Review Article

Novel Bioactive Compound Production by Microbial Biota: Potential Antimicrobials

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Abstract:

Man is always trying to make his life easier and accomplished. He has faced mass destruction in history due to epidemics like small pox, malaria and plague. In order to combat diseases, exploration of man led him to search for causative agents and their control. A time reached when it was found that microbes are themselves a source of potent metabolites which have proved to be effective as drugs and medicines showing great antibiotic activity. It is necessary to find out new sources for potential new antimicrobial compounds. Several hundred important compounds have been isolated which have antibiotic activities and diverse chemical nature. But these compounds should have minimum toxicity to be useful clinically. Because of the increasing resistance of pathogens, there was a never ending desire and need to search for more. Bioactive Compounds have been extracted from microbes which are produced as secondary metabolites. Day by day, new compounds are being discovered giving a hope of golden future of drug industry. The current article emphasizes the importance and need to search for new bioactive compounds to overcome infections caused by multiple drug resistant (MDR) and biofilm forming pathogens irrespective of the previously present knowledge.

Keywords:

Penicillin, Antibiotics, Secondary metabolites**,** Bioactive compounds, Biofilms

Introduction:

The term bioactive compound consists of two words "*Bios*" from Greek means life and "*activus*" from Latin mean full of energy and dynamic. So it is defined as "a compound which causes a reaction and triggers a response in living cells and tissues"[1]. Humans are trying to satisfy their needs. Without a doubt, one of these needs is to stay alive. The fear of getting diseases and death led the man to study the microbes in the surroundings. Moreover there is a need to do management of pests which are devastating for crops because these are becoming resistant to pesticides[2].

About 5000 antibiotic compounds have been obtained from cultured Gram-positive, Gram-negative bacteria and filamentous fungi. Among these compounds, only hundreds could be used clinically to treat animal, plant and human diseases [3]. There are about hundreds of antibiotics discovered, but bacterial resistance against these drugs has evolved continuously. Human race is witnessing multiple drug resistance (MDR) in bacteria. These bacteria are posing a serious threat to public health. World Health Organization has concluded that excessive, improper and unnecessary prescription of antibiotics has leaded this resistance in microbes[4].

Nature is attractive source giving us outstanding diversity of microorganisms, plants animals, marine organisms which have chemical diversity in their therapeutic compounds [5]. As compared to macro-organisms, microorganisms are cheap source of natural products because of large scale production opportunity of these source organisms. Many organisms produce both primary and secondary metabolites and have novel potential to fight against various serious diseases of human and animal origin[6]. There is a need to test these compounds for possible clinical use. The brief history, sources of bioactive compounds, discovery of penicillin and

need of new antibiotics especially against multi-drug resistant and biofilm forming pathogens are discussed here.

Bioactive compounds: the secondary metabolites:

Marine bacteria and fungi live close with other organisms and produce biologically active compounds due to the lack of an active defense system. This explains why they produce secondary metabolites; the bioactive compounds or rely on other associated microbes for mutual protection and benefits [7 and 8]. These compound show biological activity. It has a direct physiological or cellular effect living organism. They have the capacity to influence health [9]. These metabolites are not essential for metabolism and growth of microbes. Their production is controlled by cryptic gene clusters [10]. These secondary metabolites can be harvested from fermentation of microbes and can be obtained directly from the tissue samples of macro-organisms. It is estimated that more than 300,000 secondary metabolites exist in living organisms [11]. Many of the discovered antimicrobial products are the potential source of novel drugs from human benefits. Decade from 1950 to 1960 was called "Golden Age of Antibiotics" in which fields of microbiology and chemistry worked together. This was the period, when many new antimicrobial compounds, in particular from Streptomyces were discovered and their biotechnology perspectives were explored by industry [12].

