



Herbal Mixtures: Aspects Related to the Quality of Chinese Medicine Formulas and Perspectives for Products Registration in Brazil

**Ferdinando Lucas Góis ^a, Ademir Evangelista do Vale ^b,
Gislane Oliveira Ribeiro ^c and Erika Maria de Oliveira Ribeiro ^{a*}**

^a *Department of Life Sciences, State University of Bahia - DCV/UNEB, Rua Silveira Martins, 2555, Cabula, 41195-001, Salvador, Bahia, Brazil.*

^b *College of Pharmacy, Federal University of Bahia – FACFAR/UFBA, Av. Adhemar de Barros, s/n, Ondina, 40170-290, Salvador-Bahia, Brazil.*

^c *Agronomy School, Federal University of Goiás, Rodovia Goiânia-Nova Veneza, s/n, Campus Samambaia, Goiânia, Goiás, Brazil.*

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ABSTRACT

Traditional medicine products are easily found in different regions of the world. Given this scenario, the World Health Organization (WHO) is very interested in the rational insertion of these resources, especially in primary pharmaceutical care in emerging countries. One of the main concerns of the WHO is with the population's access to traditional medicine products without quality guaranteed by regulatory and health control agencies in the country of origin. In ancient Chinese Pharmacology and Medicine, products based on associated drugs, used by boiling in water (decoction), successfully contribute to maintaining the health of Chinese people. In Brazil, the sanitary legislation of herbal mixtures for medicinal teas allows the sanitary notification of these products as traditional herbal medicines. On the other hand, the lack of clinical services to monitor consumption

*Corresponding author: E-mail: eribeiro@uneb.br;

and the scarcity of evidence to ensure safety and efficacy, add to the inadequacy of the products to sanitary standards, the lack of inspection, and the definition of quality parameters for the evaluation of mixtures. Due to the chemical complexity of herbal mixtures, the correct identification of drugs through conventional techniques is usually possible for individual species, making it necessary to develop more comprehensive approaches. These testes allow to investigate the presence and/or absence of multiple pre-established markers, through the concept of fingerprint similarity and evaluation by chemometric tools. Liquid chromatography integrated with mass spectrometry and multivariate data analysis proved to be the most used method. Among the objectives of this critical and prospective review are: to describe the probable origin of medicinal teas, the theoretical foundation of the compositions in pharmacology and traditional Chinese medicine, the modern techniques developed in the quality control of herbal mixtures, and the perspectives for rational and safe insertion of traditional herbal medicines in Brazilian pharmaceutical care.

Keywords: Associated herbal drugs; medicinal teas; traditional herbal products; decoctions; holistic quality control.

1. INTRODUCTION

The traditional use of plants and inputs of natural origin as food or medicine is present in human history. In recent decades, the World Health Organization (WHO) has shown interest in contributing to the rational insertion of these resources in health systems in emerging countries such as Brazil [1,2]. One of the concerns of the WHO is related to the quality of formulas with a complex chemical nature, used in traditional medicine (TM) in several countries. Often, the use of associated herbal drugs (AHD's) is the only alternative where conventional pharmaceutical assistance is precarious. In trade, products with mixed drugs are easily found in the consumer market.

The latest WHO recommendations for traditional medicine were decisive for the construction of public policies aimed at TM practices in Brazil. Among the most important policies are the National Policy on Integrative and Complementary Practices (NPICP) in the Unified Health System ("SUS") and the National Policy on Medicinal Plants and Herbal Medicines (NPMPHM) [3,4]. Such initiatives highlight herbal products as strategic in the pharmaceutical assistance cycle and can integrate orthodox medicine harmoniously [5,6]. Allied to public policies and sanitary norms, the quality control (QC) of products with AHD's has evolved, with that, new approaches emerge in the investigation of these therapeutic resources.

Among the objectives of this critical and prospective review are: researching the origin of teas, the theoretical foundation of the compositions in the view of Traditional Chinese

Medicine and Pharmacology (TCMP), the modern techniques developed in quality control of TCMP's formulas, the tea market, sanitary norms, and perspectives for the registration of traditional herbal products (THP's) in Brazil.

2. THE PROBABLE ORIGIN OF TEAS

It is believed that the first record of the use of plants in the form of teas occurred in the East, between 3500 to 2600 BC, in the figure of the legendary emperor Shen-Nung or "The Divine Farmer" [7]. Legend has it that the emperor did not drink water if it was not boiled for hygienic-sanitary reasons and that, on one of his walks, he stopped to rest in the shade of a tree when some leaves fell into the container in which he had put water to boil. Shen-Nung decided to taste it and realized that the drink had left him revitalized [8,9].

Shen-Nungis also considered the author of the world's first pharmacopeia, the "Pen Ts'aoChing", with 365 registered drugs. Legend has it that many preparations he tried himself and ended up intoxicating himself. The Pen Ts'aowas compiled during the late Western Han Dynasty (25-220 CE), with different classifications in the toxicity level of plants: high, medium, small and minor. Later, in the Ming dynasty (1368-1644 CE), the "Ben Chao Gang Mu" brought a special chapter with a systematic review on drug toxicity [10,11].

