Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/12960
DOI URL: http://dx.doi.org/10.21474/IJAR01/12960

ISSN NO. 2320-5407

REVIEW ARTICLE

PRODUCTION OF ANTINEOPLASTIC DRUGS FROM SOIL MICROORGANISMS

C. Obula Reddy, Deepika Damalla, Divya Ganga and Divya Teja
Chaitanya Bharati Institute of Technology, Department of Biotechnology, Gandipet, Hyderabad-500075, Telangana, India.

Manuscript Info

Manuscript History
Received: 30 March 2021
Final Accepted: 30 April 2021
Published: May 2021

Key words:-
Cancer, Antineoplastic Drugs, Streptomyces, Cytotoxic

Abstract

As number of cancer patients increasing, the number of chemotherapy treatments are also increasing. This analysis aims to provide a cutting-edge outline of the antineoplastic medications extracted from streptomyces. Streptomyces are the main source of antibiotic production. Antineoplastic medications moderate the pace of tumor development and postpone metastasis. The utilization and performance of the methods are discussed, with focus on the antineoplastic drugs. Streptomyces produces compounds and crude extracts which shows cytostatic reaction across different human cell lines like for breast carcinoma (MCF-7, MDA-MB-231 cell lines), (HepG2 cell lines) hepatic carcinoma, (DU 145 cell lines) prostate cancer and more.

Introduction:-

Cancer:

One out of each two men and out of each three ladies will be determined to have cancer disease. In any case, notwithstanding those enormous numbers most people don't have a clue what truly implies. At the easiest level, Cancer cells will be cells that have lost the capacity to lead as the typical control that the body applies on all cells. In our body we have billions of cells that they have various capacities. It's an exceptionally confounded cycle under unfathomable incredible control and if something turns out badly and that control is lost and specific cells get away from the typical control systems and they proceed to develop and they may spread. That is the thing that we call malignancy. Those cells together, we would call it harmful in light of the fact that not exclusively would it be able to attack into contiguous organs, yet shockingly malignancy can spread to different tissues and that can be perilous. In contrast to dangerous tumors, benign tumors don't spread into, or attack any close by tissues [1].

Malignant growth can really happen any place in the body on the grounds that there are cells wherever in the body [1]. In ladies perhaps the most widely recognized tumors are breast malignancy and in men the prostate cancer disease. In the two, cellular breakdown in the lungs and colon malignancy are basic tumors. The extended occurrence of patients with disease in India among males were 679,421 (94.1 per 100,000) and among females 712,758 (103.6 per 100,000) for the year 2020. One out of 68 guys (cellular breakdown in the lungs), 1 of every 29 females (breast malignant growth)[2].

Types of cancer:

1. Carcinoma is a malignancy that starts in the skin or in tissues.
2. Sarcoma is a disease that starts without control and can attack close by tissues, bone, ligament, fat, muscle, veins, or other connective or steady tissues.

Corresponding Author:-Deepika Damalla
Address:-Chaitanya Bharati Institute of Technology, Department of Biotechnology, Gandipet, Hyderabad-500075, Telangana, India.

3. Leukemia is a malignancy that starts in blood tissue, like the bone marrow, and causes such a large number of unusual blood cells.
4. Lymphoma and various myeloma are tumors that start in the cells of the invulnerable framework.

Antineoplasic Drugs:
Antineoplastic drugs are the medications that are prescribed in order to treat cancer. These are also referred to as anti-cancer, cytotoxic or chemo drugs. These drugs are highly toxic with an extremely low therapeutic index as compared to most of the other classes of drugs [3].

Table 1:- Isolation Of Antineoplastic Drugs From Different Sources:

S.NO	SOURCE OF ANTINEOPLASTIC DRUG		NAME OF THE DRUG	REFERENCES
1	Microbial-derived antineoplastic drugs from-Marine environment	Cephalodiscusgilchristi (African marine worm)	Cephalostatins 18 and 19	George et al [4]
2		Spongia spp. (sponge from eastern Indian ocean)	Spongistatin 1	Michael et al [5]
3	Plant-derived antineoplastic drugs	I. VIGUIERASYLVATICA	Millerenolide	Peter et al [6]
4		Decachaetathieleana,	Thieleanin	Peter et al [6]
5	Microbial-derived antineoplastic drugs from-Soil environment	**Streptomyces anulatus**	Montanastatin (1) and valinomycin (2)	Barton et al [7]
6		Brevibacillus brevis EGS9	Vancomycinand methicillin	Senthil Kumar et al [8]

Isolation Of Antineoplastic Drugs:
Plant Derived Antineoplastic Agents:
Plants are the main source of highly efficient traditional cancer treatments. Vinca alkaloids, vinblastine, and vincristine, both isolated from Madagascar periwinkle, were the first agents used in clinical trials. these are mostly useful for treating carcinoma breast and leukaemia. [9]

Microbial Derived Antineoplastic Agents:
Many of best anticancer drugs come from microbes which are used to battle against other cancer cells. The function of microbial symbionts in the development of biologically effective specialised metabolites has been the subject of recent research. Only some studies have found the real producers of specialised metabolites of interest so far [10].

From soil microbes:
To date, microorganisms isolated from soil produces antibiotics which can kill other pathogenic microorganisms. The antineoplastic agents isolated from soil often shows more effect towards cancer cells. [11] The anthracyclines family, doxorubicin and daunorubicin, is one of the most well-known drugs derived from Streptomyces. These medications could take action at different levels to advance apoptosis of malignant growth cells [12].

