BACTERIAL METABOLITES AS POTENT THERAPEUTIC AGENTS - A COMPREHENSIVE REVIEW

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Abstract

Biologically active secondary metabolites are produced by bacteria in remarkable amounts. These organisms have enormous biotechnological value due to their potential to synthesise the bioactive molecules. Microbes synthesise secondary metabolites in reaction to nutrition, growth rate, feedback control, enzyme inactivation and enzyme stimulation. With the aid of biotechnology, microbes are explored to produce desired biomolecules like enzymes, proteins, and other compounds with therapeutic applications. Ever since the discovery of penicillin, microbes from various habitats are being extensively analysed for their metabolites with medicinal properties. The emergence of drug resistance and deadly side effects associated with synthesised drugs, has forced the scientific community to dig deep into natural resources to combat the drug resistance and cater to the other deadly diseases. Since the last few decades, scientists and pharmaceutical industries are focused more on natural compounds with medicinal applications. In the current review article, we try to summarize the bacterial metabolites which have been identified as potential therapeutic agents.

Keywords: - Bacterial Metabolites, Therapeutic Agents, Drug Discovery.

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INTRODUCTION

Over the past 20 years, the field of secondary metabolites has undergone a great deal of change. Adapting to the challenges of the natural environment has led to the evolution of secondary metabolism in nature. The biosynthetic genes are preserved as long as the metabolites are advantageous to the organism, and genetic alterations further enhance the process. Large-scale bioactive compound synthesis can be more easily achieved through the use of microorganisms, as they navigate the challenges of acquiring pharmaceuticals through widespread harvesting (Demain, et al 2011). Some natural compounds produced by microorganisms, such as bacteria or fungi, have bioactive qualities that make them effective against other microbes or against certain physiological situations in the body. It is believed that secondary metabolites produced by microbes are the primary source of innovative medicinal drugs with antimicrobial capabilities since the discovery of the first antimicrobial compound penicillin in the 1920s. Numerous bioactive molecules, including antibacterial, antiviral, antifungal, anti-quorum sensing, and anticancer chemicals, have been found in bacteria (Fahmy & Abdel-Tawab, 2021). Earlier studies have suggested that microbes which produce secondary metabolites are associated with their hosts. Developing novel natural compounds is made possible by the synthesis of such secondary metabolites. Microorganisms are seen as most promising candidates for the production of novel and potent secondary metabolites which may employed to combat the drug resistance. (Piel, 2009; Valliappan et al., 2014).

Microorganisms produce secondary metabolites in response to many environmental factors, including temperature, humidity, pH, nutrients, and light. When a bacterial growth is restricted by a deficiency in carbon, nitrogen, phosphate, or other nutrients, the production of secondary metabolites is frequently induced. In nature, concentration and composition of nutrients influence mechanisms that are complex that regulate global gene expression, reflecting different environmental conditions that trigger the production of certain secondary metabolites (Bibb, 2005; Sánchez et al., 2010; Van Wezel & McDowall, 2011). Secondary metabolism is often suppressed when glucose, phosphate, or ammonium concentrations are high (Masuma et al., 1986), however there can be exceptions, for example, high phosphate concentrations can trigger a variety of secondary metabolites (Tyc et al., 2017). The production of secondary metabolites is stimulated by a variety of factors and is utilized in a variety of ways in natural product discovery strategies. Based on the OSMAC (One Strain-Many Compounds) model, a single strain of bacteria is cultured under various environments. For instance, In *Streptomycetes*, the presence of scandium and/or lanthanum at low levels triggered the expression of several secondary metabolite biosynthesis genes, or even activated previously silenced biosynthesis genes, such as those involved in actinorhodin synthesis in *Streptomyces lividans* (Kawai et al., 2007).

