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Bioprospecting of Microbes for Valuable Compounds to Mankind

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Abstract: The most biological multiplicity on this planet is almost certainly concealed in soils. Many valuable bacteria had been extensively dispersed in soils worldwide, with soils from terrestrial, desserts and Antarctic. Hence, soils become an intensively utilized ecological niche for the inhabitants to generate various useful biologically active natural products such as antibiotics, antifungal, antiviral, antioxidant, neuroprotection, anticancer and other important compounds. Bacteria including Actinobacteria have been exceptionally valuable for the pharmaceutical industry due to their limitless capability to generate secondary metabolites with various biological activities and chemical structure. Therefore, this article aims to provide critical insight of bioprospecting of microbes for valuable compounds to mankind.

Keywords: Bioprospecting; microbes; compounds; metabolites; actinobacteria; soil

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INTRODUCTION

Biotechnology is an illustration of biodiversity as new products via the utilization of living organisms and bioprocesses in medicine, engineering, technology, and other fields that required bioproducts. The greater the biodiversity offered, the greater probabilities of discoveries that could be transformed into vital technologies[1]. The estimation of the environmental and economic gains that are a direct or indirect result of microbial diversity were approximate to be in the range of 16-54 trillion US dollars per year, with an average of 33 trillion US dollars per year[2].

The primary and secondary metabolism of prokaryotes has been utilized by industrial for the creation of diverse products such as antibiotics[3–6], amino acids[7,8], nucleotides[7], organic acids[9] and vitamins[10]. Bacteria like Actinobacteria are a particularly rich source of compounds with activities such as antimicrobial[6,11–22], anticancer[23–29], antioxidants[30–35], neuroprotective[36,37], enzymes[38–41] and immunosuppressive[29] as illustrated by Figure 1. Bérdy (2005)[42] reported that in 2002, over 10,000 bioactive compounds (45% of all microbial metabolites) were obtained from filamentous Actinobacteria, out of which 7600 (75%) were obtained from *Streptomyces* and 2500 (25%) from rare Actinomycetes for instance *Actinomadura*, *Streptoverticillium* and *Micromonospora*.

Despite the tremendous success of the past in obtaining

useful secondary metabolite, the probabilities of discovery novel biologically active molecules from bacteria such as Actinobacteria was reduced and appears to be reaching a saturation curve. Recently, isolating well known Actinobacteria such as *Streptomyces* from diverse environments were reported to obtain similar compound, potentially due to regular genetic exchange between species[43]. These challenges had led to intensely amplified in serious demand for new structures in pharmacology, hence propelled the investigation of new habitats with poorly explored areas and uncommon environments to become vital for the discovery of novel bacteria (e.g. Actinobacteria) and useful metabolites[44–55]. Reports from poorly explored areas from these regions (e.g. Antarctic, Australia, China, Malaysia and Jordan) suggested that the investigation of new habitats remain to be valuable in discovering novel microorganisms and useful metabolites[47,56–61]. Moreover, the progression of new selective methods allows the screening and isolation of 'rare' Actinobacteria that can lead to finding useful bioactive compounds[62–64]. The finding of "rare" Actinobacteria has increased the array and diversity of genetic resources available for biotechnological utilization[62–66]. It is apparent that the findings of novel bacteria such as Actinobacteria could increase the discovery novel bioactive metabolites[62,66–68].

