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Analysis and Characterization of Quality Systems in the Natural Medicinal Products Industry in Costa Rica and the World

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Abstract

The use of natural products has been a practice carried out by people throughout history to take care of their health and to alleviate a wide variety of ailments. The reasons for the use of natural medicine at this time, with so many advances in pharmacology, are varied, among which are the dissatisfaction of the immediate needs of people to feel better about themselves and the economic factor. It must be considered that not everything natural is good. Therefore, the products manufactured and distributed under the line of Natural Medicinal Products must go through a verification and certification process, ensuring that they contain sufficient information on their composition and effects to avoid the risks that they may bring to those who consume them. This research describes good practices in the manufacture of natural products and shows the establishment of a Quality Management System in the pharmaceutical industry in different countries of the world. Finally, the use of natural products in Costa Rica is detailed, certain aspects to establish a Quality Management System in the country, as well as its importance.

Keywords: Natural products, Natural medicine, Quality Management System, Costa Rica.

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1. Introduction

People seek their integral well-being. The search for emotional, occupational, and physical stability is a constant in most human beings. Among the most relevant aspects is the search for well-being in health issues, which is even considered as one of the human rights. This right encompasses a set of social criteria that can enable all people to enjoy the availability of health services, safe working and housing conditions, and even adequate food to maintain their bodies in the best possible way. However, everyone has also been given the freedom to look after his health and body himself. (1)

Since human beings have an individual responsibility to look after their well-being in this regard, advances in medicine have become a key aspect of achieving this. In the last decade, medicine has presented technological advances on a large scale, in areas such as cardiology and oncology, bringing equipment and treatments used in many hospitals for the care of patients. (2) However, these advances at the macro level often do not meet the immediate needs of people to feel better about themselves and their bodies, apart from the economic and social factors that can affect whether a given population has access to medicine as such. Even the myths that have been raised are that so much technology may be too much for the human body and that it may not resist so many new chemicals and products.

For this reason, people have chosen to use natural products, to take better care of their health, without having to use products containing chemicals or previous treatments. They are looking for a "healthier" lifestyle, so macrobiotics has a great advantage over pharmaceuticals. Natural medicines, such as herbal products, have also become popular in some sectors of the population. However, the thought that everything natural is good, or harmless, is deception and can bring consequences to people who use them in their bodies. Putting health at risk due to the lack of information when using this type of natural product is a fact that should be avoided, and the population should be warned about it. (3)

According to (4), natural medicine facilitates the process of medication and pain relief, treating that patient-doctor relationship, and becoming the ideal support for many sectors of the population that need quick and less expensive options to seek their well-being. For this reason, they seek to go back to past times when people used all kinds of herbs to heal their ailments. However, and as mentioned above, it is important to stress that some poisonous herbs and products could cause allergic reactions in patients, causing greater harm than the benefit they may have brought.

All this boils down to the need to effectively control and administer the products that people are consuming to improve their well-being in terms of health. Create verification systems for natural medicinal products, as well as certification for clients, so that they can be sure of what they are consuming and its repercussions, whether negative or positive for their bodies. For this reason, the concept of Quality Management Systems in medicinal products was born, which countries and regions have gradually adopted, to improve the quality of life of people.

2. Materials and methods

A bibliographic review was carried out on the markets for natural products both worldwide and in Costa Rica. Information sources such as The World Health Organization (WHO) and the health records of the Ministry of Health of Costa Rica were consulted. On the other hand, regarding the issue of Quality Management Systems, international standards were reviewed: ISO, ICH, the provisions of laws and regulations, as well as scientific publications in databases, such as Scifinder, EbscoHost, Elsevier, among others. The information obtained was classified, and the analysis was carried out by comparing and triangulating concepts and synthetic ideas.

3. Results and discussion

3.1. Principles of natural medicine

Also known as traditional medicine, according to (5) it is a set of knowledge, skills, and practices based on indigenous theories, beliefs, and experiences from different cultures, which have been used for the prevention, diagnosis, and treatment of both physical and mental illnesses. It has a wide range of products, (6) mentions that these products include herbs, herbal material, herbal preparations, and finished herbal products containing as active ingredients parts of plants or other plants, or combinations of these ingredients. They may also contain active ingredients that are not of plant origin, but animal or mineral origin.

However, according to (7), a natural or traditional medicinal product is made up of the plant, mineral, or even animal components, which have been approved for use as a medicinal product based on scientific studies carried out beforehand. According to the above mentioned, these products can go through several stages or presentations. Each of these stages can have its medicinal use or become an ingredient for the subsequent stage. The above is represented by the following diagram.

