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A Comprehensive Review of Natural Products from Microbial Sources and their Applications

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Abstract:
Secondary metabolites, or natural products produced by living organisms, are important in drug discovery and development. Many nations have used natural products in their traditional medicine remedies in the past decades. Microbes produce different types of natural compounds that are useful in the treatment of different diseases, such as cancer, bacterial and fungal infections. This review summarizes different types of natural products derived or extracted from different microbes and their applications.

INTRODUCTION

Natural products (NPs) are bioactive molecules that are helpful in the drug discovery process. Natural products, secondary metabolites, produced by living organisms, such as microorganisms, plants, and animals (Baker *et al*., 2000; Ebada *et al*., 2008; Iqbal and Ashraf, 2018) have been improving human life for thousands of years (Shen, 2015). One of the oldest records of using natural products belonged to ancient Mesopotamia (2600 BC) which described about 1000 plants and plant-derived materials, such as cedar oils (*Cedrus species*) and the juice of the *Papaver somniferum* poppy seed and the resin of *Commiphora myrrha* (myrrh) (Newman *et al*., 2000). Also, more than 700 natural compounds and around 800 complexes including *Aloe vera* (aloe) and *Ricinus communis* (castor) oil, and *Boswellia carteri* (frankincense) have been described by the ancient Egyptian Ebers Papyrus (1550 BC) (Zhong and Wan, 1999). Many natural compounds and plant-derived substances were collected by the legendary Greek physicians and pharmacist Hippocrates of Cos (circa 460–377 BC). He described the diuretic effect of *Ornithogalum caudatum* (squill) juice, the anesthetic effect of extract from *Atropa belladonna*, the emetic effect of *Veratrum album* (white hellebore) extract, the use of melon juice as a laxative and using of olive oil to speed wound healing (Cheng and Zhen, 2004; Castiglioni,1985). For decades many nations used natural products as a traditional medical remedy. One of the famous nations is Chinese and in 1979 about 5967 medicinal herbs were used in China (Petrovska, 2012; Patwardhan and Mashelkar, 2009).

Natural products from microbial sources

Since penicillin was discovered by Alexander Fleming in 1928 and its structure was explained and introduced as the first antibiotic by Fleming, Chain, and Florey in 1945 and also the discovery of streptomycin in 1943 by Waksman, Woodruff, Schatz, and Lechevalier, microorganisms have become an important substitutional source in the production of natural product drugs (Fenical, 1993; Fleming, 1980; Demain and Adrio, 2008; Gaynes, 2017; Woodruff *et al.,* 2014).

Microorganisms as sources of antioxidant compounds

Antioxidants are molecules (mainly reactive oxygen and nitrogen species (ROS and RNS) which are generated from metabolic pathways (Nathan and Cunningham, 2013; Lushchak, 2014) such as lipid β-oxidation and mitochondrial respiratory chain and are capable of causing damage to different cells or molecules such as cell organelles or nucleic acids, proteins and lipids (Netzker *et al*., 2018; Nimse and Pal, 2015; Schieber and Chandel, 2014; Krumova and Cosa, 2016). High levels of ROS and RNS can cause tissue damage due to oxidative stress and involved in many diseases like autoimmune disorders, cardiovascular diseases, diabetes, cancer, neurodegenerative diseases and aging (Amin and Edris, 2017; Ashraf *et al.,* 2020; Nimse and Pal, 2015; Chehue *et al*., 2013; Phaniendra *et al*., 2015; Xu and Leeuwenburgh, 2015; Forbes *et al*., 2007; Gupta *et al*., 2013).

In a study, ethyl acetate extracts of several *Aspergillus* and *Penicillium* species including *Rhizopus oryzae*, were evaluated. Only four extracts of *Aspergillus* and two extracts of *Penicillium* species protected linoleic acid better than the control. Also, it's reported that probiotic bacteria *Streptococcus thermophiles* have powerful antioxidant activity, protecting the body from oxidative stress caused by free radicals which increase in the body due to sugar, antibiotics, stress, aging, and toxins (Malpur *et al*., 2006; Kim, 2013).

Also, an important potential source of antioxidants is *actinobacteria*. *Streptomyces* strains isolated in the Oman Sea showed an *in vitro* inhibitory concentration (IC_{50}) against 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical inhibition, which ranges from 356.8 to 566.4 µg/mL (Gozari *et al*., 2019).

Extract from strain *Streptomyces antioxidans* at a concentration of 1.5 mg/mL, isolated from the forest of Tanjung Lumpur, exhibited antioxidant activity (79.84%) against superoxide radicals. Fatty acids, pyrazines, and phenolic compounds were the most abundant compounds in the extract (Ser *et al*., 2016). Also, similar compounds were found in a strain of *Streptomyces Monachensis*, isolated from a mangrove in Malaysia, with antioxidant activity of 83.80 and 75.50% against superoxide radical and metal chelating activity (Law *et al*., 2019).

An important factor affecting the production of antioxidant compounds is growth media. In a study, culture media containing sucrose or lactose and ammonium sulfate enhanced the production of antioxidants by *Aspergillus candidus* CCRC 31543 (Yen and Chang, 1999).

Streptomyces variabilis (isolated from the Gulf of Khambhat) was cultured in six different media which are glycerol asparagine agar (ISP5), tyrosine agar (ISP7), Gause synthetic agar (GSA), inorganic salt agar (ISP4), yeast malt extract agar (ISP2) and starch casein agar and incubated for 7–9 days at 30°C. Among these media, the GSA medium was selected due to the larger quantity of cell mass production compared to other media. After the extraction of metabolites using ethyl acetate antioxidant activity tests were performed using DPPH, metal, and hydrogen peroxide (H_2O_2) radical tests using concentrations ranging from 0.5 to 2.0 mg/mL. The best radical scavenging activity was against H_2O_2 radical at a concentration of 0.5 mg/mL with 64% antioxidant activity (Dholakiya *et al*., 2017).

Carotenoid pigments are a group of antioxidants that can be synthesized and extracted from microorganisms due to their potential coloring properties. These pigments are used as vitamins in the case of carotenes and xanthophylls which can be found on microalgae (*Haematococcus pluvialis*), bacteria (*Gordonia rubropertincta*), and yeast (*Blakeslea trispora*) (De Carvalho *et al*., 2014). Carotenoids, glycosidic carotenoids, extracted from *Rhodococcus* sp. and *Gordonia* sp. showed good antioxidant activity against DPPH radical with IC_{50} of 1.07 and 0.09 µg/mL, respectively (Ortega *et al*., 2016).

Commercially, a carotenoid pigment from a mutant strain of *Rhodobacter sphaeroides* is available to be used as a supplement like Lycogen™, it contains spheroid enone, bixin (a carotenoid found on *Bixa orellana* L.) and hydroxy spheroid enone (Wang *et al*., 2016; Li *et al*., 2017; Raddatz-Mota *et al*., 2017). Also, astaxanthin pigment from microalgae *Haematococcus pluvialis* is already available. The anticipated production cost is $552/Kg which is cheaper than the synthetic carotenoids ($1000/Kg) (Saini and Keum, 2017).

Microorganisms as sources of anti-inflammatory compounds

Several microorganisms contain natural products that exhibit anti-inflammatory properties. Natural microbial product, FK506 (Tacrolimus), isolated from *Streptomyces tsukubaensis* decreases inflammatory mediator expression through inhibition of the release of mast cell and basophil mediators. Also, it has efficacy in the treatment of chronic inflammatory disease rheumatoid arthritis (Mark *et al*., 2016; Migita and Eguchi, 2003).

In a study conducted by Breyner *et al*., 2017, seven peptides were found in the supernatant of *Faecalibacterium prausnitzii* which have *in vivo* anti-inflammatory properties in a dinitrobenzene sulfate-induced colitis model and also inhibit *in vitro* NF-κB pathway. Another natural product isolated from *Streptomyces* sp. SCSIO 10355, strepsesquitriol, inhibited the production of tumor necrosis factor in lipopolysaccharide-activated macrophages, demonstrating anti-inflammatory activity (Yang *et al*., 2013).

