A REVIEW: ISOLATION OF ACTINOMYCETES FROM DIFFERENT SOIL SAMPLE AND CHECK THEIR ANTIMICROBIAL ACTIVITY

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ABSTRACT

Antibiotics square measure the most significant commercially used secondary metabolites, created by means of several microbes. The emergence of antibiotic resistance and the need for broad-spectrum antibiotics is in focus and demand. Inside the present observe, soil samples were collected from distinctive regions and antibiotic-generating Actinomycetes have been isolated from those samples using serial dilution and plating method. Actinomycetes are gram-positive and soil-residing microbes and those microbes have traits in common with both bacteria and fungi. The inhibitory activity of the organism turned into checked against a number of the essential opportunist microorganism flora and inoculated into an applicable designed media reckoning on the microorganism needs and incubated for forty- eight hours at 37 °C. The characteristics of the isolate were studied on the morphological, cultural, and physiological levels. Though an oversized listing of antibiotics is well-known to be commercially accessible, the quest for the foremost capability one continues to be on, and this work could provide some ability facts at the antibiotic manufacturing and also the control of microbial strains. This review further summarizes the relationship with Actinomycetes and their ability to provide biologically active secondary metabolites, many of which have been isolated and become useful drugs.

Keywords*: Actinomycetes, Antibiotics, Gram- positive, Microbial strains, Resistance, Secondary metabolites, Soil-residing*

1. INTRODUCTION

Many compounds that square measure extraordinarily biologically active are isolated from microorganisms. Those lively compounds can be additional explored as new medicines or antibiotics.

1.1 The Actinomycetes

Actinomycetes are a group of prokaryotic microorganisms that are gram-positive bacteria with high guanine+ cytosine of their DNA [1], which have thread-like filaments within the soil [2]. The name

"actinomycetes'' comes from the Greek word "atkis" (lightning) and "mykes" (mushrooms), which have all the properties of bacteria and fungi [3] however but own sufficient one-of-a-kind features to delimit them into kingdom bacteria. They are moreover first-rate as a wealthy supply of bioactive secondary metabolites [4].

1.2 Distribution of Actinomycetes

Actinomycetes can exist in different habitats and are cosmopolitan in natural ecosystems. They are called gram-positive bacteria, which are characterized by the formation of air and matrix mycelium in a solid medium, and the existence of spores on the surface of a vulgaris [5]. Actinomycetes were divided into different genera according to morphological and chemical standards; Due to its importance in life sciences, ecology and biotechnology, Streptomyces is the highest and typical isolated genus in the order Actinomycetes. The genus, *Streptomycete,* is liable for the method of over 60% of illustrious antibiotics whilean extra 15% square measure became created via an expansion of related *Actinomycetes, Micromonospora, Actinomadura, Streptoverticillium and Thermoactinomycetes* [6].

1.3 Structure

Actinomycetes are characterized with the aid of the formation of normally branching threads and rods. The hyphae are normally non-septal; below sure special conditions, septa may also be discovered in few forms. Actinomycetes cell membranes can be made rigid to maintain the shape of the cells and prevent the cells from rupturing due to excessive osmotic pressure. Based on the basic materials of the cell wall, four groups have been identified in actinomycetes **[Table- 1]** [7].

Cell membrane type	**Sugar pattern**	**Genera**
I	No function sugar sample	*Streptomyces, Streptoverticillicum*, etc.
II	Araginose, Xylose (monosaccharide)	*Actinoplanes, Micromonospora* etc.
III	No sugar	*Dermatophilus, Planomonospora* etc.
IV	Galactose, Arabinose	*Mycobacterium, Nocardia,* etc.

1.4 Soil

The Actinomycetes population has been called soil inhabitant. It was found that only 10% of Actinomycetes were isolated from nature. Therefore, researchers must be forced to detect many Actinomycetes that have been found to be unable to produce new antibiotics that are effective against bacteria that are resistant to existing antibiotics [8]. Every 12 months almost 500 antibiotics had been observed, in which 60% of antibiotics are obtained from the soil [9]. Recent analyses have proven that screening of soil for antimicrobial activities has been finished in lots of parts of the arena [10].

