Technological Forecasting on Phytotherapics

Development in Brazil

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Abstract—The prospective analysis is presented as an important tool to identify the most relevant opportunities and needs in research and development from planned interventions in innovation systems. This study chose *Phyllanthus niruri*, known as "stone break" to describe the knowledge about the specie, by using biotechnological forecasting through the software Vantage Point. It can be seen a considerable increase in studies on *Phyllanthus niruri* in recent years and that there are patents about this plant since twenty-five years ago. India was the country that most carried out research on the specie, showing interest, mainly in studies of hepatoprotection, antioxidant and anti-cancer activities. Brazil is in the second place, with special interest for anti-tumor studies. Given the identification of the Brazilian groups that exploit the specie it is possible to mediate partnerships and cooperation aiming to help on the implementing of the Program of Herbal medicines (phytotherapics) in Brazil.

Keywords—*Phyllanthus niruri*, phytotherapics, technological forecasting.

I. INTRODUCTION

The prospective or prospective analysis (or forecasting) is a planning technique used to improve the information base available on the managerial decision [1]; which means to search and perform exploration work of general nature, in order to determine the most important information to orientate the study steps. Although it was created for planning in the economic sectors, the technique also has potential in the management of supply chains in Science and Technology (S&T) [1].

The determination of technological demands is a recent field on the research area, and was consolidated by the return that has on justifying the funding of activities that uses public and private investments [1]. Thus, as the practice of bioprospecting develops, the natural resources starts to have value, attracted to investors and important for its preservation, as these resources may be used for the development of new products [2].

Therefore, identifying which are the most important needs and opportunities for research and development (R & D) in the future, from planned interventions in innovation systems [3] can be an important step in established programs in Brazil as the National Policy on Medicinal Plants and Phytotherapics. This program, approved in 2006, aims on secure safe access and rational use of medicinal plants and phytotherapics by the population, based on the list of regulated plants by ANVISA (National Agency of Sanitary Surveillance) [4].

Among the medicinal plants approved by ANVISA, *Phyllanthus niruri* was chosen for this study to describe the knowledge about this species, through biotechnological prospection using the software Vantage Point. In order to suggest a strategic plan for this plant, the main publication areas and its respective patents and institutions / authors were analyzed to identify the existing studies and orientate the development of potential pharmaceutical products.

II. THE DEVELOPMENT OF PHYTOTHERAPIC DRUGS IN BRAZIL

The emergence of the pharmaceutical industry dates back to the nineteenth century, following the progress of medicine. Early in its history, most drugs were of natural origin and were developed from therapeutic practices, where its activity was based on separation and purification of products extracted from plants and / or animals [5].

Over time, these drugs have been replaced by synthetic chemical, requiring increasing scientific knowledge, which increased the need of spending on research, improvement of natural medicines and the discovery of new drugs with powerful pharmacological properties [6].

The modernization of the development of new drugs began to involve extraction, purification, chemical synthesis, fermentation procedures and the pharmaceutical process itself, using high-tech equipments and technology. Thus, the main raw material used are the pharmaceutical chemicals, derived from the chemical synthesis of organic materials, however, other feedstocks are still obtained from isolation of medicinal substances in plants or in its extract (phytotherapics), now with the use of biotechnology [7].

The use of herbal medicines (or phytotherapics) is increasing worldwide as an additional way to treat and prevent diseases, especially chronic diseases such as cardiovascular and neurodegenerative disorders [8] - [9]. Although there is a great interest in synthesis techniques, similar to combinatorial chemistry, the prospection of natural products is still a source of new drugs, and about 50% of new chemical entities, from 1981 to 2002 were natural products or derived from natural products [10] - [11]. Likewise, according to WHO, about 80% of world population consumes natural products, a market estimated at U.S.$ 50 billion / year.

In this context, the growth in the herbal market, estimated at about U.S.$ 22 billion, 3.7% of the global market, accompanies the pharmaceutical industry, considered one of the most lucrative in the world. The global pharmaceutical market moves around 856.4 billion dollars, associated with constant and high investments in research and development of new products. Brazil is considered the seventh largest market, and from 2006 to 2010 grew by 14%. It is also estimated that by 2015 Brazil will be the sixth largest market in this sector [12].
In Europe alone, the market of herbal medicines reaches billions of dollars a year, with Germany accounting for 50% of this value [13]. In Brazil, even before the importance of this market, there are no official figures on how much the herbal industry moves, it is estimated somewhere around a billion reais / year [14].

