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A Review of Antimicrobial Activity of Actinomycetes Isolated from Soil of Different Area of NCR

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Abstract

The purpose of the study was to resolve the crucial requirement to discover new antibiotics in recent Era because increase in toxicity by various Antagonistic bacterial and fungal species. Antibiotics produce from natural sources like soil. As soil contains different macroscopic as well as microscopic species, some microscopic species helps in producing antibiotics cross-streak method where used to check antagonistic activity of isolated actinomycetes against test organism. On the other hand, Solid-state fermentation and crude extraction where used for the production of antibiotics from isolates. As present investigation soil sample has been collected from different niches near NCR. The preliminary screening bacterial isolates were identified as Pseudomonas fluorescence, Streptomyces griseus, Bacillus anthracis, Bacillus subtilis, activity against gram positive and gram negative bacteria for Aspergillus niger, Penicillium griseofulvin from the soil sample. As antimicrobial resistance (AMR) hikes more attention as biggest hazardous to prevention and treatment of an increasing number of infections.

Keywords: *Solid state fermentation, crude extraction, antagonistic activity, streak methods, screening*

1.INTRODUCTION

Identification of such microorganisms raises a possibility of finding noble antibiotics with a potential clinical use [1]. Antibiotics are a natural substance of biological synthetic or semi-synthetic origin [2]. In 1928, the term antibiotics arose as antibiosis in French microbiological literature perhaps as later in 1942 the term antibiotics was introduced by Waksman. The most important antibiotics includes aminoglycosides, penicillin, Macrolides, Glycopeptides,Cephalosporins, and Tetracyclines [3]. According to the international centre of information on antibiotics, 338 species of fungi are able to produce antibiotics and these fungi compete against different other microbes and may include antimicrobial production [4].

As microbial population in soil depends upon various factors includes pH, temperature,Salt, Concentration, carbon source etc. while growing in soil microorganism compete with each other for growth advantage and evolve a mechanism to win other organism [5]. Each year nearly 500 antibiotics were found inwhich 60% of antibiotics are obtained from the soil. A Teaspoon of soil contains 10millions to 1billions bacteria active in each bit of the soil. Most of the antibiotics producers used today are the soil microbes. Bacterial pathogens (e.g., *Staphylococcus aureus, Mycobacterium tuberculosis*etc.) have been reported to frequently acquire resistance to antibiotics, exhibit multi-drug resistance in bacteria that has raised a serious concern among scientific community. Highlight a greater need to find more antibiotics as well as alternative antimicrobial substance [6].

The ability of actinomycetes to produce a variety of bio active substance has been known for long time and being utilize in research andsynthesize bio active compounds in numerous academic and industrial laboratories. These studies have tremendous impact on application against many human infections [7].

Actinomycetes are gram-positive,Saprophytic, Filamentous bacteria [1], with high guanine+ cytosine content of over 55% [8] that are responsible for the production of over 20,000 natural products extensively used in pharmaceutical and Agrochemical industry [9]. The impervious problem demands to reach new antibacterial agents effective against resistance pathogenic bacteria. So we need to screen more and more Actinomycetes from different niches for antimicrobial activity in the hope of getting some new actinomycetes strains that produce antibiotics which have not been discovered yet and are active against drug resistance. Actinobacterial strains mainly derive from soil [10] but they also abundantly present in seas and oceans [11] whereas, extreme habitats such as caves [12], deserts [13] or Antarctica ecosystemsdesignated as precious source of actinomycetes producing novel metabolites of pharmacological importance [14]. Genome sequencing can also be applied to detect the genes responsible for production of secondary metabolites besides those that were isolated

under standard cultivation conditions [15]. There, many methods have been developed to activate the antibacterial secondary metabolism, posses combined cultures and use of goadsporins [16]. An operative action in development of strains with enhanced secondary metabolism was established with the recent advancement of whole-genome sequencing, systems biology and genetic engineering. However, the "-omics" technologies (genomics, transcriptomics, proteomics and metabolomics) together with bio informatics are especially useful tools in the saturated huge production of actinomycetes secondary metabolites. Metabolic engineering of actinomycetes as several novel in silico methods to automate the scanning of secondary metabolism in bacterial genome (e.g., antibiotics & secondary metabolite Analysis Shell, anti Smash) had been introduced [17].