1.5 The importance of Actinomycetes

Actinomycetes are bacteria with biotechnological value, used to produce secondary metabolites [11]. Screening, isolation, and characterization of promising strains of Actinomycetes producing capability

secondary metabolites have been a first-rate area of studies via many groups worldwide for many years [12]. Actinomycetes in particular *Streptomyces* species are widely recognized industrially important microorganisms as they are an upscale source of several beneficial bioactive herbal products with ability packages and are prolific producers of secondary metabolites, a lot of that have industrial significance as antibiotics, anti-parasitic and antifungal agents, anticancer or immunosuppressive agents as well as industrially important enzymes [13].

Table- 2: Antibiotics and Bioactive secondary metabolites from Actinomycetes: [14], [15]

Antibiotics Bioactive Metabolites					
Source	**Total**	**With other activity**	**No antibiotic activity**	**Antibiotics plus other active compounds**	**Total bioactive metabolites**
Bacteria	2900	780	900	1680	3800
Actinomycetes	8700	2400	1400	3800	10100
Fungi	4900	2300	3700	6000	8600
Total	16500	5500	6000	11500	22500

1.6 Antibiotics

Antibiotics are natural biotechnology medicines which can be made by way of many fungi and bacteria. In 1928, the term antibiotic appeared as an association in French microbiological literature while later in1942 the term antibiotic was introduced by Waksman [16]. The demand for state-of-the-art antibiotics growing daily due to the emergence of multiple pathogens that square measure immune to antibiotics cures for erstwhile life-threatening diseases. The most important antibiotics include Aminoglycosides, Penicillin, Macrolides, Glycopeptides, Cephalosporins, and Tetracycline [17]. About 75% of antibiotics are produced by way of Actinomycetes.

Table- 3: Some clinically vital antibiotics from Actinomycetes.

Antibiotic	**Produced by**	**Activity**	**Reference**
Erythromycin	*Actinopolyspora sp*.	Antibacterial	[18]
Rifamycin	*Micromonospora rifamycinica*	Antibacterial	[18]
Avermectin	*S. avermitilis*	Antiparasitic	[19]
Antimycin	*Streptomyces antibioticus*	Antifungal	[20]
Tomaymycin	*Streptomyces achromogenes*	Antiviral	[21]
Kinamycin	*Streptomyces murayamaensis*	Antibacterial	[22]
Azalomycin	*Streptomyces hygroscopicus*	Antifungal	[23]

Lincomycin	*Streptomyces lincolnensis*	Antibacterial	[24]

2. OVERVIEW OF BIOLOGICAL ACTIVITY

Many secondary metabolites of microorganisms have antibacterial, antifungal, antiviral, antitumor, antiprotozoal, and cholesterol-lowering and various activities. They are commonly used in medicine, veterinary surveillance, agriculture, and commerce. Approximately 14,000 microbial-derived compounds show antibacterial activity. Among them, 66% are against gram-positive bacteria, 30% against gram-negative bacteria, 5% against mycobacteria, 34% of compounds have antifungal effects, 21% against yeasts, 11% against phytopathogenic fungi, 24 % Fight against various fungi [14]. Among the microbial products, the fermentation product of *Streptomyces* is the most abundant source of antibiotics and various industrial compounds [25]. Examples of antimicrobial activity include β-lactams, tetracyclines, aminoglycosides, glycopeptides, macrolides, aminocyclitoles, cyclic peptides, lincosamides, glycolipopeptides, streptogramines, ansamycines,chloramphenicols, phenylpropanoides[26].

Clavuligerus produces clavulanic acid, a related β-lactamase inhibitor. In addition, this species also produces penicillin N, cephalosporin C and hypermycin [27]. For example, cephalosporins, which are structurally equivalent to cephalosporins, are produced by completely different species of Streptomyces., *S. griseus,S. viridochromogenes* and *S. fimbriatus* can secrete cephalosporins A and B; *S. lactamdurans* produces cephalosporin C [28]. Interestingly, the actinomycete strains that produce cephalosporin C (e.g. *S.*jumonjinensie, *S. katsurahamanus, S. clavuligerus* and *Streptomyces* sp. Uncategorized) also produces clavulanic acid [29]. Clavulanic acid was discovered in 1976 and can inhibit the β-lactamase found in plasmids by *Escherichia coli, Proteus, Klebsiella, and Shigella*. and *Pseudomonas* [30]. Clavulanic acid has almost no antibacterial activity, but together with unique synthetic or semi-artificial penicillins (amoxicillin-trimox, amoxiclav) as β-lactamase inhibitors, it is usually used for pathological treatment [28].