During the middle ages, Europe received numerous shipments of spices from Asia. As teas spread throughout Europe, coming from Asia, they received different names from the dialects of each region, while maintaining their

original accent. Thus, the “*te*” of the Fujian region became the French “*thé*”, the Italian “*te*”, the English “*tea*” and the German *tee*. The Portuguese purchased tea in Macau, a Portuguese colony in China, so the “*chá*”, spoken by the Portuguese, arrived in Brazil under the name of “*chá*” [8]

2.1 The Theoretical Foundation of the Compositions, used in the Preparation of Decoctions, in the View of Traditional Chinese Medicine and Pharmacology

Chinese medicine began its basic concepts in the "Age of the Yellow Emperor" (Huang Di), in 2700 BC; however, it was in the Age of "War of the Feudal States" (476-221 BC) that, with the Naturalist School, it was founded in medical science [12]. All medical physiology, pathology, and pharmacological treatment are influenced by the *Taoist* concepts of yin and yang, “*Qi*” (Chi), and the five movements (fire, wood, metal, earth, and water) [13].

It encompasses the use of ancient practices, such as Acupuncture (*Zhen Jiu*), Moxibustion (*Wen Jiu*), Therapeutic Physical Exercises (*Ba Gua Zhang, Tai Ji Quan and Qi Gong*), Manipulation Techniques (*Tui Na*), Dietetics and Pharmacotherapy with ingredient of natural origin, mainly from herbs (*ben cao*) [14].

Dietary therapy and pharmacotherapy, together, form TCMP, following the same theoretical foundation. TCMP has its own diagnostic and application methods. It studies the basic theory, origin, methods of harvesting, processing, properties, pharmacological action, and applicability of natural substances in the human body.

The drugs in TCMP have four aspects that differentiate them in their compositions: the four *qi* (*si qi*) - cold, hot, warm, and cool; and the five flavors (*wuwuei*) - spicy, sweet, sour, bitter and salty. In addition to the senses of action: ascending (*sheng*), descending (*jiang*), superficializing (*fu*), and deepening (*chen*); action on the meridians (*guijing*) and toxicity (*du xing*) [15]. The purposes of selecting species in a mixture in TCMP's view are described in Table 1.

The consumption of associated herbal drugs, prepared through boiling in water decoction,

remains one of the oldest practices officials in use from China and India [16]. TCMP formulas are characterized by having multiple active ingredients and therapeutic targets in the body, making it challenging to define quality parameters for these mixtures. Through the concept of similarity of chromatographic, spectroscopic and/or spectrometric fingerprints, the standard chemotaxonomic profile of traditional medicine formulas can be predetermined and compared to investigate the authenticity of products available in the global market. In this sense, the correct identification of species in the mixtures using integrated analytical techniques and chemometric tools make it possible to analyze the reproducible quality of established formulas available on the market. In addition to qualitatively evaluating the presence of pre-established chemotaxonomic markers, the use of modern analytical techniques also allows to quantitatively investigate the proportion of chemical constituents based on the hierarchy of drugs in the mixtures. The holistic approach, used to assess the quality of traditional mixtures, considers the theoretical foundation, philosophical principles and chemical complexity of these mixtures in a comprehensive way. One of the challenges in the development of these methodologies is the need to establish standard markers that are related to the bioactivity of these mixtures.

2.2 The Challenges in Quality Control of TCMP's Formulas

Special attention has been given to the investigation of the authenticity and quality of TCMP formulas, mainly due to the chemical complexity of these mixtures. Side effects of conventional (allopathic) medicines, lack of curative treatment for chronic diseases, spending on research into new synthetic drugs, are also reasons for the renewed interest of the Western public in oriental medicine products [11].

The safety and effectiveness of traditional herbal medicines are among the greatest concerns of health regulators authorities worldwide and WHO. Different formulas with associated herbal drugs are found in the formal and informal market of natural products. Many products no have define parameters for quality assessment since they are present in the market informally (without registration) [17,18].

Table 1. Functions of individual drugs in the TCMP formulas.

Components of a prescription	Function in the formula
Main Drug - MD (Jun Yao)	Treating the cause and main symptoms of the disease
Supporting Drugs- SD (Chen Yao)	Reinforces MD action
Assistant Drug - AD (Zuo Yao)	Inhibit or stimulate the effects of MD and SD
Guide Drug - GD (Shi Yao)	Conducts the effects and balances the action of other drugs

One of the challenges lies in the investigation of the botanical authenticity of the drugs already associated through conventional pharmacobotanical methods, requiring comprehensive technical approaches in the QC of these mixtures. With advances in biomedical, analytical, and computational technology, modern approaches emerge in the QC of these mixtures [19,20].

Another obstacle is the choice of markers to determine the quality of associated herbal drugs. Official analytical methods can be very selective, with substances that are not commercially available or are unrelated to the bioactivity [21–23].

The QC at TCMP's formulas uses relatively innovative systems, supported by software in interpreting pre-processed data [24].

Thirteen studies were reviewed in this work with the different modern techniques used to detect chemical markers of complex herbal matrices used in traditional Chinese medicine. All TCMP formulas follow the ancient concepts of Taoist philosophy, such as the principles of yin and yang, of "Qi" and of the five movements. Often, traces of chemical components can be responsible for the global therapeutic action of these preparations and must be taken into account in the QC of these mixtures. Several methods have been developed to analyze the multiple and simultaneous presence of pre-established chemical markers of traditional formulas, through the fingerprint similarity profile. These techniques allow the qualitative and quantitative analysis of the presence of traces of constituents using integrated chromatographic and spectrometric techniques. Also known as hyphenated techniques, these approaches allow the coupling of different methods to investigate the presence and quantity of quality markers in these mixtures. Furthermore, the use of hyphenated techniques allows investigating the presence of unknown components or the use of drugs other than those described on the packaging, which can characterize fraud. The use of drugs other than the original ones, used

for commercial purposes, can directly influence the safety and efficacy of these preparations, requiring the development of methodologies that allow tracking of the chemical components of these mixtures.