Natural products play a predominant role in the development of new therapeutic agents [18]. Actinobacteria designated the protruding group of microorganism, which produce plant based compounds. Majority of these molecules emerged from *Streptomyces* genus [19].

Antibiotic	Structural class	Producing species	Antibiotic spectrum	Reference
Lassomycin	Cyclic peptide	*Lentzea kentukyensis*	M.tuberculosis	[20]
Anthracimycin	Tricarboxilic	*Streptomyces sp.*	Gram positive	[21]
Salinamide F	Depsipeptide	*Streptomyces sp.*	Gram positive/negative	[15]
Taromycin A	Lipopetide	*Saccharomonospora sp.*	Gram positive	[22]
Enterocin	Polyketide	*Salinispora pacifica*	Gram positive	[23]
Diflustatin A	Angucycline	*Micromonospora rosaria*	Gram positive	[24]

The marine environment has been traditionally another source of new Actinomycetes. Their isolation programs have ensured a continued discovery of new strains that produce new compounds or new analogs with biological activity.

Here, the secondary metabolites of Actinobacteria, which excluded antibacterial, Antifungal, Antiviral properties which plays a vital role in living niches.

2.Antibacterial activity

In the recent Era, Antibiotics confrontation of microorganism is one of the biggest ultimatum to universal health, dietary needs &development.

2.1 Spirotetronate compounds

Among novel molecules that were reported since 2011 is maklamicin, a new spirotetronate- class polyketide. It is a poly cyclic compound from the culture extract of endophytic Micromonospora sp. Maklamicin showed potent antimicrobial activities against gram- positive bacteria, including *Micrococcus luteus, Bacillus subtilis, Bacillus cereus, Staphylococcus aureus* with MIC values of 0.2,1.7,6.5,and 13µg/ml,respectively and lower activity against *Candida albicans* (MIC=50µg/ml).the compound showed moderate cancer cell cytotoxicity [25]. Another newly discovered spirotetronate antibiotics of polyketide origin is nomimicin, which was isolated from the culture extract of *Actinomadura sp.* TP-A0878. The molecules showed antimicrobial activities against M.luteus, *C.albicans* and *Kluyveromyces fragilis* with MIC values of 6.3,12.5 and 12.5µg/ml, respectively. Here nomimicin displayed weak cytotoxicity against human cancer cells [26].
Antibacterial and Antitumor activities were demonstrated by lobophorin F, a new spirotetronate molecules isolated from *Streptomyces sp.* SCSIO 01127. The MIC values towards *Bacillus thuringiensis, S.aureus* displayed 2,8 µg/ml [27].

2.2Tetracenediones

Novel polyketides named formicamycins A-L were discovered as secondary metabolite products of the *S.formicae KY5* strain isolated from Kenyan ants *Tetraponera penzigi.* Formicamycin J inhibit the growth of the clinically relevant pathogens- MRSA and vancomycin-resistant *Enterococcus faecium* (VRE) with MIC of 0.41 and 0.82 µg/ml, respectively. Other tested formicamycins were less potent.

2.3Lactams

Streptomyces zhaozhouensis CA- 185989 from marine sediments collected near Utonde, Equatorial Guinea was found to produce new bio active secondary metabolites from the class of poly cyclic tetramic acid macrolactams, isoikarugamycin and 28-N-methylikarugamycin. These novel compounds demonstrated potent antibacterial and antifungal activities and were shown to be active towards *S.aureus, C.albicans and A.fumigatus* presenting MICs between 1 and 8 µg/ml [28].

