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Ethnobotany and herbal medicine in modern complementary and alternative medicine: An overview of publications in the field of I&C medicine 2001–2013

Zorica Popović *, Rada Matić, Srđan Bojović, Milena Stefanović, Vera Vidaković

Institute for Biological Research "Siniša Stanković", University of Belgrade, Bulevar despota Stefana 142, 11060 Belgrade, Serbia

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ABSTRACT

Ethnopharmacological relevance: Ethnobotanical knowledge and traditional medicinal practices from different parts of the world are of global importance and documentation of ethnobotanical, and ethnopharmacological data is a key prerequisite for further research in the area of herbal medicine and its implementation in clinical practice.
Aims: An attempt was made to evaluate the scientific output of research related to ethnobotany and herbal medicine in journals indexed in the subject area "Integrative and Complementary Medicine" in the period 2001–2013, in order to ascertain research trends in both subdisciplines.
Materials and methods: All articles related to ethnobotany and herbal medicine, extracted from journals included in the field of I&C Medicine and published in the period 2001–2013, have been analyzed for general bibliometric data, and specific data: ethnobotanical data (geographic, floristic, pharmacological, sociological and other relevant data) and phytotherapeutic data (type of applied herbal medicine, plant species studied, pharmacological activity of studied plant species and disease and disorder type studied on a particular model).
Results: In the studied period, the number of articles dealing with ethnobotany and herbal medicine increased 6.3-fold. Articles related to ethnobotanical studies documented medicinal flora from 81 countries, either giving an overview of overall medicinal flora, or presenting the ethnomedicinal aspect of the use of plants for the treatment of ailments typical to the studied area. Additionally, the authors provided significant information on the methods of use and herbal preparations. In herbal medicine studies, plants, traditional plant remedies, herbal medicinal products and active herbal compounds were tested for many of pharmacological activities (146), with the curative activity emerging as most frequently tested. Out of 39 model systems, most of the studies were carried out under controlled *in vitro* conditions (4589 articles), followed by rat *in vivo* (2320), human *in vivo* (1285), mouse *in vivo* (955), and on agents of pathogenic diseases (887); more than 800 medical disorders were treated.

Abbreviations: Iv, In vitro cell cultures and biological molecules out of normal biological context; H, human *In vivo, in vitro, in vivo+in vitro*; R, rat *In vivo, in vitro, in vivo+in vitro*; M, mouse *In vivo, in vitro, in vivo+in vitro*; P, Parasites/pathogen, agents of diseases: viruses, bacteria, fungi, parasites; Other animal model systems, rabbit, hamster, gerbil, monkey, cattle, cat, dog, pig, chicken, snail and fish; *in vivo, in vitro*, or both, pharmacological activities (32 in total): and medical disorders affecting organ systems (23 in total); Am, Ameliorative; An, analgesic; Aa, anti-aging; Ac, anti-cancer; Ad, anti-diabetic; Ai, anti-inflammatory; Aob, anti-obesity; Aox, anti-oxidant; Apa, antiparasitic activity; Apy, anti-pyretic; Cv, cardiovascular; Cp, cell protective; C, curative; G, gastrointestinal; I, immunomodulatory; Me, metabolic; N, neural; Np, neuropsychiatric; Ph, pharmacokinetics; Pre, preventive; Pro, protective; Rg, regenerative; Rgl, regulatory; Re, relaxant; RS, reproductive and sexual activity, Res, respiratory system activity; Sk, skeletomuscular activity; St, stimulative activity; Su, suppressive activity; T, toxic activity/safety; U, urinoregulatory activity; W, wound-healing activity; AD, age-related disorders; C&T, cancer & tumor; CD, cardiovascular disorders; Cf&a, cell function & activity; Cg&d, cell growth & differentiation; DenD, dental disorders; DerD, dermatological disorders; ED, endocrine disorders; GD, gastrointestinal disorders; ID, immune disorders; InD, infectious (pathogen-caused) disorders; MenD, mental disorders; MetD, metabolic disorders; ND, neurological disorders; NonD, nonspecific objects (nonspecific or induced pain, inflammation, oxidative stress, toxicity); O, obesity, not associated with diabetes, originating from diet; PD, psychological issues; RepD, reproductive system disorders; ResD, respiratory disorders; SD, skeletomuscular disorders; GP, general pharmacology, toxicity, safety, efficiency, pharmacokinetics, synergism or antagonist effect herb–herb, drug–herb; UD, urinary disorders; Wb, well-being, herbal product type; TKM, Traditional Korean medicine; KM, Kampo medicine; TCM, Traditional Chinese medicine; HMP, herbal medicinal product; AM, Ayurvedic medicine; HAC, herbal active compound; H, herbs (medicinal plants); TTM, Traditional Thai medicine; ATM, African traditional medicine

* Corresponding author.
E-mail address: zorica.popovic@ibiss.bg.ac.rs (Z. Popović).

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Conclusions: The study revealed the regions most studied for new records of floristic and ethnomedicinal diversity, the most frequently studied plant species, and the most promising therapeutic indications for the integration of herbal remedies in the curative process, as ascertained from the selected bibliographic databases.