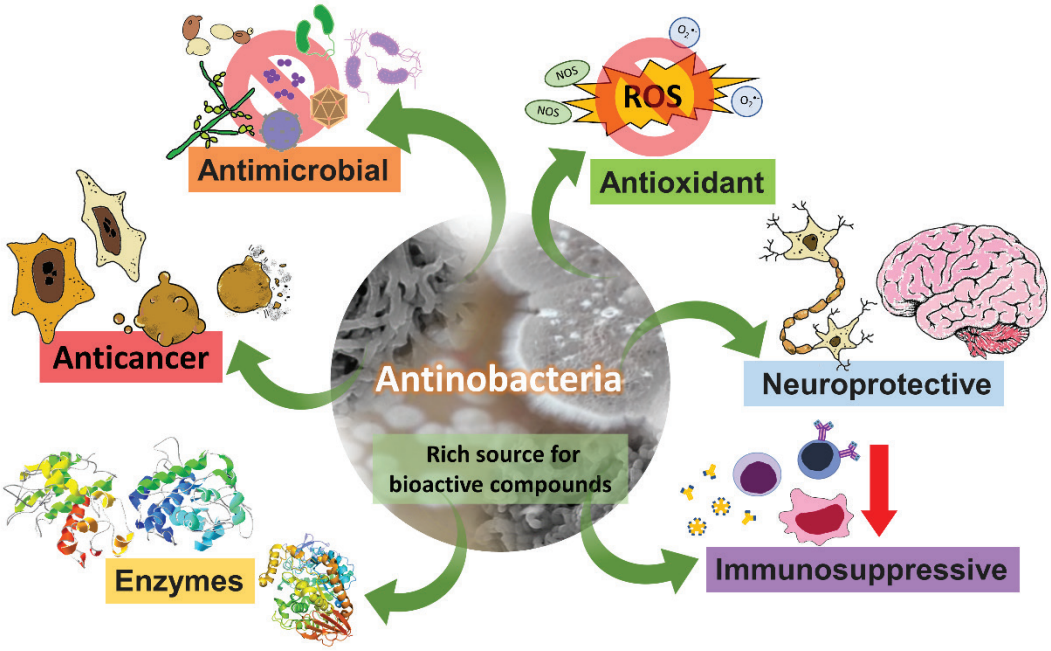

Figure 1. Actinobacteria are prolific producers for metabolites with diverse activities.

The genome sequencing of *Streptomyces coelicolor* A(3)2^{T}[69] and *Streptomyces avermitilis* MA-4689^{T}[70,71] discovered that these bacteria comprise more than 20 natural product gene clusters. This number of gene clusters is much more as compared to genomes of bacteria from another phylum[72,73]. For instance, *Bacillus subtilis* strain 168^{T} with three, *Ralstonia solanacearum* strain GMI 1000^{T} with two[74], and *Pseudomonas aeruginosa strain* PA01^{T} with four[75] *Pseudomonas aeruginosa* strain. While most other bacteria genomes lacking any detected natural product gene clusters[69]. These reports indicated the capability to produce secondary metabolites are not evenly distributed among microbes. Moreover, multiple gene clusters encoding for alike classes of secondary metabolites have been discovered in the genomes of other Actinobacteria[76,77]. Thus, explaining Actinobacteria are highly prolific sources of bioactive metabolites[78] with high capacity to utilize a extensive range of compounds and create secondary metabolites with diverse chemical structures and biological activities[79,80].

Unexplored environment — The Antarctic

The Antarctic is the area at the Earth's South Pole, contrary the Arctic region at the North Pole. The Antarctic includes the continent of Antarctica and the ice shelves, waters and island territories in the Southern Ocean situated south of the Antarctic Convergence. The area covers approximately 20% of the Southern Hemisphere, of which 5.5% (14 million km^2) is the surface area of the continent itself. The Antarctic is the coldest and windiest continent, it is a hostile, remote, and uninhabited area with its surrounding marine sites, provides an appropriate chance to investigate a still unexplored microbial biodiversity[81–87]. The uneven mixture of selection pressures has led to the evolution of novel biochemical adaptations and the likelihood of native species[88,89]. The production of metabolites such as antibiotics and toxins could confer a competitive survival benefit in this environment. Therefore, the investigation of poorly explored areas such as the Antarctic seemed as important region for discovering of potential novel bacteria and useful biological active metabolites[59,82,85,90,91].

Bacteria from Antarctic territories

The information of prokaryotic biodiversity remains very sparse across Antarctica[82,92,93]. Nevertheless, in recent decades, the improvement in both culture dependent and culture-independent methodologies allow some studies focused on Signy Island were done[94,95,96,97,98,99]. This area

act as a benchmark site within the maritime Antarctic, whose terrestrial ecosystems are demonstrative of the region[100]. Furthermore, more studies are also emerging from other sites along the Antarctic Peninsula, such as the study of the prokaryotic communities of a series of Antarctic terrestrial habitats along a latitudinal gradient as part of a larger regional microbial diversity study covering between the Falkland Islands (~50^{0}S) and Mars Oasis, Alexander Island (~72^{0}S)[101–103]. Based on the restricted habitats studied, a fairly large bacterial diversity has been reported[96–99,104,105].

