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Air, Water and Soil: Resources for Drug Discovery

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1. Introduction

Drug discovery is the process by which new candidate drugs are discovered. The chemical compounds that are present in plants and animals have been an important source of new bioactive compounds. Also, we can find organisms that live in air, water and soil that we don't see, but possess a great variety of chemical that we can use to create new medicines. Bioactive compounds offer an enormous diversity of chemical structures with strong biological effect; this is one of the reasons why natural products research cannot be replaced by synthesis chemistry as a source for new bioactive compounds. Actually, more than the half of currently used medicines came from natural sources or are related to them, specifically in the situation of anticancer drugs that more than 60% belongs from nature [1].

Based on the experience in this field, it is considered that a chemical compound isolated from natural origin should be fully assessed in order to be used to combat diseases; in this manner is important to consider the type of new chemical entities potentially applicable for partial or total synthesis, as well as its use in different kind of diseases that are treatable with these compounds (2); Therefore is very important continue the search for new secondary metabolites potentially usable as drugs by human.

2. Importance of drug discovery

The importance of look for new bioactive compounds to synthesize new drugs it's based by a main objective of saving human life that it's lose by illness. Also, it is important to recognize that the drug discovery projects, help those countries that target their efforts in this area to economically and sociality develop themselves, because when chemical compounds

are discovered from microorganism that lives in natural environments, this chemical can be exploited industrially and generate more jobs.

Now, the new drugs and innovative procedures are usually able to keep people alive for a long time with better conditions that would have previously been rapidly fatal, such as cancer and end-stage heart, liver, lung, kidney, and neurologic diseases. As a result, most people in modern countries die from long-term chronic conditions that are characterized by a prolonged period of distressing symptoms and progressive loss of function.

According with World Health Organization (WHO) of *“57 million global deaths in the last report in 2008, 36 million (63%), were due to no communicable diseases (NCDs). The four main NCDs reported are cardiovascular diseases, cancers, diabetes and chronic lung diseases. The burden of these diseases is rising disproportionately among lower income countries and populations. In 2008, nearly 80% of no communicable disease deaths -- 29 million -- occurred in low- and middle-income countries with about 29% of deaths occurring before the age of 60 in these countries. The leading causes of NCD deaths in 2008 were cardiovascular diseases (17 million deaths, or 48% of all NCD deaths), cancers (7.6 million, or 21% of all NCD deaths), and respiratory diseases, including asthma and chronic obstructive pulmonary disease (4.2 million). Diabetes caused another 1.3 million deaths”* [3]. As we can see, in the WHO's statistic data, there are less number of people that die with microbial infection, it can be said to thanks to the constant development of pharmaceutical drugs.

The discovery of new bioactive compounds from microorganism present in the ambient, needs the previously determination of diversity, because by knowing the kind of microbes that live in a certain site, we can be able to design strategies and culture methods adapted for the different types of microorganism present in nature [4]. We can be able to screen chemical bioactivity only if we can culture the microorganism, because we need the microbial biomass to obtain the compounds. To culture microorganism from natural sources is not an easy topics, because, when we try to cultivate bacteria or fungi from substrates and conditions that are in constant change, and incubate them in a static temperature and nutrients; many microbes don't resist this transformation of circumstances and die.

3. Drug resistance bacteria

Some Bacteria can innately be resistant to one or more types of antimicrobial compounds and other can be capable of acquired. In actuality, it is well know the factors that provoke mutations in bacteria that create stronger species that are able to survive to the effects of current drugs. Examples of these factors are the unnecessary use of antibiotics by humans, the use in animal feeds in low doses, availability over-the-counter in many countries, misuse by health professionals, patient failure to follow prescribed treatment, antibiotic use in agriculture, aquaria and family pets, eating raw or undercooked foods.

