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Scientific production of plant species included in the Brazilian national list of medicinal plants of interest to the unified health system (RENISUS) from 2010 to 2013

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ABSTRACT

This systematic review aimed to quantify the studies related to therapeutic action of plants listed in the Brazilian National List of Medicinal Plants of Interest to the Unified Health System (RENISUS), published between 2010 and 2013 in three scientific databases (SciELO, Science Direct and Springer). Initially, the searching of the papers was performed by reading the title, selecting those related to health. The selected work was then analyzed by reading the abstract and selecting publications that mentioned some kind of effective treatment. Finally, the text of the selected papers was fully evaluated in order to seek those that showed some kind of therapeutic action, listing plants that have confirmed efficacy and morbidity or clinical indications with the highest number of studies. From the 21,357 papers found in the search databases, 330 showed therapeutic improvement on disease. Curcuma longa (turmeric), Zingiber officinale (ginger) and Allium sativum (garlic) were the plants with the largest number of studies. Antitumor and antioxidant activities were the clinical indications most published.

Keywords: natural products, herbal medicine, medicinal plants, health, therapy.

INTRODUCTION

Historically, it has been observed that natural products have been playing an important role in the treatment and prevention of diseases. They remain as a source of innovation in the discovery of alternative therapies. Among these innovative sources, plant species for medicinal purposes are attracting attention [1,2]. It is known that conventional medicine can treat a wide range of diseases, how ever, the high costs and the number of undesirable side effects culminate to directing people to use herbal medicines, which tend to have fewer side effects [3]. For many centuries, medicinal plants have been an abundant source of biologically active compounds with numerous therapeutic activities [4]. It is estimated that 60% of the world population and 80% of the population in developing countries depend on traditional medicine [5]. The Brazilian population uses medicinal plants with certain regularity due in part to the rich Brazilian flora and culture, as well as the lack of access to health services from low-income individuals and/or from rural areas [6].In this sense, a recent study published by Newman & Cragg (2012) showed that 50% of the drugs approved in 2010 were directly or indirectly derived from natural products. Currently, there is a growing

search for new sources of bioactive molecules for the development of targeted drugs for various therapeutic activities. The same study showed that drugs from natural products and their derivatives represented over 26% of all new chemicals introduced to the market between 1981 and 2010 [7].

The abundance of different plant species in the world flora, many with important therapeutic characteristics, encourages research and discovery of new bioactive compounds for the development of new drugs [5,8].These data reinforce the importance of using medicinal plants, which is an important practice in health[1].Furthermore, it contributes significantly to primary health care being a cost-effective form of treatment for the majority of the population [9].Medicinal plants are an important tool for pharmaceutical assistance. Various announcements and resolutions of the World Health Organization (WHO) highlight the agency's position on the need to value the use of herbal medicines [10].Accordingly, there is a need for experimental studies to demonstrate the pharmacological properties and to identify the active compounds of plants. Therefore, this will provide increased benefits in the use of medicinal plants mentioned in popular culture avoiding the harms resulting from improper use [11].

Being aware of this situation, Brazil's Ministry of Health issued in February 2009 the National List of Medicinal Plants of Interest to the Unified Health System (RENISUS) [12].To select medicinal plants of interest to the Unified Health System (SUS), Brazil's Ministry of Health started from a preliminary list of 237 plant species, developed in 2005 in partnership with other ministries and with the help of consultants and researchers. The preliminary list included species used in health services, the traditional and popular knowledge, the chemical and the pharmacological studies available. From this 237 species, 100 plant species were selected with indications for use in primary care and with important information related to the plant material, form of use, therapeutic indication, and route of administration [13].Finally, the Ministry of Health reached to 71 species of interest to SUS, among which included plants used by folk medicine and plants whose effects have scientific evidence. In addition, it was prioritized the inclusion of native plants of different biomes in the country and those which could benefit the most common diseases in Brazil [12].