Rapamycin (RAPA), known as sirolimus, has an anti-inflammatory effect by providing a neuroprotective effect after spinal cord injury (Song *et al*., 2015). Also, researchers demonstrated the effect of RAPA as anti-inflammatory compound *in vitro* and *in vivo* (Zheng *et al*., 2017). These compounds are fermentation products extracted from

Streptomyces hygroscopicus, which was isolated from a soil sample collected on Easter Island in 1976 (Abraham and Wiederrecht, 1996). Also, other compounds, Salinamides A and B, obtained from marine *Streptomyces* sp. CNB-091 showed a potent topical anti-inflammatory activity through a phorbol ester-induced mouse ear edema assay (Trischman *et al*., 1994). Another anti-inflammatory compound is Phomol obtained from *Phomopsis* sp. (Weber *et al*., 2004).

Microorganisms as sources of antibiotics

There are many microorganisms from which antibiotic compounds can be derived (Yunus *et al.,* 2016). The first known medically useful antibiotic was penicillin which was produced by fungus *Penicillium notatum*. After penicillin discovery, several antibiotics were produced from different microorganisms. Streptomycin and neomycin are produced from *actinomycetes.* Chlortetracycline (aureomycin, biomycin) is produced by *Streptomyces aureofaciens*, which have activity against Gram-positive and Gram-negative bacteria (Demain, 2014). Penicillin is effective against Gram-positive bacteria, which are responsible for diseases such as diphtheria, gonorrhea, meningitis, scarlet fever, and pneumonia (Fleming, 2001; Tan and Tatsumura, 2015).

Filamentous bacteria (*actinomycetes*) (Baltz, 2007) are known to produce a considerable number of antibiotics which include β-lactams (Aoki *et al*., 1976), heptadecaglycosides (Singh *et al*., 2000), anthraquinones (Takahashi *et al*., 1988), piercings (Hayakawa *et al*., 2007), octapeptide (Radzom *et al*., 2006), tetracyclines (Hatsu *et al*., 1992), phenazines (Maskey *et al*., 2003), peptides/glycopeptides (Kimura *et al*., 1997), angucyclinone (Sun *et al*., 2007), macrolides (Tanaka *et al*., 1997), polyenes (Lemriss *et al*., 2003), anthracyclines (Maeda *et al*., 1994), benzoxazolophenanthridines (Doull *et al*., 1994) and lactones (Imai *et al*., 1987). Approximately, 75 % of the antibiotics are produced by *actinomycetes* and about 75 % of these are made by a single genus, *Streptomyces*. Strains of *Streptomyces hygroscopicus* make almost 200 antibiotics (Demain, 2014). The bacterial strain *Streptomyces griseus* produces more than 40 different antibiotics. Also, the *Bacillus subtilis* strain produces more than 60 antibiotic substances (Dworkin, 2007).

A large number of antibiotics have been produced by bacterial strains which include kanamycin, produced by *Streptomyces kanamyceticus* (Yanai *et al*., 2004), thienamycin, produced by *Streptomyces cattleya*, vancomycin, produced by *Streptomyces orientalis* (Williamson *et al*., 1985), neomycin, produced by *streptomyces fradiae* (Dulmage, 1953), streptomycin, produced by *streptomyces griseus* (Meanwell *et al*., 2008), chloramphenicol produced by *streptomyces venezuelae* (Vitayakritsirikul *et al*., 2016), erythromycin, produced by *streptomyces erythraea* and tetracycline produced by *streptomyces rimosus* (Petkovi´c, 2006). Vancomycin is effective against pathogenic bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), *Listeria monocytogenes*, *Staphylococcus epidermidis*, *Clostridium difficile* and *Streptococcus pneumonia* (Dasgupta, 2012).

Also, some FDA-approved drugs from bacteria include Tigecycline produced by *Streptomyces aureofaciens* (Zhanel *et al*., 2004), Biapenem and Ertapenem produced by *Streptomyces cattleya* (Perry and Ibbotson, 2002; Keating and Perry, 2005) and Telithromycin produced by *Saccharopolyspora erythraea* (Zhanel *et al*., 2002).

An important type of antibiotic that is also produced in high amounts for commercial use is β-lactam antibiotics. β- Lactam antibiotics are natural or derived from natural products which include Glycopeptides such as vancomycin and teicoplanin are produced at a total of 9,000 tons, cephalexin (4,000 tons), cefadroxil (1,000 tons), ampicillin (5,000 tons per year), amoxicillin (16,000 tons), and Macrolides which include azithromycin (1,500 tons) and clarithromycin (1,500 tons) (Arnold, 2014).

Even though β-lactamases are responsible for the major cause of resistance development, β-lactam compounds are still very helpful due to the discovery of β-lactamase inhibitors. Approximately, 40 different -lactam compounds are utilized in medicine. These include broad-spectrum activity doripenem (S-4661), which also has efficiency against *Pseudomonas aeruginosa*. Also, other β-lactam compounds include carbapenems, clavulanic acid, ceftobiprole, meropenem, ceftaroline tomopenem, and faropenem (Hugonnet *et al*., 2009).

Two compounds ieodoglycolipid were isolated from the marine bacterium *Bacillus licheniformis*, ieodoglucomide C and ieodoglycolipid, exhibited antibiotic properties against *Salmonella typhi*, *P. aeruginosa*, *Bacillus subtilis*, *B. cereus*, *S. aureus,* and *E. coli* with MICs ranging from 0.01 to 0.05 µM (Tareq, 2015).

Microorganisms as sources of antifungal compounds

Many microorganisms contain compounds that exhibit an antifungal activity. Polyene antifungal agent Nystatin from *Streptomyces noursei* is effective against *Aspergillus* species (Stanley and English, 1965) and clinically plays a significant role as a topical antifungal agent in treating genital, gastro-intestinal and oral candidiasis (Fjærvik and Zotchev, 2005).

Endophytic *Streptomyces aureofaciens* CMUAc130 produces two compounds, 5, 7-dimethoxy-4-phenylcoumarin and 5, 7-dimethoxy-4-p-methoxylphenyl coumarin, which exhibits antifungal activity (Taechowisan *et al*., 2007).

Additionally, Amphotericin B, an antifungal produced by *Streptomyces nodosus*, is effective against life-threatening fungal infections caused by Aspergillus species, especially in patients undergoing organ transplantation, undergoing aggressive chemotherapy, or having acquired immunodeficiency syndrome (Abu-Salah, 1996; Tevyashova *et al*., 2013).

An antifungal Peptide from *B. amyloliquefaciens* sybc H47 was extracted and analyzed by (Li *et al*., 2016). This substance showed a significant effect on a variety of pathogenic fungi including *Penicillium citrinum, Aspergillus niger, Fusarium oxysporum*, *and Candida albicans*. A list of antifungal peptides (Li *et al*., 2021) that exhibited an activity as antifungal is listed in Table 1.

Microorganisms as sources of Immunosuppressive compounds

There are some natural products produced by microbes that act as immunosuppressive agents. Both Mycophenolic acid from the fungus *Penicillium stoloniferum* and Cyclosporin A from the fungus *Tolypocladium inflatum* are used as immunosuppressive agents in organ transplantation. Cyclosporin A is used in heart, liver, and kidney transplants (Courtwright, 2009; Newman and Cragg, 2012; Viaud *et al*., 2013).

Other immunosuppressive agents are Rapamycin (sirolimus) and FK506 (tacrolimus) which are produced from *Streptomyces rapamycinicus* and *Streptomyces tsukubaensis*. Rapamycin is used as an immunosuppressant in kidney transplants and FK506 in liver, heart, pancreas, intestines, kidney, lung, cornea, trachea, small bowel, skin, bone marrow, and limb transplants. FK506 was approved by the FDA for use as an immunosuppressant (Kim *et al*., 2014; Tanaka *et al*., 1987; Nagano *et al*., 2006).