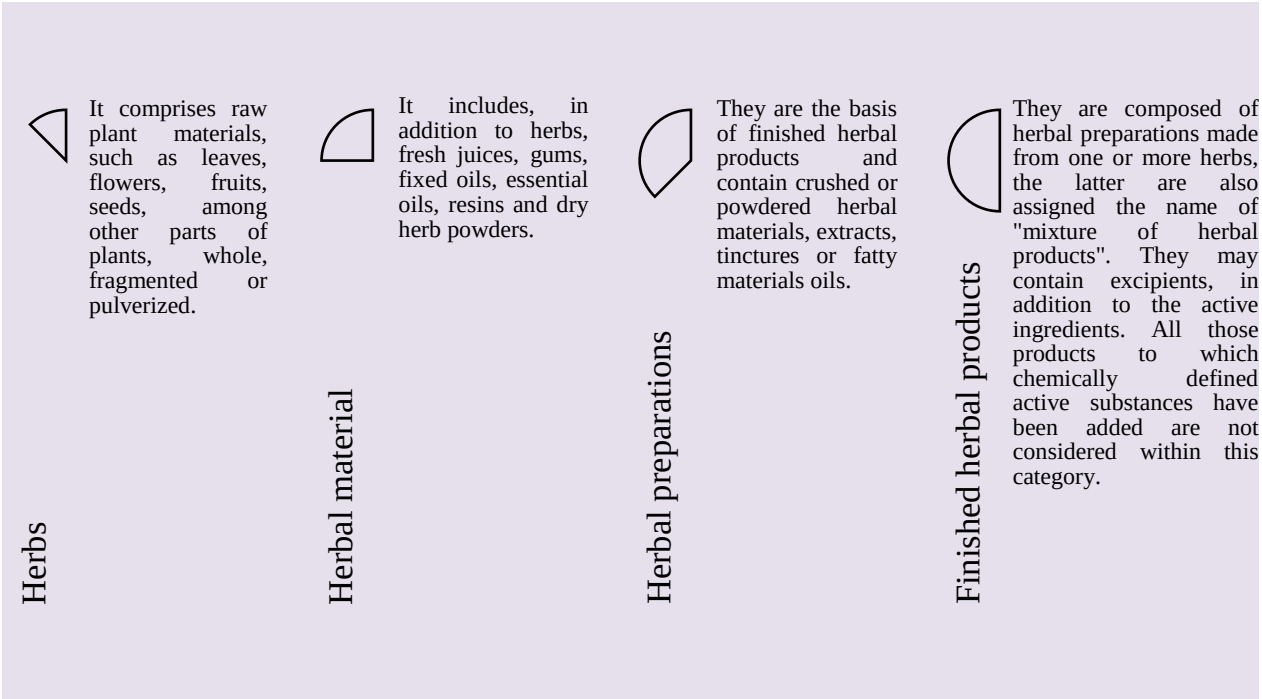

Figure 1. Stages of natural medicinal products (5)

Professionals in conventional medicine and health care agents such as doctors, dentists, nurses, pharmacists, and physiotherapists can also practice traditional medicine.

Natural products have a great advantage due to the novelty of their structures, which could hardly have been the result of human reasoning no matter how creative.

Moreover, this structure facilitates their interaction with complex biological processes such as protein-protein interactions. (8) However, they require processes that ensure the appropriate use of natural resources (plants and organisms) to avoid the loss of biodiversity.

More than 25% of drugs used during the last 20 years are directly derived from plants, while another 25% are derived from natural, chemically modified products. It is worth mentioning that only 5% to 15% of the approximately 250,000 medicinal plants have been investigated for bioactive compounds. (9) Some of the essential drugs made from plants are atropine (anticholinergic), codeine (antitussive, analgesic), colchicine (anti-gout), digitoxin/digoxin (cardiotonic), vincristine (antitumor), morphine (analgesic), quinine/artemisinin (anti-malarial), reserpine (antihypertensive), and physostigmine (cholinergic). (10)

To continue the growing research on natural medicines and to counteract the problem of the extinction of plant species, mainly in tropical countries, consortiums were organized with pharmaceutical companies. They are committed to conserving biodiversity in exchange for sharing with the population of the area the rights to the possible exploitation of the medicines and other chemical substances that may be discovered. In Costa Rica, the National Institute of Biodiversity (INBIO) was created in 1989, in consortium with the pharmaceutical company Merck, in the United States the "International Groups for Cooperation on Biodiversity" and later the Latin American Network for Research on Natural Bioactive Compounds (LANBIO). (8)

It is important to mention that these products must meet some criteria to be evaluated in the pharmaceutical field. Among these criteria is their level of acceptance as a drug depends on the review of risks of the consumption of the product, the appropriate use of user information and testing of the product, the negative and counterproductive aspects of the use of the product must be properly documented, as established by laws or agreements of the country. (7)

3.2. Global trends in natural products

Natural medicine products can be found according to (11) with a different degree of processing, both artisanal and industrial, which have generally been subjected to a certain degree of fragmentation and/or pulverization.

There are some approaches in which the consumption and production of natural products have been specializing, to satisfy the criteria that have been developing in most of the countries practicing this activity, among these tendencies we can mention (12):

- Search for sustainability and attractiveness in packaging
- Safety and efficacy of formulations
- Whole food supplements

In many areas, especially in tropical regions, the abundance of medicinal plants makes safe and effective products available for the prevention and treatment of disease through self-medication. (10)

According to the 2012 National Health Interview Survey (NHIS), which included questions regarding the use of complementary and alternative medicine by the American public, approximately 18% of adults consumed natural products, especially those in the form of dietary supplements. The results are presented below.

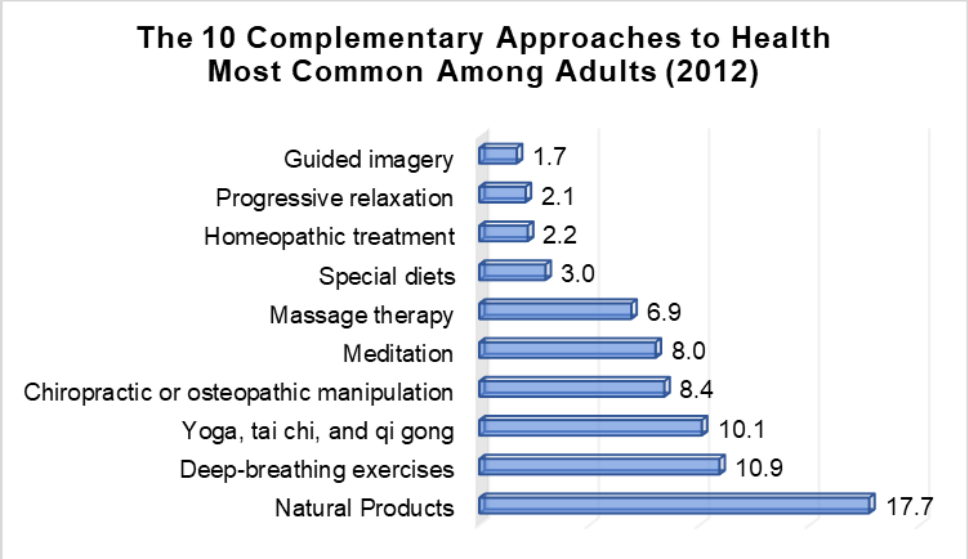

Figure 2. Survey results. Source (13)

In 2013, it was estimated that about 80% of the world's population uses traditional herbal medicine for primary health care. In Asia, millions of people maintain their health using leaves, roots, and bark. According to renowned researchers, virtually all these plants have been revealed for use in traditional medicine. (14)

