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# Antimicrobial metabolites and antibiotics obtained from different environmental sources

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**ABSTRACT**

*This article compiles the history, sources and future prospects of antimicrobial metabolites and antibiotics. It is a brief overview of the antibiotic development through years and its emergence as life saving agents for everyone. Here, we also discussed the present situation of antibiotics and development of antibiotic resistance at fast rate is increasing concern for future of public health and medical science. The current status of pharmaceuticals companies showing a development of technology gap, as research on and development of new antimicrobial agents are being deemphasized or abandoned by many pharmaceutical companies has also been discussed. Thus new ways of for development of novel antimicrobials, designing more effective preventive measures to combat high rate resistance development is the need of the hour. Focus must shift from the already existing sources of antimicrobials to the still uncovered sources which have yet not been explored.*

**Keywords:** Antibiotics, history of antibiotics, secondary metabolite, resistance, novel metabolites

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## INTRODUCTION

The term “antimicrobials” include all agents that act against all types of microorganisms – bacteria (antibacterial), viruses (antiviral), fungi (antifungal) and protozoa (antiprotozoal) and antitumor. Antimicrobial metabolites are organic compounds that are not directly involved in the normal growth, development and reproduction of organisms. Secondary metabolites or Antimicrobial metabolites are produced from organisms to inhibit other organism’s competing for same ecological niche. Secondary metabolites are produced after active growth of the organism and are structurally diversified. The distribution of secondary metabolites is also unique and some metabolites are found in a range of related microorganisms, while others are only found in one or a few species. Filamentous microorganisms such as fungi and actinomycetes are the main source of secondary metabolites with antibiotic activity. The filamentous microorganisms freshly isolated from soil are the best source of secondary metabolites. The nature has immense potential to provide broad spectrum of structurally diverse secondary metabolites (Maier *et al.*, 1999).

Waste generation and its control have taken an important role in our environment. With the doubling of population and changing lifestyle pattern of the inhabitants the quantity of municipal waste generated is increasing in an alarming rate. Most of this waste is subjected to dumping in a specified disposal yard. The greatest challenge to the environmentalists is the ecofriendly management of this waste and application of microorganisms in this context has got an age over other available technologies. Organic waste is consumed by the bacteria, used as nutrients by the bacteria, and is no longer present to produce odours, sludge, pollution or unsightly mess. When bacteria consume waste, they convert the waste into safe by products and in due course of this conversion they actually produce several metabolites to break down the complex waste into simple compounds. Soil microorganisms are increasingly becoming an important source in the search for industrially important molecules (Alexander, 1977).

Extent of microbial diversity in nature is still largely unknown, thus there might be many more useful products yet to be identified from soil microorganisms. In soil 80 to 99% of microorganisms remain unidentified whereas these biological communities are known to play a dominant role in maintaining a sustainable biosphere. Today both academic and industrial interest in soil bacteria is on the rise, in search of deriving these unique biologically active metabolites and novel commercially important products from them. Bacteria are present in diverse ecological habitats. Hence there is an immense possibility to screen effective bacterial strains from waste dump sites with valuable applications. To cope up with the demand for new organisms with properties of production of unique enzymes/molecules for industrial application and waste degradation there have been a constant effort in isolating novel bacteria from diverse environment (Saha, 2014). Accordingly, the main aim of the present review is to explore and summarize published information on rich sources of bacterial strains producing beneficial antimicrobial agents from waste water resources.

**History of Antibiotics and antimicrobial agents**

When antibiotics were first introduced in the middle of the last century, they were hailed as wonder drugs. Patients and physicians alike were amazed at the almost miraculous effect of these drugs on serious bacterial infections. For the past fifty or sixty years physicians have come to expect that antibiotics would cure almost all of their patient’s bacterial infections, and patients expect that the miracle drugs will still work wonders. Prior to 1940 infections were either treated with surgical drainage, antiseptics, silver compounds, arsenicals, or with tincture of time. Bacterial endocarditis was almost uniformly fatal, and a diagnosis of pneumonia or meningitis was practically a death sentence. The rapid succession of antibiotics over the latter half of the twentieth century was indeed miraculous and provided clinicians with many options to success- fully treat a wide range of bacterial infections (Zinner, 2007).