Microbial red pigments Prodigiosins produced by *Serratia marcescens* and Pigments produced by *Monascu*, both have immunosuppressive activity (Pandey *et al*., 2007). Also, the Everolimus compound produced by *streptomyces hygroscopicus* can suppress the immune system. (Chapman and Perry, 2004).

Table 1. Antifungal peptides and their applications.

Antifungal Peptide	Source (Microbial Species)	Fungal Species (active against)	Reference
HP 2-20	*Helicobacter pylori*	*Candida albicans* and *Hyphomyces burnetii*	Ribeiro and Medina-Acosta, 2003
EntV	*Enterococcus faecalis*	*C. albicans, C. tropicalis, C. paraplanatus,* etc.	Graham *et al*., 2017
Chitinase	Marine *streptomyces* DA11	*Aspergillus niger* and *Candida albicans*	Han *et al*., 2009
Chandrananimycin A	Marine *Actinomycetes* M045	*M. miehei*	Maskey *et al*., 2003
Fusaricidin A	*Paenibacillus polymyxa* KT-8	*Fusarium oxysporum, Aspergillus niger, Saccharomyces cerevisiae, Magnaporthe grisea*, etc	Kajimura and Kaneda, 1996; Hua *et al*., 2020
Syringostatin A, syringostatin E	*Pseudomonas syringae*	Yeasts, filamentous fungi	Sorensen *et al*., 1996
Nikkomycin Z	*Streptomyces tendae*	*Glomus, Aspergillus fumigatus,* etc.	Hector *et al*., 1990; Ganesan *et al*., 2004
Polyoxin D	Actinomycete *Streptomyces cacao*	*Candida albicans, Cryptococcus neoformans*, etc.	Becker *et al*., 1983
Iturin A	*Bacillus subtilis* CCTCCM207209	*Candida, Hyphomyces cerevisiae, Fusarium* and *Aspergillus*	Lei *et al*., 2019; Klich *et al*., 1991
Not named	*Bacillus velezensis* DTU001	*Candida, Penicillium, Aspergillus,* etc	Devi *et al*., 2019
Echinocandin B	*Aspergillus nidulans*	*Candida*	Nyfeler *et al*., 1974
VL-2397	*Acremonium persicinum*	*Aspergillus, Cryptococcus neoformans, Candida glabrata*, etc	Nakamura *et al*., 2017
Aureobasidin A (AbA)	*Aureobasidium pullulans*	*Candida, Cryptococcus neoformans, Blastomyces dermatitis* etc	Takesako *et al*., 1993; Takesako *et al*., 1991

Microorganisms as sources of anticancer compounds

Microbial compounds are one of the most important agents used in cancer treatment. The first antibiotic shown to have anticancer activity was polyketide actinomycin which was isolated from *Streptomyces parvulus* in 1940. Actinomycin D (dactinomycin) is widely used as an anticancer drug for treating many tumors, such as metastatic, non-seminomatous testicular cancer, childhood rhabdomyosarcoma, Wilms'

tumor and Ewing's sarcoma in clinical practice (Waksmanand Woodruff, 1940; Hollstein, 1974).

In addition to its immunosuppressive, anti-inflammatory, and antifungal properties, rapamycin, is a natural product derived from *Streptomyces rapamycinicus* (Kim *et al*., 2014) and inhibits angiogenesis, tumor cell proliferation, and acts as an antitumor agent on a tumor cell (Law, 2005).

Another glycopeptide anticancer agent is bleomycin which is produced by *Streptoalloteichus hindustanus*. It's used in the treatment of sarcomas, ovarian melanomas and testicular cancer, testis tumors, Hodgkin's and non-Hodgkin's lymphomas, and squamous cell carcinomas. Also, blenoxane, a derivative of bleomycin, is used with other compounds against head, neck, and testicle tumors, lymphomas, and skin carcinomas (Demain and Vaishnav, 2011). Other examples of anticancer agents are epothilone which produced from mycobacterium *Sorangium cellulosum* (Molnar *et al*., 2000), and dolastatin (marine microbial natural products) which is originated from *cyanobacteria* of the genera *Symploca and Lyngbya* (Simmons *et al*., 2008). In addition, fungal furanosteroid, represented by Wortmannin, extracted from *Penicillium funiculosum* is useful against human breast MCF-7 cancer cells (Davidson *et al*., 2013). Benzoquinone ansamycin antitumor compound, Geldanamycin and its analogs, derived from *Streptomyces hygroscopicus* var. geldanus, play an important role as an anticancer agent in multiple myeloma, breast, and prostate cancer (Singh *et al*., 2010; Gorska *et al*., 2012).

Taxol compound produced by the endophytic fungi *Taxomyces Andreae* and *Nodulisporium styliform* exhibited anticancer activity against breast and advanced forms of Kaposi's sarcoma. It's also approved for refractory ovarian cancer (Newman and Cragg, 2007). On the other side, compounds produced from brown alga, *Dictyota dichotoma* possess antitumor activity which are 4-acetoxydictylolactone, dictyolide A, B (diterpenes), and nordictyolide compounds (Asolkar *et al*., 2010; Vuong, 2017).

Myxobacteria, relatively large Gram-negative rods, are an unusual source of secondary metabolites which possess antitumor activity. Approximately 400 compounds had been isolated from *myxobacteria* and in clinical trials epothilones were active against taxol-resistant tumors. Also, *myxobacterium Sorangium cellulosum* produces 16-member ring polyketide macrolide lactones which have antitumor activity. They are active against breast cancers, including those that don't respond to taxol or other chemotherapy (Gerth *et al*., 2000; Goodin, 2008). Two compounds exhibited antitumor activity, 5, 7-dimethoxy-4-phenylcoumarin and 5, 7-dimethoxy-4-p-methoxylphenyl coumarin, were isolated from endophytic *Streptomyces aureofaciens* (Taechowisan *et al*., 2007).

In addition, the *Streptomyces* group produced about two-thirds of antitumor bioactive compounds such as brostallicin (a derivative of distamycin A), daunorubicin, nogalamycin, actinomycin A, mithramycin, actinomycin D, bleomycin, mitomycin C and Amrubicin which isolated from *streptomyces distallicus, Streptomyces facetious, Streptomyces nogalater, Streptomyces galilaeus., Streptomyces argillaceusStreptomyces antibiotics, Streptoverticillium verticillium, Streptomyces lavendulae and Streptomyces peuceticus*, respectively (Broggini *et al*., 2004; Salas *et al*., 1998; Sugiura *et al*., 2005).

Microorganisms as sources of antivirus compounds

There are many types of viruses that infect humans and some of these virus infections lead to death. Recently many researchers focused on the antiviral activity of natural products produced by microbes. Table (2) summarizes the inhibition activity of some natural products on different viruses (Frediansyah *et al*., 2022).

Table 2. Natural products as antiviral agents.

