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**Revisión | Review**

# Why do we have so many molecules and biodiversity but so few antiparasite medicines?

[Porqué tenemos tantas moléculas bioactivas y biodiversidad pero tan pocas medicinas antiparasitarias?]

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**Abstract:** Natural products are isolated from biodiversity, that is, from plants, microorganisms, insects, and marine organisms; most of the biodiversity is found in about 10-12 countries located around the Equator. For a long time, people chose this option to alleviate diseases and the industry to discover new medicines; however, from the 70's onwards synthetic products have displaced them. Today there is a rebirth of natural products research and annually hundreds of new natural and synthetic bioactive molecules are reported in specialized journals. On the other hands, new drugs are continually required and especially there is a deficit of them to treat the so-called Neglected Diseases, which affect and threaten the health of billions of people in the world. These diseases paradoxically affect almost all megadiverse countries. Thus, the richest countries in biodiversity do not benefit from the use of natural products because research, development and production of new medicines are carried out in more technologically advanced countries. Why do we have so many molecules in biodiversity and journals but so few medicines? How could new antiparasite drugs be developed quickly and cheaply in the countries affected by Neglected Diseases? A feasible alternative is the Mining in Press, that is, the search of molecules in scientific literature. In this paper we analyze the reasons why these valuable substances have not become drugs and remain curiosities of laboratories and libraries, and the advantages of using this approach as a source of drugs or templates to other bioactive molecules.

**Keywords:** Biodiversity; Natural Products; New Drugs; Limitations; Journals; Mining; Neglected Diseases

**Resumen:** Los productos naturales son aislados de la biodiversidad, es decir, de plantas, microorganismos y organismos marinos; gran parte de la biodiversidad se encuentra en cerca de 10-12 paises localizados alrededor del Ecuador. Por mucho tiempo, la gente ha seleccionado esta opción para aliviar sus enfermedades y la industria para descubrir nuevas medicinas; sin embargo, desde los años 70s los productos sintéticos los han desplazado. Hoy hay un renacimiento de la investigación de productos naturales y anualmente cientos de nuevas moléculas naturales y sintéticas bioactivas son reportados en las publicaciones especializadas. De otro lado, continuamente se requieren nuevas drogas y especialmente hay un déficit de ellas para tratar las llamadas Enfermedades Olvidadas, que afectan y amenazan la salud de miles de millones de personas en el mundo. Estas enfermedades paradójicamente afectan casi todos los países megadiversos. De esta manera, los países más ricos en biodiversidad no se benefician del uso de productos naturales, ya que la investigación, el desarrollo y la producción de nuevas medicinas se lleva a cabo en países tecnológicamente avanzados. Por qué tenemos tantas moléculas en la biodiversidad y en las publicaciones, pero tan pocas medicinas? Cómo podrían las drogas antiparasitarias ser desarrolladas de manera mas rápida y barata en los países afectados por las Enfermedades Olvidadas? Una posible alternativa es la Minería de las Publicaciones, es decir, la búsqueda de moléculas en la literatura científica. En este artículo nosotros analizamos las razones por la cuales esas valiosas sustancias no han llegado a ser drogas y permanecen como curiosidades de los laboratorios y bibliotecas, y las ventajas de usar esta aproximación como una fuente de drogas o modelos de otras moléculas bioactivas.

**Palabras clave**: Biodiversidad; Productos Naturales; Nuevas Drogas; Limitaciones, Revistas; Minería, Enfermedades olvidadas

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## INTRODUCTION

### *Why do we need more drugs?*

The search for novel drugs is a constant human necessity for many reasons such as low therapeutic arsenal, resistance, reduced efficacy, inadequate treatment scheme, secondary effects, fast metabolism, and chemical instability, among others. Additionally, many diseases are classified as chronic and sometimes diseases require personalized pharmacologic attention. In some instances, we demand new drugs owing to the appearance of recent diseases like Flu and Ebola or by the rapid increase of others such as Alzheimer's.