During the latter half of the nineteenth century, scientists such as Koch were able to identify the microorganisms responsible for diseases such as tuberculosis, cholera, and typhoid. Methods such as vaccination for fighting infections were studied. Besides their fatal effect like causing diseases, scientists were also carrying out research to try and find effective antibacterial agents or antibiotics from these microorganisms. The scientist who laid foundation of chemotherapy, the use of chemicals against infection, was Paul Ehrlich. He was thus known as the father of chemotherapy. He spent much of his career studying histology, then immunochemistry, and won a Nobel Prize for his contributions to immunology. In 1904 he switched direction and entered a field which he defined as chemotherapy. Ehrlich's 'Principle of Chemotherapy' was that a chemical could directly interfere with the proliferation of microorganisms, at concentrations tolerated by the host. This concept was popularly known as the 'magic bullet', where the chemical was seen as a bullet which could search out and destroy the invading microorganism without adversely affecting the host. The process is one of selective toxicity, where the chemical shows greater toxicity to the target micro- organism than to the host cells.

By 1910, Ehrlich had successfully developed the first example of a purely synthetic antimicrobial drug. This was the arsenic containing compound salvarsan. Although it was not effective against a wide range of bacterial infections, it did prove effective against the protozoal disease sleeping sickness (trypanosomiasis), and the spirochaete disease of syphilis. The drug was used until 1945 when it was replaced by penicillin. Over the next twenty years, progress was made against a variety of protozoal diseases, but little progress was made in finding antibacterial agents, until the introduction of proflavine in 1934. Proflavine is a yellow-coloured aminoacridine structure which is particularly effective against bacterial infections in deep surface wounds, and was used togreat effect during the Second World War.

The systematic screening approach introduced by Paul Ehrlich became the cornerstone of drug search strategies in the pharmaceutical industry and resulted in thousands of drugs identified and translated into clinical practice,

including, of course, a variety of antimicrobial drugs. During the earlier days of antibiotics research, this approach led to the discovery of sulfa drugs, namely sulfonamidochrysoidine (KI-730, Prontosil), which was synthesized by Bayer chemists Josef Klarer and Fritz Mietzsch and tested by Gerhard Domagk for antibacterial activity in a number of diseases (Domagk, 1935). Prontosil, however, appeared to be a precursor to the active drug, and the active part of it, sulfanilamide, was thus not patentable as it had already been in use in the dye industry for some years. As sulfanilamide was cheap to produce and off-patent, and the sulfanilamide moiety was easy to modify, many companies subsequently started mass production of sulfonamide derivatives. The legacy of this oldest antibiotic on market is possibly reflected in one of the most broadly disseminated cases of drug resistance: sulfa drug resistance, which is almost universally linked with class 1 integrons. Moreover, once the sulfa drug resistance is established on a mobile genetic element, it may be difficult to eliminate because the resulting construct confers a fitness advantage to the host even in the absence of antibiotic selection (Enne *et al*., 2004). Despite this, many continuously modified derivatives of this oldest class of synthetic antibiotics are still a viable option for therapy, and the action of and resistance to sulfanilamide is one of the best examples for the arms race between man and microbes. Two other classes of synthetic antibiotics successful in clinical use are the quinolo- nes, such as ciprofloxacin, and oxazolidinones, such as linezoild (Walsh, 2003).

Penicillin was discovered in 1928, it was not until 1940 that effective means of isolating it were developed by Florey and Chain. Society was then rewarded with a drug which revolutionized the fight against bacterial infection and proved even more effective than the sulfonamides. In 1944, the antibiotic streptomycin was discovered from a systematic search of soil organisms. It extended the range of chemotherapy to *Tubercle bacillus* and a variety of Gram-negative bacteria. This compound was the first example of aseries of antibiotics known as the aminoglycoside antibiotics. After the Second World War, the effort continued to find other novel antibiotic structures. This led to the discovery of the peptide antibiotics (e.g. bacitracin (1945)), chloramphenicol (1947), the tetracycline antibiotics (e.g. chlortetracycline(1948)), the macrolide antibiotics (e.g. erythromycin (1952), the cyclic peptide antibiotics (e.g. cycloserine (1955)), and in 1955 the first example ofa second major group of (3-lactam antibiotics, cephalosporin C.

As far as synthetic agents were concerned, isoniazid (a pyridine hydrazide structure) was found to be effective against human tuberculosis in 1952, and in 1962 nalidixic acid (the first of the quinolone antibacterial agents) was discovered. A second generation of this class of drugs was introduced in 1987 with ciprofloxacin. Many antibacterial agents are now available and the vast majority of bacterial diseases have been brought under control (e.g. syphilis, tuberculosis, typhoid, bubonic plague, leprosy, diphtheria, gas gangrene, tetanus and gonorrhoea).More than 23,000 bioactive metabolites of which 17,000 antibiotics were discovered from the microorganisms in the last 50 years.

