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Review

Sources of antibiotics: Hot springs

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ABSTRACT

The discovery of antibiotics heralded an era of improved health care. However, the over-prescription and misuse of antibiotics resulted in the development of resistant strains of various pathogens. Since then, there has been an incessant search for discovering novel compounds from bacteria at various locations with extreme conditions. The soil is one of the most explored locations for bioprospecting. In recent times, hypersaline environments and symbiotic associations have been investigated for novel antimicrobial compounds. Among the extreme environments, hot springs are comparatively less explored. Many researchers have reported the presence of microbial life and secretion of antimicrobial compounds by microorganisms in hot springs.

A pioneering research in the corresponding author's laboratory resulted in the identification of the antibiotic Fusaricidin B isolated from a hot spring derived eubacteria, *Paenibacillus polymyxa*, which has been assigned a new application for its anti-tubercular properties. The corresponding author has also reported anti-MRSA and anti-VRE activity of 73 bacterial isolates from hot springs in India.

Contents

1. Introduction

Novel natural products can have innumerable potential uses, especially in the area of new drug discovery. Extensive research in the drug discovery arena has resulted in the identification of several terrestrial mesophilic sites. Man has explored various extreme environments for isolating microbes that secrete novel bioactive metabolites with therapeutic potentials. Microorganisms have been isolated from extreme environments ranging from the drought conditions in the Atacama Desert [1], sea-ice brine and high salinity [2], and hot springs [3]. Actinomycetes are one of the most versatile microorganisms, owing to their adaptability to diverse ecosystems and unusual habitats [4]. Thermophilic and

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alkalophilic actinomycetes possess a diverse physiology and adapt to various hostile and unfavorable conditions. These microorganisms have unique strategies for survival [5]. The cell envelopes in these bacteria play a critical role in their adaptation to higher temperatures, especially the cell structure and function [6]. Regarding the selection of actinomycetes as the target group microorganism, they score high over the other microbes as a prolific producer of antibiotics and other biopharmaceutical products [7].

Antimicrobial agents have treated various infectious diseases for the past seven decades [8]. They have been mainly useful in lowering the duration of illness and death from infectious diseases. However, their widespread use has enabled the infectious microorganisms to circumvent the toxicity aspect and adapt themselves, thus rendering the antibiotics less effective over a period [9]. Antimicrobial resistance affects human lives tremendously. Currently, an estimated additional 10 million lives will be affected by drug-resistant strains of infectious agents such as tuberculosis, and certain bacterial infections by the year 2050, which will entail around 100 trillion US dollars' worth of the global economy. We live in a world where multiple factors affect and promote antimicrobial resistance [10].

Antibiotics have become a necessity in various medical interventions since they reduce the disease burden. Not offering antibiotics or a delay in initiating antibiotic treatments has often led to an exacerbation of disease [11]. However, antibiotic resistance is also a result of the widespread misuse and excessive prescription of antibiotics. Gross misuse has led to new strains of easily controlled infectious agents. There is a consistent demand for more and more novel scaffolds with unique bioactivity not only as antimicrobials but also as anti-cancer and anti-diabetic agents. The organisms in extreme environments have a unique ability to accumulate certain metabolites in excess or secrete certain compounds that may find commercial applications. The enzyme, thermostable polymerase is one such example of commercial success.

Moreover, such heat-induced microbial compounds display varied bioactivity, some of which aid in the alleviation of the pains afflicting humans. Hot springs/geysers are such major niches on the Earth where we find such heat-tolerating microbes. There is a need to augment research-based studies on bioactive compounds screening from hot spring microbes, apart from working on their mechanistic ways to overcome the heat.

This review article explores the diversity in the area of bioactive compounds from the versatile Actinomycetes and other microbes from hot springs.

