Phytotherapeutic drugs: prevalence, advantages, and disadvantages of use in clinical practice, profile and evaluation of users

Medicamentos fitoterápicos: prevalência, vantagens e desvantagens de uso na prática clínica e perfil e avaliação dos usuários

Clara Oliveira Esteves¹, Raquel Miguel Rodrigues², Andréia Luísa Duarte Martins³, Rayana de Almeida Vieira³, Juliana Lourenço Barbosa³, Júlia Barbosa Ferraz Vilela³

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ABSTRACT: Introduction: This study aimed at reviewing the literature on the aspects of the use of phytotherapeutic drugs, medicinal products made from the extraction of active compounds from unprocessed plants, undergoing industrial processes. Therefore, the most commonly used phytotherapeutic substances, the prevalence of this practice, the advantages and disadvantages of its use, and the profile and evaluation of Universal Health Care users were identified. Material and Methods: The bibliographic research comprised of articles published within the period from 2014 to 2018 in the SciELO and Lilacs databases. The keywords "fitoterapia" (phytotherapy) and "medicamentos fitoterápicos" (phytotherapeutic drugs) were used, three hundred and fifty-three articles were found in SciELO database, yet only twenty-one were selected for reading, and thirteen were used to write this article. In comparison, in the Lilacs database, one thousand, four hundred and ninety articles were located, forty-six selected for reading, and only eight were utilized for preparing the article. The others were eliminated based on their titles, repetition, or because they did not adhere to the inclusion criteria. Results and Discussion: Four categories were created based on the twenty-one selected articles: the most commonly used phytotherapeutic medicine, the prevalence of phytotherapy use, advantages and disadvantages of the practice, profile, and evaluation of Universal Health Care users. Conclusion: The most commonly used phytotherapeutic medicine are Guaco (Mikania glomerata), medication made of Passiflora (passion fruit), green tea, and phytotherapeutic drugs extracted from Curcuma (Turmeric). There is a low prevalence of the practice, as indicated by the majority of the studies. As a disadvantage, it is possible to mention the insufficient knowledge by health professionals and the inadequate supply of phytotherapeutic drugs by the Universal Health Care system. On the other hand, the improvement of the doctor-patient bond is a positive aspect of using phytotherapeutic medication. The user profile includes women and individuals over 50 years old, who take the majority of phytotherapeutic drugs. Further studies on phytotherapy are needed, aiming at disseminating care provision that tightens the bond between the population and its ethnic-cultural singularities.

RESUMO: Introdução: Este trabalho realizou uma revisão de literatura acerca de aspectos do uso de fitoterápicos, medicamentos compostos a partir da extração de matérias primas vegetais ativas, que passam por um processo de industrialização. Dessa forma, identificaram-se os fitoterápicos mais utilizados, a prevalência de utilização dessa prática, vantagens e desvantagens de seu uso e o perfil e avaliação de usuários do Sistema Único de Saúde. Material e Métodos: Realizou-se um levantamento bibliográfico do período de 2014 a 2018 nas bases de dados SciELO e Lilacs. Foram utilizados os descritores "fitoterapia" e "medicamentos fitoterápicos", sendo encontrados 353 artigos da base SciELO, sendo somente 21 selecionados para leitura e 13 utilizados para formar o artigo, enquanto na base de dados Lilacs 1490 artigos foram encontrados, 46 selecionados para leitura e 8 utilizados para elaborar o artigo. Os demais foram eliminados pelo título, por repetição ou por não se encaixarem nos critérios de inclusão. Resultados e Discussão: A partir dos 21 artigos selecionados, o conteúdo destes foi agrupado em quatro categorias: fitoterápicos mais utilizados, prevalência do uso da fitoterapia, vantagens e desvantagens da prática e perfil e avaliação dos usuários do Sistema Único de Saúde. Conclusão: Os fitoterápicos mais utilizados são o Guaco (Mikania glomerata), medicamentos à base de Passiflora, chá verde e fitoterápicos a base de Curcuma. A prevalência do uso é apontada como baixa pela maior parte dos estudos. Como desvantagem menciona-se o desconhecimento de profissionais de saúde e a menor oferta de medicamentos fitoterápicos pelo Sistema Único de Saúde, por outro lado, o estreitamento do vínculo médico-paciente é um aspecto positivo do uso dos fitoterápicos. Os usuários que fazem mais uso da fitoterapia são mulheres e indivíduos acima de 50 anos. São necessários mais estudos sobre a fitoterapia, buscando difundir uma produção de cuidado que se aproxime da população dentro de suas particularidades étnico-culturais.

Descritores: Fitoterapia; Medicamentos fitoterápicos.

Keywords: Phytotherapy; Phytotherapeutic drugs.

Speech Therapist and Substitute Professor in the Undergraduate Course of Medicine at the "Universidade Federal do Rio de Janeiro", Macaé
Campus. Doctoral Degree in Linguistics from the Federal University of Rio de Janeiro. ORCID: https://orcid.org/0000-0001-9979-7416. E-mail:
clarinha.esteves@gmail.com.

Physiotherapist and Assistant Professor in the Undergraduate Course of Medicine at the "Universidade Federal do Rio de Janeiro", Macaé Campus.
Doctoral Degree in Bioethics, Applied Ethics, and Collective Health from PPGBIOS at the Federal University of Rio de Janeiro, National School of Public Health, "Universidade Federal Fluminense" and "Universidade do Estado do Rio de Janeiro". ORCID: https://orcid.org/0000-0002-4593-6633. E-mail: raquelrodrigues@macae.ufrj.br.

^{6633.} E-mail: raquelrodrigues@macae.ufrj.br.

3. Graduated in Medicine from the "Universidade Federal do Rio de Janeiro", Macaé Campus. ORCID: ORCID: Martins ALD - https://orcid.org/0000-0002-1163-0900; Vieira RA - https://orcid.org/0000-0003-4950-0615; Barbosa JL - https://orcid.org/0000-0002-7754-5821; Vilela JBF - https://orcid.0000-0002-8701-2770. E-mail: duarteandreia96@gmail.com, rayanav@yahoo.com.br, lourencob.juliana@gmail.com, juliabvilela@gmail.com.

Correspondence: Raquel Miguel Rodrigues. Rua Manoel Soares da Silva, 1455, Itamambuca, Ubatuba, SP. CEP: 11680-000.