Since 2007, Brazil's public health system provides herbal remedies. Ordinance GM/MS Nº. 533 from 2012 establishes a list of 12 herbal medicines of the National List of Essential Medicines (RENAME) available at SUS (espinheira-santa, guaco, artichoke, mastic, cascara, devil's claw, soy isoflavones, cat's claw, mint, aloe, willow, plantago) derived from plants belonging to RENISUS [14].Given these preliminary considerations, the aim of this study was to conduct a systematic review to verify the amount of scientific papers published about the medicinal plants listed in RENISUS, pointing to studies showing therapeutic action. This study is directed to the field of public health and primary health care. Thus, it is important to address the lack of data on the efficacy and therapeutic use of medicinal plants in question, as well to show the plants and morbidities that require clinical research for discovering new herbal medicines.

EXPERIMENTAL SECTION

This systematic review on plant species listed in RENISUS was obtained from a literature search of three electronic databases: Science Direct, Springer and Scientific Electronic Library Online (SciELO) (Figure 1). The choice of such databases was due to the relevant content from leading national and international journals. The approach consisted to search scientific papers published since the creation of RENISUS in the period of January 2010 to February 2013.All scientific papers available as full and open access texts, regardless of language were considered. The descriptor used in the query was the scientific name of the 71 medicinal plants cited in RENISUS.

The selection criteria was to include publications proving therapeutic action from plant(s) of RENISUS, regardless of the part of the plant, or even the type of extraction employed. It is noteworthy that communications, digests, reviews and studies that addressed only the chemistry of the plant were not included. Papers that only mention the empirical use of plants as well as works made from semi-structured interviews were also excluded. Papers were counted only once even if they were doubled in databases. For full text display was accessed the available link directly on its own selected database. The collected data were stored in a hard disk, separated into three folders named: Science Direct, Springer and SciELO.

This review was performed in three steps. The primary search consisted in reading the title of the papers. It was selected only health-related publications using the keywords: disease's name, therapy, therapeutic, health, treatment, disease, medicine, prevention, patient, effects, benefits, beneficial, pain, edema, dysfunction, erectile, adjuvant,

protection, protects, infection, infected, cancer, cells. For the secondary search, the previous chosen papers were selected by the abstract that mentioned some kind of effective treatment with the plant of interest. Finally, the full text of the selected papers was evaluated in order to elect those that proved some kind of therapeutic action. Still in this step, it was listed the plants that showed therapeutic efficacy and the morbidities with higher number of studies.

