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Brazilian panorama about the registration and use of herbal medicines

[Panorama brasileño en cuanto al registro y el uso de las hierbas medicinales]

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Abstract: It was evaluated the Brazilian panorama regarding the registration and use of phytotherapics. A descriptive study about herbal medicines was carried out using the Pubmed and Portal Capes databases, and online data from the National Health Surveillance Agency (ANVISA). Of the 114-plant species described in the list of Brazilian Common Denomination (CBD), 67 have at least one formulation registered by ANVISA, with emphasis on Ginkgo biloba L. Fifteen different pharmaceutical forms were observed, the most common being tablets. There are 22 different indications, laxative was the most cited. Publications in the field of herbal medicine have increased significantly in the last 2 decades.

Keywords: phytotherapy, medicinal plants, drug registration, use of herbal medicines.

Resumen: Se evaluó el panorama brasileño sobre el registro y uso de fitoterápicos. Se realizó un estudio descriptivo de las hierbas medicinales utilizando las bases de datos Pubmed y Portal Capes, así como datos en línea de la Agencia Nacional de Vigilancia Sanitaria (ANVISA). De las 114 especies de plantas descritas en la lista de Denominación Común Brasileña (CBD), 67 tienen al menos una formulación registrada por ANVISA, con énfasis en Ginkgo biloba L. Se observaron 15 formas farmacéuticas diferentes, siendo las más comunes las tabletas. Hay 22 indicaciones diferentes, laxante fue el más citado. Las publicaciones en el campo de la medicina herbal han aumentado significativamente en las últimas 2 décadas.

Palabras clave: Fitoterapia, plantas medicinales, registro de medicamentos, uso de hierbas medicinales.

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INTRODUCTION

Along the humanity evolution the interest for the research of medicinal plants has increased, in this context, emerges the phytotherapy that can be defined as the study of plants and its application on the cure of diseases (VENTURA, 2012).

The Brazilian biome is a vast field, still little valued, for research in the area of natural products. Researches in this area related that several plants show important pharmacological activity such anti-inflammatory, antioxidant, antitumor, among others, which corroborates to the encouragement of use of phytotherapy and research in this area (VENTURA, 2012). To get an idea of plants potential on the development of new drugs, between 1983 and 1994 the FDA approved 520 new drugs, these, 196 were of natural origin (DAVID *et al.*, 2004).

According to Resolution No. 26 of May 13, 2014, which regulates the registration of herbal medicines and the registration and notification of traditional herbal products, the herbal product is that used for prophylactic, curative or palliative purposes obtained exclusively of vegetal raw material, not considering those with isolated active substances although they have vegetal origin. In this resolution, the National Agency of Sanitary Surveillance (ANVISA) defines two new terms used in phytotherapy, herbal medicine and traditional herbal product (BRASIL, 2014a).

Since the 1970s, the World Health Organization (WHO), with the creation of the Traditional Medicine Program (which includes phytotherapy, homeopathy, traditional Chinese medicine/acupuncture and anthroposophic medicine) has started to encourage the preservation of the culture of several populations, linking the popular knowledge to medicine, thus promoting other forms of care (WHO, 2002).

In Brazil, the ANVISA (National Health Surveillance Agency), according to Law 9782/1999, which defines the National Health Surveillance System and creates the National Sanitary Surveillance Agency, is responsible for regulating, recording and monitoring the marketing of these products at the national level (BRASIL, 1999). Currently many Laws govern the use of herbal medicines in Brazil. The RDC No 26 of 2014 is the current resolution and provides about the registration of herbal medicines and the registration and notification of traditional herbal products (BRASIL, 2014a). Other Laws, such as, Law No 5991 of 1973, provides about the Sanitary Control of the Trade of Drugs, Medicines, Pharmaceutical Supplies and Related, which legally bases the control of these medicines (BRASIL, 1973).

There are countries that accept herbal medicines with several compounds, provided they have a good clinical response. Signaling a change of attitude for the recognition of these drugs, provided that they have a good clinical observation. This chance is linked to the understanding that the human body is a complex organism and that few diseases can be attributed to a single cause. The Ministry of Health, when recommending and indicating 66 medicinal plants approved by ANVISA, whose use is consecrated in the culture of Brazilian popular medicine, had a correct and coherent attitude. The next step is to supervise the commercialization of these herbal medicines to preserve the health of the consumer.

Between 2011 and 2014, the phytotherapeutics segment grew by 20% in the number of units sold and 24% in sales, a result that is very positive considering the scenario of the global economy (IMS Health apud VALÉCIO, 2015).