2.4 Xanthones

Antimicrobial substance is buanmycin, a new pentacylic xanthone isolated from the culture of marine *Streptomyces*, strain from a tidal mud flat in Buan (Republic of Korea). Buanmycin was shown not only to display strong inhibitory activity against both Gram-positive (*S.aureus, B.subtilis, k.rhizophila)* and Gram-negative bacteria (*Salmonella enterica , P.hauseri*) with MIC Values 0.42-12.5 µg/ml. Four novel xanthones (citreamicin θ A and citreamicin θ B, citreaglycon A and dehydrocitreaglycon) were obtained by. From[29] a marine *Streptomyces caelestis* strain. They also showed cytotoxicity against HeLa cells [30].

3.Antifungal activity

Amongthe novel antifungal secondary metabolites produced by Actinomycetes is sceliphrolactam. It has shown potent antifungal activity against amphotericin B-resistant*C. albicans* with MIC of 4µg/ml [31].

Neomaclafungin A was the main metabolite from the fermentation broth of *Actinoalloteichus* sp. that was isolated from the marine sediment collected from Usa Bay, Kochi Prefecture, Japan. Besides neomaclafungin A, also other neomaclafungins (B-I) were isolated, but in lower concentrations. All novel compounds possess a macrolide ring similar to that of Maclafungin, but with different moieties substituted in C-24 and C-33 position. The MIC values for these new Neomaclafungins (A-I) against *dermatophyte Trichophyton mentagrophytes* were between 1-3 µg/ml [32].

Other three novel members (15-glycidylfilipin III; 16α, 17α- epoxyfilipan V; 16β, 17β- epoxyfilipin V) of the polyene macrolide class were isolated from the cultures of a soil actinomycete, *S. lavenduligriseus* . Only 15-glycidylfilipin III showed significant inhibition of *C. albicans* mycelia growth. with MIC value of 6.25 µg/ml compared to MIC =3.13 µg/ml for the control, nystatin. The other compounds displayed considerably weaker fungicidal effects which ruled out the hypothesis that microbial secondary metabolites with an epoxide function are more toxic or have stronger cytostatic properties than analogs without the epoxide function [33].

In 2017, a Streptomyces sp. strain was isolated from a soil sample collected from a coal mine at a depth of 20 cm in Nanchang, Jiangxi, People's Republic of china. Six new cyclic octa depsipeptides, enduspeptides A-F, were produced by this strain. The most potent antifungal activities against C. glabrata with IC_{50} values of 5.33, 1.72 and 8.13 µg/ml were shown by endopeptides A, B and C, respectively [34].

4.Antiviral activity

The study of marine Actinomycetes strain, *Streptomyceskaviengensis*, isolated from the coast of New Ireland enabled Raveh and coworkers to identify a novel metabolite with significant antiviral activity. The compound, antimycin A1a, was found to be an antimycin A derivative and shows high potency against the Western equine encephalitis virus with IC_{50} value of less than 4Nm and selectivity index of greater than 550. Analysis of its mechanism of action revealed distruption of mitochondrial electron transport and pyrimidine biosynthesis. Moreover, the previously known antimycin A demonstrated a broad spectrum activity towards a wide range of RNA viruses, including members of the Togaviridae, Flaviviridae, Bunyaviridae, Paramyxoviridae, and Picornaviridae families[35].

Ahmpatinin Bu is a linear peptide and a novel pyrrolidine derivative with an unusual amino acid, 4-amino-3-hydroxy-5-(4-methoxyphenyl) pentanoic acid. It was produced by Streptomyces sp. Ahmpatinin iBu showed significant inhibitory activity against HIV-1 protease resulting in IC_{50} = 1.79 nM[36].

HIV-1 protease is essential in the life cycle of HIV and has been used as a promising target for AIDS therapy. In 2013, a new inhibitor of HIV-1 protease, 4862F was isolated from the culture broth of Streptomyces albosporus. It was identified as N,N,N-(trimethylated)- Tyr-L-Leu-L-Val-L-Leu-(dehydrated)-His and found to inhibit HIV-1 protease with an IC50 of 15.26 nM.