INTRODUCTION

In Brazil, the use of medicinal plants is mainly based on indigenous practices that, when associated with African and Portuguese cultures, generated a vast popular experience¹. The World Health Organization (WHO) recognizes and encourages these practices, as they make up what is called Traditional and Complementary Medicine.

According to WHO, the majority of the population from developing countries "depend on traditional medicine for their primary care, considering that 80% utilize traditional practices for their basic health care and 85% among those people use plants or preparations made from them". WHO had already warned regarding the necessity of regulating the use of medicinal plants and phytotherapy at the Alma-Ata conference in 1978, these treatmentswere based solely on empirical knowledge and popular experience until then, as mentioned.

Thus, the National Policy of Medicinal Plants and Phytotherapy, was stated in Decree # 5,813, dated June 22nd, 2006, and implemented actions capable of promoting improvements in the well-being of the Brazilian population and thereby fostering, among other results, improvement in healthcare (1). That policy complies with Primary Care as proposed by WHO, which focuses its attention on the person and not just the disease and addresses the most common problems in the community, providing prevention, treatment, and rehabilitation services, maximizing health and well-being². An Inter-ministerial Ordinance # 2,960, dated December 9th, 2008, approved the National Policy of Medicinal Plants and Phytotherapy and created the National Committee of Medicinal Plants and Phytotherapy, it grants safe and rational use of medicinal plants and phytotherapic medicine by the population, making sure it is done safely, effectively, and with quality1.

Nineteen other integrative practices have been added to the Universal Healthcare System aside from phytotherapy, as stated by the National Policy of Integrative and Complementary Practices – PNPIC (Decree GM/MS #971 and Decree #849/2017). According to Lucas Gaspar Ribeiro, who was the coordinator of the Work Group (GT) of PICS at the Brazilian Association of Medicine of Family and Community in 2018, integrative practices are recommended for preventive or curative purposes, in multiple situations, such as supportive care or primary therapies for acute or chronic clinical conditions. The presence of these practices in the Universal Healthcare System is responsible for reducing the unnecessary use of medicines and, consequently, their adverse effects and, thus, improves the resolution and effectiveness of treatments and provides increased quality of life to users. The increased demand for these services by healthcare users has also been encouraging. When considering the results; from data collected from e-SUS and Electronic Citizen Medical Records in 2016, there have been over two million Integrative Practical appointments registered in the Basic Healthcare Units (UBS), and among them, eighty-five thousand were considered phytotherapy³.

The National Essential Medicine Listing (Rename) includes a dozen phytotherapeutic drugs, originating from standardized plant species: Artichoke (Cynara scolymus L.), "Aroeira" (Mastic) (Schinus terebinthifolius Raddi); Aloe Vera (L.) Burm.f); Chitticum bark (Rhamnus purshiana D.C.); "Espinheira-santa" (Maytenus officinalis Mabb.); Guaco (Mikania glomerata Spreng.); Devil's Claw (Harpagophytum procumbens); Spearmint (Mentha x piperita L.); Soy isoflavone (Glycine max (L.) Merr.); Plantago (Plantago ovata Forssk.); Willow (Salix alba L.); Cat's claw (Uncaria tomentosa (Willd. ex Roem. & Schult)⁽⁴⁾.

Despite their effectiveness and low operating costs⁵, phytotherapy is not uniformly employed throughout the entire country. It is still quite often an unfamiliar topic for health professionals. These difficulties arise, ranging from the correct understanding of the difference between phytotherapeutic drugs and medicinal plants. These concepts are confused by the population as well as by healthcare professionals. There is disagreement by ANVISA⁶ stating that the population uses medicinal plants for therapeutic purposes, the effectiveness of which is being proven through chemical and pharmacological studies. Phytotherapeutic drugs are obtained by extracting the active materials from unprocessed plants through an industrialized process and present effectiveness based on clinical evidence⁷.

Besides that, according to ANVISA⁶, the industrialization process of phytotherapy standardizes the quality through the purification of microorganisms and foreign substances, thereby making it possible to provide enhanced safe usage.

The riches of the Brazilian plant species and biomes, associated with ethnic-cultural diversity, imply extensive usage of plants for curative purposes8. Factors, such as easy access to these plants and cultural compatibility, are extremely relevant to progress in using phytotherapeutic drugs, attributing an excellent price-performance ratio to such practices⁵. Primary care services are the leaders in prescribing phytotherapy treatments, seeking to establish ties between users and healthcare teams⁷. Thus, using phytotherapies promotes the tightening of these bonds due to respect for the users' culture and, thereby, "adding meaning to the provision of healthcare and increasing adhesion to its practices"7. That effect arises because cultural competence, one of the derivative aspects of primary healthcare, allows for the recognition of the cultural particularities of social groups, as well as an understanding of their different necessities and convictions about the health-disease process. Thereby, this facilitates the adhesion to the treatment by the user and, consequently, making increased effectiveness possible to its prescription².

Primary Care Professionals can provide specific services, varying according to place, time period, and that take into consideration variables and relationships. Furthermore, they can modulate the agency the patient will have in making decisions regarding aspects related to the treatment, avoid repetition of exams, medications, and organize prescriptions from all specialists².

However, it is necessary to emphasize that the actual institutionalization of the Integrative Practices in the Universal Healthcare System is an enormous challenge, due to the reduced number of qualified human resources, insufficient funding, and limited institutional spaces for developing new practices and services. Regardless, due to cultural as well as scientific issues, there is a barrier to the inclusion of Integrative Practices to biomedicine⁹. The purpose of this work, through a literature review, is to identify the most commonly used phytotherapeutic drugs, the prevalence of alternative practices use, investigating their advantages and disadvantages, and elucidating the profile of Universal Healthcare users and evaluating their.

MATERIAL AND METHODS

This study is based on a literature review, it searched for articles through the Scientific Electronic Library Online (SciELO) database, performed in the timeframe ranging from April 2019 to May of the same year, and, in the LILACS database, in July 2019.

Advanced research was performed in each database by inserting the keywords separately and jointly, corresponding to the classification of Health Science Keywords (DeCS), in Portuguese, as: "Medicamentos Fitoterápicos" (Phytotherapeutic Drugs) and "Fitoterapia" (Phytotherapy). The inclusion criteria for articles were as follow: they had to be written in Portuguese and must have been published in the last five years. They had to

identify the most commonly used herbal medications, the prevalence of their use as an alternative practice, stating their advantages and disadvantages, and mention the profile of the Universal Health Care System Users and their evaluation of it.