It can be describe several strategies of antibiotics resistance in different bacterial genera. Pathogens bacteria that have become resistant to the current antibiotic drug are an increas-

ing public health problem. Some examples of diseases that have become very hard to treat with the current drugs are wound infections, septicemia, tuberculosis, pneumonia, and gonorrhea, to name a few. One part of the problem is that bacteria and other microbes that cause infections are remarkably adaptable and have developed several mechanisms to be immune to antibiotics and other antimicrobial drugs.

Also, it's been reported that over-prescription and the improper use of antibiotics has led to the generation of antibiotic resistance bacteria that use to be susceptible at those antibiotics [5].

4. Mechanisms of bacteria to become antibiotics resistant

- a. **Avoiding entrance of antibiotic into the bacteria cell:** Bacteria and other microbes can actually change the properties of its membrane by changing its grade of permeability by reducing the number of ion channels which are the entrance of some drugs to diffuse into the cells. Another way to get rid of antibiotics in some bacteria is use adenosine triphosphate (ATP) to obtain energy to activate this ion channels and pump it out of the cells.
- b. **Editing transmembrane protein expression:** The mechanism of several antibiotics it's to interact specifically with molecules in the membrane of the microbes and preventing it from interacting with other molecules (usually proteins) inside the cell. Some bacteria respond by changing the chemical structure or the expression of the molecule (replacing it with another molecule) so that the antibiotic can no longer recognize it or bind to it.
- c. **Bacterial enzymes that destroy antibiotics:** Some bacteria can be resistant to antibiotics by neutralizing them directly. For example, some organisms may obtain new genes that encode proteins like enzymes that neutralize antibiotics agents before they get to their targets. An example of this enzymes can be found in the β -lactamases like penicillinases, cephalosporinases, carbenicillinase, cloxacilane, carbapenemase, metalloenzyme that destroy the β -lactams (penicillins, monobactams, carbapenems, and cephalosporins). The β -lactamases can be isolated from Gram Negative Bacteria: *Escherichia coli*, *Enterobacter cloacae*, *Citrobacter freundii*, *Serratia marcescens*, and *Pseudomonas aeruginosa*. The mechanism of action of β -lactamases is the breaking of β -lactam ring of the antibiotic, thus destroying the drug [6]. Other example of this is *Pseudomonas sp.* erythromycinesterases that degrade erythromycin by hydrolysis of the lactone ring of erythromycin [7].

5. Cancer

Cancer is an illness that comprises more than hundred types. This disease appears when old cells are not replaced by new cells and are accumulated in a mass of tissue known as tumor" [4]. To cite some statistics data; cancer is responsible for one of every four deaths in the United States.

It's second only after heart disease as a cause of death in this country. About 1.2 million Americans were diagnosed with cancer in 1998. Of that number, more than 500,000 are expected to die of this disease. Cancer can attack anyone, but the chances of getting the disease increase with age. The most common forms of cancer are skin, lung, colon, breast and prostate cancer. Cancer is a disorder that affects the genes. There were an estimated 12.7 million cancer cases around the world in 2008, of these 6.6 million cases were in men and 6.0 million in women. This number is expected to increase to 21 million by 2030. Lung cancer is the most common cancer worldwide contributing nearly 13% of the total number of new cases diagnosed in 2008. Breast cancer (women only) is the second most common cancer with nearly 1.4 million new cases in 2008 and colorectal cancer (Figure 1) is the third most common cancer with over 1.2 million new cases in 2008 [8].

