Introduction

Actinobacteria is a phylum of bacteria that comprises Gram-positive genera with high guanine and cytosine (G + C) content in their genomes and a few Gram-negative species [1,2]. Although actinobacteria are commonly present in terrestrial and aquatic ecosystems, they have a wide range of habitats, including extreme geographical locations such as deserts, hot springs, salt lakes, caves, and deep-sea [3–6]. In light of their abundance in such extreme environments accompanied by their well-known biosynthetic capabilities, scientists are interested in their metabolic versatility, discovering novel bioactive secondary metabolites, and their extracellular enzymes, which can be potentially propitious for pharmaceutical development [7–11].
Furthermore, actinobacteria have astonishing capabilities in adapting contaminated soil and efficiently decomposing organic materials such as hemicellulose and lignin through the actions of their metabolites [12]. Apparently, these bacteria can be bioindicators to toxic contaminants due to their higher sensitivity in detecting toxic elements [13]. Their unique tolerance to these contaminants accompanied by their degradation, biostimulation, and bioaugmentation abilities have enabled them to be great candidates for the bioremediation of heavy metals and organic pollutants [14–16]. Additionally, actinobacteria are incredible producers of agro-active and plant growth-promoting (PGP) compounds such as siderophores and indole acetic acid [17,18]. Actinobacteria have a major contribution to the agriculture industry whereby numerous strains (either single strains or in consortia) or their associated compounds have been applied as biofertilizers, biopesticides, and biological control agents [19–22]. The utilization of actinobacteria to manage plant diseases and pests that damage agricultural crops is effective, cost-saving, and eco-friendly, thus, they can substitute and mitigate the use of harmful chemical fertilizers and pesticides.

Actinobacteria can be categorized into two genera, *Streptomyces* and non-*Streptomyces* [23]. *Streptomyces* is the largest genus of Actinobacteria, and these bacteria are predominantly found in soil, but can also be present in various habitats such as marine/mangrove environments and plants [24–27]. Streptomycetes are unique filamentous Gram-positive bacteria that produce vegetative hyphae [28–30]. About 80% of clinically used antibiotics are derived from actinobacteria, in which a good number of them are isolated from the genus *Streptomyces* [19,31–33]. Astoundingly, streptomycetes remain as inexhaustible sources of antimicrobials to date [34,35]. In addition, about 17% of known active secondary metabolites are produced by this genus and many of them are of great medical significance [36–39]. For instance, Ivermectin, an antiparasitic agent is derived from *Streptomyces avermitilis* for treating lymphatic filariasis, was found to have a potent inhibitory effect on the growth of the formidable coronavirus disease 2019 (COVID-19) causative virus (SARS-CoV-2) [40,41]. Besides, streptomycetes are also recognized as producers of antifungal, antitumor/anticancer, antioxidant, and antiviral agents [42–44].

In recent decades, the non-*Streptomyces* which is known as the rare actinobacteria (e.g., *Micromonospora*, *Microbacterium*, *Jishengella*, *Salinispora*, *Saccharopolyspora*, *Sinomonas*, *Nocardiopsis*, etc. [45–49]), has piqued the scientists’ interest in discovering new unprecedented bioactive compounds produced by them. On the premise that extremophilic actinobacteria are a promising potential source of new drugs, we attempt to provide an overview of their bioprospecting aspects in this review.

2. Types of Extremophiles

Extremophiles are organisms that live in extreme habitats. They often have unique survival mechanisms to withstand harsh conditions such as high temperature, extreme pH, salinity, pressure, and aridity [50,51]. Extremophiles can be divided into two broad categories, namely, the extremotolerant and the extremophilic. In some cases, the scientific community applied the term “extremophilic organism” to exclusively define organisms requiring one or more extreme growth conditions. In comparison, extremotolerant organisms are those that are able to tolerate one or more physicochemical parameters [52]. Extremophile—the suffix ‘-phile’ originated from the Greek word ‘philos’, which conveys the meaning of ‘love’ and ‘preference’ of extreme environments [11,53]. Some examples of different types of extremophiles are listed in the following [54,55]: (a) thermophile—an organism that grows best at high temperatures and is commonly found in hot places such as the desert; (b) psychrophile—an organism that grows best at low temperatures; (c) halophile—an organism that thrives in habitats with high salt concentrations, such as sea and salt lakes; (d) alkaliophile—an organism that grows best in an alkaline environment; (e) acidophile—an organism that grows best in an acidic environment; (f) barophile—an organism that thrives at high-pressure conditions and is commonly found in deep-sea habitats; and (g) xerophile—an organism that grows best in an extremely arid area such as the desert. This review aims to collect information on actinobacteria present in various
extreme environments and their potential to produce metabolites with bioactive properties such as antibacterial, antifungal, anticancer, and many more.

3. Actinobacteria in Extreme Environments

3.1. Extremophilic Actinobacteria in Hot Springs

Hot springs are usually formed by magma that heats the rainwater or underground water geothermally near the active volcanoes [56,57]. They are usually of low salinity (<0.5%) and have a wide range of pH values ranging from 0.5 to 9 [58]. Hot springs are for balneotherapy or recreational purposes and are a breeding ground for extremophilic actinobacteria. A thermophile is a type of extremophile that survives growth optimally at a temperature of more than 50 °C [59]. To prevent the protein from aggregating at high temperatures, they have special ‘heat shock’ proteins called chaperones responsible for unfolding the denatured protein damaged by heat [60].

In a study by Liu and colleagues [61], sediments were taken from Tengchong County of Yunnan Province in China. Fifty-eight actinobacteria isolates were recovered from 10 hot springs distributed among Hehua, Rehai, and Ruidian, in which two novel genera, *Thermoactinospora* and *Thermocatellispora*, were also identified. The sampling sites’ temperature and pH ranged from 62 °C to 99 °C, and 2.5 to 9.0, respectively. It has been reported in another study that most of the thermophilic actinobacteria found in the Rehai were able to synthesize thermostable polymer-degrading enzymes which allow the bacteria to withstand the protein-denaturing temperature [62]. In particular, one of the strains produced cellulase, β-1,4-endoglucanase (Cel5A), which was highly tolerant to a high concentration of salt [62], and thus, indicates that the bacteria could be polyextremophilic and have a halotolerant property. Surprisingly, Liu, et al. [61] found that 53/58 strains were affiliated to 12 genera, namely, *Actinomadura*, *Micromonospora*, *Microbispora*, *Micrococcus*, *Noncardiopsis*, *Nonomuraea*, *Promicromonospora*, *Pseudonocardia*, *Streptomyces*, *Thermoactinospora*, *Thermocatellispora*, and *Verrucosispora*, in which several isolates exhibited antibacterial activities against various common pathogens including *Acinetobacter baumannii*, *Micrococcus luteus*, and *Staphylococcus aureus*. Furthermore, one strain, *Micromonospora* YIM 78104, demonstrated a particular broad antibacterial property. This study suggested a variety of actinobacterial species that are yet to be explored from hot springs, in which their secondary metabolites may contribute to the development of new antibiotics.

Gholami, et al. [56] isolated a novel strain, *Kocuria rosea* MG2, from the Ab-e-Siah spring in Ramsar City in Iran with the highest natural radioactivity. Ab-e-Siah spring is a radioactive hypothermal spring with a recorded radon concentration of 146.5 Bq. l-1 [63]. Its temperature ranged from 28 to 35 °C with a pH value of 6.8 [56]. In this study, the MG2 strain was identified as *Kocuria rosea* by 16S rRNA gene sequencing. Multiple stress tests were carried out, and the results were captivating. It was found that this strain was polyextremophile and able to survive under multiple stresses such as high levels of UV-C radiation, hydrogen peroxide, and desiccation. It also exhibited maximal growth at pH 9.2. It was suggested that carotenoids played an essential role in the photoprotective mechanism of the bacteria [56]. Carotenoids can absorb maxima at 450 nm, which makes them an effective antioxidant [64]. This study provides a basis for advanced research on developing antioxidant agents with natural biomolecules.