From the industrial standpoint, innovative drugs are new economic opportunities. Until the 1970s, natural products were the preferred option for the industry to develop new medicines, but later they were displaced by synthetic products and combinatorial chemistry, although interest in natural products has recently been renewed.

On the other hand, the WHO has declared more than twenty diseases as Neglected Diseases; among them are leishmaniasis and trypanosomiasis (WHO, 2017). Malaria has received special attention in recent years and therefore is not found in this group. These diseases affect several billions of people and require more pharmacological solutions. Thus, the Nobel Prize for Medicine was awarded in 2015 to the researchers who participated in the development of the antimalarial artemisinin and the antiparasite avermectin (The Nobel Assembly at Karolinska Institutet, 2015). However, more efforts are required, since developing a medicine, whether of natural or synthetic origin, requires a high investment of money and time, as well as very expensive human teams and instrumental equipment. Any methodology that reduces these factors will be an additional opportunity for a drug to reach society quickly and cheaply. Traditionally, this has been done with approximations based on the organic synthesis and on biodiversity. Nevertheless, a lot of valuable information about old and new bioactive molecules can be found in scientific information from journals. In this article we discuss the role of megabiodiversity and the potential of scientific information in the discovery of new drugs, especially for Neglected Diseases.

### *Where can drugs come from?*

Drugs have diverse origins, like chemical entities or biological information. In the first case, they can be found from synthetic and natural resources, while biological information or functional evidence commonly is obtained from traditional uses and toxicology; thus, molecules from Biodiversity must be considered like chemical entities and carriers of biological information. Additionally, it must be taken into account that natural substances must be optimized and therefore used as templates to develop new medicines

There is great concern worldwide because fewer drugs are being discovered (Bennani, 2011; Jarvis, 2016); moreover, innovation has been replaced by the development of the so-called "Me Too" medicines (Gagne & Choudhry, 2011), that is, chemical entities that maintain the same structural pharmacophore but have slight structural modifications to change the pharmacokinetic properties.

The main sources of drugs as chemical entities are shown below:

- ***From biodiversity***
  - Plants
  - Marine organisms
  - Microorganisms, including endophytes
  - Insects
  - Tissue or microorganism culture elicitation and challenges
  - Metabolic Engineering
- ***From Organic Synthesis***
  - Combinatorial Chemistry
- ***From Molecular Modeling***
  - *In silico*
  - Virtual libraries
- ***From Serendipity***
  - Biological activity
  - Metabolism (biotransformation)
  - Unexpected organic synthesis
- ***From Old Drugs***
- ***Drug Second Uses***
- ***From the Literature***

Most of the research on natural products has been done on plants, and although a high percentage has not been studied, the interests are currently focusing on marine organisms (Blunt *et al.*, 2018), fungi (mainly endophytes) (Hillman *et al.*, 2017) and unconventional natural sources including insects

(Seabrooks & Hu, 2017), since they offer more attractive possibilities, especially to obtain new chemical skeletons and biological activities. Therefore, the richness in biodiversity is not having many species, but a great variation of them, since plant species of the same genus or tribe contain very similar compounds with similar pharmacologic actions. However, marine organisms, microorganisms, and synthetic molecules lack traditional medicine and there is not enough knowledge in chemotaxonomy to carry out studies to develop new drugs quickly.

It is also noteworthy that modifications on a partial sequence of the genome of a microorganism or plant can generate new natural molecules that had never been present in the original organism and elicitation in roots or cell cultures is an easier method to find these type of compounds. Besides, Omics allow valuable and accurate pharmacological targets to be defined

On the other hands, combinatory chemistry has been a faster way to obtain hundreds or even thousands of substances subsequently bioassayed through HTS or UHTS; although, the results have not been promising because synthesis is carried out on a solid phase, so bioavailability is usually low. Alternative source of new molecules is the use of software to design new molecular structures to build a virtual library. Molecular modeling allows the identification of a pharmacophore to establish relationships between the structure and activity; nevertheless, sometimes structures are so complex that is not feasible an efficient organic synthesis.