A fermentation product from the genus *Streptomyces.* More than forty naturally occurring carbapenems have been isolated. These are broad-spectrum antibiotics used in clinical treatments and have been relatively proven against β-lactamase. Compounds such as penicillin and cephalosporins inhibit microbial cell wall biogenesis [28]. It is also relatively immune to β-lactamase [26]. In 1944, Waxman discovered streptomycin, an aminoglycoside antibiotic in the subculture of *S. griseus* [29]. The compound has antibacterial properties against gram-negative bacteria and weaker activity against gram-positive bacteria It is widely used to treat tuberculosis [29]. Gentamicin is produced by fermentation in Micromonospora acnes and Micromonospora violaceus [30]. It is a broad-spectrum antibiotic with strong activity against Gram-negative bacteria.

Streptomyces spp. additionally produces macrolide structures, which avoid the growth of bacteria with the aid of interacting with their ribosomes [28]. Erythromycin is a metabolite of *Saccharopolyspora erythraea* [31].

3. ANTIMICROBIAL PROPERTIES OF NOVEL ANTIBIOTICS

The antibacterial activity of secondary metabolites is currently receiving more and more attention [28]. This is due to the urgent need to discover new antibiotics to combat the spread of multi-drug resistant clinical strains, and the treatment of the following diseases has failed. Due to their chemical and functional diversity, biologically active metabolites are the subject of scientific research, which may lead to the development of new and more effective antibacterial drugs [32]. Approximately 70% of the known antibiotics are from Actinomycetes, most of which are from the genus *Streptomyces*. [33].

Streptomycin is a group of antibacterial compounds derived from *Streptomyces.* They are structurally unrelated compounds that can inhibit the synthesis of bacterial ribosomal supra molecules during the peptidyl transfer step. Staying is a streptococcal antibiotic that was extracted from a terrestrial strain of S. griseus in the 1960s [34], but its antibacterial properties have recently been studied. Gentamicin has antibacterial effects on *S. pyogenes* and *Streptococcus agalactiae* [35]. Virginiae produces two streptococcal antibiotics, virginiamycin M_1 (VM_1) and virginiamycin S (VS) [28]. Both compounds show strong synergy

[36]. Virginiamycin is active against Gram-positive bacteria; it also regulates the natural flora in animals and acts as a growth stimulant. Due to the emergence of strains resistant to virginiamycin, its use has been restricted [30].

The chemically modified streptoquinupridine/dalfopristin is approved as an antibiotic for the treatment of complex skin infections caused by the vancomycin-resistant strain *E. faecium* and other gram-positive pathogens [30].

Natural metabolites also include cyclic lipopeptides and daptomycin, a compound produced by *Streptococcus roseosporus*, used to treat infections, skin infections, diabetic foot infections, and skin burns caused by Gram-positive bacteria; Patients who cannot tolerate other powerful antibiotics to treat these types of infections [37]. Daptomycin shows antibacterial activity against penicillin-resistant *Streptococcus pneumoniae*, vancomycin-resistant *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus* and other multi-drug resistant strains [38]. The mechanism of action of daptomycin involves irreversible binding to bacterial cell membranes, causing them to depolarize.

One of the recently discovered antibacterial action mechanisms is the inhibition of bacterial carboxylic acid synthesis. Fatty acids are necessary for bacteria to store energy and are close to the composition of cells. Selectively inhibit fatty acid synthesis. Bacteria make these two compounds highly active for recording. Positive bacteria, methicillin-resistant Staphylococcus aureus strains, and vancomycin-resistant *Enterococcus faecalis* [39].

Another new compound, pagamycin, comes from the soil Actinomycetes strain *Amycolatopsis* sp. [28]. It is a cyclic peptide antibiotic, and the MIC value of MRSA is higher than that of the VRE strain [28]. The mechanism of action includes rapid functional changes of bacterial membranes [40].