1. Introduction

Ethnobotany is a specific field of scientific study in plant research, a scientific investigation of inter-relations between people and plants that relies on a multidisciplinary approach involving anthropology, archeology, botany, ecology, economics, medicine, religious, cultural and several other disciplines (Soejarto et al., 2009; Sharma and Kumar, 2013). From ancient civilizations, ethnobotanical and ethnomedicinal knowledge has been more or less preserved through the ages in written or oral form; over time some traditional knowledge of herbal medicine has been incorporated into the system of official, i.e. Western medicine, while some remained less known and has survived only among small, more or less isolated ethnic groups (Gurib-Fakim, 2006). Modern ethnobotanists strive to collect all available data on the usage of plants, to document the biodiversity of medicinal plants and the methods of their use. This type of research has been launched in many countries (especially underdeveloped ones), mainly because of its possible contribution to healthcare; however, its results also benefit the preservation of biodiversity, the raising of environmental consciousness, and different sociological and economic aspects. The expansion of ethnobotanical fieldwork has led to increased data collection, and prompted modern pharmacology to evaluate the medicinal properties and pharmaceutical potential of documented medicinal flora through the exploration, isolation and testing of plants and their bioactive chemical compounds (Soejarto et al., 2009).

The research of plant resources in traditional medicine was intensified in the 20th century with the aim of finding new cures for a spectrum of different conditions (Benzie and Wachtel-Galor, 2011; Bone and Mills, 2013), and helping to bring research relating to phytotherapy or herbal medicine into the focus of the current search for new drugs (Harvey, 1999; Heinrich and Gibbons, 2001; Weldegerima, 2009). The richness and diversity of flora can be a unique source of potential medicines. However, apart from documenting the pharmacological properties of plants through ethnobotanical/ethnomedicinal research and random screenings of a number of species for their biological activities, only a small percentage of the plant species living on Earth (250,000–500,000) has been investigated phytochemically, or studied for their pharmacological properties (Rates, 2001). Approximately 50,000 species of higher plants are believed to have been used medicinally (Idu, as cited in Idu, 2013), and data indicated by Payne et al. (as cited in Rates, 2001) imply that only 5000 have been studied with evidence for medicinal use.

Increased research activities in the area of discovery, isolation, implementation and studies of the effectiveness of herbal medicines have resulted in a rapid growth of scientific literature dealing with these topics. This area attracts a great deal of scientific interest in a number of highly ranked journals, particularly in the field of Integrative and Complementary Medicine (I&C Medicine). Periodically, any research discipline should be considered in a broader perspective, based on relevant publications, their quantitative and qualitative indicators and the predominant tendencies within the subject area. Such overviews are important for improving the publishing efficiency of researchers, adjusting the editorial policy of journals and helping researchers to more fully comprehend the current situation in the relevant area in order to plan their future research, which is usually conceived as an expansion of past work in the field. Emerging trends in the publication of studies on medicinal plants, particularly from a biological aspect, are evident in the increasing number of articles and the impact factors of journals publishing such research (Gilani and Atta-ur-Rahman, 2005). Scientific (and public) interest in herbal medicine has grown exponentially with the increase in the number of reports documenting the safety and effectiveness of different herbal preparations (Pal and Shukla, 2003; Albuquerque, 2013). However, quantification of the scientific output and future directions within herbal medicine have been the subject of very few studies. Calixto (2005) presented the expensive year-to-year growth in scientific output in Latin American countries over 25 years and the simultaneous increase in the publication of both basic and clinical studies. Varah and Desai (2015) analyzed the global publication of ethnobotanical genomics over the past decade through indexes of productivity (number of articles) and quality (number of citations and the h-index), and confirmed the expansion of this subdiscipline as crucial for recording existing biodiversity and describing new species. Moral-Muñoz et al. (2014) presented a keyword analysis of 18,536 articles published in 21 journals in the ISI subject category I&C Medicine from 1974 to 2011, and demonstrated that the study of medicinal plants is a growing area of research, with a good rate of publication and citation of published documents. The need for such periodical overviews of the literature in ethnopharmacology and herbal medicine is emphasized as one of the basic prerequisites for improving the quality of research in this area (Albuquerque and Hanazaki, 2009). Despite the methodological limits of bibliometric studies, they are important tools for assessing the size and distribution of scientific literature in numerous research areas over a particular time period (García-García et al., 2008), and are helpful in ascertaining the relevance of topics in the scientific literature and understanding how research fronts evolve and interact (Natale et al., 2012). I&C Medicine covers “resources on the practical use of allopathic, alternative and/or complementary medicine and treatments used in the prevention and treatment of diseases, healing illnesses, and health promotion”. The aim of this study was to extract research articles (original research articles and short communications) dealing with ethnobotany and herbal medicine, which basically relies on traditional usage of plants, from journals indexed in I&C Medicine, and to evaluate the position and research trends in this botanical–medicinal area at the beginning of the 21st century.

