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Diversified role and applications of marine actinomycetes in the field of biology

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ABSTRACT

Actinomycetes are the most profitable and biotechnologically valued prokaryotes representing the genera consisting of *Streptomyces*, *Arthrobacter*, *Actinomyces*, *Cornyebacterium*, *Micrococcus*, *Micromonospora* and other diverse species of microorganisms. Actinomycetes represent a group of one of the most powerful secondary metabolite producers which possess a wide range of biological activities. *Streptomyces*, an important genus under actinomycetes, alone serves as the huge producer of a number of biologically active molecules. This genus possesses a huge potential of synthesizing various different and novel active metabolites. Due to the gradual reduction of the chances of isolation of novel compounds within *Streptomyces* coming from terrestrial environs resulting in the increase of resistant pathogenic microorganisms, marine actinomycetesmay form a platform for novel drug synthesis, which in-turn may form an extraordinary tool for combating a wide range of resistant microbes. The role of marine actinomycetes extends to diverse fields such as antibiotic production, production of antibacterial and antifungal compounds, synthesis of enzymes and enzyme inhibitors, synthesis of anticancer drugs and various other lifesaving molecules. Marine actinomycetes also play an important role in biofouling and nanoparticle synthesis. Thus speakingsuccinctly, marine actinomycetes are biologically very important as they serve their useful purpose in various fields of biology.

***Keywords*:** Marine actinomycetes; Biologically active metabolites, Novel compounds, Resistant pathogenic microorganisms, Biofouling, Nanoparticles

1. INTRODUCTION

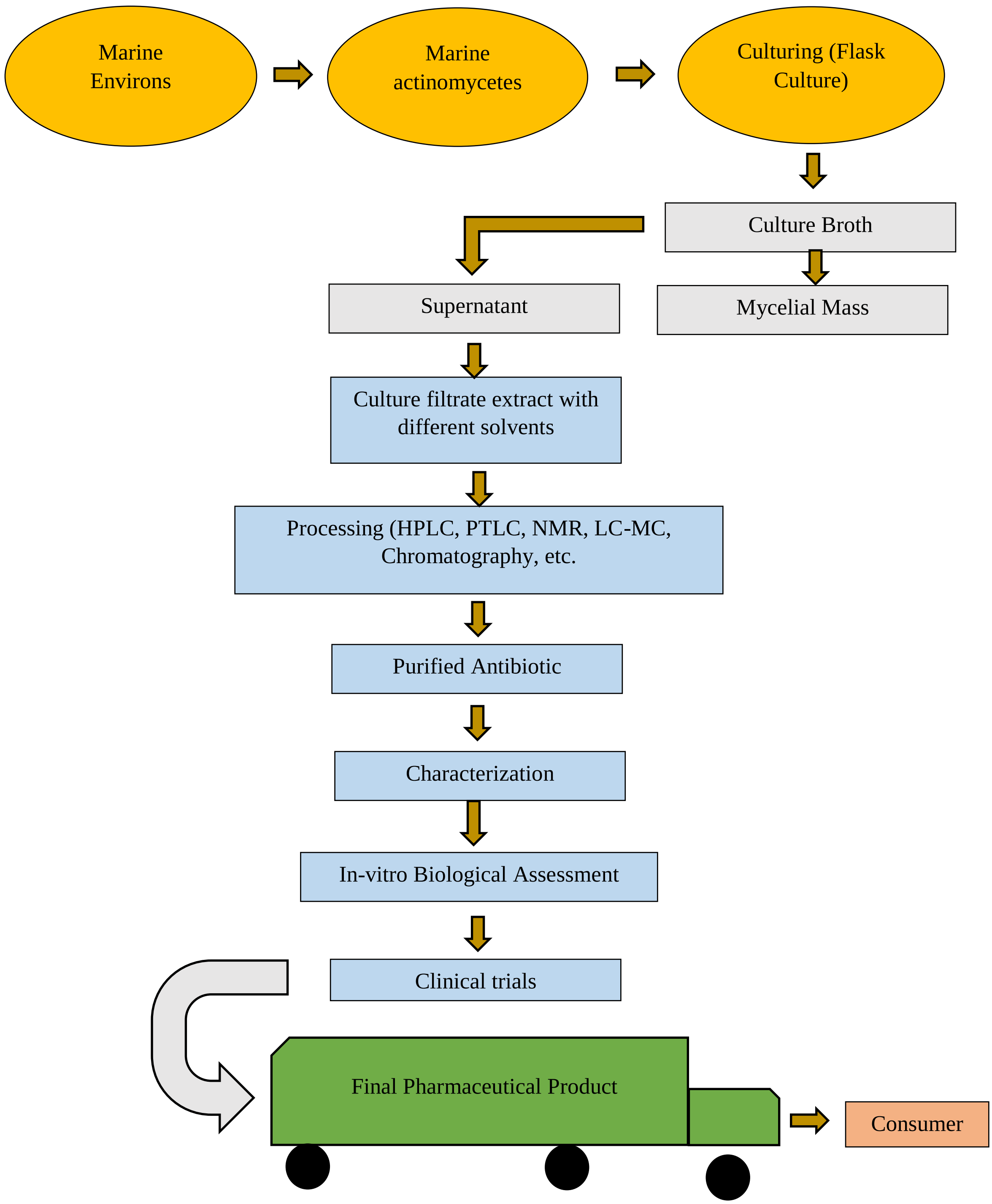

Figure 1. Flow chart showing the actinomycetes cultured to synthesize a pharmaceutical product

Being the richest inhabitant of microorganisms, marine biosphere represents an unreached section of opportunity and moreover 70% of the earth's surface is covered by oceans. Marine microbes are rapidly evolving as important and novel sources of various biologically active compounds and hence are receiving a great interest for their considerable benefits. Due to the fact that the marine environment is saline in nature, it can be a pivotal source for rare and novel microbial products. Accompanied by other microbes, actinomycetes as well can play a substantial role in various areas such as pharmaceutical and medical industries, because of their capability to produce various biologically active compounds [1,2].