In 2006, the herbal industry in Brazil accounted for 4% of the pharmaceutical industries present in the country (171 phytotherapeutic laboratories were responsible for marketing 727 registered products/medicines), of which 50% were in the Southeast region and 10% in the South region of the country. The North region that is known for its biodiversity in fauna and flora presented only 2% of these industries (HASENCLEVER et al., 2009). In addition, it is a very concentrated market, in 2007, only 20 laboratories were responsible for the sale of 84.70% of the total segment, accounting for 67.44% of total sales. The most representative laboratories in that year were Altana Pharma (German origin), Farmasa (national capital) and Marjan Farma (national) (FREITAS, 2007). It is observed, in this scenario, the need for the development of the phytotherapeutic drug industry, together with research in this area (YUNES et al., 2001). ABIFISA has its contribution in Brazil as an organ that is active in the defense of collective and individual interests in this segment.

Based on the importance and growth of this science worldwise and in Brazil, the aim of this article was to carry out a survey of the legislation that covers phytotherapics, the herbal medicines that are registered in our country, the evolution of the number

of published studies involving the theme and the billing of this sector.

METHODOLOGY

It is a descriptive study that evaluated the use and record of herbal medicines in Brazil. A research was carried out based on secondary data obtained from DATAVISA (ANVISA website – BRASIL, 2016a), taking into account the name of the plant species used, its pharmaceutical form and its therapeutic indication. The medicinal plants described in the list of Common Brazilian Denominations (DCB) present in RDC No. 64 of December 28, 2012 (BRASIL, 2013) and updated by RDC No. 38, of August 26, 2015, were searched (BRASIL, 2015a).

A survey was also carried out in Portal Capes using some descriptors as "phytotherapy", "herbal medicine", "phythoterapic", "legislation" to obtain information about the evolution in the use of herbal medicines by the population, the sector growth, the current legislations involving this theme, the use of these drugs in the single health system.

A survey was carried out in the Pubmed database with the only the descriptor "phytotherapy", and with the descriptors "phytotherapy" AND "Brazil", in order to verify the evolution of the number of publications in this area worldwide and local (Brazil), were considered the first articles published (1947 and 1969, respectively) to the most recent, published until January 2017. In addition, some of the best-selling herbal medicines in the year 2014 come from the international pharmaceutical marketing consultant IMS Health do Brasil.

Based on the survey conducted by DATAVISA and articles published from 1969 to January 2017, it was possible to evaluate the evolution of the topic in Brazil.

RESULTS AND DISCUSSION

Legislation

The Laws have always been important guides in the formation of the society. They help the organization by establishing order before a population. In Brazil, when it comes to health, we have a well-founded legislation and are guided mainly by ANVISA and the Ministry of Health (MS). In the case of herbal medicines can be cited as important laws that establish the control and registration of this type of product and which provide information about its potential use.

In the 1970s, laws such as Law No. 5991 of 1973, which established the Sanitary Control of the Trade in Drugs, Medicines, Pharmaceutical Supplies and Related Products were drawn up, and provided other provisions, which included important concepts in the scope of Phytotherapy (BRASIL, 1973).

The National Policy of Medicinal Plants and Phytotherapy (PNPMF) (BRASIL, 2006a) should be mentioned, and within Unified Health System (SUS) the National List of Essential Medicines (RENAME), the Document No. 31 of Primary Care and the National Policy on Integrative Practices (PNPIC) (BRASIL, 2012b), summarize in their texts the importance of valuing traditional knowledge, stimulating knowledge and research in the field of alternative medicine and rational use in the field of phytotherapy.

In this context, the RDC No. 26 of 2014 deserves to be highlighted, since it is the current resolution dealing with the registration of herbal medicines, registration and notification of traditional herbal products. In addition, it brings important definitions such as Phytotherapeutic and Traditional Phytotherapeutic Product, which changed after its publication several drug registration processes in our country and created a new class of products. According to this RDC, herbal medicine is that "obtained by the use of plant raw materials that have safety and efficacy based on clinical studies". Traditional herbal product is defined as being "obtained from plant raw materials, its safety and effectiveness being based on data of safe and effective use described in technical-scientific literature and can be used without supervision" (BRASIL, 2014a).

The publication of RDC 26/2014 had an impact on the industry because it changed the register of herbal medicines. In addition to including the term traditional herbal product, it establishes that for the registration of both classes (herbal medicines and traditional phytotherapeutic products) some adjustments are made, leading the industry to adapt to the new Resolution.

At the moment to register these products it is necessary that the applicant requires to the Brazilian Pharmacopoeia the inclusion of the constituents of the phytotherapic in the list of the DCB, if these are not already in the same one. The technical report, stability study report, production and quality control report, plant drug analysis report, the finished product analysis report, safety and efficacy/effectiveness reports are requested as mandatory documents.