2. Materials and methods

2.1. Data sources and searches

Five researchers searched Scopus and Web of Science (‘All databases’ option) bibliographic databases during 2014 to extract all articles included in the field of I&C Medicine (Thompson Reuters) published in the period from January 1, 2001– December 31, 2013 (24 journals in total). Three researchers independently reviewed the titles, abstracts and keywords from the obtained database (24,453 articles), and the overall sample was sorted according to the Cochrane Library (Wieland et al., 2011) into 5 categories and over 70 subcategories: (1) Alternative Medicine Systems (subcategories: Homeopathy, Naturopathy, Anthroposophic Medicine, Traditional Medicine Systems (Chinese, Japanese, Indian, etc.), comprising 14.8% papers of the total sample; (2) Natural product-based therapy (subcategories: Herbal Medicine (i.e. the use of plants either by documenting traditional usage or in experimental research), Animal Active Compounds, Minerals, Fungi, Ozone/Oxygen/CO_2, Diet, Nutritional Supplements), 63.5% papers of the total sample; (3) Energy therapies (Acupuncture, Acupressure, Qi Gong, Reiki, Healing Touch), 10.3% papers of the total sample; (4) Manipulative & Body-based Methods (Massage, Reflexology, Kinesiology, Osteopathy, Tapping, etc.), 5.3% papers of the total sample; (5) Mind-Body Interventions (Exercise, Tai Chi, Aromatherapy, Spirituality, Yoga, etc.), 6.1% papers of the total sample.

2.2. Study selection

Three researchers independently reviewed the titles, abstracts and keywords from the obtained database (24,453 articles) to select all articles dealing with herbal medicine and ethnobotany. The aim of this selection was to obtain all published outputs relating to (1) Ethnobotany/Ethnomedicine and (2) Herbal medicine, with clear evidence of their biological activity documented by testing *in vitro* or on animal/human models. The following prefixes/words were used as criteria for the inclusion of articles: ethno-, phyto-, fito-, traditional, common or Latin name of plant species (or genus and family), herbal medicine, active herbal compound, herbal formulation and preparations originating from traditional medicine (Chinese, Japanese, Korean, Thai, African and Indian). The selected database, comprised of all articles dealing with herbal medicine and ethnomedicine, was used in further analyses (13,789 articles in total), which represented more than half of the total number of papers in I&C Medicine, i.e. 56.77%. All analyzed articles had titles and abstracts in English.

The next exclusion criterion, after reading the abstracts, was the elimination of reviews and meta-analyses if they were based on data collected by other authors, research articles dealing with research methodology, trade in medicinal plants, sociological studies on preference of herbal remedies, procedures for active herbal compound isolation, plant chemodiversity, opinions and duplicates. The final database included 11,921 articles (11,476 dealing with herbal medicine and 445 with ethnobotany).

2.3. Data survey

Two researchers independently reviewed abstracts or full-text articles in order to determine the criteria set for classification, which was verified by a third reviewer. Microsoft Excel 2010 was used to create a unifying database and to conduct standard reports and queries of the data. Data analysis and synthesis was conducted for the whole sample and separately for two sub-bases: Ethnobotany/Ethnomedicine and Herbal medicine. Document information including title, year of publication, source journal, number of authors and their countries of origin, were downloaded for each article. Authors' affiliations were analyzed to evaluate the contribution of different countries. The term 'single country' was assigned if researchers' addresses were from the same country and the term 'international collaboration' was designated to those articles that were co-authored by researchers from more than one country. Specific data input for Ethnobotany/Ethnomedicine included narrowly specified studied geographic regions, informant structure, type of study in terms of the documented flora (total medicinal flora or a list of ethnomedicinal plants used in the prevention and treatment of particular ailments), number of documented plants, their uses and traditional herbal preparations and remedies. In the Herbal medicine sub-base, additional coding was performed for the type of applied herbal medicine, plant species studied (common names were changed to appropriate Latin names) and their classification (genera, family), activity of studied plant species (one or more pharmacological activities) and the diseases and disorder types studied on a particular model (cell-line disease models, *in vitro* or *in vivo* experimental animal and human models). Taking into consideration that over the years much of the plant nomenclature has changed, we checked all the Latin names using The Plant List (http://www.theplantlist.org/) and EOL list (http://www.eol.org), which provide the accepted Latin name for plant species. All incorrect, ambiguous or synonymous taxon names were corrected. The number of citations an article has received to date was taken from Google Scholar (https://scholar.google.com/) and Thomson Reuters (ISI) Web of Science databases (https://webofknowledge.com/) in the period 3–30 April 2015. The impact factor (IF) of a journal was determined as reported in year 2014 ISI, Journal Citation Reports (JCR), which is the latest data available.