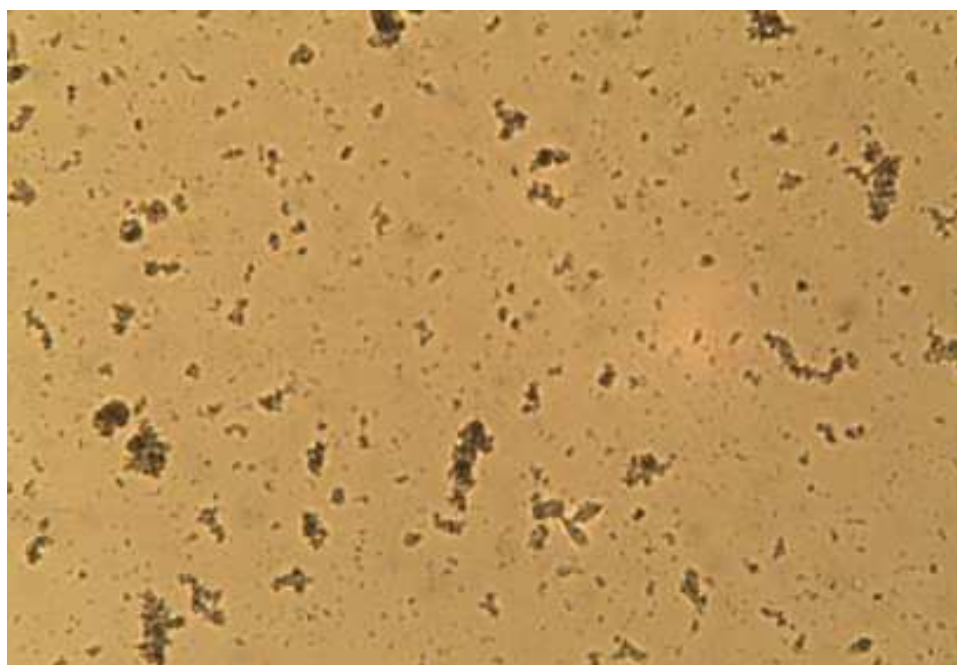


Figure 1. Cancer Colorectal HCT-116 cell culture in McCoy medium at 40 X amplification

6. Natural source for drug discovery

6.1. Drug discovery from air microorganisms

The atmosphere is well characterized for possess a good light intensity, extreme temperature variations, low concentration of organic matter and water, hence become a very hostile place for microorganism. However, there are a numerous quantity of microbes founded in the atmosphere, most of them introduced by human activity.

Bioaerosols are airborne particles that are biological in foundation. Bioaerosols can be formed from nearly any process that involves biological materials and generates enough energy to separate small particles from the larger substance, such as wind, water, air, or me-

chanical movement. Plants, soil, water, and animals (including humans) all serve as sources of bioaerosols and are present in most places where any of these sources live.

Microorganisms are frequently considered passive habitants of the air, dispersing via airborne dust particles (Figure 2). However, latest studies suggest that many airborne microorganisms are metabolically active, even up to altitudes of 20,000 m. Also, it has been suggested, that some airborne microbes may modify atmospheric conditions [9].



Figure 2. Fungal strains from air samples in Valle de las Palmas, Mexico.

Several studies reported a great variety of microorganism present in air samples, for example, a study realized in Mexico, in 2007, showed 21 species of bacteria founded in air samples from landfill, some of them are pathogenic and opportunistic bacteria, the most abundant are *Pasteurella haemolytica*, *Serratia plymuthica*, *Escherichia coli* y *Klebsiella pneumonia* and 19 fungal species, 7 of them allergenic, *Cladosporium herbarum*, *Aspergillus* sp y *Penicillium* sp. [10]. Despite this, *Serratia plymuthica*'s well known to possess 2-amino-3-(oxirane-2,3-dicarboxamido)-propanoyl-valine has been shown to inhibit the growth of the human pathogen *Candida albicans* efficiently [11].

Another studies found airborne microbes collected at indoor air with filters installed in two shopping centers in Singapore. The most common microorganism appears to be several species of *Brevundimonas* (50%) [12] other study has identified *Brevundimonas diminuta* as producer of a nematocidal metabolite known as (R)-(-)-2-ethyhexan-1-ol which have a strong activity against *C. elegans* and *B. xylophilus* [13].

6.2. Drug discovery from soil microorganisms

Soil microorganisms (Figure 3), such as bacteria and fungi, play central roles in soil fertility and promotion of plant health. It is assessed that in 1 g of soil there are 4000 different bacterial "genomic units" based on culture independent identification methods. In the other hand, an estimated 1,500,000 species of fungi, but they are more difficult to cultivated by standard methods [14].

