

## A WORLDWIDE COMPARATIVE-DIAGNOSTIC STUDY OF MEDICINAL NATURAL PRODUCTS REGULATORY STATUS

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### ABSTRACT

Herbal products encompass a variety of preparations of plant origin that are the oldest form that humanity has been using to treat diseases, a practice that has grown enormously in the last decade. The aim of this study is to determine the natural medicinal products regulatory status of the main health authorities worldwide, to be used as a basis for improvement and optimization of legislation. Materials and Methods: A comparative study assessment of the natural medicinal products regulatory status in major health authorities in 2015, searching database of various government health agencies around the world, using keywords to find case law, regulations and laws on the subject and by information triangulation technique it was established the current regulatory situation. Results: It is well known that herbal

products are not completely free of side effects, so is surprising that very few countries have a national policy to regulate and promote the safety and quality of medicinal plant materials. Depending on the country concerned, a herbal product could be defined as food, dietary supplement or herbal medicine. This disparity in the regulations that apply in different countries, influences access to products and international distribution plus it is not guaranteed that natural medicinal products meet the requirements of safety, efficacy and quality.

**KEYWORDS:** regulatory, natural medicinal products, dietary supplement.

### INTRODUCTION

The use of herbs for medicinal purposes is an ancient custom and, either by an idealization of nature or the poverty, using plants to cure various diseases is a practice that has been increasing in recent years. The number of higher plants cataloged on earth is about 250,000

and it is estimated that between 35 000 and 70 000 species have been used by some cultures for medicinal purposes.<sup>[1, 2]</sup>

In developed countries, the widespread use of herbal medicine was reduced at the end of the twentieth century due to the development and production of synthetic drugs. However, in recent decades, herbal medicine has begun to be increasingly used, even in industrialized countries.<sup>[3]</sup>

The World Health Organization (WHO) defines as finished medicinal herbal medicines and labeled products whose active ingredients are aerial or underground parts of plants or other plant materials or combinations thereof, unwrought or as plant preparations. Plant material includes juices, gums, fatty oils, essential oils or any other substances of this nature<sup>[3]</sup> understood.

It is estimated that about 25% of prescribed drugs worldwide are derived from plants and are in use 121 active compounds from them. Of the total of 252 drugs on the essential drug list of the WHO, 11% is exclusively of vegetable origin. Almost 80% of the population of Africa and Asia depends on traditional medicine for primary health care.<sup>[4]</sup>

According to WHO, the percentage of the population that has used such drugs at least once is 48% in Australia, 31% in Belgium, 70% in Canada, 42% in the US and 49 % in France. Also in Japan 85% of doctors prescribe medicine not only modern but also traditional medicinal herbs which are covered by health insurance. In China, traditional medicine accounts for about 40% of all health care provided. While in Africa, more than 80% of the population depends on herbal medicines. In Latin America traditional medicine has been used by 71% of the Chilean population and 40% of the Colombian population.<sup>[5]</sup>

The herbal products are not completely free of side effects. Clinical studies have shown that the occurrence of undesirable side effects is possible with the use of herbal medicines; these effects could be due to the inadvertent use of the wrong plant species, adulteration with other medicines, contamination with toxic substances undeclared overdose, misuse by consumers and concomitant use with other drugs, causing adverse drug interactions.<sup>[4]</sup>

It is well known that there are many contaminants and residues in medicinal plants that can cause harm to consumers, such as radionuclides, toxic metals or microorganisms. Some arise

from past or present use of agents or materials that pollute the environment and then to plants, such as emissions from factories or residues of certain pesticides.<sup>[6]</sup>

Despite its existence and continued use for many centuries, and its popularity and extensive use of the last decade, traditional medicine has not been officially recognized in most countries. Consequently, education, training and research in this area has not been accorded due attention and support.<sup>[5]</sup>

The practice of traditional medicine vary widely from country to country and from region to region, as they are influenced by factors such as culture, history, personal attitudes and philosophy.<sup>[5]</sup>

### **Policies to regulate herbal medicines must have 3 main objectives<sup>[7]</sup>**

1. minimize the damage caused by dangerous products,
2. increasing medical and economic benefits of using herbs, and
3. to rationalize the use of herbs based on scientific evidence.