There is an agreement that spatial distinction between soil organisms is not random but displays expectable patterns over dissimilar spatial scales. The small-scale difference is found to exhibit superior diversity than large scale difference[106–108]. Small-scale difference might be more vulnerable to local environmental effects such as areas of increased substrate availability[109]. Scientists indicated that water content, organic content (loss on ignition) and total N showed substantial direct correlations with microbial counts from soil at 6 different sites on Signy Island, whereas pH exhibited an inverse association[94]. Some recent culture-independent reports have demonstrated that soil prokaryote biodiversity on Signy Island have high association with elements such as conductivity, pH, lead and copper content. Moreover, significant overlap was reported across sites evidently affected by penguins, seals, and the existence of vegetation[99]. The direct effect of soil properties for instance soil pH, nutrients and moisture on bacterial diversity were demonstrated[110–113], and remarkably these parameters also exhibited close connection to specific functional genes for instance glutamate dehydrogenase and nitrate reductase[102].

Studies of the bacterial ecology of Antarctic soils by means of culturing dependent methods demonstrated that bacterial abundance and diversity can differ with soil factors for instance moisture, pH, available nutrients, salinity, elevation, slope, solar radiation, and drainage[114]. Suzuki et al. (1997)[115] isolated an obligate psychrophilic Actinobacteria, *Cryobacterium psychrophilum* from the Antarctica soil. This bacterium grew best at 9–12^{o}C and did not grow at temperatures higher than 18^{o}C. While psychrophilic strains of *Modestobacter multiseptatus* with optimum growth temperatures of 11-13^{o}C have also been isolated from transantarctic mountain soils[116].

Normally, the early studies on the bacterial diversity of Antarctic soils were disadvantaged by the readiness of appropriate approaches. With the accessibility of DNA-based culture-independent assays, analysis of mineral soils of the Antarctic area has discovered that the soil bacterial communities have low diversity compared with temperate soils and may be dominated by a few bacterial phylotypes. Bacteria reported from the soils typically group with the phyla *Actinobacteria*, *Acidobacteria*, *Bacteroidetes*, *Deinococcus-Thermus*, *Firmicutes*, *Cyanobacteria* and *Proteobacteria*[117-119]. Apart from *Deinococcus* and *Cyanobacteria*, they are among the phyla normally described from non-Antarctic soils[120]. The phyla *Actinobacteria* and *Bacteroidetes* appear to be prevalent in Antarctica while other phyla less broadly spread (e.g. *Acidobacteria)*. Remarkably some bacteria have no close relatives demonstrating soils of the Antarctic (e.g. Ross Sea Region) are extremely potential as a natural reserve of novel and cold-adapted bacteria[118]. The closest relatives include members of the genera *Arthrobacter*, *Brevundimonas*, *Leptolyngby*a, *Hymenobacter*, *Nocardioides*, *Sphingomonas* and *Sporosarcina*[117–119] all of which have been isolated from Antarctic soil.

The Barrientos Island of Antarctic is situated at 62˚24'S, 59˚47'W, north entrance to English Strait between Robert and Greenwich Islands. The north coast of the 1.5km island is dominated by steep cliffs, reaching a height of nearly 70 metres, with a gentle slope down to the south coast. The eastern and western ends of the island are black sand and cobbled beaches. The western end has columnar basalt outcrops as a notable feature. The whole center of the island is covered by widespread moss carpet. Lichens *Xanthoria* spp., *Caloplaca* spp. and other crustose lichen species are present. Moreover, the green alga *Prasiola crispa* is prevalent. Soil samples were collected from this island and molecular identification, which was based on 16S rDNA sequences analysis, discovered eight genera of Actinobacteria namely *Actinomyces*, *Actinobacterium*, an uncultured *Actinomycete*, *Streptomyces*, *Leifsonia*, *Frankinea*, *Rhodococcus* and *Mycobacterium*. The uncultured *Actinomyces* sp. and *Rhodococcus* sp. appear to be the prominent genera of Actinobacteria in Barrientos Island soil[121]. Molecular methods were applied to investigate correlations between actinobacteria abundance and environmental features, for instance vegetation and type of rookery. There was a substantial positive association between type of rookery and the abundance of actinobacteria; soil samples collected from active chinstrap penguin rookeries had the highest actinobacteria abundance. Vegetation type, for instance moss, which could provide a microhabitat for bacteria did not associate significantly with actinobacteria abundance[121].

