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Antimicrobial and anticancer potential of soil bacterial metabolites - a comprehensive and updated review

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ABSTRACT

The majority of natural products currently used in the medical field are derived from microbial or plant sources. The bioactive compounds derived from natural sources exhibit tremendous structural and chemical diversity. According to previous research, only a small percentage of the world's plant and microbial diversity has been examined for bioactivities. The compounds originating from secondary metabolites of microorganisms are more useful for the development of novel drugs due to their biological friendliness and drug-likeness than any other compounds. Thus, recent research suggests that microorganisms obtained from diverse habitats and natural resources offer various bioactive secondary metabolites with incredibly wider chemical entities, hopefully, an alternative remedy for many diseases. Soil bacteria are capable of producing a variety of natural bioactive compounds for the treatment of various diseases. The three genera *Bacillus* spp., *Streptomyces* spp., and *Pseudomonas* spp. have been the prime focus to produce different types of antibiotics. However, to date, there are no reviews that evaluated the antimicrobial and anticancer properties of soil bacterial metabolites. Hence, the current review aimed to assess the antimicrobial and anticancer potential of soil bacterial metabolites.

1. INTRODUCTION

Man is dependent on natural products to maintain good health and protect against various diseases from time immemorial. Natural products are the richest source for drug discovery and currently, 65% of the approved drugs in medical fields are obtained from them [1,2]. The database of natural products contains more than 210,000 biologically active compounds with abundant chemical diversity [3]. In the year 2013, 1453 new compounds had been approved by the United States Food and Drug Administration of which approximately 40% were derived from natural products and their derivatives [4]. Scientific communities have given more importance to natural products as drugs derived from them provide better treatment compared to synthetic products [5]. Besides, the compounds derived from natural sources contain abundant structural diversity compared to synthetic compounds and play an important role in new drug discoveries [6]. Especially, compounds derived from microorganisms play a significant role in treating infectious diseases and cancer [2,7]. Among microorganisms, bacteria and fungi are the main candidates focused on the production of bioactive compounds [8,9], as they have existed on earth for billions of years and have evolved many biosynthetic pathways by novel mechanisms to synthesize secondary metabolites. The various applications of microbial natural products are demonstrated in Figure 1. The discovery of bioactive compounds from microbes involves various steps, including isolation, structural elucidation, and establishing the biosynthetic pathway leading to the formation of secondary metabolites [7,9].

According to an estimate, 0.1% of bacterial species and 5% of fungal species of the world are known to man, which only a small fraction has been screened for bioactivity [10,11]. Antimicrobial agents isolated from actinomycetes include streptomycin, gentamycinand rifamycin, whereas anti-cancer agents comprise mitomycin, aclarubicin, neocarzinostatin, doxorubicin, mithramycin, and carzinophilin [12]. Previously, there are no reviews that evaluated the antimicrobial and anticancer properties of soil bacterial metabolites. Therefore, the current review aimed to assess the antimicrobial and anticancer potential of soil bacterial metabolites.

2. CANCER-A DEADLY DISEASE

In recent years, the incidence of cancer is increasing at a phenomenal rate. According to a World Health Organization (WHO) estimate, cancer affects approximately 10 million people by 2020, or nearly one in six deaths. Breast, lung, colon, rectum, and prostate cancers are the most frequent cancers. Tobacco use, a high body mass index, alcohol consumption, and a lack of physical activity account for almost one-third of cancer fatalities. In low- and lower-middle-income

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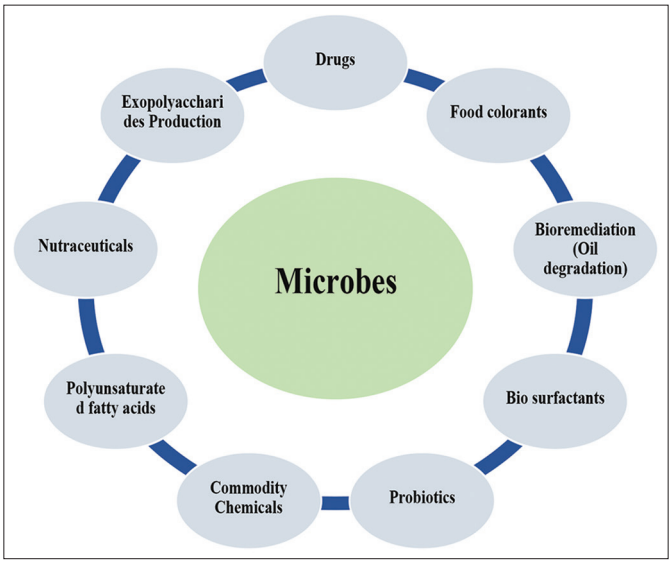

Figure 1: Various applications of microbial natural products.

countries, cancer-causing diseases such as the human papillomavirus and hepatitis account for roughly 30% of cancer cases. Many tumors are curable if identified early and treated properly [13,14].