3.3. A natural product is not synonymous with a quality product

The fact that a product indicates that it is natural does not mean that it is safe to use as a medicine. There are natural products that have hidden drug ingredients, which may be contaminated or maybe a health fraud. This is defined (15), as the promotion, advertising,

distribution, or sale of products that are presented as effective in diagnosing, treating, preventing, or curing disease (or other conditions) or having a beneficial effect on health even though such items have not been scientifically proven to be effective and safe for such purposes. However, people continue to purchase them as consumers seek easy, less expensive solutions to serious health problems, even if these are not previously certified or proven remedies. (16)

There have been cases, where people suffering from health problems such as cancer, and who maintain regular pharmaceutical treatments, use natural medicine as an alternative remedy. According to Dr. Nicole Kornspan M.P.H., an FDA consumer safety officer, anyone who suffers from, or has a family member, friend, or acquaintance who suffers from any type of cancer. For this reason, people are prone to seek remedies for it, not only in already regulated drugs but also in natural treatments. However, the use of these products could alter existing treatments, if they are not consulted with a physician, and are not endorsed by an entity. (17)

This is why, before taking any medicine, you should read the label, which should contain a list of the substances used in the preparation of the medicine, to prevent an allergen from affecting the consumer. Also, check the expiration date, as it can lose its properties over time. It should be noted that medications could have side effects in people; this is related to allergies, so we recommend self-medication, or sharing medication between people, more if one of these is pregnant. (18)

How can you be sure if a product may be a fraud? In this case, you need to verify that the products do not attempt to cure a wide variety of diseases, as this is a synonym for not being objective and consistent with what the product is capable of doing. In addition, review the personal testimonials of patients who have used them previously, and verify that their origin is completely natural. Finally, avoid the promise of "get better in 30 days", or when a product claims to perform a health-enhancing action 40 minutes faster than pharmaceutical drugs, it is a warning sign, as it is probably misleading advertising. (16)

It is also important to mention that the aim is for medicinal products to be approved by a third-party entity that certifies their use in the market. Excessively high doses of this type of product can also generate complications in patients. If a product is not properly legalized, consumers are not completely sure, just by reading the label, that what it says is correct. Due to tests on various products sold in retail stores or by mail order, the FDA found products containing up to 31 times the prescription dose of a component that contained a pharmaceutical product already registered and controlled. (19)

Adverse reactions to natural products are also a reality. A study in Cuba in 2003 and 2007 showed some of the systems affected by such products and their percentage of affectation, so there is the possibility that the organism rejects these compounds as with synthetic medicines. The data obtained from the study are illustrated below.

Table 1. Suspected RAM products in 2007 (20)

Suspicious product	Severity		
	Mild	Moderate	Grand Total
	n/%	n/%	n
Garlic (*Allium sativum* L.)	28/65,1	15/34,9	43
Vimang® (*Mangifera indica* L.), aqueous extract of trunk bark: syrup, tablet or cream	33/78,6	9/21,4	42
Aloe (*Aloe vera* L.)	30/83,3	6/16,7	36
Mint (*Mentha* spp.)	26/89,6	3/10,3	29
Eucalyptus (*Eucalyptus* spp.)	12/52,2	11/47,8	23
Ginger (*Zingiber officinale* Roscoe)	13/72,2	5/27,8	18
Noni (*Morinda citrifolia* L.)	9/75,0	3/25,0	12
Guava (*Psidium guajava* L.)	7/58,3	5/41,7	12
Passionflower (*Passiflora incarnata* L.)	8/80,0	2/20,0	10
Sweet orange (*Citrus sinensis* [L.] Osbeck)	2/22,2	7/77,8	9
Others	78/62,4	47/37,6	125
Total by severity /%	246/68,5	113/31,5	359

n: number of reports, %: percentage of total reports by product and by severity.

Table 2. Products are classified by system and severity (20)

Product	Affected system						Total
	Skin	DS	CNS	CVS	RS	General	
	n/%	n/%	n/%	n/%	n/%	n/%	
Garlic (*Allium sativum* L.)	5/11,6	5/11,6	5/11,6	8/18,6	2/4,6	18/41,9	43

Vimang® (*Mangifera indica* L.), aqueous extract of trunk bark: syrup, tablet or cream	2/4,8	10/23,8	6/14,3	15/35,7	2/4,8	7/16,7	42
Aloe (*Aloe vera* L.)	2/4,3	5/13,9	3/8,3	8/22,2	1/2,8	17/47,2	36
Mint (*Mentha* spp.)	1/3,4	9/31,0	9/31,0	7/24,1	1/3,4	2/6,9	29
Eucalyptus (*Eucalyptus* spp.)	2/8,7	11/47,8		3/13,0	4/17,4	3/13,0	23
Ginger (*Zingiber officinale* Roscoe)	4/22,2	6/33,3			3/16,7	5/27,8	18
Noni (*Morinda citrifolia* L.)		2/16,6	7/58,3		1/8,3	2/16,6	12
Guava (*Psidium guajava* L.)	2/16,6	7/58,3		1/8,3	1/8,3	1/8,3	12
Passionflower (*Passiflora incarnata* L.)	3/30,0	1/10,0	6/60,0				10
Sweet orange (*Citrus sinensis* [L.] Osbeck)	3/33,3	1/11,1		2/22,2	2/22,2	1/11,1	9
Others	10/8,0	32/25,6	18/14,4	21/16,8	9/7,2	35/28,0	125
Total	34/9,4	89/24,8	54/15,0	65/18,1	26/7,2	91/25,3	359

DS: digestive system; CNS: central nervous system; CVS: cardiovascular system; RS: respiratory system; n: number of reports; %: percentage of total reports by product and by the system.

Another fact to consider is that, although natural products come from renewable sources, this can also mean an impact on the environment due to their manufacturing process. The preservation of natural resources and the reduction of environmental pollution are not a priority in the manufacture of many of these products, so quality should not be demanded exclusively in the veracity of the components and labeling but should include environmental issues for the selection of alternative medicines.

