome sequence of bioactive streptomycete isolated from mangrove forest in East Malaysia, *Streptomyces monashensis* MUSC 1J^{T}. Prog Drug Discov Biomed Sci 2019; 2(1): a0000045.
90. Ser, H-L, Palanisamy, UD, Yin, W-F, *et al.* Presence of antioxidative agent, Pyrrolo [1, 2-a] pyrazine-1, 4-dione, hexahydro-in newly isolated *Streptomyces mangrovisoli* sp. nov. Front Microbiol 2015; 6: 854.
91. Lee, L-H, Zainal, N, Azman, A-S, *et al. Streptomyces pluripotens* sp. nov., a bacteriocin-producing streptomycete that inhibits meticillin-resistant *Staphylococcus aureus*. Int J Syst Evol Microbiol 2014; 64(9): 3297–3306.
92. Ser, H-L, Palanisamy, UD, Yin, W-F, *et al. Streptomyces malaysiense* sp. nov.: a novel Malaysian mangrove soil actinobacterium with antioxidative activity and cytotoxic potential against human cancer cell lines. Sci Rep 2016; 6(1): 1–12.
93. Qin, S, Li, W-J, Dastager, SG, *et al.* Actinobacteria in special and extreme habitats: diversity, function roles, and environmental adaptations. Front Microbiol 2016; 7: 1415.
94. Gomez-Escribano, JP, Alt, S, and Bibb, MJ. Next generation sequencing of actinobacteria for the discovery of novel natural products. Mar Drugs 2016; 14(4): 78.
95. Ser, H-L, Tan, W-S, Ab Mutalib, N-S, *et al.* Genome sequence of *Streptomyces pluripotens* MUSC 135^{T} exhibiting antibacterial and antioxidant activity. Mar Genomics 2015; 24: 281–283.
96. Ser, H-L, Ab Mutalib, N-S, Yin, W-F, *et al.* Genome seq*uence of Streptomyces antioxidans* MUSC 164^{T} isolated from mangrove forest. Prog Microbes Mol Biol 2018; 1(1): a0000001.
97. Ser, H-L, Tan, W-S, Ab Mutalib, N-S, *et al.* Genome sequence of *Streptomyces mangrovisoli* MUSC 149^{T} isolated from intertidal sediments. Braz J Microbiol 2018; 49(1): 13–15.
98. Ser, H-L, Chan, K-G, Tan, W-S, *et al.* Complete genome of mangrove-derived anti-MRSA streptomycete, *Streptomyces pluripotens* MUSC 135^{T}. Prog Microbes Mol Biol 2018; 1(1): a0000004.
99. Ser, H-L, Tan, W-S, Ab Mutalib, N-S, *et al.* Draft genome sequence of mangrove-derived *Streptomyces* sp. MUSC 125 with antioxidant potential. Front Microbiol 2016; 7: 1470.
100. Ser, H-L, Tan, W-S, Cheng, H-J, *et al.* Draft genome of amylolytic actinobacterium, *Sinomonas humi* MUSC 117^{T} isolated from intertidal soil. Mar Genomics 2015; 24: 209–210.
101. Ser, H-L, Tan, W-S, Cheng, H-J, *et al.* Draft genome of starch-degrading actinobacterium, *Microbacterium mangrovi* MUSC 115^{T} isolated from intertidal sediments. Prog Drug Discov Biomed Sci 2018; 1(1): a0000005.
102. Ser, H-L, Tan, W-S, Yin, W-F, *et al.* Whole genome sequence of *Streptomyces humi* strain MUSC 119^{T} isolated from intertidal soil. Prog Drug Discov Biomed Sci 2019; 2(1): a0000020.
103. Ser, H-L, Tan, W-S, Mutalib, N-SA, *et al.* Genome sequence of *Streptomyces gilvigriseus* MUSC 26^{T} isolated from mangrove forest. Braz J Microbiol 2018; 49(2): 207–209.
104. Ser, H-L, Law, J-F, Tan, W-S, *et al.* Whole genome sequence of *Streptomyces colonosanans* strain MUSC 93J^{T} isolated from mangrove forest in Malaysia. Prog Microbes Mol Biol 2020; 3(1): a0000061.
105. Ventura, M, Canchaya, C, Tauch, A, *et al.* Genomics of *Actinobacteria*: tracing the evolutionary history of an ancient phylum. Microbiol Mol Biol Rev 2007; 71(3): 495–548.