In soil there is a constant exchange of organic substances and flow of energy. Feeding, predation, degradation of macromolecular substrates and absorption of nutrients have been important in chemical processes in soil. One of the most important microorganism in drug discovery found in natural habitat mainly in soil are the actinomycetes which are very diverse family of bacteria, they are an important source of bioactive compounds with high value in pharmaceutical industry. It's have been reported that almost 80% of the world's antibiotics come from the genera *Micromonospora* and *Streptomyces*. Beside this, the majority of the actinomycetes in soil that are potential drug sources remain uncultivable, and therefore in cannot be screened for novel antibiotic discovery [5].

Has been reported that microorganisms found in soil are a plentiful source of chemically diverse bioactive compounds, and have been an important source for the discovery of antibacterial agents including penicillins, cephalosporins, aminoglycosides, tetracyclines, and polyketides [2].

Also, from 117 actinomycetes strains isolated from the wasteland alkaline and garden soil samples in India, were found 15 actinomycetes strain that showed antimicrobial activity against at least two pathogen bacteria between them *Staphylococcus aureus*[5].

According to reference [15], environmental factors, such as carbon and energy sources, mineral nutrients, growth factors, ionic composition, available water, temperature, pressure, air composition, electromagnetic radiation, pH, oxidation–reduction potential, surfaces, spatial relationships, genetics of the microorganisms and interaction between microorganisms, can alter the microbial diversity, activity and population dynamics of microorganisms in soil. It is important to mention that almost 80–90% of the microorganisms habiting soil are on solid surfaces [15].



Figure 3. Bacteria strains from soil samples in Valle de las Palmas, Mexico.

6.3. Drug discovery from water microorganisms

The world's oceans comprise about 70 % of the earth's surface, where the extensive drug discovery efforts involving soil bacteria have not been extended to this ecosystem [16]. This environment have special attention since is known that typical microbial abundance of 10^6 per ml in the water column and 10^9 per ml in ocean bottom sediments. Actinobacteria is among the most dominant population and successful phyla of all environments [17]. This class takes into account 5 subclasses, 9 orders, 55 families, 240 genera and 3000 species [18].

From all actinobacteria, Marine Actinobacteria have become the most important source of secondary metabolites with medical application, such as anticancer, antibiotics, antitumor, anti-inflammatory, and antifungal compounds [16-17, 19].

Actinobacteria, called commonly actinomycetes are Gram positive bacteria having a higher guanine plus cytosine (G+C) percentage in its DNA than any other bacteria. Most of these organisms are aerobic (oxidative), some are facultative or forced anaerobes (fermentation) [20]. These microorganisms grow as networks called mycelium. They structures are filamentous. Sometimes are on the surface, for that is called aerial mycelium, or substrate mycelium if it attaches to the substrate surface [21]. The individual filaments of the mycelium or hyphae are divided into units as a result of growth of the cell wall into the hyphae at regular intervals along this structure. This process is called septation and each of the resulting septa contains one DNA molecule. The mycelium bacterium is analogous to the mycelium forming filamentous fungi [22]. Actinobacteria produce spores in specialized hyphae many of which are developed on the aerial filament, sometimes these spores are flagellated. The Actinobacteria inhabit the soil where play an important role in soil chemistry, the characteristic odor of soil is due to special metabolites that are known as Geomins [23]. Actinobacteria also inhabit aquatic environments including those marine. Actinomycetes are the most economically and biotechnologically valuable prokaryotes [24].

Almost 60 years in actinomycetes researches, more than 15000 bioactive compounds have been discovery for academic and pharmaceutical researchers many of which are used as drugs today. Fact more than half of the antibiotics discovered to date are obtained from the soil-derived actinomycete bacteria *Streptomyces* and *Micromonospora* genus spores [25].