Actinomycetes are a class of gram positive bacteria prevailing all over the globe, being nearest to bacteria in abundance and playing an important role in producing diverse range of secondary metabolites such as antibiotics, anticancer and antitumor agents, enzymes and various other important products. Marine actinomycetes, among various other microbes, have played an important role in being the greatest source of novel compounds [3,4]. Due to the fact that marine environment comprises of an enormous treasure of resources, marine actinomycetes play an important role by being an important part of it. Apart from this fact, marine actinomycetes differ considerably from their terrestrial correlatives because of different environmental conditions prevailing in a marine environment, hence they can be a source of different and novel compounds [5,6].

Actinomycetes have played an important role in the development of a large number of bioactive compounds, which after isolation, processing and characterization have been transformed into drugs for treating various diseases in both humans and animals. Keeping this fact in view, actinomycetes are considered to be the effective sources for the production of various antibiotics and other biologically active compounds. Each strain of actinomycetes has the innate capability of producing approximately around 10-20 secondary metabolites [7]. Actinomycetes are extraordinary producers of antibiotics and among actinomycetes the major role is played by*Streptomyces,* which alone represent an outstanding 80% of the natural products produced by actinomycetes [8]. *Streptomyces* have been a source to various analytics, including anti-bacterial, anti-fungal and anti-cancer drugs.*Streptomyces* accompanied by actinomycetes keep maintaining the pace as a source of novel metabolites exhibiting various biological activities such as anti-infectant and anti-cancer activity, apart from being the source of various other pharmaceutically useful compounds [9]. Fig. 1 displays the general process of synthesis of a pharmaceutical compound from actinomycetes.

In this review, we have focused on the applications of marine actinomycetes and the areas where they play an important role.

2. MARINE ACTINOMYCETES AND THEIR APPLICATIONS IN DIVERSE BIOLOGICAL FIELDS

Actinomycetes in general and marine actinomycetes in particular have their applications over vast range of areas, be it the synthesis of a biologically active product, synthesis of a drug to cure diseases, synthesis of enzymes, synthesis of antibacterial, antifungal and anticancer products or their role in biofouling. All these areas are very important in today's world. The role of marine actinomycetes and their applications in these particular areas are discussed hereunder.

2. 1. Synthesis of bioactive secondary metabolites

Actinomycetesare the most cost-effective and biologically valuable prokaryotes representing a genera consisting of *Streptomyces*, *Actinomyces*, *Arthrobacter*, *Cornyebacterium*, *Frankia*, *Micrococcus* and various others. Actinomycetesrepresent a group of one of the most dynamic and powerful producers of secondary metabolites possessing widely different biological activities [10-13]. *Streptomyces* represents a genus which alone serves as a source of vast number of biologically active molecules.Fig. 2 depicts the different biological activities of the secondary metabolites produced by the genus *Streptomyces*. This genus possesses huge potential as a source of various secondary active metabolites. Due to the gradual reduction of the chances of isolation of novel compounds within *Streptomyce*s coming from terrestrial environs, it has resulted in an increasedresistance to pathogens [14,15]. Marine actinomycetes may form a platform for novel drug synthesis which in turn may form an extraordinary tool for combating a wide spectrum of resistant microbes [16,17].