### **MATERIALS AND METHODS**

This paper is a worldwide comparative-diagnostic study on the natural medicinal products regulatory status in 2015, for this a search was conducted in the databases of various government health agencies around the world, using key to finding the law, regulations and laws in the field, using the technique of triangulation of information to establish the current regulatory situation words.

As a reference for the major health authorities to investigate the information in "National Policy on Traditional Medicine and Regulation of Herbal Medicines - Report of a WHO Global Survey"<sup>[8]</sup> was used in 2005, which states where there is a regulatory status of natural medicinal products, secondly it was determined which is the most recognized at regional level, with respect to the population under their jurisdiction, and health levels measured from its infant mortality rate and life expectancy health Authority, with priority given to submit lower infant mortality and increased life expectancy, finally the information collected was classified by region and triangle to conclude an overall regulatory status.

### **RESULTS AND DISCUSSION**

Legislative controls regarding medicinal plants have not evolved around a structured model control. There are different ways that countries define plants or herbs or products derived

from the same drugs, and some countries have adopted different approaches to licensing, distribution, manufacturing and marketing to ensure their safety, quality and efficacy ; in fact according to the survey "National Policy on Traditional Medicine and Regulation of Herbal Medicines - Report of a WHO Global Survey" of 2005, only 92 countries have a national policy in this area, representing 65% of the member states. Depending on the country concerned, an herbal product could be defined as food, dietary supplement or herbal medicine. This disparity in the regulations that apply in different countries affects access to products and international distribution.<sup>[8, 9]</sup>

### **A summary of the regulatory situation in some regions is as follows**

World Health Organization (WHO)

The World Health Organization is the governing body of world health policies, therefore, the definitions of this entity as a reference point used to establish the comparative analysis of regulatory status in other regions of the planet.

It is defined as traditional medicine, "the entire set of knowledge, skills and based on theories, beliefs and experiences indigenous to different cultures practices, whether explicable or not, used for health maintenance and prevention, diagnosis, improvement or treatment of physical or mental illness"

The definition of herbal medicine "includes herbs, herbal materials, herbal preparations and finished herbal products, that contain as active ingredients parts of plants, or other plant materials, or combinations of these elements."

Herbs: include gross, such as leaves, flowers, fruits, seeds, stems, wood, bark, roots, rhizomes and other plant parts, whole, fragmented or powdered plant materials.

Other important definitions established by WHO document drawn General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine.<sup>[10]</sup>

"Herbal Materials: includes, in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries these products can be processed by various local procedures, such as steaming, roasting or stir-baking with honey, alcoholic beverages or other materials."

"Herbal Preparations are the basis for finished herbal products and may consist of crushed or ground herbal materials, or extracts, tinctures and fatty oils of herbal materials. They

produced by extraction, fractionation, purification, concentration and other biological or physical processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages or honey or other materials."

"Finished herbal products: consist of herbal preparations made from one or more herbs. If you use more than one herb, you can also use the term "blend of herbal products. "Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, not considered to be herbal finished or in admixture products that have been added chemically defined active substances, including synthetic compounds or isolated constituents of herbal materials."

The description of the regulatory status of natural medicinal products in different regions of the planet now be used.

**Asia:** In most Asian countries traditional medicine is used regularly by a high percentage of the population and are often used in combination with western medicine; health authorities in different countries have made efforts to establish laws and regulations to ensure the quality, safety and efficacy of these medicines, and also define the professional profile and technical expertise for trade and dispensing of pharmaceuticals. In Japan, a country where the per capita consumption in natural products is the highest in the world, this class of drugs are regulated in the same way as western medicines and must present data from clinical trials of three phases. Moreover, in the Republic of Korea only standardized medicinal plants can be distributed legally. In Hong Kong, herbal remedies are subject to import and export controls, quality and advertising; for which it specified that traditional Chinese medicine cannot be advertised for certain diseases that require proper diagnosis, such as cardiovascular disease.<sup>[11]</sup>

In 1993 the Japanese Standards for Herbal Medicines, which contains 248 articles were published: 165 Japanese Pharmacopoeia (XII) and 83 of the Japanese Codex; herbal medicine and materials or herbal ingredients listed in the Standards should be used to make or imported herbal medicines.