**Explored sources of antimicrobial agents**

**Soil as source of antimicrobial agents**

Many soil-inhabiting bacteria are known to produce secondary metabolites that can suppress microorganisms competing for the same resources (Garbeva *et al.*, 2011). Microbial population play's a prominent role for biotechnology and pharmaceutical industries as it offers countless new genes and biochemical pathways to probe for enzymes, antibiotics and other useful molecules. There are a number of microorganisms which produce a number of medically and industrially useful compounds which is primarily bioactive secondary metabolites.

Secondary metabolites are produced by some organisms such as bacteria, fungi, plants, actinomycetes and so forth. Among the various groups of organisms that have the capacity to produce such metabolites, the actinomycetes occupy a prominent place (J Antibiot, 2005). Actinomycetes are prokaryotes of Gram-positive bacteria but are distinguished from other bacteria by their morphology, DNA rich in guanine plus cytosine (G+C) and nucleic acid sequencing and pairing studies. They are characterized by having a high G+C content (>55%) in their DNA (Gonzalez-Franco, 2009). Actinomycetes are of universal occurrence in nature and are widely distributed in natural and man-made environments. They are found in large numbers in soils, fresh waters, lake, river bottoms, manures, composts and dust as well as on plant residues and food products. However, the diversity and distribution of actinomycetes that produce secondary metabolites can be determined by different physical, chemical and geographical factors (Gurung *et al*., 2009). Actinomycetes provide many important bioactive substances that have high commercial value. Their ability to produce a variety of bioactive substances has been utilized in a comprehensive series of researches in numerous institutional and industrial laboratories. This has resulted in the isolation of certain agents, which have found application in combating a variety of human infections. That is why more than 70% of naturally occurring antibiotics have been isolated from different genus of actinomycetes. Out of

this different genus, *Streptomyces* is the largest genus known for the production of many secondary metabolites (Maleki, 2011).

**Waste water as source of antimicrobial agents**

In the urban route, the anti-infectives excreted [for some compounds, as much as 90% in the parent form (Jjemba 2006), washed off (in the case of topical formulations), or discarded by people in households, hospitals, or industries will end up in sew- age. Once in wastewater, anti-infectives are discharged directly to surface waters or transported by sewers to wastewater treat- ment plants (WWTPs). During this process, the anti-infective loads in sewage may be diluted by the mixing with used water containing none of these substances (Alexy 2004). Anti-infectives may also reach the aquatic environment directly because of leak- ing sewers and sewer overflows (Sedlak *et al.* 2004). Compounds arriving at WWTPs may be eliminated from wastewater, depending mainly on their capacity to associate with particulate matter (which influences their removal by physicochemical or biological treatments) and their susceptibility to bio- logical transformation (which certainly affects their elimination by biological treatment) (Ternes and Joss 2006). Partial biodegradation and mineralization of anti-infectives in WWTPs is possible, as bacteria may cometabolize these substances or use them as a source of carbon and energy to grow (Ternes *et al.* 2004). Substances having a lower affinity for solids and higher resistance to biotransformation will be subsequently dis- charged into streams (Roberts and Thomas 2006). Substances sorbed to sludge during treatment in WWTPs can also reach the environment by the application of sewage sludge in agricultural fields or by leaching in landfills. For these reasons, WWTPs are the main entry point of urban anti-infectives into the aquatic environment (Glassmeyer *et al*. 2008; Ternes *et al.* 2004).

**Aquatic environment as source of antimicrobial agents**

In the agricultural route, anti-infectives present in animal excreta may reach the aquatic environment by drainage and runoff to surface water and by percolation to ground- water. Studies have shown that compounds may be transported by the aqueous phase or bound to particulates in suspension (Kay et al. 2004, 2005), and this pathway is enhanced mainly because of land application of manure (Alexy 2004; Kumar et al. 2005). Substances retained and progressively accumulated in soils can be gradually released into the aqueous phase; agricultural soils may therefore act as environmental reservoirs for anti-infectives (Lee et al. 2007; Rooklidge 2004). These sub- stances can also reach natural waters directly by leaking from manure storage structures or constructed lagoons (Meyer 2004) or through dust (Hamscher et al. 2003). Compounds used in aquaculture are often released directly into surface waters by leaching from food pel- lets, fish feces, or pond sediments (Cabello 2006; Lee et al. 2007). Anti-infectives sprayed on fruit plants may reach the aquatic environment; however, this pathway has not yet been documented. Therefore, agricultural activities may be considered among the main non- point sources of anti-infectives in the aquatic environment.