Discovery of penicillin: the fungal metabolite:

Penicillin was the first compound discovered by Alexander Fleming in 1929 which showed the antibacterial effect against *Staphylococcus aureus*. He observed a contaminated agar plate streaked with *S. aureus* having a fungal colony. Colonies around the fungal growth were lysing and the area was transparent. The mode of action of this compound released by fungal growth was very interesting. It was causing harm to polymers of cell wall in bacteria. Fleming found that it was also effective against many Gram positive bacteria in laboratory conditions. He understood the importance of this metabolite produced by fungi named *Penicillium*. This compound was named as "Penicillin". He was unable to purify it [13]. Later, two British scientists, Florey and Chain purified this antibiotic during Second World War (1939-1945) and all three scientists got prestigious Nobel Prize. It was the drug which saved many lives including thousands of soldiers and hundreds of civilians. It laid the base of antibiotic era and drug industry [14].

The resistance against penicillin became apparent. Development of penicillin resistant pathogens limited its effectiveness. In 1940, two scientists Abraham and Chain reported resistance of *E. coli* against penicillin which produced penicillinase which resulted in its inactivity. In 1942, resistance against penicillin was also reported in hospitalized patients undergoing treatment for infections caused by *Staphylococcus aureus*. *Enterbacteriaceae* also showed high rates of penicillin resistance. So outstanding success of penicillin as discussed above moved interest of scientists to the search for other antibiotic-producing microorganisms, especially from soil environments [15].

Discovery of streptomycin: the actinobacterial metabolite:

Another great success was the discovery of actinomycetes bacteria, *one of the most important phyla of Gram Positive bacteria, which are very active in production of antimicrobial substances* [16 and 17]. *After the discovery of penicillin, S.A. Waksman discovered* S**treptomycin** was obtained from soil actinomycetes, *Streptomyces griseus in 1943, which was later used successfully to treat tuberculosis* [18]. *More than two thirds of novel natural antibiotics are of Streptomyces origin, which belong to Actinomycetes group of bacteria.* The examples include Daptomycin and Lincomycin which are formed by complex secondary metabolisms [19]. It is believed that each *Actinobacteria* has the inherent ability to produce approximately 20 secondary metabolites. It is because they are originated

with a novel metabolome, making them a novel source of unique antimicrobial products [20]. Extremophile actinomycetes are promising sources of antimicrobial compounds due to their unique nature, diverse community structure and unexplored metabolic pathways [21].

Microbes: Sources of secondary metabolites:

Apart from the above mentioned discoveries, there are several other reports mentioning importance of microbes as source of secondary metabolites [22]. However, our knowledge on this subject is still lacking. There is need to explore the microbial diversity and its products as potential antimicrobial agents. No discrimination of terrestrial, endophytic or marine microbiota is required in this regard. But substantial evidence encourages exploring more vigorously marine mirobiota as newly emerged antimicrobial sources. Marine microbiota is a great treasure which is occupying about three quarters of the earth's surface. Water column of ocean contains about 10^6 bacteria per milliliter. Marine natural products are now playing a very active part in medical and pharmaceutical research [23]. The first documented marine bioactive microbial secondary metabolite was isolated by Burkholder and his co-workers in 1966 from a marine *Pseudomonas* spp. [24]. Between 2009-2011, about 230 structurally diverse bioactive compounds from marine sources were reported [25]. It was reported that gene analysis of a marine bacteria *Bacillus subtilis spizisenii* obtained from Indian Ocean has shown presence of many genes which make them capable of producing secondary metabolites [2]. Shifting the research goals on unexplored group of bacteria like *Firmicutes* etc. can help to find new antimicrobial productions [26].