The Pharmaceutical Education Center of Japan issues a certificate for pharmacists specializing in Kampo medicines and herbal materials according to their own qualification criteria. This certification must be renewed every three years.

Moreover, the Chinese government has strengthened its commitment to the integration of traditional and allopathic medicine on several occasions. Article 21 of the Constitution of the People's Republic of China, adopted in 1982, promotes traditional Chinese medicine and allopathic. The Office of Traditional Medicine was established as part of the Central Health Administration in 1984. In 1986, the State Administration of Traditional Chinese Medicine was established.<sup>[12]</sup>

### **Oceania**

In 1974, the Australian Parliament created the Research Committee of chiropractic, osteopathy, homeopathy and naturopathy. The Committee published an extensive report in 1977.

In 2000, the Therapeutic Goods Administration established the Guidelines on levels and types of data required to support statements about therapeutic products. The Evaluation Committee of Complementary Medicines recognizes two types of evidence to support claims on therapeutic products: scientific evidence and traditional use. The extent of evidence needed depends on the claims made by the product. For the Committee, the traditional use refers to evidence in writing or orally recorded for a substance that has been used for three or more generations for health-related purposes. The regulations include provisions for the use of drugs that combine a number of traditions, and the use of treatments are recent modifications of traditional therapies. Traditional therapies include traditional Chinese medicine, traditional ayurvedic medicine, traditional European herbal medicine, traditional homeopathic medicine, aromatherapy, and other traditional medicines.<sup>[12]</sup>

### **Africa**

Considering the high value of medicinal plants for primary health care, African countries began in 1985, the development of a legal framework for the practice of traditional medicine and adopting control measures for the plant material, developing campaigns public information and providing professional education to ensure proper and safe use of these products. At present, work on the establishment of collaborative centers of excellence / WHO for research and development of traditional medicines used in the treatment of priority diseases and the promotion of preclinical research and clinical evaluation, development, production Local and marketing of traditional medicines standardized.<sup>[13]</sup>

In South Africa the National Department of Agriculture regulates traditional drugs through the National Commission on Plant Genetic Resources, which is a member of a traditional healer. The National Department of Health produced the National Drug Policy. For the purposes of the implementation of the National Drug Policy regarding traditional medicines, the National Department of Health created the National Reference Center for traditional medicines. Traditional medicines are included in the section Drug Policy Programme for Reconstruction and Development of the Government.

In 1998, Parliament passed Law 132, the Regulatory Authority of drugs and medical devices, including registration and regulation of traditional medicines. provisions to be applied when registering allopathic medicines either, traditional and complementary / alternative sets. This is done by setting up committees of independent experts for the two main types of medicine. In the case of traditional medicines, issues of safety and quality take precedence over claims of effectiveness. The aim is to regulate and do not prevent access.<sup>[12]</sup>

### **Europe**

In 1989 the European Scientific Cooperative on Phytotherapy (ESCOP for short) was established with the purpose of establishing the criteria for the evaluation of herbal medicines, support scientific research and contribute to the acceptance of herbal medicine in Europe. Europe also has, with a system of mutual recognition of decisions marketing authorization to allow free movement of medicines in the market of the European Union.<sup>[14]</sup>

In order to protect public health while ensuring the free movement of medicinal herbal within the European Union, the way drugs herbal are registered and marketed has been in change since 2004 and to date.