In addition, information from doctor's offices can provide valuable information from the follow-up of secondary effects and the unpredicted symptoms after the product has been launched to the market. Another important component in the search for new drugs is serendipity (Ban, 2006; Baumeister *et al.*, 2013) from unexpected activities, astonishing reactions, and surprising metabolism or unpredicted symptoms.

These seems to suggest that there are more potential sources of new molecules and biodiversity is only one of them, like Tulip has already expressed it (Tulp & Bohlin, 2002): "Thus, it seems that biodiversity is not a unique and valuable source of molecules and information for new drugs, Thus, there are no obvious advantages of "biodiversity prospecting", which will, possibly, endanger fragile ecosystems in the search for rare species". As discussed below, it does not seem to be important for megadiverse countries either.

***The role of megadiverse countries in new drug discovery***

Natural products have been the most abundant source of bioactive substances; therefore, it is assumed that rich countries in biodiversity are the source of many medicines. This would be favored because in these same countries there is a rich ethnomedic tradition and they are still used as raw drugs. However, that's not true. A rapid analysis of some drugs developed from natural products (Table No. 1) (Mark & Butler, 2004; Kingston, 2011; Mishra & Tiwari, 2011; Dias *et al.*, 2012; Cragg & Newman, 2013; Harvey *et al.*, 2015; Patridge *et al.*, 2015; Campbell *et al.*, 2017) shows that most of them originated mainly in the United States, Europe, and Asia (Japan and China), and only a few from megadiverse countries. In this last case the situation is dramatic, because they contribute with raw material and ethnomedic knowledge, but the process of development new medicines has not been carried out there. Moreover, when an active natural product with biological activity has been detected, the development process is undertaken in an industrialized country, such as steroids, which were first developed in Mexico, but the advanced research was carried out in USA. Another exception was the antimalarial artemisinin, discovered and developed in China.

The richness in biodiversity and the poor role played by scientists of the megadiverse countries in the development of new medicines is illustrated with the rapamycin, whose name was taken from the native name of the island, Rapa Nui. This medicine was discovered from a microorganism in Pascua Island (Chile) by a Brazilian team studying natural products on behalf of a USA-based pharmaceutic (Jeffery et al., 2017) Furthermore, research into natural products in these countries is of the phytochemical type that is, more focused on the isolation and identification of secondary metabolites and with scarce support in biological activity. As Harvey said, "there is a widening gap between natural-product researchers in countries rich in biodiversity and drug discovery scientists immersed in proteomics and high-throughput screening" (Dias et al., 2012).

Although the statement has been made many times that natural products contribute more than 70% of the medicines available in the market (Farnsworth,

1993) we must be very careful with that figure. This high percentage is true if anticancer drugs and antibiotics are considered, but in very few cases the intact natural product is used, like alkaloids of Vinca.

Likewise, the structural analogues of a lead are considered like new drugs, as is the case of statins, penicillins or cephalosporins; this is the case of drugs called "Me Too". It is clear that these substances are not new medicines, since they have the same pharmacological target and the same mechanism of action.