A total of three hundred and fifty-three articles were found in the SciELO database and, among those, there were seventy-seven articles that included the keyword "medicamentos fitoterápicos" (phytotherapeutic drugs), nine articles were excluded due to repetition, while two hundred and seventy-six articles were found including the keyword "fitoterapia" (phytotherapy), and six of them were excluded due to repetition. After applying the inclusion criteria, seventy-eight articles remained. Amidst those, fifty-seven were eliminated by the title, as they did not meet the inclusion criteria, four of them for having included both keywords. Out of the twenty-one selected articles, thirteen were chosen to be read and used for preparing this literary review.

A total of one thousand, four hundred, and ninety articles were found in the LILACS database, among those, four hundred and fifty-nine articles were detected through the inclusion of the keyword "medicamentos fitoterápicos" (phytotherapeutic drugs), one article was excluded due to repetition. One thousand and thirty-one articles were found by researching the keyword "fitoterapia" (phytotherapy), out of which four were excluded due to repetition. Afterwards, with the inclusion criteria, three hundred and forty-five articles were focused on. Among those, two hundred and ninety-nine were eliminated due to their title, as they did not meet the inclusion criteria, and, in the midst of these, eleven included both keywords. Amid the forty-six lingering eligible articles, eight already were in the SCIELO database, thus they were excluded. Among the thirty-eight remaining articles, eight were picked for reading and used for preparing this literary review.

The selected articles from the two databases encompass bibliographic reviews and original articles.

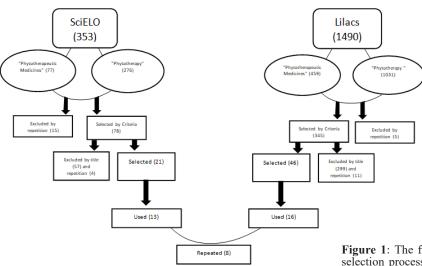


Figure 1: The flowchart describes the article selection process applied to this bibliographic review

RESULTS AND DISCUSSION

The purpose of this study was to present and discuss findings in literature regarding the use of phytotherapeutic

drugs through the analysis of original studies. The articles were read, carefully selected, and described in this context, according to Table 1.

Table 1: The listing of the selected articles based on their names, authors, publication magazine, article title, publication year

Authors	Title/Year	Findings	Conclusion
Mattoset al. ¹⁰	Medicinal plants and phytotherapeutic drugs in Primary Health Care: perception of professionals. 2018	96.2% of professionals believe in the medicinal effect of plants and phytotherapeutic drugs with allopathic medications. 70.7% of professionals report the population displays an interest in this practice. Nine out of twelve plants or herbal medicines (75%) are known by less than half (41.4%) of health professionals.	The city of Blumenau did not implement the National Policy entirely. Professionals agree with the Ministry of Health's initiave, they believe in the therapeutic effect of plants; however, they do not prescribe them due to lack of knowledge.
Caccia-Bava et al. ⁷	Availability of phytotherapeutic drugs and medicinal plants at the São Paulo State primary care units: results from the National Program of Improved Access and Basic Care Quality (PMAQ). 2017	11% of the São Paulo State Healthcare units provide phytotherapeutic drugs and medicinal plants. Marilia city is noteworthy, in which fortyfour out of forty-five healthcare units provide them; Campinas provides them at 65.1% of the units and Sorocaba, 50%. Guaco is the most commonly used medication. 12% of the interviewed professionals certify that their team holds health educational activities focusing on the use of medicinal plants and herbal medicines.	It has been proven that phytotherapy is present in cities well-rated in human development indicators. The increase in scientific publications optimistic about these medications was emphasized, in counterpart to detrimental essays regarding the use of industrialized medications instead of manipulated medications or herbal drugs.
Machado et al. ¹³	Research and extension activities in phytotherapy performed by the "Rede FitoCerrado" (FitoCerrado Network): the rational use of medicinal plants and herbal medications by the elderly in Uberlândia-MG. 2014	Ginkgo biloba and Aesculus hippocastanum (horse chestnut) are mentioned as the most commonly used herbal medications. 5.5% of those interviewed took herbal medications, and 76.7% reported on taking some medicinal plants. 60.7% of the elderly declared that they did not inform the doctor of using medicinal plants and herbal medications.	The importance of performing extension activities for improving the usage of phytotherapy among the elderly and also for making scientific knowledge available to the population.
Varela; Azevedo ¹¹	Knowledge of herbal medicine and its practice by doctors in the family healthcare strategy. 2014	It emphasizes the use of phytotherapeutic drugs by professionals who did not have access to these subjects in college, but they prescribe them based on their clinical experience. As follows: (1) anxiolytics and sedatives: Remilev, Calman, Floriny, and Passiflorine, Ansiopax; (2) Ginseng for anxiety and insomnia; (3) female demographic: Mencirax, isoflavone, and Promensil; (4) Kronel, with antimicrobial, anti- inflammatory, and healing activities.	The article demonstrated that the majority of interviewed doctors were familiar with herbal medications and recommended them to ESF users from Caicó. Despite the lack of instruction regarding this type of medication in the training of professionals, they are receptive to herbal medication practices in ESF.
Nascimento Júnior et al. ¹²	Evaluation of the knowledge and perception of professionals from family healthcare strategy about the use of medicinal plants and phytotherapy in Petrolina-PE, Brazil. 2016	66.7% of the 96 graduated professionals did not know the difference between phytotherapeutic and homeopathic medicines. Despite that, 36.5% confirmed that they prescribe them; the majority of doctors are between 31 and 40 years old. 67% of these professionals were not taught during their training how to these medications. Guaco (Mikania glomerata S.), Maracugina, (Passiflora alata A., Erythrina mulungu M., and Crataegus oxyacantha L.) and Tensart (Passiflora incarnata L.) were the most commonly cited.	Training and motivation are necessary, so that healthcare professionals become able to prescribe Medicinal Plants and Phytotherapeutic drugs. It is essential to include subjects such as Phytotherapy in their curriculum, in order to cover this subject and prepare professionals, as well as promoting periodic update courses.
Borcard et al. ¹⁷	Ethnopharmacological study regarding the urban forest as a subsidy for the implementation of Phytotherapy in the Universal Healthcare System. 2015	80% of the interviewed parties classify their interest level in learning more about PNPIC, PEPIC, and Phytotherapy ranging from 8 to10. One hundred and two residents were also interviewed, 47% of them confirmed that they use PM/Phytotherapy; and they did not inform the doctor of their use. 32 Local Specialists were interviewed, 95% of them shared their knowledge with others, mainly with neighbors and family members.	There is little knowledge of PM/ Phytotherapy and its policies in PHCS (primary healthcare services), as self- teaching is the most common mean for obtaining this type of knowledge. The importance of this knowledge and its perpetuation into future generantions is evident to local specialists.
Feitosa et al. ²¹	Phytotherapy Subject Matter in the Field of Healthcare Courses. 2016	70.8% of the interviewed students are in favor of adding medicinal plants and phytotherapy subjects to their undergraduate medicine course. The majority (81.3%) of the students confirmed they were unfamiliar with PNPIC.	Even though they were unfamiliar with the integrative regulatory practices, most displayed self-taught interest on the subject.