Biological activity of secondary metabolites: Broad spectrum action:

Secondary metabolites have broad spectrum of pharmacological biological activity which could be antimicrobial, antitumor and antiviral. There are certain guidelines to differentiate between active and inactive natural products with bioactive potential. In general, mostly microbial compounds play active role in physiological and pathological processes of host. For example, gut bacteria play an essential role in host health overall. It is because their unique metabolites make them to synthesize several molecules such as clostridial cluster IV and XIV, vitamins and aromatic compounds that are essential to control cardiac diseases, synthesis of cholesterol and metabolic diseases including obesity and diabetes [27]. Studies on microbes with antibacterial, antiviral, anticoagulant, antitumor potential, cardiovascular and pharmaceutical properties led them ideal for more in-depth investigations [28] (Table 1).

Microbial Source	Name of Compound	Pharmacological Effect	Reference
Aspergillus terreus	Mevinolin	Cholesterol lowering agent	[29]
Aspergillus parasiticus	Sequoiatone A& B	Anti-tumor	
Nocardia spp.	Ansamitocin	Anti-tumor, Antifungal	
Pseudomonas phenolica	MC21-A	Bactericidal	
Salinospora tropica	Salinosporamide	Apoptotic activity in myeloma cells	[11]

Saccharomonospora	Lodopyridone	Cytotoxic effects on colon adenocarcinoma	
Salinispora arenicola	Arenimycin	Antibacterial	
Shewanella spp.	Eicosapentaenoic acid	Anti-thrombotic, Anti-Atherosclerotic agent	
Streptomyces caespitosus	Mitomycin C	Anticancer (Lung and Colon Cancer)	[5]
Streptomyces pneuceticus	Epirubicin	Anticancer (Breast Cancer)	

Table 1: List of some microbial products and their pharmacological effects

Usually, a bioactive compound is broad spectrum compound, since it is essentially active against both Gram-positive and Gram-negative bacteria. It is considered to be equally effective against any disease affecting humans, animal or even plants. This might be due to the facts that it targets cellular organelles or enzymes [30 and 31]. It was reported that cell free filtrate of *Pseudomonas aeruginosa* has shown antimicrobial activity against *Xanthomonas oryzae* which is a rice bacterial blight [32].
Halobacillin a cyclic acyl peptide of *bacillus spp.* has been proved to be a very good bio-surfactant. It inhibits the growth of tumor cells in human colon. Living isolated microorganisms can be grown and their centrifuged extracts can be used for antimicrobial activity screening assay. Later, using molecular approaches such as DNA sequencing or genome mining can be used to screen target microorganisms and identify them. If the product of interest found then such microbes can be further studies regarding their structure and elucidated antimicrobial activity [33, 34].

Chemical nature of bioactive compounds:

All the bioactive compounds discovered up till now have exhibited a variety of chemical nature. They have several uncommon and complex specific chemical structures. There are many examples of different structural elements and unique chemical groups such as macro lactone, cyclopeptide skeleton etc. The chemical structures indicate novel arrangement of different functional groups in antibiotics and microbial secondary compounds [31]. An example is marine Bacillus, various structurally unique secondary metabolites including polyketides, polypeptides, fatty acids, lipopeptides, lipoamides and isocoumarins have been isolated from this microorganism [2]. Gram negative bacteria are sources of bioactive compounds like pyrrole, benzaldehyde, phloroglucinol, phenazine, quonoline, pseudopeptide pyrrolidinediole quinolone, phenanthren etc. Marine strain brevibacillus laterosporus has been studied for its antimicrobial activity against *Enterococcus* spp. It has been found that it yielded Tauramamide, a lipopeptide. *Pseudomonas stutzeri*'s ethylacetate extract has shown inhibitory effects against pathogenic bacteria *Bacillus subtilis*. The chemical investigation of the extract revealed that it contained a metabolite named zafrin [35]. It was reported an antibiotic Bacitracin which is a polypeptide extracted from *B. subtilis* found in sugar cane fermentation [36]. It inhibits growth of *Micrococcus flavus*. Many peptides have been extracted from *Bacillus cereus*, *B. subtilis*, and *Bacillus licheniformes* which have shown antifungal effect. A bacterial genus *Marinispora* was isolated from Cocos Lagoon, Guam in a

sediment sample and studied chemically. It harbors a sequence of unique 2-alkylidene-5-alkyl-4-oxazolidinones, lipoxazolidinone compounds. Interestingly, antimicrobial activities of these are broad spectrum identical to the commercial antibiotic "linezolid" [37] (Table 2; Figure 1).