Daptomycin (IC_{50} = 1µM) and Nanchangmycin (IC_{50} = 0.1µM) showed a previously not described anti-ZIKV activity. Both of these drugs are bio active secondary products of Streptomyces spp., for which antiviral activity was unrecognized before. Daptomycin is a lipopeptide antibiotic used in the treatment of infections caused by gram-positive bacteria and it was found in the culture broth of *S. roseosporus.* In turn, nanchangmycin is produced by *S. nanchangensis* and was shown to have insecticidal activity against silkworms and antibacterial activity in vitro[37].

5.Discussion

Actinomycetes were extensively present in the soil that were easily isolated from the sample. A lot of actinomycetes were isolated that were collected from different region near NCR. Maximum number of colonies was obtained from the sample. Tested strains showed high activity against Gram positive bacteria,moderate activity against Gram-negative bacteria *C.violaceum and E.coli(ToLC),* yeast and fungus and low activity against gram –negative bacteria , *P.aeruginosa and E.coli(DSM 1116).* This results from the present study are in agreement with

many studies [38]. They reported that actinomycetes usually show good activity against Gram-positive bacteria but lacking activity against Gram –negative bacteria. The reason for different sensitivity could be described by the morphological differences of their outer membrane [39]. There is also the possibility that Gram-negative bacteria might have acquired the resistant genes from the neighbouring resistant bacterial cells in the previous environment [40].

In the study shows that Bacillus species with the highest number of isolates produces clear zone of inhibition against test microorganism. (Ahmed, 2013) who screened soil microorganism for antibiotic production and reveals that *Bacillus species* exhibited antibacterial activity of all bacteria isolated.It has been reported that bacitracin produced by *Bacillus* species inhibits both *E.coli* and *S.aureus*[41] identified 14 isolates of antibiotics producing *Bacillus* species from soil. There is an argument with [42] who documented that strains of *Bacillus* had greater effects on Gram –positive bacteria as compared to Gram –negative bacteria.

Collected several wild type *B. Subtilis*, having the potential to produce more than a dozen of antibiotics[43]. *Bacilli* are predominant soil bacteria widely used in industrial application, particularly antibiotics production having medically. Agriculturally and veterinary importance [44]. Majority of *Aspergillus* strains shows antibiotic activity against beta lactamase producing *E.coli*, methicillin-resistant *S.aureus*, *Enterococcus faecalis and Candida albicans* [45] . Many *Aspergillus* species have been able to produce antioxidants [46].As per report that some *Aspergillus* species are utilized industrially for various enzymes production [47]. The study upto yet now states that antibiotics producing bacteria and fungi are novel and have commercial value.

6.Conclusion

The actinomycetes were isolated from soil sample of NCR regions registered that they have antibacterial, Antiviral and antifungal properties. Some antimicrobial properties display cytotoxicity towards distinct tumor cell lines. Some compound forming Actinobacteria include: *Amycolatopsis, Pseudonocardia, Kibdelosporangium, Actinoalloteichus*, (Family Pseudonocardiaceae*), Micromonospora*(Family Micromonosporaceae*),Actinomadura, Actinoallomurus* (family Thermomonosporaceae*), Actinokineospora* (family Actinosynnemataceae*),Kocuria* (family Micrococcaceae*),Actinomyces*(family Actinomycetaceae*), Kribella*(family Nocardioidaceae) and *Nocardia* (family Nocardiaceae). The massive amount of novel natural productwas obtained by bacteria.

All agents demonstrate the highest prospects of actinomycetes as leader promoter of novel bioactive molecules, and valued in clinical sector in terms of drug development. As use of contemporary strategy using the "-omics "technology with bioinformatics, are valid prospective in searching for novel bioactive compounds. Whereas paying attention towards the education of society on the proper handling of antibiotics in Agriculture sector as well as treatment of animal diseases and human.

Different actinomycetes mediates different biochemical,morphological & chemical nature that plays a dissimilar role towards test organism, whereas some inhibits and other favours the growth. Further studies are in progress.

REFRENCES

1. Berdy., J. (2005). Bioactive microbial metabolites. The Journal of antibiotics, 58(1), 1-26.

2. Nikodinovic, J., Barrow, K. D., & Chuck, J. A. (2003). High frequency transformation of the amphotericin-producing bacterium Streptomyces nodosus. Journalof microbiological methods, 55(1), 273-277.