Is intended for evaluation of applications for marketing all Member States can refer to a single set of information on a plant substance or the herbal preparation that includes the therapeutic uses and safe conditions of use recommended. a subcategory of drugs also introduces herbal for which must be demonstrated safety and efficacy.<sup>[15]</sup>

### **In the European Union the herbal medicines can register in three ways**

As a result of traditional medicinal use accepted on the basis of data on safety and efficacy sufficient, it is granted a traditional use (simplified registration procedure) by a Member State.

As a result of well-established medicinal use, it is demonstrated by scientific literature that the active ingredients have been well known medicinal use within the Union for at least ten years, with recognized efficacy and an acceptable level of safety. As a result the product is granted a marketing authorization usually by a Member State or the European Medicines Agency.

A product can be authorized after evaluation of an application for marketing authorization consisting of only studies of safety and effectiveness conducted by the company ("stand alone") or a combination of own studies and bibliographic data ('mixed') application. As a result the product is granted a marketing authorization by a Member State or the Agency through the centralized procedure if all requirements are met.<sup>[16]</sup>

Regardless of the regulatory pathway to market access, the quality of herbal medicine should always be shown.<sup>[17]</sup>

In some countries like France, Belgium, Spain, Switzerland, medicinal plants are classified in lists and registration requirements vary according to the list in which the plant is located, also changes the mode and site of authorized sales: prescription medical, without prescription, sale only in pharmacies or other point of sale.<sup>[11]</sup>

In Belgium for example, combinations of more than three floors of a single list or if the plants belong to different lists are accepted. They also have available a list of indications for traditional uses of different plant groups.

Moreover, in Germany, Austria, Bulgaria, Ireland; products containing ingredients herbal medicines are considered when labeling or accompanying documents indicate prevention, cure or remedy, or when any of the ingredients is recognized as having medicinal properties. For the record must be submitted documentation with pharmaceutical and chemical characteristics, application, usual dose, mechanism of action, side effects and interactions with other medications. The quality control is performed according to the European Pharmacopoeia.<sup>[13]</sup>

It is possible to market natural products that do not have sufficient scientific evidence of efficacy under the name "traditional use" quality records "traditional" products are not checked by the health authority and the person who sells is not allowed to give recommendations on the use of the products.



## America

In 1994, the Congress of the United States of America, approved the law Dietary Supplement Health and Education Act (DSHEA), to regulate botanicals. DSHEA classifies herbs, vitamins, minerals and amino acids as nutritional or food supplements and allows these products to be marketed without evidence of efficacy, safety or quality, provided they are not recommended to diagnose, treat, cure or prevent any disease. As a result, consumers have no guarantee of the quality of the product they are consuming. Moreover, in contrast to prescription drugs, the Federal Food and Drug Administration must first demonstrate that a herbal preparation is not safe before it can be withdrawn from the market.<sup>[18, 19]</sup>

Due to the problems presented with plants such as St. John's wort; *Hypericum perforatum*, echinacea and ephedra genus, in 2006 the Law dietary supplement and Consumer Protection drug without a prescription, which requires manufacturers, packers or distributors of supplements reporting of approved serious adverse events FDA. Serious adverse events are defined as death, a life-threatening event, hospitalization, persistent or significant disability or incapacity, congenital anomaly or birth defect or an adverse event requiring medical or surgical intervention. These reports are used to identify adverse trends and help alert the public about the security problems.<sup>[20]</sup>

Unlike the United States, Canada, natural medicinal products are regulated as drugs and there is a lot of natural products with therapeutic indications that are legally marketed.<sup>[19]</sup>

Moreover, the law in Argentina does not differentiate between natural medication and chemical and drug since 1993, the obligation to register drugs of natural origin was established.<sup>[21]</sup>

The herbalists are authorized to sell the plant drug mixtures but also must have a pharmacist as technical director. It is important to mention that people who plant and harvest medicinal plants must be authorized by the Ministry of Health.<sup>[22]</sup>

Always in South America, in August 1992, it was created in Chile, the Traditional Medicine Unit to integrate traditional medicine with proven efficacy in health programs, and help establish their practice. Natural products are classified.<sup>[23]</sup>

- Medicines to cure, relieve or prevent diseases
- Food products with medicinal and therapeutic properties
- Food products with nutritional purposes

According to the regulation, control of medicines, food and cosmetics products for medical use, herbal products with therapeutic indications or dosage recommendation are considered drugs. Its distribution is restricted to pharmacies and drugstores.