Based on the statistical report of global cancer, approximately 12.7 million cases of cancer were detected and 7.6 million cancer mortality occurred in the year 2011 [15,16] and 8.8 million of death in 2015 [17]. Cancer is caused by both external (chemicals, radiation, tobacco, alcohol abuse, and infectious organisms) and internal (familial history, hormones, immune conditions, inherited mutations, and mutation occur from metabolism) factors. The other factors that cause cancer include infections 15–20%, diet, obesity 30–35%, tobacco 25–30%, stress, lack of physical activity, radiation, and environmental pollutants [18].

3. ANTIMICROBIAL RESISTANCE (AMR)

Antimicrobial agents have saved millions of lives from microbial infections for more than seven decades. However, AMR is a major problem faced by the medical world and this has caused adverse effects on human beings [19]. Pathogens are regularly becoming resistant towards antimicrobial agents. This problem is further increased due to the independent and continuous use of antibiotics that cause serious health diseases in humans [20]. Recently, the AMR reports predicted that due to multidrug-resistant (MDR) infections the death rate will be 10 million in the year 2050 [21]. It referred to the evolution of pathogenic microbes such as fungi, bacteria and viruses that developed resistance against the antimicrobial drugs [22,23]. At present, 60% of the Gram-negative bacteria have developed resistance to all classes of antimicrobial agents including carbapenems, cephalosporin, and fluoroquinolones. [24,25]. Similarly, Gram-positive bacteria *Staphylococcus aureus* significantly increased its resistance to the antibiotic methicillin and referred to as methicillin-resistant *S. aureus* [26]. According to the world health organization report in 2017, three groups of bacterial genus namely *Pseudomonas*, *Acinetobacter,* and various *Enterobacteriaceae* members including *Escherichia coli*, *Klebsiella*, *Proteus,* and *Serratia* developed resistance to most of the antibiotics [27-29].

The fungal infection is yet another serious issue in the medical field and has the potential to harm every individual. Approximately, 1.2 billion people are suffering from various fungal diseases universally [30]. The most common disease-causing pathogenic fungi are *Aspergillus* and *Candida*. The infection caused by *Aspergillus* in human is extremely alarming. Particularly, *Aspergillus niger* causes various diseases to humans which includes pulmonary diseases, fungal ear infections, temporary hearing loss, and skin diseases [31]. The *Candida* spp. is the common cause of fungal nosocomial bloodstream infections. Among the *Candida* spp. *Candida albicans* is the most prevalent species involved in nosocomial bloodstream infections, gastrointestinal tract infection, mucosal oral cavity diseases, intestinal infections, and skin problems [32].

4. NEED FOR ALTERNATIVE DRUGS TO TREAT CANCER AND MICROBIAL INFECTIONS

The available cancer therapies such as radiation therapy, surgery, chemotherapy, hormone therapy, and immunotherapy often fail to achieve complete cancer remission. These types of treatments cause significant side effects to humans, such as blood clots, hair loss, pain, anemia, fatigue, thrombocytopenia, diarrhea, constipation, neurological complications, and unpleasant to fatal infections [33,34]. Moreover, the currently available anticancer drugs are limited in their safety and efficacy. Successful cancer therapy depends on its preferential wipeout of cancer cells without side effects or negligible toxicity to the normal cells [35,36].

After the revolution, in the 1960s the “golden era,” most of the important antibiotics such as cephalosporins, macrolides, tetracyclines, and aminoglycosides were discovered and major problems of chemotherapy have been solved. The history is being repeated now because the exciding compounds are losing their efficacy due to the increase in AMR and failure to treat the MDR bacteria and fungi. It becomes a universal problem for public health [37,38]. In addition, the widely used antifungal drugs like azoles cause significant side effects and frequently decrease the efficacy against fungal pathogens [39]. For this reason, the discovery of new bioactive compounds with safety and efficacy to treat cancer and microbial infections is an exclusively important objective.