It is clear from the mandatory records, legal basis and definitions present in these resolutions, that phytotherapy in Brazil is a subject that has been taking on importance in recent years. With well-established guidelines and laws related to the subject, which stimulate the research and development of this sector, besides stimulating the adoption of herbal medicine in the public health system. The chemistry of natural products is the oldest studied in Brazil, in addition, the country has a vast biome still to be researched, this scenario contributes to research in this sense and the Laws, guidelines and regulations are indispensable in this scenario.

Having strict legislation that guides the processes of development, production, quality control and inspection of these products is of extreme importance to ensure that the products that are on the market are effective and safe, and consequently, stimulate the prescription of them, with consequent increase in consumption and market growth.

Use of phytoterapics in the Brazilian Health System (SUS)

The insertion of herbal medicines into basic health care in the outcome of a struggle that precedes the creation of the Unified Health System (SUS), regulated by Law 8080 of 1990, several health professionals contributed fundamentally to the creation of policies that allowed the inclusion of this therapy in public health services in Brazil (BRASIL, 2006a).

In 2006, the publication of two policies was instrumental in guiding legislation, programs and projects that allowed the development of strategic lines that strengthened the use and access to medicinal plants and herbal medicines in primary health care. By means of Ordinance No. 971, of May 3, 2006, the National Policy for Integrative and Complementary Practices in the SUS (PNPIC) was created, which contemplates Phytotherapy as a therapeutic option. In the same year, the National Policy of Medicinal Plants and Phytotherapy (PNPMF) was established by decree No. 5.813, of June 22, 2006, with the objective of providing safe access and rational use of medicinal plants and phytotherapics In our country (BRASIL, 2006b, 2006c).

In this way, the Ministry of Health, in order to contribute with the expansion of alternative therapies, allows the inclusion of some phytotherapics from 2007 in the National Relation of Essential Medicines (RENAME), integrating the Basic Component of Pharmaceutical Assistance, which was being improved over the years (BRASIL, 2007).

In 2007, two phytotherapics were included in the basic component of Pharmaceutical Assistance: *Mikania glomerata* (Guaco) e o *Maytenus ilicifolia* (Espinheira Santa) (Brasil, 2007). In 2009, six herbal medicines were added to the National List of Medicines and Complementary Supplies for Pharmaceutical Care in Primary Care, totaling a list of eight herbal medicines due to the inclusion of *Cynara scolymus* (artichoke), *Schinus terebenthifolius* (aroeira), *Rhamnus purshiana* (cascara sagrada), *Harpagophytum procumbens* (devil's claw), *Glycine max* (soy isoflavone) and *Uncaria tomentosa* (cat's claw) (BRASIL, 2009). In 2012, four new drugs, *Aloe vera* (aloe vera), *Mentha piperita* L. (peppermint), *Plantago ovata* Forssk (plantago) and *Salix alba* L. (willow), were added in this list, totaling 12 herbal medicines listed in RENAME (BRASIL, 2012a).

Currently, there are 12 phytotherapics that make up the cast established in RENAME, and it did not present any changes since 2012 (Table 1) (BRASIL, 2015).

The availability of phytotherapics to SUS patients, regulated through public policies, allows these patients another treatment option, besides favoring popular participation, by rescuing the knowledge acquired by the population (Figueredo *et al.*, 2014).

However, some difficulties and challenges can be observed in the attempt to implant phytotherapeutic programs, such as doubts and knowledge about the efficacy and safety of treatment by health professionals, which favors the use of synthetic medicines, the need for adequate physical structure, and acceptance of the professionals involved (Araújo *et al.*, 2014; Figueredo *et al.*, 2014).

In the search for improvements, the Ministry of Health directed financial resources, around R$ 3.4 million, to be applied in projects approved by means of public notice. With the objective of supporting and strengthening the structuring of primary care through the availability of herbal medicines, the purchase of inputs, hiring and training of professionals, in addition to enabling the purchase of necessary equipment. The investments aim to strengthen projects, which make it possible to increase the supply of herbal medicines in the SUS. Some of the

selected projects were in cities of the states of Rio de Janeiro, Minas Gerais, São Paulo, Paraná and Rio Grande do Sul (BRASIL, 2016b). Thus, it can be noticed an expansion in investments in this sector by the Ministry of Health and in an attempt to expand the number of herbal medicines supplied to the Brazilian population by the single health system. However, there is a need to increase the list's list of RENAME, which since 2012 remains stagnant.