**Table No. 1**

**The origin and fate of some natural drugs and derivatives**

| ***Drug or Natural Product*** | ***Origen*** | ***Discovery Approach*** |
|---|---|---|
| ***From Europe/USA*** | | |
| Aspirin-COX inhibitors | Europe/USA | Traditional medicine |
| Aescin | Europe | Traditional medicine |
| Artemisinin | China | Screening |
| Atropine | Europe | Traditional medicine |
| Calycheamicin | USA | Screening |
| Camptothecin | China/USA | Screening |
| Cyclosporine | Europe | Screening |
| Colchicine | Europe | Medical extrapolation |
| Digoxin | Europe | Traditional medicine |
| Daunorubicin | Europe | Screening |
| Ergot | Europe | Screening |
| Galanthamine | Europe /USA | Screening |
| Galegin | USA | Chemical extrapolation |
| Khellin | Europe | Traditional medicine |
| Penicillin | Europe | Medical extrapolation |
| Podophyllotoxin | USA | Screening |
| Rifampin | Europe | Screening |
| Statins | Japan/USA | Screening |
| Sylibin | Europa | Traditional medicine |
| Taxol | USA | Screening |
| Warfarin | USA | Medical extrapolation |
| ***From Megadiverse Countries*** | | |
| Ecteinascidin | Caribbean Sea/USA | Screening |
| Acyclovir | Caribean Sea/USA | Chemical extrapolation |
| Capsaicin | Bolivia, Mexico | Medical extrapolation |
| Epothilone | Congo | Screening |
| Chloramphenicol | Venezuela/USA | Screening |
| Captopril | Brazil/ Europe | Medical extrapolation |
| Pilocarpine | Brazil | Medical extrapolation |
| Quinine | Amazonian Forest | Traditional medicine |
| Steroids | Mexico | Medical extrapolation |
| Tubocurarine | Amazon Forest | Medical extrapolation |
| Vincristine | Jamaica/Puerto Rico | Serendipity |

***Used as traditional medicine or site material origin vs. country of development**

The discovery of new biologically active molecules is a long, twisted, and expensive process. Difficulties in developing new medicines have increased along with the expenses involved, which nearly amount to US$ $2.87 billion (DiMasi *et al.*, 2016). Such a high investment requires the study of

faster and more effective possibilities to identify a hit molecule and transform it into a lead and finally in a drug. Until a few years ago, the search for new medicines was based on extensive extract screening and the synthesis of thousands of substances; in the latter case, it is considered that from every 10,000 molecules that undergo the process to develop a medicine, only one is released to the market (The Pharmaceutical Industry and Global Health, 2017). However, the current drug searching process is supported by new knowledge and technologies like HTS and UHTA bioassays and others. Furthermore, proteins are crystallized massively, and thousands of analogues can be designed in silico and synthesized efficiently in a few days by combinatorial chemistry. Besides, there are supplementary powerful analytical tools to check molecule stability and to determine the structure. Currently, without sacrificing a single mouse, it is possible to differentiate promissory molecules, their ADMET properties and their toxicological implications using specific in silico software. For this reason, an explanation on increasing costs in drug development do not have any support.

Although in the last 15 years pharmaceutical companies have once again shown the interest in biodiversity (Rouhi, 2003; Harvey *et al.*, 2015; Boufridi & Quinn, 2018), several drawbacks consigned by the companies to natural products converge:

- Often, biodiversity material is far away of the civilization and eventually the national accesses regulation is very slow, with many bureaucratic procedures which have increased with the Convention for Biological Diversity.
- Collection and specimen availability is especially dramatic regarding marine natural products, which additionally have not traditional medicine.
- Low material available for preclinical and clinical assays; the latter require kilograms of the bioactive molecule. Sometimes plant organs are forbidden to collect due to represent a great threat to the plant survival, such as roots or bark. In addition, other conditions such as temperature, season, plant age, and geographic affects the contents of secondary metabolites.
- Low concentrations of metabolites, some of them unstable or soluble only in organic solvents.
- The time-consuming nature of the purification processes.
- Long time investing in structural elucidation
- Complex structures usually with several chiral centers. Thus, the presence of several chiral centers is a great challenge to optimize a molecule. For this reason, many synthetic drugs available in the market have very little chirality compared to natural ones, because the purification and separation processes in each stage are very expensive and the yields are very low.
- Finally, natural products are only chemical structures not drugs. The drug has to be optimized in its pharmacokinetic, pharmacodynamic and toxicological aspects to make them more effective, bioavailable, stable and innocuous.