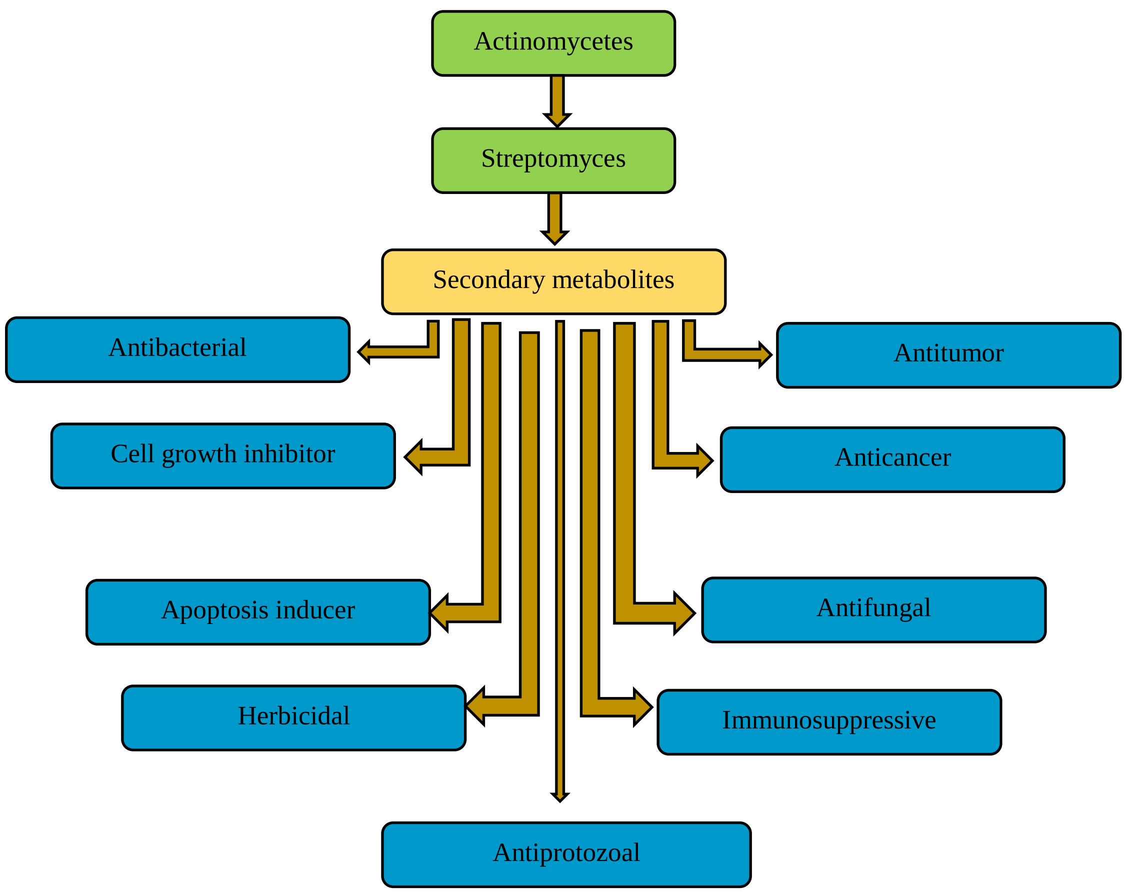

Figure 2. Different biological activities of secondary metabolites produced by the genus *Streptomyces*

A continuous research is going on over and over again in order to find some new species of marine actinomycetes that have not been isolated earlier. Regardless of the continuous developments that are being made in isolating and culturing rare species of marine actinomycetes,a very large number of these microorganisms still remain untraced, undetected and uncultured [18,19].

Marine actinomycetesare known for their role as efficient producers of novel bioactive secondary metabolites possessing a wide range of biological activities including antibacterial, antifungal, anticancer, antitumor, etc.Fig. 3 displays different secondary metabolites that are produced by marine actinomycetes [20].

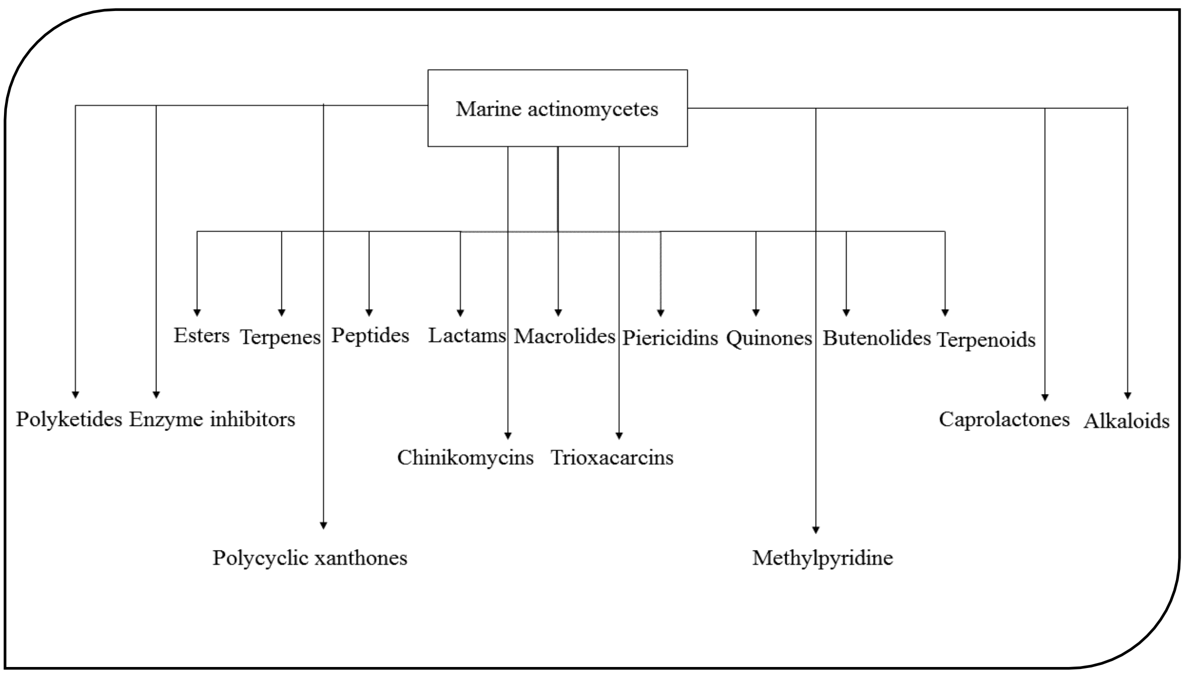

Figure 3. Different secondary metabolites produced by marine actinomycetes

2. 2. Production of antibiotics

Actinomycetesare mostly known for their wide range of applications in diverse fields. As far as the production of antibiotics is concerned, two-third of the antibiotics that are developed in the current times are derived from actinomycetes. Some of those antibiotics include anthracyclines, chloramphenicol, tetracycline, nucleosides, erythromycin, vancomycin, gentamicin, etc. These antibiotics are used to cure a wide range of human diseases including respiratory disorders, leprosy, tuberculosis and various other deadly diseases [21]. Among actinomycetes, the genus *Streptomyces* has got the capabilityto produce a wide spectrum of antibiotics as they possess an extraordinary potential of synthesizing secondary metabolites and antibiotics as well [11]. Apart from this fact, the source of antibiotics that were of actinomycete origin until 1974, was confined to the genus *Streptomyces* [22].