3. Demain., A. L. (2009). Antibiotics: natural products essential to human health. Medicinal research reviews, 29(6), 821-842.

4. Hyde., K. D. (2001). Increasing the likelihood of novel compound discovery from filamentous fungi. Bio-exploitation of filamentous fungi, 77-91.

5. Hibbing, M. E., Fuqua, C., Parsek, M. R., & Peterson, S. B. (2010). Bacterial competition: surviving and thriving in the microbial jungle. Nature reviews microbiology, 8(1), 15-25.

6.Donadio, S., Carrano, L., Brandi, L., Serina, S., Soffientini, A., Raimondi, E., ... & Gualerzi, C. O. (2002). Targets and assays for discovering novel antibacterial agents. Journal of biotechnology, 99(3), 175-185.

7.Khanna, M., Solanki, R., & Lal, R. (2011). Selective isolation of rare actinomycetes producing novel antimicrobial compounds. Int J Adv Biotechnol Res, 2(3), 357-75.

8.Ventura, M., Canchaya, C., Tauch, A., Chandra, G., Fitzgerald, G. F., Chater, K. F., & van Sinderen, D. (2007). Genomics of Actinobacteria: tracing the evolutionary history of an ancient phylum. Microbiology and molecular biology reviews, 71(3), 495-548.

9.Manteca , A., Alvarez, R., Salazar, N., Yagüe, P., & Sanchez, J. (2008). Mycelium differentiation and antibiotic production in submerged cultures of Streptomyces coelicolor. Applied and environmental microbiology, 74(12), 3877-3886.

10. Guo, X., Liu, N., Li, X., Ding, Y., Shang, F., Gao, Y., ... & Huang, Y. (2015). Red soils harbor diverse culturable actinomycetes that are promising sources of novel secondary metabolites. Applied and Environmental Microbiology, 81(9), 3086.

11.Hassan, H. M., Degen, D., Jang, K. H., Ebright, R. H., & Fenical, W. (2015). Salinamide F, new depsipeptide antibiotic and inhibitor of bacterial RNA polymerase from a marine-derived Streptomyces sp. The Journal of antibiotics, 68(3), 206-209.

12. Jiang, Z. K., Guo, L., Chen, C., Liu, S. W., Zhang, L., Dai, S. J., ... & Sun, C. H. (2015). Xiakemycin A, a novel pyranonaphthoquinone antibiotic, produced by the Streptomyces sp. CC8-201 from the soil of a karst cave. The Journal of antibiotics, 68(12), 771-774.

13. Goodfellow, M., Busarakam, K., Idris, H., Labeda, D. P., Nouioui, I., Brown, R., ... & Bull, A. T. (2017). Streptomyces asenjonii sp. nov., isolated from hyper-arid Atacama Desert soils and emended description of Streptomyces viridosporus Pridham et al. 1958. Antonie van Leeuwenhoek, 110(9), 1133-1148.

14. Singh, B. P., Gupta, V. K., & Passari, A. K. (Eds.). (2018). Actinobacteria: Diversity and Biotechnological Applications: New and Future Developments in Microbial Biotechnology and Bioengineering Elsevier.

15. Thong, W. L., Shin-ya, K., Nishiyama, M., & Kuzuyama, T. (2016). Methylbenzene-containing polyketides from a Streptomyces that spontaneously acquired rifampicin resistance: Structural elucidation and biosynthesis. Journal of natural products, 79(4), 857-864.

16. Onaka, H. (2017). Novel antibiotic screening methods to awaken silent or cryptic secondary metabolic pathways in actinomycetes. The Journal of antibiotics, 70(8), 865-870.

17. Medema, M. H., Blin, K., Cimermancic, P., de Jager, V., Zakrzewski, P., Fischbach, M. A., ... & Breitling, R. (2011). antiSMASH: rapid identification, annotation and analysis of secondary metabolite biosynthesis gene clusters in bacterial.