5. SOIL MICROORGANISMS

Soil is a rich reservoir of microorganisms that differentially favors the diversity of microbes according to the geographical region and environmental factors. The soil microbes are the key components of the forest biomes and they are playing a vital role in the soil aggregation, nitrogen fixation and cycling of nutrients through lignin and cellulose breakdown [40,41]. Soil microbes, such as fungi and bacteria control the ecosystem by decomposition and maintain the health of the ecosystem. The majority of the currently used drugs are derived from the soil microorganisms belonging to the genera *Bacillus, Streptomyces, Micromonospora, Penicillium,* and *Cephalosporium* [42]. More than 500 bioactive compounds are discovered every year among which almost 60% is obtained from the soil microbes [43,44].

6. SOIL BACTERIA

The soil bacteria are the key contributors to productivity in the ecosystem and nutrient cycling. It is the most diverse and abundant microbial community in soil [45]. Besides, soil bacteria are the main source of production of bioactive secondary metabolites with enormous biological properties [46,47]. It has been used for a variety of applications ranging from crop production to drug discovery. Members of the genus *Bacillus* are commonly found in soil and produce a variety

of bioactive secondary metabolites that are effective against a variety of life-threatening diseases [42]. As per literature, many bacterial strains isolated from soil samples, for example, *Bacillus pumillus, Bacillus lentus, Enterobacter aerogenes, Bacillus alvei, Micrococcus roseus,* and *Bacillus amyloliquefaciens* have shown strong bioactivity against the various pathogens [48-50]. Nowadays, most of the research workers focused on soil microbial communities and diversity of soil bacteria especially from *Bacillus* communities [51]. The isolation of pure compounds from bacterial strains is not a simple process. Because each crude extract contains several compounds, constructing a crude extracts library takes less time than constructing a purified compounds library, and the range of diversity may be comparable to that of a large systematic compound library. To detect the target component in the various compound mixtures, however, a sophisticated and robust screening technology with high specificity and sensitivity is required. To eliminate known and redundant compounds, suggest which peak should be efficiently purified, and accumulate knowledge for structure determination, a dereplication technique is necessary [52]. The dereplication process for bacterial natural product screening method is shown in Figure 2.

7. BACTERIAL METABOLITES

Bacterial secondary metabolites are a major source of the drugs that lead, with attractive bioactivities. In particular, a variety of secondary metabolites is produced by bacteria, generating approximately half of the discovered antibiotics [53]. In the group of bacteria, the *Streptomyces*, *Pseudomonas,* and *Bacillus* species are the most frequent producer of bioactive compounds. Among these, *Bacillus* strains have a great potential to use in various application fields including antibiotics, enzymes producers, vitamins, probiotics, and bioprotection products. They also contributed significant roles in the biodegradation of pollutants in the environment [54].

The most prominent species of *Bacillus* including *Bacillus lichaniformis, Bacillus subtilis, Bacillus circulans, Bacillus amyloliquefacience, Bacillus polymixa, Bacillus pumilus,* and *Bacillus cereus* [55,56]. These organisms commonly produce isocoumarins, lipopeptides, polyketides, aminoglycoside, aminopolyol, phospholipids, phosphon oligopeptide, and terpenoids [57,58]. Similarly, the most important antibiotics rifamycin and gramicidin are reported from *Streptomyces* and *Bacillus* [59]. American physician William Coley reported that the bacterial strains had produced several safe vaccines against carcinomas, lymphomas, sarcomas, and melanomas cancers [60]. This has prompted the development of many new drugs from bacteria for various diseases [61]. The process involved in the isolated of bioactive compounds is shown in Figure 3.

8. ANTIMICROBIAL METABOLITES FROM SOIL BACTERIA

Today both industrialists and academicians focus interest on soil bacteria due to its discrete advantages over the other microbes. The soil bacteria not only produce unique bioactive metabolites but also commercially important natural products [62]. They are employed in various fields such as fermentation process (cheese, brewing, baking and butter manufacturing), chemical manufacturing (acetone, ethanol, organic acid, perfume, enzymes, etc.), and drug discovery. Therefore, the application of soil bacteria's open up new areas of biotechnological exploitations, which lead to the essentials of isolation and cultivation of these organisms [63,64]. They produce a variety of vaccines, antibiotics, steroids, and therapeutically useful compounds with strong biological activities [65]. Streptomycin was the first aminoglycoside antibiotic derived from the soil bacterium *Streptomyces griseus*. Following that, important antibiotics such as macrolide, chloramphenicol, glycopeptide (e.g., vancomycin), and tetracycline were derived from the soil bacteria [66,67].