Microbial Strain (Source)	**Compound Name and Type**	**Viral Target**	**$IC_{50}/EC_{50}/ED_{50}$**	**Target Inhibition**	**Ref.**
Cladosporium sp. 7951	aspulvinone D (polyphenol)	SARS-CoV-2	IC_{50}: 10.3 µM	Virus replication	Liang *et al*., 2022
Cladosporium sp. 7951	aspulvinone M (polyphenol)	SARS-CoV-2	IC_{50}: 9.4 µM	Virus replication	Liang *et al*., 2022
Cladosporium sp. 7952	aspulvinone R (polyphenol)	SARS-CoV-2	IC_{50}: 7.7 µM	Virus replication	Liang *et al*., 2022
AspAspergillus fumigatus MR2012	neoechinulin A (alkaloid)	SARS-CoV-2	IC_{50}: 0.47 µM	Virus replication	Alhadrami *et al*., 2022
Aspergillus niger No.LC582533	aurasperone A polyphenol	SARS-CoV-2	IC_{50}: 12.25 µM	Virus replication	ElNaggar *et al*., 2022
Penicillium purpurogenum JS03-21	purpurquinone B (polyketide)	H1N1	IC_{50}: 61.3 µM	ND	Wang *et al*., 2011
Penicillium purpurogenum JS03-22	purpurquinone C (polyketide)	H1N1	IC_{50}: 64 µM	ND	Wang *et al*., 2011
Penicillium purpurogenum JS03-23	purpurester A(polyketide)	H1N1	IC_{50}: 85.3 µM	ND	Wang *et al*., 2011
Penicillium purpurogenum JS03-24	TAN-931(polyketide)	H1N1	IC_{50}: 58.6 µM	ND	Wang *et al*., 2011
Penicillium camemberti	3-deoxy-4b-deoxypaxilline (alkaloid)	H1N1	IC_{50}: 28.3 µM	ND	Fan *et al*., 2013
P. camemberti OUCMDZ-1492	TTD (alkaloid)	H1N1	IC_{50}: 34.1 µM	ND	Fan *et al*., 2013
P. camemberti OUCMDZ-1492	paspaline (alkaloid)	H1N1	IC_{50}: 77.9 µM	ND	Fan *et al*., 2013
P. camemberti OUCMDZ-1492	DPT (alkaloid)	H1N1	IC_{50}: 32.2 µM	ND	Fan *et al*., 2013
P. camemberti OUCMDZ-1492	emindole SB (alkaloid)	H1N1	IC_{50}: 26.2 µM	ND	Fan *et al*., 2013
P. camemberti OUCMDZ-1492	DCA (alkaloid)	H1N1	IC_{50}: 38.9 µM	ND	Fan *et al*., 2013
Podospora vesticola XJ03-56-1	alachalasin A (alkaloid)	HIV-1	EC_{50} = 8.01 µM	ND	Zhang *et al*., 2008
Epicoccum nigrum	epicoccin G (alkaloid)	HIV-1	EC_{50} = 13.5	ND	Wang *et al*.,

XZC04-CS-302			µM		2020
Stachybotrys chartarum MXH-X73	Stachybotrin D (terpenoid)	HIV-1	EC_{50} = 8.4 µM	replication	Ma *et al*., 2013
Truncatella angustata XSB-01-43	truncateol O (terpenoid)	HIV-1 and H1N1	IC_{50} = 39.0 µM (HIV) and 30.4 µM (H1N1)	ND	Zhao *et al*., 2018
Aspergillus fumigatus	penicillixanthone A (polyketide)	HIV-1	IC_{50} = 0.26 µM	entry	Tan *et al*., 2019
Penicillium raistrickii IMB17-034	raistrickindole A (alkaloid)	HCV	EC_{50}: 5.7 µM	ND	Li *et al*., 2019
Trichoderma harzianum LZDX-32-08	harzianoic acid A (terpenoid)	HCV	IC_{50}: 5.5 µM	entry	Zhao *et al*., 2017
Aspergillus versicolor	cyclo (L-Tyr-L-Pro) (peptide)	HCV	IC_{50}: 8.2 µg/mL	replication	Ahmed *et al*., 2017
Metarhizium anisopliae var. dcjhyium	destruxin A (peptide)	HBV	IC_{50}: 1.2 µg/mL (mix A+B+E)	ND	Dong *et al*., 2013
M. anisopliae var. echium	destruxin B (peptide)	HBV	IC_{50}: 1.2 µg/mL (mix A+B+E)	ND	Dong *et al*., 2013
M. anisopliae var. dcjhyium	destruxin E (peptide)	HBV	IC_{50}: 1.2 µg/mL (mix A+B+E)	ND	Dong *et al*., 2013
Aspergillus sp strain XS-2009	22-O-(N-Me-l-valyl)-21- epi-aflaquinolone B (alkaloid)	RSV	IC_{50}: 0.042 µM	ND	Chen *et al*., 2014
Aspergillus sp strain XS-2009	aflaquinolone D (alkaloid)	RSV	IC_{50}: 6.6 µM	ND	Chen *et al*., 2014

Note: ND: not yet described, TTD: (6S,7R,10E,14E)-16-(1H-indol-3-yl)-2,6,10,14-tetramethylhexadeca-2,10,14-triene-6,7-diol, * DPT: 4a-demethylpaspaline-3,4,4a-triol and DCA: 4a-demethylpaspaline-4a-carboxylic acid.

CONCLUSION

Different microbial strains can produce different types of bioactive natural products. They are active against cancer, and microbial infections and also act as immunosuppressant agents. To develop and focus on their useful applications in the treatment of numerous human diseases, additional experimental studies are required.

CONFLICT OF INTEREST

The author declares that this article's content has no conflict of interest.

REFERENCES

Abraham, R.T., Wiederrecht, G.J., 1996. Immunopharmacology of rapamycin. Annu. Rev. Immunol., 14(1): 483–510.

Abu-Salah, K.M., 1996. Amphotericin B: an update. Br. J. Biomed. Sci., 53(2): 122–133.

Ahmed, E., Rateb, M., El-Kassem, A., Hawas, U.W., 2017. Anti-HCV protease of diketopiperazines produced by the Red Sea sponge associated fungus *Aspergillus versicolor*. Appl. Biochem. Microbiol., 53(1): 101–106.

Alhadrami, H.A., Burgio, G., Thissera, B., Orfali, R., Jiffri, S.E., Yaseen, M., et al., 2022. Neoechinulin A as a promising SARS-CoV-2 Mpro inhibitor: *In vitro* and in silico study showing the ability of simulations in discerning active from inactive enzyme inhibitors. Mar. Drugs., 20(3): 163.

Aoki, H., Sakai, H.I., Kohsaka, M., Konomi, T., Hosoda, J., Kubochi, Y., et al., 1976. Nocardicin A, a new monocyclic β-lactam antibiotic. J. Antibiot., 29(5): 492–500.

Amin, R.A., Edris, S.N., 2017. Grape Seed Extract as Natural Antioxidant and Antibacterial in Minced Beef. PSM Biol. Res., 2(2): 89-96.

Arnold, L., 2014. Demain. Importance of microbial natural products and the need to revitalize their discovery. J Ind Microbiol Biotechnol., 41(2): 185–201.

Ashraf, A.,Ali, M.A., Iqbal, M.N., 2020. Monolluma quadrangula as the Protective and Curative Plant against Diabetes Mellitus. PSM Microbiol., 5(3): 89-91.

Asolkar, R.N., Kirkland, T.N., Jensen, P.R., Fenical, W., 2010. Arenimycin, an antibiotic effective against rifampin-and methicillin-resistant *Staphylococcus aureus* from the marine actinomycete *Salinispora arenicola*. J. Antibiot., 63(1): 37–39.

Baker, W., van den Broek, A., Camon, E., Hingamp, P., Sterk, P., Stoesser, G., Tuli, M.A., 2000. The EMBL nucleotide sequence database. Nucleic Acids Res., 28(1): 19–23.

Baltz, R.H., 2007. Antimicrobials from actinomycetes: back to the future. Microbe., 2(3): 125–131.

Becker, J.M., Covert, N.L., Shenbagamurthi, P., Steinfeld, A.S., Naider, F., 1983. Polyoxin D inhibits growth of *zoopathogenic* fungi. Antimicrob. Agents Chemother., 23(6): 926–929.

Breyner, N.M., Michon, C., De Sousa, C.S., Vilas Boas, P.B., Chain, F., Azevedo, V.A., et al., 2017. Microbial anti-inflammatory molecule (MAM) from *Faecalibacterium prausnitzii* shows a protective effect on DNBS and DSSinduced colitis model in mice through inhibition of NF-kappaB pathway. Front. Microbiol., 8: 114.

Broggini, M., Marchini, S., Fontana, E., Moneta, D., Fowst, C., Geroni, C., 2004. Brostallicin: A new concept in minor groove DNA binder development. Anticancer. Drugs., 15(1): 1–6.

Castiglioni, A., 1985. A History of Medicine. New York, NY, USA: Jason Aronson.

Chapman, T.M., Perry, C.M., 2004. Everolimus. Drugs., 64(8): 861–872.

Chehue Romero, A., Olvera Hernández, E.G., Flores Cerón, T., Álvarez-Chávez, A., 2013. The exogenous antioxidants. In: Morales-González JA, editor. Oxidative Stress and Chronic Degenerative Diseases—A Role for Antioxidants. Croatia: InTechOpen., 33.