2.4. Statistical procedure

The Statistica 8.0 program (StatSoft inc. 2007) was used to run descriptive analyses and principal component analysis. Analysis of principal components was performed to assess the correlations: (1) between the number of plants documented in ethnobotanical studies (total medicinal flora or medicinal flora relating to specific disorders) and the geographic region studied; (2) between herbal product type and organ system disorders, and (3) between model systems, pharmacological activities and medical disorders. For this purpose, some of the data from the total data set were grouped as follows: 6 model systems (*Iv,* H, R, M, P, As), 32 pharmacological activities (Am, An, Aa, Ac, Ad, Ai, Aob, Aox, Apa, Apy, Cv, Cp, C, G, I, Me, N, Np, Ph, Pre, Pro, Rg, Rgl, Re, Rs, Res, Sk, St, Su, T, U, W) and 23 medicinal disorders affecting organ systems (AD, C&T, CD, Cf&a, Cg&d, DenD, DerD, ED, GD, ID, InD, MenD, MetD, ND, NonD, O, PD, RepD, ResD, SD, GP, UD, Wb). Similar pharmacological effects (beneficial, adaptogenic, alleviating, etc.) were grouped as one activity (i.e. ameliorative).

3. Results

The total number of articles in I&C Medicine showed an increasing trend; in each of the 5 categories a certain increase in the number of published papers was noted. However, the highest increase in scientific output was evidenced in category (2), which basically accounts for the emerging trend of publications in I&C Medicine (Fig. 1). Out of the 24 analyzed journals from the subject area of I&C Medicine, 20 published articles dealt with ethnobotany and herbal medicine; the number of articles, cited reference count, average citation rate per article and impact factors are shown in Table 1. In total, 11,921 published articles were analyzed. In the studied period, the number of articles dealing with ethnobotany and herbal medicine increased 6.3-fold, from 376 (2001) to 2367 (2013), following the exponential growth function. To envisage trends in the coming period (up to 2020), 17 prediction models were tested. Among them, statistical procedure selected exponential trend as the best-fitting model (Fig. 2). The average number of authors per article also increased over the study period from 4.6 (2001) to 6.3 (2013).

International collaborations accounted for 16.75% of all the articles, while 83.25% were by authors from a single country. Out of 2310 internationally collaborative articles, 1967 (85.15%) were a collaboration of authors from two countries, 315 (13.64%) from three countries, and 28 (1.21%) from four and more countries. The

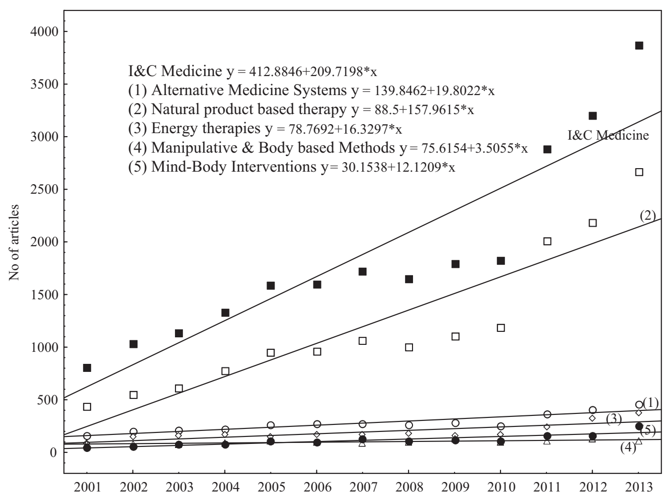

Fig. 1. Number of published articles in I&C Medicine and 5 categories related to specific alternative therapies from 2001 to 2013.

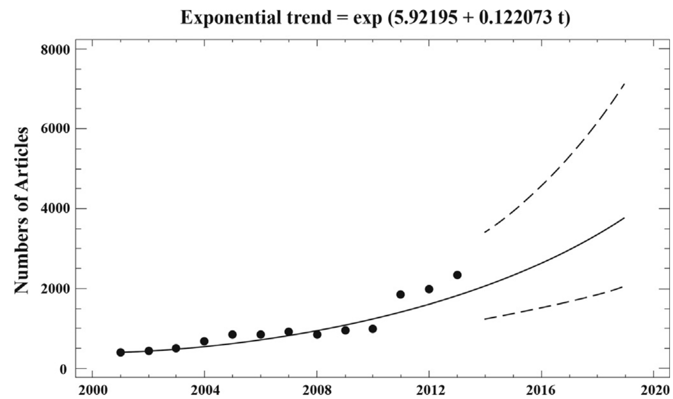

Fig. 2. Actual and predicted increase in the number of articles in Ethnopharmacology and Herbal medicine. Points and continuous line show the actual increasing trend 2001–2013; the continuous line 2013–2020 shows the predicted increasing trend with 95.0% limits (discontinuous lines).

Table 1
Studied journals sorted by the number of analyzed articles.