Marine actinomyceteshave been deeply studied for their potential as novel antibiotic producers. Various novel antibiotics are being produced bymarine actinomycetes. Abyssomicin C, a novel antibiotic produced by a marine *Verrucosispora* strain, has got the ability to act as a powerful antibacterial agent against gram-positive bacteria in conjunction with the clinical isolates of multi-resistant *Staphylococcus aureus* as well as vancomycin resistant *Staphylococcus aureus*.A new species of marine *Streptomyces* has shown the ability to produce novel antibiotics known as Chlorinated dihydroquinones. Essramycin is another novel antibiotic, active against gram-positive and gram-negative bacteria, which has been isolated from *Streptomyces* sp. Other new antibiotics include Caboxamycin, Himalomycins A and B, Glyciapyrroles, Bisanthraquinone, etc., all of these possessing antibacterial activity against various bacterial species [23-26].

Apart from the production of various novel antibiotics possessing antibacterial activities, marine actinomycetes are under study for the production of antibiotics that are effective against pathogenic fungi. Chandrananimycin A, a novel antibiotic isolated from *Actinomadura* species is endowed with a powerful quality of acting as an antifungal agentagainst *Mucor michei*,apart from having antialgal activity against *Chlorella vulgaris* and *Chlorella sorokiniana*, the two microalgae. Chandrananimycin A has also been antibacterially active against *Staphylococcus aureus* and *Bacillus subtilis*. This novel antibiotic has also been known to act as anticancerous agent [27].

In short, marine Actinomycetes possess the extraordinary potential as the producers of novel antibiotics which can be of tremendous help in saving human lives.

2. 3. Production of enzymes and enzyme inhibitors

The physiological, biochemical and molecular differences between marine actinomycetesand their terrestrial correlatives makes marine ones quite diverse as far as synthesis of biologically active compounds is concerned. This poses a difference even on the synthesis of enzymes as marine actinomycetes possess a great tendency to synthesize various biologically active enzymes [28]. Actinomycetesin general and marine actinomycetes in particular have got a great capability to synthesize enzymes which are industrially important such as amylases, cellulases, hemicellulases, lignolytic enzymes, lipases and xylanases.

Amylases: Actinomycetessecrete amylases to the outside cell environs in order to perform extracellular digestion. This quality of enzyme secretion to carryout extracellular digestion is also possessed by bacteria and fungi. Among amylases, α-amylase (E.C. 3.2.1.1), a hydrolysing enzyme which carries out the hydrolysis of starch and glycogen to yield glucose and mannose, is of great biotechnological importance showing its applications in food, fermentation, textile and paper industries [29].

Cellulases: Cellulases are cellulolytic enzymes which are a group of glycosyl hydrolases and depending on their sequence homologies, they are categorized into various families but cellulases in general terms are divided into exoglucanases (E.C. 3.2.1.74), endoglucanases (E.C. 3.2.1.4), cellulobiohydrolases (E.C. 3.2.1.91) and β-glucosidases (E.C. 3.2.1.21). Actinomycetessuch as *Cellulomonas fimi*, *Microbiospora biospora* and *Thermobifida fusca*, producing cellulases have been deeply studied [30-32].

Cellulase systems in microbes are of two types, either it can be complexed or non-complexed [33]. Complexed systems are known by another name as cellulosomes, which are a characteristic feature of anaerobic bacteria. Aerobic bacteria including most of the actinomycetespossess a non-complexed or free system which involves theextracellular secretion of these enzymes through specific pathways [34].

Hemicellulases: Accompanied by the synthesis of cellulases, most of the hemicellulases are associated with the family of glycosyl hydrolases, while as some of them belong to glycosyltransferases [30,33]. Hemicellulose contains xylan and mannan as the most plentiful components and their degradation by hemicellulases leads to an enhancement in cellulose hydrolysis. Some of the hemicellulases are 1,4-β-xylanases (E.C. 3.2.1.8), β-D-xylosidases (E.C. 3.2.1.37), acetyl xylan esterases (E.C. 3.1.1.72), mannanases (E.C. 3.2.1.78), β-mannosidases (E.C. 3.2.1.25) etc. [30].

Lignolytic enzymes: Laccases (E.C. 1.10.3.2), manganese peroxidases (E.C. 1.11.1.13) and lignin peroxidases (E.C. 1.11.1.14) constitute a complex of three principal enzymes which help in carrying out the process of lignin degradation. Laccases come under oxidoreductases and are extracellular inducible enzymes operating by the use of simple oxygen as an oxidizing agent apart from using it as a cofactor. Manganese and lignin peroxidases are conjointly called as heme peroxidases. Lignin peroxidases are specific in degrading high redox potential compounds while as manganese peroxidases act as low redox potential heme peroxidases. Both of these enzymes require $H_2O_2$for their activity [35-37].

Xylanases: Being the second most plentiful polysaccharide in the cells walls and amounting around 30-35% total dry weight of plants growing on land as well as being the major constituent of hemicellulose, xylan presents a tough layer which needs to be digested if any biological or chemical process (requiring constituents of xylan) has to be carried out. This process is carried out by a group of enzymes acting cooperatively which are known as xylanases. Xylan hydrolysis is carried out by xylanolytic enzyme system generally consisting of hydrolytic enzymes viz; β-1,4-endoxylanase, β-xylosidase, α-L-arabinofuranosidase, α-glucuronidase, acetyl xylan esterase and phenolic acid esterase. Xylanolytic enzyme system has been found to be predominant in fungi,actinomycetesand bacteria [38-42].