TABLE 1 – PHYTOTHERAPY PRESENT AT RENAME 2014

Generic designation	Brazilian Common Name (DCB)	Indication/Action	Pharmaceutical Form/ Description
Artichoke	*Cynara scolymus L.*	Treatment of symptoms of functional dyspepsia (postprandial discomfort syndrome) and mild to moderate hypercholesterolemia. It presents collagenous and choleretic action.	Capsule, tablet, dragee, oral solution and/or tincture
Aroeira	*Schinus terebinthifolius* Raddi	It presents healing, anti-inflammatory and topical antiseptic action for gynecological use	Gel and/or ovule
Aloe Vera	*Aloe vera* (L.) Burm. f.	Topical treatment of 1st and 2nd degree burns and as a coadjuvant in cases of psoriasis vulgaris	Cream
Cascara sagrada	*Rhamnus purshiana* DC.	Supporting in cases of eventual intestinal constipation	Capsule and/or tincture
Espinheira Santa	*Maytenus officinalis* Mabb.	Coadjuvant in the treatment of gastroduodenal gastritis, ulcer and symptoms of dyspepsia	Capsule, emulsion, oral solution and/or tincture
Devil's claw	*Harpagophytum procumbens*	Treatment of acute low back pain and as a coadjuvant in cases of osteoarthritis. It has anti-inflammatory action	Capsule or tablet
Guaco	*Mikania glomerata* Spreng.	It has expectorant and bronchodilator action	Capsule, oral solution, tincture and/or syrup
Peppermint	*Mentha x piperita* L.	Treatment of irritable bowel syndrome. Antiflatulent and antispasmodic action	Capsule
Soy isoflavone	*Glycine max* (L.) Merr.	Supporting the relief of climacteric symptoms	Capsule or tablet
Plantago	(*Plantago ovata* Forssk.)	Supporting in cases of habitual intestinal constipation. Treatment of Irritable Bowel Syndrome	Powder for oral dispersion
Willow	(*Salix alba* L.)	Treatment of acute low back pain. It has anti-inflammatory action	Tablet
Cat's claw	*Uncaria tomentosa* (Willd. ex Roem. & Schult.) DC.	Supporting in cases of arthritis and osteoarthritis. It has anti-inflammatory and immunomodulatory action	Capsule, tablet and/or gel

SOURCE: BRASIL (2015)

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Panorama of the registry of phytoterapics: datavisa data

The registration of herbal medicines acts as an instrument by which the Ministry of Health determines its registration with the competent body, so that criteria related to the efficacy, safety and quality of these products are met, so that they can be commercialized (BRASIL, 2014a).

With regard to registration of these products, according to RDC No. 26 of 2014, the herbal medicinal product may be of common or simplified registration. While the traditional herbal product can be a common, simplified or just notified, where prior communication is required to ANVISA "informing that it is intended to manufacture, import and/or commercialize traditional herbal products." Details regarding the registration of these products are presented in Table 2.

TABLE 2 - REGISTRATION OF PHYTOTHERAPY PRODUCTS

CATEGORY	SAFETY AND EFFECTIVENESS / EFFECTIVENESS	
Herbal medicine	Common Registry	Presentation of clinical and non-clinical data demonstrating safety and efficacy.
	Simplified Registry	a) Presence in the List of herbal medicines of simplified registration, according to Normative Instruction (IN) No. 2, of May 13, 2014; or b) Presence in well-established use monographs of phytomedicines of the European Community.
Traditional Herbal Product	Notified	For the products listed in the Pharmacotherapeutic Form of the Brazilian Pharmacopoeia and that have a specific monograph of quality control published in pharmacopoeia recognized by ANVISA.
	Registry	Proof of safe and effective use for a minimum period of 30 years; Or by simplified registration.
	Simplified Registry	a) Presence in the List of herbal medicines of simplified registration, according to Normative Instruction (IN) No. 2, of May 13, 2014; or b) Presence in well-established use monographs of phytomedicines of the European Community.

SOURCE: BRASIL (2014a)

The resolution also emphasizes the list of plants present in Normative Instruction (IN) No. 2 of 2014, which lists plants recognized as safe and effective as being of simplified registration. Being indicated 27 plants used in the manufacture of phytotherapic medicines and 16 plants for the production of traditional herbal products. In total, IN lists 43 plants that can be commonly used in the production of herbal medicines without the need for additional evidence of efficacy and safety (BRASIL, 2014b).

These standards are valid only for industrialized products, and no registration or notification is required for preparations developed by traditional communities that are non-profit making and non-industrialized (BRASIL, 2014a).

Such registration regulations allow Brazil to have a market with products developed through current standards, making it more attractive and promising nationally and internationally, while not

ignoring the traditional knowledge related to culture in using products of natural origin.