From Marine Microbes:
Apart from sponges, algae, and corals, marine bacteria and fungi are wellknown to create specialised metabolites with complex and various chemical structures, which can be used to develop new drugs. Secondary metabolites can available in prokaryotes and eukaryotes, including unicellular bacteria (e.g., Bacillus spp. and Pseudomonas spp.), eukaryotic fungi (e.g., Penicillium spp. and Aspergillus spp.), filamentous actinomyces, and filamentous actinomyces (e.g., Streptomyces spp) [13].

Chemically Derived Antineoplastic Agents:
Alkylating agents are chemicals that cause DNA strands to split, causing cancer cells to multiply. The first chemicals used to treat cancer were nitrogen mustards.

Antineoplastic Drug Classification[14]:
Anticancer drugs have historically been classified into the following groups based on their biochemical mechanisms of action:

Alkylatingagents, Antimetabolites, Antitumour antibiotics, Plant alkaloids, Miscellaneous agents, Hormonal agents.[14]

Few Soil Microbes Producing Antineoplastic Drugs:
Fungi:
Natural products extracted from fungi have lengthy been a precious source of prescription drugs. fragrant compounds, amino acids, anthracenones, butanolides, butenolides, cytochalasans, macrolides, naphthalenones, pyrones, and terpenes, to call some, are some of the metabolites produced by using fungi. Aspergillus ustus produces phenylahistin, which incorporates aromatic amino acid phenylalanine and protonated amino acid. It represents suppressing activity on P388 cells in G2/M phase cell cycle. [15]

Anticancer polyketides with different spiro ring structures have been found in filamentous growths. [16,17] The antifungal compound griseofulvin from P. griseofulvum is one of the most notable. Griseofulvin was first considered for cancer disease therapy in 1973, after being presented economically in 1965. [18]after it had been perceived to actuate cell accumulation and cell division within the human cervical neoplastic cell line Hela, and additionally prevents centrosomal clump in human squamous cancer SCC-114 cell line [19,20].

In laboratory mice affected with COLO 205 tumours, it was also shown that combining griseofulvin with the antineoplastic agent nocodazole enhanced the results of nocodazole and stopped tumour extension in vivo. [21].

Bacteria:
Staphylococcal superantigens-like (SSL) are a sort of bacterial protein framed by Staphylococcus aureus and equipped for confining few eukaryotic receptors in malignant growth cells. SSL10 connects with CXCR4, a GPCR found in T-ALL lymphoma and cervical carcinoma cells in people. CXCL12 is the most well-known ligand for CXCR4, yet SSL10 movement hindered the chemotactic reaction of HeLa (cervical carcinoma) cells to this ligand. [22] Some bacterial proteins are similarly candidate therapeutic experts for harmful development treatment. This is the circumstance of the amino destructive adulterating compound arginine deiminase of Mycoplasma arginini (Ma-ADI), a tumor advancement inhibitor and perhaps a medicinal expert for the treatment of in vitro and in vivo tumors. for instance, hepatocellular carcinoma, melanoma, leukemia, renal cell carcinoma and prostate threat [23]**.**

Actinobacteria:Streptomyces
Many microorganisms have been studied for producing anti-cancer leads or compounds. The anti- cancer activity of these natural, microbial compounds is capable of inducing apoptosis, regulate functions of the immune system and inhibit the proliferation of the cells. Actinobacteria is one of the largest taxonomic groups, with a wide range of species. It has been known as a primary source for the extraction of natural and bioactive products, like anticancer agents and a variety of other auxiliary metabolites[24,25,26]. Streptomyces is a highly recognized representative of the class of Actinobacteria. In fact, 80% of the natural products from this class are extracted from the Streptomyces genus. Screening potentially anti-cancerous and antineoplastic compounds from Streptomyces that are mangrove derived is the most initial step [27,28]. Studies consisting of experiments have shown that Streptomyces in the mangrove areas demonstrated a certain level of cytotoxic activity that works against cancerous cell lines in humans.For this, it is important that pure and raw extracts of Streptomyces species are isolated [29].

Novel compounds that have antineoplastic potential and properties can be extracted from Streptomycetes that are mangrove derived. Two major compounds, namely, azalomycin F5a and azalomycin F4a 2-ethylcrude extracts[30] have been derived from Streptomyces wherein, both these compounds exhibit extremely high levels of cytotoxicity against cancer of the colon. Also, compounds like indolocarbazoles and streptocarbazoles A and B have been extracted from the Streptomyces species, exhibiting impressive amounts of cytotoxic effects against cancers in humans like Leukemia, HeLa and lung cancer cells [30]. An in-depth analysis has also revealed that one of these

compounds can successfully cause an arrest in the cell cycle in humans, facilitating, antineoplastic property. A significant observation has been made in which the Streptomyces' isolated extract composed of ethyl acetate has demonstrated potential cytotoxicity against two cell lines responsible for breast cancer. A specific fraction of the Streptomyces extract is also capable of causing arrest in cell division cycle in the Gap1 and Gap2 phases, controlling cell proliferation and induces apoptosis that is mitochondria mediated [31].