Industrially produced enzymes in general and hydrolytic enzymes in particular have been generally synthesized in submerged fermentation (SmF) in addition to solid state fermentation (SSF) [43-45]. Actinomycetes have got the capability of synthesizing xylanases and some of the species of actinomycetes have been utilized for synthesizing xylanases in SnF and SSF by making use of different agricultural wastes as primary substrates [46-51]. Different comparative studies have been carried out on the production of xylanases byactinomycetes in SmF and SSF. For example, a study on the use of wheat bran and eucalyptus kraft pulp as a primary substrate, *Streptomyces* sp. QG-11-3 was utilized, showing higher enzyme titre production when grown in SSF compared to SmF [52]. One more study carried out on the production of xylanases by *Streptomyces* sp. using wheat bran as a primary substrate in SSF, resulted in the production of an enzyme having a specific activity of 2.18 [46]. Various other studies have been carried out on xylanase production in SmF using xylan from various sources such as wheat bran, rice bran straw, etc. The production of biomass hydrolysing enzyme system consisting of xylanases and other enzymes by a strain of *Streptomyces* sp. MDS was reported. This strain had the ability to make use of a wide range of cellulosic substrates such as carboxymethyl cellulose, xylan, wood straw, rice straw, etc. [53]. Another species, *Streptomyces lividans* NRC was reported to possess the ability of producing xylan in SmF by utilizing wheat bran as a primary substrate [54]. One more study regarding the production of extracellulase xylanase by a strain of *Streptomyces albus* ATCC

3005 using oat spelt xylan as a primary substrate was reported and the maximum production was attained (11.97 U/mL) in 120 hours [55].

Production of enzyme inhibitors: Actinomyceteshave got the capability to synthesize low molecular weight enzyme inhibitors. While as the first enzyme inhibitor was reported by Umezawa from a *Streptomyces* strain, but ever since there have been as many as 60 enzyme inhibitors that have been reported. For example, leupreptines inhibit trypsin, plasmin and papain. One more inhibitor namely antipain inhibits papain, chymotrypsin, trypsin and cathepsnin B. Having the ability to inhibit a variety of enzymes, these inhibitors from actinomycetesfind their role in cancer treatment. For example, a strain of *Streptomyces* has been reported to produce an enzyme inhibitor called revistin, inhibiting reverse transcriptase. One more example includes Alistragin, an inhibitor present in the culture filtrates of *Streptomyces roseoviridis* [22,56].

2. 4. Actinomycetes and cancer

Until now, cancer is considered as the deadliest disease and a serious health problem. Moreover, the second leading cause of cancer deaths in women is due to breast cancer. Treatment for cancer, in the present scenario, involves therapeutic methods such as surgery, chemotherapy, radiotherapy and immunotherapywhich individually or in combination, are helpful in specific cases considering the situation of a cancer patient. There have not been any deep studies on anti-cancer compounds derived from marine actinomycetesbut still there has been some discovery of compounds from marine actinomyceteswhich possess anti-cancer activity [57-60].

Salinispora tropica, a marine actinomycetes, has been utilized as a source for pure bioactive compounds which exhibited little suppressive effects in various malignant cells. One specific compound, Salinosporamide A, which is a novel bicyclic beta-lactone gamma-lactam has been reported to be extracted from *Streptomyces tropica* (an obligate marine actinomycetes). This compound has shown a role in inducing apoptosis in multiple myeloma cells. This compound is an orally active proteasome inhibitor different from the anticancer drug, Bortezomib (commercially available anticancer drug) [61-64].

Salinosporamide A has been tested for its anticancer and antimalarial drug activity by Prudhomme et al, 2008 [61] and it showed an inhibitory activity both *invitro* and *invivo* against parasite development. The mode of inhibition developed by this drug is unknown, however it is probably due to proteasome complex inhibition [61]. Recent antibiotics, known as Caprolactones have been isolated from *Streptomyces* sp. showing decent phytotoxic and anticancer activity[65].

2. 5. Actinomycetes and biofouling

Any solid surface that is present in a marine environment like seawater, in this particular scenario, will eventually become covered by a layer of organic film and fouling microbes such as marine bacteria, fungi, diatoms, algae and other seawater microbes [66]. Due to the presence of these biofouling microbes, serious problems such as settling of these microbes on ships, power plants, pipelines and other marine constructions would occur [67]. Most of the countries, in order to solve this menace, had made the use of antifouling paints containing organotin such as tri-n-butyltin (TBT)which contains copper and organonitrogen compounds. But due to the side effects caused by the application of TBT, it was decided to ban this particular antifouling agent by International Maritime Organization (IMO) and Marine Environmental Protection Committee (MEPC). It was also decided to ban other chemical substances containing tin as a biocide [68]. The replacement for this effective antifouling agent, TBT, is not yet currently available. So, there is a pressing need to find an alternative antifouling product that is environment friendly and non-toxic.

Actinomycetesare a source to many valuable secondary bioactive metabolites such as antibiotics, enzymes, antibacterial, antifungal and anticancer compounds. Being surrounded by a marine environment, the marine actinomycetes represent a different class when it comes to the synthesis of bioactive compounds due to the environmental differences with their terrestrial correlatives[69]. Marine actinomycetes are not exploited too much for research but they possess loads of potential. Antifouling agents have been reported from bacteria, fungi, plants, etc. but such studies about marine actinomycetes are very less. For example, a potent bioactive compound has been reported from marine actinomycetes that acts against biofouling bacteria [70].