Bacteria produce specialized metabolites as an outcome of interactions with other microbes in their immediate environment. Studies have demonstrated that secondary metabolites produced by soil bacteria can be utilized as weapons in biowarfare, allowing producers to gain an edge over other bacteria in the same ecological niche (Cornforth & Foster, 2013; Foster & Bell, 2012). A variety of cellular functions are influenced by antimicrobial compounds at subinhibitory concentrations, including development of cells, formation of biofilms, motility, virulence, and nutrient uptake (Linares et al., 2006; Romero et al., 2011). Some studies have found that antibiotics promote bacterial growth under nutrient-deficient conditions by serving as a source of nutrients, but these findings are controversial since others have not confirmed them. Additionally, secondary metabolites with antimicrobial activity may also stimulate sporulation, which has important ecological implications (D'Costa et al., 2006; Dantas et al., 2008; Ueda et al., 2000).

BACTERIAL SECONDARY METABOLITES AND THEIR ANTIMICROBIAL POTENTIAL-

Secondary metabolites produced by microbes are composed of peptides, polyketides, carbohydrates, lipids, terpenoids, steroids and alkaloids, all of which are themselves made from primary metabolites. Secondary metabolites of microbes and their structure and function have a long and illustrious history connecting these two branches of metabolism. In fact, the pharmaceutical industry used these molecules as a source of drugs and leads for the development of new medicines for most of the 20th century (Newman, 2008). Since the discovery of peptides synthesized by microorganisms independently of ribosomes and RNA, large number of natural bacterial metabolites with anti-bacterial (Table 1), anti-fungal (Table 1), and antiviral (Table 2) activities have been discovered.

APPLICATIONS OF SECONDARY METABOLITES-

1. Antibacterial activity:

Bacillus spp. producing secondary metabolites have been recognized as antibiotics that are predominantly peptides. Several examples such as, *B.licheniformis 26-103RA* strain synthesize lichenin; *B. megaterium* synthesiz megacin; *B. coagulans* synthesize antilisterial coagulin; *B. polyfermenticus* synthesize polyfermenticin SCD; *B.cereus* synthesize cerein. These all are examples of Bacteriocins produced by *Bacillus* strains (Sansinenea & Ortiz, 2011). Similarly other microorganisms such as, *Nonomuraea spp.* inhibited a carbapenem resistant *Enterobacter iaceae by* synthesizing Sealutomicin A compound (Igarashi et al., 2021).

Streptomyces spp. can synthesize several secondary metabolites such as; bonactin which inhibits the growth of bacteria against both Gram-negative and Gram-positive bacteria (Schumacher et al., 2003); Caboxamycin demonstrated antibacterial effect against Gram-positive bacterial pathogens (Hohmann et al., 2009); Lobophorin I inhibited the growth of bacteria, such as, *B. subtilis* and *S. aureus* (Pan et al., 2013) and many other compounds as mentioned above (Table 1.).

Table 1. Bacterial secondary metabolites with their antimicrobial effect.