The majority of the actinomycetes isolated from marine sources was largely of terrestrial origin and had been washed to shore and existed in the ocean as metabolically inactive spores [25]. Recently, phylogenetic analyses of the 16S rRNA genes indicate that existing new taxa widely distributed in ocean sediments [26], including some that appear to be unique and obligate marine actinomycete bacteria [27]. These strains represent the most significant source of naturally occurring microbial antibiotics [17, 28- 30] and antitumor compounds [28- 30] with specific metabolic and physiological capabilities that had not been observed in terrestrial microorganisms before [31-32]. Members of this group are producers of clinically useful antitumor drugs such as anthracyclines, glycopeptides, aureolic acids, enediynes, antimetabolites, carzinophilin, mitomycins and others [19].

The studies related with new biodiversity and drugs discovery had been examined from waters all around the world such as San Diego Bay, Bahamas, Fiji and Guam Islands among

others. Recently, one study in the Gulf of California [32] found Operational Taxonomic Units (OTUs) belonging *Streptomyces* and *Actinomadura* genus and a potentially represent a new genus-level taxon in the family *Streptomycetaceae*. In addition, several previously described marine species were isolated including *Micromonospora krabiensis*, *Saccharomonospora marina*, *Streptomyces fenhuangensis*, *Verrucosipora maris* and *Verrucosipora sediminis* suggesting that these species may have broad geographic distributions.

The genes involved in secondary metabolism are responsible for the biosynthesis of small molecules that mediate important functional traits such as allelopathy, chemical communication and iron acquisition [33]. These compounds have been used to assess biogeographical patterns among bacteria [34].

Polyketide synthase (PKSI) genes are called Type I and are responsible for the production of many important secondary metabolites including the antibiotic erythromycin [35] and the anticancer agent epothilone [35-36].

Bacteria can maintain complex assemblies of PKS genes [37], many of which are not expressed under normal laboratory conditions [38]. Recently, a study found that HGT plays an important role in the evolution of PKSI genes and that ketosynthase (KS) domains within polyketide synthase genes are phylogenetically important making predictions about production of secondary metabolites by complex biosynthetic pathways [39-40]. Other method used for providing further evidence for endemism associated with secondary metabolites [33], is the terminal restriction fragment length polymorphism (T-RFLP) used to demonstrate that subpopulations of bacteria cluster together based on collection site [41].

According to [32] targeting KS domains provides a rapid method to assess PKS diversity and novelty within individual strains. The results revealed evidence of common pathways shared with other *Salinispora* strains but also sequences that share low levels of identity with any characterized pathways and thus may be associated with the production of new secondary metabolites. It is noteworthy that the new sequence type "L" also possesses a KS sequence that has not previously been observed in "*S. pacifica*".

Secondary metabolites are linked to an organism's fitness and therefore represent an emerging marker to study population structure and function, taxonomically meaningful patterns of secondary metabolite production have been detected in bacteria [42] and fungi [43].

Progress has also been made in drug discovery from actinomycetes by using high throughput screening and fermentation, metabolic profiling technologies, genome scanning, mining genomes for cryptic pathways, and combinatorial biosynthesis to generate new secondary metabolites related to existing pharmacophores [17, 44]. Metagenomic screening of DNA from environmental samples [45-46] provides an alternative way of discovering new antibiotic biosynthetic genes.

According to [47] recently published new web tools that provide automated methods to assess the secondary metabolite gene diversity; those are the Natural Product Domain Seeker (NaP-DoS) analysis based on the phylogenetic relationships of sequence tags derived from polyketide synthase and non-ribosomal peptide synthetase (NRPS) genes. These results are compared

with an internal experimentally database. NaPDoS provides a rapid mechanism used to infer the generalized structures of secondary metabolites biosynthetic gene richness and diversity within a genome or environmental sample by extract and classification of ketosynthase and condensation domains from PCR products, genomes, and metagenomic datasets increasing exponentially the investigations in this field of science with benefits in the field of drug discovery.

Table 1 shows a list of microorganisms isolated from different sources which produce anti-oxidant, antibacterial, anticoagulant, antiviral, anti-inflammatory, immune system, antidiabetic and nematocidal activities, as well as their action mechanisms.

