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Characterization of Thermophilic Novel-Rare Actinobacteria and Compost as an Unique Secondary Metabolite Producer: A Review

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Abstract. This review aims to explain in more detail about the Actinobacteria and it secondary metabolites. Some species of Actinobacteria can live in extreme environments such as high acid, high base, high salt and even high temperatures. Actinobacteria mainly of the genus *Streptomyces sp*. has been known to produce bioactive compounds such as antibacterial, antifungal, anticancer, antitumor, anticytotoxic, anti-inflammatory, anti-parasitic, anti-malarial, antiviral and antioxidant. This study reviews various research findings on Actinobacteria species and their ability to thrive in extreme environments. It also reviews the findings of bioactive compounds isolated from Actinobacteria and their potential applications. Some species in the genera *Streptomyces*, *Thermonospora*, *and Thermoactinomyces* have optimal growth temperatures above 55°C and are categorized as thermophilic. More than 30,000 bioactive compounds that have been isolated are derived from Actinobacteria and 80% are from the genus *Streptomyces sp.* Benzastatin C and 3-Chloro-Tetrahidroquinolon are new antivirals isolated from *Streptomyces nitrosporeus*. Essramycin is a novel antibiotic that shows activity against Gram positive and Gram negative bacteria. Chandrananimycin A isolated from *Actinomadura sp*. and *N*-(2-hydroxyphenyl)-2-Phenazinamin (NHP) isolated from *Nocardia dassonvillei* are novel antibiotics that can be used as antifungals, antialgas, antibacterials and anticancer. The potential of Actinobacteria in producing bioactive compounds can advance the field of science and technology in the future and become an alternative to overcome the problem of resistance to pathogenic microorganisms are increasing.

Keywords: Actinobacteria, Bioactive compound, Secondary metabolites

INTRODUCTION

Actinobacteria or Actinomycetes is an unicellular microorganism, Gram positive and aerobic [1]. Its fungi-like morphology has mycelium causing Actinobacteria to be initially classified in groups between bacteria and fungi. However, further studies show that Actinobacteria filaments are prokaryotic [2,3]. Actinobacteria generally live in environments with neutral pH with optimum

temperatures ranging from 25-30°C but there are some species that can live in extreme environments such as environments with high acid levels (Acidophilic), high alkaline levels (Alkalophilic) or high salt content (Halophilic) even optimum temperature growth above 55°C (Thermophilic) for example genus *Streptomyces, Thermonospora* and *Thermoactinomyces* [2,4,5,6]. High levels of Guanine and Cytosine in Actinobacteria DNA cause an unique life cycle when compared with other prokaryotic bacteria [7, 8]. Some bacteria included in the Actinobacteria class are listed in Table 1 below.

Table 1. Classification of Actinobacteria groups

Groups	Characteristics	References
Nocardioformactinomycetes	Aerobic, can live in an acid or base, rod or round, containing mycolic acid, cell wall chemotype IV.	[3,9,10]
Multilocular sporangia actinomycetes	Aerobic or anaerobic, has mycelium, has no hyphae, cell wall chemotype III.	[3, 11]
Actinoplanetes	Aerobic, immovable or non-motile, having spores stored in vesicles, not having mycelium, chemotype II cell wall.	[3,12,13]
Streptomycetes and its group	Aerobic, having mycelium and branched substrate.	[3,14,15,16]
Thermomonospora and its group	Aerobic, having mycelium and a branched substrate, chemotype III cell wall.	[3,17]
Thermoactinomycetes	All species are thermophilic, cell walls contain Meso-DAP but do not have a typical amino acid or sugar.	[3]
Other groups	All species produce spores for growth.	[3]

Actinobacteria is known to live in some places, namely the soil [18], compost [19,20], waste [21,22,23] as well as territorial waters [24]. Areas that have extreme environments such as high plaines, volcanic areas and waters with high salt content can also be a habitat of Actinobacteria [7,25,26]. Actinobacteria known for its ability to survive in extreme environmental conditions, is due to the flexibility of its metabolites. Such capabilities spark speculation that physiological or biochemical pressures under extreme conditions can lead to the production of natural compounds [27] such as potential secondary metabolites [24,25,28].