Bacillus is the most common bacteria found in the soil and many species of this genus produce a variety of antimicrobial compounds [68]. The bactericidal and fungicidal compounds derived from the soil *Bacillus* spp. includes megacin from *Bacillus megaterium* [69], polyfermenticin from *Bacillus polyfermenticus* [70],

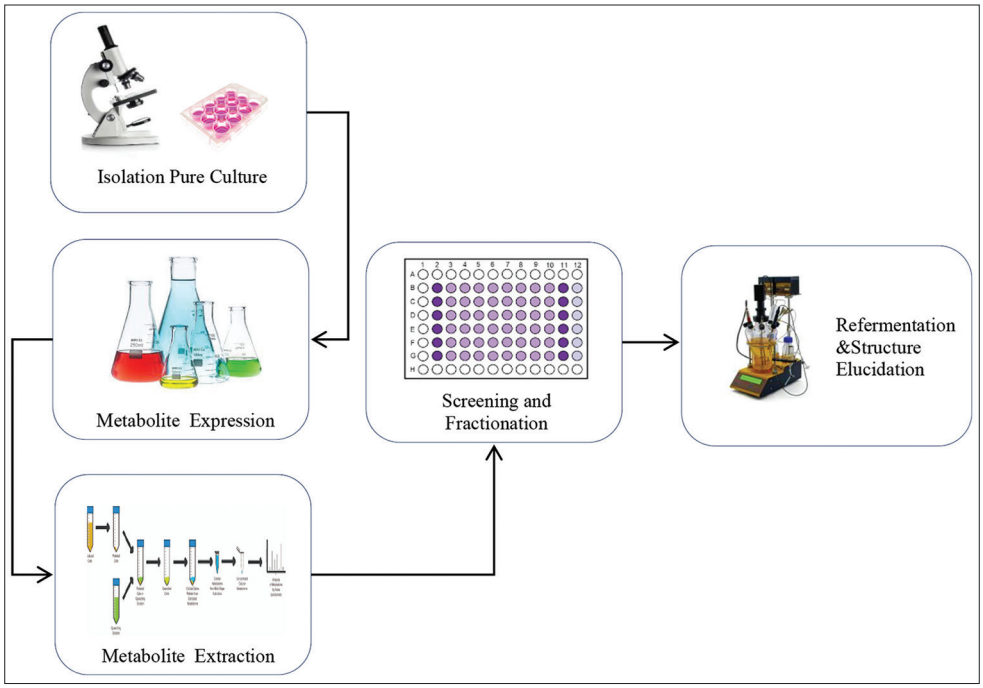

Figure 2: Dereplication process for bacterial natural product screening.