Table 1: The listing of the selected articles based on their names, authors, publication magazine, article title, publication year

Continuation

Authors	Title/Year	Findings	Conclusion
Oliveira; Lucena ¹⁸	Usage of medicinal plants by the residents of Quixadá–Ceará. 2015	57.41% report that they use medicinal plants, among those people, 93.37% drink tea as a medication, and 6.63% use it as food. The age bracket ranging from 51 to 60 years old knows more information on medicinal plants. 97% are unfamiliar with the toxicity risks from prolonged use of some medicinal plants, such as "boldo."	Residents in Quixadá-Ceará frequently use medicinal plants. Tea is mainly drunk by women and it is done for healing purposes and disease prevention. The population is unaware as to the usage and dosages.
Soares et al. ²²	Pharmacological evaluation and assessment of the labeling of "boldo" plant drugs (<i>Peumus boldus</i> Molina) and chamomile (<i>Matricaria recutita</i> L.) for sale in Fortaleza, CE. 2015	35.7% of the samples of "boldo" tea and 57.7% of the samples of chamomile exceeded the maximum concentration of foreign material; 100% of the "boldo" samples and 96.6% of chamomile presented errors or missing information on the labels.	It is necessary to improve inspection and intervention in the production and sale of these products to adhere to current applicable standards.
Dias et al. ²³	Using herbal medications based on "aroeira" (mastic) as an assistant in the treatment of gingivitis: Systematic Review. 2015	Five reviews related to the use of herbal medications on the treatment of oral lesions confirm the applicability of "aroeira" (mastic) against gingivitis, except 1), one randomized clinical study, one experimental study, and one descriptive observational study.	"Aroeira" (mastic) was concluded as displaying antifungal and antimicrobial activities and reduction of gum bleeding rates.
Kuba; Vattimo ²⁴	Using oriental herbal medications in renal lesions: integrative review. 2015	It performed a bibliographic review on the evaluation of 12 studies, 11 of those reported on herbal medications effectiveness in either preventing or improving renal lesions.	It is necessary to know the risks, interactions, toxicity, active mechanisms, and adverse effects of these medications.
Piriz et al. ²⁵	Medicinal plants in the healing process of wounds: a literature review. 2014	It performed a bibliographic review on 57 selected articles. It identified a total of 52 medicinal plants and an herbal mixture that were studied experimentally or clinically on its auxiliary effects in the healing process, confirming that the majority (88.5%) displayed efficacy.	The utilization of medicinal plants considers an important alternative in the treatment of wounds, showing the need for performing further studies and updating the subject.
Figueredo et al. ²⁷	The National Policy on Medicinal Plants and Herbal Medications: construction, perspectives, and challenges. 2014	Based on the performed analysis, it was noticed that the implementation of the National Policy on Medicinal Plants and Herbal Medications made little progress regarding the hindrances to its use in SUS (Universal Health Care system), due to the insufficient knowledge of the healthcare professionals.	Despite the challenges, it focused on the Policy, as it is important for providing means of complementary treatment, which is accessible and favors public engagement.
David; Bello ¹⁴	Prescription of herbal medication by nutritionists in compounding pharmacies. 2017	Camellia sinensis was the most commonly used, due to its main purpose of controlling weight. Its anti-obesity effect consists of a decrease in adipose tissue, since it reduces adipocytes.	Due to the recent regulation for nutritional health professionals, it is important to identify their preferences on the selection of herbal medication.
Marques et al. ¹⁵	Characterization of medicinal plants and phytotherapeutic drugs for the treatment of osteoporosis used in Brazil. 2016	The article mentions Glycine max (Soybeans), Trifolium pratense (Red clover), Cimicifuga racemosa (Black cohosh), and Curcuma longa (Turmeric) as alternatives in the treatment of osteoporosis in Brazil.	Phytotherapeutic Drugs are presented as alternative medications.
Sousa; Tesser ¹⁶	Traditional and Complementary Medicine in Brazil: insertion in the Universal Healthcare System and integration with primary care. 2017	Traditional and Complementary Medicine can be inserted in two or more factors of the network, focusing its supply in primary care, and most of that supply should be performed through the Universal Healthcare System.	The suggestion of expanding traditional and Complementary Medicine in SUS (Universal Healthcare System) so as to not waste preexisting experiences.
Araújo et al. ²⁰	Difficulties faced by nurses in the applicability of herbal medications in primary healthcare: an integrative review. 2015	Absence of planning, insufficient skills of healthcare professionals, and non-valorization by the administration and the respective healthcare team.	Increased investment by administrators in implementing integrative and complementary practices, as well as in the preparatory process.
Darroz et al. ²⁶	Utilization of herbal medications in the treatment of intestinal constipation. 2014	Psyllium Mill, a laxative that increases the stool bulk, castor oil, and anthraquinone compounds as secretagogic laxatives; were cited. They include Aloe vera, Chitticum bark (Rhamnus purshiana), Chinese rhubarb (Rheum palmatum), and Alexandrian senna (Cássia angustifolia).	There are awareness programs for discussing adverse effects from taking laxatives and the need for changes in diet and lifestyle.
Sá et al. ¹⁹	Evaluating the impact on the Brazilian policy of medicinal plants and phytotherapeutic compounds in healthcare college education. 2018	The PNPMF depends on intrinsic and extrinsic factors regarding education in order to achieve the expected results. There has been little impact on healthcare college curriculums in Ceará State. Except for what has been done in pharmacy courses.	It is essential to improve instruction on phytotherapy in college teaching, as well as other integrative practices.