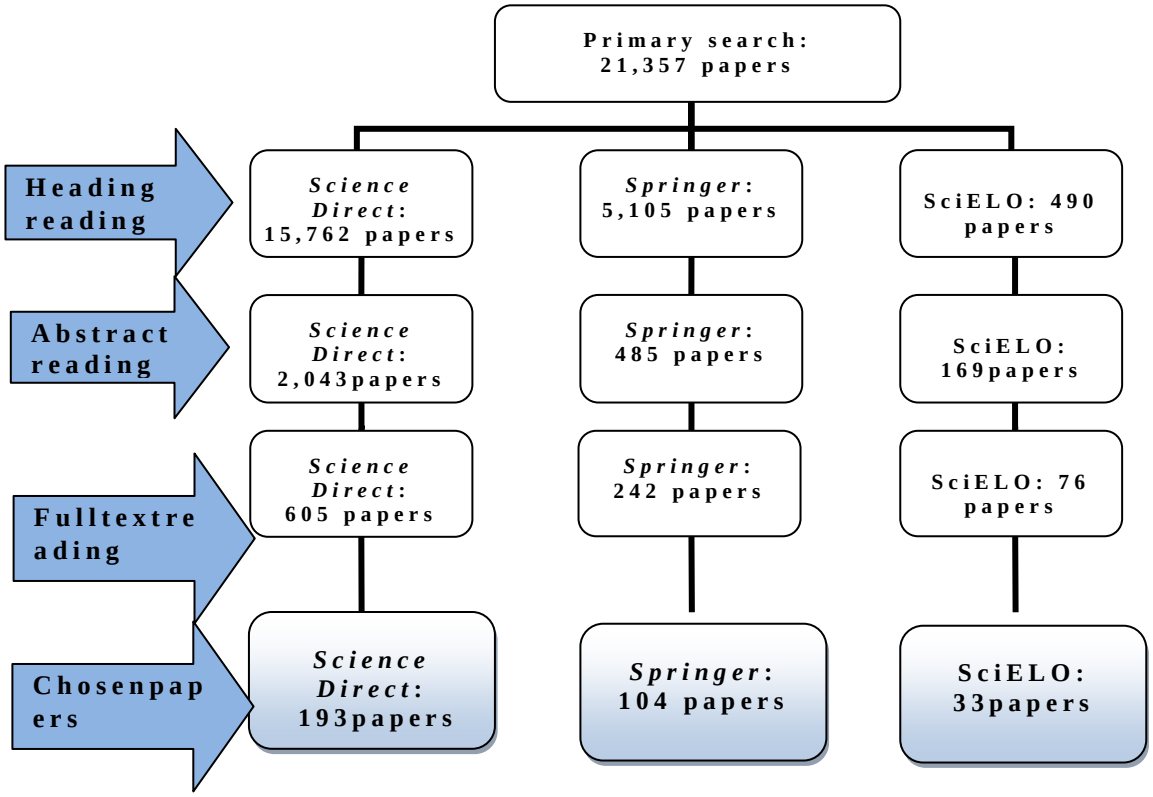

Figure 1. Flowchart of the selection steps of papers of interest

RESULTS AND DISCUSSION

The initial screening resulted in 21,357 publications in all three databases. After completing the evaluation of the titles of these productions, we selected 2,697 papers that had links with health or any morbidity. From these selected papers, 923 abstracts addressed plants with effective treatment. After reading the full text of these publications, applying the inclusion and exclusion criteria, the study focused on 330 articles of interest (1.54% of all articles published in the three databases). It was possible to assess the plants that have therapeutic evidence (Table 1), and which morbidities or conditions these plants are indicated for.

Table 1. Total number of papers per plant

Plant species listed in RENISUS	Science Direct	Springer	SciELO	TOTAL
Curcuma longa L.	62	45	0	107
Zingiber officinale Roscoe	23	9	0	32
Allium sativum L.	11	5	1	17
Chamomilla recutita (L.) Rauschert	7	4	2	13
Momordica charantia L.	7	0	4	11
Phyllanthus L. - *Phyllanthus amarus* Schumach. - *Phyllanthus niruri* L. - *Phyllanthus tenellus* Roxb. - *Phyllanthus urinaria* L.	9	1	0	10
Aloe L. - *Aloe barbadensis* Mill. - *Aloe vera* (L.) Burm. f.	4	3	1	8
Mentha L. - *Mentha crispa* L. - *Mentha piperita* L. - *Mentha villosa* Becker	4	4	0	8
Psidium guajava L.	3	4	1	8
Punica granatum L.	4	2	2	8
Achillea millefolium L.	4	2	1	7
Passiflora L. - *Passiflora alata* Curtis - *Passiflora edulis* Sims - *Passiflora incarnata* L.	3	3	1	7
Uncaria tomentosa (Willd. ex Roem. &Schult.) DC.	4	1	2	7
Calendula officinalis L.	3	2	1	6
Glycine max (L.) Merr.	5	1	0	6
Schinus areira L. *Schinus terebinthifolius* Raddi	2	1	3	6
Baccharis trimera (Less) DC	3	0	1	4
Bauhinia L. - *Bauhinia affinis* Vogel - *Bauhinia forficata* Link - *Bauhinia variegata* L.	1	2	1	4
Bidens pilosa L.	1	1	2	4
Persea Mill. - *Persea americana* Mill. - *Persea gratíssima* C.F. Gaertn.	3	0	1	4
Lippia sidoides Cham.	3	0	0	3
Alpinia Roxb. - *Alpinia speciosa* (Blume) D. Dietr. - *Alpinia zerumbet* (Pers.) B.L.Burtt&R.M.Sm.	1	2	0	3
Ananas comosus (L.) Merr.	1	1	1	3
Cordia L. - *Cordia curassavica* (Jacq.) Roem. &Schult. - *Cordia verbenacea* DC.	2	1	0	3
Eucalyptus globulus Labill.	2	1	0	3
Eugenia uniflora L. *Myrtus brasiliana* L.	2	0	1	3
Foeniculum vulgare Mill.	2	0	1	3
Kalanchoe pinnata (Lam.) Pers.	1	2	0	3
Apuleia ferrea (Mart.) Baill.	2	0	0	2
Croton spp L. - *Croton cajucara* Benth. - *Croton zehntneri* Pax&K.Hoffm.	0	2	0	2
Cynara scolymus L.	0	1	1	2
Mikania Willd. - *Mikania glomerata* Spreng. - *Mikania laevigata* Sch.Bip. ex Baker	1	0	1	2
Morus L.	2	0	0	2
Tabebuia avellanedeae Lorentz exGriseb.	1	1	0	2
Tagetes minuta L.	0	1	1	2
Vernonia condensata Baker	2	0	0	2
Anacardium occidentale L.	1	0	0	1
Arrabidaea chica (Bonpl.) B. Verl.	1	0	0	1