Table 2:- Antineoplastic Drugs Produced From Soil Microbes:

S.NO	TYPE OF MICROBE	NAME OF ANTINEOPLASTIC DRUG	TYPE OF CANCER CURED	REFERENCES
1.	Yukon (Fungus)	Dilactone 2	Breast, lung, prostate, pancreas, colon cancers	Tan et al [32]
2.	Kitasatosporia spp. (bacteria)	Terpentecin	Leukaemia L-1210, P388 and Ehrlich ascites carcinoma	sawa et al [33]
3.	Streptomyces galilaeus (actinobacteria)	Aclarubicin	acute non lymphocytic leukemia	Demant et al [34]
4.	Streptomyces peucetius (bacteria)	Daunorunicin	Acute myeloid leukemia	Karl et al [35]
5.	Aspergillus flavus (Fungi)	Solamargine	Melanoma	Hawari et al [36]
6.	Streptomyces antibioticus (actinobacteria)	Pentostatin	hairy cell leukemiachronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), and cutaneous T-cell lymphoma	Roback et al [37]
7.	Streptomyces achromogenes (actinobacteria)	Streptozocin	metastatic pancreaticislet cell carcinoma	Abdollahi et al [38]
8.	Chromobacteriumviolaceum (bacteria)	Romidepsin	non-Hodgkin's lymphoma, Hodgkin's lymphoma, or multiple myeloma.	Savini et al [39]

AnticancerousAvtivity:

Other than the MTT assay,the SRB (Sulforhodamine B) method can also be used that estimates the total content of protein that is present in the cells and hence, the total number of cells that are viable in the soil microorganisms along with the level of cellular protein present in them can be measured that gives an idea about the cytotoxicity.[40] A colorimetric assay known as the CCK-8 assay is also employed for measuring the viability of cells in vitro for the purpose of proliferation and cytotoxicity experimentation.

Another critical technique called as metagenomics is widely being employed for identifying microorganisms that belong to different environments and have been uncultivable for prolonged periods of time. In such a technique, DNA belonging to the microbes is isolated from an environment sample that has been chosen. The sequence of DNA then obtained will represent the microorganism that is present in the sample [41]. The process of extraction involves the screening for bioactivity performed for raw or crude extracts belonging to Streptomyces. It is followed by the purification process and then finally the partial characterization that is done using methods like IR spectra (infrared spectra) and UV absorption (ultra-violet absorption). For accurate and successful extraction, it is important that conditions developed for culturing are appropriately optimized. This optimization of the conditions for culture is to be done based on the recommendations provided by the "International Streptomyces Project". Post optimization of culture conditions, the isolate has to be identified using comparative properties. The extract then prepared from the cell culture broth containing the isolate can be analyzed using the above-mentioned assays or array techniques like HPLC diode technique [42]. There is very limited amount of knowledge as to the mechanisms that are involved for successful antineoplastic or anti-cancerous activities in cells and furthermore, living beings.

Insilico-Docking Studies:

Concentrates from common items, particularly microorganisms, have demonstrated to be a significant wellspring of different atoms in a few medication disclosures endeavors, prompting the revelation of various significant medications. The disclosure of different bioactive particles has come about because of the ID of microbial strains with promising natural exercises and the refinement of the bio-atoms answerable for the exercises. The MTT (3-[4, 5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) method was utilized to assess the in vitro cytotoxicity of the extracellular and intracellular focuses on HeLa cells. MTT testing was utilized to screen the most perplexing concentrates on MCF-7 cells. Two incredibly powerful thinks were picked for Hoechst 33342 staining and cell cycle examination to see whether the compound interceded apoptosis on HeLa cells, in view of the aftereffects of in vitro anticancer examinations of both extracellular and intracellular concentrates [43]. Utilizing the web-based programming apparatuses PEP-FOLD and iCn3D, the 3D development of the peptide NMANF2 was illustrated. The objective receptors of M. tuberculosis, cellular breakdown in the lungs (A540), and colon disease (HT-29) cells were recovered in 3D structure from the RCSB PDB. Hex 8.0.0 docking writing computer programs was utilized to examine and imagine in silico sub-atomic docking among ligands and proteins from M. tuberculosis and disease cell lines (A540 and HT-29) [44,45].

Discovery of Novel Compounds with Anticancer/Cytotoxic Activity from Mangrove-Derived Streptomyces sp

Table 3:- Compounds With Anticancer/Cytoxic Activity Isolate From Streptomyces Spp During The Years 2012-2020, A Summary Of Studies On The Anticancer/Cytotoxic Behaviour Of Streptomyces SPP.

S.no	Author	Strain	Source	Compounds / crude extract	Cell Lines
1.	Fredimoses et al. [46]	Streptomyces sp. ACT01, ACT02, ACT03, ACT04, ACT05	Mangrove sediment (India)	Crude ethyl acetate extract	MCF-7, MDA-MB-231 cell lines
2.	Yang et al. [47]	Streptomyces antibioticus strain H74-21	Sediments from mangrove site (China)	Streptomyceamide C*	MCF-7 cell lines
3.	Sudha et al. [53]	Streptomyces avidinni strain SU4	Marine sediments	Isooctyl phthalate 1,2-benzenedicarboxylic acid, bis (2-methyl propyl) ester	Hep-2 cell lines, VERO cell lines.
4.	Hanan M. abd Elnaby [54]	Streptomyces rochei MHM13	Marine sediments (Egypt)	Different concentrations of AgNPs.	Hep – G2, HCT – 116, A-549 and MCF- 7, PC3 Cell lines
5.	Suganya et al. [68]	Streptomyces olivaceus strain MSU3	Mangrove soil (India)	Crude ethyl acetate extract	MCF-7 cells, HT-29 cells.