Contrary to the traditional views and perceptions, the studies above have proven that in extremophile actinobacteria from hot springs, it is not necessary to be thermophilic. They may even be polyextremophilic, in which further investigation is required. Actinobacteria from hot springs can have various mechanisms to combat the harsh conditions of hot springs. The biometabolites they synthesized could be a potential new source of medicine such as antibiotics and antioxidants.

3.2. Extremophilic Actinobacteria in Deserts

Deserts cover about one-fifth of the Earth’s surface [65]. Deserts are incredibly arid (average annual rainfall less than 25 cm) [66] and have a wide range of temperatures and
weather conditions with low nutrient status, making it difficult for most organisms to survive [67]. Although the general impression of a desert is patches of hot and empty land, some deserts are cold all year round. They can be classified into four categories: subtropical, cold, coastal, and semi-arid [68]. Though deserts were once thought to be lifeless due to their extreme environments, recent studies have proven this perception is wrong. A wide range of actinobacteria are cultivatable in these places. To survive in such a harsh environment, living forms, including bacteria, need to have unique survival mechanisms to adapt to the extreme environment. Therefore, they tend to produce various interesting secondary metabolites which assist them in their survival.

Many studies have been carried out to investigate the actinobacteria isolated from deserts and analyze their bioactive potentials. Abenquines are new bioactive metabolites that Schulz, et al. [69] discovered. *Streptomyces* sp. strain DB634 was isolated from the soil taken from Salar de Tara of the Atacama Desert, Chile, which is known to be one of the driest places on earth with an average annual rainfall of about 15 mm; every one square meter only receives a depth of 15 mm water each year [70]. It also has the highest level of ultraviolet radiation on earth [71]. For the above reasons, its soil has been compared to that of Mars. In the study, four abenquines (A–D) were then isolated from the fermentation broth of *Streptomyces* sp. strain DB634 and found to be structurally related to aminobenzoquinones. Other studies have revealed that benzoquinones possess antioxidant and anticancer properties in addition to anti-inflammatory effects [72]. Abenquines A and D demonstrated selective inhibition of phosphodiesterase type 4b (PDE4B), which is known to upregulate CYLD expression, a key modulator in suppressing inflammatory reactions [69,73]. Hence, these two abenquines can be a potential source for developing a new anti-inflammatory agent for inflammatory diseases. Besides, inhibition of PDE4 downregulates the production of cyclic adenosine monophosphate (cAMP), which is the cardinal regulator of both the innate and adaptive immune response, and it is also capable of suppressing T-cell stimulating cytokines [74,75]. Therefore, abenquines could be an alternative therapeutic option for T-cell mediated autoimmune disorders such as celiac disease and rheumatoid arthritis, although more studies are warranted to understand its pharmaceutical applications.

Four types of ansamycin-type polyketides, the chaxamycins A–D (Table 1), were identified from the *Streptomyces* sp. strain C34 isolated from Salar de Tara of Atacama soil [76]. Ansamycin is a lipophilic antibiotic that possesses antitumor activity [76]. It exerts its activity by selectively inhibiting the heat shock protein (Hsp90) by interrupting its ATPase activity, which induces tumor cell death [76]. Its selective action against Hsp90 also leads to the degradation of proteins essential for cancer cells’ survival [77]. Moreover, the increase of antibiotic-resistant bacteria has driven scientists towards the research for new antibiotics. Thus, the antimicrobial properties of chaxamycins A–D were evaluated with *Staphylococcus aureus* and *Escherichia coli* by the agar diffusion method. Chaxamycin D exhibited a selectively high antibacterial activity against methicillin-resistant *S. aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA), the majority with MIC values of less than 1.21 \(\mu\)g/mL [76]. This study exemplifies that actinobacteria isolated from deserts are promising bioprospecting resources for new antibiotics and cancer drugs.

Habitats with extreme aridity such as the Atacama Desert have drawn microbiologists’ interest due to the variety of flora found there. The compounds synthesized by these florae are viewed as the scaffolds for new drugs. Wichner, et al. [78] discovered six novel glycosides—lentzeosides A–F from the Atacama Desert (Table 1), which demonstrated anti-HIV integrase activity. The soil samples were collected from a high-altitude location (>5000 m) where *Lentzea* sp. H45 was isolated. The compounds lentzeosides A–F produced by the strain were then tested for inhibitory activity against HIV-1 integrase at different concentrations [78]. HIV-1 integrase is a vital enzyme for completing the HIV viral replication cycle at the post-entry phase and, therefore, has been the target for antiretroviral drug development [69]. The three FDA-approved antiretroviral drugs, elvitegravir, raltegravir, and dolutegravir are all integrase strand transfer inhibitors [79]. Results showed that
lentzeoside C, D, and E achieved IC\textsubscript{50} values at 21, 16, and 21 µM, respectively, which were lower than lentzeoside A, B, and F. This indicates that lentzeoside C, D, and E exhibit a more potent inhibitory activity, whereas lentzeoside A, B, and F demonstrate a moderate inhibitory effect on HIV integrase [78]. Hence, this newly discovered group of lentzeoside is a good product for antiretroviral therapy.

Table 1. Summary of bioactivity of actinobacterial strains isolated from the Atacama Desert.

| Sampling Site | Strain | Extremophilic Properties | Sample Type | Bioactivity | Compound | IC\textsubscript{50} or MIC | Reference |
|---------------|--------|--------------------------|-------------|-------------|----------|-----------------|----------|
| Salar de Tara of the Atacama Desert, Chile | Streptomyces sp. DB634 | Polyextremophilic | Desert soil | Anti-inflammatory activity via human recombinant cyclic AMP (cAMP)-specific phosphodiesterase (PDE-4B2) inhibition | Abenquines A and D | IC\textsubscript{50} Abenquines A: 4.6 ± 0.2 µM; Abenquines D: 4.2 ± 0.3 µM | [69] |
| Salar de Tara of the Atacama Desert, Chile | Streptomyces sp. C34 | Polyextremophilic | Desert soil | Antibacterial activity against E. coli, S. aureus (MRSA and MSSA) | Chaxamycin D | MIC E. coli and S. aureus: <1.21 µg/mL | [76] |
| At a high-altitude location (>5000 m) in Atacama Desert | Lentzea sp. H45 | Polyextremophilic | Desert soil | Inhibition of HIV-integrase | Lentzeosides A–F | MIC Lentzeoside A > 100 µM; Lentzeoside B > 100 µM; Lentzeoside C: 21 µM; Lentzeoside D: 16 µM; Lentzeoside E: 21 µM; Lentzeoside F > 100 µM | [78] |
| Saudi Arabian desert | Streptomyces sp. DA3-7 | Thermotolerant (proposed) | Desert soil | Antibacterial activity against E. coli, S. typhimurium, S. aureus, P. vulgaris, P. aeruginosa, E. fecalis, K. pneumoniae, Anti fungal activity against C. albicans, S. cerevisiae, C. neoformans | Pyridine-2,5-diacetamide | MIC E. coli: 31.25 µg/mL; S. typhimurium, S. aureus, P. vulgaris, P. aeruginosa, E. fecalis: 62.5 µg/mL; K. pneumoniae: 125 µg/mL; C. neoformans: 31.25 µg/mL; C. albicans and S. cerevisiae: 62.5 µg/mL | [80] |

\* Not available.

Nithya, et al. [80] evaluated the antimicrobial activity of 134 actinobacterial isolates collected from the Saudi Arabian desert. Among these isolates, the ethyl acetate extract of Streptomyces sp. DA3-7 demonstrated a broad-spectrum antagonistic effect on various pathogens, including Pseudomonas aeruginosa, Staphylococcus aureus, Klebsiella pneumoniae, Enterococcus faecalis, Escherichia coli, Proteus vulgaris, and Salmonella typhimurium; as well as Fungi Candida albicans, Cryptococcus neoformans, and Saccharomyces cerevisiae. It is likely that Streptomyces sp. DA3-7 could be a thermotolerant bacterium as it was able to tolerate maxima at 40 °C. It has been established that thermotolerant microbes achieve optimal growth at 40 °C [81,82]. Furthermore, the extract also displayed cytotoxic activity against the MCF-7 breast adenocarcinoma cell line (IC\textsubscript{50} = 85 µg/mL). The active compound, pyridine-2,5-diacetamide, was isolated from the crude extract, and it was found that MIC values of pyridine-2,5-diacetamide were the lowest against E. coli and C. neoformans (both 31.25 µg/mL) (Table 1), which is lower than that of the standard therapeutic drugs ketoconazole (50 µg/mL) and streptomycin (10 µg/disc), respectively [80].