In Barrientos Island, the selective isolation of culturable bacteria using 12 different isolation media were performed and total 96 bacteria isolates were isolated with 39 and 57 isolates belonged to phylum *Actinobacteria* and *Proteobacteria*, respectively. Through 16S rRNA gene analysis, 13 (*Arthrobacter*, *Brevibacterium*, *Demetria*, *Gordonia*, *Rhodococcus*, *Janibacter*, *Leifsonia*, *Dermacoccus*, *Kocuria*, *Lapillicoccus*, *Micromonospora*, *Microbacterium*, *Nocardioides*) and 8 (*Bradyrhizobium*, *Caulobacter*, *Sphingomonas*, *Methylobacterium*, *Paracoccus*, *Ralstonia*, *Rhizobium*, *Staphylococcus*) different genera of *Actinobacteria* and *Proteobacteria*, respectively were discovered[122,123]. Comparatively *Actinobacteria* (13 genera) had substantial higher diversity than *Proteobacteria* (8 genera)[122,123], hence showed that *Actinobacteria* are proficient to prosper in an extensive range of diverse soil environments, and they could resist the pressure of harsh environment as they could persist in the viable but inactive state for a extended time with form of spore[124]. Their extensive disseminations in Antarctic suggest that their dispersals are extremely endemic,

predominantly in soil and sediment[112,125]. Therefore, allowing the bio-prospecting of bacteria from sampling soil from widespread array of geographic sites, such as the Antarctic areas to be benefitted. Results showed that *Streptomyces* agar (SA) was the most suitable medium for isolating actinobacteria from soil of Barrientos Island with 54% isolation rate, while starch casein agar (SCA) was the most suitable medium to isolate proteobacteria with 19% isolation rate[122,123].

Furthermore, researchers studied actinobacteria and proteobacteria isolates from Barrientos Island for ability of producing antibacterial and antifungal secondary metabolites[122,123]. By means of high-throughput screening models, about 23%, 9%, 6% and 1% of isolates inhibited growth of *Candida albicans* ATCC 10231^T, *Staphyloccoccus aurues* ATCC 51650^T, methicillin-resistant *S. aurues* (MRSA) ATCC BAA-44^T and *Pseudomonas aeruginosa* ATCC 10145^T, respectively. A total 34 bioactive isolates were isolated and categorized into 13 genera, particularly 9 genera were actinobacteria. The high bioactivities of actinobacteria isolates (38%) as compared to proteobacteria isolates (25%) in this study[122,123] showed that *Actinobacteria* still remain as the better source for bioprospecting of novel bioactive metabolites owing to their tremendous capability to produce secondary metabolites with varied chemical structure and biological activities[79,80,126]. These findings provided vital baseline data that Barrientos Island is a good source of isolation for bioactive actinobacteria and proteobacteria with good antibacterial and antifungal metabolites[122,123].

In Barrientos Island, the application of the polyphasic taxonomic such as on the basis of phylogenetic, chemotaxonomic, phenotypic and signature nucleotide pattern of the 16S rRNA gene, these results indicated that strain 39^T is unlike all the genera in the family *Dermacoccaceae*. Hence, it is recommended that strain 39^T to be categorized in a novel genus in the family *Dermacoccaceae*, as *Barrientosiimonas* gen. nov., the type species of which is *Barrientosiimonas humi* gen. nov., sp. nov. The strain was named after Barrientos Island, the origin of the sampling site[127].