2. Biodiversity and the need for new bioactive compounds

The use of various supporting technologies for detecting new microorganisms, novel chemical structures, and novel biocatalytic activities has invigorated the natural product screening ventures. In this regard, the advent of new technologies such as combinatorial chemistry, combinatorial biosynthesis, metabolic pathway engineering, gene shuffling, and directed evolution of proteins are supportive tools to enhance the properties and activity of the novel bioactive compounds [7]. Bioactive natural products may not be isolated and available with the desired potency and pharmacological properties; however, bioinformatics can be useful in designing new analogs with optimized biological properties [12].

There is an intense need for new, novel, and useful compounds. Drug resistance, life threatening mutating viruses, a rise in the incidence of fungal infections, and postoperative issues in organ transplant patients are key inducers for creating this need. The World Health Organization (WHO) has reported that 35 million people were living with HIV at the end of 2013. That same year, around 2.1 million people became newly infected [13]. The Ebola outbreak in 2014–2015 in West Africa has further weakened the health care system in affected countries. The fear of nosocomial Ebola transmission resulted in a low turnout (10%) at the health care centers [14]. There is an alarming increase in the number of resistant and multidrug-resistant pathogens. Of these, the Gram-negative bacteria are currently a colossal threat. Methicillin-resistant *Staphylococcus aureus* (MRSA) incidence is decreasing and stable in most countries; however, bacteria from the *Enterobacteriaceae* sp. pose a greater threat in the form of resistance to the extended spectrum beta-lactamase (ESBL) and carbapenem antibiotics. Apart from the bioprospecting activities, ways to combat drug resistance is required [15].

More than 20 new antibiotics were discovered and marketed between 1940 and 1962. Thereafter, the discovery and marketing of new compounds slackened. The development of analogs safely catered to the management of the drug resistance issue until about two decades ago. The analog pipeline suddenly seems to have dried up, resulting in an acute unmet need for new antibiotics. Hence, there is an intense need for newer and novel classes of bioactive compounds [16].

3. Hot springs, geysers and microbes

The Encyclopaedia Britannica defines hot springs as springs with water at temperatures substantially higher than the air temperature of the surrounding region. Shallow intrusions of magma (molten rock) in volcanic areas heat the groundwater, which is later discharged by hot springs. Some thermal springs, however, are unrelated to volcanic activity. In such cases, the water is heated by connective circulation. Groundwater percolating downwards reaches a depth of a kilometer or more where the temperature of the rocks is high because of the natural temperature gradient of the Earth's crust–about 30 °C (54°F) per kilometer in the first 10 km (6 miles) [17]. Additionally, a geyser is defined as a hot spring that intermittently spouts jets of steam and hot water. The term geyser is derived from the Icelandic word *geyser* (to gush). Geysers result from the heating of groundwater by shallow bodies of magma and are present in areas that have a history of volcanic activity. The sudden release of pressure because of near-boiling water in the deep, narrow conduits beneath a geyser, results in the spouts [18].

Thomas Brock (1966) was one of the pioneers who discovered the growth of microbes in the boiling hot springs of Yellowstone National Park [19]. Brock et al. isolated a thermophilic and heterotrophic microorganism, *Thermus aquaticus* [20]. Consistent exposure to high temperatures, high free water content, high moisture content, and a typical chemical composition facilitates the growth of a typical range of hyperthermophilic microorganisms [21]. However, each hot spring differs from others in temperature, chemical composition, gradients of temperature and light [22].

The chemical constituents of the hot springs vary to a large extent, even among hot springs within close proximities, thereby resulting in a biodiversity in their microflora [23]. Hot springs enable the growth of microbial mats by providing favorable conditions. The diverse spectrum of colors in the microbial mats is probably because of a combination of scattering from the water and the microbial mats lining the base of these hot springs [24]. Additionally, quinones influence the color of the microbial mats. Hiraishi et al. (1998) observed a change in the quinone profile with varying growth temperatures. Table 1 summarizes the quinone profile of hot spring microbial mats with varying growth temperatures. The microbial flora of such mats include prokaryotes such as chemotrophic sulfur bacteria, cyanobacteria, and anoxygenic phototrophic bacteria, which varies with temperature, pH, sulfide concentrations, and other environmental factors [25].