6.	Shen et al. [69]	Streptomyces antibioticus strain H12-15	Sediments from mangrove district (China)	Neoantimycin A* Neoantimycin B* Antimycin A1ab Antimycin A2a Antimycin A9	MCF-7 cells SF-268 cells NCI-H460 cells.
7.	Chan et al. [80]	Streptomyces sp MUM256	Mangrove soil (Malaysia)	Crude methanol extract	HCT-116 Cells
8.	Seretal. [93]	Streptomyces Sp. MUSC5	Mangrove soil (Malaysia)	Crude methanol extract	MCF-7 cells, HCT – 116 cells, CaCO -2, SW480, DU145 cells
9.	Tae su et al. [95]	Streptomyces Sp. VN1	Coastal region (centralVietnam)	Cinnamamide,spirotetronate antibiotic lobophorin A, diketopiperazines cyclo-L-proline- L-tyrosine, and a unique furan-type compound	AGS, HCT 116, A375M, U87MG
10.	Mutalib et al [96]	Streptomyces monashensis sp. Strain MUSC 1JT	mangrove soil (East Malaysia)	Crude methanol extract	HCT-116, SW480 cells.

NOTE: NOTE: Lung cancer cell lines A549 and NCl-H460; colon cancer cell lines HCT-116, HT-29, and SW480; leukemia cell line HL-60; breast cancer cell lines MCF-7 and MDA-MB-231; glioblastoma cell line SF-268; prostate cancer cell line DU 145; cervical cancer cell line HeLa[97].

Conclusion:-

Natural products, such as those used in cancer treatment, have a significant impact on enhancing and improving human wellbeing. Streptomyces are promising producers of anti-cancerous property compounds and are reported from various habitats such as soil, plant parts and even from air [98]. In this review, the secondary bioactive metabolites extracted from Streptomyces have been highlighted to possess enormous potential as antineoplastic pharmaceuticals along with addressing the urgent need of expanding the current research done in this field, involving approaches of several types like the identification and purification of targeted compounds along with in depth study of these microorganisms present in the soil followed by the analysis of active strains consisting of the biosynthetic category of gene clusters.

References:-

1. Bast RC, Croe CM, Hait WN, Hong WK, Kufe DW, Piccart-Gebhart M, Pollock RE, Weichselbaum RR, Yang H, Holland JF (2016). Holland-Frei Cancer Medicine. Wiley. ISBN 978-1-118-93469-2.
2. Nandakumar A, Gupta PC, Gangadharan P, et al: Geographic pathology revisited: Development of an atlas of cancer in India. Int J Cancer 116: 740 - 754, 2005 Crossref, Medline.
3. Wainwright, E.N. &Scaffidi, P. (2017). Epigenetics and cancer stem cells: Unleashing, hijacking, and restricting cellular plasticity. Trends Cancer, 3, 372–386.
4. George R. Pettit, Rui Tan, Jun-ping Xu, Yoshitatsu Ichihara, Michael D. Williams, and Michael R. Boyd, Antineoplastic Agents. 398. Isolation and Structure Elucidation of Cephalostatins 18 and 19, Journal of Natural Products 1998 61 (7), 955-958,DOI: 10.1021/np9800405.
5. George R. Pettit, Zbigniew A. Chicacz, Feng Gao, Cherry L. Herald, Michael R. Boyd, Jean M. Schmidt, and John N. A. Hooper,Antineoplastic agents. 257. Isolation and structure of spongistatin1,The Journal of Organic Chemistry 1993 58 (6), 1302-1304,DOI: 10.1021/jo00058a004
6. Peter G. Taylor, Omar A. Dupuy Loo, José A. Bonilla, Renato Murillo,Anticancer activities of two sesquiterpene lactones, millerenolide and thieleanin isolated from Viguiera sylvatica and Decachaetathieleana,Fitoterapia,Volume 79, Issue 6,2008,Pages 428-432,
7. Antineoplastic agents. Part 409: Isolation and structure of montanastatin from a terrestrial actinomycete1Dedicated to the memory of Professor Sir Derek H. R. Barton (1918–1998), a great chemist and friend.1,Bioorganic& Medicinal Chemistry,Volume 7, Issue 5,1999,Pages 895-899,