A study with a TCMP formula, the Bانشa (BHT), demonstrated the first application of paper spray mass spectrometry (PS-MS) as a methodology for obtaining fingerprints (Table 3). The PS MS method made it possible to trace the origin, establish authenticity and assess the quality of two BHT manufacturers in the eastern market [25-26]. The negative ion PS-MS spectrum yielded the best phytochemical profile information and was suitable for BHT fingerprint analysis. In addition to identifying the active principles, several compounds present in the BHT were detected simultaneously without any sample pre-treatment and the need for chromatographic separation, providing comprehensive information for evaluating the quality of commercial mixtures. In another study of a traditional Korean medicine formula, Ojeoksan (OJS), the results showed variation of 19 pre-established markers, such as gallic acid and chlorogenic acid, between samples of OJS obtained in the laboratory and commercially. The method used was reverse-phase high performance liquid chromatography coupled with diode array detection (RP-HPLC-DAD) [27].

The technique developed to analyze the OJS formula made it possible to investigate the reproducibility of this mixture in the Korean market using a comprehensive analytical technique and a chemometric tool to interpret the data.

2.3 Obtaining Fingerprints of TCMP's using Modern Analytical Techniques

In general, FP's be obtained through hyphenated analytical techniques, based on the physical properties of substances (atoms or molecules), present in the mixtures, with the interaction of electromagnetic radiation in modern platforms.

Efficient analytical techniques for separating and detecting chemical substances in complex matrices, such as those derived from TCMP's formulas, are used to characterize the identity of these products by means of FP's. Separation techniques such as thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC), gas chromatography (GC), and Capillary Electrophoresis (CE) are integrated with spectrometric techniques for detecting such ultraviolet and visible (UV-Vis), mass spectrometry (MS), infrared (IR), or nuclear magnetic resonance (NMR)[25–27].

The detection of substances through "Tandem" systems, as those that use more than one mass sequence analyzer (MS-MS) are called, is among the most promising methods [28]. MS, integrated with LC or CG, has advantages such as increased sensitivity and elucidative capacity in the study of complex matrices, as described in Table 2.

Liquid chromatography with mass spectrometer detection (LC-MS) has gone through a long stage of development and is currently one of the most widely used methods in investigating the authenticity of TCMP formulas. Among the reasons are: the modernization of the LC columns, due to the increase in vacuum caused by the high pressure in the LC and the reduced pressure in the MS. Ultra-High Performance Liquid Chromatography (UHPLC) with higher pressure limits, lower extra-column dispersion, solvent waste and versatility will, over time, replace conventional HPLC in the analysis of multidrug formulas [29]

To obtain fingerprints, different techniques for separating chemical components can be used together with techniques for detection, such as: liquid chromatography coupled with mass spectrometry (LC-MS), diode array (LC-DAD) or nuclear magnetic resonance (LC-NMR), as shown in table 2. The techniques that use LC in an integrated manner with other analytical techniques have advantages such as: sensitivity to detect traces of substances in complex matrices, versatility, ease of learning and handling the equipment. Among the disadvantages are: being destructive to the samples, higher solvent consumption, need for pre-treatment and time available (long term) for analysis. The techniques that use thin layer chromatography (TLC) coupled with other analytical techniques allow the initial screening to be carried out, as there is little variation in

chemical constituents, lower cost, versatility, high speed and sensitivity [30].

Obtaining fingerprints using gas chromatography (GC) is the best tool for investigating volatile compounds, with high sensitivity and selectivity for non-polar compounds. Among the disadvantages of GC coupled with other techniques are: being destructive, the high cost and not feasibility of detecting polar compounds, which are very present in tea mixtures. On the other hand, capillary electrophoresis (CE) techniques have advantages such as: wide detection range and ability to separate substances in complex matrices [24]. Among the CE disadvantages are the high operating cost.

Associated herbal drugs (AHD's), used in the preparation of decoctions, consist of an expressive number of associated plants, and it is necessary to guarantee the authenticity of the species, individually, before being mixed. However, the presence of AHD's in the market depends on the standards in force in the country of origin [30]. In some places, tea blends do not have defined quality parameters and depend on pre-marketing regulatory approval [23,31,32].

The evaluation of the quality of these mixtures is more difficult than that of isolated drugs due to the greater number of substances present and the natural variation in the chemical composition of the plants. These variations can happen due to seasonal issues, related to cultivation, soil, harvest, light, relative humidity, geographic area, and phytochemistry, such as linked to the processing of the raw material [33]. The consequence is that batches of the same product can significantly differ in pharmacological activity in the body, with changes in pharmacodynamics and pharmacokinetics [25].