***Why do we have so many molecules and biodiversity but so few antiparasite medicines?***

Latin and Central America, are the most biodiverse regions of the world; Brazil, Colombia, México, Bolivia, Peru, Ecuador, Costa Rica, and Panamá in addition to China, India, Australia, Madagascar, Congo, among others, account for more than 70% of Earth's total biodiversity. Several medicines such as tubocurarine, chloramphenicol and quinine have been developed from this richness (Mark & Butler, 2004; Kingston, 2011; Mishra & Tiwari, 2011; Dias *et al.*, 2012; Cragg & Newman, 2013; Harvey *et al.*, 2015; Patridge *et al.*, 2015; Campbell *et al.*, 2017). Additionally, each country possesses countless knowledge in ethnomedicine owing to abundant practices from indigenous, afroamerican and mestizo people. Comprehensive ethnomedicine has been recorded in several classical texts on traditional medicine, national vademecum and natural pharmacopeia in many of those countries. Despite their richness in fauna and flora, several endemic diseases known as Neglected Diseases have high rates of incidence in all megadiverse countries, except Australia. These diseases are leishmaniasis, trypanosomiasis, soil-transmitted helminthiases, schistosomiasis, cysticercosis/taeniasis, dengue, chikungunya, rabies, leprosy, among others.

Like was exposed before, there is a great concern about the development of new drugs, and the same critic problem occurs when parasitic diseases are considered, in addition to poverty, poor sanitary conditions and malnutrition. Why, given such high biodiversity, profuse ethnomedical information and high levels of diseased parasite population, has been impossible to improve significantly the health in

biodiverse countries? Several research groups from universities and others public and private research centers in some megadiverse countries have carried out projects to search for molecules to battle some of the diseases previously mentioned, using data linked to natural products from traditional medicine. Regardless of these efforts, the results are far from being proper pharmacological solutions, although in some cases bioactive substances have been identified and tested.

Several facts involved in delays of drug development process for neglected diseases in the megadiverse countries can be noticed, as follows:

***The Position of Pharmaceutical Industry***

The pharmaceutical industry is not interested in the high investment of time and money required to produce suitable drugs that offer a very low profit in return. Drug development from natural products is also a very sensitive topic pertaining to the corporate image and stock price of multinational pharmaceutical corporations; the threat of being called biopirate is always present. In addition, the portfolio of industry is far of the neglected diseases.

***The Research Policies of the Biodiverse Countries***

Usually there is a lack of national policies in science and technology, chronic money deficiency, absence of modern equipment and technologies, and teams of multidisciplinary sciences. Neither there is a long-term planning in science and technology.

But in addition, the procedures to access to genetic and biological resources are so complicated and with many requirements that take too long to be approved. And this affects not only bioprospecting but also basic research and education.

***The Attitude of the Researchers***

There is a lack of policy continuity in the investigations, which are often linked to undergraduate and postgraduate studies; when the student finishes a work in natural products, that line is also finished. Besides, academic research is carry out under the same parameters of the industry, looking for a pure molecule with a new skeleton, active at low concentrations, nontoxic, druggable and easy to synthesize, so, publishable, or patentable. This is the same landscape but with few human, economic and technical resources.

The publishable attitude is over to find a possible use or solution to a specific trouble and then basic science research is the only end. Due to low possibilities of development, basic research is a vicious circle; only a paper is the final result and the cycle repeats itself: new research in bioactive molecules, new publications and new graduate and undergraduate students.

***The Use/Abuse of Ethnomedical Information*** (Gertsch, 2009)

The ethnomedical information must be evaluated carefully. Ethnomedical recommendations of plant and natural products usually include a wide collection of pharmacological applications. Some information about uses and traditional practices seem to be weak, controversial o uncertain; there are different common names and plants uses in several countries or regions within the same country. And to stablish a relationship among the morphology of a root, fruit, or leaf to a specific organ in the human body seems too irrational. Moreover, a plant is recommended, for example to treat diabetes, but without specifications about TD1 or TD2.

***The misuses of biological activity***

Besides, it is common to find misleading titles and content in scientific articles about the results in the lab, for example, an assay against L1210 or KB cells is expressed as an anticancer result when in reality is only a cytotoxic activity. Most recently, anticancerigen is similar to anticancer, or inhibition of renin-angiotensin enzyme is equivalent to an antihypertensive agent. Relief of some symptoms is shown as disease control i.e., diabetic complication treatment as anti-diabetic, and acetylcholinesterase inhibitors as anti-Alzheimer drugs and COX inhibitor is an anti-inflammatory. Moreover, the titles of several papers have claimed for antimalarial substances, but only one *in vitro* assay is carried out on the plasmodium survival, so the substances should be classified as anti-plasmodials. A similar situation is found for anti-tuberculosis vs. anti-mycobacterial, anti-leishmanial and leishmanicidal. Thus, a lot of false expectations are generated in the scientific field and in the society.