Journal	NA	AA	GS	WoS	IF
Journal of Ethnopharmacology	5502	5.64	39.57	18.84	2.998
Phytomedicine	1766	5.50	31.63	16.23	3.126
Evidence-Based Complementary and Alternative Medicine	1721	6.39	10.29	3.61	1.880
Chinese Journal of Natural Medicines	767	4.46	5.53	0.33	1.114
American Journal of Chinese Medicine	746	6.03	16.43	9.05	2.755
Chinese Journal of Integrative Medicine	741	5.10	5.18	1.58	1.217
BMC Complementary and Alternative Medicine	669	5.79	20.48	3.94	2.020
African J. of Traditional, Complementary and Alt. Medicines	554	4.49	11.42	2.34	0.500
Journal of Traditional Chinese Medicine	369	4.87	3.37	0.87	0.716
Journal of Alternative and Complementary Medicine	256	4.70	27.93	12.06	1.585
Chinese Medicine	141	5.35	20.64	2.49	1.490
Forschende Komplementarmedizin	103	3.95	14.29	6.03	1.079
Integrative Cancer Therapies	100	4.75	25.82	7.47	2.361
Alternative Medicine Review	75	1.99	48.88	12.25	3.833
Complementary Therapies in Medicine	71	3.89	18.52	8.59	1.545
Alternative Therapies in Health and Medicine	59	4.29	26.69	11.10	1.243
European Journal of Integrative Medicine	51	5.29	5.33	2.10	0.777
Holistic Nursing Practice	36	1.75	10.58	1.72	0.622
Explore: The Journal of Science and Healing	31	3.29	15.26	8.03	1.000
Journal of Herbal Medicine	30	3.57	4.37	1.73	1.188

NA: number of articles; AA: Average number of authors per article; GS: average citation rate per article according to Google Scholar; WoS: average citation rate per article according to Web of science; IF: impact factor in 2014 JCR.

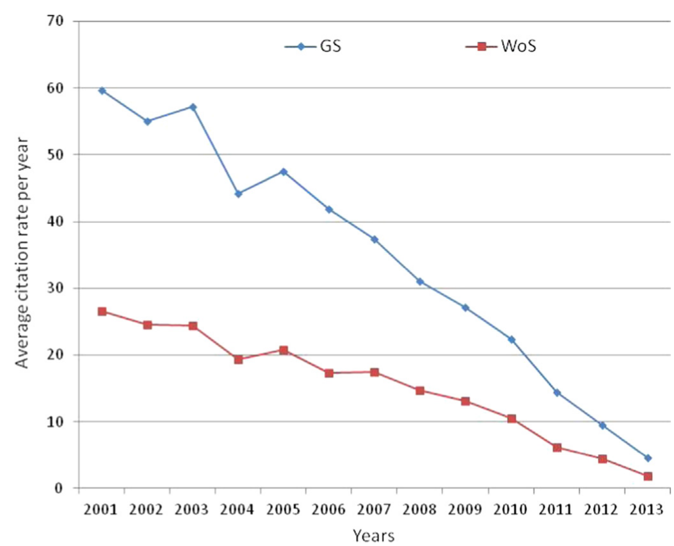

Fig. 3. Average citation rate for articles related to herbal medicine and ethnobotany in 20 journals included in the area of I&C Medicine (GS: Google Scholar; WoS: Web of Science).

rate of international collaboration has increased over the study period (from 58 articles in 2001 to 392 in 2013). The analyzed articles were written by authors from 143 countries, most of them from China (4263 articles; 25.92%), followed by India (1323; 8.05%), USA (1079; 6.56%), South Korea (1069; 6.50%), Taiwan (776; 4.72%), Brazil (769; 4.68%), Japan (580; 3.53%), Germany (553; 3.36%), Nigeria (360; 2.19%) and South Africa (358; 2.18%).

The total citation scores for the analyzed articles dealing with ethnobotany and herbal medicine are 354,845 according to Google Scholar (GS) and 158,421 according to Web of Science (WoS) database. Out of all the analyzed articles, 734 articles (5.32%) were not cited at all in GS and 2851 (20.68%) in WoS database. The majority of these uncited articles (60.35% and 49.63%, respectively) were published in the last three years of the study. Average citation rates for the analyzed articles are shown in Fig. 3. According to both citation databases, citation rates decreased over the studied period; however, it is a well-known fact that the number of citations is highly correlated with the length of time elapsed since the publication of the article. Overall, the average citation rate was 25.73 (GS) and 11.49 (WoS).

3.1. Ethnobotanical studies

Among the 24 researched journals from the I&C Medicine area, only two were significantly oriented toward the publication of papers related to ethnobotany and ethnomedicinal practices. The leading journal in the publication of such articles was the Journal of Ethnopharmacology (368 published articles over the investigated period, or 82.7%), followed by the African Journal of Traditional, Complementary and Alternative Medicine (13.9%). The journals Evidence-Based Complementary and Alternative Medicine, Phytomedicine, Alternative Medicine Review, Complementary Therapies in Medicine and Holistic Nursing Practice published an insignificant number of articles on this subject (3.6% in total).