Some TCMP formulas were randomly selected to exemplify modern analytical techniques used in phytochemical tests to assess the authenticity of mixtures through the detection of chemical compounds. Among the studied compositions are the formulas: GX II (05 drugs), XSLJZT (10 drugs), BHT (07 drugs), and DBT (02 drugs), which had: 57, 06, 59, and 18 compounds detected, respectively, with use from HPLC integrated to MS. The formulas: GJK (06 drugs), GQD (04 drugs), and SST (03 drugs), obtained: 13, 50 and 6 compounds successfully identified through UHPLC integrated

techniques, with high detection power of substances in complex plant matrices (Table 3).

Another fast, sensitive, precise, accurate and reliable method was developed using ultra-high performance liquid chromatography coupled with triple quadrupole mass spectrometry (UHPLC-QqQ-MS/MS) to analyze the reproducibility of the Guanjiakang formula (GJK), with six drugs mixed together. In this method, the quantitative and simultaneous investigation of 13 chemical components of the GJK formula, which are related to the bioactivity of the extracts, was carried out in three different batches. Simultaneous determination showed extreme variation in 13 components of the GJK formula, such as alkaloids and triterpenoid saponins [34]. Another blend of oriental medicine, the Palmultang formula (PLMT), with eight drugs: Ginseng radix, Glycyrrhizae radix, Hoelen, Atractylodis rhizoma, Angelicae gigantis radix, Cnidii rhizoma, Paeoniae radix and Rehmanniae radix; a quali-quantitative analytical method was developed. The developed analytical method allowed the simultaneous analysis of 11 main constituents: hydroxymethylfurfural (5-HMF), albiflorin, paeoniflorin, ferulic acid, nodakenin, ginsenoside Rg1, decursinol, glycyrrhizin, 6-gingerol, ginsenoside Rg3 and decursin; of the eight drugs already mixed. In the method developed using high-performance liquid chromatography with detection by diode arrays (HPLC-DAD) and liquid chromatography coupled with a tandem mass spectrometer (LC-MS-MS), the presence and quantity of the 11 constituents of the formula PLMT has been successfully investigated through the concept of similarity of chromatographic and spectroscopic fingerprints [35]. In another example, the Guan Xin II (GX II) decoction, a five drug TCMP formula widely used for the treatment of coronary heart disease, was investigated using high-performance liquid chromatography coupled with diode array detection and spectrometer of masses with evaporative electrospray (HPLC-DAD-ESI-MSn). In this study with the GX II, a total of 57 compounds, including phenolic acids, glycosides, flavonoids and alkaloids were characterized based on their mass spectra and comparison with reference standards [36].

The developed QC method proved to be able to identify standard markers of mixed drugs, a prerequisite for the safety and efficacy of these

preparations and for future pharmacokinetic studies.

2.4 Standardization in Quality Control of Herbal Mixtures

The therapeutic properties of herbal compositions must be guaranteed batch by batch and, for this, standardization is necessary. Compositions may need adjustments with the addition or removal of certain species, in order to comply with the expected effect, reduce toxicity or meet pharmacopoeia criteria [18].

Quality assurance of THP's involves the conversion of botanical materials into reproducible products, in which modern analytical techniques, seen previously, with associated traditional knowledge, are employed. In Brazil, if the THP's does not report a serious adverse reaction for thirty years in pharmacovigilance systems, safety and efficacy can be guaranteed [46]. Standardization is fundamental for the reproducibility of batches of THP's on the market.

In QC, it requires planning and documentation at all stages of the manufacturing process, before and after drugs are mixed. The entire production process must be described in a manual of good manufacturing and quality control practices (GMQCP), with the presence of reports with validated identity and purity test methods [30].

The use of poorly processed or different herbs from those alleged on the packaging makes it difficult to establish an identity standard for these mixtures in the consumer market, in addition to characterizing fraud [47].

Standardization should cover compliance with guidelines ranging from plant germination in the production chain, using Good Agricultural and Collection Practices (GACP), to GMQCP. Seeks to transform individual fresh plants into traditional products with defined identity, safety, and quality [1].

Thus, standardization in the QC of herbal mixtures must involve three well-established aspects: 1) identity - there must be only one drug; 2) purity - there must not be any other component, besides the constituents of the drug itself; and 3) content - the metabolites must be within the pre-established quantitative limits [48].

Table 2. Advantages of elementary and integrated (hyphenated) analytical techniques used in the phytochemical study of herbal mixtures

Elementary Techniques	Hyphenated techniques	Advantages
Thin Layer Chromatography (TLC)	<ul style="list-style-type: none"> ✓ TLCQA-UV (<i>software</i>MATLAB 4.2c). ✓ HPLC-MS (<i>High Performance Liquid Chromatography-Mass Spectroscopy</i>) ✓ HPLC-DAD (<i>High Performance Liquid Chromatography- Diode Array Detection</i>); 	<ul style="list-style-type: none"> ✓ Minor change in chemical constituents ✓ Simple for initial screening; ✓ Lower cost ✓ Analysis of multiplesamples (versatility) High speed and sensitivity
Liquid Chromatography(LC)	<ul style="list-style-type: none"> ✓ HPLC-NMR (<i>High Performance Liquid Chromatography-Nuclear Magnetic Resonance</i>); ✓ HPLC-ELSD (<i>High Performance Liquid Chromatography -Evaporative Light Scattering Detection</i>) 	<ul style="list-style-type: none"> ✓ Versatile; ✓ Easy to learn and use; ✓ Wide range of detectable chemical components; ✓ High sensitivity; ✓ Suitable for mixtures;
Gas Chromatography(GC)	<ul style="list-style-type: none"> ✓ CG-MS (<i>Gas Chromatography- Mass Espectroscopy</i>) 	<ul style="list-style-type: none"> ✓ Best technique for volatile compounds; ✓ Standardized extractive methods; ✓ High sensitivity to impurities ✓ Highly selective; ✓ Not suitable for polar compounds; ✓ Powerful separation technique; ✓ Wide detection range; ✓ Selective in the analysis of complex mixtures;
Capillary Electrophoresis (CE)	<ul style="list-style-type: none"> ✓ CE-DAD (<i>Capillary Electrophoresis-Diode Array Detection</i>) 	