Microorganism	Bioactive Compounds	Bioactivity	Mechanism	Reference	Natural Source
<i>Brevundimonas diminuta</i>	(R)-(-)-2-ethylhexan-1-ol	Nematicidal	Inhibitor against <i>C. elegans</i> and <i>B. xylophilus</i>	[48]	Air
<i>Pasteurella haemolytica</i>	A1-Derived Leukotoxin and Endotoxin	Immune system	Induce Intracellular Calcium Elevation in Macrophages	[49]	Air
<i>Streptomyces strain PM0324667</i>	NFAT-133	Antidiabetic	induced glucose uptake in L6 skeletal muscle cells	[50]	Soil
<i>Clostridium cellulolyticum</i>	Closthioamide	Antibiotic	<i>Staphylococci</i> Multiresistente inhibition	[51]	Soil
<i>Gordonia sputi DSM 43896</i>	G48 JF905613 Compound	Antimicrobial	<i>C. albicans</i> , <i>S. aureus</i> inhibition	[52]	Soil
<i>Actinomycetes</i>	3Ba3 Compound	Antibacterial	<i>E. amylovora</i> , <i>P. viridiflova</i> , <i>A. tumefaciens</i> , <i>B. subtilis</i> ATCC 663, <i>E. coli</i> ATCC 29998 3 inhibition	[53]	Soil
<i>Micromonospora sp.</i>	Diazepinomicin/ ECO-4601	Antimicrobial	Unespecific	[54]	Soil
<i>Eurotium Herbariorum</i>	<i>E. Herbariorum</i> NE-4	Antioxidant	Antioxidant <i>in vitro</i>	[55]	Water
Sponge	Batzelladine L y M	Antibacterial	<i>S. aureus</i> and methicillinresistant, <i>S. aureus</i> inhibition	[56]	Water
Bivalve mollucs	Anticoagulant polypeptide (TGAP)	Anticoagulant	Inhibition of factor II toIIa conversion	[56]	Water
Fungus	8'-O-Demethylnigerone	Antituberculosis	<i>M. tuberculosis</i> inhibition	[56]	Water
Algae	Dolabelladienetriol	Antiviral	Inhibition of HIV-1 replication	[56]	Water
Soft coral	Durumolides A-C	Anti-inflammatory	Modulation of LPS-activated murine macrophage cell line	[56]	Water
Sea cucumber	Frondoside A	Immune system	Lysosomal activity, phagocytosis and ROS activation	[56]	Water

Table 1. Microorganism isolated from natural sources that produce bioactive compounds

7. Conclusion

Bioactive compounds isolated from aerial, terrestrial and marine organisms have extensive past and present use in the treatment of many diseases and serve as compounds of interest both in their natural form and as templates for synthetic modification. To found new compounds useful to develop new pharmaceutical drugs, a good potential source and diverse bioactive chemicals is microorganism present in natural sources as air, soil and water.

Chemical compounds from natural sources are the major protagonists in chemical diversity for pharmaceutical discovery over the past century. The interesting chemicals identified as natural products are derived from the biodiversity in which the interactions between microbial entities and their environment formulate the diverse complex chemical entities within the organisms that enhance their survival and competitiveness. Hence, it is important to study inter and intraspecific interactions between microorganism in natural environments, this will make the screening for bioactive compounds in microbes easier.

Microbial interactions can influence the secretion of bioactive compound. Has been reported, various types of contacts among bacterial species and other organism. For example, these relations can be negative (parasitism, competition and predation) or positive (metabiosis and symbiosis) for these microorganisms. Between interactions in microorganism we can emphasize competition. Some bacteria are reduced by different species when the environmental resources are limited; therefore they produce compounds that impress negatively in their competitors [4].

Finally, air, soil and water are the home of microorganism that compete all the time to survive, resist changes in temperature, pressure, nutrient, carbon and nitrogen content, microorganisms that are obligated to produce weapons against predators, change and mutate to scape of detection of other microbes. All this, are the reason why we can find an unimaginable number and variety of chemical that are effective to be part of a pharmaceutical drug formulation.

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