8. Arumugam T, Senthil Kumar P, Hemavathy RV, Swetha V, Karishma Sri R. Isolation, structure elucidation and anticancer activity from Brevibacillus brevis EGS 9 that combats Multi Drug Resistant actinobacteria. MicrobPathog. 2018 Feb;115:146-153. doi: 10.1016/j.micpath.2017.12.061. Epub 2017 Dec 24. PMID: 29278781.
9. Hong WK, Sporn MB: Recent advances in chemoprevention of cancer. Science 1997; 278:1073-1077.
10. Rohde S, Nietzer S, Schupp PJ (2015) Prevalence and mechanisms of dynamic chemical defenses in tropical sponges. PLoS One 10: e0132236.
11. Ainsworth TD, Heron SF, Ortiz JC et al (2016) Climate change disables coral bleaching protection on the Great Barrier Reef. Science 352:338–342
12. [Molecular mechanisms of anthracyclines action], Szuławska A, Czyz M PostepyHig Med Dosw (Online). 2006; 60():78-100.
13. Bérdy J (2005) Bioactive microbial metabolites. A personal view. J Antibiot 58:1–26.
14. Immerman HJ. Hepatotoxic effects of oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 673-708.
15. Kanoh K, Konho S, Asari T, Harada T, Katada J, Muramatsu M, Kawashima H, Sekiya H, Uno I. (-)-phenylahistin: a new mammalian cell cycle inhibitor produced by **Aspergillus usts**. Bioorg Med Chem Lett. 1997; 7:2847–2852.
16. Brian, P.W. Studies on the biological activity of griseofulvin. Ann. Bot. **1949**, 13, 59–77.
17. Hector, R.F. An overview of antifungal drugs and their use for treatment of deep and superficial mycoses in animals. Clin. Tech. Small Anim. Pract. **2005**, 20, 240–249.)
18. 51. Grisham, L.M.; Wilson, L.; Bensch, K.G. Antimitotic action of griseofulvin does not involve disruption of microtubules. Nature **1973**, 224, 294–296
19. Panda, D.; Rathinasamy, K.; Santra, M.K.; Wilson, L. Kinetic suppression of microtubule dynamic instability by griseofulvin: implications for its possible use in the treatment of cancer. Proc. Natl. Acad. Sci. USA **2005**, 102, 9878–9883.
20. Rebacz, B.; Larsen, T.O.; Clausen, M.H.; Rønnest, M.H.; Löffler, H.; Ho, A.D.; Krämer, A.Identification of griseofulvin as an inhibitor of centrosomal clustering in a phenotype-based screen. Cancer Res. **2007**, 67, 6342–6350.
21. Ho, Y.-S.; Duh, J.-S.; Jeng, J.-H.; Wang, Y.-J.; Liang, Y.-C.; Lin, C.-H.; Tseng, C.-J.; Yu, C.-F.;Chen, R.-J.; Lin, J.-K. Int. J. Cancer**2001**, 91, 393–401.
22. Walenkamp AME. Bacterial proteins against metastasis. In: Fialho AM, Chakrabarty AM, eds. Emerging Cancer Therapy: Microbial approaches and Biotechnological Tools. Nutley N.J.: John Wiley 2009.
23. Lind DS. Arginine and cancer. J Nutr 2004; 134:2837- 41
24. Are, C.; McMasters, K.M.; Giuliano, A.; Yanala, U.; Balch, C.; Anderson, B.O.; Berman, R.; Audisio, R.; Kovacs, T.; Savant, D. Global forum of cancer surgeons: Perspectives on barriers to surgical care for cancer patients and potential solutions. Ann. Surg. Oncol 2019, 26, 1577–1582.
25. Chalbatani, G.M.; Dana, H.; Memari, F.; Gharagozlou, E.; Ashjaei, S.; Kheirandish, P.; Marmari, V.; Mahmoudzadeh, H.; Mozayani, F.; Maleki, A.R. Biological function and molecular mechanism of pirna in cancer. Pract. Lab. Med. 2019, 13, e00113.
26. Tan, L.T.-H.; Chan, K.-G.; Pusparajah, P.; Yin, W.-F.; Khan, T.M.; Lee, L.-H.; Goh, B.-H. Mangrove derived streptomyces sp. Mum265 as a potential source of antioxidant and anticolon-cancer agents. BMC Microbiol. 2019, 19, 38.
27. Miyadoh S,1997. Atlas of actinomycetes. Asakura Publishing Co, Tokyo, Japan.
28. Aderem A. 2005. Systems biology: its practice and challenges. Cell 121:511–513. doi: 10.1016/j.cell.2005.04.020.
29. Hopwood DA, 2007. Streptomyces in nature and medicine: the antibiotic makers. Oxford University Press, New York, NY.
30. Salam, N., Jiao, J.-Y., Zhang, X.-T., & Li, W.-J. (2020). Update on the classification of higher ranks in the phylum actinobacteria. International Journal of Systematic and Evolutionary Microbiology, 70, 1331–1355. doi: 10.1099/ijsem.0.003920.
31. Murphy SL, Kochanek KD, Xu J, Heron M. Deaths: Final Data for 2012. National Vital Statistics Reports. Vol 63. No 9. National Center for Health Statistics; 2015.
32. Pettit GR, Tan R, Herald DL, Hamblin J, Pettit RK. Antineoplastic agents. 488. Isolation and structure of yukonin from a yukon territory fungus. J Nat Prod. 2003 Feb;66(2):276-8. doi: 10.1021/np020144m. PMID: 12608865.