In 2009, Carlson et al. [41] isolated the results of tiradamycin C (6) (Figure 1) and D from *Streptomyces* sp., which showed strong activity against vancomycin-resistant *Enterococcus faecalis*. These compounds have been classified as dienoyl tetramic acid [41]. Tirandamycin disrupts the transcription process by inhibiting bacterial RNA polymerase [42]. Marinomycins are polyenes derived from Polychtiden and are compounds of the new genus Mani spora (MAR-2) [28]. Marinomycin A (7) (Figure 1) shows strong anti-tumor properties (for 6 to 8 melanoma cell lines) and antibacterial properties in vitro [28]. It represents a MIC value of 0.1-0.6 μM against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis* [43].

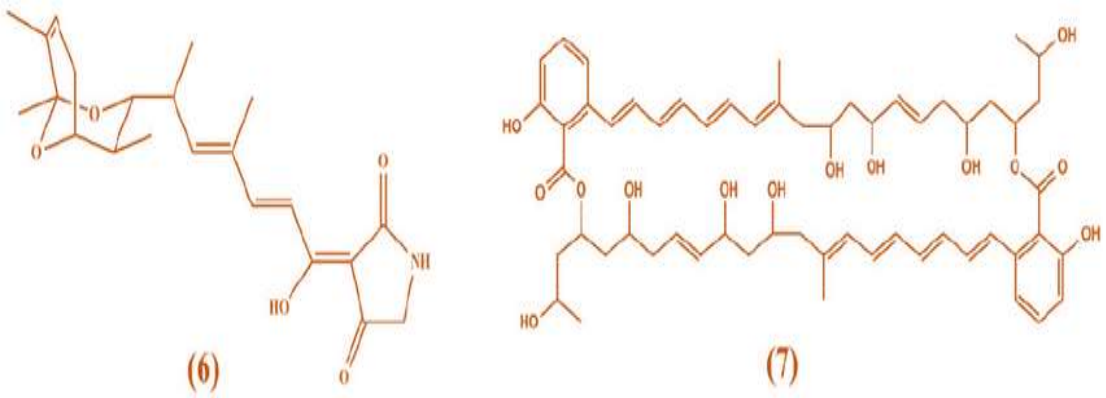

Figure- 1: The structure of tirandamycin C (6) and marinomycin A (7)

Verrucosipora is a rare Actinomycetes genus that produces a family of polycyclic poly ketides. One of these compounds, abismycin, was isolated from *Verrucosispora Maris* [44]. It has antibacterial properties and inhibits the biosynthesis of para-aminobenzoic acid [45]. Therefore, its activity destroys the biosynthesis of vitamin B earlier than the known synthetic sulfa drugs [46]. Abisomycin C shows effective antibacterial activity against Gram-positive bacteria, including multi-drug resistant strains of *Staphylococcus aureus* [45].

Albidopyrone is a new type of α-pyrone containing metabolites produced by *Streptomyces.* Isolated. Albidopyrone inhibits protein tyrosine phosphatase B [47]. *Micromonospora rifamycinica* produces rifamycin S and its geometric isomers, which are antibiotics against Gram-positive bacteria (including MRSA) [28].

The nucleoside amide antibiotics sansanmycin F and G were obtained from SS fermentation broth isolated from *Streptomyces* [28]. Sansanmicin F has weak antibacterial activity against *Pseudomonas aeruginosa.* Both of these compounds are effective against *Mycobacterium tuberculosis* [48].

Bafilomycin is a secondary metabolite of *Streptomyces* spp. It has antibacterial, antifungal, antitumor and antiparasitic effects [49]. Their antibacterial activity has been evaluated, so the data obtained indicate that the effect of these macrolide antibiotics on gram-positive bacteria belongs to Class A.