Table 3. Modern analytical techniques used to identify chemical substances in TCMP's formulas

TCMP's formulas	Number of drugs in the composition	Number of samples analyzed	Technique used	Number of identified compounds	References
Guanjiekang (GJK)	06	03	UHPLC–QQQ–MS/MS	13	[34]
Palmul-tang (PLMT)	08	12	HPLC-DAD, LC-MS-MS	11	[35]
Guan Xin II (GX II)	05	2	HPLC-DAD-ESI-MSn	57	[36]
Xiang-Sha-Liu-Jun-Zi-Tang (XSLJZT)	10	06	HPLC–MS-ESI	06	[37]
Xiao–Xu–Ming (XXMD)	12	1	HPLC–HRMS/MTSF	68	[38]
Bansha Herbal Tea(BHT)	7	2	PS-MS	59	[39]
Gegen-Qinlian (GQD)	4	24	UHPLC-MS/MS	50	[40]
Gyeji-tang (GT)	3	1	HPLC-DAD	16	[41]
DangguiBuxue Tang (DBT)	2	6	HPLC-DAD-ELSD e LC-ESI-MS	18	[42]
Samhwangsasim-tang (SST)	3	9	UHPLC-PAD	6	[43]
Ojeok San (OJS)	17	10	RP-HPLC-PDA	19	[44]
Erzhiwan (EZW)	2	4	HPLC	6	[45]
Er-xian decoction (EXD)	6	1	HPLC-HRMS/MS	71	[29]

Among the indispensable requirements in the QC of herbal mixtures, before and after the drugs are mixed, the following stand out: detailed description of the botanical source, origin, and geographic location by GPS; harvest, collection, and processing conditions; comparison with pharmacopeia standards through identity tests (macroscopic, microscopic, FT-IR, TLC, HPLC, GC...), quali-quantitative assays of therapeutic and/or toxic substances (HPLC, UHPLC, MS, NMR...); physicochemical characterization (moisture content, extractable substances, total and insoluble ash...), purity tests (microbiological, mycotoxins, foreign matter, pesticides, toxic metals), in addition to *omic's* approaches [49].

In the case of already associated drugs, confirmation of botanical identity can be based on multiple and simultaneous analyses of metabolites through the concept of similarity of chemotaxonomic markers. This theory emerged

in Germany and has been successfully applied in the standardization of industrialized herbal medicines. In the concept of similarity, the phytochemical profile of a test product must be constructed and compared with the phytochemical profile of an authentic, clinically evaluated, or traditionally established product [24].

The use of statistical tools, such as chemometrics, can be integrated into the comparison of information present in databases, with test samples found in the consumer market [25]. In Brazil, the phytochemical profile of samples from mixtures used in the preparation of medicinal teas is required by the National Health Surveillance Agency (NHSA) in the pre-marketing of traditional herbal products (THP) [46]. In the method developed, it is necessary to detect at least one chemotaxonomic marker of individual drugs in the mixtures, as exemplified in Fig. 1.