Bacteria as source of new natural products

The natural products have been demonstrated to be the richest source for discovery of novel bioactive compounds[128]. Previously, the majority bioactive products of microbial origin obtained from few taxonomic groups and mainly terrestrial environments[42,48]. In these decades, microbial natural products research inspired the progress of integrated methods merging specific isolation methods and the access to geographically diverse sources and to different ecological niches[128]. Lately the advancement of technologies enables other initiatives like targeting the exploitation of the metabolic potential of environmental gene libraries without undertaking the need of culturing microbes[129–131].

The microbial secondary metabolites comprise of antitumor agents, antibiotics, pesticides, enzyme inhibitors, toxins, and pigments. The biosynthesis of these metabolites is usually coded by genes clusters on chromosomal DNA and irregularly on plasmid DNA[132]. The discovery of new classes of antibiotics are vital to fight the increased occurrence of multiple resistances among pathogens to the available drugs presently in clinical use[133]. The utmost producers of natural product antibiotics are Actinobacteria as nearly two thirds of natural products have been derived from Actinobacteria[20], with streptomycetes accountable for more than 80% of them.

The phylum *Actinobacteria* signify a significant constituent of the microbial population in most soils[134–138]; such as the Antarctic region[117-119,139]. Also, *Actinobacteria* present in rhizosphere soil were reported for discovery of antimicrobial agents and other useful metabolites[140–151]. The genus *Streptomyces* exhibited potential as bio-control agent of commercial crops against fungal pathogens[17,152]. Moreover, *Streptomyces* spp. derived from grapes exhibited antifungal activity that is pathogenic to fungi and yeast from the same habitat[153]. While the genus *Arthrobacter,* a pervasive genus repeatedly discovered in Antarctic and Arctic areas is recognized for secondary bioactive metabolite production and for bioconversions[154,155]. Rojas et al. (2009)[128] examined Antarctic bacteria for creation of novel metabolites discovered a novel molecules associated to cyclic thiazolyl peptides active on gram positive pathogens produced by *Arthrobacter agilis* derived from Lake Hoare and Lake Fryxell from the McMurdo Dry Valley area in Antartic[128].

The Antarctic γ- and β-Proteobacteria strains R-12535 and R-7687 derived from Lake Reid in the Larsemann Hills and Lake Hoare in the McMurdo Dry Valleys produced bioactive metabolites that inhibited the growth of gram positive and negative pathogens such as *E. coli* and *S. aureus*[128]. Moreover, the MS spectra of bioactive metabolites obtained from the γ- and β-Proteobacteria strains R-12535 and R-7687 indicated no relatedness with any known compounds, suggesting a chemical novelty related to the bioactivity of these Antarctic bacteria. These studies demonstrated the high occurrences of antimicrobial activities discovered from Antarctic bacteria, which exhibited them as a prolific source of antimicrobial agents[42,62,156]. These findings support the notion that bacteria from Antarctic habitats comprise a rich metabolic diversity and the production of antimicrobial agents could provide a competitive benefit in this situation[157].

Other than antimicrobial agents, bacteria such as Actinobacteria produced enzymes that are vital and extensively used in medical therapy, bio-organic chemistry, molecular biology, detergent manufacturing, food processing, the textile and pharmaceutical industries[158]. For instance, Thermophilic *ThermoActinomyces candidus* could yield extracellular enzyme keratinase that could degrade wool[159]. The antimicrobial agents and keratin-degrading producing *Actinobacteria* (*Streptomyces, Nocardioides, Saccharomonospora, Nonomuraea* and *Nocardiopsis*) have been utilized to transformed poultry farm feather waste by composting into pathogen-free

and odourless bio-fertilizer with complete biological degradation[160].

Crawford (1978)[161] reported that streptomycetes can decay lignin by producing the enzyme lignin peroxidase. The extracellular lignin peroxidase derived from *Streptomyces viridosporus* has been studied[162] and it was the first report of a lignin peroxidase from a bacterium. In nature, lignin physically covers cellulose to form lignocellulose (65% cellulose, 25% lignin, and small quantities of hemicellulose glucans), and is resilient to degradation by most microorganisms. *Streptomyces viridosporus* T7A could depolymerizes lignin while degrading cellulose[161] and generates a modified water-soluble, acid-precipitable polymeric lignin (APPL) as a key lignin degradation product[163]. Pasti et al. (1990)[164] revealed novel *Streptomyces* strains, the *S. rochei* and *S. chromofuscus* that were discovered to be superior or equivalent in lignocellulose-degrading capability to *Streptomyces viridosporus* T7A.