Name of compound	Source strain	Nature of activity	Reference
Halobacilin	*Bacillus* sp.	Anticancer	[2]
Mixirin	*Bacillus* sp.	Anticancer	
Loloatin	*Bacillus* sp.	Antibacterial	
Bacillamide	*Bacillus* sp.	Anti-algal	
Basilliskamide	*Bacillus* sp.	Antifungal	
Mojavensin	*Bacillus mojavensis*	Antifungal	
Macrolactin	*Bacillus amyloliquefaciens*	Antibacterial	
Bactriacin	*Bacillus* sp.	Antibacterial	[36]
Amphotericin B	*Streptomyces nodosus*	Antifungal	[31]
Vancomycin	*Streptomyces orientalis*	Antibacterial	
Polymyxin B	*Bacillus polymyxa*	Antibacterial	
Gentamicin	*Micromonospora purpurea*	Broad Spectrum	
Rifamycin	*Streptomyces mediterranei*	Tuberculosis	
Erythromycin	*Streptomyces erythreus*	Antibacterial	
Neomycin	*Streptomyces fradiae*	Broad Spectrum	
Streptomycin	*Strepomyces griseus*	Antibacterial	
Istamycin	*Streptomyces tenjimariensis*	Antibacterial	[28]
Altemicidin	*Strepomyces sioyaensis*	Anticancer	
Marinone	*Strepomyces*	Antibacterial	
Asplasmomycin	*Strepomyces griseus*	Antibacterial	

Thiomarinol	*Alteromonas Rava*	Antibacterial	

Table 2: List of some bioactive compounds from microbes

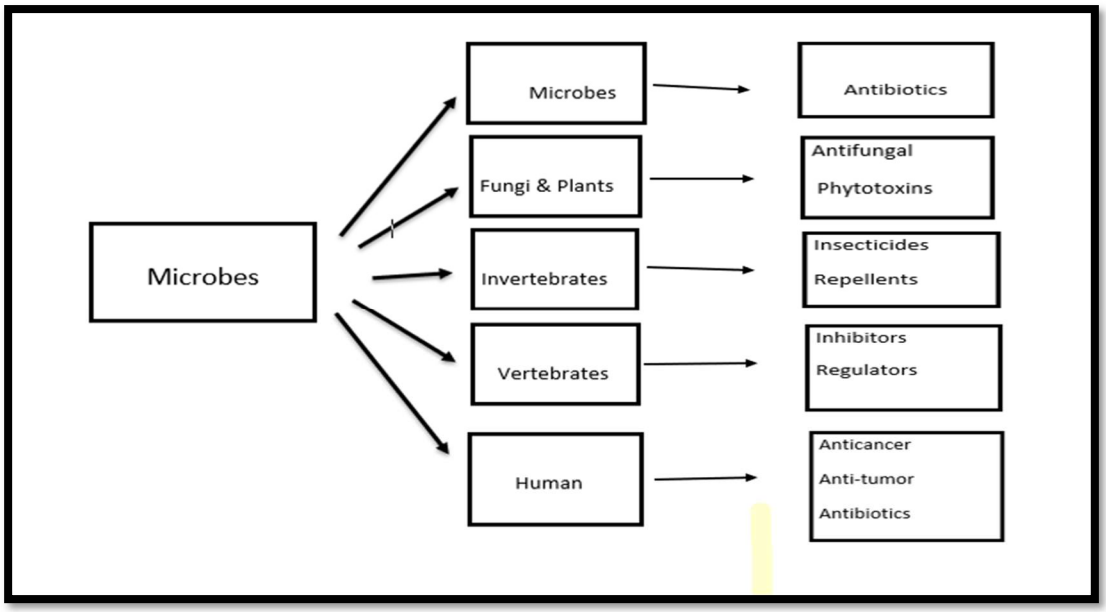

Figure 1: Microbial interactions and types of products

Multidrug resistance and biofilm formation: need of new drugs:

Infectious diseases and increasing pathogenicity is a consistent problem. This poses a serious challenge to human, animals and environment. This problem increases thousand times, when bacteria form biofilms. Approximately, 90% of bacteria prefer biofilm mode which is a natural mode of their life style [38] (Figure 2). Biofilms are groups of same or different bacteria attached to an inert surface. Once they mature, they secrete an extracellular polymeric substance (EPS), also called as matrix. Once the EPS is produces, it offers shield to the community. Now, single-cell organisms enjoy community benefit, have more protection against unfavorable conditions and offer more threat to any antimicrobial treatment [39]. WHO (World Health Organization) has published its first ever list of antibiotic resistant "priority pathogens", it include 12 families of bacteria considered as greatest threat to human life. This list has been drawn to guide and promote fresh research and development on new antibiotics. These bacteria are having built in mechanisms to resist antibiotic treatments and can pass on these abilities genetically to other bacteria becoming drug resistant [40] (Table 3).

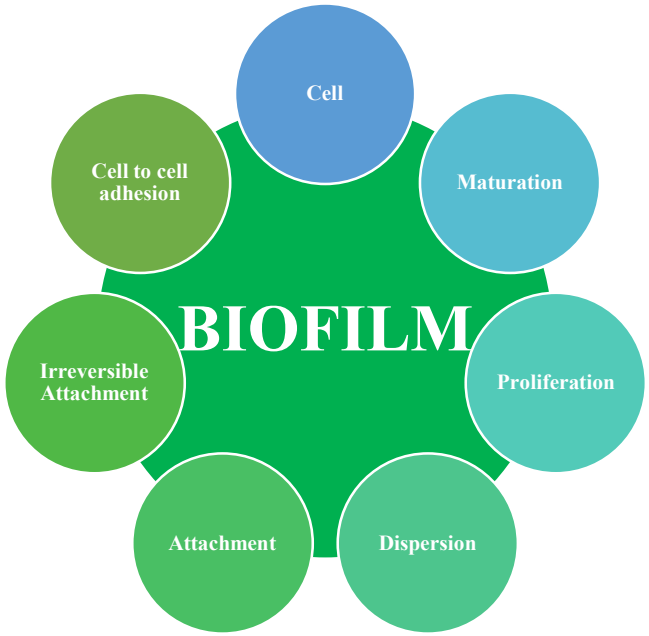

Figure 2: Steps involving biofilm formation

Priority	Name of Bacteria	Drugs
Critical	*Acinetobacter baumannii*	Carbapenem
	Pseudomonas aeruginosa	Carbapenem
	Enterobacter spp.	Carbapenem
High	*Enterococcus faecium*	Vancomycin
	Staphylococcus aureus	Vancomycin & Methicillin
	Helicobacter pylori	Clarithromycin
	Campylobacter spp	Fluoroquinolone
	Salmonella spp.	Fluoroquinolone
	Neisseria gonorrhoeae	Cephalosporin & Fluoroquinolone
Medium	*Shigella* spp.	Fluoroquinolone
	Streptococcus pneumonia	Penicillin
	Haemophilus influenza	Ampicillin

Table 3: WHO List of antibiotic resistant "priority pathogens"

Research on antibiotic development is no longer an economical benefit for pharmaceutical industries because of their short curative use and these are not profitable to treat chronic cardiovascular diseases, diabetes, asthma and psychological disorders. Data obtained from Center of Disease Control and Prevention (CDC) and United States Food and Drug Administration (FDA) and Centre for Drug Evaluation and Research showed that number of antibiotics approved faced continuous decline in recent decades. Coordinated efforts, renewal of research efforts and formation of new policies can solve the problem [41] (Figure 3).