The number of articles constantly increased over the period, with the most being published in the last three years (43.4%). All in

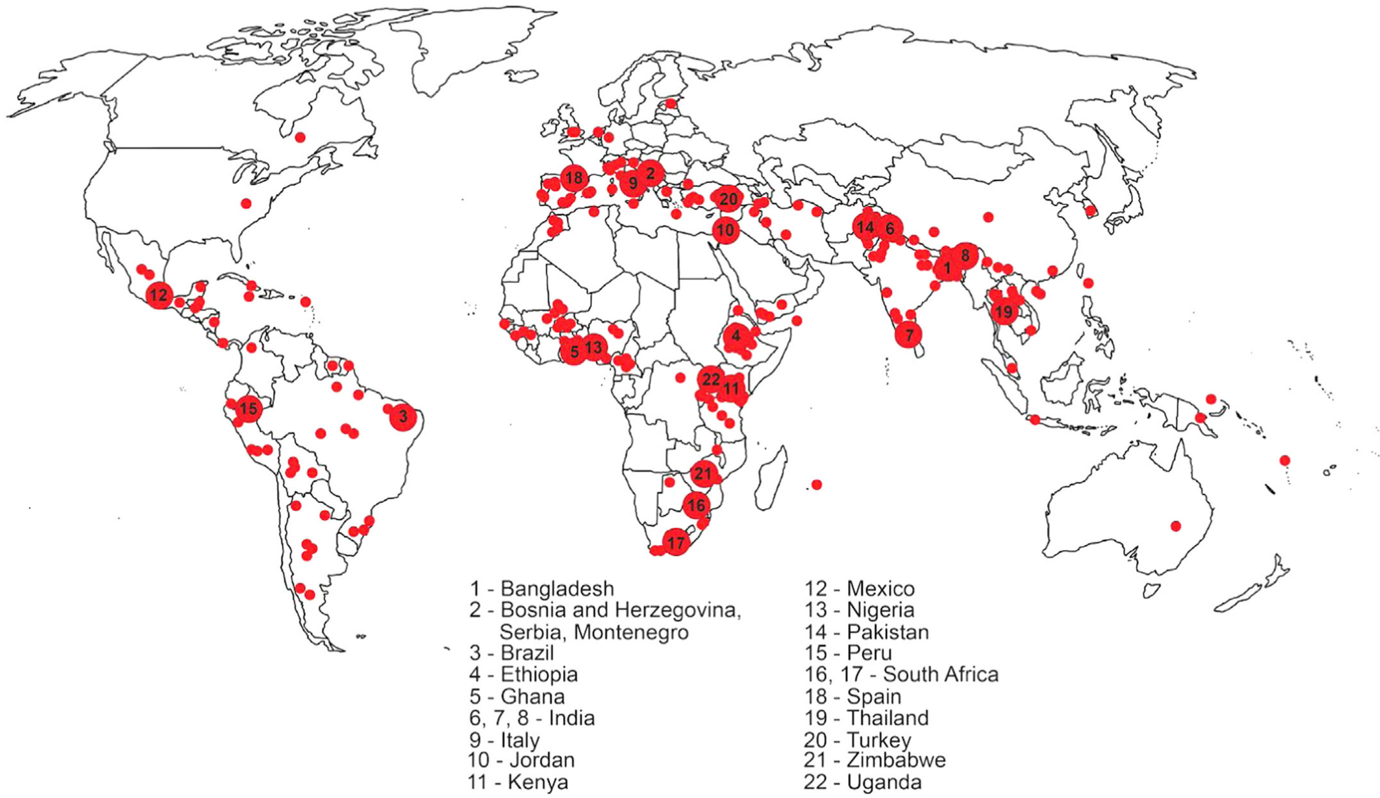

Fig. 4. Map with locations presented by ethnobotanical research in journals indexed in I&C Medicine from 2001–2013. Circles indicate the number of articles from a particular locality: smaller circles represent one published article, larger circles are for >5 articles published (5 articles from Bosnia and Herzegovina, Serbia and Montenegro are presented together because the smaller circles overlapped).

all, authors from 70 countries contributed with their studies; the largest number of articles was published by research teams from a single country (68.3%), whereas the rest of the articles were the result of cooperation between authors from two or three countries (26.01% and 5.62%, respectively). Authors from India contributed the largest number of articles (9.66%), followed by authors from South Africa (6.29%), Spain (6.01%), Italy (4.72%), USA (4.49%), UK (4.27%), Nigeria (3.60%), Kenya (3.37%) and Switzerland (3.37%). The total citation score for the analyzed articles on ethnobotany was 22,483 according to GS and 11,326 according to the WoS database. Out of all the analyzed articles, 6 (1.34%) were not cited at all in GS and 26 (5.84%) in the WoS database. Overall, the average citation rate was rather high −50.87 (GS) and 25.62 (WoS).

Of the total number of articles, the largest number geographically covered African and Asian countries (33.60% and 30.95%, respectively). Nigeria, South Africa, Kenya, Uganda and Ethiopia in Africa, as well as India, Pakistan and Turkey in Asia were comprehensively explored, i.e. several regions in these countries were studied for the collection of ethnobotanical data. In Europe (16.93% of the articles), the largest amount of ethnobotanical data was documented in Spain and Italy. In 16.40% of the articles, the authors surveyed different regions of Central and South America; most were located in Brazil, Peru and Mexico. The largest number of locations was explored in India, Brazil, Italy, Spain and Nigeria. Data on the location of ethnobotanical studies per country are given in Fig. 4.