33. Tamamura T, Sawa T, Isshiki K, Masuda T, Homma Y, Inuma H, Naganawa H, Hamada M, Takeuchi T, Umezawa H. Isolation and characterization of terpentecin, a new antitumor antibiotic. J Antibiot (Tokyo). 1985 Dec;38(12):1664-9. doi: 10.7164/antibiotics.38.1664. PMID: 3841535.
34. Jensen PB, Jensen PS, Demant EJ, et al. (October 1991). "Antagonistic effect of aclarubicin on daunorubicin-induced cytotoxicity in human small cell lung cancer cells: relationship to DNA integrity and topoisomerase II"
35. Karl K. Kwok, … James N. Gibson, in Pharmacology and Therapeutics for Dentistry (Seventh Edition), 2017
36. El-Hawary, S.s.; Mohammed, R.; AbouZid, S.f.; Bakeer, W.; Ebel, R.; Sayed, A.m.; Rateb, M.e. (2016-04-01). "Solamargine production by a fungal endophyte of Solanum nigrum". Journal of Applied Microbiology. 120 (4): 900–911.
37. Roback et al., 2006. "Pentostatin is a purine analog that inhibits DNA synthesis and is used for the treatment of hairy cell leukemia" Handbook of Clinical Neurology, 2014.
38. M. Abdollahi, A. Hosseini, in Encyclopedia of Toxicology (Third Edition), 2014,NationalCenter for Biotechnology Information (2021). PubChem Compound Summary for CID 29327, Streptozocin.
39. V. Savini, ... P. Fazii, in The Microbiology of Skin, Soft Tissue, Bone and Joint Infections, 2017.
40. Levine, O., &Zbuk, K. (2019). Colorectal cancer in adolescents and young adults: Defining a growing threat. Pediatric Blood Cancer, 66, e27941.
41. Siegel, R.L., Miller, K.D., & Jemal, A. (2020).Cancer statistics, Cancer Journal for Clinicians, 70, 7–30. doi: 10.3322/caac.21590.
42. Tan, L.T.-H., Ser, H.-L., Yin, W.-F., Chan, K.-G., Lee, L.-H., & Goh, B.-H. (2015).Investigation of antioxidative and anticancer potentials of streptomyces sp. Mum256 isolated from Malaysia mangrove soil, Frontiers in Microbiology, 6, 1316.
43. Angel TreasaThomas, Venkata Rao, Mallikarjun,NaseerMaliyakkal,TukaramKedar Kisan, Alex Joseph, NayanabhiramaUdupa,In vitro anticancer activity of microbial isolates from diverse habitats,Brazilian Journal of Pharmaceutical Sciences vol. 47, n. 2, apr./jun., 2011
44. Khusro, A., C. Aarti and P. Agastian, 2016. Anti-tubercular peptides: A quest of future therapeutic weapon to combat tuberculosis. Asian Pac. J. Trop. Med., 9: 1023-1034.
45. Khusro, A., 2016. Therapeutic potential of anti-tubercular peptides: A million-dollar question. EC Microbiol., 4: 697-698.
46. Ravikumar, S.; Fredimoses, M.; Gnanadesigan, M. Anticancer property of sediment actinomycetes againstmcf-7 and mda-mb-231 cell lines. Asian Pac. J. Trop. Biomed. 2012, 2, 92.
47. Fu, S.;Wang, F.; Li, H.; Bao, Y.; Yang, Y.; Shen, H.; Lin, B.; Zhou, G. Secondary metabolites from marine-derivedStreptomycesantibioticus strain h74-21. Nat. Prod. Res. 2016, 30, 2460–2467.
48. I. Trabelsi, D. Oves, A. Manteca, O. Genilloud, A. Altalhi, and M. Nour, Curr. Microbiol. 73, 220 (2016).10.1007/s00284-016-1053-5
49. S.B. Zotchev, J. Biotechnol. 158, 168 (2012) .10.1016/j.jbiotec.2011.06.002
50. K. Shiomi, K. Hatae, H. Hatano, A. Matsumoto, Y. Takahashi, C.L. Jiang, H. Tomoda, S. Kobayashi, H. Tanaka, and S. Qmura, J. Antibiot. 58, 74 (2005).10.1038/ja.2005.10
51. S.N. Fu, F. Wang, H.Y. Li, Y.X. Bao, Y. Yang, H.F. Shen, B.R. Lin, and G.X. Zhou, Nat. Prod. Res. 30, 2460 (2016).10.1080/14786419.2016.1201668
52. P.J. Zhao, G.H. Li, and Y.M. Shen, Chem. Biodiver. 3, 337(2006).10.1002/(ISSN)1612-1880
53. SSudhaaSelvamMMasilamanib;Asian Pacific Journal of Tropical BiomedicineVolume 2, Issue 10, October 2012, Pages 770-773.
54. Hanan M.Abd-ElnabyaGehan,M.Abo-ElalaaUsama,M.Abdel-RaoufbMoazM.Hameda,The Egyptian Journal of Aquatic Research,Volume 42, Issue 3, September 2016, Pages 301-312
55. Abdeen, S., Geo, S., Sukanya, S., Praseetha, P.K., Dhanya, R.P., 2014.Biosynthesis of Silver nanoparticles from Actinomycetes for therapeutic applications. Int. J. Nano Dimension 5 (2), 155–162.Abd-Elnaby, H., Abo-Elala, G., Abdel-Raouf, U., Abdelwahab, A.,
56. Hamed, M., 2016. Antibacterial and anticancer activity of marineStreptomycesparvus: optimization and application. Biotechnol. Biotechnol. Equip. 30 (1), 180–191.
57. Abou-Elela, G.M., El-Sersy, N.A., Wefky, S.H., 2009. Statisticaloptimization of cold adapted a´ -amylase production by free and immobilized cells of Nocardiopsisaegyptia. J. Appl. Sci. Res. 5 (3),286–292.
58. Bhosale, R.S., Hajare, K.Y., Mulay, B., Mujumdar, S., Kothawade,M., 2015. Biosynthesis, characterization and study of antimicrobial effect of silver nanoparticles by Actinomycetes spp. Int. J. Curr. Microbiol. Appl. Sci. 2, 144–151.