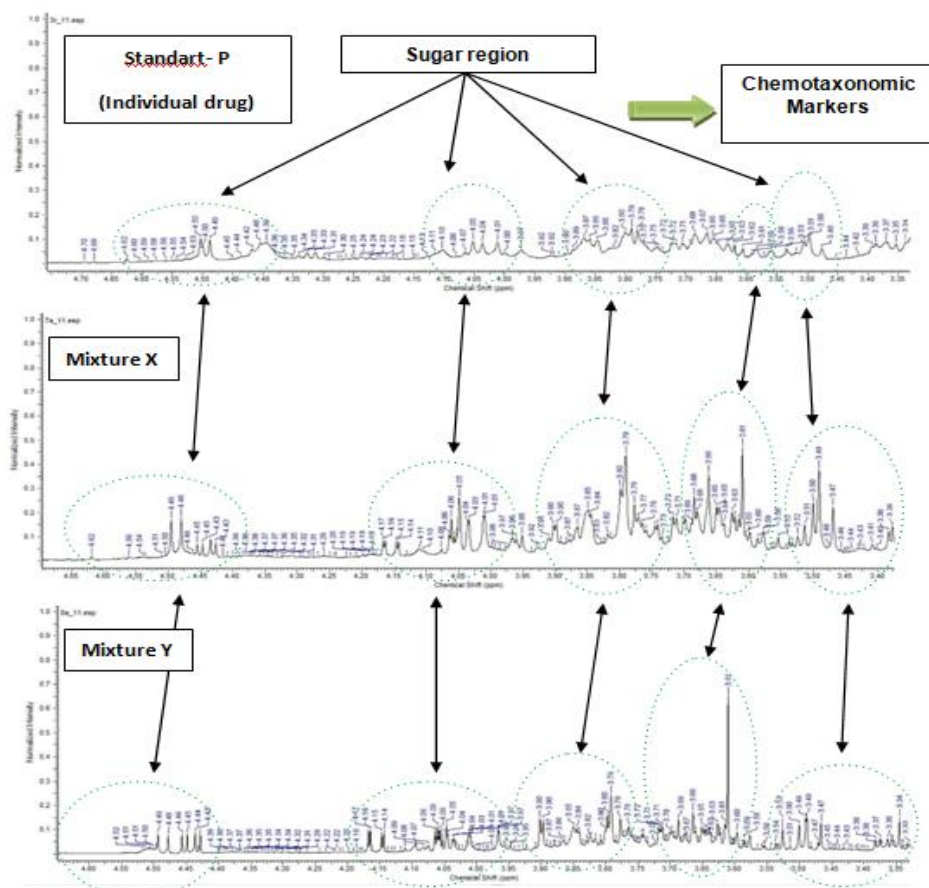


Fig. 1. The similarity of the metabolic profile of the standard- P (*Hibiscus sabdariffa* L.) and of the X and Y mixtures, in the same region ($^1\text{H-NMR}$, 500MHZ, CD_3OD , δ 3.30 - 4.70 ppm)

2.5 Holistic Quality Control: A More Sensible Approach

With current WHO recommendations for the manufacture of safe and reproducible THP's, development in QC has achieved good results using sophisticated and comprehensive analytical techniques.

Such approaches are not limited to a few markers, as the formulas act synergistically and traces of chemical substances may be responsible for the global therapeutic action of these compositions [50].

It is not possible to consider only a single technique, but a multi-technical approach combined with historical records of practical and effective use over the years. The investigation of metabolites that play a central role in mediating pharmacological effects in traditional decoctions is already being used in the holistic quality control (HQC) of these products.

Screening extracts for the detection of biomarkers in cell lines, animal models, and human volunteers are also being developed, making the investigation broader [51–53].

Omics techniques (metabolomics, proteomics, genomics), integrating high-throughput screening, systems biology, and multivariate data analysis, are preferred approaches in investigating the biochemical interaction between DNA, RNA, and protein [54].

Reductionist strategies are recommended for synthetic substances, and the choice of multiple markers and obtaining FP's with the full profile of these complex mixtures, is a more comprehensive analysis [55].

In the HQC, the factors influencing a TMP' sare considered without disregarding its chemical complexity, cultural and philosophical principles, and its practical and effective use in populations over the years.

One of the holistic methods developed in the TCMP formulas, aiming to guarantee the authenticity of the products, is the choice of quality markers or "Q-markers". The choice of these markers starts in the production chain and extends to multiple therapeutic targets in the body [56].

In a model developed at Harvard University, in the United States of America (USA), interconnected databases, known as "herbalomes", successfully contribute to regulatory authorities in China and the USA in investigating the identity and purity of TCMP's formulas [57].

In another system, characterized by eight elements in a modular format, different technologies are used in the research of MT products. Called "iVarious", it is considered a new paradigm of systematic research in QC of old products [58]. It is considered an innovative idea of technological demonstration to establish quality standards for these products.

Different strategies are based on comprehensive evaluation methods and the use of state-of-the-art tools in the modern QC of traditional products. Phytochemistry is closely related to traditional medicine and is undergoing a revolution as new technologies emerge [16].

The integration between philosophy, science, and technology with botany, systems biology, and phytochemistry, continues as a holistic strategy in evaluating the authenticity and quality of THP's, used in the preparation of medicinal teas [59].

2.6 The tea Products Market

Global consumption of products with *Camellia sinensis* (L) Kuntze (Green Tea), for example, surpassed 4.84 million tons in 2013, according to the Food and Agriculture Organization of the United Nations (FAO). The consumption of green tea products in China exceeded 8% in 2013, reaching 1.61 million tons, the highest in the world. In India, consumption expanded 2.4% in 2009 and 6.6% in 2013, reaching one million tons. In this same study, the sale of teas in the United States of America (USA) had increased by 5.9%, with annual sales of 1.7 billion dollars, mainly for products considered to be dietary [60].

In Latin America and the Caribbean, the consumption of tea products is in the order of 95 thousand tons per year. Brazil is in eighteenth place, with seven thousand tons of Green Tea consumed a year. In Brazil, another plant traditionally consumed for teas is Yerba Mate (*Ilex paraguariensis*) [8]. The state of Paraná produces, on average, two hundred thousand tons of Yerba Mate [61].

The market for tea products is growing in Brazil, with a greater focus on beverages considered dietetic and non-medicinal (phytotherapeutic) [62].

According to the Ministry of Health (MH) in Brazil, there are 2,160 Basic Health Units (BHU) that provide herbal medicines in Primary Care Programs Around: 260 UBS dispense fresh plants, 188 herbal drugs, 333 manipulated herbal medicines, and 1,647 industrialized products [63]. In another study in ANVISA (regulatory agency) databases, until September 2016, there were no records of medicinal teas reported as THP in the agency [64].