To illustrate the reality of some of the procedures, the results of a study on the manufacture of medicinal syrups of botanical origin are listed in Figure 5.

Table 3. Results of syrup production (21)

Components	Factors	Impact value	Affectation percentage
Air resource	Air quality (combustion gases, MP, odors)	-4,00	-3,3 %
	Noise and vibration level	-0,80	-0,7 %
Water resource	Water quality (effluent generation)	-0,40	-0,3 %
Soil resource	Soil quality	-4,00	-3,3 %
Waste	Solid waste generation	-4,00	-3,3 %
Geomorphodynamic process	Erosion	-4,00	-3,3 %
	Geomorphology	-4,00	-3,3 %
	Instability	-4,00	-3,3 %
Biotic environment	Flora	-4,00	-3,3 %
	Fauna	-4,00	-3,3 %
	Ecosystems	-4,00	-3,3 %
Socioeconomic	Commercial activities	36,00	30,0 %
	Employment	15,00	12,5 %
	Landscape aspects	-4,00	-3,3 %
	Population risks	-4,00	-3,3 %
	Basic services	-4,00	-3,3 %
	Communities quality of life	8,00	6,7 %
	Occupational health and occupational safety	-12,00	-10,0 %
Total impact		-2,20	-1,8 %

3.4. Good practices in the manufacture of natural products

The Good Manufacturing Practices (GMP), besides contributing to improving the quality of the pharmaceutical products available in the market, have allowed an important advance in the conceptual interpretation and the practical application of the true meaning of quality assurance in the pharmaceutical industry. (22) The World Health Organization establishes a series of good practices for the proper handling of products of natural origin, since, unlike conventional pharmaceuticals, which are generally made from synthetic products, through reproducible manufacturing techniques and procedures, herbal medicinal products are prepared from material that may be subject to contamination and deterioration. (23) Therefore, strict controls are required to ensure the safety and effectiveness of the finished products. Some of the general aspects defined by the organization are discussed below.

3.4.1. Local

Storage areas: materials should be stored from separate locations. The area should be well ventilated and protected from the entrance of insects or other animals, such as rodents. Measures considered effective in preventing or limiting the spread of animals and micro-organisms within the plant material and in preventing cross-contamination should be implemented. In addition, containers should be placed in such a way that air can circulate between them. Cleanliness and ensuring optimal conditions in terms of factors such as humidity and temperature should be a priority.

Production area: implement equipment that facilitates the task of cleaning and prevents cross-contamination whenever dust is generated, especially caution when sampling, weighing, mixing, and processing medicinal plants.

Concerning quality control, this should be carried out exclusively by personnel trained in herbal medicinal products, so that they can perform the appropriate tests to identify possible adulteration, the presence of fungi, lack of uniformity, etc. For the tests, it is suggested to carry out sampling of the materials and stability tests.

3.4.2. Quality evaluation

These are guidelines agreed by WHO on the procedure to be followed for the evaluation of the quality of natural products. Given the increasing popularity of traditional medicine, professionals sought appropriate methods to ensure the safety and active ingredients.

Pharmaceutical evaluation: refer to a pharmacopeia monograph, if available. If it does not exist, a monograph should be established using the criteria set by the official pharmacopeia.

Raw plant material: provide the complete botanical definition, including genus, species, and name of the author who has described it. The part of the plant from which the medicinal product is prepared is defined and described, and whether the material is fresh, dried, or traditionally processed.

Plant preparations: a detailed description of the manufacturing process is required, if available, specifying the substances added to adjust the preparation to a certain active, characteristic, or other purposes. Add the identification method, and if possible, the analysis. If it is not possible to identify an active substance, it is sufficient to identify a characteristic substance or mixture of substances to ensure uniformity in the quality of the preparation.

Finished product: a detailed description of the manufacturing process and the formula, including the excipients quantity, is given. The specifications of the finished product, a method of identification, and, if possible, the quantification of the plant material in the finished product are defined. The process is the same as above for the identification of the active substance.

3.4.3. Quality Management System

The word "management" comes from the Latin "gestus", which refers to an attitude or movement of the body, which in turn, is derived from "gerere", which refers to carrying out, following up, conducting an action, or even executing. After a series of changes and studying its history and possible definitions in greater depth, the word "management" also refers to the power to act, administer it or make it circulate. (24)

Now, regarding the concept of quality, as mentioned in (25), quality refers to a quality or qualities that determine the value of an object. The adequacy of a product to meet specific characteristics is what determines its main function.

Once the two previous words have been defined, the concept of quality management is born, which was the result of the evolution of industrial quality over time. Firstly, it began with a stage of achieving quality employing quality inspection. Then, it evolved, and changed the concept to quality control, using more tools so that the products comply and are constant. Once the products comply, this permanence must be ensured, so quality assurance is born. Finally, the concept evolves to quality management, more integrally and completely. (26)

According to (27), the concept of quality management is based on a collection of methods that can be used individually, at a specific time or continuously, to control the quality of products or processes.

A quality management system allows assuring the quality of the activities of an organization, assuring the fulfillment of the needs and expectations of the clients or interesting parts of the same one, as well as the handling to the internal thing of its processes. For this reason, it must be well defined, with established objectives and scope, to improve the performance of the company. (28)

A survey conducted in the study obtained from (29), points to the use of quality management tools in some companies interviewed. The following graph visually shows these results, giving an overview of the use of these tools in these companies.

So, in this way, it is possible to visualize graphically and descriptively, the different types of programs, methodologies, tools, compared to each other and making it clear that the more you know about them, the less frequently they are used. As in the case of Six Sigma, AMEF, Poka Yoke, which are more technical, instead of the improvement groups, surveys, diagrams, and audits, which are easier to apply or to seek their application eventually. These techniques for collecting information are known as soft techniques and are generally the most used, the others are called hard techniques. (29)

3.5. Quality Management System in the pharmaceutical industry

In the constant search for improvement, safety, confidence, and development in the field of health, the implementation of a QMS can represent an increase in the quality of life of users, since the failure to comply with specifications or the presence of defects in products can have serious consequences, both in terms of health and credibility.