3.3. Extremophilic Actinobacteria in Deep-Sea Sediment

The marine creatures commonly known to us are coastal ocean species, and most of the live forms in the deep sea remain enigmatic to humans. Most of this vast blue realm is
unexplored, and only a small fraction of the ocean has been mapped \[83\]. The pressure, oxygen level, temperature, and nutrients of the deep-sea vary depending on the area. Nevertheless, in such an extreme environment where the pressure is immense, and no light can penetrate, certain groups of actinobacteria have acclimatized and demonstrated great biosynthetic capacity \[84,85\]. Research on deep-sea actinobacterial diversity is limited, which is often due to the difficulty of sampling. Thanks to the breakthrough of technologies, more unique species are brought to light.

Eighteen marine actinobacteria were isolated from seawater, corals, and echinoderms in Avilés Canyon, Spain. Samples were collected at a depth of 1500 to 4700 m. As determined by 16S rRNA sequencing, they mostly belonged to the genus *Streptomyces*, and the remaining were *Pseudonocardia*, *Micromonospora*, and *Myceligenans* \[86\]. Cytotoxic assays of ethyl acetate extract of the strains against HeLa, a breast cell line, and HCT116, a human colon tumor cell line, were also carried out. The extracts of the two strains *Streptomyces cyaneofuscatus* M-157 and M-192 showed the highest cytotoxic activity against the cancer cells. Even more so, both extracts were still active even after dilution at 1:100. Both *Streptomyces xiamenensis* M186 and *S. cyaneofuscatus* M190 were also able to produce β-elemene, a compound that has been used to treat brain and breast cancer clinically \[87,88\]. Metabolite profiling analysis showed that three compounds, cosmomycin, daunomycin, and galtamycin which possess antitumor activity, were detected in the ethyl acetate extract of *S. cyaneofuscatus* M192 \[86\]. Besides, antibiotic assays with ethyl acetate extracts from different strains also showed potent antibacterial activity against a wide range of pathogens and fungi such as *Gram-negative Escherichia coli*, *Micrococcus luteus*, and *Saccharomyces cerevisiae*. Two of the strains, *Micromonospora tulbaghiae* M194 and *Streptomyces halstedii* M204, showed a moderate antifungal effect on *S. cerevisiae* \[86\]. Notably, only the strains of *S. cyaneofuscatus* produce compounds with antagonistic activity against antibiotic-resistant *M. tuberculosis*. Based on these findings, these strains’ extract exerted good antimicrobial activity towards several pathogens and cytotoxic effect against HeLa and HCT116 cancer cells (Table 2). In short, this study presented a preliminary finding that marine actinobacteria can be a great potential source of antifungal and anticancer agents other than antibacterial. Therefore, it will be worthy of investigating the compounds responsible for these observed bioactivities.

Unarguably, the active metabolites of actinobacteria are indeed a great source of new drugs. Nevertheless, the application of elicitor to the culture medium is crucial to stimulate the stress response for metabolites’ production. Factors such as type, concentration, and duration of exposure of the elicitor are also cardinal to determine the production of the metabolites \[89\]. Xu, et al. \[90\] evaluated fifty actinobacteria strains cultivated from deep-sea at various sites where the depths ranged from 150 fsw to 2790 fsw. Nineteen of the isolates belonged to the genus *Streptomyces* while the others were rare actinobacteria. Notably, 27 strains showed positive antimicrobial activity, whereby the activity of 15 strains was enhanced by the elicitor lanthanum chloride (LaCl$_3$) (2 mM) while 11 of them were attenuated by it. For instance, *Streptomyces* sp. R818 exerted a potent antifungal (MIC of 25 µg/mL) and synthesized antimycin-like metabolite, urauchimycin D, only when LaCl$_3$ was used as the elicitor. Until now, metronidazole or vancomycin remains the first-line therapy for *C. difficile* infection \[91\]. Interestingly, the antibacterial activity against *C. difficile* was detected in *Salinispora* M864 after the fermentation with LaCl$_3$. It exerted its activity with an MIC value (0.125 µg/mL) four times less than that of metronidazole and vancomycin (0.5 µg/mL) \[90\]. Herein, a pertinent elicitor is essential for obtaining the desired bioactivity effectively. The significant bioactivities of the strains are summarized in Table 2.
### Table 2. Bioactivity of actinobacterial strains isolated from the deep-sea environment.

| Sampling Site                  | Actinobacteria                      | Strain          | Extremophilic Properties                  | Sample Type | Bioactivity                                                                 | Extract    | Compound       | IC₅₀ or MIC | Reference |
|-------------------------------|-------------------------------------|-----------------|------------------------------------------|-------------|-----------------------------------------------------------------------------|------------|----------------|-------------|-----------|
| Avilés Canyon in Asturias, Spain | Streptomyces cyanosulfures          | M-169 and M-185 | Halotolerant, psychrotolerant, and barotolerant | Coral       | Antibiotic activity (>2 pathogens); moderate cytotoxic activity against HeLa and HCT 116 cells | Ethyl acetate extract | N.A.         |             |             | [86]      |
|                              | Micromonospora tulbagiae            | M-194           |                                          | Coral       |                                                                             |            |                |             |           |
|                              | Streptomyces carnosus               | M-207           |                                          | Coral       |                                                                             |            |                |             |           |
|                              | Streptomyces carnosus               | M-220           |                                          | Polychaete  |                                                                             |            |                |             |           |
|                              | Streptomyces sulfureus              | M-231           |                                          | Decapod     |                                                                             |            |                |             |           |
|                              | Microligenerans cantabricum         | M-193           |                                          | Starfish    |                                                                             |            |                |             |           |
|                              | Micromonospora aurantiaca           | M-235           |                                          | Ofiuroid    |                                                                             |            |                |             |           |
|                              | Streptomyces cyanosulfures          | M-179           |                                          | Polychaete  | Antibiotic activity (>2 pathogens); strong cytotoxic activity (>50%) against HeLa and HCT 116 cells |            |                |             |           |
|                              | Streptomyces albidoflavus           | M-192           |                                          | Actinia     |                                                                             |            |                |             |           |
|                              | Micromonospora tulbagiae            | M-227           |                                          | Sea water   | Antibiotic activity against M. luteus and Streptococcus pneumoniae; moderate cytotoxic activity against HeLa and HCT 116 cells |            |                |             |           |
|                              | Micromonospora saelicesensis        | M-228           |                                          | Seawater    | Antibiotic activity against M. luteus only; moderate cytotoxic activity against HeLa |            |                |             |           |
| HBOI collection              | Streptomyces setonii                | M-178           | Sponge                                   |             | Antibiotic activity against Neisseria gonorrhoea only; strong cytotoxic activity (>50%) against HeLa and HCT 116 cells |            |                |             |           |
|                              | Streptomyces halstedii              | M-204           | Ofiuroid                                 |             | Antimicrobial activity against Clostridium perfringens and Candida krusei only; strong cytotoxic activity (>50%) against HeLa and HCT116 cells |            |                |             |           |
|                              | Streptomyces xiamenensis            | M-186           | Coral                                    |             | Strong cytotoxic activity (>50%) against HeLa and HCT 116 cells            |            |                |             |           |
|                              | Microligenerans cantabricum         | M-201           | Coral                                    |             | Moderate cytotoxic activity against HeLa and HCT 116 cells                 |            |                |             |           |
|                              | Streptomyces sp.                    | R818            | Halophilic                               | Sponge      | Antifungal activity against C. albicans                                     |            |                | N.A.        |           |
|                              | Salinispora sp.                     | M864            | Halophilic                               | Sponge      | Antibacterial activity against C. difficile                                  | Ethyl acetate extract | N.A.        | C. difficile: 0.125 µg/mL |           |

* Not available.
3.4. Extremophilic Actinobacteria in Caves

There is an abounding number of caves on earth, and the most common types are the limestone, calcareous, and basaltic caves [92]. Depending on the types of caves, the processes of formation range widely. For instance, stone caves are formed by erosion and weathering over millions of years [93], while limestone caves are formed by natural acid dissolving the stone [94]. Some caves, such as moonmilk caves, are formed by microbial degradation of carbonate [92].