In this latest research that investigated herbal medicines registered at ANVISA, Ginkgo (*Ginkgo biloba*) and Indian Nut (*Aesculus hippocastanum*) were the most used in the industrialization of herbal medicines in Brazil. In addition, of the 12 herbal medicines listed in the current National List of Essential Medicines "RENAME" and most of the species that make up the current Brazilian Pharmacopoeia - 6th editions, the species are exotics [33,65].

The result is the need to import raw materials for the manufacture of herbal medicines, even though the country has a wide range of plants, a favorable climate, technological potential, and associated traditional knowledge.

In Brazil, relevant information about native plants was compiled by European naturalists of the 19th century, such as the French botanist Auguste de Saint-Hilaire (1779-1853) [66,67]. However, native plants lack evidence to support their safe use, persisting in informality.

2.7 Divergences in the Global Health Regulation of Herbal Products

Several meetings have been held in order to harmonize the quality control of herbal mixtures around the world. One of them is the International Conference of Medicines Regulatory Authorities (ICDRA's), organized by the WHO since the 1980s [68]. At the fifty-first meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, held in 2017, recommendations for selecting quality markers were discussed [69]. The purpose of the document was to contribute to the technical guidance and development of analysis methods for the QC of THP, in order to meet standardization requirements [33,70].

One study compared five Good Manufacturing Practice (GMP) recommendations for herbal medicines: WHO, Food and Drug Administration of China (SFDA), European Medicines Agency (EMA), United State Food and Drug Administration (USFDA), and Pharmaceutical Inspection Cooperation Scheme, from Singapore (PIC/S) [30].

In Europe, EMA harmonized criteria for marketing products based on traditional use. In the US, products made with vegetable input, but without claim of therapeutic property on the label, can be considered diet products, with less rigor in pre-marketing. In 2011, the Food Safety Modernization Act (FSMA) required the USFDA to adopt a stricter stance after adverse events occurred with herbal dietary supplements.

After the approval of the Chinese Constitution-1982, the TCMP's decoctions were initially regulated and several updates took place over time. Even with the expansion of requirements for the manufacture of THP for export purposes, the standards for traditional products had to adapt. In 2010, the SFDA differentiated decoctions for local consumption from products for export [30]. In traditional decoctions, the SFDA norms centralize their actions towards a quality final product, with less focus on production processes.

A comparative study of pharmacopoeia standards in eastern countries revealed that there is great variation in drug purity parameters, such as limits for toxic metals, pesticides, and microbial contamination. In addition, the same drug can be described with a different nomenclature, making it difficult to analyze the authenticity of these products. The Western Pacific Regional Forum for Harmonization of Herbal Medicine (FHH) attempted to standardize crude drug monographs in the pharmacopoeias of six Asian countries (Japan, China, Korea, Singapore, Vietnam, and Hong Kong)[18]. This measure aimed to contribute to the promotion of more uniform products.

Among Southeast Asian countries, India is also among the leaders in the development of guidelines and analytical methods for determining the quality of traditional products [71].

A coordinated vision of the integration of traditional knowledge requires the acceptance of paradigm shifts in Latin America. The insertion of

TM in public health in South American countries still faces challenges with regard to the sanitary regulation of products. Strategies have been recommended, such as constructive dialogue between States and traditional communities, aiming at preserving knowledge of native flora and its sustainable development [6].

2.8 Perspectives for Sanitary Regulation of THP's for Medicinal Teas in Brazilian Market

According to the Resolution of the Collegiate Board (RCB) of the National Health Surveillance Agency (NHTSA) n. 26, of May 13, 2014, medicinal tea is defined as: "*traditional herbal products consisting exclusively of isolated or associated plant drugs (more than one species), subject to health notification*" [46]. In Brazil, registering a traditional product is still an arduous and bureaucratic process, which makes it difficult to insert these resources in pharmaceutical assistance programs and in the formal herbal medicine market. Due to the greater demand for sanitary adequacy of herbal mixtures as therapeutic formulas in the Brazilian market (traditional product), many times, manufacturers decide to adapt products as diet products (as food). As a result, most products made with associated drugs are found in Brazil as a food supplement and not a traditional product, as it should. Unlike in China, where TCMP formulas for local consumption are exempt from health registration, the insertion of traditional medicine decoctions in the Brazilian market requires the registration or health notification of the products at the regulatory agency.

Several laboratory tests are required by NHTSA in the notification of AHD's for medicinal teas as THP's. Reports with quality control tests of raw materials and finished products, certificates of Good Manufacturing Practices Traditional Herbal Products (GMPTHP) are required. The GMPTHP allows: facilities, methods, processes, and quality assurance and control systems to be adequate 344 [72].

Even with the advances achieved in analytical technology and in the sanitary regulation of THP's in Brazil, it is estimated that 400 million people in Latin America practice herbal medicine informally [6]. The levels of implementation and enforcement of health standards that determine the influence of standards in each country [64,73].

Herbal medicines with simplified sanitary registration at NHTSA, for the most part, are made with imported vegetable raw material, far from preparations with native plants, used by traditional communities in Brazil. Plants used in traditional indigenous communities, caboclo-ribeirinhos, and quilombolas are not part of the main repertoire of species listed in official Brazilian monographs [74].

One of the services that can contribute to the generation of clinical evidence in the use of THP's is Pharmaceutical Care (PC). PC services bring drug users closer to a health professional, the pharmacist, contributing to the documentation of consumption through well-defined clinical protocols [4,62].