Sr. No.	Name of the Compound	Micro-organism	Applications	References
1.	Chlorocatechelin A,bacitracin A, Indole-3-lactic acid, Phenylacetic acid,Aborycin & Chalcomycin polyketide ansalactams A–D, Fijimycin A	*Streptomyces spp.*	Antibacterial and Antifungal	(Kishimoto et al., 2014; Lee et al., 2014; Ser et al., 2015; Sajid et al., 2011; Shao et al., 2019; (Sun et al., 2011)
2.	Ambiguine-K and M isonitrile	Marine *Cyanobacterium Fischerella ambigua*	Antibacterial	(Mo et al., 2009)
3.	Alkylphenols, Anaephenes A-C	*Cyanobacterium Hormoscilla spp.*	Antibacterial	(Brumley et al., 2018)
4.	Oxatetracyclo ketone bacilysin	*B. stercoris MBTDCMFRI Ba37* *B. amyloliquefaciens MTCC 10456*	Antibacterial Antifungal	(Nair et al., 2021) (Vairagkar & Mirza, 2021)
5.	Thiopeptide-class antibiotic, Micrococcin	*B. stratosphericus*	Antibacterial	(Wang et al., 2020)
6.	Red-pigmented Prodigiosin	*Hahella spp.*	Antibacterial	(Nakashima et al., 2005)
7.	Janthinopolyenemycins A and B	*Janthinobacterium spp.*	Antifungal	(Anjum et al., 2018)
8.	Branimycins B and C	*Pseudonocardia carboxydivorans M-227*	Antibacterial	(Braña et al., 2017)
9.	1-acetyl-beta-corboline	*Pseudomonas UJ-6*	Antibacterial	(D. S. Lee et al., 2013)
10.	Arisostatin B	*Micromonospora spp*	Antibacterial	(Furumai et al., 2000)
11.	Sealutomicin A	*Nonomuraea sp. MM565M-173N2*	Antibacterial	(Igarashi et al., 2021)
12.	Pentadecanoic acid Tetradecanoic acid, and n-hexadecanoic acid	*Actinomycete AMA50*	Antifungal	(Sangkanu et al., 2021)
13.	Streptothiazolidine A	*Streptomyces spp. SY1965*	Antifungal	(Yi et al., 2020)
14.	7 surfactin, 1, Anteiso-C15 Ile2	*B. velezensis SH-B74*	Antifungal	(Ma et al., 2020)
15.	Chitinase	*Pseudomonas spp.*	Antifungal	(Liu et al., 2019)
16.	Different lipid compounds and fatty acids	*Brevibacillus antibioticus spp. TGS2-1T*	Antibacterial and Antifungal	(Choi et al., 2019)
17.	Bis (2-ethylhexyl) phthalate and 4-bromophenol	*Nocardiopsis spp. SCA21*	Antibacterial	(Siddharth & Rai V, 2019)
18.	3-hydroxy-N-methyl-2- oxindole derivatives	*Salinispora arenicola*	Antibacterial	(da Silva et al., 2019)
19.	Polyketide compounds	*S. felleus*	Antibacterial	(Almalki, 2020)
20.	Salinaphthoquinones	*S. arenicola*	Antibacterial	(Da Silva et al., 2019)
21.	Meroterpenoids	*Streptomyces spp.*	Antibacterial	(Ryu et al., 2019)
22.	Terrosamycins A and B	*Streptomyces spp. RKND004*	Antibacterial	(Yi et al., 2020)
23.	Mycenolide A	*Streptomyces spp. 4054*	Antibacterial	(Sproule et al., 2019)
24.	Tunicamycin derivatives	*S. xinghaiensis SCSIO S15077*	Antibacterial and Antifungal	(de Oliveira et al., 2020)
25.	N-acetylborrelidin B	*S. mutabilis spp. MII*	Antibacterial and Antifungal	(Hamed et al., 2018)
26.	Extracellular enzymes	*Actinobacteria*	Antibacterial and Antifungal	(Arumugam et al., 2017)
27.	Peptidic compounds	*Aneurinibacillus spp. YR247*	Antifungal	(Kurata et al., 2017)
28.	Diketopiperazines	*Rheinheimera japonica KMM 9513 T*	Antibacterial	(Kalinovskaya et al., 2017)
29.	Isoprenoid quinones	*R. japonica spp.*	Antibacterial	(Romanenko et al., 2015)
30.	Mollemycin A	*Streptomyces spp. CMB-M0244*	Antibacterial	(Raju et al., 2014)
31.	Iodinin	*Streptosporangium spp. DSM 45942*	Antibacterial and Antifungal	(Sletta et al., 2014)
32.	Lobophorin I	*Streptomyces spp. 12A35*	Antibacterial	(Pan et al., 2013)
33.	Pseudonocardians A–C	*Pseudonocardia spp. SCSIO 01299*	Antibacterial	(S. Li et al., 2011)
34.	Caboxamycin	*Streptomyces spp. NTK 937*	Antibacterial	(Hohmann et al., 2009)

35.	Bonactin	*Streptomyces spp. BD21-2*	Antibacterial	(Schumacher et al., 2003)
36.	Methylamine	*Pseudoalteromonas haloplanktis TAC125*	Antibacterial	(Sannino et al., 2017)