Moonmilk has long been regarded as a medication. From the 16th to 19th centuries, moonmilk was used as a medication to treat calcinosis and cardialgia, according to swiss naturalist Conrad Gesner (1516–1555) [95]. Though not all moonmilk caves’ formation involves microbial activity, many do hold a wide range of microbes such as bacteria, especially streptomyces, fungi, and algae in markedly high density [92,96]. Forty isolates were obtained by Adam, et al. [97] from the moonmilk cave Grotte des Collemboles, Comblain-au-Pont located in Belgium. These isolates were associated with the genera *Agromyces*, *Amycolatopsis*, *Kocuria*, *Micrococcus*, *Micromonospora*, *Nocardia*, *Rhodococcus*, and *Streptomyces*. The extremophiles have to develop unique survival strategies that allow them to dwell in the moonmilk cave exclusively [92]. This characteristic is evidenced by the highly territory-selective behavior of the isolates. For instance, 58% of the isolates in pure cultures died after the second round of inoculation in the study. It is likely to be caused by the absence of neighboring cultures and the substances emanated by them, a common mutualistic survival strategy adopted by organisms dwelling in an oligotrophic environment [97]. The antibacterial activity of the isolates was evaluated via the cross-streak method. Overall, the isolates showed a more potent inhibitory activity against Gram-positive bacteria than Gram-negative bacteria. Among all isolates, one extremely rare actinobacterium *Amycolatopsis* sp. MMun171 (actinobacterial abundancy <0.001%) exhibited the most robust antibacterial activities against both Gram-positive and Gram-negative microbes (*E. coli*, *P. aeruginosa*, *Citrobacter freundii*, *K. pneumoniae*, *Bacillus subtilis*, *S. aureus*, and *M. luteus*) under all culture conditions [97] (Table 3). This finding rekindles the hope of researchers to search for novel antibiotics from extremophiles in unique niches. However, since many isolates (58%) were lost during the purification process in the first study, it is necessary to mimic their environmental niche with specific growth factors to increase microbial growth.

A wide diversity of taxonomy, including some rare taxa, were isolated from the Shuanghe Karst Cave in Guizhou province in China. It is the longest cave in Asia, with a total cave passage of 130 km [98]. Karst caves are formed by the slow dissolution of limestone, gypsum, and dolomite by acid rainwater [99]. The cave is an extreme habitat because it is dim, humid, and cold but is also oligotrophic as a minimal source of organic material is present. A total of 45 isolates categorized into 23 species and 7 genera in which most of them were *Streptomyces* (52%), followed by *Actinoplanes* (13%), *Nocardioidei*, *Agromyces*, *Rhodococcus*, *Oerskovia*, and *Micromonospora* (all >1%) were investigated by Long, et al. [100]. The antimicrobial activity of these isolates was screened, and 16 out of 45 isolates showed inhibitory activity against at least one of the tested pathogens *E. coli*, *S aureus*, and *Botrytis cinerea*. Besides, *Streptomyces radius* S142 and *Actinoplanes friulensis* S761 displayed the strongest activity against all pathogens. This result is in line with a previous study in which an amphomycin-like new lipopeptide compound, friulimicins, derived from *A. friulensis* demonstrated an intense antibiotic activity, even against multidrug-resistant strains [101]. In short, these studies have exemplified the high diversity of rare actinobacteria in caves, and the bioactive compounds produced by these extremophiles in these particular niches do offer a promising means to tackle the antibiotic resistance crisis.
Table 3. Summary of bioactivity of actinobacterial strains isolated from caves.

| Sampling Site                              | Actinobacteria          | Strain         | Sample Type | Bioactivity                                                                 | Reference |
|--------------------------------------------|-------------------------|----------------|-------------|----------------------------------------------------------------------------|-----------|
| Moonmilk cave Grotte des Collemboles,     | *Amycolatopsis* sp.     | MMun171        | Moonmilk    | Antibacterial activity against *E. coli*, *P. aeruginosa*, *K. pneumoniae*,  | [97]      |
| Belgium                                    | *Kocuria rhizophila*    | MMun160        |             | *B. subtilis*, *S. aureus*, and *M. luteus*                               |           |
| Shuanghe Karst Cave, Guizhou province,     | *Streptomyces* sp.      | MMun141, MMun146, MMun156 |             | Strong antibacterial activity, particularly against *B. subtilis*, *S. aureus*, and *M. luteus* | [100] |
| China                                      | *Streptomyces badius*   | S142           | Bat guano   | Antimicrobial activity against *E. coli*, *S. aureus*, *B. cinerea*          |           |
| *Actinoplanes friulensis*                  | S761                    | Rock soil      |             |                                                                           |           |

3.5. Extremophilic Actinobacteria in Salt Lakes

Salt Lakes are one of the unique niches that have drawn the interest of scientists in recent years. A salt flat is the basis of the formation of salt lakes. The salt flat is usually formed in arid areas where evaporation outpaces precipitation, leaving the salt behind [102]. When there is open water such as rain and stream entering the landscape that dissolves the salt precipitate, a salt lake is formed [102]. Interestingly, they display a broad diversity in their sedimentary process, morphology, hydrology, and ecosystems [103]. Depending on the content of the lakes, their composition of ecosystems varies greatly. Given their high saturation of ions, microbial dwellers often develop unique strategies to cope with extreme conditions.

Generally, the resistance mechanism and DNA-repair system of extremophilic bacteria in the salt lake were investigated by Albarracin, et al. [104]. A group of bacteria belonging to the *Acinetobacter* genus was obtained from the high-altitude Andean lakes (HAAL), Puna Desert. HAALs is a collection of salt lakes located at the Dry Central Andes where UV-B radiation is exceptionally high. It is also characterized by high arsenic toxicity, salinity, extreme temperatures, and pH [105]. The potent photo-repair ability of the extremophiles might be due to a particular gene HQ443199 of Ver 3, which encodes class-I photolyase responsible for repairing UV-induced DNA lesions in cis-syn cyclobutane pyrimidine dimer (CDP) and pyrimidine (6-4) pyrimidone photoproducts (6-4PPs), which are commonly damaged by high UV-intensity [106]. A study by Wu et al. [107] revealed a rich diversity of actinobacteria (*Actinomyces*, *Bifidobacterium*, *Corynebacterium*, etc.) present in the sediments of two salt lakes, Qaidam Lake and Qinghai Lake, China. Nonetheless, the coping mechanism of these extremophilic actinobacteria requires further investigation.

In extreme environments where nutrients and resources are scarce, organisms tend to produce antimicrobial secondary metabolites to inhibit other competitors’ growth for survival. Therefore, niches such as HAALs are storehouses of potential sources of antibiotics. The extremophilic profile and antimicrobial activity of actinobacteria in HAAL are investigated in a study conducted by Rasuk, et al. [105]. Fifty-one isolates were from various lakes of HAALs and were found to be members of the following genera: *Arthrobacter, Blistococcus, Brevibacterium, Citrococcus, Kocuria, Microbacterium, Micrococcus, Micromonospora, Nesterenkonia, Rhodococcus*, as well as *Streptomyces*. Their polyextremophilic properties were evaluated. Results showed that all 51 isolates demonstrated high resistance to UVB radiation. Furthermore, several isolates were able to tolerate and grow in an extremely high pH value of 12, indicating that they are incredibly alkaliphilic. Regarding their halotolerant property, all strains could tolerate 5% NaCl, but only 21 of the isolates were able to tolerate up to 25% NaCl. The antagonistic activities were studied against *S. aureus*, *E. coli*, *Bacillus* sp., *E. faecalis*, and two fungi species (*Rhodotorula* sp.). The data showed that all isolates displayed antagonistic activity against at least one of the tested pathogens (Table 4), suggesting inhibitory activity was relatively common among extremophiles in salt lakes.


such as HAALs. Especially, those of *Streptomyces* sp., *Microbacterium* sp., and *Micrococcus* sp. are capable of producing cytotoxic compounds against other organisms.