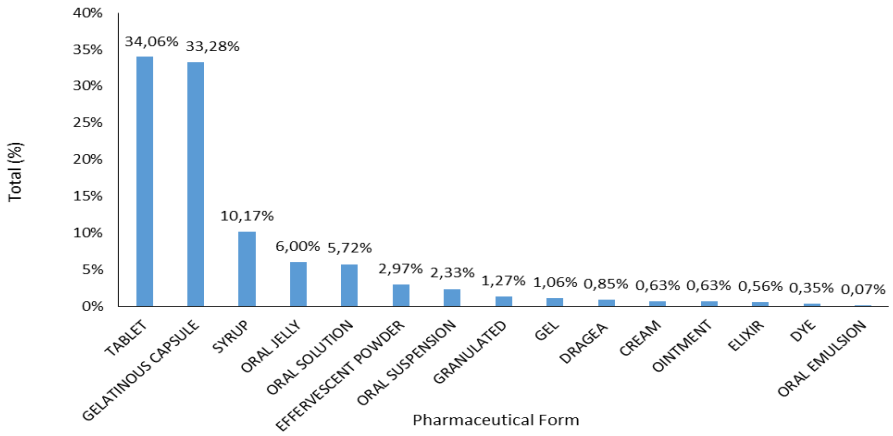
The list of medicinal plants described in the DCB has 114 plant species, of which 67 species have at least 1 active registration in DATAVISA (an online consultation tool provided by ANVISA in order to provide information on processes, products and companies subject to health regulation). Of the 47-remaining species, 25 of them do not present any results regarding the presence of registered formulations when they are researched and the remaining (22) have already been registered at some time, but currently there is no registered formulation for these medicinal plants.

According to Normative Ruling No. 2 of May 13, 2014, 25 of the species present in the list of DCB (21.93% of the total) are classified as herbal medicine of simplified registration and another 15 species of the same list are defined as Traditional Phytotherapic product of simplified registration (13.16% of the total), these do not need of additional safety and efficacy data (BRASIL, 2013).

Based on this survey conducted in DATAVISA in May 2016, taking into consideration which formulations have a registration still valid, that is, with a registration deadline equal to or greater than May 2016, a total of 1.415 formulations were obtained with active registration by ANVISA in Brazil, 81.48% of the formulations are classified as simple (obtained from a single plant species), the others, 18.52% are defined as composite formulations (they have on your composition more than one plant species).

Among the plant species with the highest number of phytotherapics registered are: ginkgo - *Ginkgo biloba* L. (10.53% of the total), the guaco - *Mikania glomerata* Spreng. (7.52% of the total), the valerian - *Valeriana officinalis* L (7.14%), the senna - *Senna alexandrina* Mill. (6.22% of the total), the Indian chestnut - *Aesculus hippocastanum* L. (5.35%), the artichoke - *Cynara scolymus* L. (5.65% of the total), the Santa - *Maytenus ilicifolia* Mart. ex Reiss (4.52%), the thistle-marian - *Silybum marianum* (L.) Gaertn. (3.67% of the total), ivy - *Hedera helix* L. (3.39%) and plantago - *Plantago psyllium* L. (3.25%). Some of them, such as the ivy (*Hedera helix* L.), the senna (*Senna alexandrina* Mill.) and the ginko (*Ginkgo biloba* L.) are also among the best-selling medicines in the country in 2014 (TABLE 3).

As for the pharmaceutical form, there were 15 varieties (Graphic 1), and the three most common pharmaceutical forms were the presentations of tablet (34.09%), gelatinous capsule (33.30%) and syrup (10.17%), these representing more than half of the registered formulations (77.49%). The remainder (22.51%) corresponds to the pharmaceutical forms of oral jelly, oral solution, effervescent powder, oral suspension, granules, gel, dragea, cream, ointment, elixir, tincture and oral emulsion. More than half (72.48%) of the analyzed pharmaceutical forms are solid, 19.20% are liquid and 8.32% are semi-solid. The pharmaceutical presentation is intimately linked with the time and manner in which the product will be absorbed by the organism, and the correct choice depends on the study of each plant raw material, its chemical composition and the intended effect.