In each of the analyzed articles the authors used the ethnobotanical approach (botanical species determination and collection of voucher specimens) to present a different number of species (from 1 to 4554 species). Besides a large database with a long list of species and families, the authors also documented comprehensive data on the traditional usage of plants and the preparation and application of remedies/preparations (4297 usages and 4858 remedies documented, respectively). In most of the papers, information on the usage of plants was gathered from the local populace (local inhabitants/informants, alone or accompanied by traditional healers), fewer papers contain data obtained by interviewing only traditional healers, practitioners and/or herbalists (5.12%), and only some articles contain information collected from herb sellers (0.67%). In total, 68 different ethnic groups were described with their locations, population size, way of life, and some of them served as the source of information more than once: Bapedi tribe (5 articles), Yoruba tribe (3), Mapuche community (3).

Principal component analysis was performed in order to establish correlations between variables; on the correlation matrix, 379 geographic areas were mapped from the dataset and 21 variants of medicinal flora composition (samples × variables). PCA explained 9.79% of the total variance for the two main axes (axis 1, 4.91% and axis 2, 4.88%, respectively) (Fig. 5). The greatest impact on the formation of axis 1 was due to the number of plants documented in Cameroon, Guinea, Uganda, Togo, Ghana, Vietnam, Nigeria, Ethiopia, Kenya (medicinal flora with antimalarial properties), and Nigeria, India, Kenya, Congo, South Africa, Brazil (medicinal flora with antidiabetic properties). The greatest impact on the formation of axis 2, beside the countries that participated in the formation of axis 1 (mentioned above, medicinal flora with antidiabetic properties), was also due to the number of plants documented in the Dominican Republic, Thailand, India, Pakistan, Guatemala and Cameroon (medicinal flora used for urogenital disorders).

3.2. Herbal medicine studies

From the 24 analyzed journals in the I&C Medicine area, 20 published articles dealt with herbal medicine research. The Journal

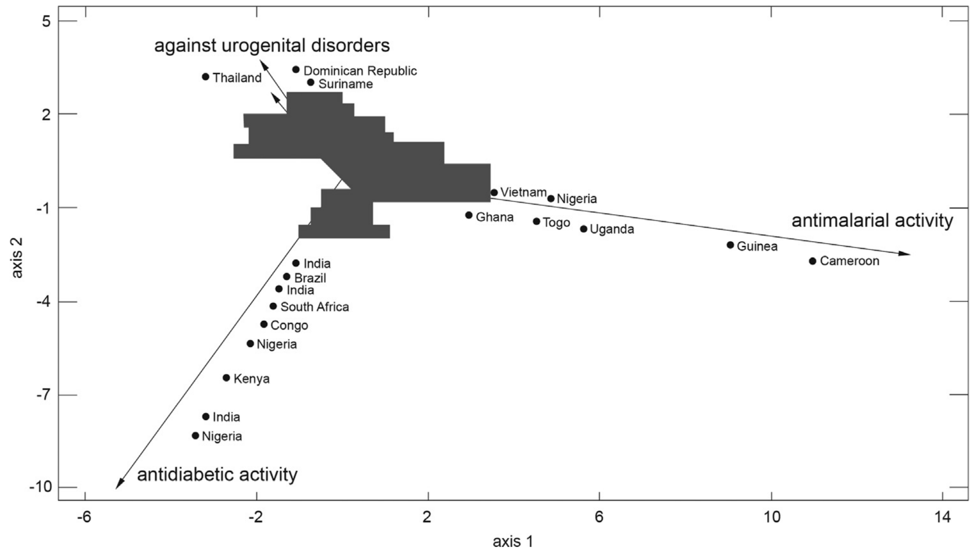

Fig. 5. Graphical visualization of PCA of 379 geographic areas and 21 medicinal flora compositions on the plane of axes 1–2. The shaded area in the center indicates regions within all other countries (66) and medicinal flora with other pharmacological properties (18 pharmacological properties: anti-epileptic, analgesic, gastrointestinal, immunoprotective, ethnoveterinary, anti-inflammatory, antimicrobial, antidiarrheic, antiparasitic, antihypertensive, toxic, anti-HIV; against respiratory disorders, gastrointestinal disorders, snake bite, for insect control, for wound healing, edible plants).

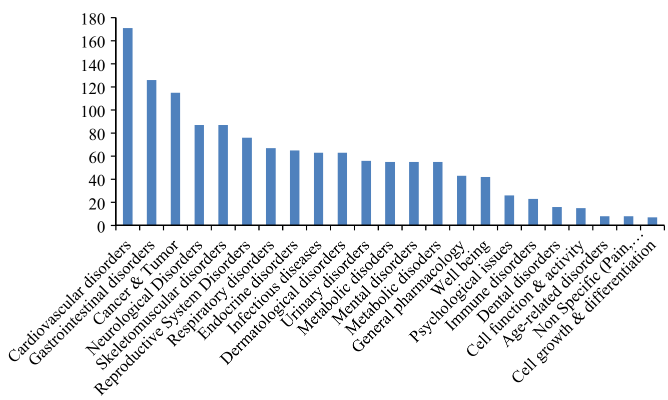

Fig. 6. Number of articles regarding the curative activity of herbal medicines for therapy of different disorders.

of Ethnopharmacology published the largest number of these articles (41.78% of the total number), followed by Phytomedicine (14.29%) and Evidence-Based Complementary and Alternative Medicine (12.98%). In total, 11,476 articles were included in the analysis. The number of articles dealing with herbal medicine increased 6.0-fold during the studied period, from 329 (2001) to 1976 (2013).