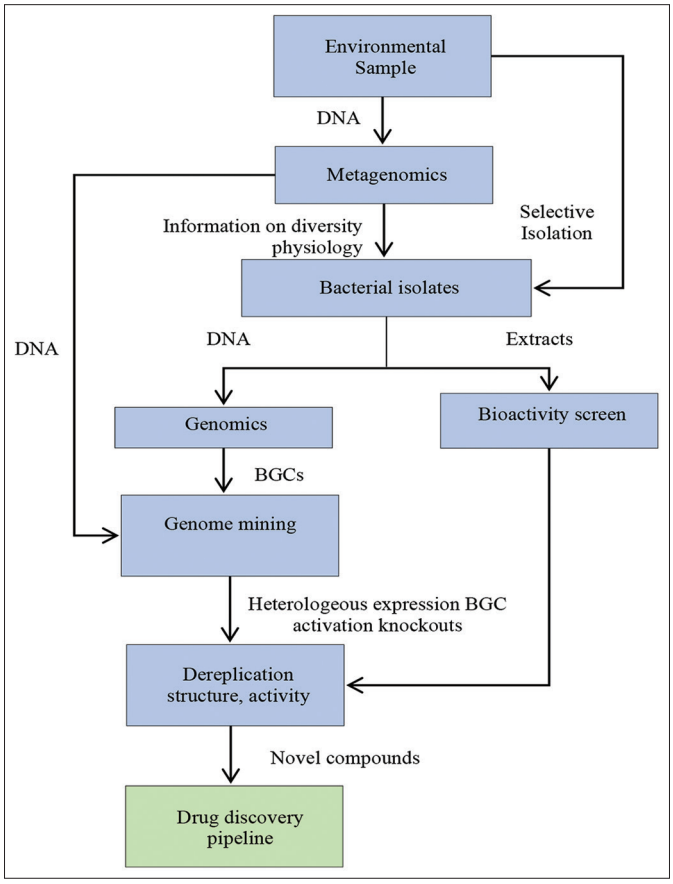

Figure 3: Overview of the workflow for the discovery of bioactive compounds from bacteria.

cerein and zwittermicin 14 from *B. cereus* [71], bacilysin 1, subtilin, ericin, mersacidin, sublancin, subtilolysin, amicoumacin 4 and iturin 7 produced by *B. subtilis* [72], lichenin from *Bacillus licheniformis*, difficidin 10, bacilysin 1, macrolactin 12, iturin 7 from *B. amyloliquefaciens* [73], amicoumacin 4 and bacilysin 1 from *B. pumilus* [74], Zwittermicin 14, thuricin, tochicin, kurstakin, and entomocin from *Bacillus thuringiensis* [71]. In addition to these, mitomycin C an antitumor compound derived from *Streptomyces caespitosus* was discovered by Japanese microbiologists in the year 1950. The mitomycin C is used in the treatment of lungs, breast, hepatic carcinoma, head, neck, bladder, and colorectal cancers [75].

Erythromycin isolated from the soil bacterium *Saccharopolyspora erythraea* is the first generation of macrolide and the macrolide antibiotics potential against both Gram-positive and Gram-negative bacteria [76]. The compound cyclopentapeptides derived from *Streptomyces flavovirens* isolated from the Antartic soil samples showed potent antitumor and antimicrobial activity [77,78] reported laterosporulin 10 (LS10) a type of anticancer agent derived from *Brevibacillus* spp. showed anticancer activity against five different human cell lines such as lung carcinoma (H1299), cervical cancer (HeLa), breast cancer (MCF-7), fibrosarcoma (HT1080), and embryonic kidney cancer (HEK293T). Similarly, 700 antibiotics have been derived from *Micromonospora* spp., including 150 aminoglycosides [79]. Hover *et al*., [80] reported a new class of antibiotic malacidins discovered from the soil bacteria, which are active against different types of MDR pathogens. The list of antimicrobial compounds isolated form bacterial strains is detailed in Table 1.

Singh and Wahla [127] disclosed the secondary metabolites extracted from *Streptomyces werraensis* KBR01 isolated from the rhizosphere soil samples showed antifungal activity against *Fusarium oxysporum*. Recently, it was found by the disc diffusion method that several *Streptomyces* spp. isolated from the rhizosphere soil showed excellent antifungal activity against *C. albicans* [128]. Likewise, Andargie and Li, [129] revealed antifungal compounds extracted from *Streptoverticillium morookaense* isolated from the soil samples of pine forest at China, showed potential antimicrobial activity against the tested pathogens *Ustilaginoidea virens, Bipolaris maydis* and *Rhizoctonia solani*. Adlin Jenifer *et al*., [130] reported the strain *Nocardiopsis* sp. isolated from the soil samples collected from Kovalamsolar salterns, Tamil Nadu, showed antimicrobial activity against *E. coli, Pseudomonas aeruginosa, A. niger*, etc. Pattnaik [131] described that the strain *Micromonospermae chinospora* isolated from the soil samples of Western Odisha, showed potential antibacterial activity against *S. aureus.* A study by Mahdiyah *et al*. [132] isolated several bacterial strains from peat soil samples showed strong antibacterial activity against methicillin-susceptible *S. aureus* (ATCC 29213) and *E. coli* (ATCC 35218). Kumar *et al*. [1] isolated the bacterial strain *B. subtilis* from soil samples were collected from Avalanche reserve forest of south zone Nilgiris district. The bioactive metabolites of the strain showed strong antimicrobial activity against *E. aerogenes, Enterococcus faecalis, Alcaligenes faecalis* and *C. albicans.* Zhou *et al.* [133] isolated several *Bacillus* strains from rhizosphere soil that have antimicrobial activity against *Phytophthora infestans, R. solani, Pseudomonas syringae, Erwinia carotovora, Verticillium dahlia* and *Botrytis cinerea.* Recently, a study by Osama *et al.* [12] isolated the four *Streptomyces* spp. (SH8, SH10, SH12, and SH13) from the top layer of agricultural soil in Beni-Suef Governorate, Egypt. All the four isolated showed a broad spectrum of antimicrobial activity against *C. albicans* (ATCC 60193), *Listeria monocytogenes* (ATCC 7644), *E. coli* (clinical isolate), *Salmonella enterica* (ATCC 14028), *B. subtilis* (environmental sample), and *S. aureus* (ATCC 43300).