Chen, M., Shao, C.L., Meng, H., She, Z.G., Wang, C.Y., 2014. Anti-respiratory

syncytial virus prenylated dihydroquinolone derivatives from the gorgonian-derived fungus *Aspergillus* sp. XS-20090B15. J. Nat. Prod., 77(12): 2720–2724.

Cheng, Z.F., Zhen, C., 2004. The Cheng Zhi-Fan Collectanea of Medical History; Peking Univ. Med. Press: Beijing, China.

Courtwright, D.T., 2009. Forces of Habit: Drugs and the Making of the Modern World; Harvard University Press: Cambridge, MA, USA, ISBN 0674029909.

Dasgupta, A., 2012. Advances in antibiotic measurement. Adv. Clin. Chem., 56, 75–104.

Davidson, D., Amrein, L., Panasci, L., Aloyz, R., 2013. Small molecules, inhibitors of DNA-PK, targeting DNA repair, and beyond. Front. Pharmacol., 4:5.

De Carvalho, J., Cardoso, L., Ghiggi, V., Woiciechowski, A., Vandenberghe, L., Soccol, C., 2014. Microbial pigments. In: Brar SK, Dhillon GS, Soccol CR, editors. Biotransformation of Waste Biomass into High Value Biochemicals. NY: Springer, 73-97.

Demain, A. L., Vaishnav, P., 2011. Natural products for cancer chemotherapy. Microb. Biotechnol., 4(6): 687–699.

Demain, A.L., 2014. Importance of microbial natural products and the need to revitalize their discovery. J. Ind. Microbiol. Biotechnol., 41(2):185–201.

Demain, A.L., Adrio, J.L., 2008. Contributions of microorganismsv to industrial biology. Mol. Biotechnol., 38(1): 41–55.

Devi, S., Kiesewalter, H.T., Kovács, R., Frisvad, J.C., Weber, T., Larsen, T.O., Kovács, Á.T., Ding, L., 2019. Depiction of secondary metabolites and antifungal activity of *Bacillus velezensis* DTU001. Synth. Syst. Biotechnol., 4(3): 142–149.

Dholakiya, R.N., Kumar, R., Mishra, A., Mody, K.H., Jha, B., 2017. Antibacterial and antioxidant activities of novel actinobacteria strain isolated from Gulf of Khambhat, Gujarat. Front. Microbiol., 8: 2420.

Dong, C., Yu, J., Zhu, Y., Dong, C., 2013. Inhibition of hepatitis B virus gene expression & replication by crude destruxins from *Metarhizium anisopliae* var. dcjhyium. Indian J. Med. Res., 138 (6): 969-976.

Doull, J.L., Singh, A.K., Hoare, M., Ayer, S.W., 1994. Conditions for the production of jadomycin B by *Streptomyces venezuelae* ISP5230: Effects of heat shock, ethanol treatment and phage infection. J. Ind. Microbiol., 13(12):120–125.

Dulmage, H.T., 1953. The production of neomycin by *Streptomyces fradiae* in synthetic media. Appl. Microbiol., 1 (2): 103-106.

Dworkin, M., 2007. Lingering puzzles about *myxobacteria*. Microbe., 2:18–24.

Ebada, S.S., Edrada, R.A., Lin, W., Proksch, P., 2008. Methods for isolation, purification and structural elucidation of bioactive secondary metabolites from marine invertebrates. Nat. Protoc., 3(12): 1820-1831.

ElNaggar, M.H., Abdelwahab, G.M., Kutkat, O., GabAllah, M., Ali, M.A., El-Metwally, M.E., et al., 2022. Aurasperone A Inhibits SARS CoV-2 *In Vitro*: An Integrated *In Vitro* and In Silico Study. Mar. Drugs., 20(3): 179.

Fan, Y., Wang, Y., Liu, P., Fu, P., Zhu, T., Wang, W., Zhu, W., 2013. Indole-diterpenoids with anti-H1N1 activity from the aciduric fungus *Penicillium camemberti* OUCMDZ-1492. J. Nat. Prod., 76(7): 1328–1336.

Fenical, W., 1993. Chemical studies of marine bacteria: Developing a new resource. Chem. Rev., 93(5): 1673–1683.

Fjærvik, E., Zotchev, S.B., 2005. Biosynthesis of the polyene macrolide antibiotic nystatin in *Streptomyces noursei*. Appl. Microbiol. Biotechnol., 67(4): 436–443.

Fleming, A., 1980. Classics in infectious diseases: on the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of *B. influenzae* by Alexander Fleming, Reprinted from the British Journal of Experimental Pathology 10:226-236, 1929. Rev. Infect. Dis., 2(1): 129–139.

Fleming, A., 2001. On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of *B. influenzae*. 1929. Bull. World Health Organ., 79(8): 780–790.

Forbes, B.A., Sahm, D.F., Weissfeld, A.S, 2007. Laboratory methods and strategies for antimicrobial susceptibility testing, Bailey and Scott's Diagnostic Microbiology. 12th ed. St. Louis., Mosby Elsevier., 5(1): 187-214.

Frediansyah, A., Sofyantoro, F., Alhumaid, S., Al Mutair, A., Albayat, H., Altaweil, H.I., et al., 2022. Microbial Natural Products with Antiviral Activities, Including Anti-SARS-CoV-2: A Review. Molecul., 27(13): 4305.

Ganesan, L.T., Manavathu, E.K., Cutright, J.L., Alangaden, G.J., Chandrasekar, P.H., 2004. *In-vitro* activity of nikkomycin Z alone and in combination with polyenes, triazoles or echinocandins against *Aspergillus fumigatus*. Clin. Microbiol. Infect. Off. Publ. Eur. Soc. Clin. Microbiol. Infect. Dis., 10(11): 961–966.

Gaynes, R., 2017. The discovery of penicillin–New insights after more than 75 years of clinical use. Emerg. Infect. Dis., 23(5): 849-853.

Gerth, K., Steinmetz, H., Hofle, G., Reichenbach, H., 2000. Studies on biosynthesis of epothilones: the biosynthetic origin of the carbon skeleton. J. Antibiot., 53(12): 1373–1377.

Goodin, S., 2008. Novel cytotoxic agents: epothilones. Am. J. Health Syst. Pharm., 65(10 Suppl 3): S10–S15.

Gorska, M., Popowska, U., Sielicka, A., Kuban-Jankowska, A., Sawczuk, W., Knap, N., et al., 2012. Geldanamycin and its derivatives as Hsp90 inhibitors. Front. Biosci. (Landmark Ed)., 17(6): 2269–2277.

Gozari, M., Bahador, N., Jassbi, A.R., Mortazavi, M.S., Hamzehei, S., Eftekhar, E., 2019. Isolation, distribution and evaluation of cytotoxic and antioxidant activity of cultivable *actinobacteria* from the Oman Sea sediments. Acta. Oceanol. Sin., 38(12): 84-90.

Graham, C.E., Cruz, M.R., Garsin, D.A., Lorenz, M.C., 2017. *Enterococcus faecalis* bacteriocin EntV inhibits hyphal morphogenesis, biofilm formation, and virulence of Candida albicans. Proc. Natl. Acad. Sci., 114(17): 4507–4512.

Gupta, C., Prakash, D., Gupta, S., 2013. Functional foods enhanced with microbial antioxidants. Acad. J. Nutr., 2(2): 10–18.

Han, Y., Yang, B., Zhang, F., Miao, X., Li, Z., 2009. Characterization of antifungal chitinase from marine *Streptomyces* sp. DA11 associated with South China Sea sponge *Craniella australiensis*. Mar. Biotechnol., 11(1): 132–140.

Hatsu, M., Sasaki, T., Gomi, S., Kodama, Y., Sezaki, M., Inouye, S., Kondo, S., 1992. A new tetracycline antibiotic with antitumor activity. J. Antibiot., 45(3): 325–330.