### Table 4. Summary of bioactivity of actinobacterial strains isolated from salt lakes.

| Sampling Site | Actinobacteria | Sample Type | Bioactivity | Reference |
|---------------|----------------|-------------|-------------|-----------|
| Laguna Diamante, Antofalla, Laguna Santa Maria, Laguna Socomp, Tolar Grande, and Salina Grande, Argentina | Actinobacterial strains of 11 genera *Streptomyces*, *Micrococcus*, *Microbacterium*, *Nesterenkonia*, *Kocuria*, *Rhodococcus*, *Arthrobacter*, *Micromonospora*, *Blastococcus*, *Brevibacterium*, and *Citricoccus* | Soil, stromatolite, sediment, water, and flamingo feces | Antibacterial activity against *E. coli*, *Bacillus*, *E. faecalis*, *S. aureus*, and *Rhodotorula* sp. (at least 1) | [105] |

Undoubtedly, salt lakes are a cradle for polyextremophiles and hold great potential for pharmaceutical applications. The actinobacteria obtained from HAALs are highly UV-resistant and exhibit good antimicrobial activity. The UV-resistance and DNA-regulatory proteins are potentially beneficial to the development of antioxidants and, therefore, should be further investigated.

### 4. Discussion

Based on the different extreme environments discussed in this review, deserts and the deep sea are the most favorable environments for the isolation of bioactive actinobacteria. Compounds with potential applications in medicine have been yielded from these two habitats. One of the reasons is their high abundance in these habitats. Actinobacteria has a dominant diversity and distribution in arid areas [108], and it is the most dominant phylum (72 to 88%) in the Atacama Desert [109]. Similarly, it has been suggested that actinobacteria make up to about 10% of the bacteria colonizing aggregates in the sea, and their antagonistic activity is significant for their survival [110]. Besides, hot springs posed another excellent source for the isolation of bioactive thermophilic actinobacteria based on the literature findings. However, the research on extremophilic actinobacteria’s medical applications from salt lakes was thus far minimal. More research is needed as salt lakes are potentially an excellent source for beneficial bioactive compounds.

For most studies, it is anticipated that future research scope should identify compounds responsible for the observed bioactivities. A typical approach to extract and purify the bioactive compounds from the bacteria would be through bioassay-guided fractionation [111–113]. With the chromatography separation techniques, pure compound isolation can be achieved following elucidation of compound structure [114,115].

Additionally, whole-genome sequencing via next-generation sequencing technology (NGS) can also provide means for evaluating the bacteria’s bioactive capability by studying the biosynthetic gene cluster related to the compounds [116–118]. In particular, the streptomycetes possessed a prolific potential to synthesize a significant number of valuable secondary metabolites. It has been reported that the genome of the *Streptomyces* spp. can carry more than 20 to 30 biosynthetic gene clusters affiliated with secondary metabolite production [3,119–121]. By utilizing the genome sequencing technique and bioinformatics software, the biosynthetic gene clusters of many actinobacteria can thus be identified [122–125]. A simple illustration is detecting the gene cluster encoding the biosynthesis of ansamycin compounds in the genome sequence of *Streptomyces* sp. LZ35 [126]. The availability of NGS offers accurate results, which pushes forward the sequencing capacity at an affordable price. As more and more actinobacteria are discovered from the aforementioned special niches, discovering new bioactive compounds can also be accomplished through a genomic approach.
5. Conclusions

In conclusion, actinobacteria present in extreme environments are great resources that can contribute to microbial drug discovery. Many studies have proven the bioactive potential of these extremophilic actinobacteria. Nevertheless, further in-depth studies are required to explore the bioactive capabilities of these extremophilic actinobacteria. With this, extremophilic actinobacteria represent an alternative rich source of bioactive compounds that can be harvested to develop novel medicines.

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References
1. Law, J.W.F.; Letchumanan, V.; Tan, L.T.H.; Ser, H.L.; Goh, B.H.; Lee, L.H. Editorial: The rising of “Modern Actinobacteria” era. Prog. Microbes Mol. Biol. 2020, 3, a0000064. [CrossRef]
2. Verma, M.; Lal, D.; Kaur, J.; Saxena, A.; Kaur, J.; Anand, S.; Lal, R. Phylogenetic analyses of phylum Actinobacteria based on whole genome sequences. Res. Microbiol. 2013, 164, 718–728. [CrossRef]
3. Law, J.W.F.; Tan, K.-X.; Wong, S.H.; Ab Mutalib, N.-S.; Lee, L.-H. Taxonomic and characterization methods of Streptomyces: A review. Prog. Microbes Mol. Biol. 2018, 1, a0000009. [CrossRef]
4. Lee, L.-H.; Cheah, Y.-K.; Sidik, S.M.; Ab Mutalib, N.-S.; Tang, Y.-L.; Lin, H.-P.; Hong, K. Molecular characterization of Antarctic actinobacteria and screening for antimicrobial metabolite production. World J. Microbiol. Biotechnol. 2012, 28, 2125–2137. [CrossRef]
5. Qin, S.; Li, W.-J.; Dastager, S.G.; Hozzein, W.N. Actinobacteria in special and extreme habitats: Diversity, function roles, and environmental adaptations. Front. Microbiol. 2016, 7, 1415. [CrossRef] [PubMed]
6. RangseeKaew, P.; Pathom-Aree, W. Cave actinobacteria as producers of bioactive metabolites. Front. Microbiol. 2019, 10, 387. [CrossRef] [PubMed]
7. Law, J.W.F.; Ser, H.-L.; Duangdai, A.; Saokaew, S.; Bukhari, S.I.; Khan, T.M.; Ab Mutalib, N.-S.; Chan, K.-G.; Goh, B.-H.; Lee, L.-H. 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. [CrossRef] [PubMed]
8. Lee, L.-H.; Zainal, N.; Azman, A.-S.; Eng, S.-K.; Goh, B.-H.; Yin, W.-F.; Ab Mutalib, N.-S.; Chan, K.-G. Diversity and antimicrobial activities of actinobacteria isolated from tropical mangrove sediments in Malaysia. Sci. World J. 2014, 2014, 698178. [CrossRef]
9. Lee, L.-H.; Chan, K.-G.; Stach, J.; Wellington, E.M.; Goh, B.-H. The search for biological active agent (s) from actinobacteria. Front. Microbiol. 2018, 9, 824. [CrossRef]
10. Stennett, H.L.; Tiwari, K.; Williams, S.E.; Curnow, P.; Race, P.R. The extremophilic pharmacy: Drug discovery at the limits of life. In Biotechnological Applications of Extremophilic Microorganisms; De Gruyter: Berlin, Germany, 2020; pp. 43–72.
11. Giddings, L.-A.; Newman, D.J. Bioactive Compounds from Extremophiles. In Bioactive Compounds from Extremophiles: Genomic Studies, Biosynthetic Gene Clusters, and New Dereplication Methods; Springer International Publishing: Cham, Switzerland, 2015; pp. 1–47.
12. Chadlia, H.; Fatma, A.; Atef, J. Actinobacteria: A promising source of enzymes involved in lignocellulosic biomass conversion. Adv. Biotech. Microbiol. 2019, 13, 555874.
13. Madrova, P.; Vetrovsky, T.; Omelka, M.; Grunt, M.; Smutna, Y.; Rapoport, D.; Vach, M.; Baldrick, P.; Kopecky, J.; Sagova-Mareckova, M. A short-term response of soil microbial communities to cadmium and organic substrate amendment in long-term contaminated soil by toxic elements. Front. Microbiol. 2018, 9, 2807. [CrossRef]
14. Olajuyigbe, F.M.; Ehiosun, K.I. Assessment of crude oil degradation efficiency of newly isolated actinobacteria reveals untapped bioremediation potentials. Bioremediation J. 2016, 20, 133–143. [CrossRef]
15. Polti, M.A.; Aparicio, J.D.; Benimeli, C.S.; Amoroso, M.J. Simultaneous bioremediation of Cr (VI) and lindane in soil by actinobacteria. Int. Biodeterior. Biodegrad. 2014, 88, 48–55. [CrossRef]
16. Rathore, D.S.; Sheikh, M.; Singh, S.P. Marine Actinobacteria: New Horizons in Bioremediation. In Recent Developments in Microbial Technologies; Prasad, R., Kumar, V., Singh, J., Upadhyaya, C.P., Eds.; Springer: Singapore, 2021; pp. 425–449.
17. Anwar, S.; Ali, B.; Sajid, I. Screening of rhizospheric actinomycetes for various in-vitro and in-vivo plant growth promoting (PGP) traits and for agroactive compounds. *Front. Microbiol.* 2016, 7, 1334. [CrossRef]

18. Anilkumar, R.R.; Edison, L.K.; Pradeep, N. Exploitation of fungi and actinobacteria for sustainable agriculture. In *Microbial Biotechnology*; Patra, J.K., Vishnuprasad, C.N., Das, G., Eds.; Springer: Singapore, 2017; pp. 135–162.