18. Newman, D. J., & Cragg, G. M. (2016). Natural products as sources of new drugs from 1981 to 2014. Journal of natural products, 79(3), 629-661.

19. Barka, E. A., Vatsa, P., Sanchez, L., Gaveau-Vaillant, N., Jacquard, C., Klenk, H. P., ... & van Wezel, G. P. (2016). Taxonomy, physiology, and natural products of Actinobacteria. Microbiology and molecular biology reviews: MMBR, 80(1), 1.

20.Gavrish, E., Sit, C. S., Cao, S., Kandror, O., Spoering, A., Peoples, A., ... & Lewis, K. (2014). Lassomycin, a ribosomally synthesized cyclic peptide, kills Mycobacterium tuberculosis by targeting the ATP-dependent protease ClpC1P1P2. Chemistry & biology, 21(4), 509-518.

21. Jang, K. H., Nam, S. J., Locke, J. B., Kauffman, C. A., Beatty, D. S., Paul, L. A., & Fenical, W. (2013). Anthracimycin, a potent anthrax antibiotic from a marine-derived actinomycete. Angewandte Chemie, 125(30), 7976-7978.

22. Yamanaka, K., Reynolds, K. A., Kersten, R. D., Ryan, K. S., Gonzalez, D. J., Nizet, V., ... & Moore, B. S. (2014). Direct cloning and refactoring of a silent lipopeptide biosynthetic gene cluster yields the antibiotic taromycin A. Proceedings of the National Academy of Sciences, 111(5), 1957-1962.

23. Bonet, B., Teufel, R., Crüsemann , M., Ziemert, N., & Moore, B. S. (2015). Direct capture and heterologous expression of Salinispora natural product genes for the biosynthesis of enterocin. Journal of natural products, 78(3), 539-542.

24. Yang, J., Yang, Z., Yin, Y., Rao, M., Liang, Y., & Ge, M. (2016). Three novel polyene macrolides isolated from cultures of Streptomyces lavenduligriseus. The Journal of antibiotics, 69(1), 62-65.

25. Igrashi Y, Ogura H, Furihata K, oku N, Indananda C thamdhaipenet A 2011. Maclamycin, an antibacterial polyketide from an endophytic. micromonospora spp J Nat producer 74(4) :670-674.

26. Igarashi, Y., Iida, T., Oku, N., Watanabe, H., Furihata, K., & Miyanouchi, K. (2012). Nomimicin, a new spirotetronate-class polyketide from an actinomycete of the genus Actinomadura. The Journal of antibiotics, 65(7), 355-359.

27. Niu, S., Li, S., Chen, Y., Tian, X., Zhang, H., Zhang, G., ... & Zhang, C. (2011). Lobophorins E and F, new spirotetronate antibiotics from a South China Sea-derived Streptomyces sp. SCSIO 01127. The Journal of antibiotics, 64(11), 711-716.

28. Lacret, R., Oves-Costales, D., Gómez, C., Díaz, C., De la Cruz, M., Pérez-Victoria, I., ... & Reyes, F. (2015). New ikarugamycin derivatives with antifungal and antibacterial properties from Streptomyces zhaozhouensis. Marine drugs, 13(1), 128-140

29. Liu, X., Gan, M., Dong, B., Zhang, T., Li, Y., Zhang, Y., ... & Si, S. (2013). 4862F, a new inhibitor of HIV-1 protease, from the culture of Streptomyces I03A-04862. Molecules, 18(1), 236-243.

30. Liu, L. L., Xu, Y., Han, Z., Li, Y. X., Lu, L., Lai, P. Y., ... & Qian, P. Y. (2012). Four new antibacterial xanthones from the marine-derived actinomycetes Streptomyces caelestis. Marine drugs, 10(11), 2571-2583.

31. Oh, D. C., Poulsen, M., Currie, C. R., & Clardy, J. (2011). Sceliphrolactam, a polyene macrocyclic lactam from a wasp-associated Streptomyces sp. Organic letters, 13(4), 752-755.