To ensure compliance with the regulations established by the WHO, there are regulatory bodies called Drug Regulatory Agencies (MRAs) which perform a variety of functions, including licensing, manufacturing and distribution inspection, product evaluation, and health records. Below are some of these agencies worldwide.

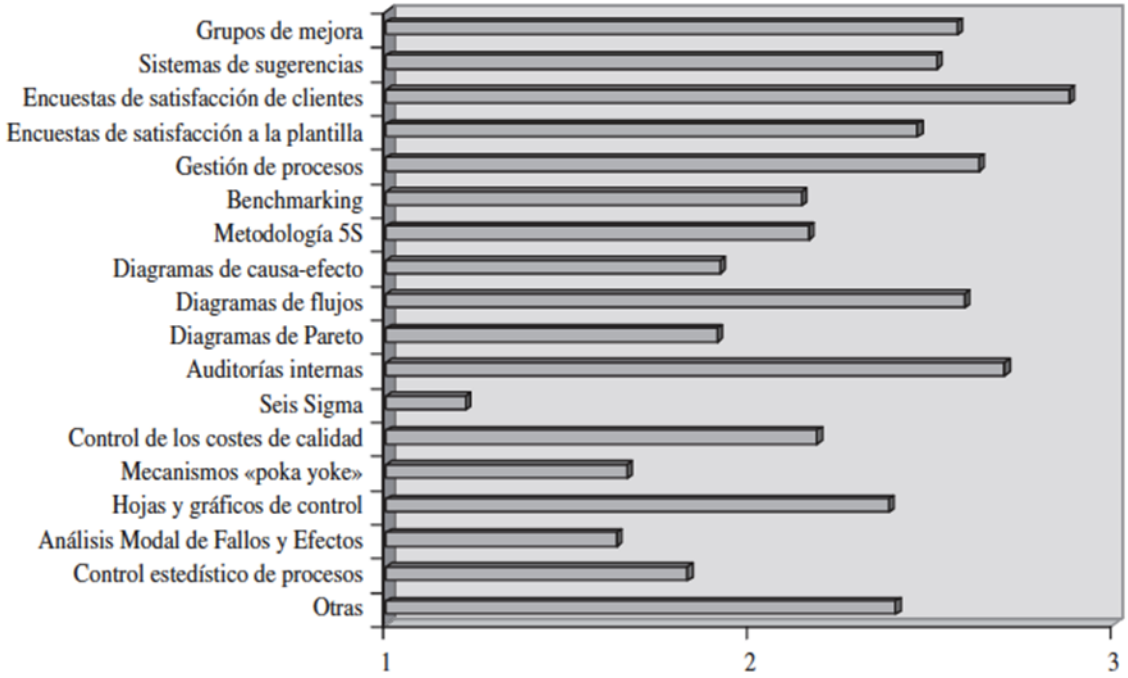

Figure 3. Use of quality management tools (29)

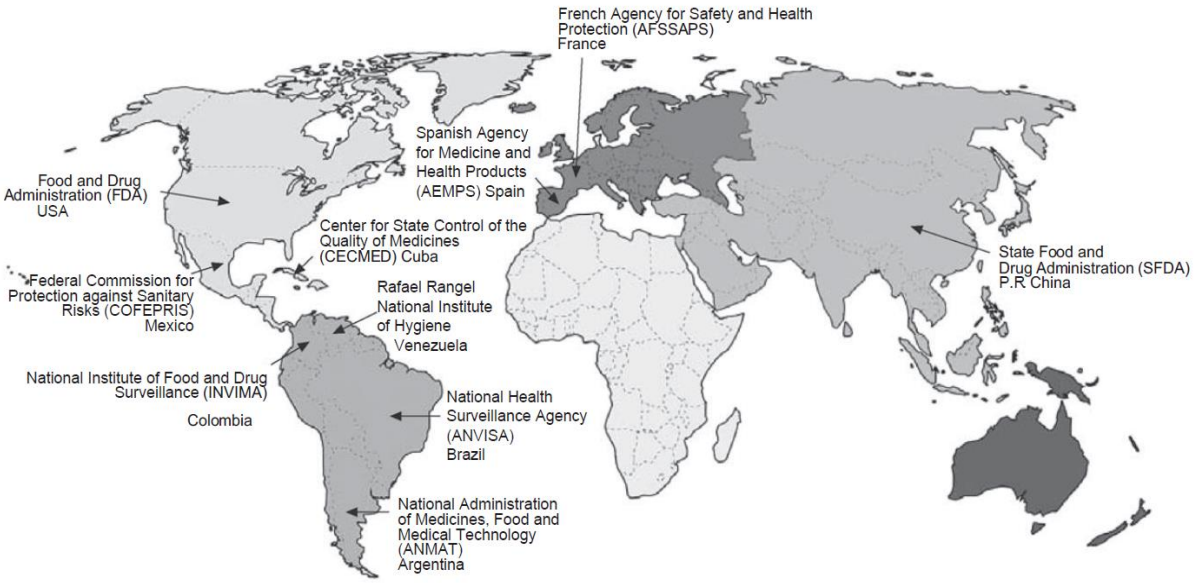

Figure 4. Some MRAs worldwide (30)

The WHO is responsible for evaluating the performance of the agencies, as well as their weaknesses, strengths, and adequate drug control in each country. However, it was considered to include as part of this tool a module of indicators regarding the presence of a GSC that covers all its regulatory functions. (30) The indicators are (30):

a. Management commitment to implement a QMS relevant to all regulatory functions.

- Policy statement and development plan.
- Identification and designation of necessary financial support and human resources.

b. Presence of a QMS.

- Definition of organizational chart and responsibilities.
- Written documentation to carry out all functions.
- Documented and implemented audit system.
- Management system to ensure traceability of actions.

The above corresponds to some of the guidelines indicated in the ISO 9001 standard, based on the principles of customer focus and processes in the search

for continuous improvement. The aim is to obtain results that allow us to identify improvement actions to correct current errors or prevent possible risks.