Hayakawa, Y., Shirasaki, S., Shiba, S., Kawasaki, T., Matsuo, Y., Adachi, K., Shizuri, Y., 2007. Piericidins C 7 and C 8,

New Cytotoxic Antibiotics Produced by a Marine *Streptomyces* sp. J. Antibiot., 60(3): 196–200.

Hector, R.F., Zimmer, B.L., Pappagianis, D., 1990. Evaluation of nikkomycins X and Z in murine models of coccidioidomycosis, histoplasmosis, and blastomycosis. Antimicrob. Agents Chemother., 34(4): 587–593.

Hollstein, U., 1974. Actinomycin. Chemistry and mechanism of action. Chem. Rev., 74(6): 625–652.

Hua, B., Feng, H., Han, J., Qiao, Z., Wang, X., Zhang, Q., Liu, Z., Wu, Z., 2020. Isolation and Characterization of a New Fusaricidin-Type Antibiotic Produced by *Paenibacillus bovis* sp. nov BD3526. Curr. Microbiol., 77(12): 3990–3999.

Hugonnet, J.E., Tremblay, L.W., Boshoff, H.I., Barry, C.E., Blanchard, J.S., 2009. Meropenem-clavulanate is effective against extensively drug-resistant *Mycobacterium tuberculosis*. Sci., 323(5918): 1215-1218.

Imai, H., Suzuki, K.I., Morioka, M., Numasaki, Y., Kadota, S., Nagai, K., et al., 1987. Okilactomycin, a novel antibiotic produced by a *Streptomyces* species. J. Antibiot., 40(11): 1475–1482.

Iqbal, M.N, Ashraf, A., 2018. Recombinant Protein Production in Plants: Biofactories for Therapeutics. Int. J. Mol. Microbiol., 1(1): 38-39.

Kajimura, Y., Kaneda, M., 1996. Fusaricidin A, a new depsipeptide antibiotic produced by *Bacillus polymyxa* KT-8. Taxonomy, fermentation, isolation, structure elucidation and biological activity. J. Antibiot., 49(2): 129–135.

Keating, G.M., Perry, C.M., 2005. Ertapenem. Drugs, 65(15): 2151–2178.

Kim, S.K., 2013. Marine microbiology: bioactive compounds and biotechnological applications. Weinheim: Wiley-VCH.

Kim, Y.H., Park, B.S., Bhatia, S.K., Seo, H.M., Jeon, J.M., Kim, H.J., et al., 2014. Production of rapamycin in *Streptomyces hygroscopicus* from glycerol-based media optimized by systemic methodology. J. Microbiol. Biotechnol. 24(10): 1319–1326.

Kimura, K., Kanou, F., Takahashi, H., Esumi, Y., Uramoto, M., Yoshihama, M., 1997. Propeptin, a New Inhibitor of Prolyl Endopeptidase Produced by *Microbispora*. J. Antibiot., 50(5): 373–378.

Klich, M.A., Lax, A.R., Bland, J.M., 1991. Inhibition of some mycotoxigenic fungi by iturin A, a peptidolipid produced by *Bacillus subtilis*. Mycopathologia, 116(2): 77–80.

Krumova, K., Cosa, G., 2016. Overview of reactive oxygen species. In: Nonell S, Flors C, editors. Singlet Oxygen: Applications in Bioscience and Nanoscience. EU: Royal Society of Chemistry., 3.

Law, B. K., 2005. Rapamycin: an anti-cancer immunosuppressant? Crit. Rev. Oncol. Hematol., 56(1): 47–60.

Law, J.W.F., Se,r H.L., Ab Mutalib, N.S., Saokaew, S., Duangjai, A., Khan, T.M., et al., 2019. *Streptomyces monashensis* sp. nov., a novel mangrove soil *actinobacterium* from East Malaysia with antioxidative potential. Sci. Rep., 9(1): 1-18.

Lei, S., Zhao, H., Pang, B., Qu, R., Lian, Z., Jiang, C., et al., 2019. Capability of iturin from *Bacillus subtilis* to inhibit *Candida albicans in vitro* and *in vivo*. Appl. Microbiol. Biotechnol., 103(11): 4377–4392.

Lemriss, S., Laurent, F., Couble, A., Casoli, E., Lancelin, J.M., Saintpierre-Bonaccio, D.,

et al., 2003. Screening of nonpolyenic antifungal metabolites produced by clinical isolates of *actinomycetes*. Can. J. Microbiol., 49(11): 669–674.

Li, J., Hu, Y., Hao, X., Tan, J., Li, F., Qiao, X., Chen, S., Xiao, C., Chen, M., Peng, Z., 2019. Raistrickindole A, an anti-HCV oxazinoindole alkaloid from *Penicillium raistrickii* IMB17-034. J. Nat. Prod., 82(5): 1391–1395.

Li, T., Li, L., Du, F., Sun, L., Shi, J., Long, M., Chen, Z., 2021. Activity and Mechanism of Action of Antifungal Peptides from Microorganisms: A Review. Molecul., 26(11): 3438.

Li, X., Zhang, Y., Wei, Z., Guan, Z., Cai, Y., Liao, X., 2016. Antifungal Activity of Isolated *Bacillus amyloliquefaciens* SYBC H47 for the Biocontrol of Peach Gummosis. PLoS ONE, 11(9): e0162125.

Li, Z., Kong, L., Hui, B., Shang, X., Gao, L., Luan, N., et al., 2017. Identification and antioxidant activity of carotenoids from superfine powder of *Rhodobacter sphaeroides.* EJFA., 29(11): 833-845.

Liang, X.X., Zhang, X.J., Zhao, Y.X., Feng, J., Zeng, J.C., Shi, Q,-Q., et al., 2022. Aspulvins A H, Aspulvinone Analogues with SARS-CoV-2 Mpro Inhibitory and Anti-inflammatory Activities from an Endophytic *Cladosporium* sp. J. Nat. Prod., 85(4): 878–887.

Lushchak, V.I., 2014. Free radicals, reactive oxygen species, oxidative stress and its classification. Chem.-Biol. Interact., 224: 164-175.

Ma, X., Li, L., Zhu, T., Ba, M., Li, G., Gu, Q., et al., 2013. Phenylspirodrimanes with anti-HIV activity from the sponge-derived fungus *Stachybotrys chartarum* MXH-X73. J. Nat. Prod., 76(12): 2298–2306.

Maeda, A., Nagai, H., Yazawa, K., Tanaka, Y., Imai, T., Mikami, Y., et al., 1994. Three new reduced anthracycline related compounds from pathogenic *Nocardia brasiliensis*. J. Antibiot., 47(9): 976–981.

Malpur, P.P., Shah, A.S., Juvekar, A.R., 2006. Antioxidant and anti-inflammatory activity of extract obtained from Aspergillus candidus MTCC 2202 broth filtrate. Ind. J. Exp. Biol., 44(6): 468–473.

Mark, G., Papich, D.V.M., MS, DACVCP, 2016. In Saunders Handbook of Veterinary Drugs (Fourth Edition). Elsevier In.

Maskey, R.P., Kock, I., Helmke, E., Laatsch, H., 2003. Isolation and Structure Determination of Phenazostatin D, a New Phenazine froma Marine Actinomycete Isolate *Pseudonocardia* sp. B6273. Z. Für Naturforsch. B., 58, 692–694.

Maskey, R.P., Li, F., Qin, S., Fiebig, H.H., Laatsch, H., 2003. Chandrananimycins A approximately C: Production of novel anticancer antibiotics from a marine *Actinomadura* sp. isolate M048 by variation of medium composition and growth conditions. J. Antibiot., 56(7): 622–629.

Meanwell, R.J.L., Shama, G., 2008. Production of streptomycin from chitin using *Streptomyces griseus* in bioreactors of different configuration. Bioresour. Technol., 99(13): 5634–5639.

Migita, K., Eguchi, K., 2003. FK506: anti-inflammatory properties. Curr. Med. Chem., 2:5.