4. THE ANTICANCER ACTIVITY OF METABOLITES, NOW AND IN THE PAST

Actinomycin D is one of the main natural metabolites used to treat tumors [28]. It is isolated from the antibiotic S. Actinomycin D works by binding to the DNA in the transcription initiator complex and preventing the transcription extension of RNA polymerase [28]. Actinomycin D is still used to treat Wilms tumor in children, but its many side effects limit its use [30], [51]. Leomycin is another anticancer agent. This metabolite, *Streptococcus rotatum*, was approved by the FDA for clinical treatment in 1973 [52]. Mitomycin from *S. Caesptitosus* shows high anti-tumor activity. However, due to its toxicity, its therapeutic use is limited [53].

Marinomycin A, Daryamid C, Lucentamycine (A, B), Mansuramycine (13) and Tatrolon are other anti-tumor compounds obtained from strains of actinomycetes in marine sediments [54]. In 2007, Cho et al. [55] An isolated new compound, lucentamycin AD. Its chemical structure includes a peptide containing 3-methyl-4-ethylene proline. They were isolated from Nocardiopsis lucentensis marina [28]. Lucentamycin A and B show strong activity against HCT-116 human colon cancer cells [54], [55]. Mansuramycin AD is an isoquinoline quinone isolated from the marine strain Mei37 Streptomyces [28]. They show anti-tumor activity against cancer cells, breast cancer, melanoma, and prostate adenocarcinoma [54]. Tartrolon is a compound with a large dilactone structure and also has interesting biologically active properties. Tartrolon D (14) is derived from *Streptomyces* sp. (figure 2). It shows cytotoxicity to human tumor cell lines: lung (A549, large intestine (HT29) and breast (MDA-MB-231) [56].

Carboxamycin (15) is derived from *Streptomyces* sp. (Figure 2), showing anti-tumor activity against gastric adenocarcinoma (AGS), hepatocellular carcinoma (HepG2) and breast cancer (MCF7) and antibacterial properties against gram-positive bacteria. [51].

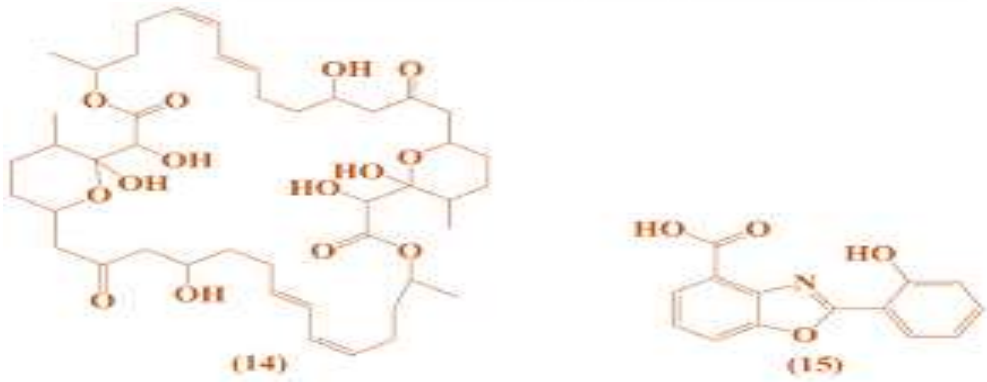

Figure- 2: The structure of tartrolon D (14) and carboxamycin (15)

5. ANTIFUNGAL ACTIVITY

Amphotericin B is one of the most famous metabolites of actinomycetes. It is a polyene macrolide antibiotic that was isolated from the broth of *Streptococcus nodus* in 1955 [57]. It is a broad-spectrum antifungal antibiotic, but its many side effects limit its clinical application. [57].

Two types of antifungal nucleosides can competitively inhibit fungal chitin synthase: Polytoxin and Nicomycin [58], [59]. Polytoxin is a secondary metabolite of *S. cacaoi var. asoensis* and has antifungal activity [28]. It also showed activity against plant pathogenic fungi (such as Alternaria kikuchiana, Picularia oryzae) in the 1960s [58]. Nicomycin (Nicomycin Z) is more effective against *Candida albicans* than polyoxin [28]. Nicomycin is produced by *S. tendae* and *S. anochromogenes*. Nicomycin was isolated from S. tendae in the 1970s and was found to be effective against Rhizopus cancer and Botrytis cinerea [58]. Nicomycin X and Z are peptidyl glycoside antibiotics, produced by *S. ansochromogenes* [28]. Nicomycin acts as a chitin synthase inhibitor in fungi and insects [60].