Graphic 1
Pharmaceutical form of the phytoherapics registred in the anvisa

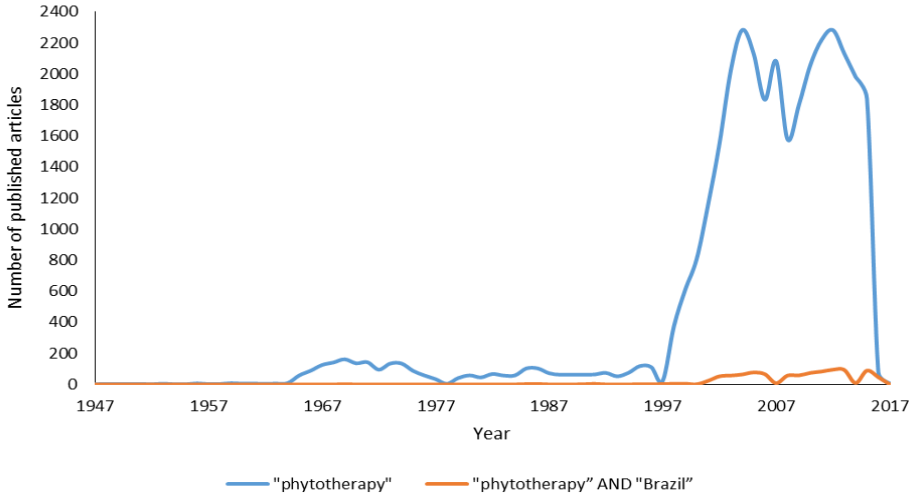
Regarding the use for which they were defined during ANVISA registration, 22 different indications of use were observed (Table 3). The most common being: laxative (13.64% of the total), anxiolytic, anti-inflammatory, antivaricose and psychoanaleptic (all representing 7.57% of the total), and, expectorant, cholagogue and choleretic (both accounting for 6.06% of the total), these classifications represent 56.04% of the indications described. It can also be observed that among the most commercialized herbal medicines (Table 4), there are medicines indicated as laxative, anxiolytic, expectorant and cholagogue.

Table 3
Pharmaceutical indications suggested during the registration of phytotherapic in ANVISA

PHARMACEUTICAL INDICATION	TOTAL (%)
Laxative	13.64%
Antivirose	7.57%
Psychoanalytical	7.57%
Antinflammatory	7.57%
Anxiolytic	7.57%
Cholagogue and choleretic	6.06%
Expectorant	6.06%
Aide in the treatment of the climacteric	4.54%
Healing	4.54%
Analgesic	3.03%
Digestive tract	3.03%
Hepatoprotective	3.03%
Antispasmodic	3.03%
Antiinfection / immunomodulatory	1.51%
Cerebral vasodilator	1.51%
Urinary tract infection	1.51%
Simple androgen	1.51%
Gynecology and obstetrics	1.51%
Antiemetic and antinauseant	1.51%
Immunostimulant	1.51%
Diuretic	1.51%
Iodine therapy	1.51%
Antidepressant	1.51%
Antacids and simple anti-ulcer	1.51%
Antilipemic	1.51%
Anti-phlogistic and anti-pruritic	1.51%
Cardiovascular apparatus	1.51%
Stimulating appetite	1.51%

Publications about the phytotherapy theme

When searching the publications about phytotherapy in the Pubmed database, 34538 articles were initially found when using only the descriptor "phytotherapy". Among the main subjects related to these descriptors are the adverse effects associated with it, its history, its efficacy, use, research, phytotoxicity, among others. When the descriptor "Brazil" was included in this research ("phytotherapy AND" Brazil), 1139 articles were found, a small part of this total (3.29% of the articles obtained in the first moment) but that has been growing over the years, as observed in Graphic 2. Among the main themes of these publications can be mentioned the in vitro and in vivo biological activities of plants, ethnobotanical studies and chemical composition of plant extracts.



Graphic 2
Number of publications in function of the year

When comparing the publications using the 2 descriptors as a function of time, it is observed that the first published article that contains the descriptor "phytotherapy" was published in the year 1947 (1 article) (according to Graphic 2) referring to the use of medicinal herbs Asteraceae family in the treatment of epilepsy, published in the "Australasian Journal of Pharmacy". In the 1940s there was an increase in the number of studies involving epilepsy, and in the year 1947 another 306 studies on this topic were published. The article refers to the traditional use of plants of this family in the treatment of this pathology.

Some historical events have aided in the growth of studies and researches in the segment of medicinal plants, accompanying the increase of publications at world and national level.

Publications began to increase in the 1970s, from 1966 to 1976, 1,306 articles were published (3.78% of the total published), many of them are clinical studies involving herbal medicines, their application in the treatment of specific diseases. One of the milestones of this period was the creation of the Traditional Medicine Program by the WHO, as an alternative practice of health care. Some years later, in 1978, Alma Ata was declared a landmark for phytotherapy in a period when the world began to worry about the use of alternative practices for treatment and maintenance of health (WHO, 1978).

However, in the 1980s, the discovery of new drugs based on their mechanism of action and molecular modeling (through the use of softwares), made the substances of synthetic origin more exploited, and that studies with medicinal plants in the background (Argenta *et al.*, 2011).