Antibacterial compounds

Antibacterial is one of the secondary metabolites activity produced by microorganisms in the stationary phase which can inhibit the growth or kill other microorganisms [35,41,42,43,44,45,46]. As many as 23,000 antibiotics that have been isolated from microorganisms, and more than 10,000 of which are produced by Actinobacteria, its about 75% of antibiotics are produced by Actinomycetes [16] and are known to be largely produced from the genus *Streptomyces* [14]. Streptomycetes produce about 34% of the bioactive compounds of the 45% that have been isolated from actinomycetales species, the other eleven percent are produced by other actinomycetes [47].

Three isolated Actinobacteria isolates from the Algerian desert were able to produce antibacterial activity that showed some pathogenic bacteria [48]. Twelve isolates of Actinobacteria isolated from samples of farmland of the Egyptian region could produce antibiotics showing activity against bacteria *Escherichia coli, Staphylococcus aureus, Bacillus cereus, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella Typhi, Candida albicans, Aspergillus niger,* and *Aspergillus flavus* [49]. Other research reported that *Streptomyces sp.* able to produce antibiotics Essramycin which is a novel antibiotic triazolopyrimidin. The antibiotics showed activity against Gram positive and Gram negative bacteria with MICs of 2-8 µg/mL [50].

Antibiotics can also be produced by Actinobacteria that live in extreme environments. Thermophilic Actinobacteria will produce antibiotics that can produce activity at high temperatures, as well as halophilic Actinobacteria that can produce antibiotics that can produce activity at high salt levels [51]. Actinomycetes strains isolated from Lake Tana, Ethiopia, can also produce antibiotics that still show activity against pathogenic bacteria even though they are at 5% salinity [52]. Another study proved that the bacteria *Burkholderia gladioli* OR 1 isolated from the agricultural land of the volcanic area of Khuda Lahora village was able to produce antibiotics that still showed activity against pathogenic bacteria *Staphylococcus, Enterobacter, Enterococcus, Acinetobacter* and *Citrobacter* even at 121ºC [53]. Therefore the nature and environmental conditions of a microorganism will affect the characteristics of the antibiotics produced [54].

Antifungal compounds

Actinobacteria is still considered to be the most potent bacterial group in producing antifungal because of its ability to produce secondary metabolites with various chemical structures and biological activities. For the pharmaceutical industry, the main challenge today is the new, safe and more effective antifungal search for controlling mycotic diseases [53, 55, 56]. Not only in the field of health, antifungal properties are also widely used in the field of environment, agriculture, food technology and the manufacture of cosmetics [57-59]. Although many antifungals have been isolated from various microorganisms, identification to find novel antifungals that are effective against pathogenic microorganisms continues to be carried out [60,61].

The novel discovery of the new Chandrananimycin A antibiotic isolated from *Actinomadura sp.* and *N*-(2-hydroxyphenyl)-2-Phenazinamin (NHP) isolated from *Nocardia dassonvillei* are two examples of the many novel antibiotics that have been found. Chandrananimycin A not only can be used as an antifungal, but also functions as an anti-aging, antibacterial and anticancer agent. The antibiotic activity shown by Chandrananimycin A may inhibit the growth of *Mucor miehei*, *Chlorella vulgaris* and *Chlorella sorokiniana*, *Staphylococcus aureus* and *Bacillus subtilis* bacteria. While NHP showed antifungal activity in inhibiting the growth of *Candida albicans* with MIC of 64µg/mL [62,63]. Streptomyces sp. isolated from the South China Sea also showed antifungal activity against *Candida albicans* and *Aspergillus niger* [64].