The water-absorbing bacteria are responsible for the production of rapamycin (sirolimus). Rapamycin was originally isolated from a soil-borne actinomycete strain on Easter Island [61]. Rapamycin has an antifungal effect on *Candida*. Compared with amphotericin B, it shows stronger antifungal properties in systemic candidiasis in mice [62]. Several secondary biologically active metabolites have been obtained from *Streptomyces* TK-VL_333 [28]. Among them, 1H-indole-3-carboxylic acid (T_1) has antifungal activity against *Candida albicans, Epidermophyton flocculus, Aspergillus niger* and *Fusarium oxysporum*. It also shows antibacterial activity [63].

6. ANTIPARASITIC PROPERTIES

Milbemycin is a 16-membered macrolide isolated from *Streptococcus hygroscopicus* subspecies *Aureolacrimosus* [28]. They have strong repellent, insecticidal and acaricidal properties, and have a wide range of activities [64].

Avermectins are antiparasitic compounds found in soil by S. avermitilis. Macrolides are effective against invertebrate parasites of cattle [65].

Two new compounds were isolated from *S. nanchangensis*: nanchangmycin, a polyether effective against chicken coccidia parasites; and the 16-membered macrolide melinomycin, which has antiparasitic activity close to that of avermectin [28]. Each product is active against harmful nematodes and insects [66].From the absolute antiparasitic activity of *S. axinelle*against *Trypanosoma brucei*, previously known tetromycin B and some structurally new tetromycin derivatives were isolated (Figure 3) [67].

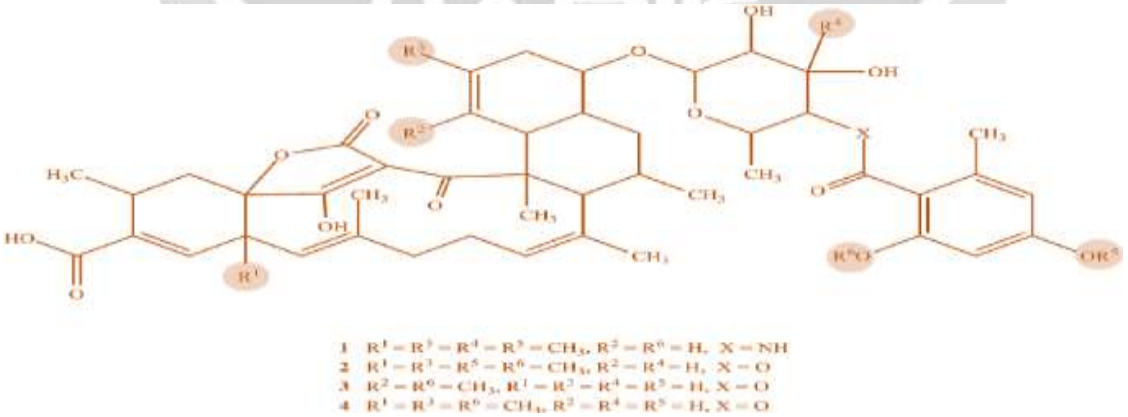

Figure- 3: Chemical structure of tetromycin

Valinomycin and butenolide are antiparasitic compounds derived from the genus *Streptomyces.* Valinomycin can be a cyclic depeptide isolated from various soil actinomycetes, such as *S. fullvissimus*, *S. roseochromogenes* or *S. griseus var. flexipartum* is similar to marine species [28]. Butenolide is an α, β-unsaturated lactone with anti-trypanosomal activity [68].

7. ANTIVIRAL PROPERTIES

In 1971, Takatsuki, Tamura, etc. [69] tunicamycin (TM) from the fermentation broth of *S. lyososuperficus* nov. sp. Later they were also isolated from strains of actinomycetes. Streptovirin was isolated from *S. griseoflavus* subspecies *Thuringiensis* [28]. Each compound has similar activity against enveloped viruses, and streptavidin is also an effective inhibitor of *Bacillus.* Corynetoxin was isolated from *Corynebacterium rathayi* in 1982 [58].