In Colombia since 1995 the Government issued a decree establishing the procedure for registration of natural products with therapeutic indications and the required technical documentation on manufacturing processes, quality control, and if toxicity studies is required and monographs material, including its traditional use, application method, dosage, contraindications, adverse reactions and literature. With special authorization selling individually packaged plant material is allowed and not mixed, as long as you can not declare a therapeutic activity.<sup>[24]</sup>

In Cuba natural products are part of the national health system are prescribed and dispensed in community pharmacies and hospital, and there is an herbal form of apitherapy, there numerous national and regional natural products industry and quality standards.

In 1992, the Ministry of Health officially recognized homeopathic products. A good standard manufacturing practice for the manufacture of homeopathic remedies has been accepted. In 1995, the Traditional Medicine Program was instituted, giving priority to the cultivation of medicinal plants, professional education, research of traditional medicine, and the integration of traditional medicine into the national health system.<sup>[25]</sup>

There is a program of regional companies that distribute natural medicinal products standardized according to the national form.

In Central America, the Technical Committee of Standardization and Technical Regulations through entities Standardization and Technical Regulations of the countries of the region, made up of representatives of the academic, consumer, private enterprise and government; are the bodies responsible for carrying out the study or adoption of Technical Regulations and as for natural medicinal products, in 2013 went into effect three Technical Regulations

RTCA 11.03.64: 11 Requirements for Health Registry "

RTCA 03.11.56: 09 Quality Verification

RTCA 11.04.41: 06 Labeling Requirements.

These regulations apply to natural medicinal products for human use marketed in the State party in Central America and in them the conditions and requirements under which sanitary

registration will be granted the analytical tests are established, and; physicochemical and microbiological tests, to be carried out to verify the quality of natural medicinal products for human use by the health authority in each country. The technical evaluation also revising the labeling included.<sup>[26]</sup>

For purposes of these regulations is meant as a medicinal natural product that processing, industrial and product labeling with medicinal properties, which contains in its formulation ingredients derived from plant, animal, mineral or mixtures thereof. It may contain excipients in addition to the natural material. Products that includes active substances chemically synthesized or isolated from natural material as responsible for the synthesis pharmacological activity, are not considered as natural medicines. Regarding the dosage form or route of administration, they are all accepted while its proven safety and efficacy, except for those intended for ophthalmic and parentally use.

Natural products for medicinal purposes can be marketed through two ways: selling product prescription or over the counter product.

The documentation to be submitted for the sanitary registration, whose term is five years, including a monograph with the technical scientific description of the safety profile and effectiveness, according to the level of evidence of a medicinal natural product, the Certificate of Good Practices manufacturing, each of the establishments involved in the manufacture of the product, qualitative and quantitative formula, efficacy and safety information and labeling of packaging or primary, secondary and package insert.

The traditional use must be supported by documentary evidence stating that they natural drug that is used in a product, has been used for three or more decades for medicinal purposes.

## CONCLUSIONS

Regulation and national and international health controls should ensure that natural products meet the requirements of safety, efficacy and quality.

It should be remembered that natural products subjected to industrial processes, must meet standards or quality guidelines for cultivation, collection and processing, to avoid that during the process of production and marketing contamination, adulteration or deterioration is generated, which jeopardize the health of the population.

Therefore, the health authorities must maintain standards and controls necessary to minimize the damage caused by dangerous products and rationalize the use of substances with pharmacological activity based on scientific and traditional evidence. The documentation on the scientific evidence on the safety and efficacy of these products as well as compliance with quality processes, by companies should be available to the entire population and be subject to verification by the health authorities, so that in the not too distant future can be sold only high quality herbal products, and traditionally scientifically proven.

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