Molnar, I., Schupp, T., Ono, M., Zirkle, R., Milnamow, M., Nowak-Thompson, et al., 2000. The biosynthetic gene cluster for the microtubule-stabilizing agents epothilones A and B from *Sorangium cellulosum* So ce90. Chem. Biol., 7(2): 97–109.

Nagano, J., Iyonaga, K., Kawamura, K., Yamashita, A., Ichiyasu, H., Okamoto, T., et al., 2006. Use of tacrolimus, a potent

anti-fibrotic agent, in bleomycin-induced lung fibrosis. Eur. Respir. J., 27(3): 460–469.

Nakamura, I., Yoshimura, S., Masaki, T., Takase, S., Ohsumi, K., Hashimoto, M., et al., 2017. ASP2397: A novel antifungal agent produced by *Acremonium persicinum* MF-347833. J. Antibiot., 70(1):45–51.

Nathan, C., Cunningham Bussel, A., 2013. Beyond oxidative stress: An immunologist's guide to reactive oxygen species. Nat. Rev. Immunol., 13(5): 349-361.

Netzker, T., Flak, M., Krespach, M.K., Stroe, M.C., Weber, J., Schroeckh, V., et al., 2018. Microbial interactions trigger the production of antibiotics. Curr. Opin. Microbiol., 45: 117-123.

Newman, D.J., Cragg, G.M., 2007. Natural products as sources of new drugs over the last 25years. J. Nat. Prod., 70(3): 461–477.

Newman, D.J., Cragg, G.M., 2012. Natural products as sources of new drugs over the 30 years from 1981 to 2010. J. Nat. Prod., 75(3):311–335.

Newman, D.J., Cragg, G.M., Snader, K.M., 2000. The influence of natural products upon drug discovery. Nat. Prod. Rep., 17(3): 215–234.

Nimse, S.B., Pal, D., 2015. Free radicals, natural antioxidants, and their reaction mechanisms. RSC Adv., 5: 27986-28006.

Nyfeler, R., Keller-Schierlein, W., 1974. Metabolites of microorganisms. 143. Echinocandin B, a novel polypeptide-antibiotic from *Aspergillus nidulans* var. echinulatus: Isolation and structural components. Helv. Chim. Acta., 57(8): 2459–2477.

Ortega Cabello, L., Pérez Méndez, H.I., Manjarrez Alvarez, N., López-Luna, A., Solís Oba, A., et al., 2016. Comparación de la actividad antioxidante de carotenoides en extractos crudos y pre-purificados de actinobacterias marinas. Rev. Mex. Cienc. Farm., 47(2): 60-65.

Pandey, R., Chander, R., Sainis, K.B., 2007. Prodigiosins: a novel family of immunosuppressants with anti-cancer activity. Ind. J. Biochem. Biophys., 44(5): 295–302.

Patwardhan, B., Mashelkar, R.A., 2009. Traditional medicine-inspired approaches to drug discovery: Can Ayurveda show the way forward? Drug Discov. Today., 14(15-16): 804–811.

Perry, C.M., Ibbotson, T., 2002. Biapenem. Drugs., 62(15): 2221–2234.

Petkovi´c, H., Cullum, J., Hranueli, D., Hunter, I.S., Peri´c-Concha, N., Pigac, J., et al., 2006. Genetics of *Streptomyces rimosus*, the oxytetracycline producer. Microbiol. Mol. Biol. Rev., 70(3): 704–728.

Petrovska, B.B., 2012. Historical review of medicinal plants' usage. Pharmacogn. Rev., 6(11): 1-5.

Phaniendra, A., Jestadi, D.B., Periyasami, L., 2015. Free radicals: Properties, sources, targets and their implications in various diseases. Indian J. Clin. Biochem., 30(1): 11-26.

Raddatz-Mota, D., Pérez-Flores, L.J., Carrari, F., Mendoza-Espinoza, J.A., de León-Sánchez, F.D., Pinzón-López, L.L., Godoy-Hernández, G., Rivera-Cabrera, F., 2017. Achiote (*Bixa orellana* L.): A natural source of pigment and vitamin E. J. Food Sci. Technol., 54(6): 1729-1741.

Radzom, M., Zeeck, A., Antal, N., Fiedler, H.P. F., 2006. A novel cyclic octaketide produced by Streptomyces strain Tü 6319. J. Antibiot., 59(3): 315–317.

Ribeiro, P.D., Medina-Acosta, E., 2003. Prevention of lethal murine candidiasis using HP (2-20), an antimicrobial peptide derived from the N-terminus of *Helicobacter pylori* ribosomal protein L1. Peptides, 24(11): 1807–1814.

Saini, R.K., Keum, Y.S., 2017. Progress in microbial carotenoids production. Indian J. Microbiol., 57(1): 129-130.

Salas, J.A., Méndez, C., 1998. Genetic manipulation of antitumor-agent biosynthesis to produce novel drugs.Trends Biotechnol., 16(11): 475–482.

Schieber, M., Chandel, N.S., 2014. ROS function in redox signaling and oxidative stress. Curr. Biol., 24(10): R453-R462.

Ser, H.L., Tan, L.T.H., Palanisamy, U.D., Abd Malek, S.N., Yin, W.F., Chan, K.G., et al., 2016. *Streptomyces antioxidans* sp. nov., a novel mangrove soil actinobacterium with antioxidative and neuroprotective potentials. Front. Microbial., 7: 899.

Shen, B.A., 2015. New golden age of natural products drug discovery. Cell., 163(6): 1297–1300.

Simmons, T.L., Coates, R.C., Clark, B.R., Engene, N., Gonzalez, D., Esquenazi, E., et al., 2008. Biosynthetic origin of natural products isolated from marine microorganism-invertebrate assemblages. Proc. Natl. Acad. Sci., 105(12): 4587–4594.

Singh, M.P., Petersen, P.J., Weiss, W.J., Kong, F., Greenstein, M., 2000. Saccharomicins, novel heptadecaglycoside antibiotics produced by *Saccharothrix espanaensis*: Antibacterial and mechanistic activities. Antimicrob. Agents Chemother., 44(8): 2154–2159.

Singh, S. B., Genilloud, O., Peláez, F., 2010. “2.05 – Terrestrial Microorganisms – Filamentous Bacteria,” in Comprehensive Natural Products II, eds H.-W. Liu and L. Mander (Oxford: Elsevier)., 2: 109–140.

Song, Y., Xue, H., Liu, T. T., Liu, J. M., Chen, D., 2015. Rapamycin plays a neuroprotective effect after spinal cord injury via anti-inflammatory effects. J. Biochem. Mol. Toxicol., 29(1): 29–34.

Sorensen, K.N., Kim, K.H., Takemoto, J.Y., 1996. *In vitro* antifungal and fungicidal activities and erythrocyte toxicities of cyclic lipodepsinonapeptides produced by Pseudomonas syringae pv. syringae. Antimicrob. Agents Chemother., 40(12): 2710–2713.

Stanley, V. C., English, M. P., 1965. Some effects of nystatin on the growth of four *Aspergillus species*. J. Gen. Microbiol., 40(1):107–118.

Sugiura, T., Ariyoshi, Y., Negoro, S., Nakamura, S., Ikegami, H., Takada, M., Yana, T., et al., 2005. Phase I/II study of amrubicin, a novel 9 aminoanthracycline, in patients with advanced non-small-cell lung cancer. Invest. New Drugs., 23(4): 331–337.

Sun, C.H., Wang, Y., Wang, Z., Zhou, J.Q., Jin, W.Z., You, X.F., et al., 2007. Chemomicin A, a new angucyclinone antibiotic produced by *Nocardia mediterranei* subsp. kanglensis 1747-64. J. Antibiot., 60(3): 211–215.

Taechowisan, T., Lu, C., Shen, Y., Lumyong, S., 2007. 4-arylcoumarin inhibits immediate-type allergy. Food Agric. Immunol., 18(3-4): 203-211.

Takahashi, I., Takahashi, K.I., Asano, K., Kawamoto, I., Yasuzawa, T., Ashizawat, T., et al., 1988. DC92-B, a new antitumor antibiotic from Actinomadura. J. Antibiot., 41(8):1151–1153.