2. Antifungal activity:

Microorganisms such as *Streptosporangium spp. DSM 45942* synthesize Iodinin which exhibited antifungal activity (Sletta et al., 2014); Anteiso-C15 Ile2,7 surfactin synthesize by *B. velezensis SH-B74* affected the appressoria formation of Magnaporthe oryzae, a rice blast fungus (Ma et al., 2020); Chitinase enzyme synthesized by *Pseudomonas spp*. exhibits efficacy against fungi *Fusarium* and *Verticillium dahlia CICC 2534* (Liu et al., 2019); Peptidic compounds synthesized by *Aneurinibacillus spp. YR247* exhibit efficacy against fungi *A. brasiliensis NBRC945* (Kurata et al., 2017).

3. Antiviral activity:

Globally, viruses pose a serious health risk to humans and their safety. Antiviral substances can be produced by marine-derived *Streptomyces*. It was found that from endophytic *Streptomyces species* at 50 and 171 μM, anthranoside C and wailupemycins, were isolated which inhibit influenza H1N1 virus by 47.8 and 50% respectively. In addition, butanolide and neoabyssomicin D derivatives from *Streptomyces koyangensis* displayed antiviral activity against herpes simplex virus with EC 50 25.4 μM (El-Gendy et al., 2021; Teng et al., 2020). Porcine epidemic diarrhea virus was strongly inhibited by Xiamycin C (Kim et al., 2016). Similarly, *S. koyangensis SCSIO 5802* synthesize Neoabyssomicins which exhibit viral inhibitory activity against vesicular stomatitis virus and HSV (H. Huang et al., 2018) and Abyssomicin Y compound synthesized by *Verrucosispora spp.* also showed antiviral activity (Zhang et al., 2020).

Table 2. Bacterial secondary metabolites with their anticancer/antiviral effect.

Sr. No.	Name of Compound	Micro-organism	Applications	References
1.	Anthracyclines (aclarubic in, doxorubicin and daunomycin), peptides (actinomycin D and bleomycin), enediynes (neocarzinostatin), aureolic acids(mithramycin), itomycins, carzinophilin, antimetabolites (pentostatin)	*Actinomycetes spp.*	Anticancer drugs	(Krishnan et al., 2014)
2.	Bleomycin	*Streptoalloteichus hindustanus*	A therapeutic agent in regard to cancers of various types, including ovarian, testicular, and Hodgkin's lymphoma.	(Demain & Vaishnav, 2011)
3.	Diterpenoid derivative	*Actinobacteria*	Cell proliferation inhibition in liver and colon cancer cells HCT-116 as well as in lung cancer cells A549.	(Fu et al., 2020)
4.	urukthapelstatin A	*Merchercharimyces asporophorigenes YM11-542*	The compound inhibits the growth of A549 cells and is cytotoxic to a variety of cancer cells.	(Matsuo et al., 2007)
5.	trehalose analogs lentztre haloses A, B and C	*Actinomycete strain Lentzea sp. ML457-mF8*	Inhibition of diseases associated with autophagy, such as neurodegenerative disease, heart, arteriosclerosis, diabetes disease.	(Dimasi et al., 2017)
6.	Propionate and Butyrate	*Firmicutes phylum*	Prostate, colon, and lung cancer cells exhibit apoptosis, antiproliferative, and epigenetic activity.	(Górska et al., 2019)
7.	Jadomycins	*Streptomyces venezuelae*	Activation of ROS in breast cancer cells.	(Hall et al., 2015)
8.	Lentztrehaloses A, B and C	*Lentzea sp. ML457-mF8*	The autophagocytosis process in ovarian and human melanoma cancer.	(Wada et al., 2015)
9.	Mensacarcin	*Streptomyces bottropensis*	Melanoma cell lines undergoing apoptosis.	(Plitzko et al., 2017)
10.	Violacein	*Chromobacterium, Janthinobacterium, Alteromonas, Duganella, Massilia, Pseudoalteromonas and Collimonas*	HeLa cells show cell growth inhibition.	(Alem et al., 2020)
11.	Actinomycin D	*Streptomyces parvulus*	Wilms' tumour, childhood Ewing's sarcoma rhabdomyo sarcoma, and	(Pham et al., 2019)