**Future prospects of antimicrobials and antibiotics**

21st Century 'omics technologies also can advance the synthesis and production of natural products. Despite the great synthetic diversity derived from the development of combinatorial chemistries and high-throughput screening methods over the past fifty years, natural products and related structures continue to be extremely important elements of pharmacopoeias. Looking forward, natural products and related structures are likely to become even more important for development of improved and new medicines, due to the variety of functionally relevant secondary metabolites of microbial and plant species whose chemical and genetic diversity are being revealed by ultra-fast DNA sequencing and related genomics and bioinformatics tools. Here to fore, methods for identifying and characterizing the activities of secondary metabolites have been inefficient and often tedious, but recent advances in genomics, informatics, and associated 21st century 'omics technologies are dramatically accelerating the pace of discovery and analysis (Linh Ngo, 2013).

As resistance to available antibiotics continues to increase, it will become necessary to develop new agents with novel targets or mechanisms of action. Combination of currently available antibiotics might remain useful in the treatment of resistant pathogens, but it is possible that physicians will run out of options at some time in the future. Several experimental molecules are in the literature and are under consideration for clinical development. For example, bacteriocins such as two-peptide antibiotics and other molecules are being studied for potential antibacterial chemotherapy (Cotter *et al.*, 2005) as are molecules that block receptors on the bacterial surface that mediate cell adhesion (the initial phase of infection). Other approaches include hybridization and other modifications of existing antibiotics; bacteriophages are also under investigation to possibly revive interest in the mass antibacterial agents. There is no doubt that as antibiotic resistance increases worldwide, enormous challenges

will be placed on physicians and industry alike to find new products to continue the antibiotic miracle long into the future. Every attempt should be made today to preserve and optimize the agents in our therapeutic armamentarium. There are several indications that new approaches are required to combat emerging infections and the global spread of drug-resistant bacterial pathogens. One is the pattern in rates of death from infectious disease in the 20th century: from 1900 to 1980, the rate dropped from 797 per 100,000 people to 36 per 100,000 people, a reduction by a factor of more than 20 and a testament in part to the efficacy of antibiotics (Armstrong *et al*., 1999).

However, from 1980 to 2000, that rate doubled, largely because of HIV but also due to the spread of drug-resistant bacterial pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci, multiple-drug-resistant gram-negative bacteria, and multiple-drug-resistant tuberculosis (Cohen, 2000). While the rise in mortality is due partly to infection in more seriously ill or immune-compromised patients, there is no doubting the need for new strategies and new molecules to treat pathogens that are resistant to nearly the full array of contemporary antibiotics. We are at a critical point, not seen since the pre-antibiotic era, at which infections caused by some bacterial pathogens are untreatable.

A second indication of the need for novel antibacterial therapeutics is the almost 40-year innovation gap between introductions of new molecular classes of antibiotics: fluoroquinolones in 1962 and the oxazolidinone linezolid in 2000 (Walsh, 2003).

A third indication is the recent trend by several large pharmaceutical companies to leave the antibacterial and antifungal therapeutic arenas, suggesting a future decrease in scientific expertise in antibacterial-drug discovery and development skills. A technology gap is developing and widening, as research on and development of new antimicrobial agents are being deemphasized or abandoned by many pharmaceutical companies.