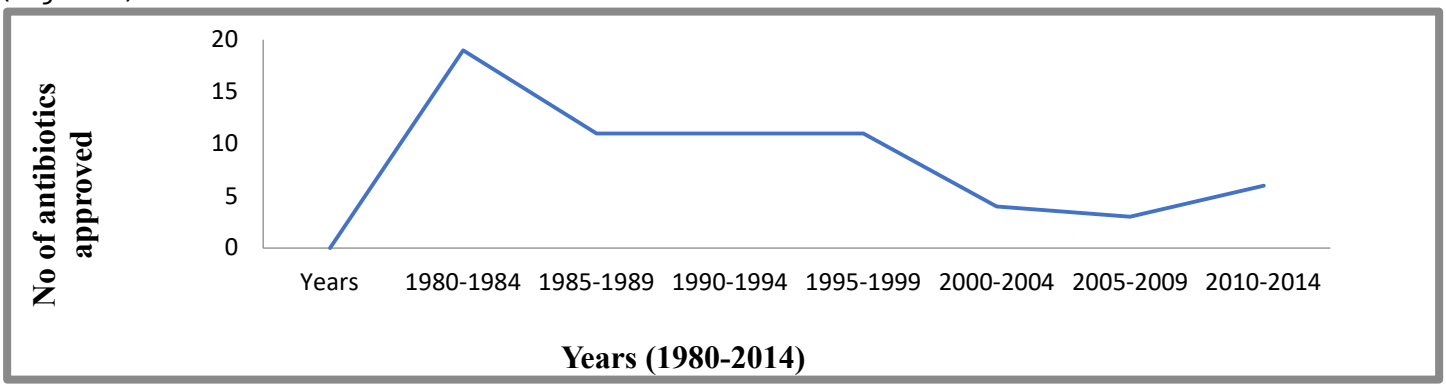

Figure 3: Development and approval of new antibiotics in past few decades

Therefore, it is important to search for alternative drugs which are capable to control biofilm forming pathogenic infections. The matrix of biofilm comprises EPS, flagella, pili, and

other biotic or abiotic components from environment. Presence of novel bioactive compounds in bacteria such as *Bacillus* and *Paenibacillus* which have antimicrobial and anti-biofilm activities have been reported [42]. Even compounds found in their extracellular polysaccharide (EPS) can be involved in anti-biofilm activities [43]. Secondary metabolites produces by many marine organisms can be used as promising anti-fouling agents with the potential to solve the causative factors of bio-fouling [44]. For example, marine cyanobacteria are active bio-control agents. Not only they serve as antibacterial agents but also have antimicrobial property against wide range of bacteria and fungi. It is estimated that almost 50% of Cyanobacteria harbored antimicrobial substance. Their blooms contain secondary metabolites with novel structure and activity [45].

Conclusions:

Ever since the origin of human civilization, there is continuous exploration of new and novel antimicrobial agents from various sources. Universe is full of novel microbial species which are yet to be discovered. There is a need to investigate more microbial potential for production of secondary metabolites which can act as bioactive compounds because already discovered antibiotics and drugs are losing efficacy against pathogens. It is also necessary to find their potency against pathogenic microbes because of their increasing resistance. Hundreds of antibiotics are purified up-till now but some are medically useable. Microbial biofilm forming capacity of microbes is another problem in dealing with treatment of diseases as they behave differently while in biofilm. Biofilm formation and biofilm forming microbes are the permanent reason of bio-fouling at commercial level which has no permanent solution, making the problem worse with every passing day. Microbial secondary metabolites undoubtedly have enormous pharmaceutical applications. These are the most suitable and ecofriendly natural alternate to synthetic chemicals that can offer solution to many obstacles in the field of medicine, food and environment.

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