32. Sato, S., Iwata, F., Yamada, S., & Katayama, M. (2012). Neomaclafungins A–I: oligomycin-class macrolides from a marine-derived actinomycete. Journal of natural products, 75(11), 1974-1982.

33. Yang, J., Yang, Z., Yin, Y., Rao, M., Liang, Y., & Ge, M. (2016). Three novel polyene macrolides isolated from cultures of Streptomyces lavenduligriseus. The Journal of antibiotics, 69(1), 62-65.

34. Chen, Y., Liu, R. H., Li, T. X., Huang, S. S., Kong, L. Y., & Yang, M. H. (2017). Enduspeptides AF, six new cyclic depsipeptides from a coal mine derived Streptomyces sp. Tetrahedron, 73(5), 527-531.

35. Raveh, A., Delekta, P. C., Dobry, C. J., Peng, W., Schultz, P. J., Blakely, P. K., ... & Miller, D. J. (2013). Discovery of potent broad spectrum antivirals derived from marine actinobacteria. PloS one, 8(12), e82318.

36. Chen, M. H., Chang, S. S., Dong, B., Yu, L. Y., Wu, Y. X., Wang, R. Z., ... & Si, S. Y. (2018). Ahmpatinin i Bu, a new HIV-1 protease inhibitor, from Streptomyces sp. CPCC 202950. RSC advances, 8(10), 5138-5144.

37. Barrows, N. J., Campos, R. K., Powell, S. T., Prasanth, K. R., Schott-Lerner, G., Soto-Acosta, R., ... & Garcia-Blanco, M. A. (2016). A screen of FDA-approved drugs for inhibitors of Zika virus infection. Cell host & microbe, 20(2), 259-270.

38. Cwala ., Z., Igbinosa, E. O., & Okoh, A. I. (2011). Assessment of antibiotics production potentials in four actinomycetes isolated from aquatic environments of the Eastern Cape Province of South Africa. African Journal of Pharmacy and Pharmacology, 5(2), 118-124.

39. Pandey., A., Ali, I., Butola, K. S., Chatterji, T., & Singh, V. (2011). Isolation and characterization of Actinomycetes from soil and evaluation of antibacterial activities of Actinomycetes against pathogens. International journal of applied biology and pharmaceutical technology, 2(4), 384-392.

40. Reller., L. B., Weinstein, M., Jorgensen, J. H., & Ferraro, M. J. (2009). Antimicrobial susceptibility testing: a review of general principles and contemporary practices. Clinical infectious diseases, 49(11), 1749-1755.

41. Hassan., S. A., Hanif, E., & Zohra, R. R. (2014). Isolation and screening of soil bacteria for potential antimicrobial activity. Fuuast Journal of Biology, 4(2), 217-219.

42. Aslim, B., Sağlam, N., & Beyatli, Y. (2002). Determination of some properties of Bacillus isolated from soil. Turkish Journal of Biology, 26(1), 41-48.

43. Sonenshein , A. L., Hoch, J. A., & Losick, R. (Eds.). (2002). Bacillus subtilis and its closest relatives: from genes to cells.

44. Akbar l., A., Ali, I., & Anal, A. K. (2016). Industrial perspectives of lactic acid bacteria for biopreservation and food safety. Journal of Animal & Plant Sciences, 26(4).
45. Svahn , K. S., Göransson, U., El-Seedi, H., Bohlin, L., Larsson, D. J., Olsen, B., & Chryssanthou, E. (2012). Antimicrobial activity of filamentous fungi isolated from highly antibiotic-contaminated river sediment. Infection ecology & epidemiology, 2(1), 11591.
46. Miyake ., Y., Ito, C., Itoigawa, M., & Osawa, T. (2009). Antioxidants produced by Eurotium herbariorum of filamentous fungi used for the manufacture of karebushi, dried bonito (Katsuobushi). Bioscience, biotechnology, and biochemistry, 73(6), 1323-1327.
47. Gugnani ., H. C. (2003). Ecology and taxonomy of pathogenic aspergilli. Front Biosci, 8(1-3), 346.