The provision of clinical services for monitoring use is also important for the dissemination of information on adverse reactions of herbal medicines in the pharmacovigilance systems, with a view to recall the products. It should also be analyzed which sanitary category the tea products are in the Brazilian market, whether dietary or medicinal, since the sanitary parameters to assess quality in the two categories are different [72].

The sanitary registration of traditional herbal products in Brazil is required because it guarantees greater quality and safety of these preparations for the Brazilian market, since the botanical identity of the drugs before being mixed is required in the notification/sanitary registration of traditional products. In addition to ensuring the authenticity of the products, the tests required for the sanitary registration of herbal mixtures as traditional herbal products in Brazil require tests to determine the stability of the drugs on the shelves, which allows for greater safety for consumers of herbal mixtures in Brazil. The company requesting registration or notification must submit a completed accelerated stability study report and accompanied by the ongoing long-term stability study of three pilot batches. Such studies allow traditional herbal products to be placed on the market with well-defined safety and quality criteria.

In THP's, a kind of leaflet accompanies the product, ensuring that information about the risks and benefits is provided to consumers. On the other hand, diet teas cannot claim therapeutic properties and are exempt from the NHTSA health registration requirement.

One of the biggest challenges in THP manufacturing is the need to import raw

materials by the herbal industries in Brazil, although the country has a valuable medicinal flora, favorable climate, traditional knowledge, and biotechnological capacity. In addition, the need of the Brazilian population for THP's with the assurance of safety, efficacy, and quality by the NHTA is also not compatible with the high rates of fires registered in its biomes in the last two years.

In 2019, the Queimadas Program of the National Institute for Space Research ("INPE") registered more than two hundred thousand fires in the Legal Amazon and in the Pantanal biome; it set a historic record, with more than eight thousand fires. In September 2020, the Amazon biome registered more than thirty-two thousand hot spots (NISR, 2020). The data demonstrate the need for a firm presence of the State in actions to preserve the biodiversity and integrity of traditional peoples.

Harmonization of sanitary parameters in products used in the preparation of teas with associated drugs, development of more comprehensive analytical methods, generation of evidence to confirm traditional use, in addition to reducing deforestation, are challenges for the consolidation of public policies for TM in Brazil.

3. CONCLUSION

A large part of the associated medicinal teas, present in the formal and informal market in Brazil, do not have a defined quality standard or are suitable as diet products (foods). There are few herbal teas blends reported as THP by ANVISA. The lack of regularized products such as medicinal teas hinders the inclusion of these resources in the Brazilian pharmaceutical assistance program, as recommended by the NMPHM and the WHO.

The absence of a defined quality profile and the lack of documentation to validate the traditional use can favor the entry of products without guaranteed safety and quality, making the practice of TM informal in Brazil. Using the example of TM in eastern countries, such as China, which serve a large part of the population with TCMP's formulas, can serve as an example for Brazil in consolidating its own public policies.

Herbal mixtures, used in the preparation of medicinal teas are already present in the history of mankind and in commerce in countless

Brazilian cities, requiring broader approaches to guarantee the quality and safety of these THP's.

Establishments that sell THP's in Brazil, for example, should keep health professionals available to the population during all hours of operation, in order to rationalize the practice of herbal medicine. The irresponsible and unaccompanied consumption of THP's such as herbal mixtures for medicinal teas cannot be credited to the practice of herbal medicine itself.

Over time, information collected in well-defined clinical pharmaceutical care protocols and consistent pharmacovigilance systems will be able to correlate the complex chemical composition of these mixtures, with evidence. Initiating the investigation of the risks and benefits inherent to the consumption of THP's, in practice, may contribute to the validation of the safe use of these old therapeutic resources in health regulatory bodies.

The development of sophisticated analytical methods for investigating the authenticity of ancient formulas, such as those used in TCMP, also contributes to a more comprehensive analysis of these mixtures. The use of botany, *omics*, and phytochemical approaches are recommended strategies for the more comprehensive HQC of these mixtures.

In addition to sanitary regulation and the HQC, the preservation of native flora and the enhancement of popular knowledge associated with the use of plants are essential for the sustainable development of the production chain of THP's 100% native. Thus, both the WHO recommendations for TM, as well as public policies for phytotherapeutic care in primary care in Brazil, can be fully consolidated.

It is concluded that this review with the different modern analytical techniques used to assess the quality of formulas from traditional Chinese pharmacology and medicine was useful to confirm the use of the fingerprint similarity concept to assess the quality of complex mixtures. Due to the large number of mixed compounds, sensitive techniques such as LC-MS proved to be one of the most used methods to assess the presence and quantity of standard chemical markers in traditional mixtures of oriental medicine.

The use of chemometric tools, such as principal component analysis (PCA), proved to be a powerful tool to hierarchically investigate the presence of pre-established chemical components in these mixtures.

Furthermore, due to the chemical complexity of complex matrices, the need to detect traces of substances responsible for the global bioactivity of these mixtures is essential for the establishment of gold standard methodologies.

Thus, holistic approaches are the most recommended to assess the quality of TCMP herbal mixtures, since it considers the chemical complexity in a comprehensive way, the theoretical foundation and the philosophical principles inserted in these practices. It is hoped with this study that comprehensive approaches can also be developed to assess the quality of traditional products, similar to those used in TCMP, in the Brazilian consumer market.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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