Table 4. Functions and indicators (30)

Features	Indicators
Licensing and marketing authorization activities	Percentage of requests for health registration procedures evaluated in time
	Percentage of response to health license procedures for pharmaceutical operations
Regulatory inspections	Percentage of compliance with planned inspections
	Percentage of State Pharmaceutical Inspection Reports Delivered on Time
Batch release	Percentage of a batch released by documentation and testing
Regulatory oversight of clinical trials	Number of inspections to authorized clinical trials carried out
Postmarketing activities (adverse event monitoring)	Percentage of investigations against adverse events carried out on time
	Percentage of sanitary measures issued monitored
Access to laboratories	Percentage of analytical capacity of the national control laboratory
National regulatory system	Percentage of approved regulations disseminated in time
	Percentage of compliance with the calibration/verification plan
Some improvement actions undertaken ● Review and adjustment of the regulated times ● Application of mechanisms and records to control service times ● Organization of seminars and workshops with the participation of drug manufacturers, distributors, marketers, importers, and exporters ● Review of the documentary base of the processes ● Automation of control activities ● Improvement of feedback mechanisms for undesirable effects after vaccination or availability of drugs on the market ● Statement on the test request form of the priority level of the products involved in suspected adverse reactions ● Increase in controls by the heads of areas and processes in the exit registers and the fulfillment of the evaluation plans ● Creation of the operational committee for health decision-making, which involves executives and external experts ● Increase in the level of competence of specialists through the management of training activities and internal training in Medicines Regulatory Authority ● Establishment of mechanisms that provide more information on the effectiveness of the training received ● Give timely response to complaints and claims from external customers	

3.5.1. United States

The Food and Drug Administration is an entity that is responsible for ensuring public health, ensuring the safety and efficacy of medicines, used in both humans and animals, biological products, medical devices, food supply, cosmetic products, and emitting radiation. In addition to this, it is a source of information accessible to the public. (31) For example, it campaigns to raise public awareness of eliminating the risk of keeping unused opioid drugs at home, giving them the tools to get rid of them. (32)

3.5.2. Central America

To control good manufacturing practices, the Central American Technical Regulations on Pharmaceuticals are created, covering natural medicinal products for human use. This document includes the participation of five countries: Guatemala, Honduras, El Salvador, Nicaragua, and Costa Rica. It is responsible for establishing the guidelines of the BPM that regulate the procedures involved with the elaboration of natural medicinal products that are used by humans. It is responsible for ensuring the safety and effectiveness of them, ensuring the quality of the inputs. (33)

RTCA 11.03,69:13 provides that laboratories must have a health permit for operation, under the regulatory authority of each country, and must ensure compliance with the specifications of the same. It also covers topics related to the organizational structure of the company, its facilities, equipment, materials and products, sampling, documentation, production, and control of processes, guarantee and quality control, handling of complaints, claims and withdrawals, audits, and verification. (33)

3.5.3. Mexico

There is COFEPRIS, an entity that treats national pharmaceutical policy and the consumption of such medicines. Its functions include dealing with the issuance of standards and regulations, monitoring, verification, and health promotion. A little more focused on the medicines sector, it is responsible for regulating the import of raw materials or ready medicines, from foreign countries, as well as the regulation at the national level, of medicines and their manufacturing procedures, updating the Pharmacopeia, advertising, certification, analysis, standards, in short, everything related to the marketing and distribution of pharmaceutical products. (34)

Mexico has the burden of being a benchmark for other countries, due to its experience with the quality of this type of product and the development of research protocols. With the process of inserting new drugs in

general, four categories can be observed: new, generic, free-to-counter, and herbal medicines. (34)

In this case, we will take the category of herbalists. Herbalism is known as the study and use of plants as medicinal products. Many of the plants have healing properties that alleviate discomfort in the human body, so their use has become popular, as people believe that being completely natural, they do not generate collateral damage such as medicines created with chemicals. (35)

To register a product in this category, you need to meet the following requirements:

Table 5. Requirements for the sanitary registration of medicinal products in Mexico (34)

Requirements	Specifications
Therapeutic indications	Correct fundamentals in studies
Terms of use	When ingesting or putting on the product, content per dose.
Pre-registration information	-
Labeling	-
Pre-clinical and clinical studies	-
Formula	Qualitative and quantitative
Raw materials	Drugs and additives
Pharmaceutical development	Pharmaceutical form, formulation, processes related to its manufacturing or fabrication, process controls as such.
Facilities	Comply with the requirements of good practice.
Manufacturing Information	Process mapping
Assurance of the sterilization process	Specify type and evaluation of procedures
Control of packaging materials	Quality testing
Control of the finished product	Through analytical methods
Stability studies	According to NOM177.
Samples	Even if the requirement is
Drug control	Certificates of analysis with impurity levels and solvents, if applicable.

3.5.4. Bolivia

As for this country, according to (7), concerning its good manufacturing practices, all procedures related to the production and creation of products of the pharmaceutical family must comply with these, as appropriate and applicable. In addition, this is provided that the Directorate of Medicines and Health Technology has issued the necessary regulations for this type of product. There are also some guidelines as to the form of the products, examinations before their commercialization, labeling, analytical methodology, quality control of the same, raw material used in their respective elaboration, among other attributes, which must have a correct verification, according to the entity established in that nation.

3.5.5. Spain

In this country, some laws promote quality in pharmaceutical products in general. For example, Law 29/2006, on guarantees and rational uses of medicines, which establishes the authorization of a new medicinal product, if it meets the following requirements: it meets the quality requirements, it is safe from toxic effects and it is effective in the therapeutic indications that it offers. In addition, there is the Royal Spanish Pharmacopoeia, which is the code that establishes the quality of the principles of medicines for human use and even for use in animals. (36)

The standards applicable in this country are GMP, for the industrial production of medicines, LPG, for pre-clinical development and quality control of production, and GCP, for clinical trials. The regulatory bodies are AEMPS, EMA, and FDA. Apart from this, some standards are used for the correct manufacturing of drugs, these are the NCF or GMP. These standards touch on points such as quality management, personnel, premises and equipment, buildings, auxiliary areas, equipment, documentation, production, manufacturing and third-party analysis, complaints and withdrawal of marketed products, and self-inspection. (36)

3.5.6. India

A study was carried out in four states in India, regarding the certification of wild medicinal and aromatic plants (37) mentions the attempt to create a standard that could be established in the country and supported internationally. Some of the benefits of this standard, or the implementation of this system, would be sustainable harvesting ensuring availability of the resources used, quality of the product, commercialization outside the borders, respect for traditional rights and practices. All this, generating benefits not only for the producers but for all the interested parties. The International Centre for Community Forestry in Bhopal undertook an assessment project for the creation of this standard. However, over the years, other international standards have been applied and some national standards have been implemented, which have maintained order in the production of these products.