The picture of the Brazilian reality is based on its economic history, which has always highlighted the use of plant products such as the redwood (Pau-Brasil), sugar cane, coffee, and, recently, the soybean. Moreover, it is remarkable the importance of using plants in Brazil, especially considering the source of our pharmaceutical industry, focused on the use of various plant-derived inputs. This remains true today with most of the national industry using plants as a basic input. However, the impact on the Brazilian economy concerning the production of plant-derived drugs is not significant, although it is one of the largest consumer markets [15]. This is contradictory, considering that Brazil is a country whose biodiversity associated with a rich ethnic and cultural diversity, has a valuable traditional knowledge using medicinal plants. So has the potential to develop research which may result into appropriate treatments and technologies [16].

According to [16] Brazil has 55,000 species of plants that have been cataloged (does not account the vegetation of wetland, savannah and caatinga, not yet documented) of 10,000 plants which have indication for medical use. Brazil fails to win U.S. $ 250 billion a year by not exploiting their biodiversity. Given these two realities, that most people consume herbal medicine, and that Brazil is rich in biodiversity with cataloged plants with potential use as drugs, a very positive picture is presented to the national laboratories, which are increasing their investments in phytomedicines (products developed from extracts of native plants and sold by prescription).

In this scenario, the National Policy on Medicinal Plants and Phytotherapics, approved by the Decree No. 5.813 of June 22th 2006, aims to ensure the Brazilian population safe access and rational use of medicinal plants and herbal medicines, promoting the sustainable use of biodiversity and the development of the productive chain and the national industry. Besides establishing guidelines and priority lines for development of technologies and innovations, as well as the strengthening of productive chains, and development of the Productive Complex of Health [17].

However, Brazil has extreme rigidity on the environmental and health legislation, requiring a high level of complexity in research to obtain registration of herbal medicines [18]. Besides it requires prior authorization of the study in the Council of Management of the Genetic Patrimony - CGEN [19] and in the Brazilian Institute of Environment and Renewable Natural Resources - IBAMA [20], for collect, bioprospecting or marketing. Thus, the bureaucracy is an obstacle in advancing the development of Herbal Medicines in Brazil and the inspectors often relegate the scientific knowledge acquired in previous studies, which in turn were carried out without prior authorization.

Given the importance on the implementation of the National Program of Phytotherapics in Brazil, established by the Ministry of Health and the study of technological prospection, it is urgent to establish guidelines to leverage this program in accordance with the reality of the Brazilian scientific production. It is crucial to establish a model of study, to be called competitive intelligence, to promote a technology management with a decision making power, subject to the Brazilian legislation with the guidelines recommended by the World Health Organization.

III. TECHNOLOGICAL FORECASTING

According to [21], Analysis of Future Technologies are systematic processes that analyze and produce judgments about characteristics of emerging technologies, development routes and potential impacts in the future. This concept incorporates a variety of methods of technological forecasting. The technological forecast, in turn, seeks to identify the major changes and / or technological guidelines, through pre-defined methods and approaches to map the opportunities and realize the risks involved in changing the paradigm in order to meet social and economic demands [22].

In this scenario, the Analysis of Future Technologies combines methods such as competitive intelligence. According to [23], it is a proactive and systematic process that seeks to discover the forces that govern the business, reduce risk and drive the decision maker to act in advance, and protect the generated knowledge. It consists on steps of collecting and searching data and the use of public and published information available on trends, events and actors outside the company boundaries, as the internal competitive environment of the company; filtered and integrated analysis and their dissemination [21].

From this perspective, the prospecting is a way to try to anticipate the advances and be able to influence the orientation of technological trajectories, ie, put yourself forward and ensure the competitiveness and survival of research and extension institutions and the users of its results [24]. Within the context of herbal medicines, this tool allows you to target your search according to what has already been produced, and establish partnerships or co-operations that leverage innovation as determined by the needs of public and private institutions and government agencies.

Based on this knowledge has been possible to establish a diagram (Fig. 1) in order to set an implementation model of the development of herbal medicines in Brazil. Thus, the first step in establishing the priority project - the plant under study - is to outline a strategic plan for the development of activities, based on studies of technological foresight of the investigated material. Then the formulation of a problem determines the direction of the research, defining methods to be implemented and combined with competent researchers in the areas of interest. At this stage, competitive and innovative projects can be established, with achievable action plans and monitored by goals, in that the generated knowledge will be protected. It is very important the constant communication between the involved agents, in order to disseminate information, exchange experiences and increase knowledge about the topics discussed.
Concurrent with the process, it should be prospecting companies active in developing the proposal, to be able to establish the technology transfer. At the end of the entire process it must be guaranteed that the Phytomedicine be available to the Ministry of Health.