			metastatic non-seminomatous testicular cancer are treated clinically	

4. Antioxidant activity:

Free radicals, or reactive oxygen species (ROS), are an important class of molecules that contribute to many diseases, including heart disease, cancer, ischaemia, diabetes mellitus, early aging, arterial sclerosis, inflammation, liver damage , skin damage, Alzheimer's disease, and arthritis (Valentão et al., 2002). According to the free radical theory of aging, molecules that scavenge free radicals or use antioxidants may be effective in delaying intrinsic aging. For example; Exfoliates from *Streptomyces* produce Carquinostatin A, which contains reactive N-H and O-H groups and protects the brain. Additionally, it exhibits the antioxidant effect comparable to that of vitamin E in rat liver microsomes. It has also been reported to inhibit glutamate toxicity in primarily cultured hippocampal neurons (Shin-Ya et al., 1990). Similarly, An extract of *Streptomyces LK-3(JF710608)* exhibits antioxidant effect because it consists of cyanidin-3-O-rutinoside, daidzein- 8-C-glucoside (puerarin), sesamol, (-) gallocatechin gallate, and, as well as delphinidinas (Karthik et al., 2013). Moreover, Thiazostatins A and B are nitrogen-containing antioxidants produced by *S. tolurosus*.

Table 3. Microbiological sources of antioxidants

Sr. No.	Name of Compound	Micro-organism	Applications	References
1.	3''-Dihydroxyterphenyllin and 3-Hydroxyterphenyllin	*Aspergillus candidus*	Lipid peroxidation inhibition	(Sheu & Chiang, 2001)
2.	Versicolone A	*Aspergillus Versicolor*	ABTS Scavenger	(T. X. Li et al., 2020)
3.	Kojic acid	*Aspergillus Versicolor*	ABTS Scavenger	(T. X. Li et al., 2020)
4.	Phomapyrone C	*Aspergillus Versicolor*	ABTS Scavenger	(T. X. Li et al., 2020)
5.	4,5,6-trihydroxy-7- methyl-1,3-dihydroisobenzofuran	*Cephalosporium spp.*	Radical- scavenger of DPPH	(X. Z. Huang et al., 2012)
6.	(Z)-1-((1-Hydroxypenta-2,4- Dien-1-yl) Oxy)Anthracene-9,10-Dione	*Nocardiopsis alba*	Radical- scavenger of DPPH	(Janardhan et al., 2014)
7.	Phenazoviridin	*Streptomyces spp.*	Lipid peroxidation inhibition activity.	(Kato et al., 1993)
8.	5-(2,4- Dimethylbenzyl) Pyrrolidin -2-One	*Streptomyces spp.*	Radical-scavenger of DPPH	(Saurav & Kannabiran, 2012)

CONCLUSION & FUTURE ASPECTS

Biologically produced secondary metabolites are also called "natural products". There is a need to maintain the feasibility and productivity of natural products research since they provide a variety of bioactive lead compounds for drug discovery. The current study finds a huge scope in the further study in the microbial secondary metabolism for the identification of novel drugs. The microbes from diverse habitats provide a strong platform which can answer may questions posed by deadly disease and drug resistance menace.

There is a need for extensive research to expand the drug discovery perspective and to develop an understanding of a drug's mechanism so it is suitable for treating various diseases. Using new advances in DNA technology, cultivation and fermentation beneficial microbial strains can be explored for the benefit of mankind to address problems posed by obsolete drugs.

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LIST OF ABBREVATIONS

OSMAC, One Strain-Many Compounds; RNA, Ribonucleic Acid; MTCC, Microbial Type Culture Collection & Gene Bank; HSV, Herpes Simplex Virus; ROS, Reactive Oxygen Species; ABTS, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); DPPH, 2,2-diphenyl-1-picrylhydrazyl; DNA, Deoxyribonucleic Acid.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ETHICAL APPROVAL

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included within this review article.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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