Recently, the relationship between the influenza virus JBIR-68 (25) and the new skeleton (5'-O-geranyl-5,6-dihydrouridine) has been identified from the genus *Streptomyces* [28]. significantly inhibits the growth of influenza virus; however, the mechanism of antiviral activity is unclear [70].

8. DISCUSSION

This research aims to isolate microorganisms, especially rare Actinomycetes, from mandatory niches, and ideally have high genetic potential to produce secondary metabolites. In a study conducted in soil samples taken from the Garden of Sathyabama University, Chennai, India 13 out of 22 [59%] Actinomycetes isolates showed potential antimicrobial activity against one or additional check bacteria and /or fungus [71]. In a study conducted in soil samples of various sites of Chambal territory and alternative components of Madhya Pradesh, India solely 5 out of 85 Actinomycetes isolates showed antimicrobial activity [72].

In a study, Actinomycetes isolated from soil samples of Jeddah and Al-Madina Al-Munawarah, Saudi Arabia showed antimicrobial activity against aureus *Staphylococcus, Escherichia coli, and Salmonella typhimurium* [73].

Ahmed et al.,2013 who screened soil microorganisms for antibiotic production and divulges that solely *Bacilli* species exhibited antibacterial activity of all bacteria isolated [74]. On agar media, cultural characteristics displayed by bacteria were accustomed to determine bacteria due to their specific and completely different growth patterns [75]. It has been reportable that *Bacillus* species and their reproductive structure forming bacteria carry genes for the assembly of antibiotics and breakdown of various carbon sources [76]. It has been reported that Bacitracin produced by *Bacillus* species inhibits each *E. coli and S. aureus* [76].

In a study fourteen *Bacillus* strains that produce antibiotics from the soil were identified [77]. For the synthesis of secondary metabolites Bacillus species are renowned for outstanding diversity each in its function and structure [78]. There is an argument with Aslim et al., 2002 who documented those strains of *Bacillus* had larger effects on gram-positive bacteria as compared to gram-negative bacteria [79].

In another study, 5 different pigments like green, orange, white, yellow, and brown were extracted from Actinomycetes isolates and were sublimate and tested for the antimicrobial activity that showed that each one extracted pigment inhibited the growth of *E. coli, Staphylococcus aureus, Bacillus subtilis,* and *Salmonella typhi* except the yellow pigment that showed inhibitory impact against solely gram-negative bacteria [80].

Kumari et al., [2013] study that the most effective genus of Actinomycetes that turns out antibiotic is *Streptomyces,* starch casein broth was found to be the foremost appropriate media for antibiotic production due to the environmental factors that affect the temporal arrangement and extent of production of antibiotics and technique of cultivation, such as carbon and nitrogen sources, oxygen tension, temperature, pH and alternative secondary metabolites.

9. CONCLUSION

At present, there is a demand to go looking out novel antimicrobial producing strains as a result of the pre-existing medication have unsuccessful due to the development of resistance among the microorganisms.

Secondary metabolites with antimicrobial activity are wide utilized in the treatment of infectious diseases. However, it is likely that most of the new metabolites of real bacteria isolated at intervals in the past 5-10 years have weaker biological activity than the old and recognized compounds. The MIC value of newly discovered antibacterial molecules isolated from Actinomycetes is likely to have reached a peak in the identification of antibiotics isolated in the 1950s and 1960s. From a numerical point of view, it is difficult to find compounds with high antibacterial activity. For example, among the 10 million strains of Actinomycetes detected and isolated from soil samples, one strain can produce daptomycin, 50 types of

erythromycin, 150 types of vancomycin, 1,000 types of tetracycline and actinomycin and 100,000 streptomycin [81]. So far, the main types of biologically active compounds have been separated from the soil due to the easy availability of the environment. The current analysis seeks new strains from less accessible places, like seas and oceans.

This study was an effort to isolate versatile strains of Actinomycetes and to examine their antimicrobial activity. The isolates that showed broad-spectrum activity against the check microorganisms could be thought about as candidates concerning checking out potential antimicrobial compounds.

10. ACKNOWLEDGEMENT

The authors are thankful to the IAMR (Institute of Applied Medicines and Research) college, Ghaziabad, Uttar Pradesh for approving this topic.

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