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**REFERENCES**

[1] Alexander M, “Introduction to soil microbiology”, *John Wiley and Sons Inc*, New York, USA, **1977**.
[2] Alexy R. **2004**. What do we know about antibiotics in the environment? In: Pharmaceuticals in the Environment: Sources, Fate, Effects and Risks (Kümmerer K, ed). Berlin:*Springer*, 209–221.
[3] Amrita Saha and Subhas Chandra Santra, “Isolation and Characterization of Bacteria Isolated from Municipal Solid Waste for Production of Industrial Enzymes and Waste Degradation”, *Journal of microbiology & experimentation*, Vol. 1, pp. 01-08, **2014**.
[4] Ana Cecilia González-Franco and Y Loreto Robles Hernández, “Actinomycetes as biological control agents of phyto pathogenic fungi”, *Tecnociencia Chihuahua*, vol.3(2), pp. 64–73,**2009**.
[5] Armstrong GL, Conn LA and Pinner RW. “Trends in infectious disease mortality in theUnited States during the 20th century” , *J. Am. Med. Assoc.*,Vol.281 (1), pp. 61–66, **1999**.
[6] Cabello FC. **2006**. Heavy use of prophylactic antibiotics in aqua- culture: a growing problem for human and animal health and for the environment. *Environ Microbiol* 8(7):1137–1144.
[7] Cohen M. L., “Changing patterns of infectious disease” *Nature*;406(6797):762–7. **2000**.
[8] Domagk, G. (**1935**). Ein Beitrag zur Chemotherapie der bakteriellen Infektionen. *Dtsch. Med. Wochenschr*. 61, 250.
[9] Enne, V. I., Bennett, P. M., Livermore, D. M., and Hall, L. M. (**2004**). Enhancement of host fitness by the sul2-coding plas- mid p9123 in the absence of selective pressure. *J. Antimicrob. Chemother*. 53, 958–963.
[10] Glassmeyer ST, Kolpin D, Furlong ET, Focazio MJ. **2008**. Environmental presence and persistance of pharmaceuticals: an overview. In: Fate of Pharmaceuticals in the Environment and in Water Treatment Systems (Aga DS, ed). Boca Raton, *FL:CRC Press*.
[11] Hamscher G, Pawelzick HT, Sczesny S, Nau H, Hartung J. **2003**. Antibiotics in dust originating from a pig-fattening farm: a new source of health hazard for farmers? *Environ Health Perspect* 111:1590–1594.
[12] Jjemba PK. **2006**. Excretion and ecotoxicity of pharmaceutical and personal care products in the environment. *Ecotoxicol Environ Saf* 63(1):113–130.
[13] Kay P, Blackwell PA, Boxall ABA. **2004**. Fate of veterinary antibiotics in a macroporous tile drained clay soil. *Environ Toxicol Chem* 23(5):1136–1144.

[14] Kumar K, Gupta SC, Chander Y, Singh AK. **2005**. Antibiotic use in agriculture and its impact on the terrestrial environment. *Adv Agron* 87:1–54.
[15] Lee LS, Carmosini N, Sassman SA, Dion HM, Sepúlveda MS. **2007**. Agricultural contributions of antimicrobials and hor- mones on soil and water quality. *Adv Agron* 93:1–68.
[16] Linh T. Ngo, "21 Century Natural Product Research and Drug Development and Traditional Medicines", *Nat Prod Rep*., Vol. 30(4), pp. 584–592, 2013.
[17] Maleki H, "Characterization of *Streptomyces* isolates with UV, FTIR spectroscopy and HPLC analyses", *Bioimpacts.*, Vol. 1(1), pp. 47–52, 2011.
[18] Meyer MT. **2004**. Use and environmental occurrence of veteri- nary pharmaceuticals in the United States agriculture. In: Pharmaceuticals in the Environment: Sources, Fate, Effects and Risks (Kümmerer K, ed). Berlin:*Springer*, 155–163.
[19] Paolina Garbeva, Olaf Tyc, Mitja NP, Remus-Emsermann, Annemieke van der Wal, Michiel Vos, Mark Silby, Wietse de Boer. No apparent costs for facultative antibiotic production by the soil bacterium Pseudomonas fluorescens Pf0-1. *PLOS ONE*. **2011**; 6: e27266.
[20] Roberts PH, Thomas KV. **2006**. The occurrence of selected pharmaceuticals in wastewater effluent and surface waters of the lower Tyne catchment. *Sci Total Environ* 356(1–3):143–153.
[21] Rooklidge SJ. **2004**. Environmental antimicrobial contamination from terraccumulation and diffuse pollution pathways. *Sci Total Environ* 325(1–3):1–13.
[22] Sedlak DL, Huang CH, Pinkston K. **2004**. Strategies for select- ing pharmaceuticals to assess attenuation during indi- rect potable water reuse. In: Pharmaceuticals in the Environment: Sources, Fate, Effects and Risks (Kümmerer K, ed). Berlin:*Springer*, 107–120.
[23] Stephen H. Zinner. Antibiotic use: present and future. *New Microbiologica*, 30, 321-325, **2007**
[24] Tara Devi Gurung, Chringma Sherpa, Vishwanath Prasad Agrawal and Binod Lekhak "Isolation and characterization of antibacterial actinomycetes from soil samples of Kalapatthar, Mount Everest Region", *Sci Technol*., vol. 10, pp. 173–182, **2009**.
[25] Ternes TA, Joss A, Siegrist H. **2004**. Scrutinizing pharmaceuticals and personal care products in wastewater treatment. *Environ Sci Technol* 38(20):392A–399A.
[26] Ternes TA, Joss A. **2006**. Human Pharmaceuticals, Hormones and Fragrances: The Challenge of Micropollutants in Urban Water Management. London: IWA Publishing.
[27] Walsh, C. T. (**2003**). Antibiotics: Actions, Origins, and Resistance. Washington, DC: *ASM Press*.