Casearia sylvestris Sw.	0	0	1	1
Chenopodium ambrosioides L.	1	0	0	1
Jatropha gossypiifolia L.	0	0	1	1
Justicia pectoralis Jacq.	1	0	0	1
Maytenus Molina - *Maytenus aquifolium* Mart. - *Maytenus ilicifolia* Mart. exReissek	1	0	0	1
Mentha pulegium L.	1	0	0	1
Ocimum gratissimum L.	1	0	0	1
Plectranthus barbatus Andr.	0	1	0	1
Ruta graveolens L.	0	1	0	1
Trifolium pratense L.	0	0	1	1
Vernonia Schreb. - *Vernonia polyanthes* Less. - *Vernonia ruficoma* Gardner	1	0	0	1
TOTAL	**193**	**104**	**33**	**330**

From the 71 plants in RENISUS list, 48 have studies demonstrating therapeutic activity for any clinical indication from in vitro or in vivo preclinical studies. From this total, 18 papers were published in 2010, 137 in 2011, 164 in 2012 and 11 studies published between January and February 2013. It was found that 150 researches are from *in vitro* preclinical studies, 157 from *in vivo* preclinical studies and 23 from *in vivo* and *in vitro* preclinical studies.

Remarkably from the 330 selected papers, 48 publications (14.54% publications describing therapeutic potential) were performed by Brazilian researchers. These data demonstrate that at least during the assessed period, Brazilian researchers developed considerable amount of studies with significant results. Furthermore, from the 49 plants with some therapeutic potential, 7 are available at SUS as herbal medicine: *Cynara scolymus* (artichoke), *Schinus terebenthifolius* (Brazilian peppertree), *Glycine max* (soy isoflavone), *Uncaria tomentosa* (cat's claw), *Maytenus ilicifolia* (espinheira-santa), *Mentha piperita* (mint) and *Aloe vera* (aloe). Likewise, 18 species are native to Brazil: *Phyllanthus niruri* (shatterstone), *Psidium guajava* (guava), *Uncaria tomentosa* (cat's claw), *Schinus terebinthifolius* (Brazilian peppertree), *Baccharis trimera* (gorse), *Bauhinia forficata* (Brazilian orchid tree), *Bidens* pilosa (black-jack), *Lippia sidoides* (rosemary pepper), *Ananas comosus* (pineapple), *Cordia verbenaceae* (manjack), *Eugenia uniflora* (pitanga), *Mikania glomerata* (guaco), *Tagetes minuta* (southern marigold), *Anacardium occidentale* (cashew), *Arrabidaea chica* (crajiru), *Casearia sylvestris* (guacatonga), *Justicia pectoralis* (tilo) and *Maytenus ilicifolia* (espinheira-santa).