Fig. 1 Implementation model for the development of herbal medicines (phytotherapics) in Brazil (adapted [25])

IV. FORECASTING STUDY ON PHYLANTHUS NIRURI

According to the model proposed earlier, before formulating the action plan for implementation of the herbal medicine, we suggest the prospection of the major institutions, researchers and areas of knowledge in a defined timeline to direct the strategic planning. The species chosen was Phyllanthus niruri L., popularly known as "stone break". It belongs to the Euphorbiaceae family, which comprises about 315 genera and 8,000 species [3], geographically distributed in Asia, Africa and the Americas [26].

This plant is traditionally used in folk medicine in India for treating diarrhea, fever, cramps, renal problems, and as a diuretic and expectorant [27]. In Brazil it is also used in folk medicine as a diuretic and solvent of kidney stones [28]. Its chemical constituents are well established, especially tannins, flavonoids and lignans [26].

The description of the pharmacological activities of this plant as inhibiting the formation of kidney stones [29], anti-inflammatory [30], antifungal, antiviral, antibacterial [31], antioxidant, hepatoprotective [32] hypoglycaemic, hypotensive and analgesic [33] and anti-cancer [34] revealed a variety of applications and possibilities of products in the pharmaceutical industry.

In accordance with Fig. 2, there was a considerable increase in the interest of studies on Phyllanthus niruri in recent years, shown by an increase in the number of scientific publications.

This interest can also be seen in patent deposition (Fig. 3). In the same figure it can be seen that since 1986 there are patent applications on the plant Phyllanthus niruri, in a way that every year a patent has been recorded. In both graphs, the year 2011 showed the highest number of records and papers, which may be related to investments in R & D in recent years, as well as partnerships between the Brazilian laboratories, universities and international research institutes.

India was the country that most carried out research on the species Phyllanthus niruri (Fig. 4), probably because it is a species traditionally used in their folk medicine.

Moreover, the research developed in India cover all areas listed (Fig. 5), showing their interest, especially in studies of hepatoprotective activities, antioxidant and anti-cancer. In second place was Brazil, with research on anti-cancer
activities, antioxidant, hepatoprotective, anti-viral and renal activities, with special interest for anti-tumor studies of the plant *Phyllanthus niruri*.

Fig. 5 List of bioactivities on *Phyllanthus niruri* publications and their respective countries (Vantage Point 7.1)

Fig. 6 shows a trend of interest in researches on the potential anti-cancer and antioxidant activities of *Phyllanthus niruri*, in recent years. More recently a new area of knowledge about the plant began to be exploited, its potential in the area of cosmetics, including an increase in the publication of articles and patent applications, where there are 16 patents in this bioactivity (data not shown).

Fig. 6 List of bioactivities on *Phyllanthus niruri* publications over the years (Vantage Point 7.1)

Finally, the diagram on Figure 7 shows the interaction between the Brazilian institutions. This data is very important to identify the universities involved in the study of *Phyllanthus niruri*, and their partnerships and cooperation in order to direct funding, define of methods and technology to implement the studies. In this figure, the thicker the line is the greater amount of work is shared between the universities. It also shows that the groups at the Federal University of Santa Maria, of Parana, of Sao Paulo, of Pernambuco and the Oswaldo Cruz Foundation work without partnerships, or at least, not yet published work with other institutions. Thus, we can identify the institutions and suggest interaction / communication between them.

Fig. 7 Diagram of brazilian institutions and their collaborations on *Phyllanthus niruri* publications (Vantage Point 7.1)

V. CONCLUSION

The prospective study of *Phyllanthus niruri* shows the importance of obtaining prior knowledge, both in relation to biological activities, and institutions that work with the plant. This type of analysis allows us to create perspectives of which areas of bioactivity may be of real interest for capital investment and help us to suggest which institutions can establish cooperation and partnerships. In order to change the Brazilian reality, in which basic research in the pharmaceutical sector are weak and causing low technological impact on generating innovations [2], the government and financial institutions are making credit lines for small businesses and research institutions, with the prospect of achieving success in the context of innovation in their projects approved.

In considering the *Phyllanthus niruri*, we can infer that many of the pharmacological activities are well established, since efficacy has been demonstrated experimentally in their renal activity, anticancer and antioxidant. However, studies in the pharmaceutical, technological, toxicological and clinical development need to be done. Based on technological forecasting and competitive intelligence the bottleneck of drug research, in certain way, can be strengthened.

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REFERENCES