19. Law, J.W.-F.; Ser, H.-L.; Khan, T.M.; Chua, H.-B.; Pusparajah, P.; Chan, K.-G.; Goh, B.-H.; Lee, L.-H. The potential of *Streptomyces* as biocontrol agents against the rice blast fungus, *Magnaporthe oryzae* (Pyricularia oryzae). *Front. Microbiol.* 2017, 8, 3. [CrossRef]

20. Zamoum, M.; Goudjal, Y.; Sabaou, N.; Barakate, M.; Mathieu, F.; Zitouni, A. Biocontrol capacities and plant growth-promoting traits of endophytic actinobacteria isolated from native plants of Algerian Sahara. *J. Plant Dis. Prot.* 2015, 122, 215–223. [CrossRef]

21. Jayakumar, J. *Streptomyces avermitilis* as a biopesticide for the management of root knot nematode, *Meloidogyne incognita* in tomato. *Karnataka J. Agric. Sci.* 2009, 22, 564–566.

22. Xiong, Y.-W.; Gong, Y.; Li, X.-W.; Chen, P.; Ju, X.-Y.; Zhang, C.-M.; Yuan, B.; Lv, Z.-P.; Xing, K.; Qin, S. Enhancement of growth and salt tolerance of tomato seedlings by a natural halotolerant actinobacterium *Glutamicibacter halophytocola* KLBMP 5180 isolated from a coastal halophyte. *Plant Soil* 2019, 445, 307–322. [CrossRef]

23. Hu, D.; Sun, C.; Jin, T.; Fan, G.; Mok, K.M.; Li, K.; Lee, S.M.-Y. Exploring the potential of antibiotic production from rare actinobacteria by whole-genome sequencing and guided MS/MS analysis. *Front. Microbiol.* 2020, 11, 1540. [CrossRef]

24. Anandan, R.; Dharamadourad, D.; Manogaran, G.P. Anandan, R.; Dharamadourad, D.; Manogaran, G.P. An introduction to actinobacteria. In *Actinobacteria-Basics and Biotechnological Applications*; IntechOpen: Rijeka, Croatia, 2016.

25. Law, J.W.-F.; Pusparajah, P.; Ab Mutalib, N.-S.; Wong, S.H.; Goh, B.-H.; Lee, L.-H. A review on mangrove actinobacterial diversity: The roles of streptomycetes and novel species discovery. J. Pept. Med. Mol. Biol. 2019, 2, a0000024. [CrossRef]

26. Lee, L.-H.; Law, J.W.-F.; Khan, T.M.; Chan, K.-G.; Ab Mutalib, N.-S.; Goh, B.-H. IDDF2019-ABS-0323 Unveiling the Anti-Colon Cancer Potential of Sarawak Mangrove-Derived Novel Streptomyces. Gut 2019, 68, A42–A43.

27. Kemung, H.M.; Tan, L.T.-H.; Chan, K.-G.; Ser, H.-L.; Law, J.W.-F.; Lee, L.-H.; Goh, B.-H. Antioxidant activities of *Streptomyces* sp. strain MUSC 14 from mangrove forest soil in Malaysia. *BioMed Res. Int.* 2020, 2020, 642607. [CrossRef]

28. Ser, H.-L.; Tan, L.T.-H.; Law, J.W.-F.; Chan, K.-G.; Duangjai, A.; Saokaew, S.; Pusparajah, P.; Ab Mutalib, N.-S.; Khan, T.M.; Goh, B.-H. Focused review: Cytotoxic and antioxidant potentials of mangrove-derived *Streptomyces*. *Front. Microbiol.* 2017, 8, 2065. [CrossRef]

29. Ser, H.-L.; Law, J.W.-F.; Chaiyakunapruk, N.; Jacob, S.A.; Palanisamy, U.D.; Chan, K.-G.; Goh, B.-H.; Lee, L.-H. Fermentation conditions that affect clavulanic acid production in *Streptomyces clavuligerus*: A systematic review. *Front. Microbiol.* 2016, 7, 522. [CrossRef]

30. Tan, L.T.-H.; Chan, K.-G.; Chan, C.K.; Khan, T.M.; Lee, L.-H.; Goh, B.-H. Antioxidative potential of a *Streptomyces* sp. MUM292 isolated from mangrove soil. *BioMed Res. Int.* 2018, 2018, 4823126. [CrossRef] [PubMed]

31. Law, J.W.-F.; Ser, H.-L.; Ab Mutalib, N.-S.; Saokaew, S.; Duangjai, A.; Khan, T.M.; Chan, K.-G.; Goh, B.-H.; Lee, L.-H. *Streptomyces monasenshis* sp. nov., a novel mangrove soil actinobacterium from East Malaysia with antioxidative potential. *Sci. Rep.* 2019, 9, 1–18.

32. Lee, L.-H.; Zainal, N.; Azman, A.-S.; Eng, S.-K.; Ab Mutalib, N.-S.; Yin, W.-F.; Chan, K.-G.; Goh, B.-H.; Lee, L.-H. Screening for antioxidative compounds from mangrove-derived *Streptomyces* sp. isolated from a Brazilian tropical forest soil. *Prog. Microbes Mol. Biol.* 2019, 2, a0000024. [CrossRef] [PubMed]

33. Hopwood, D.A. *Streptomyces in Nature and Medicine: The Antibiotic Makers*; Oxford University Press: New York, NY, USA, 2007.

34. Hopwood, D.A. *Streptomyces in Nature and Medicine: The Antibiotic Makers*; Oxford University Press: New York, NY, USA, 2007.

35. Karpiński, T.M. Marine macrolides with antibacterial and/or antifungal activity. *Mar. Drugs* 2019, 17, 241. [CrossRef]

36. Cheah, Y.-K.; Lee, L.-H.; Chiang, C.; Catherine, C.-Y.C.; Wong, V.-L.C.M. Isolation, identification and screening of actinobacteria in volcanic soil of a reclamation site (the Anti-Mariana): A microorganism possessing antifungal activity. *Pol. Polar Res.* 2015, 36, 67–78. [CrossRef]

37. Harir, M.; Bendif, H.; Bellahcene, M.; Fortas, Z.; Pogni, R. *Streptomyces Secondary Metabolites*; IntechOpen: London, UK, 2018; pp. 99–122.