9. ANTICANCER METABOLITES FROM SOIL BACTERIA

The anticancer metabolites isolated from the soil bacterial strains can be considered as a safe alternative for synthetic drugs. Malkov *et al*. [134] reported a Gram-positive bacteria *B. oligonitrophilus* KU-1 isolated from the soil samples of Kazan city, Russia exhibited the effective anticancer activity against colon cancer cell line. Abraham *et al*. [135] isolated antitumor compound doxorubicin from the soil bacterium *Streptomyces peucetius* var. caesius which showed anticancer activity against skin cancer. Similarly, a new bacterial strain AAA5 isolated from the humus soil of Western Ghats, India, has been identified as *Streptomyces aurantiacus.* It produced a quinone-related antibiotic resistomycin showing potential anticancer activity against HeLa (cervical carcinoma) and HepG2 (hepatic carcinoma) cell lines with growth inhibition 0.005 and 0.006 g/mL, respectively [136].

Rebeccamycin is a Lentzea aerocolonigenes-derived indolocarbazole-based antitumor antibiotic. Rebeccamycin was discovered in a Panama soil sample from an actinomycete culture of C-38383.Different study groups called it *Saccharothrix aerocolonigenes* and *Lechevalieria aerocolonigenes* after it was first placed under *Streptomyces* sp. and titled *Nocardia aerocolonigenes* [137]. Hou *et al*. [138] reported *Streptomyces* sp. isolated from the soil samples collected at Huiquan Square in China, produced a new polyketide glycoside, gilvocarcin HE showing moderate anticancer activity against P388, K562 and MCF-7 cell lines with IC_{50} values of 45, 39, and 36 µg/mL, respectively. Similarly, Balachandran *et al*. [139] reported the bacteria ERI-135

Table 1: List of antimicrobial compounds isolated from bacterial strains.