The selected articles were arranged in four categories, based on the content analysis and the purpose of the discussion: A) Most commonly used phytotherapeutic substances; B) Determination of prevalence of phytotheray usage; C) Advantages and disadvantages of using phytotherapeutic medication; D) The profile and evaluation of users in the Universal Healthcare System regarding the usage of phytotherapeutic drugs. The following topics will discuss such categories.

Most commonly used phytotherapeutic substances

The Universal Healthcare System started to implement phytotherapy in 2006, when the Ministry of Health launched the National Policy of Integrative and Complementary Practices (PNPIC)¹⁰, studies regarding the use of this practice became more frequent, making it possible to make comparisons.

The first analyzed article⁷ evaluated the availability of phytotherapeutic drugs in primary healthcare units in the state of São Paulo, "recommending Guaco (Mikania glomerata) traditionally broadly presented due to its expectorant and bronchodilator actions".

One study¹¹ carried out in the family healthcare strategy framework in Caicó, in Rio Grande do Norte state, focused on the proven anxiolytic and sedative activity, such as Remilev, made of valerian (*Valeriana officinalis*); Calman, Floriny, and Passiflorine, prepared with "passiflora" (passion fruit) (*Passiflora incarnata*); Ansiopax, extracted from kava kava (*Piper methysticum*); Ginseng (*Panax ginseng C. A. Mey.*), used in treating anxiety and insomnia.

Varela and Azevedo¹¹ also identified the use of phytotherapeutic medicine targeted to a female demographic, as Mencirax, made from a dry extract of "cimicifuga" (black cohosh) (*Cimicifuga racemosa L.*); Kronel, prepared from "aroeira" (mastic) (*Schinus terebinthifolius Raddi*), which provides antimicrobial, anti-inflammatory, and healing properties; isoflavone, eases vasomotor symptoms, caused by menopause, and Promensil, prepared with red clover (*Trifolium pratense*), however, it provides questionable efficacy, as it does not promote significant improvement of menopausal symptoms; and tibolone.

There was another research study¹² performed on the family healthcare strategy in Petrolina-PE, the medications cited in the interviews were: Guaco® (Mikania glomerata S.) (4 mentions); Maracugina® (made from passion fruit) (*Passiflora alata A., Erythrina mulungu M. and Crataegus oxyacantha L.*) (2 mentions); Tensart® (Passion Fruit) (*Passiflora incarnata L.*) (2 mentions)¹², thus, these are in agreement with the other analyzed articles. And finally, a study¹³ performed in Uberlândia-MG, focused on *Ginkgo biloba* and *Aesculus hippocastanum*, as the most commonly used Phytotherapeutics.

Green tea, Camellia sinensis, according to one of

the research essays¹⁴ is primarily prescribed by nutritionists to promote weight loss. The literature¹⁵ also mentions phytotherapeutic drugs made of *Curcuma* (Turmeric) due to its bone protective properties, presenting as an alternative treatment for osteoporosis.

Prevalence of phytotherapeutics usage

Around 25% of Brazilian cities, in 2008, offered some approaches among Traditional and Complementary medicines, based on the context and local needs¹⁶. In 2014, only 16.1% primary healthcare units in São Paulo state offered these drugs, as evidenced by a research study¹³ performed on 292 elderly people who were over 60 years old and were enrolled in Physical and Recreational programs for the Elderly in Uberlândia-MG. It confirmed that 5.5% of the interviewed participants used phytotherapeutic drugs, while the majority of the interviewed did not know that term. Conversely, 76.7% reported that they used some medicinal plants.

Patients commonly use medicinal plants, yet they do not report it to their doctors, as confirmed in one study¹⁷ performed among the 102 users of the Primary Healthcare Unit in Juiz de Fora (MG), whereas 47% confirmed that they did not report this fact. Medicinal plants are lower priced when compared to phytotherapeutic and allopathic drugs. Also, they are associated with traditions and public knowledge, as evidenced in the same study (18) that interviewed 32 local specialists in that same region. 95% of these people confirmed that they shared their knowledge with others, especially family members and neighbors.

In the study, as mentioned earlier¹⁷ in Juiz de Fora (MG), 142 healthcare professionals were interviewed, and none of them knew how to define the term phytotherapy. 58.4% were self-taught on their knowledge about the subject, and only 13% confirmed to have obtained that knowledge in university¹⁷. One study¹² on 96 bachelors in Family Healthcare Strategy in Petrolina-PE confirmed that 66.7% did not know the difference between phytotherapeutic and homeopathic medications and, despite that, 36.5% confirmed that they prescribed these drugs. The majority of these doctors were aged between 31 and 40. While in a similar research study¹⁰ performed from 2014 to 2015 in Blumenau-SC, analyzing 157 Family Healthcare professionals in the city, 85.4% of them did not know about the presence of phytotherapeutic medicine listed on the National Listing of Essential Medications and, despite this, 84.7% had already previously prescribed them to their patients.

In Caicó (RN), there was a research study¹¹ performed in 2011, including nine doctors that suggested that they had little knowledge of phitotherapy and had little instruction on this subject in their undergraduate course. But, contrary to other studies, the professionals, despite not having technical preparation, confirmed that they were

knowledgeable on specific drugs due to the many years they had practiced medicine and their experiences, and they reported that they had prescribed them to their patients, especially anxiolytic/sedative phytotherapeutic drugs to substitute benzodiazepines

Regarding the prevalence of phythotherapy related knowledge by healthcare professionals, the southeast region presents the largest number of specialists in phytotherapy (42%), probably due to the higher concentration of healthcare professionals in these big healthcare centers. There are 20% in the northeast region, followed by 15% in the southern region, then 13% in the central-western, and, finally, 10% in the northern region¹⁹.

Almost all the studies indicated that the majority of the components of either group — healthcare professional and users — use,or have already used, some medicinal plants, mainly as teas. Regardless, they do not recommend the use of phytotherapy for various treatments.