Takesako, K., Ikai, K., Haruna, F., Endo, M., Shimanaka, K., Sono, E., et al., 1991. Aureobasidins, new antifungal antibiotics.

Taxonomy, fermentation, isolation, and properties. J. Antibiot., 44(9): 919–924.

Takesako, K., Kuroda, H., Inoue, T., Haruna, F., Yoshikawa, Y., Kato, I., et al., 1993. Biological properties of aureobasidin A, a cyclic depsipeptide antifungal antibiotic. J. Antibiot., 46(9): 1414–1420.

Tan, S. Y., Tatsumura, Y., 2015. Alexander Fleming (1881–1955): discoverer of penicillin. Singapore Med. J., 56(7): 366–367.

Tan, S., Yang, B., Liu, J., Xun, T., Liu, Y., Zhou, X., 2019. Penicillixanthone A, a marine-derived dual-coreceptor antagonist as anti-HIV-1 agent. Nat. Prod. Res., 33(10): 1467–1471.

Tanaka, H., Kuroda, A., Marusawa, H., Hatanaka, H., Kino, T., Goto, T., et al., 1987. Structure of FK506, a novel immunosuppressant isolated from *Streptomyces.* J. Am. Chem. Soc. 109(16): 5031–5033.

Tanaka, Y., Komaki, H., Yazawa, K., Mikami, Y., Nemoto, A., Tojyo, T., et al., 1997. Brasilinolide A, a new macrolide antibiotic produced by *Nocardia brasiliensis*: Producing strain, isolation and biological activity. J. Antibiot., 50(12): 1036–1041.

Tareq, F. S., Lee, H. S., Lee, Y. J., Lee, J. S., Shin, H. J., 2015. Ieodoglucomide C and ieodoglycolipid, new glycolipids from a marine-derived bacterium *Bacillus licheniformis* 09IDYM23. Lipids., 50(5): 513–519.

Tevyashova, A.N., Olsufyeva, E.N., Solovieva, S.E., Printsevskaya, S.S., Reznikova, M. I., Trenin, A.S., et al., 2013. Structure-antifungal activity relationships of polyene antibiotics of the amphotericin B group. Antimicrob. Agents Chemother., 57(8): 3815–3822.

Trischman, J.A., Tapiolas, D.M., Jensen, P.R., Dwight, R., Fenical, W., Mckee, T.C., et al., 1994. Salinamides A and B: anti-inflammatory depsipeptides from a marine *streptomycete*. J. Am. Chem. Soc., 116(2): 757–758.

Viaud, S., Saccheri, F., Mignot, G., Yamazaki, T., Daillère, R., Hannani, D., et al., 2013. The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. Sci., 342(6161): 971–976.

Vitayakritsirikul, V., Jaemsaeng, R., Lohmaneeratana, K., Thanapipatsiri, A., Daduang, R., Chuawong, P., et al. 2016. Improvement of chloramphenicol production in *Streptomyces venezuelae* ATCC 10712 by overexpression of the aroB and aroK genes catalysing steps in the shikimate pathway. Antonie Van Leeuwenhoek, 109(3): 379–388.

Vuong, Q.V., 2017. Utilisation of Bioactive Compounds from Agricultural and Food Production Waste; CRC Press: Boca Raton, FL, USA, ISBN 1351647598.

Waksman, S.A., Woodruff, H.B., 1940. Bacteriostatic and bactericidal substances produced by a soil *actinomyces*. Proc. Soc. Exp. Biol. Med., 45(2): 609–614.

Wang, H., Wang, Y., Wang, W., Fu, P., Liu, P., Zhu, W., 2011. Anti-influenza virus polyketides from the acid-tolerant fungus *Penicillium purpurogenum* JS03-21. J. Nat. Prod., 74(9): 2014–2018.

Wang, Q., Zhang, K., Wang, W., Zhang, G., Zhu, T., Che, Q., Gu, Q., Li, D., 2020. Amphiepicoccins AJ: Epipolythio dioxopiperazines from the fish-gill-derived fungus *Epicoccum nigrum* HDN17-88. J. Nat. Prod., 83(2): 524–531.

Wang, C.C., Ding, S., Chiu, K.H., Liu, W.S., Lin, T.J., Wen, Z.H., 2016. Extract from a mutant *Rhodobacter sphaeroides* as an enriched carotenoid source. Food Nutr. Res., 60(1): 29580.

Weber, D., Sterner, O., Anke, T., Gorzalczancy, S., Martino, V.,. Phomol, A.C., 2004. A new anti-inflammatory metabolite from an endophyte of the medicinal *plant Erythrina crista-galli.* J. Antibiot., 57(9): 559–563.

Williamson, J.M., Inamine, E., Wilson, K.E., Douglas, A.W., Liesch, J.M., Albers-Schönberg, G., 1985. Biosynthesis of the beta-lactam antibiotic, thienamycin, by *Streptomyces cattleya*. J. Biol. Chem., 260(8): 4637–4647.

Woodruff, H.B., Selman, A. Waksman, 2014. Winner of the 1952 Nobel Prize for physiology or medicine. Appl. Environ. Microbiol, 80(1): 2-8.

Xu, J., Leeuwenburgh, C., 2015. Free radicals and oxidative stress: Basic concepts and misconceptions. In: Miller J, Le Prell CG, Rybak L, editors. Free Radicals in ENT Pathology. SWT: Humana Press, 10-15

Yanai, K., Murakami, T., 2004. The kanamycin biosynthetic gene cluster from *Streptomyces kanamyceticus*. J. Antibiot., 57(5): 351–354.

Yang, X.-W., Peng, K., Liu, Z., Zhang, G.-Y., Li, J., Wang, N., et al., 2013. Strepsesquitriol, a rearranged zizaane- type sesquiterpenoid from the deep sea-derived actinomycete *Streptomyces* sp. SCSIO 10355. J. Nat. Prod., 76(12): 2360–2363.

Yen, G.C., Chang, Y.C., 1999. Medium optimization for the production of antioxidants from *Aspergillus candidus*. J. Food Prot., 62(6): 657-61.

Yunus, F.N., Khalid, Z.Z., Rashid, F., Ashraf, A., Iqbal, M.N., Hussain, F., 2016. Isolation and Screening of Antibiotic producing Bacteria from Soil in Lahore City. PSM Microbiol., 01(1): 01-04.

Zhanel, G.G., Homenuik, K., Nichol, K., Noreddin, A., Vercaigne, L., Embil, J., et al., 2004. The glycylcyclines. Drugs., 64(1):63–88.

Zhanel, G.G., Walters, M., Noreddin, A., Vercaigne, L.M., Wierzbowski, A., Embil, J.M., et al., 2002. The ketolides., 62(12): 1771–1804.

Zhang, Y., Tian, R., Liu, S., Chen, X., Liu, X., Che, Y.J.B., 2008. Alachalasins AG, new cytochalasins from the fungus *Stachybotrys charatum*. Bioorg. Med. Chem., 16(5): 2627–2634.

Zhao, J.L., Zhang, M., Liu, J.M., Tan, Z., Chen, R.D., Xie, K.B., Dai, J.G., 2017. Bioactive steroids and sorbicillinoids isolated from the endophytic fungus *Trichoderma* sp. Xy24. J. Asian. Nat. Prod. Res., 19(10): 1028–1035.

Zhao, Y., Liu, D., Proksch, P., Zhou, D., Lin, W., 2018. Truncateols OV, further isoprenylated cyclohexanols from the sponge-associated fungus *Truncatella angustata* with antiviral activities. Phytochemistry., 155: 61–68.

Zheng, H., Fu, Y., Huang, Y., Zheng, X., Yu, W., Wang, W., 2017. mTOR signaling promotes foam cell formation and inhibits foam cell egress through suppressing the SIRT1 signaling pathway. Mol. Med. Rep., 16(3): 3315–3323.

Zhong, G., Wan, F., 1999. An outline on the early pharmaceutical development before Galen. Chin. J. Med. Hist., 29(3): 178–182.