2. 6. Actinomycetes and nanoparticles

Due to wide range of applications in various fields, nanoparticles are gaining a considerable attention. There are various biological sources that prove useful in synthesizing nanoparticles such as bacteria, fungi as well as actinomycetes, particularly marine ones. Biosynthesis of nanoparticles from actinomycetes has been reported by various researchers. For example, biosynthesis of silver nanoparticles from actinomycetes has been reported byS. Abdeen et al, 2014 [71].

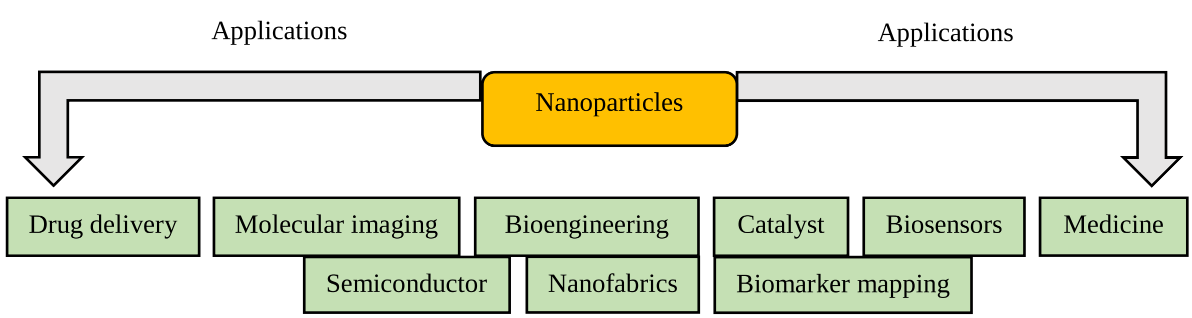

Figure 4. Diagrammatic representation of various applications of nanoparticles

A green approach for synthesizing silver nanoparticles from a marine Streptomyces sp.-MS26 has been reported byA. Zarina& Anima Nanda, 2014 [72]. A study carried out by S. Deepa et al, 2013 [4] has reported the extracellular synthesis of silver nanoparticles from a Thermoactinomyces sp. at room temperature. One more study carried out by Prakasham et al, 2012 [73] has reported the synthesis of silver nanoparticles from a marine isolate, *Streptomyces albidoflavus*. A study on the synthesis of gold nanoparticles from a marine *Streptomyces cyaneus* has been carried out by El-Batal & Al Tamie, 2015 [74]. Various other studies on biological synthesis of different nanoparticles have been reported.

Biosynthesis of various metal nanoparticles such as zinc, copper, gold, iron and titanium have an important role to play in overcoming the menace of antibiotic resistance because various resistant pathogenic microbes pose a threat in treating various deadly diseases. Antibiotics in combination with biosynthesized nanoparticles, can help in minimizing the doses of antibiotics which in-turn help in curing the deadly diseases [72].

Apart from the applications that nanoparticles find in combination with antibiotics, there are various other important ones that are listed in figure 4. Biosynthesis of nanoparticles is very much economical and a suitable process requiring less energy apart from being environment friendly[75]. Recently, gold nanoparticles have gained a considerable interest and are under extensive research because of their wide range of biological and biomedical applications [74].

3. SUMMARY AND FUTURE PERSPECTIVES

Marine actinomycetes, being the richest source of novel and important compounds, represent a genera of less exploited marine microbes. These uniquely efficient microbes possess a lot of potential in various fields of research, be it the synthesis of a novel drug, an enzyme or their role in cancer and biofouling, as discussed in this paper.

Actinomycetesin general and marine actinomycetesin particular have been a source to various lifesaving antibiotics such as chloramphenicol, tetracycline, erythromycin and other important antibiotics. Genus *Streptomyces,* which comes under actinomycetes, represents a genus of extraordinary potential having the capability to synthesize secondary metabolites and various lifesaving antibiotics. Until 1974, the only source available for antibiotic production was this genus *Streptomyces.*

Marine actinomycetes have a different capability of synthesizing products when compared to their terrestrial correlatives such as synthesis of enzymes, bioactive secondary metabolites and antibiotics, because of the different environs surrounding them. Marine actinomyceteshave served as a source of novel antibacterial, antifungal and anticancer compounds. Therefore, they play an important role in biological sciences. The role of marine actinomycetesalso extends in controlling the menace of biofouling.

In a nutshell, marine actinomyceteshave an extensive role in diverse fields particularly in the field of biological sciences. A continuous and rapid research about these valuable marine microbes then may result in the development of novel drugs to cure deadly diseases such as cancer. The developments in research techniques in near future will be quite useful in carrying out an efficient research in this less exploited region. Figure 5 graphically displays the number of new compounds isolated from marine microbes per year from 2001 to 2010, which shows the capability of marine microorganisms in synthesizing novel compounds.

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References

[1] V. S. Bernan, M. Greenstein, G. T. Carter, Curr. Med. Chem. *Anti-infective agents* 3 (2004) 181-195.

[2] P. Dhevagi, E. Poorani, *Indian Journal of Biotechnology* 5 (2006) 514-520.

[3] S. Silambarasan, E. P. Kumar, T. Murugan, D. Saravanan, R. Balagurunathan, JAPS 2 (10) (2012) 099-103.

[4] S. Deepa, K. Kanimozhi, A. Panneerselvam, *Int. J. Curr. Microbiol. Appl. Sci* 2 (9) (2013) 223-230.