Advantages and disadvantages of using phytotherapeutic medicine

Based on the analysis of the first article¹⁰, a detrimental outlook was placed on the outlook of users regarding medicinal plants, as they do not consider they might have any harmful effects since they are natural, leading to the user not informing the doctor of such use. Yet, medication interactions may occur with allopathic drugs, as well as other toxic effects to the organism when used in excess^{13,18}. Unfamiliarity is also stressed¹⁰, regarding the interviewed professionals on plants listed in RENAME, thereby hindering their prescription. However, the study^{10,} besides revealing that professionals believe in the practice and confirm their utilization by the local population, some medicinal plants have been emphasized, as they have already gone through all the research study steps and, thereby, they are considered sufficiently effective to be part of the medication arsenal of healthcare professionals. Additionally, the phytotherapeutic practice allows for the population to be in contact with its history, recovering traditional and cultural habits.

An increase in scientific publications on phytotherapy has been noted since 2003, through analyzing a study⁷ on the availability of phytotherapeutic drugs in primary healthcare in São Paulo State, especially on their insertion in primary healthcare, fostered by the regulatory approval of the practice in Brazil and after publications from PNPIC and PNPMF. The article⁷ emphasizes the importance of using phytotherapeutic drugs in primary healthcare in the cities of São Paulo, evolving from the main factor of the existence of municipal laws assuring that these programs remain independent from changes in political administrations, as states law # 13,888 dated July 19, 2010, authorizing the implementation of the Phytotherapeutic Municipal Program in the Public Healthcare Network in the city of Campinas

and law # 14,903, dated February 6, 2009, on the creation of the Phytotherapeutic and Herbal Medicine Program in São Paulo City. In counterpart, research study⁷ negatively emphasizes the use of industrialized phytotherapeutic medicine instead of compounded ones or herbal drug medications, displaying the need for this segment of the Brazilian industry so that the use of these medications is not negatively impacted due to their absence on the market.

According to the research study ¹³ on the Fitocerrado network on phytotherapeutic medicine, the mistakes in the preparation and identification of herbal species and excessive use might impose hazards, causing an overdose, absence of efficacy, undesirable effects; that can compromise the user's health. Problems, such as the absence of dialogue among Universities publishing scientifically about the subject and the population, propagating empirical knowledge, such as therapeutic recommendations, toxicity, contraindications, and possible interactions; are also emphasized in the article¹².

The study analysis ¹¹ on phytotherapeutic knowledge and practices among doctors in primary healthcare stated that this practice is beneficial to the economy, as around US\$22 billion are transacted annually by the world-wide phytotherapeutic market, and Brazil is abundant in a great diversity of plants used as medication precursors, showing its great potential in this market. The preference of professionals is furthermore positively reinforced while prescribing phytotherapeutic medicine in cases of insomnia and anxiety, which are considered as adequate, instead of using benzodiazepines and even associated with antihypertensive drugs for preventing anxiety, as sometimes it is associated to this condition.

However, this research study¹¹ also states disadvantages as undergraduate medical courses fails to introduce the budding doctor to integrative practices, and, thereby, causes a low degree of adhesion of the professional to this therapy alternative. Associated to that, family members and friends become the source of information on phytotherapy, that can bring about various harmful effects, since there is not any medical basis, instead of getting that information from a healthcare professional.

Araújo et al.²⁰ pointed out that nurses find it challenging to apply Phytotherapy in Primary Healthcare and that contributes to those negative aspects, being that the main hindrances encountered are: the absence of planning in the implementation of these and other integrative practices in primary healthcare: the lack of professional healthcare training and the recognition by the administration and the respective healthcare team²⁰.

In counterpart, there is a research study²¹ on the insertion of phytotherapeutic contents in the segment of healthcare courses, focused on interviewing students from medical, nursing, and dentistry courses, which are favorable to the addition of course contents about phytotherapy in the undergraduate curriculum, even though they do not

entirely know the efficacy and the recommendations of this practice. This way, a professional can be expected to be more assured of acting in the Universal Healthcare System, thereby preserving the right of the users to choose alternative treatments.

The negative aspects of the practice are stated in the article²² on the pharmacological evaluation and phytotherapeutic labeling, emphasizing the presence of dirt and foreign organic matter in evaluated samples exceeding the acceptable limit and errors on the labels, such as the absence of the scientific names of the botanical species, batch identification, and preparation manner, among other items. It is necessary to employ stricter surveillance in controlling Phytotherapeutics to assure the quality and desired effect in the health of the consumer.

There is a positive emphasis on using phytotherapeutic medicine in specific bodily processes that were observed throughout the analyses. The antimicrobial property of aroeira (mastic) extract²³ is proven to show promising results in controlling microorganisms related to oral pathologies²³ that justify its use in the treatment of gingivitis. Similarly, the relevance of phytotherapy in renal alterations²⁴ is emphasized, mainly by acting in changing the nephrite genetic expression, modulation of the renal system - renal angiotensin, antioxidant effects, and modulation in the production of nitric oxide²⁴. Likewise, the benefit is emphasized in "the aqueous extract of Stryphnodendron adstringens (Mart.) Coville, which is traditionally used in Brazil for its healing properties"²⁵.

This study¹⁵ on phytotherapeutic medicine used primarily in the treatment of osteoporosis in young women, reveals the benefits of medications such as isoflavone, or even phytotherapeutic drugs made of turmeric to "avoid major deterioration of the osseous structures and produce beneficial changes in osseous remodeling"¹⁵, and diminishing osteoclastogenesis. Another study²⁶ stresses the advantage of using phytotherapy in the treatment of intestinal constipation, emphasizing medications distilled from Senna, Chinese rhubarb, and Chitticum bark that act as laxatives, as well as castor oil and derivatives of aloe vera.

One study²⁷ on the construction, perspective, and challenges of PNPMF also expresses the benefits from the use of medicinal plants and phytotherapeutic medicine as they can be used in the manufacturing of industrialized medications, compounded medication, or by using plants, through homemade preparations²⁷. The article²⁷ states that phytotherapeutic substances from eleven plants are included in the list of pharmaceutical treatment medications in primary healthcare, and it identifies funding as one of the hindrances in obtaining access to the practice. The authors report that the Universal Healthcare System is inserted in a model that uses synthetic medication, and the implementation of a new dynamic would imply new costs. Even though phytotherapy is a low-cost

treatment, its structuring would incur investments in professional qualification, setting up phytotherapeutic drug manipulation, and the supply of precursor materials.