Curcuma longa (turmeric) was the most cited plant totalizing 107 published studies. From these papers, 42 mentioned antitumor activity, as evidenced by *in vitro* and *in vivo* preclinical studies [15,16,17]. Moreover, 11 studies mentioned antioxidant action by *in vitro* [18] and *in vivo* preclinical studies [19,20]. Other 10 studies indicated anti-inflammatory action by *in vivo* preclinical studies [21,22]. *Zingiber officinale* (ginger) was mentioned in 32 papers related to therapeutic activity, among which were found 6 studies focused on antioxidant therapy according to *in vitro* [23] and *in vivo* [24] preclinical studies. Four other articles indicated anti-inflammatory action with *in vitro* [25] and *in vivo* [26] studies. Seventeen papers studied *Allium sativum* (garlic), including 3 *in vivo* studies that showed the hypoglycemic action of the plant [27]. We also found 2 studies that addressed the hepatoprotective activity using *in vitro* and *in vivo* models [28,29]. *Chamomilla recutita* (chamomile) also cited as *Matricaria chamomilla* and *Matricaria recutita* was the subject of 13 studies. Three studies highlighted the anti-inflammatory action [30,31,32]. *Momordica charantia* (melon) had 11 studies reporting some therapeutical activity, including 4 antitumor studies [33,34]. Table 2 shows the above-mentioned plants as the most cited in the databases, although none is native to Brazil.

Cancer is the most cited morbidity with 72 studies, including 42 works with *Curcuma longa* and other 3 papers with *Momordica charantia*. From all papers about antitumor activity, 29 studies assessed it on a general way, without citing a specific cancer [35,36]. Some of the *in vitro* and *in vivo* studies used plants such as *Curcuma longa* (16 papers) and *Momordica charantia* (3 papers). There were 9 *in vitro* and/or *in vivo* studies about breast cancer [37,38] using the plants *Curcuma longa*, *Punica granatum*, *Glycine max*, *Allium sativum*, *Anacardium occidentale* and *Croton sp*, with one study found for each plant, except for *Curcuma longa* with 4 papers. *Curcuma longa* treatment of lung cancer was the subject of five articles [39,40]. Hepatocellular cancer was mentioned in 4 papers, which 3 studies discussed the use of *Curcuma longa* [41]. Three studies reported a therapeutic effect of *Curcuma longa* on glioblastoma [42]. Pancreatic cancer was referred in 2 publications [43,15]. According to Park et al. (2012)

and Dayan et al. (2012), *Curcuma longa* showed therapeutic effects against oral cancer [44,45]. In addition, there were 2 articles about leukemia treatment with *Chamomilla recutita* [46] and *Curcuma longa* [47]. The following cancers had only one publication with therapeutic potential using *Curcuma longa*: lumen [48], cellular [49], larynx [50], prostate [16] and papillary [51]. The use of *Kalanchoe pinnata* for cervical cancer [52] and the use of *Bidens pilosa* for colorectal [53] were also described only once.

The antioxidant potential of the RENISUS plants indicating some kind of therapeutic activity was revealed in 58 works. *Curcuma longa* was challenged in 11 *in vitro* and/or *in vivo* studies, while *Zingiber officinale* was the subject of 6 other papers and *Psidium guajava* in other 3 [54,55]. About the anti-inflammatory potential described by Marmitt et al. (2015a) [56], 44 studies were conducted demonstrating therapeutic activity through the use of plants such as *Curcuma longa* (10) *Zingiber officinale* (3), *Chamomilla recutita* (3) [57,58].

Cardiovascular diseases were the main topic of 34 publications. According to Prakash et al. (2011), 17 studies addressed turmeric therapeutic potential [59]. However, garlic had only 4 studies linking its therapeutic activity with any cardiovascular disease [60]. In addition, ginger's cardiovascular effect was cited in 3 papers [61].