3.6. Natural products and GSC in Costa Rica

According to a study conducted in 2001, by then in Costa Rica, specifically in an urban area, it was documented that regardless of sex, age, and schooling, 85% of people attending public health services had consumed multiple preparations with medicinal plants in

their homes, 78.6% of which were ingested simultaneously with medication. The people interviewed confirmed that they only had expectations of the benefits of consuming these products and did not expect any side effects or toxicity. On the other hand, in a semi-urban area, 88% of the people who went to the same services mentioned above confirmed the use of preparations with medicinal plants, 65% of them consumed them together with their medicines and only 38% had informed their doctor. (38)

According to data from the Ministry of Health, there are currently 920 registered natural products in Costa Rica. Of all these products, 470 are of Costa Rican origin, representing approximately 51.1%. The distribution according to the pharmaceutical form is illustrated below:

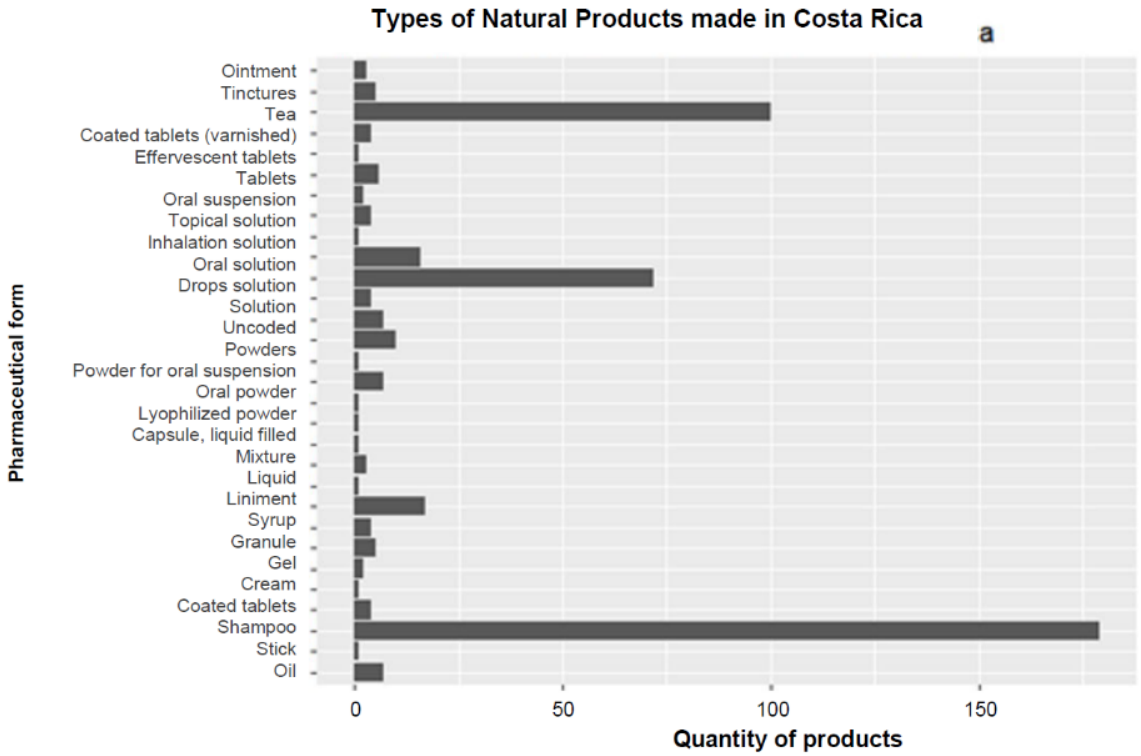

Figure 5. Types of Costa Rican natural products. Source: Ministry of Health of Costa Rica

Out of the many production companies, only the Laboratory Zepol S.A. has a quality certification assigned by INTECO, specifically the INTE/ISO 9001: 2015.

3.6.1. Costa Rican Market

In terms of the international market for natural products, Costa Rica is above Bolivia, the Dominican Republic, and Guatemala, but it is still below countries like Mexico and Brazil at the Latin American level. (39)

According to (39) indigenous, Caucasian, and Afro-American groups have been the driving force behind traditional medicine in Costa Rica. In total, there are 500 species of medicinal plants in the country of which 406 species are used traditionally. They are commonly grown in three different ways: home gardens, marketing gardens, and commercial farms. Some medicinal plants are grown nationally that have high economic and commercial value are ipecac, moringa, cat's claw, aloe vera, "hombre grande" and "juanilama".

3.6.2. Applicable laws

According to the Costa Rican government page, Resolution No. 270-2011 is established, which covers the Regulations RTCA 11.03.56.09 and RTCA 11.04.41.06, of pharmaceutical products: natural medicinal products for human use focused on quality verification and labeling requirements. These came into force in 2012 and must be complied with by all those institutions or laboratories engaged in the manufacture of medicinal products based on natural products (Resolution No. 270-2011, 2012). (40)

Quality control of a commercialized eyewash in Costa Rican macrobiotics that claims to contain natural raw materials

An example of pharmaceutical formulations not included in the RTCA guidelines is ophthalmic solutions, including eye drops. Due to their nature, as established by the General Health Law, these should be offered exclusively in pharmacies, however, some of them claim to be manufactured from natural raw materials, and therefore are available over the counter in the country's macrobiotics. The greatest risk associated with the distribution of these products is that clients do not receive the necessary information about the risks, benefits, and safe administration. (41) This author conducts a study to determine compliance with quality requirements according to USP 38 and RTCA 11.04.41:06 for eye drops sold in the Costa Rican market. The results are illustrated below.