The profile and evaluation of users of the Universal Healthcare System regarding the use of phytotherapeutic medicine

Although there is a limitation in the field of research and there is no data on the subject on a national level, it is possible to find a public standard regarding the use of phytotherapeutic medicine. However, there is a greater prevalence of use among women and individuals over 50 years of age. According to a study¹³ performed in Uberlândia (MG), the main contributing factors for the increased use among the elderly include low cost; easy access, difficult access to medications in healthcare services; fewer adverse effects when compared to conventional medicines; cultural tradition, and preference for natural products¹³.

Regarding the evaluation of the practice by users who were interviewed for the study²⁸ in the Universal Healthcare System, they confirmed that the pharmacological action from synthetic medications is quicker than medicines made from plants, especially as they are "*stronger*," they also believe that they are more effective in more severe cases. In counterpart, even though phytotherapeutic drugs are slower acting, they are gentler. On the other hand, in a study²⁹ performed in Palmares (RJ), 98% of those interviewed were unaware of the concept of phytotherapy and the possibility of this type of treatment in the Universal Healthcare System. Thus, despite the expansion of the practice, it is possible to infer that the users also need to be better informed regarding this subject.

CONCLUSION

According to the evaluated profile and methodology of the study, it is possible to establish Guaco (Mikania glomerata) and phytotherapeutic medicine made of Passiflora (passion fruit) as the most commonly used plant based treatments; the former, due to its bronchodilator and expectorant action and the latter for its anxiolytic properties. The literature also mentions green tea, Camellia sinensis, which is prescribed by nutritionists for promoting weight loss, and phytotherapeutic substances distilled from Turmeric, due to its osseous protective effect.

Regarding the prevalence of phythotherapy related knowledge by healthcare professionals, the southeast region has displayed a more significant number of specialists in phytotherapy (42%), probably due to the higher concentration of health professionals in large city centers. However, in the general, the studies have pointed out unawareness by users and health professionals regarding phytotherapy, and related to that is the fact that the Universal Healthcare System offers a smaller quantity

of phytotherapeutic drugs compared to allopathic drugs. In counterpart, the tightening of the bond with the patient, related to their cultural roots and family members, is emphasized as a positive aspect in taking Phytotherapeutics. The user profile taking phytotherapy includes women and individuals over 50 years of age. Users declared that they prefer taking phytotherapeutic medicine in less severe situations, as they believe their actions are slower and

gentler. However, the literature states that the greatest majority of users are unaware of the possibilities of using phytotherapy. Thus, it emphasizes the necessity for fostering more studies on the practice, seeking to expand knowledge, and encouraging alternative forms of careful production, so that it adjoins the population within its ethnic-cultural peculiarities.

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REFERENCES

- Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos Departamento de Assistência Farmacêutica. Política Nacional de Plantas Medicinais e Fitoterápicos [citado 02 jul. 2019]. Disponível em: http://bvsms.saude.gov.br/bvs/publicacoes/politica_ nacional fitoterapicos.pdf.
- Starfield B. Atenção primária equilíbrio entre necessidades de saúde serviços e tecnologia. Brasília: Unesco/Ministério da Saúde; 2002. Disponível em: https://www.nescon. medicina.ufmg.br/biblioteca/imagem/0253.pdf.
- Ribeiro GL, organizador. SBMFC entrevista Lucas Gaspar Ribeiro: Vamos falar sobre PICS? Rio de Janeiro, 26 jan. 2018. Disponível em: https://www.sbmfc.org.br/noticias/ sbmfc-entrevista-lucas-gaspar-ribeiro-vamos-falar-sobrepics/.
- Brasil. Ministério da Saúde. Relação Nacional de Medicamentos Essenciais - Rename [citado 25 jul. 2019]. Disponível em: https://www.conass.org.br/wp-content/ uploads/2018/11/RENAME-2018.pdf.
- Santos RL, Guimaraes GP, Nobre MSC, Portela AS. Análise sobre a fitoterapia como prática integrativa no Sistema Único de Saúde. Rev Bras Plantas Med (Botucatu). 2011;13(4):486-91. http://dx.doi.org/10.1590/S1516-05722011000400014.
- Brasil. Ministério da Saúde. Agência Nacional de Vigilância Sanitária (ANVISA). Fitoterápicos [citado 02 jul. 2019]. Disponível em: http://portal.anvisa.gov.br/fitoterapicos.
- 7. Caccia-Bava MCG, Bertoni BW, Pereira AMS, Martinez EZ. Disponibilidade de medicamentos fitoterápicos e plantas medicinais nas unidades de atenção básica do Estado de São Paulo: resultados do Programa Nacional de Melhoria do Acesso e da Qualidade da Atenção Básica (PMAQ). Ciên Saúde Coletiva (Rio de Janeiro). 2017;22(5):1651-9. doi: http://dx.doi.org/10.1590/1413-81232017225.16722015.
- 8. Pereira JBA, Rodrigues MM, Morais IR, Vieira CRS, Sampaio JPM, Moura MG, et al. O papel terapêutico do Programa Farmácia Viva e das plantas medicinais. Rev