Hypoglycemic effect of some plants was reported by 33 studies, from which we can highlight the use of *Morus sp* (3), *Curcuma longa* (3), *Momordica charantia* (2) [62,63,64]. Antibacterial activity [65] was described in 19 studies using medicinal plants such as *Mentha sp* (3) and *Calendula officinalis* (2) [66,67]. Moreover, 33 papers mentioned the neuroprotective effect of some plants, including 20 about *Curcuma* longa [68,69]. Finally, some morbidities or conditions were cited only once using some RENISUS medicinal plant: chronic asthma [70], depression [71], epilepsy [72], mitochondrial dysfunction [73], ovarian damage [74], metabolic syndrome [75], irritable bowel syndrome [76] and endometriosis [77].

It was also found that 18 studies reported that certain RENISUS plants presented cytotoxicity, for example, *Curcuma longa* (5) and *Zingiber officinale* (2) [78,79]. For more details about the performed bioassays, the original references should be consulted. It should be noted that this screening evaluated only a period of scientific production after the creation of RENISUS. However, before and after that period, several species had their therapeutic potential proven.

The activity of curcumin, the pigment responsible for the chemopreventive and antineoplastic activity of *Curcuma longa*, has not had its action confirmed by clinical studies against cancer yet. Curcumin is one of the active phytochemicals found in high concentration in Zingiberaceae species [80], which explains the amount of data found for *Curcuma longa* and *Zingiber officinale*.

It is necessary to highlight that the Brazilian scientific production has been growing since 1985, when it was published more than 2000 papers, which represented 33% of Latin American production and 0.47% of world production. In 2007, there were about 20 thousand Brazilian publications in international journals. Brazil's situation about scientific production is in full evolution, which provides a glimpse that there is a basis for the country to launch a technological innovation period if exists a collaboration with the industry [81]. The increase in the research area is in agreement with the results found in this review. From the 330 selected studies, 48 important scientific data were developed by Brazilian researchers during the period of this review. In addition, from the 49 plants with therapeutic potential, 18 species are native to Brazil and 7 species are available at SUS as herbal medicine.

Besides RENISUS, the increase in scientific production may be related to the establishment in 2006 of the National Policy on Integrative and Complementary Practices (PNPIC) [82] and the National Program of Medicinal Plants and Herbal Medicines (PNPMF) of the Ministry of Health [83] that substantially helped with the development of integrative practices in primary care. These programs have provided financial support. Since 2012, Brazil's Ministry of Health launches an annual grant for projects for Local Productive Arrangements (APLs) focused on medicinal plants. The grant released in August 2015, allocated R$ 4 million for the PNPMF [84]. In total, since 2012, 66 projects in all regions of the country have received resources from the Ministry of Health, with a total investment of R$ 26 million [85].

In this context, seeking to enhance the source of existing natural products in the country, in October 2014, the Ministry of Health approved the grant SCTIE/MS 1/2014 [86], by which it was intended a total budget around R$ 7

million, divided among 19 projects in the medicinal and herbal plants area. The projects are being developed within SUS of all Brazilian regions [84].

CONCLUSION

In this study, we investigated the medicinal plants of RENISUS and the morbidities that have larger amount of publication and consequently, those species and morbidities that need to be more explored scientifically.

From the 21,357 publications about RENISUS plants found in the search databases, 330 have evidences of therapeutic action. *Curcuma longa* (turmeric), *Zingiber officinale* (ginger) and *Allium sativum* (garlic) are the plants with larger number of studies. Clinical indications that have greater number of scientific studies in the databases are anti-tumor activity with 72 searches performed and the antioxidant activity with 58 publications. In conclusion, it is assumed that these results can provide theoretical basis for discussion in the field of public health on alternative treatments based on medicinal plants as therapeutic adjuvants. Thus, the correct use of medicinal plants with scientific evidence added to conventional therapy can contribute to improve health.

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