[5] S. Valli S. S. Sugasini, O. S. Aysha, P. Nirmala, P. V. Kumar, A. Reena. *Asian Pac J Trop Biomed* 2 (6) (2012) 469-473.

[6] C. Imada, N. Koseki, M. Kamata, T. Kobayashi, N. Hamada-Sato, *Actinomycetologica* 21 (2007) 27-31

[7] S. D. Bentley, K. F. Chater, A. M. Cerdeno-Tarraga, Nature 417 (6885) (2002) 141-147

[8] P. Lalitha, K. Karikalan, K. Thirugnanasambantham, *International Journal of Current Research* 5 (12) (2013) 4053-4056.

[9] M. J. Bibb, *Current Opinion in Microbiology* 8 (2) (2005) 208-215.

[10] T. Bull, Microbial diversity and bioprospecting, ASM Press, 2004.

[11] J. Berdy, *J Antibiot* (Tokyo) 58 (2005) 1-26.

[12] J. Mann, Natural products as immunosuppressive agents. *Nat Prod Rep* 18 (2001) 417-430.

[13] W. Pecznska, M. Mordaski, Academic Press London (1988) 219-283.

[14] F. Carlos, Multiple drug resistant bacteria, Horizon, Scientific Press, 2003.

[15] U. N. Ekwenye, E. Kazi, *Afr J Biotechnol* 6 (2007) 877-880.

[16] K. S. Lam, *Curr Opin Microbiol* 9 (2006) 245-251.

[17] W. Fenical, P. R. Jensen, *Nat Chem Biol* 2 (2006) 666-673.

[18] J. E. Stach, L. A. Maldonado, A. C. Ward, M. Goodfellow, A. T. Bull, *Environ Microbiol* 5 (2003) 828-841.

[19] T. J. Mincer, W. Fenical, P. R. Jensen, *Appl Environ Microbiol* 71 (2005) 7019-7028.

[20] R. Solanki, K. Monisha, L. Rup, *Indian J. Microbiol* 48 (2008) 410-431.

[21] S. Mukesh, *Int. J. Curr. Microbiol. App. Sci* 3 (2) (2014) 801-832.

[22] V. Chavan, S. S. Mulaje, R. Y. Mohalkar, *IJPSR* 4 (5) (2013) 1730-1742.

[23] J. Riedlinger, A. Reicke, H. Zähner, B. Krismer, A. T. Bull, W. A. C. Maldonado, M. Goodfellow, B. Bister, D. Bischoff, R. D. Süssmuth, H. P. Fiedler, *J Antibiot* 57(4) (2004) 271-9.

[24] M. Panchanathan, V. Jayachandran, S. Kannan, K. Se-Kwon, *Microbiological Research* 169 (2014) 262-278.

[25] E. Soria-Mercado, A. Prieto-Davo, P. R. Jensen, W. Fenical, *J Nat Prod* 68 (6) (2005) 904-910.

[26] M. M. El-Gendy, M. Shaaban, K. A. Shaaban, A. M. El-Bondkly, H. Laatsch, *J Antibiot* 61 (3) (2008) 149-157.

[27] R. P. Maskey, F. Li, S. Qin, H. H. Fiebig, H. Laatsch, *J Antibiot* 56 (7) (2003b) 622-634.

[28] P. R. Jensen, F. M. Lauro, *Antonie Van Leeuwenhoek* 94 (2008) 51-62.

[29] K. Selvam, B. Vishnupriya, B. V. Subhash, *International Journal of Pharmaceutical & Biological Archives* 2 (5) (2011) 1481-1487.

[30] M. G. del-Pulgar, A. Saadeddin, *Critical Reviews in Microbiology* 40 (3) (2014) 236-247.

[31] S. Sadhu, T. K. Maiti, *British Microbiology Research Journal* 3 (3) (2013) 235-258.

[32] B. Wilson, *Critical Reviews in Biotechnology* 12 (1-2) (1992) 45-63.

[33] L. R. Lynd, P. J. Weimer, W. H. Van Zyl, I. S. Pretorius, *Microbiology and Molecular Biology Reviews* 66 (3) (2002) 506-577.

[34] S. Anita, K. A. Neeraj, S. Anuja, Y. Anita, Hindawi Publishing Corporation Enzyme Research (2015) 1-15.

[35] M. G. Mason, A. S. Ball, B. J. Reeder, G. Silkstone, P. Nicholls, M. T. Wilson, *Applied and Environmental* Microbiology 67 (10) (2001) 4512-4519.

[36] J. Plácido, S. Capareda, *Bioresources* and *Bioprocessing* 2 (23) (2015) 1-12.

[37] B. Fisher, S. S. Fong, *AIMS Bioengineering* 1 (2) (2014) 92-112.

[38] M. D. Joshi, G. Sidhu, J. E. Nielsen, G. D. Brayer, S. G. Withers, L. P. McIntosh, *Biochem* 40 (34) (2001) 10115-39.

[39] D. W. Goheen, *J. Chem. Educ* 58 (6) (1981) 465.

[40] P. Biely, *Trends Biotechnol* 3 (11) (1985) 286-290.

[41] Elegir, M. Sykes, T. W. Jeffries, *Enzyme and Microbial Technology* 17 (10) (1995) 954-959.

[42] D. Dey, J. Hinge, A. Shendye, M. Rao, *Can J Microbiol* 38 (1992) 436-442

[43] Pandey, *Biochem Eng. J* 13 (2) (2003) 81-84.