Besides, a lot of the applications are about relieving a symptom more than curing the disease as presented in national natural pharmacopeias.

***The overestimation of bioassays and in vitro assays*** (Houghton *et al.*, 2007)

Frequently, *in vitro* tests are inadequate to explain

therapeutic effects. Moreover, the strain, time and type of incubation, plant variety, extraction procedure, concentration used and type of solvent or carrier, all influence the results. In addition, the stage of the organism under study might be inappropriate, such as the use of promastigotes instead of amastigotes, which are an infective stage. There is a possibility of false positive results, especially those coming from polyphenol type molecules, which seem to lack a defined target; also, the formation of artifacts or decomposition products from the original molecules. Occasionally, the concentration used to obtain good results is very high, which could induce problems in obtaining the raw material or undesirable secondary effects.

For more accurate results the use of animal model diseases are recommended but they are expensive and require expensive animal facilities and bioethical committees restrict this type of bioassay. Frequently the therapeutic scheme is not defined; due to a fast response, the intraperitoneal route is the first election, but oral use is preferred; primary studies concerning bioavailability are indispensably to asses a good absorption and effect.

Even phytochemical screening is used to detect types of natural products, with imprecise results and false positives and negatives. There are very few bioguided trials, and efforts are focused towards purifying molecules and assigning their structure and it does not correlate with their biological activity. Finally, it is considered that more than 50% of the experiments in life science research are not reproducible (Arnaud, 2014).

### *Toxicity*

During the development of the bioassays, it is quite frequent to determine the effects of a substance or an extract over different cell lines, U937, Vero and HepG2 cells, among others. Although there is no consensus concerning the concentration at which toxicity begins, results are erroneously taken as an indication of general toxicity, not only like a specific cytotoxic (Upegui *et al.,* 2014). Consequently, interest in a possible follow-up to the molecule is lost, although those results only indicated a specific effect on that particular cell and not on whole organism. Moreover, animals possess natural barriers against xenobiotics such as hepatic metabolism or control of intestinal absorption. This landscape is well different when comparing a naked cell challenge to a high concentration of a pure compound during several hours or days.

### *Some strategies to discover bioactive molecules*

Some valuable efforts have been made to find new molecules to combat those neglected diseases, but few reach the stage of clinical assays. Most of the efforts are invested in basic research based on the search for new molecules (Wink, 2012; Pohlit *et al.*, 2013; Gilbeert, 2013; Goupil & McKerrow, 2014; Njoroge *et al.,* 2014; Nagle *et al.,* 2014; Zulfiqar *et al.,* 2017). For example, 340 natural products and 476 synthetic compounds were reported as leishmanicidal; several of them, such as canthin-6-one, γ-fagarine, flavokavin B, quercetin, nerolidol, maesabalides among others, were identified as important compounds against *Leishmania* spp. (Hussain *et al.,* 2014). Likewise, an array of different strategies to determine antiparasite bioactivity was considered in the lab of the author of this review. Specifically, against Leishmaniasis, Malaria, Trypanosomiasis and Tuberculosis the following approaches were used: Traditional Medicine (Correa *et al.,* 2014), Bioguided Search Correa *et al.,* 2006), Assay of Previous Bioactive Molecules from a Library (Cardona *et al.,* 2006), Directed Chemical Transformations (Pabon *et al.,* 2013), Synthesis of an Antiparasite Lead Molecule (Echeverri *et al.,* 2004; Cardona *et al.,* 2006), Structural Analysis of Analogues of Synthetic Molecules (Baquero *et al.,* 2015), Use of Coevolutive Relationships of Parasite–Vector Insects (Genes *et al.,* 2011), and finally, Assays with Animal Model Diseases (Pabon *et al.,* 2013; Upegui *et al.,* 2015; Echeverri *et al.,* 2015). Some of these results were as follows:

- Sapogenins from *Sapindus saponaria* topically applied to a diseased hamster model had excellent antileishmanial activity in a month of treatment, with a positive evaluation up to two months after the treatment was finished. A mixture of these saponins with hydrazones derived from chromans is very active against *L. panamensis in vivo*, and the concentration, frequency of the application, and therapeutic scheme has been optimized (Echeverri *et al.,* 2015); and now we are waiting to start clinical trials.
- A semisynthetic analogue of diosgenone given orally caused a 38% reduction of parasitaemia in mice infected with *Plasmodium berghei* (Pabon *et al.,* 2013). Given these conditions, it was necessary to subject the molecule to new transformation processes until the optimal pharmacokinetic and

pharmacodynamics parameters were set and minimal toxicity was achieved. Usually, hundreds or thousands of derivatives must be synthesized and transformed until optimal pharmacologic and toxicological properties are reached, like chloroquine or captopril.

- The well-known xanthone α-mangostin obtained from *Garcinia mangostana* was tested in vitro against *P. falciparum* and *in vivo* against *P. berghei*; in the latter case, there was a parasitaemia reduction of 80% with daily doses of 100 mg/kg given twice a day for seven days. Doses were intraperitoneal, and no toxicity symptoms were detected in organic and hematologic parameters (Upegui *et al.*, 2015). Raw material for purification of kilograms or even tons is available from fruit endosperm, currently an industrial waste.
- Finally, using photodynamic therapy, a topical formulation containing hypericin 0.5% was applied to hamsters to effectively control cutaneous leishmaniasis (Montoya *et al.*, 2015).

However, there could be a faster, easier and cheaper way, based on the search of results in specialized journals, and later stages of development, as described below.

### *The challenge to find new drugs. mining in press (mip) for bioactive molecules*

Topics related to natural products are published in a variety of journals, in fields such as chemistry, pharmacy, medicine, agriculture and food, among other. A quick look at the publications related to natural products in the last six months (Journal of Ethnopharmacology, Phytotherapy Research, Phytomedicine, Planta Medica, Journal of Natural Products, Fitoterapia, Natural Products Communication, Natural Products Research, Phytochemistry, Pharmaceutical Biology, Journal of Medicinal Chemistry, European Journal of Medicinal Chemistry, Bioorganic Medicinal Chemistry, Journal of Agriculture Food Chemistry, among others) report a great deal of new molecules with interesting biological activities, with high predominance of anti-cancer, anti-inflammatory, cardiovascular, anti-diabetic and recently an explosion of antioxidant compounds. However, there are also only a few cases of anti-parasites.

A brief analysis indicates that every month, information on nearly 180 natural bioactive molecules (from approximately 15 articles/month × at least 2 bioactive molecules/article × 6 most known journals) are generated, many of which pertain to diseases that have a reduced pharmacological stock but affect hundreds of millions of people. Also, organic synthesis may contribute with a much greater quantity of molecules and many other additional molecules are found in libraries such as those from NCI and the pharmaceutical industry (Lipinski *et al.*, 2015).

Several authors have proposed literature as a source of information for valuable molecules (Banville, 2006; De Souza, 2007); this point of view could be a good response of poor countries to their own diseases. Thus, scientific literature especially related to natural products and synthetic bioactive molecules, provides tens or hundreds of molecules with multiple biological activities weekly or monthly. Usually, there are well-described assays that have as surplus a known structure and, occasionally, the preparation and biological analysis of some of their derivatives. Extracting this information, sorting it out from redundant and nonessential data, discarding inaccurate assays and inadequate concentrations, or analyzing whether the organisms were used in their right stages is a real mining process. Because searching In Press is a persistent, difficult and detailed search process of scientific literature to extract valuable information from the less useful, it could be termed as Mining In Press (MIP). This has been previously conducted to explore natural product sources (Hale, 2005; Banville, 2006; De Souza, 2007) mostly from the genomic point of view (Bachmann *et al.*, 2014; Milshteyn *et al.*, 2014). It is like the process known as "Repurposing Drugs" (Cragg *et al.*, 2014; Corsello *et al.*, 2017) or simply "Old Drugs", but in this case, the molecule is at the beginning of the development process.