38. Kemung, H.M.; Tan, L.T.-H.; Chan, K.-G.; Ser, H.-L.; Law, J.W.-F.; Lee, L.-H.; Goh, B.-H. Investigating the antioxidant potential of *Streptomyces* sp. MUSC 11 from mangrove forest soil in Malaysia. *Prog. Drug Discov. Biomed. Sci.* 2019, 2, a0000033. [CrossRef] [PubMed]

39. Tan, L.T.-H.; Chan, K.-G.; Khan, T.M.; Buhiari, S.I.; Saokaew, S.; Duangjai, A.; Pusparajah, P.; Lee, L.-H.; Goh, B.-H. *Streptomyces* sp. strain KLBMP 5182 isolated from mangrove soil. *World J. Microbiol. Biotechnol.* 2020, 40, 225–229. [CrossRef]
44. Ser, H.-L.; Yin, W.-F.; Chan, K.-G.; Khan, T.M.; Goh, B.-H.; Lee, L.-H. Antioxidant and cytotoxic potentials of *Streptomyces gilligrosus* MUSC 26\textsuperscript{T} isolated from mangrove soil in Malaysia. *Prog. Microbes Mol. Biol.* 2018, 1, a000002. [CrossRef]

45. Azman, A.-S.; Othman, I.; Velu, S.S.; Chan, K.-G.; Lee, L.-H. Mangrove rare actinobacteria: Taxonomy, natural compound, and discovery of bioactivity. *Front. Microbiol.* 2015, 6, 856. [CrossRef]

46. Azman, A.-S.; Othman, I.; Fang, C.-M.; Chan, K.-G.; Goh, B.-H.; Lee, L.-H. Antibacterial, anticancer and neuroprotective activities of rare *Actinobacteria* from mangrove forest soils. *Indian J. Microbiol.* 2017, 57, 177–187. [CrossRef] [PubMed]

47. Lee, L.-H.; Azman, A.-S.; Zainal, N.; Yin, W.-F.; Ab Mutalib, N.-S.; Chan, K.-G. *Sinomonas humi* sp. nov., an amylytic actinobacterium isolated from mangrove forest soil. *Int. J. Syst. Evol. Microbiol.* 2015, 65, 996–1002. [CrossRef]

48. Lee, L.-H.; Azman, A.-S.; Zainal, N.; Eng, S.-K.; Ab Mutalib, N.-S.; Yin, W.-F.; Chan, K.-G. *Microbacterium mangrovi* sp. nov., an amylytic actinobacterium isolated from mangrove forest soil. *Int. J. Syst. Evol. Microbiol.* 2014, 64, 3513–3519. [CrossRef]

49. Xie, Q.-Y.; Wang, C.; Wang, R.; Qu, Z.; Lin, H.-P.; Goodfellow, M.; Hong, K. *Shigella endophytica* gen. nov. sp. nov., a new member of the family *Micromonosporaceae*. *Int. J. Syst. Evol. Microbiol.* 2011, 61, 1153–1159. [CrossRef]

50. Kohli, I.; Joshi, N.C.; Mohapatra, S.; Varma, A. Extremophile—an adaptive strategy for extreme conditions and applications. *Curr. Genom.* 2020, 21, 96–110. [CrossRef]

51. Merino, N.; Aronson, H.S.; Bojanova, D.P.; Feyh-Buska, J.; Wong, M.L.; Zhang, S.; Giovannelli, D. Living at the extremes: Extremophiles and the limits of life in a planetary context. *Front. Microbiol.* 2019, 10, 780. [CrossRef] [PubMed]

52. Rampelotto, P.H. Extremophiles and Extreme Environments. *Life* 2014, 3, 482–485. [CrossRef] [PubMed]

53. Rothschild, L.J.; Mancinelli, R.L. Life in extreme environments. *Nature* 2001, 409, 1092–1101. [CrossRef] [PubMed]

54. Prieur, D. Extremophiles. In *Encyclopedia of Astrobiology*; Gholami, M., Etemadifar, Z., Bouzari, M., Eds.; Springer: Berlin/Heidelberg, Germany, 2011; pp. 572–575.

55. Pikuta, E.V.; Hoover, R.B.; Tang, J. Microbial extremophiles at the limits of life. *Crit. Rev. Microbiol.* 2007, 33, 183–209. [CrossRef] [PubMed]

56. Singh, S.P.; Shukla, R.J.; Kikani, B.A. Molecular diversity and biotechnological relevance of thermophilic actinobacteria. In *Thermophilic Bacteria: Special Topics on the Physical and Biological Aspects of Thermophilic Bacteria*; Dandawate, P.J., Vyas, A., Padhye, S., Singh, M., Baruah, J., Eds.; Springer: Berlin/Heidelberg, Germany, 2011; pp. 572–575.

57. Des Marais, D.J.; Walter, M.R. Terrestrial hot spring systems: Introduction. *Astrobiology* 2009, 19, 1419–1432. [CrossRef] [PubMed]

58. Schmidt, T.M. *Encyclopedia of Microbiology*; Academic Press: San Diego, CA, USA, 2019.

59. Kristjansson, J.K. *Thermophilic Bacteria*; CRC Press: Boca Raton, FL, USA, 1991.

60. Singh, S.P.; Shukla, R.J.; Kikani, B.A. Molecular diversity and biotechnological relevance of thermophilic actinobacteria. In *Thermophilic Microbes in Environmental and Industrial Biotechnology*; Springer: Berlin/Heidelberg, Germany, 2013; pp. 459–479.

61. Liu, L.; Salam, N.; Jiao, J.-Y.; Jiang, H.-C.; Zhou, E.-M.; Yin, Y.-R.; Ming, H.; Li, W.-J. Diversity of culturable thermophilic actinobacteria in hot springs in Tengchong, China and studies of their biosynthetic gene profiles. *Microb. Ecol.* 2016, 72, 150–162. [CrossRef]

62. Bedlund, B.P.; Cole, J.K.; Williams, A.J.; Hou, W.; Zhou, E.; Li, W.; Dong, H. A review of the microbiology of the Rehai geothermal field in Tengchong, Yunnan Province, China. *Geosci. Front.* 2012, 3, 273–288. [CrossRef]

63. Dabbagh, R.; Ghafourian, H.; Baghvand, A.; Nabi, G.; Riahi, H.; Nakhl, A. Discovery of the second highest level of radioactive mineral spring in Iran. *J. Radioanal. Nucl. Chem.* 2006, 269, 91–94. [CrossRef]

64. Singh, S.P.; Shukla, R.J.; Kikani, B.A. Molecular diversity and biotechnological relevance of thermophilic actinobacteria. In *Thermophilic Bacteria*; Gholami, M., Etemadifar, Z., Bouzari, M., Eds.; Springer: Berlin/Heidelberg, Germany, 2011; pp. 572–575.

65. Li, L.; Salam, N.; Jiao, J.-Y.; Jiang, H.-C.; Zhou, E.-M.; Yin, Y.-R.; Ming, H.; Li, W.-J. Diversity of culturable thermophilic actinobacteria in hot springs in Tengchong, China and studies of their biosynthetic gene profiles. *Microb. Ecol.* 2016, 72, 150–162. [CrossRef]

66. Australian Bureau of Statistics. *Year Book Australia, 1992 No. 75*; Australian Bureau of Statistics: Canberra, Australia, 2003. Available online: shorturl.at/cvGX0 (accessed on 3 March 2021).

67. Makhalanyane, T.P.; Valverde, A.; Gunninge, E.; Frossard, A.; Ramond, J.-B.; Cowan, D.A. Microbial ecology of hot desert edaphic systems. *FEMS Microbiol. Rev.* 2015, 39, 203–221. [CrossRef] [PubMed]

68. Logan, R.F. Causes, climates, and distribution of deserts. In *Desert Biology: Special Topics on the Physical and Biological Aspects of Arid Regions*; Academic Press: New York, NY, USA, 1968; Volume 1, pp. 21–50.

69. Schulz, D.; Beepe, P.; Ohlendorf, B.; Erhard, A.; Zinecker, H.; Dorador, C.; Imhoff, J.F. Auenquinones A–D: Aminoquinone derivatives produced by *Streptomyces* sp. strain DB634. *J. Antibiot.* 2011, 64, 763–768. [CrossRef] [PubMed]

70. Dandawate, P.; Vyas, A.; Padhye, S.; Singh, M.; Baruah, J. Perspectives on medicinal properties of benzoquinone compounds. *Mini Rev. Med. Chem.* 2010, 10, 436–454. [CrossRef] [PubMed]

71. Komatsu, K.; Lee, J.; Miyata, M.; Lim, J.H.; Jono, H.; Koga, T.; Xu, H.; Yan, C.; Kai, H.; Li, J. Inhibition of PDE4B suppresses inflammation by increasing expression of the deubiquitinase CYLD. *Nat. Commun.* 2013, 4, 1684. [CrossRef]

72. Bielekova, B.; Lincoln, A.; McFarland, H.; Martin, R. Therapeutic potential of phosphodiesterase-4 and-3 inhibitors in Th1-mediated autoimmune diseases. *J. Immunol.* 2000, 164, 1117–1124. [CrossRef]
102. Baxter, B.K. Great Salt Lake microbiology: A historical perspective. *Int. Microbiol.* **2018**, *21*, 79–95. [CrossRef]