Table 6. Results of the eye drops (41)

Packaging	Information required on eye drops labeling that declares to contain natural raw materials	Compliance	
		Yes	No
Primary	Product name	X	
	Lot number		X
	Expiration date	X	
	Name or logo of the manufacturer laboratory	X	
Secondary	Product name	X	
	Pharmaceutical form		X
	Indications		X
	How to use		X
	Qualitative composition of active ingredients		X
	Registration or registration number		X
	Name of the manufacturer laboratory and country of origin	X	
	Net volume of the finished product in the packaging declared in the International System	X	
	Lot number		X
	Storage conditions	X	
	Expiration date		X
	Contradictions and warnings		X
	Interactions		X
	Adverse effects		X
	General legends		X
	Special legends		X
	Dosage		X
	Route of administration		X
	Use during pregnancy, lactation, in elderly and children under two years of age		X

Recently, in September 2020, the RTCA 11.03.69: 2013 was approved in Costa Rica, which is the first Regulation for Good Manufacturing Practices specifically for the elaboration of natural medicinal products. It establishes compliance criteria with different levels of rigor classified as critical, qualifying, and informative, it also has a phased compliance guide in which between 95% to 100% of the critical criteria must be met, and 80% compliance with the qualifying criteria must be met.

3.6. Importance of a Quality Management System

It is important to clarify that the complexity that accompanies the implementation of a Quality Management System, in terms of internal changes in the organization, processes, and standards required of the product or service provided to customers, is directly related to obtaining benefits in organizational behavior and competitive advantages in the market, given the perceived quality in all phases of the supply chain.

Some of the benefits perceived by (42) are the strengthening of strengths and the improvement of weaknesses in the company, which has a positive impact on productivity, more in detail, as (43) say, training the company's workers. By having more information about the processes, they know them better and can approach their execution more agilely, with fewer reductions, etc. In addition, maintaining a good flow of information with the template helps to increase the motivation and commitment of the template. It also facilitates the correction of errors or inconveniences in the organization, since, it comprises several quantitative statistical techniques that detect sources of error, calculate the magnitude of errors and alert when indications that quality has deteriorated. (44) Based on the analysis of the processes carried out, the quality of the products is improved as it is thought of the needs of the customer. It is worth mentioning, according to that others definitions have referred to quality from the customer's perspective (45): "Quality is to reach and exceed the expectations of our customers the first time and all others", "Quality means providing our external and internal customers with innovative products and services that fully meet their requirements". If the quality of a product or service depends exclusively on the level of customer satisfaction that receives it, is then known that a product, service, or company has no quality in itself; is the customer who decides whether it has quality. In general, the company is driven towards excellence in all its fields.

Also, (46) concludes that promoting quality represents the opportunity to boost business competitiveness through the connection between product or service and customer, this being a way to be in tune with the changes in the market and the dynamic environment that demands precise strategies and actions today, with the least possible risk.

Finally, continuous improvement also involves a constant evolution in the company, necessary evolution, as it emphasizes (47), today, companies cannot consider innovation as an occasional event. If a company is unable to transform its products, way of production,

manage management models, and flexible structures in a context of uncertainty, it will not be able to survive.

In the pharmaceutical industry, the issue of the quality of the processes involved in the manufacture, distribution, and sale of medicines that will reach patients has been a necessity that has led to the creation of requirements and guides for proper management. This is added to other characteristic aspects of the industry such as the high complexity of the processes and the effort and costs associated with the separate implementation of activities linked to executive responsibilities of the organization, whose differences are smaller than in other sectors. (48) This has aroused awareness at different levels not only the organization but also the government, which has made it one of the most regulated industries in the world since the 1950s.

An example of these systems is that predictable results and therefore continuous process improvement are allowed. In addition, they emphasize that its implementation has objectives such as ensuring good pharmaceutical management, optimizing resources, improving availability, and therefore ensuring the quality and rational use of the drug. (49)

4. Conclusions

Plants have been used over time as an ally in the health systems of many countries. By their nature and characteristics, they have been used to alleviate and improve the quality of life of people who use this type of "medicine" as a viable alternative in their health process.

As for plants as such, countries must protect their resources, that is, to ensure the correct use of areas intended to harvest from their fruits to produce all kinds of medicines, to prevent any species of flora from being harmed by the desire and needs of the human being. The exploitation of natural resources, for tests or treatments that have not been verified, damages the ecosystem and can generate a natural impact in areas that are surrounding the geographical space used for such purposes.

80% of people worldwide use traditional herbal medicine, which is the last point of caring for areas where used plants are produced and grown as medicines. This alarming figure indicates that most people resort to such natural solutions, so it is evident the importance of controlling which products if and that products are not suitable for use for these purposes. In addition, 20% of adults in countries like the United States tend to self-medicate, indicating that the use of this type of drug, and even more unsupervised, is a recurring and everyday occurrence in the lives of thousands of people.

Expanding population's general knowledge about the fact that "natural is not synonymous with good, healthy or quality product". In this way, an awareness campaign is generated about the use of natural medicinal products, as to which are the ones that can be used, which ones should be avoided, which require a prior medical diagnosis, and what kind of information should come on the label or packaging of the products that consumers purchase. For, because of human survival, and the need of some people, they seek less expensive natural alternatives, and that could bring serious consequences on their bodies.

There are currently organizations, such as WHO, as well as drug regulatory agencies, standards, and even laws applicable to natural products in each country. It is important that when consuming medicinal products, people check their regulatory status or, in the case of producers, use the appropriate regulatory agency. This is because, at least in Costa Rica, few producing places are certified with standards such as ISO 9001, and it is an endorsement of the processes and activities behind the drugs.

It is the responsibility of both the consumer and the customers, to verify that the medicines and products are carried out by producers who have a quality management system, which approves and supports, as mentioned above, the process by which the product to be purchased is made.

As a country, the use of products that are already under the necessary rules for their proper circulation should be encouraged and responsible care for the health of individuals should be promoted.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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