There is a considerable increase in publications on phytotherapy in the world in 1995 (121 articles), in addition to studies related to the efficacy of these products, studies have been published regarding their safety. In addition to the development and growth of the pharmaceutical industry in the 1990s, in the period from 2002 to 2005 the WHO again stimulated the use of traditional medicine and complementary medicine (Argenta *et*

al., 2011). In the period between 1981 and 2006, 50% of the drugs approved by the FDA were directly or indirectly derived from natural products (Ferreira & Pinto, 2010). An expansion is observed in subsequent years, with a greater number of publications in 2012, 2318 articles were published (6.61% of the total), that is, almost double the number of articles published in 10 years between 1966 and 1976 (Anti-oxidant, antimicrobial, anti-fungal, anti-tumor) in vitro and in vivo, identification of chemical substances from plants, evaluation of its clinical efficacy. The last 20 years were responsible for 89.32% of the articles published so far in this area. One of the justifications for this fact is due to changes in medicine in the 21st century, which incorporates the principle of sustainable development, being associated with the concepts of preservation, care and traceability, making the idea of medicine associated with products of natural origin Resurgence and consequently there is an increase in the prescription of herbal products (Regis, 2014).

As for the Brazilian scenario, the first article found dates from 1969 (1 article), a year in which there is an increase in world publications. This publication depicts the use of hallucinogenic substances of natural origin, citing the use of some of these plants by Brazilian indigenous tribes. In this period in Brazil, public investments in medicinal plants began, which occurred through the Medicines Center (CEME), instituted by Decree No. 68806/1971. From the CEME the creation of some programs was important, such as the Program of Research of Medicinal Plants, whose objective was to develop research on plants present in Brazil (Brasil, 1971; Oliveira, 1997). Prior to the establishment of the CEME in the late 1970s, WHO created programs to stimulate and encourage the rational use of traditional and complementary medicine, and to publish documents such as the WHO Strategy on Traditional Medicine 2002-2005, reaffirming the interest in the development of these practices that include phytotherapy.

The publications became more expressive from the year 2001, with 23 publications (2.02% of the total), which mainly discuss the in vivo and in vitro use of medicinal plant species. In the same direction as the increase in national publications, in Brazil some National Health Conferences such as the 12th, which occurred in 2003, enable and stimulate the production of medicines obtained from the national flora in order to expand the scenario of phytotherapy in Brazil.

The expansion of studies on herbal medicines that we can observe from 2007 onwards is in line with its recognition in SUS in 2006, a period in which policies and guidelines are published that reinforce the great importance of medicinal plants by stimulating the use of natural resources.

Over the years, it has been noticed that the advances obtained in the field of herbal medicines in our country are closely related to the achievements obtained for these products in the public system, the SUS, since from the 80's and after the creation of the SUS through Of the Federal Constitution, it is clear the institutionalization of phytotherapics as well as the autonomy of research developed in the area.

Similar to that observed in world publications, publications involving phytotherapy in Brazil reached their peak in 2012, with 95 published articles (8.34% of the total, close to the number observed in the world scenario). In the last 2 decades, 84.64% of the articles on phytotherapy have been published in Brazil, showing the same tendency observed for the world scenario in relation to the growth in the number of studies involving phytotherapy.

These studies point to the expansion and interest in scientific research and in studies on medicinal plants in Brazil and in the world, mainly regarding the biological activities of several plant species. This shows a growth in research groups in this area, and an increasing interest in discovering the properties of medicinal plants and exploiting them, in order to make possible its application in an efficient and safe way, which makes it extremely important to Conducting clinical trials with these plants. Thus, phytotherapy and the study of medicinal plants are considered a promising field in scientific research.

Analysis of the growth of the phytotherapic market in Brazil

The Brazilian market currently markets several herbal medicines, which in turn gain the preference of patients and the population for being an alternative to the use of allopathic drugs, less aggressive and with fewer adverse effects than synthetics, in order to contribute to growth in Sales of these products (David *et al.*, 2004).

The great biodiversity present in our country, which corresponds to around 15 to 20% of the world total, with approximately 60000 listed higher vegetal species, and the popular knowledge about the vegetal

species, that contributes to the expansion of this Sector, which even in times of economic instability in the country, present good growth prospects (Brasil, 2006).

According to the International Federation of the Pharmaceutical Industry (Valécio, 2015), the Brazilian pharmaceutical industry has increased its sales of medicines over the past years, six times higher than the performance of developed markets.

Herbal medicines contribute significantly to the drug market. The growth of this sector is around 10% per year, and in 2001, it is estimated to have reached US $ 550 million (Knapp, 2001; Brazil, 2006). The industry moves worldwide $ 21.7 billion per year. Carvalho *et al*. (2008) presented an estimate of Brazil's participation in the phytotherapic sector, which would reach US$ 160 million per year, moving annually around R$ 1 billion in its production chain.