Anticancer compounds

Cancer is a very serious health problem for humans. In women, breast cancer is the second leading cause of death in the world. Treatment methods that are currently used to treat cancer include surgery, radiotherapy, immunotherapy and chemotherapy, each of these methods can have an effect on certain situations but when multiple methods of treatment are combined it will provide more efficient results in the treatment of cancer. Anticancer drugs that have been found come from secondary metabolites produced by microalgae. These drugs have been found to play an important role in the synthesis and identification of other pharmaceutical compounds [35,65,66,67,68]. In addition to microalgae, Actinomycetes is also one of the potential sources for the discovery of new bioactive compounds as anticancer that have diverse clinical effects. To date, more than 60% of anticancer have been found, 50% of them are sourced from metabolites produced by Actinomycetes [43,69]. New antibiotic, Caprolactones, isolated from *Streptomyces sp.* show cytotoxic properties and activity against cancer cells simultaneously [70]. Another research conducted by Ravikumar et al. (2012) reported that the Actinomycetes isolates ACT01 and ACT02 (GQ478246 and GQ478247) isolated from sediment samples can also be used as anticancer agents especially against breast cancer cells.

Antitumor compounds

Novel-antibiotics from the bacterium *Streptomyces sp.* show activity as antitumor by fighting cancer cells in human body cells but do not show activity as antibacterial or antiviral [71]. Another novel antibiotic that shows activity as an antitumor is Marinomycins. The antibiotic was isolated from *Marinispora sp*. Marinomycins showed antitumor activity against 6 of 8 melanoma cells tested [72].

Anticytotoxic compounds

Streptomyces produces many bioactive compounds such as antimicrobials, antifungals, antioxidants, anticancer and antitumors that have cytotoxic properties [73,74]. The presence of cytotoxic activity indicates the ability of a survival cell despite the presence of nearby toxic compounds [75,76]. As many as 25 bacterial strains isolated from the Bay of Bengal in Tamilnadu were able to produce antibiotics which showed antibacterial activity against Gram positive and Gram negative bacteria and antifungals against pathogenic fungi. This antibiotic is purified using chromatography methods. The BC1 fraction of the purification results showed very strong cytotoxic LC_{50} of 0.15 µg/mL [77]. The isolates of *Amycolatopsis alba* can produce Pyridinium antibiotics that exhibit cytotoxic activity against cervical cancer cells (HeLa), breast cancer cells (MCF-7) and brain cancer cells (U87MG) [78].

Anti-inflammatory compounds

Antiinflammation defined as a compound that can reduce or suppress inflammation caused by various stimuli including physical injury, heat, reaction of antibodies or infection due to bacteria. Bacterial infections are still one of the deadliest diseases in tropical countries. From 1940 to 2004, there were 335 reported deaths in the world. Bacterial resistance to several types of antibiotics is also the cause of the difficulty of curing infections caused by bacteria. This then becomes the focus of researchers to find and develop new antibiotics to overcome the problem of resistance. One source that is known to have the potential to produce new antibiotics is Actinobacteria microorganisms [79,80,81,82,83]. Moore et al. (1999) reported that the antibiotics of Sulfonamides A and B produced by the isolate *Cassiopeia xamachana* CNB-091 showed both antibacterial and anti-inflammatory activity simultaneously [84].

Antiparasite compounds

Anti-parasite is a compound used to treat diseases caused by parasites such as *Leishmania major* which causes Leishmaniasis and *Trypanosoma brucei* causes of African sleeping sickness disease. Leishmaniasis is a disease caused by the protozoa of the genus *Leismania* which has infected 350 million people in 88 countries. Several types of antibiotics that have been used for the treatment of leishmaniasis are Amphotericin B, Pentamidine and Miltefosin. But the use of these drugs can provide side effects and dependence for a long time. The large number of deaths caused by these parasites and the emergence of antibiotic resistance are important reasons for finding new and effective drugs [65,85]. Valinomycin, Staurosporin and Butenolida is a new novel anti-parasit produced as a secunder metabolite by *Streptomyces sp*. from the Mediterranean Sea. These three compounds exhibit anti-parasitic activity against *L.major* (IC_{50} Valinomycin < 0,11µM; IC_{50} Staurosporin 5,30 µM) and *T.brucei* (IC_{50} Valinomycin 0,0032 µM; IC_{50} Staurosporin 0,022 µM; IC_{50} Butenolida 31,77 µM) [86].