103. Last, W.M. Geolimnology of salt lakes. *Geosci. J.* **2002**, *6*, 347–369. [CrossRef]

104. Albarracín, V.H.; Pathak, G.P.; Douki, T.; Cadet, J.; Borsarelli, C.D.; Gätter, W.; Farias, M.E. Extremophilic *Acinetobacter* strains from high-altitude lakes in Argentinean Puna: Remarkable UV-B resistance and efficient DNA damage repair. *Orig. Life Evol. Biosph.* **2012**, *42*, 201–221. [CrossRef] [PubMed]

105. Rasuk, M.C.; Ferrer, G.M.; Kurth, D.; Portero, L.R.; Farias, M.E.; Albarracín, V.H. UV-resistant actinobacteria from high-altitude Andean Lakes: Isolation, characterization and antagonistic activities. *Photochem. Photobiol.* **2017**, *93*, 865–880. [CrossRef] [PubMed]

106. Zhang, M.; Wang, L.; Zhong, D. Photolyase: Dynamics and mechanisms of repair of sun-induced DNA damage. *Photochem. Photobiol.* **2017**, *93*, 78–92. [CrossRef] [PubMed]

107. Wu, J.; Peng, Z.; Guan, T.-W.; Yang, H.; Tian, X. Diversity of actinobacteria in sediments of Qaidam Lake and Qinghai Lake, China. *Arch. Microbiol.* **2021**, *1–11*. [CrossRef]

108. Mohammadipanah, F.; Wink, J. Actinobacteria from arid and desert habitats: Diversity and biological activity. *Front. Microbiol.* **2016**, *6*, 1541. [CrossRef]

109. Crits-Christoph, A.; Robinson, C.K.; Barnum, T.; Fricke, W.F.; Davila, A.F.; Jedynak, B.; McKay, C.P.; DiRuggiero, J. Colonization patterns of soil microbial communities in the Atacama Desert. *Microbiome* **2013**, *1*, 28. [CrossRef]

110. Grossart, H.-P.; Schlingloff, A.; Bernhard, M.; Simon, M.; Brinkhoff, T. Antagonistic activity of bacteria isolated from organic aggregates of the German Wadden Sea. *FEMS Microbiol. Ecol.* **2004**, *47*, 387–396. [CrossRef]

111. Zeng, Q.; Huang, H.; Zhu, J.; Fang, Z.; Sun, Q.; Bao, S. A new nematicidal compound produced by *Streptomyces albogriseolus* HA10002. *Antonie Van Leeuwenhoek* **2013**, *103*, 107–1111. [CrossRef]

112. Zhang, W.; Wei, S.; Zhang, J.; Wu, W. Antibacterial activity composition of the fermentation broth of *Streptomyces djakartensis* NW35. *Molecules* **2013**, *18*, 2763–2768. [CrossRef]

113. Kumar, P.S.; Yuvaraj, P.; Paulraj, M.G.; Ignacimuthu, S.; Al-Dhabi, N.A. Bio-Prospecting of soil *Streptomyces* and its bioassay-guided isolation of microbial derived auxin with antifungal properties. *J. Mycol. Med.* **2018**, *28*, 462–468. [CrossRef] [PubMed]

114. Mbah, J.A.; Ngemenya, M.N.; Abawah, A.L.; Biabaka, S.B.; Nubed, L.N.; Nyongkela, B.D.; Lemuh, N.D.; Efange, S.M. Bioassay-guided discovery of antibacterial agents: In vitro screening of *Peperomia vulcanica*, *Peperomia fernandopoioana* and *Selceria striatinux*. *Ann. Clin. Microbiol. Antimicrob.* **2012**, *11*, 10. [CrossRef] [PubMed]

115. Steinbeck, C.; Kuhn, S. NMRShiftDB—compound identification and structure elucidation support through a free community-built web database. *Phytochemistry* **2004**, *65*, 2711–2717. [CrossRef]

116. Law, J.W.-F.; Chan, K.-G.; He, Y.-W.; Khan, T.M.; Ab Mutalib, N.-S.; Goh, B.-H.; Lee, L.-H. Diversity of *Streptomyces* spp. from mangrove forest of Sarawak (Malaysia) and screening of their antioxidant and cytotoxic activities. *Sci. Rep.* **2019**, *9*, 1–15. [CrossRef] [PubMed]

117. Gosses, J.T.; Ghosh, S.; Sproule, A.; Overy, D.; Cheeptham, N.; Boddy, C.N. Whole genome sequencing and metabolomic study of cave *Streptomyces* isolates ICC1 and ICC4. *Front. Microbiol.* **2019**, *10*, 1020. [CrossRef]

118. Ser, H.-L.; Ab Mutalib, N.-S.; Yin, W.-F.; Goh, B.-H.; Lee, L.-H.; Chan, K.-G. Genome sequence of *Streptomyces antioxidans* MUSC 164T isolated from mangrove forest. *Prog. Microbes Mol. Biol.* **2018**, *1*, a000001. [CrossRef]

119. Ōmura, S.; Ikeda, H.; Ishikawa, J.; Hanamoto, A.; Takahashi, C.; Shinose, M.; Takahashi, Y.; Horikawa, H.; Nakazawa, H.; Osono, T. Genome sequence of an industrial microorganism *Streptomyces avermitilis* strain MUSC 93J. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 12215–12220. [CrossRef] [PubMed]

120. Lee, N.; Kim, W.; Hwang, S.; Lee, Y.; Cho, S.; Palsson, B.; Cho, B.-K. Thirty complete *Streptomyces* genome sequences for mining novel secondary metabolite biosynthetic gene clusters. *Sci. Data* **2020**, *7*, 1–9. [CrossRef]

121. Ser, H.-L.; Chan, K.-G.; Tan, W.-S.; Yin, W.-F.; Goh, B.-H.; Ab Mutalib, N.-S.; Lee, L.-H. Complete genome of mangrove-derived anti-MRSA streptomyctete, *Streptomyces pluripotens* MUSC 135T. *Prog. Microbes Mol. Biol.* **2018**, *1*, a000004. [CrossRef]

122. Ser, H.-L.; Law, J.W.-F.; Tan, W.-S.; Yin, W.-F.; Chan, K.-G.; Lee, L.-H. Genome sequence of bioactive streptomyctete isolated from mangrove forest in East Malaysia, *Streptomyces monashensis* MUSC 1J1. *Prog. Drug Discov. Biomed. Sci.* **2019**, *2*, a0000045. [CrossRef]

123. Ser, H.-L.; Law, J.W.-F.; Tan, W.-S.; Yin, W.-F.; Chan, K.-G.; Lee, L.-H. Whole genome sequence of *Streptomyces colonosanans* strain MUSC 93J isolated from mangrove forest in Malaysia. *Prog. Microbes Mol. Biol.* **2020**, *3*, a0000061. [CrossRef]

124. Ser, H.-L.; Tan, W.-S.; Ab Mutalib, N.-S.; Cheng, H.-J.; Yin, W.-F.; Chan, K.-G.; Lee, L.-H. Genome sequence of *Streptomyces pluripotens* MUSC 135T exhibiting antibacterial and antioxidant activity. *Mar. Genom.* **2015**, *24*, 281–283. [CrossRef] [PubMed]

125. Ser, H.-L.; Tan, W.-S.; Cheng, H.-J.; Yin, W.-F.; Chan, K.-G.; Ab Mutalib, N.-S.; Goh, B.-H.; Lee, L.-H. Draft genome of starch-degrading actinobacterium, *Microbacterium mangrovei* MUSC 115T isolated from intertidal sediments. *Proc. Drug Discov. Biomed. Sci.* **2018**, *1*, a0000005. [CrossRef]

126. Li, S.; Li, Y.; Lu, C.; Zhang, J.; Zhu, J.; Wang, H.; Shen, Y. Activating a cryptic ansamycin biosynthetic gene cluster to produce three new naphthalenic octaketide ansamycins with n-pentyl and n-butyl side chains. *Org. Lett.* **2015**, *17*, 3706–3709. [CrossRef] [PubMed]