59. Brause, R., Moeltgen, H., Kleinermanns, K., 2002. Characterization oflaser-ablated and chemically reduced silver colloids in aqueous solution by UV/VIS spectroscopy and STM/SEM microscopy.Appl. Phys. B Lasers Opt. 75, 711–716.
60. Chauhan, R., Kumar, A., Abraham, J., 2013. Biological approach tothe synthesis of silver nanoparticles with Streptomyces sp JAR1 and its antimicrobial activity. Sci. Pharm. 81 (2), 607–621.
61. Cochran, W.G., Snedecor, G.W., 1989. Statistical Methods. IowaState University Press, Ames (IA), USA.
62. Deepa, S., Kanimozhi, K., Panneerselvam, A., 2013. Antimicrobialactivity of extracellularly synthesized silver nanoparticles from marine derived actinomycetes. Int. J. Curr. Microbiol. Appl. Sci. 2 (9), 223–230.
63. Golinska, P., Wypij, M., Ingle, A.P., Gupta, I., Dahm, H., Rai, M.,2014. Biogenic synthesis of metal nanoparticles from actinomycetes:biomedical applications and cytotoxicity. Appl. Microbiol.Biotechnol. 98 (19), 8083–8097.
64. Hall, T.A., 1999. BioEdit: a user-friendly biological sequence alignmenteditor and analysis program for Windows 95/98/NT. Nucl. Acids Symp. Ser. 4, 95–98.
65. Iravani, S., 2014. Bacteria in nanoparticle synthesis: current status andfuture prospects. Int. Scholarly Res. Not. 2014, 1–18.
66. Jaidev, L.R., Narasimha, G., 2010. Fungal mediated biosynthesis ofsilver nanoparticles, characterization and antimicrobial activity.Colloids Surf. B 8, 430–433.
67. Kaler, A., Jain, S., d Banerjee, U.C., 2013. Green and rapid synthesisofanticancerous silver nanoparticles by Saccharomyces boulardii and insight into mechanism of nanoparticle synthesis. BioMed Res.Int. 2013, 1–8.
68. Sanjivkumar, M.; Babu, D.R.; Suganya, A.; Silambarasan, T.; Balagurunathan, R.; Immanuel, G. Investigationon pharmacological activities of secondary metabolite extracted from a mangrove associated actinobacteriumStreptomycesolivaceus (msu3). Biocatal. Agric. Biotechnol. 2016, 6, 82–90.
69. Hu, C.; Zhou, S.-W.; Chen, F.; Zheng, X.-H.; Shen, H.-F.; Lin, B.-R.; Zhou, G.-X. Neoantimycins a and b,two unusual benzamido nine-membered dilactones from marine-derived Streptomyces antibioticus h12-15.Molecules 2017, 22, 557.
70. Manivasagan, P.; Kang, K.H.; Sivakumar, K.; Li-Chan, E.C.Y.; Oh, H.M.; Kim, S.K. Marine actinobacteria:An important source of bioactive natural products. Environ. Toxicol. Pharmcol. 2014, 38, 172–188.
71. Ramesh, S.;William, A.Marine actinomycetes: An ongoing source of novel bioactive metabolites.Microbiol. Res.2012, 167, 571–580.
72. William, F.; Paul, J.R. Developing a new resource for drug discovery: Marine actinomycete bacteria.Nat. Chem. Biol. 2006, 2, 666–673.
73. Tan, H.S.; Che, Q.; Li, D.H.; Gu, Q.Q.; Zhu, T.J. Progress in the research of antimycin-type compounds.Chin. J. Antibiot. 2015, 40, 892–900.
74. Van Tamelen, E.E.; Dickie, J.P.; Loomans, M.E.; Dewey, R.S.; Strong, F.M. The chemistry of antimycin A.X.Structure of Antimycins. J. Am. Chem. Soc. 1961, 83, 1639–1646.
75. Imamura, N.; Nishijima, M.; Adachi, K.; Sano, H. Novel antimycin antibiotics, urauchimycins A and B,produced by marine actinomycete. J. Antibiot. 1993, 46, 241–246.
76. Hayashi, K.; Nozaki, H. Kitamycins, new antimycin antibiotics produced by Streptomyces sp. J. Antibiot. 1999,52, 325–328.
77. Yan, L.L.; Han, N.N.; Zhang, Y.Q.; Yu, L.Y.; Chen, J.;Wei, Y.Z.; Li, Q.P.; Tao, L.; Zheng, G.H.; Yang, S.E.; et al.Antimycin A18 produced by an endophytic Streptomyces albidoflavus isolated from a mangrove plant.J. Antibiot. 2010, 63, 259–261.
78. Nobuo, H.; Kazuo, K.; Hiroyuki, N.; Takuro, S.; Ikutaro, S. Antimycins A10~A16, seven new antimycinantibiotics produced by Streptomyces spp. SPA-10191 and SPA-8893. J. Antibiot. 2005, 58, 460–467.
79. Tzung, S.P.; Kim, K.M.; Basanez, G.; Giedt, C.D.; Simon, J.; Zimmerberg, J.; Zhang, K.Y.J.; Hockenbery, D.M.Antimycin A mimics a cell-death inducing Bcl-2 homology domain 3. Nat. Cell Biol. 2001, 3, 183–191.
80. Tan, L.T.-H.; Chan, C.-K.; Chan, K.-G.; Pusparajah, P.; Khan, T.M.; Ser, H.-L.; Lee, L.-H.; Goh, B.-H. Streptomycessp. Mum256: A source for apoptosis inducing and cell cycle-arresting bioactive compounds against coloncancer cells. Cancers 2019, 11, 1742.
81. Ferlay,J.; Soerjomataram, I.; Dikshit, R.; Eser, S.; Mathers, C.; Rebelo, M.; Parkin, D.M.; Forman, D.; Bray, F.Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012.Int. J. Cancer 2015, 136, E359–E386.
82. Arnold, M.; Sierra, M.S.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global patterns and trends incolorectal cancer incidence and mortality. Gut 2017, 66, 683–691.