Antimalaria compounds

Malaria is a disease caused by protozoa of the plasmodium genus. To date, more than 300 million cases of malaria have been detected and annually cause 2 million deaths in the world. The problem that is the focus of the researchers is that *Plasmodium falciparum* a vector that causes malaria, is increasingly resistant to all types of malaria drugs that have been circulating. For that needed new types of drugs to overcome these problems and the search for the drug continues to be done [87]. Maskey et al. (2004) reported that the complex compounds Trioxacarcins A, B and C isolated from *Streptomyces ochraceus* and *Streptomyces bottropensis* showed very high anti-malarial activity against pathogenic microorganisms that caused malaria disease [62].

Antivirus agent

Antivirus not only able be applied to chemotherapy healing of diseases caused by viruses in humans and animals but can also be used as a means of controlling enteropatogenic viral contamination in humans and transmission of diseases in waters due to waste pollution so it is very useful for surrounding communities who utilize coastal waters for recreation and others [88]. *Streptomyces nitrosporeus* isolated by Lee et al. (2007) able to produce several compounds that show antiviral activity namely Benzastatin C and 3-Chloro- Tetrahidroquinolon. Both showed very strong antiviral activity against herpes simplex virus type I, herpes simplex type 2, and Vesicular Stomatitis Virus (VSV) [89].

Antioxidant compounds

Reactive oxygen is one of the radical compounds in the body that is produced during normal cell metabolism and can cause cell or tissue damage, autoimmune diseases, degenerative diseases to cancer if excessive amounts [90]. Therefore, it takes a compound that can bind to free radicals that inhibit the oxidation reaction, the compound is called antioxidant substances. There are two types of antioxidants, natural antioxidants and synthetic antioxidants. Synthetic antioxidants like Butyl Hydroxilanisol (BHA), Butyl hydroxitoluene (BHT) and Propylgallat has been widely used but this antioxidant has the potential to be harmful to health because it is feared it can give side effects for users, while the use of natural antioxidants has been known to be beneficial to use even in terms of food because it has a very low degree of toxicity [91,92,93]. This then led the researchers to look for natural sources as new antioxidant producers and Streptomyces sp. has been recognized as one of the potential sources for producing antioxidant compounds [73], [94]. Four *Streptomyces* isolates namely BC01, BC02, BC03 and BC04 isolated from mangrove forest soil in Visakhapatnam region showed antioxidant activity when testing using DPPH and FRAP methods [95]. Lee at al. (2014) in his study reported that ethyl acetate extract from strain MJM 10778 *Streptomyces sp*. isolated from Hambak mountain, Korea, showed high antioxidant activity against DPPH, NO and ABTS radical compounds with value of IC_{50} respectively 92.8µg/mL; 0,082 µg/mL and 134,9 µg/mL. Based on research that has been done by both of them, it can be concluded that Actinomycetes is a potential source of antioxidant production [96].

CONCLUSION

Actinobacteria is currently known to be one of the secondary metabolites producing microorganisms of potential bioactive compounds. These secondary metabolites are generated at the stationary phase. Some types of secondary metabolites that Actinobacteria can produce are antibacterial, antifungal, anticancer, antitumor, anticytotoxic, anti-inflammatory, antiparasitic, antimalarial, antiviral and antioxidant. These secondary metabolites have different characteristics and characteristics depending on the environment in which Actinobacteria lives. Extreme living environment will affect Actinobacteria to produce secondary metabolites with unique activities, for example in the thermophilic environment Actinobacteria will produce secondary metabolite that are high temperature resistant or in the halophilic environment Actinobacteria will produce secondary metabolites that have activity at high salt levels. Generally, the secondary metabolites produced are still in the form of crude extracts with various kinds of bioactive compounds. Therefore, to obtain one type of bioactive compound such as antibacterial or antifungal, separation must be carried out and purification.

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