It is estimated that 10% of Brazilians consume some type of herbal medicine. In the year 2013, the main public responsible for consuming these products was composed of women over the age of 35 and working outside (Instituto Simone Terra apud Valécio, 2015). The category of herbal medicines available for sale in pharmacies in Brazil is wide. From a survey of the 10 most herbal medicines sold in Brazil in 2014 according to IMS Health (Table 4), some of these are also among the herbal products with the highest number of records according to data from DATAVISA, as is the case of ivy (*Hedera helix* L), senna (*Senna alexandrina* Mill.), and ginkgo (*Ginkgo biloba* L.).

In a complementary way, it can be observed that other phytotherapics listed as the most sold (Table 4) have a therapeutic classification that is similar to the most frequent indications suggested during the registration of herbal medicines in ANVISA (Table 3), among them, laxative, anxiolytic, expectorant and cholagogue.

Table 4
Top 10 best-selling phytotherapics in 2014

Phytotherapic/Laboratory	Indication	Plant specie- (DCB)
1 – Seakalm (Natulab)	Anxiolytic	*Passiflora incarnata*
2 – Abrilar (FQM)	Expectorant	*Hedera helix L.*
3 – Tamarine (Farmasa)	Laxative	*Senna alexandrina Mill.* *Cassia fistula* *Coriandrum sativum*
4 – Gerovital (EMS)	Multivitamin	*Panax ginseng C. A. Mey.*
5 – Calman (Ativus)	Anxiolytic	*Passiflora incarnata* *Salix alba* *Crataegus oxyacantha*
6 – Eparema (Takeda)	Cholagogue	*Peumus boldus Molina* *Frangula purshiana (DC.) A. Gray* *Rheum palmatum L.*
7 – Pasalix (Marjan Farma)	Anxiolytic	*Passiflora incarnata* *Salix alba* *Crataegus oxyacantha*
8 - Natus Gerin (Legrand)	Multivitamin	*Panax ginseng C. A. Mey.*
9 – Maracugina (Hypermarcas)	Anxiolytic	*Passiflora alata* *Erythrina mulungu* *Crataegus oxyacantha*
10 – Ginkomed (Cimed)	Cerebral vasodilator	*Ginkgo biloba L.*

SOURCE: Adapted from IMS Health (2014)

The Brazilian scenario shows great growth potential in the herbal medicines market, and in 2014, approximately 56 million units were sold, totaling R$ 1.1 billion, with growth of 6.1% sales in relation to the year 2013 (ANVISA, 2015).

The herbal medicines market is growing at a slower pace than the pharmaceutical market in general, due to the increased investment in the development and launch of synthetic drugs. However, this market has expanded and gained interest in investment by several companies (Valécio, 2015).

In view of the potential for growth, investments have been made in the development of herbal medicines. It also receives support from the Ministry of Health, which through public policies has improved and strengthened the use, research, and development of herbal medicines.

Since much of the investment is made in the launching of products with synthetic origin, it is natural to have a slower growth in the herbal medicines market, compared to the pharmaceutical industry in general (Valécio, 2015).

There is an increasing increase when one observes the billing in the category of phytotherapics marketed in Brazilian pharmacies. The increase in the financial sector similarly accompanies the increase in the number of publications on herbal products depending on the year. The industry's interest is linked to this growth, since, through research, new assets are sought for innovative purposes. As a result, we obtain a great variety of products that move the Brazilian market.

Together, there is an increase in the popular interest in using less aggressive and legally recognized alternative therapies, being easily accessible to patients who attend the SUS, also contributes significantly to a greater consumption of these products both by the public network and by particular prescriptions.

This reflects the triad alignment presented in this article, the records increasing as a result of the increase of researches and articles published in the area, linked to the financial interest of large industries in promoting the commercialization of these products in order to meet the needs of the population.

The Brazilian industry believes in the growth potential of this segment and seeks to develop and launch new products, based on the vast biodiversity of our country, and the significant number of scientific publications on medicinal plants and herbal medicines, which has grown considerably over the years (Carvalho *et al.*, 2011). Some reasons contribute to the development of the market, and the population's interest in herbal medicines, which are the patients' preference for natural therapies, the belief that natural medicines have fewer side effects, a tendency towards self-medication as a preventive treatment, and the lowest cost to consumers (Calixto, 2001).

Final considerations

The use of medicinal plants is a field that is expanding in the world and in Brazil, a fact that can be attributed to the presence of a vast biome with great potential to be explored in a conscious way, to the growing use of phytotherapics by the population and to the development of research in this area. It is observed that many public policies and laws currently support and promote the rational use of these.

In Brazil over the last two decades there has been an increase in research and publications in this field. On the rise is also the pharmaceutical industry in this segment that already makes more than 1 billion reais in our country.

In this way, the search for less aggressive therapies, contribute to the expansion of the number of consumers in this segment, which provides a good growth and commercial development of herbal medicines.

Where the pharmaceutical industries that market herbal products go to a scenario where they develop strategies in order to invest in this line of innovative and sustainable products.

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