Bacteria	Compound	Biological effects	References
Bacillus megaterium	Megacin	Bactericidal	[81]
Bacillus cereus	Cerein	Bactericidal	[82]
Bacillus subtilis, Bacillus pumilus	Amicoumacin 4	Antibacterial	[83]
Bacillus amyloliquefaciens	Bacillaene 11	Antibacterial	[84]
Pseudomonas fluorescens	Nunapeptin, Nunamycin	Antifungal	[85]
Scaphirhynchus albus	Malacidin	Antimicrobial	[80]
Escherichia coli	Cadaside	Antibacterial	[86]
Streptomyces malaysiensis	Azalomycin F	Antifungal	[87]
Streptomyces spp. MA37	Accramycin A	Antibacterial	[88]
Amycolatopsis spp. MST-108494	Amycolatopsins A–C	Antibacterial	[89]
Bacillus polyfermenticus	Polyfermenticin	Antimicrobial	[90]
Bacillus spp.	Bogorol A	Antibacterial	[91]
Bacillus spp.	Loloatin B	Antibacterial	[92]
Bacillus amyloliquefaciens	Macrolactin S	Antibacterial	[93]
Bacillus amyloliquefaciens	Macrolactin V	Antibacterial	[93]
Bacillus laterosporus	Basiliskamides	Antifungal	[94]
Streptomyces misionensis	Streptenols	Antibacterial	[95]
Streptomyces spp.	Dibohemamines	Antimicrobial	[96]
Thermoactinomyces vulgaris	Thermoactinoamide A	Antimicrobial	[97]
Streptomyces clavuligerus	Cephalosporins	Antibacterial	[98]
Streptomyces cattleya	Thienamycin	Antibacterial	[99]
Streptomyces erythraea	Erythromycin	Antibacterial	[100]
Streptomyces orientalis	Vancomycin	Antibacterial	[101]
Streptomyces griseus	Streptomycin	Antibacterial	[102]
Marantochloa purpurea	Gentamycin	Antibacterial	[103]
Streptomyces spp.,	Tetracyclines	Antibacterial	[104]
Pseudomonas fluorescens	Mupirocin	Antibacterial	[105]
Streptomyces roseosporus	Daptomycin	Antibacterial	[106]
Streptomyces nodosus	AmphotericinB	Antifungal	[107]
Nocardiopsis alba	Z)-1-((1-hydroxypenta-2,4-dien1-yl) oxy) anthracene-9,10-dione	Antibacterial	[108]
Streptomyces spp. HW-003	AMRSA1	Antibacterial	[109]
Streptomyces spp.C34	Chaxamycins	Antibacterial	[110]
Streptomyces kanamyceticus	Bekanamycin	Antibacterial	[111]
Streptomyces triticiradicis sp.	2,3-dihydroxybutanone	Antifungal	[112]
Streptomyces fradiae	Neomycin	Antibacterial	[113]
Streptomyces venezuelae	Chloramphencol	Antibacterial	[114]
Streptomyces griseus	Albomycin	Antibacterial	[115]
Streptomyces laurentii	Thiostrepton	Antibacterial	[116]
Streptomyces spp.	Clindamycin	Antibacterial	[117]
Actinoplanes spp. ATCC33706	Ramoplanin	Antibacterial	[118]
Verrucosispora AB-18-032	Abyssomicins	Antibacterial	[119]
Micromonospora spp.	Micromonosporin	Antibacterial	[120]
Nocardia spp.	Thiolactomycin	Antibacterial	[121]
Streptomyces aureofaciens	Chlortetracycline	Antibacterial	[122]
Streptomyces rimosus	Oxytetracycline	Antibacterial	[123]
Streptomyces mediocidicus	Mediomycin B	Antifungal	[124]
Kibdelosporangium aridum	Aridicins A, BandC	Antimicrobial	[125]
Streptomyces spp.	Bonactin	Antibacterial	[126]

Table 2: List of anticancer compounds isolated from bacterial strains.

Bacteria	Compound	Biological effects	References
Kibdelosporangium spp.	Kibdelon	Anticancer	[146]
Bacillus spp. CND-914	Halobacillin	Anticancer	[147]
Bacillus spp.	Mixirin	Anticancer	[148]
Bacillus silvestris	Bacillistatins	Anticancer	[149]
Streptomyces verticillus	Bleomycin	Anticancer	[150]
Microbacterium mangrovin MUSC115	(3R,8aS)-3-methyl-1,2,3,4,6,7,8,8aoctahydropyrrolo[1,2- a] pyrazine-1,4- dione	Anticancer	[151]
Streptomyces peucetius	Doxorubicin	Anticancer	[152]
Streptomyces vinaceus	Citreamicindelta	Anticancer	[153]
Micromonospora chersina	Dynemicin	Anticancer	[154]
Streptomycespeuceticus	Amrubicin	Anticancer	[155]
Micromonospermae chinospora spp.	Gemtuzumabozogamicin	Anticancer	[156]
Streptomyces spp. *KML-2*	Chromomycinand 1-(1H-indol-3-yl)-propane-1,2,3-triol	Anticancer	[157]
Streptomyces spp. *VN1*	Furan-type	Anticancer	[158]
Streptomyces bulli GJA1	Angucyclinones	Anticancer	[159]
Streptomyces aurantiacus AAA5	Resistomycin	Anticancer	[136]
Streptomyces peucetius and *Streptomyces* spp.	Daunorubicin	Anticancer	[160]

identified as *Methylobacterium* spp. isolated from the Doddabetta forest soil showed anticancer activity against human lung cancer cell line (A 549). The antitumor compound glycopeptides mixture of antibiotics bleomycin isolated from *Streptomyces verticillus* has been used in the treatment of ovarian cancer, head carcinomas, testicular carcinomas, and neck carcinomas [140,141].