- Bras Plantas Med (Botucatu). 2015;17(4):560-1. doi: http://dx.doi.org/10.1590/1983-084X/14 008.
- Tesser CD. Práticas integrativas e complementares e racionalidades médicas no SUS e na Atenção Primária à Saúde: possibilidades estratégicas de expansão. J Manag Primary Health Care. 2017;8(2):216-32. doi: https://doi. org/10.14295/jmphc.v8i2.528.
- Mattos G, Camargo A, Souza CA, Zeni ALB. Plantas medicinais e fitoterápicos na Atenção Primária em Saúde: percepção dos profissionais. Ciên Saúde Coletiva (Rio de Janeiro). 2018;23(11):3735-44. doi: http://dx.doi. org/10.1590/1413-812320182311.23572016.
- Varela S, Azevedo MD. Saberes e práticas fitoterápicas de médicos na estratégia saúde da família. Trab Educ Saúde (Rio de Janeiro). 2014;12(2):273-90. doi: http://dx.doi. org/10.1590/S1981-77462014000200004.
- 12. Nascimento Júnior BJ, Tínel LO, Silva ES. Avaliação do conhecimento e percepção dos profissionais da estratégia de saúde da família sobre o uso de plantas medicinais e fitoterapia em Petrolina-PE, Brasil. Rev Bras Plantas Med (Botucatu). 2016;18(1):57-66. doi: http://dx.doi.org/10.1590/1983-084X/15 031.
- Machado HL, Moura VL, Gouveia NM, Costa GA, Espindola FS, Botelho FV. Pesquisa e atividades de extensão em fitoterapia desenvolvidas pela Rede FitoCerrado: uso racional de plantas medicinais e fitoterápicos por idosos em Uberlândia-MG. Rev Bras Plantas Med (Botucatu). 2014;16(3):527-33. doi: http://dx.doi.org/10.1590/1983-084X/13 072.
- 14. David RB, Bello GB. Prescrição de fitoterapia por nutricionistas em farmácias magistrais. BRASPEN (São Paulo). 2017;32(3):288-92. Disponível em: http://pesquisa.bvsalud.org/portal/resource/pt/biblio-906071.
- 15. Marques MAA, Lima DA, Andreotti CE, Gasparotto Junior RA, Lourenço ELB. Caracterização das plantas medicinais e medicamentos fitoterápicos para tratamento da osteoporose utilizados no Brasil. Arq Ciên Saúde UNIPAR (Umuarama). 2016; 20(3):183-8. doi: https://doi.org/10.25110/arqsaude. v20i3.2016.5870.

- 16. Sousa IMC, Tesser CD. Medicina Tradicional e Complementar no Brasil: Inserção no Sistema Único de Saúde e integração com a atenção primária. Cad Saúde Pública (Recife). 2017;33(1):1-15. doi: http://dx.doi. org/10.1590/0102-311x00150215.
- 17. Borcard GG, Conde BE, Alves MJM, Chedier LM, Pimenta DS. Estudo etnofarmacológico em entorno de floresta urbana como subsídio para a implantação da Fitoterapia no Sistema Único de Saúde. Rev Bras Plantas Med (Botucatu). 2015;17(4):928-36. doi: http://dx.doi.org/10.1590/1983-084X/14 117.
- Oliveira DMS, Lucena EMP. O uso de plantas medicinais por moradores de Quixadá-Ceará. Rev Bras Plantas Med (Botucatu). 2015;17(3):407-12. doi: http://dx.doi. org/10.1590/1983-084X/13 095.
- 19. Sá KM, Lima AS, Bandeira MAM, Andriola WB, Nojosa RT. Avaliando o impacto da política brasileira de plantas medicinais e fitoterápicos na formação superior da área de saúde. Rev Ibero-Americana Estud Educ (Araraquara). 2018;13(3):1106-31. doi: https://doi.org/10.21723/riaee. v13.n3.2018.11160.
- Araújo AKL, Filho ACAA, Ibiapina LG, Nery IS, Rocha SS. Dificuldades enfrentadas por enfermeiros na aplicabilidade da fitoterapia na atenção básica: uma revisão integrativa. Rev Online Pesq Cuidado Fundamental (Rio de Janeiro). 2015;7(3):2826-34. doi: http://doi.org/10.9789/2175-5361.2015.v7i3.2826-2834.
- Feitosa MHA, Soares LL, Borges GA, Andrade MM, Costa SDM. Inserção do Conteúdo Fitoterapia em Cursos da Área de Saúde. Rev Bras Educ Med (Rio de Janeiro). 2016;40(2):197-203. doi: http://dx.doi.org/10.1590/1981-52712015v40n2e03092014.
- Soares FP, Freire NM, Souza TR. Avaliação farmacognostica e da rotulagem das drogas vegetais boldo-do-chile (Peumus boldus Molina) e camomila (Matricaria recutita L.) comercializadas em Fortaleza, CE. Rev Bras Plantas Med (Botucatu). 2015;17(3):468-72. doi: https://dx.doi. org/10.1590/1983-084X/10 115.

- 23. Dias JN, Silva MPCF, Lima IPC. O uso de fitoterápicos à base de aroeira como coadjuvante no tratamento da gengivite: Revisão Sistemática. Rev Bras Plantas Med (Botucatu). 2015;17(4):1187-91. doi: http://dx.doi. org/10.1590/1983-084x/14 164.
- 24. Kuba G, Vattimo MFF. O uso de fitoterápicos orientais nas lesões renais: revisão integrativa. Rev Bras Plantas Med (Botucatu). 2015;17(4):1192-8. doi: http://dx.doi.org/10.1590/1983-084x/14 149.
- Piriz MA, Lima CAB, Jardim VRM, Mesquita MK, Souza ADC, Heck RM. Plantas medicinais no processo de cicatrização de feridas: uma revisão de literatura. Rev Bras Plantas Med (Botucatu). 2014;16(3):628-36. doi: http:// dx.doi.org/10.1590/1983-084X/12 178.
- Darroz JV, Fuso LC, Borges NM, Gomes AJPS. Utilização de fitoterápicos no tratamento de constipação intestinal. Arq Ciên Saúde UNIPAR (Umuarama). 2014;18(2):113-9. doi: https://doi.org/10.25110/arqsaude.v18i2.2014.5176.
- Figueredo CAD, Gurgel IGD, Gurgel Junior GDG. A Política Nacional de Plantas Medicinais e Fitoterápicos: construção, perspectivas e desafios. Physis Rev Saude Coletiva (Rio de Janeiro). 2014;24(2):381-400. doi: http:// dx.doi.org/10.1590/S0103-73312014000200004.
- Gadelha CS, Júnior VMP, Bezerra KKS, Maracajá PB, Martins DSS. Utilização de medicamentos fitoterápicos e plantas medicinais em diferentes segmentos da sociedade. Rev Verde Agroecol Desenv Sustentável (Pombal). 2015;10(3):1-15. doi: http://dx.doi.org/10.18378/rvads. v10i3.3564.
- 29. Valverde AV, Silva NCB, Almeida MZ. Introdução da Fitoterapia no SUS: contribuindo com a Estratégia de Saúde da Família na comunidade rural de Palmares, Paty do Alferes, Rio de Janeiro. Rev FITOS (Rio de Janeiro). 2018;12(1):27-40. doi: http://doi.org/10.5935/2446-4775.20180004.

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