MIP could be of special importance in countries where there are reports of neglected diseases because the pharmaceutical industry has little interest in developing medicines for those diseases, which cause millions of deaths a year. It would be easier and cheaper to develop new substances to combat tropical diseases from MIP than to start the process from the basics. Additionally, given that the scientific material is in the public domain, there is no need to either pay royalties or restrict the scope of their use and study due to existing patents. The scientific field can be strengthened through transformations from hits to leads, and bioavailability assays, metabolic studies, and elucidation of mechanisms of action and toxicity

can provide sufficient resources for good and innovative publications.

On the other hands, many preclinical research centers are being established worldwide in collaboration with academics (Cavalla, 2013; Vaudano, 2013; Cragg *et al.*, 2014; Michaudel *et al.*, 2015; Arvidsson *et al.*, 2016; Abou-Gharbia *et al.*, 2017) because drug development is more than an academic exercise. Some of these initiatives have been focused on Neglected Diseases. Likewise, searching strategies have been proposed, but with very demanding requirements of the activity criteria, including extremely low effective concentrations and Selectivity Index that are too high (Nwaka & Hudson, 2006).

Although this review has been focused on drug development, other areas of research and chemical product development may benefit, such as dyes, flavoring, stabilizers, antioxidants, agrochemicals, and surfactants. This means that any molecule or extract that displays an adequate level of activity could provide the research community valuable and sufficient information to explore its possibilities.

In some cases, MIP offers a great number of benefits in the search of new drugs as shown below:

- There are well-known and standardized processes of purification and synthesis.
- It is also possible to find relevant data concerning chemical and physical stability, solubility, yielding, etc
- There are *in vitro* assay models.
- Molecules have known structures.
- Eventually, some molecules are transformed to establish a preliminary structure–activity relationship, especially on synthetic molecules.
- Sometimes there are animal model assays, so it is possible to develop approximations of their bioavailability.
- Preliminary toxicity levels in some blood, renal, and hepatic parameters could be available.

## CONCLUSIONS

The discovery and development of new medicines is a long and complex path whose requirements, time and investment have increased over the last few years -ironically, a time when better, faster, and more precise ways to isolate or design promissory molecules and massive bioassays are available to find bioactive molecules.

Biodiversity, formerly the primary source of new bioactive molecules, has not been useful for the development of the pharmaceutical industry in megadiverse countries and as a solution to their health problems. On the other hand, searching for new medicines from natural sources in these countries is limited due to economic, social, and political concerns, despite being affected by the Neglected Disease. Furthermore, there are diverse sources of potentially active molecules along with Biodiversity for drug development. However, a high economic and health potential is wasted in hundreds of reports periodically published by scientific journals since these results are not explored further to develop new medicines.

In this paper, several approaches to explain the presence of high amounts of bioactive molecules but only a few drugs were presented. Similar to the search for bioactive molecules by *in vitro*, *in vivo* or *in silico* methods, this approach can be called Mining In Press, because it considers information from specialized journals and offers two interesting perspectives for industry and society.

For the industry, this method provides valuable biological information and chemical structures that can be transformed into other more active molecules, which can be eventually patented. For the society, this method can be an important tool for countries with neglected diseases in which new prescription drugs can be developed faster and at a lower cost than undergoing a complete screening.

Despite these observations, thousands of molecules, or new chemical entities (NCE), new molecular entities (NM) or new active substances (NAS), as redefined by the FDA (Branch & Abranat, 2014), are now waiting for an opportunity to be transformed into drugs. Meanwhile, millions of people are daily infected by neglected diseases, and thousands are dying consequently.

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