Parthiban *et al*. [142] reported *B. thuringiensis* S13 isolated from the soil of Mandapam, coastal area South India, produced exopolymer with strong anticancer activity against lung cancer cell line (A549) with an IC_{50} value of 133.27 µg/mL. Kumar *et al*. [143] reported the medicinal valuable unknown compounds were derived from the two soil bacterial strains *B. pumilus* and *B. cereus* by a fractionated method. All the isolated fractions were tested against liver cancer cell lines by MTT assay, showed high anticancer activity. Xu *et al*. [144] reported the natural compound 7-Cyano-7-deazaguanine isolated from the soil bacterium *Streptomyces qinglanensis* showed potent antitumor activity against HepG2 and HeLa cell lines. Similarly, another anticancer compound bovocin HC5 derived from the bacterium *Streptomyces bovis* divulged cytotoxicity against human liver hepatocellular carcinoma (HepG2) and human breast cancer (MCF7) [145]. The list of anticancer compounds isolated form bacterial strains is detailed in Table 2.

The biosurfactant produced by *P. aeruginosa* isolated from the oil-contaminated soil showed anticancer activity against HeLa cell lines by significantly controlling cell proliferation of the cells [161]. The compound 5-methyl phenazine-1-carboxylic acid betaine, derived from the *P. putida* soil bacterium, exhibited promising anticancer activity against human breast cancer and lung cancer cell lines [162]. In addition, Ramasubburayan *et al*. [163] reported that crude extract of *B. subtilis* RG isolated from the soil samples of the Southeast coast of India showed significant antitumor activity against human breast cancer cell lines (MCF7). Kim *et al*. [164] reported that the metabolites of bacterial strain *B. amyloliquefaciens* isolated from the rhizosphere soil of Korean ginseng showed strong antiproliferative and anticancer activity against the colorectal cancer cell lines of humans such as HT-29, LoVo, SW480, and HCT116. Recently, a study by Osama *et al*. [12] isolated the four *Streptomyces* spp. (SH8, SH10, SH12, and SH13) from the top layer of agricultural soil in Beni-Suef Governorate, Egypt. Among the four isolates, the isolates SH4 and SH12 showed anti-cancer activity against breast cells MCF-10A and the hepatoma cell line hepatoma G2 (HepG2). In addition, Kumar *et al*. [165] reported that the bioactive metabolites of soil bacterium *B. subtilis* showed significant anticancer activity against breast cancer cell line (MCF-7) by MTT assay. The *in silico* analysis showed the compound metaraminol having the maximum docking score −7.27 Kcal/mol against the breast cancer targeted protein estrogen receptor alpha (ERα).

10. CONCLUSION AND FUTURE DIRECTION

The current review highlights the antimicrobial and anticancer properties of soil bacterial metabolites demonstrated by existing studies. For scientists, finding potent secondary metabolite producers like soil bacteria is an exciting and demanding platform. Members of soil bacteria generate industrially valuable compounds such as enzymes, antibiotics, and pigments despite living under extreme circumstances. In its early phases, the use of soil microorganisms as a hotspot for novel bioactive optional metabolites. Therefore, more, research is required for the identification of novel soil bacterial strains as well as novel compounds from them.

Around the world, new potent small molecules with significant anticancer potential and a manageable safety profile are desperately needed. Many anticancer medications now being used in clinical trials have a variety of side effects. Reduced toxicity in non-targeted tissues and an improved site-targeted strategy are urgently needed. As a result, there is a significant need for bioactive cytotoxic natural compounds, which are preferable to produced molecules. Blockbuster anticancer drugs such as camptothecin, doxorubicin, topotecan, vinblastine, savincristine, paclitaxel, and others have been used in nano-based platforms such as polymeric nanoparticles, polymer-drug conjugates, dendrimers, liposomes, and immunoliposomes to

improve targeted tissue delivery while reducing toxicity to healthy cells. Nature's small molecules, as well as synthetic chemicals, have made major contributions to today's commercially available pharmaceuticals. Natural compounds have a minor advantage over manufactured products due to their lower toxicity profile, despite their large contribution. It's vital to remember that drugs based on natural compounds are not completely free of side effects. Actinomycin D's approval for the treatment of particular cancers has been delayed due to its side effects, which include tissue necrosis, myelosuppression, dermatotoxicity, and gastrointestinal enterotoxicity. Computational approaches for discovering new natural compounds and chemical derivatization give a broad platform for developing anticancer drugs in the near future. In view of all of these aspects, natural products hold a lot of promise for the development of novel drug seeds to address unmet needs in cancer therapy.

11. AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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13. CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

14. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

15. DATA AVAILABILITY

All data generated and analyzed are included within this review article.

16. PUBLISHER'S NOTE

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