The enzyme chitinase were discovered from the culture filtrate of *Streptomyces cinereorube*[165]. The enzyme was inhibited by Ag^{+}, Hg^{+}, Hg^{2+} and ρ-chloromercuribenzoate. This enzyme is stable in pH range 4.0-10.0 and the optimum pH and temperature for chitinase activity were 4.5 and 50°C, respectively. Gomes et al. (2000)[166] reported that *Streptomyces* spp. obtained from a Brazilian forest soil exhibited exceptional endochitinase activity and very active against three phytopathogenic fungi, namely *Fusarium solani*, *Magnaphorte grisea* and *Aspergillus parasiticus*.

Streptomyces ipomoea CECT3341 and *S. scabies* CECT3340 in liquid culture produces great levels of enzyme mannanase[167]. The potential of mannanase enzyme in refining the bleachability of pine kraft pulp was demonstrated. With bio-bleaching examinations by means of treatment of the enzyme to result in the release of chromophoric and color material from the pine kraft pulp, together with an increase in pulp brightness and an absence of differences in the viscosity values.

Berens et al. (1996)[168] effectively obtained the enzyme endoxylanases from the thermophilic actinobacteria *Microtetraspora flexuosa* SIIX. These thermostable enzymes reported to have optimal activities at pH 6.0 and 80°C. The hydrolysis of hemicellulose generated mostly xylobiose and xylotriose, the latter will be hydrolysed to xylobiose and xylose. Researchers demonstrated the production of endoxylanase from *Streptomyces noboritoensis*[169]. Moreover, a cellulase-free and endoxylanase-producing streptomycete, *Streptomyces thermocoprophilus* sp. nov. was discovered by Kim et al. (2000)[170].

Busch and Stutzenberger (1997)[171] discovered the *Thermomonospora fusca*, a facultative thermoalkalophilic Actinobacteria that produces an extracellular α-amylase which generates maltotriose as the key product. The optimum pH and temperature for the amylase activity were 6.0 and 65°C, respectively. The enzyme activity was not blocked by the addition of glucose due to the preference of the Actinobacteria for maltotriose.

Pasti and Belli (1985)[172] reported isolation of *Streptomyces* sp. and *Micromonospora* sp. from termite gut whereby these strains produce enzyme cellulose that contributed to their cellulolytic activity. A total of 4 different termites were reported for the isolation of cellulolytic Actinobacteria, namely *Armitermes, Macrotermes*, *Odontotermes* and *Microcerotermes* spp. All Actinobacteria strains effectively degraded both soluble and insoluble cellulose with some shown persistent activity up to a week. Waldron et al. (1986)[173] reported the isolation of *Microbispora bispora* from soil samples of hot springs, geysers and composts was found to grow at 55°C and create thermo-stable extracellular endoglucanase in good concentration with broad pH range of 5.5–7.2.

All these reports indicated the practicality of various enzymes produced by various bacteria such as Actinobacteria. The value of bacteria in the production of enzymes is heightened by their comparatively high produces, cost efficiency and susceptibility to genetic manipulation. These enzymes enabled bacteria to have a key role in numerous areas for instance the biodegradation of plant litter especially the recalcitrant lignocellulose component [174] and the decomposition of soil organic matter[175].

CONCLUSION

As a conclusion, the research of microbial diversity and the isolation of novel microorganisms signify a key chance for developments in biology[67,176–181]. The search and discovery of novel microbes that produce new useful secondary metabolites remains important in the fight against antibiotic resistant pathogens[182], and new emerging diseases[183–185].

Author Contributions

N-SAM, SHW, H-LS, LT-HT and JW-FL performed the literature search, critical review and performed the writing of this review. Guidance, support, and proofreading were contributed by AD, SR and VL. N-SAM and VL founded the review writing project.

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