[44] M. Maciel, L. P. S. Vandenberghe, C. W. I. Haminiuk, R. C. Fendrich, B. E. D. Bianca, T. Q. D. Brandalize, A. Pandey, C. R. Soccol, *Food Technol. Biotechnol* 46 (2) (2008) 183–189.

[45] Pandey, C. R. Soccol, D. Mitchell, *Proc Biochem* 35 (10) (2000) 1153-1169.

[46] K. Bajaj, N. P. Singh, *Appl Biochem Biotechnol* 162 (6) (2010) 1804-1818.

[47] S. Ninawe, M. Kapoor, R. C. Kuhad, *Bioresour Technol* 99 (5) (2008) 1252-8.

[48] L. R. Alberton, L. P. S. Vandenberghe, R. Assmann, R. C. Fendrich, J. Rodriguéz-León, C. R. Soccol, *Braz. Arch. Biol. Technol* 52 n. special (2009) 171-180.

[49] H. Ding, Z. Q. Jiang, X. T. Li, L. T. Li, I. Kusakabe, *World J Microbiol Biotechnol* 20 (1) (2004) 7-10.

[50] Kumar, R. Gupta, B. Shrivastava, Y. P. Khasa, R. C. Kuhad, *Journal of Molecular Catalysis B: Enzymatic* 74 (3) (2012) 170-177.

[51] B. B. Romdhane, I. M. Achouri, H. Belghith, *Appl Biochem Biotechnol* 162 (6) (2010) 1635-1646.

[52] Q. K. Beg, B. Bhushan, M. Kapoor, G. S. Hoondal, Enzyme Microbial Technol 27 (7) (2000c) 459-466.

[53] G. D. Saratale, R. G. Saratale, S. E. Oh, *Biomass and Bioenergy* 47 (2012) 302-315.

[54] N. H. Abd El-Nasser, A. M. Amal, A. K. Abeer, Australian *J. of Basic and Applied Sciences* 4 (10) (2010) 1358-1368.

[55] V. T. Antonopoulos, M. Hernandez, M. E. Arias, E. Mavrakos, *Appl Microbiol Biotechnol* 57 (1-2) (2001) 92-7.

[56] M. Goodfellow, S. T. Williams, M. Mordarski, Academic Press, London, 1988.

[57] S. Ravikumar, M. Gnanadesigan, N. Thajuddin, V. Chakkaravarthi, B. Banerjee, *J Pharm Res* 3 (10) (2010a) 2415-2417.

[58] J-P Gillet, T. Efferth, J. Remacle, *Biochim Biophys Acta (BBA)-Rev Cancer* 1775 (2) (2007) 237-262.

[59] S. Ravikumar, M. Fredimoses, M. Gnanadesigan, *Asian Pacific J Tropical Biomed* 2 (2) (2012a) 92-96.

[60] P. Manivasagana, J. Venkatesana, K. Sivakumar, S-K Kim, *Microbiological Research* 169 (2014) 262-278.

[61] Prudhomme, E. McDaniel, N. Ponts, S. Bertani, W. Fenical, P. Jensen, L. R. Karine, *PLoS ONE* 3 (6) (2008) e2335.

[62] R. H. Feling, G. O. Buchanan, T. J. Mincer, C. A. Kauffman, P. R. Jensen, W. Fenical, Angew Chem Int Ed 42 (3) (2003) 355-357.

[63] P. R. Jensen, P. G. Williams, D. C. Oh, L. Zeigler, W. Fenical, *Appl Environ Microbiol* 73 (4) (2007) 1146-1152.

[64] Chauhan, L. Catley, G. Li, K. Podar, T. Hideshima, M. Velankar, C. Mitsiades, N. Mitsiades, H. Yasui, A. Letai, H. Ovaa, C. Berkers, B. Nicholson, T. H. Chao, S. T. Neuteboom, P. Richardson, M. A. Palladino, K. C. Anderson, *Cancer Cell* 8 (5) (2005) 407-419.

[65] Stritzke, S. Schulz, H. Laatsch, E. Helmke, W. Beil, *J Nat Prod* 67 (3) (2004) 395-401.

[66] S. Clare, *Biofouling* 9 (1996) 211-229.

[67] T. Hattori, Y. Shizuri, *Fish Sci* 62 (1996) 955-958.

[68] Y. Xu, H. He, S. Schulz, X. Liu, N. Fusetani, H. Xiong, X. Xiao, P. Qian, *Bioresource Technology* 101 (2010) 1331-1336.

[69] R. Balagurunathan, M. Radhakrishnan, R. I. K. International Publishing House Pvt Ltd (2010) 436.

[70] M. Bavya, P. Mohanapriya, R. Pazhanimurugan, R. Balagurunathan, *Indian Journal of Geo-Marine Sciences* 40 (4) (2011) 578-582.

[71] S. Abdeen, S. Geo, Sukanya., P. K. Praseetha, R. P. Dhanya, *Int. J. Nano Dimens* 5 (2) (2014)155-162.

[72] Zarina, N. Anima, J. Pharm. Sci. & Res 6 (10) (2014) 321-327.

[73] Prakasham, S. Reddy, S. K. Buddana, S. K. Yannam, G. S. Guntuku, *J. Microbiol. Biotechnol* 22 (5) (2012) 614-621.

[74] I. El-Batal, M. S. S. Al Tamie, *J. Chem. Pharm. Res* 7 (7) (2015) 1020-1036.

[75] S. Tikariha, S. Singh, S. Banerjee, A. S. Vidyarthi, *Int. J. Pharm. Sci. & Rsch* 3 (2012) 1603-1615.

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