83. Lee, M.-T.G.; Chiu, C.-C.;Wang, C.-C.; Chang, C.-N.; Lee, S.-H.; Lee, M.; Hsu, T.-C.; Lee, C.-C. Trends and Outcomes of Surgical Treatment for Colorectal Cancer between 2004 and 2012-an Analysis using National Inpatient Database. Sci. Rep. 2017, 7, 2006.
84. Chatterjee, K.; Zhang, J.; Honbo, N.; Karliner, J.S. Doxorubicin cardiomyopathy. Cardiology 2010, 115, 155–162.
85. Steele, T.A. Chemotherapy-induced immunosuppression and reconstitution of immune function. Leuk. Res.2002, 26, 411–414.
86. Jin, J.; Wu, X.; Yin, J.; Li, M.; Shen, J.; Li, J.; Zhao, Y.; Zhao, Q.; Wu, J.; Wen, Q. Identification of geneticmutations in cancer: Challenge and opportunity in the new era of targeted therapy. Front. Oncol. 2019, 9,263.
87. Khoo, X.-H.; Paterson, I.C.; Goh, B.-H.; Lee,W.-L. Cisplatin-Resistance in Oral Squamous Cell Carcinoma:Regulation by Tumor Cell-Derived Extracellular Vesicles. Cancers 2019, 11, 1166. Eng, S.-K.; Loh, T.H.T.; Goh, B.-H.; Lee, W.-L. KRAS as Potential Target in Colorectal Cancer Therapy.
88. In Natural Bio-active Compounds; Springer: New York, NY, USA, 2019; pp. 389–424.
89. Chan, C.K.; Tang, L.Y.; Goh, B.H.; Kadir, H.A. Targeting apoptosis via inactivation of PI3K/Akt/mTOR signaling pathway involving NF-B by geraniin in HT-29 human colorectal adenocarcinoma cells. Prog. Drug Discov. Biomed. Sci. 2019, 2, a0000030.
90. Pan, P.; Skaer, C.; Yu, J.; Zhao, H.; Ren, H.; Oshima, K.;Wang, L.S. Berries and other natural products in the pancreatic cancer chemoprevention in human clinical trials. J. Berry Res. 2017, 7, 147–161.
91. Kotecha, R.; Takami, A.; Espinoza, J.L. Dietary phytochemicals and cancer chemoprevention: A review of the clinical evidence. Oncotarget 2016, 7, 52517–52529.
92. Cancers 2019, 11, 1742 22 of 2512.Tan, L.T.H.; Low, L.E.; Tang, S.Y.; Yap, W.H.; Chuah, L.H.; Chan, C.K.; Lee, L.H.; Goh, B.H. A reliable and aordable 3D tumor spheroid model for natural product drug discovery: A case study of curcumin.Prog. Drug Discov. Biom. Sci. 2019, 2, a0000017.
93. HefaMangzira Kemung1,2, Loh Teng-Hern Tan2, Kok-Gan Chan3,4, Hooi-Leng Ser 2, Jodi Woan-FeiLaw2, Bey-Hing Goh1,5,6: progress in microbes and molecular biology, 2020;3(1):a0000087.
94. Zhang J and Piantadosi CA, Mitochondrial oxidative stress aftercarbon monoxide hypoxia in the rat brain. J Clin Invest 1992; 90(4):1193–1199.
95. Hue Thi Nguyen1, Anaya Raj Pokhrel 1, Chung Thanh Nguyen1, Van Thuy Thi Pham1,Dipesh Dhakal 1, HaetNim Lim1, Hye Jin Jung1,2, Tae-Su Kim1, Tokutaro Yamaguchi 1,2 &Jae Kyung Sohng1,2; scientific reports (2020) 10:1756
96. Law, J.W.-F.; Ser, H.-L.; Ab Mutalib, N.-S.; Saokaew, S.; Duangjai, A.; Khan, T.M.; Chan, K.-G.; Goh, B.-H.;Lee, L.-H. STREPTOMYCES monashensis sp. Nov., a novel mangrove soil actinobacterium from east Malaysia with antioxidative potential. Sci. Rep. 2019, 9, 3056.
97. Are, C.; McMasters, K.M.; Giuliano, A.; Yanala, U.; Balch, C.; Anderson, B.O.; Berman, R.; Audisio, R.;Kovacs, T.; Savant, D. Global forum of cancer surgeons: Perspectives on barriers to surgical care for cancer patients and potential solutions. Ann. Surg. Oncol 2019, 26, 1577–1582.
98. AtinAdhikariaEric, M.KettlesonaStephen, VesperbSudhirKumara, David L.Pophamc, ChristopherSchaffera, ReshmiIndugulaa, Kanistha, Chatterjeea, KarteekK.AllamaSergey, A.GrinshpunaTiinaReponena;Science of The Total Environment,Volumes 482–483, 1 June 2014, Pages 92-99.