International collaborations accounted for 16.75% of all the articles, while 83.33% of the articles were by authors from a single country. Out of 1913 internationally collaborative articles, 1638 (85.63%) were a collaboration of authors from two countries. The analyzed articles were written by authors from 132 countries, most of them from China (3,338 articles; 24.37%), followed by India (1171; 8.55%), South Korea (1033; 7.54%), USA (782; 5.71%), Taiwan (741; 5.41%) and Brazil. The total citation score for the analyzed articles on herbal medicine is 288,622 according to Google Scholar (GS) and 129,458 according to the Web of Science (WoS) database. Out of all analyzed articles, 547 articles (4.77%) were not cited at all in GS and 1977 (17.23%) in the WoS database. Overall, the average citation rate was 25.15 (GS) and 11.28 (WoS).

One of the objectives of this study was to identify all of the model systems used to study the pharmacological activities of herbs or their isolated bioactive compounds. This analysis revealed that 39 different model systems were used in herbal medicine studies (*in vitro*, animal/human *in vitro*, animal/human *in vivo*). Most of these studies were carried out under controlled *in vitro* conditions (4598), followed by rat model, *in vivo* (2320), human *in vivo* (1285), mouse *in vivo* (955), and on different bacteria, viruses, fungi, protozoa and multicellular organisms as models of pathogenic diseases (887). Few studies were conducted on rat, human and mouse under *in vitro* conditions (955, 469 and 388, respectively).

The terminology of pharmacological activities displayed a vast diversity (among which those with the same meaning were merged in the first processing stage according to a pre-set system, e.g. analgesic=antinociceptive, anxiolytic=anti-anxiety, etc.). In total, 146 different pharmacological properties were ascertained, most frequently tested of which were C (1296), Rgl (1144), Ai (805), Am (753), Su (635), Aox (577) T (546), followed by Ac (522), Pro (390), HepatoPro (336), Ad (309), I (235), Cv (243), An (200) and St (185). Out of the total number of studies examining the biological effects of plants and active substances in the control of pathogens *in vitro* or *in vivo* (885), most were oriented toward assessing antimicrobial activity against bacteria and fungi (395), followed by antibacterial activity (193), antimalarial+antiprotozoal+antiplasmodial activity (103+46+31, i.e. 180), antifungal activity (89), antiviral activity (162). Curative activity was the most studied activity (11.20%), evaluated through clinical trials. The largest number of clinical studies documented the effects of herbal medicines on cardiovascular disorders (13.19% of curative activity), gastrointestinal disorders (9.72%) and cancer and tumor (8.87%) (Fig. 6).

The objects of research (ailment, disorder, medical state) also exhibited a vast diversity; more than 800 different outputs were detected. Inflammation processes related to medical conditions (arthritis, respiratory or gastrointestinal inflammation, etc.) or nonspecific induced inflammations were the most studied object (805 studies), followed by cancer and tumor (732), myocardial ischemia, circulation disorders and hypertension (364), liver injuries and hepatotoxicity (337), diabetes and diabetes-related complications (309), hematological biochemistry and histopathology (267), immune response (235), hyperglycemia (215), gastric ulcer (122), depression and anxiety (106), cerebral ischemia (105), well-being and quality of life among healthy individuals (71), behavior (55). In terms of pathogen control, the most studied

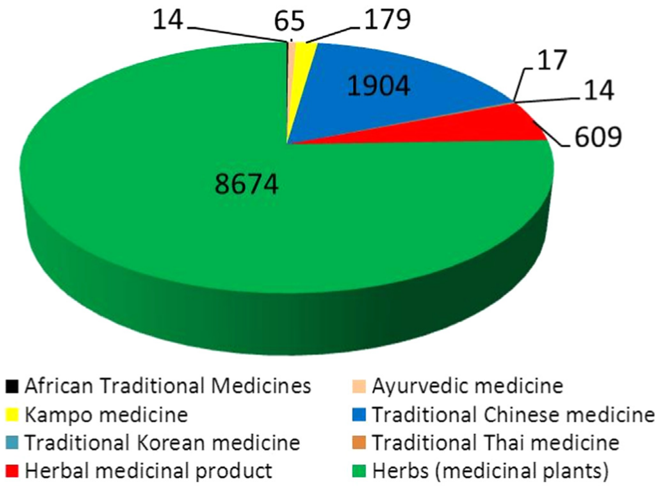

Fig. 7. Contribution of eight categories of herbal medicine type in total sample.

infectious diseases were malaria (147), HIV/AIDS (102), bacterial/fungal skin and wound infections (68), herpes virus (43).

The plant material used in the studies was very varied, i.e. the researchers used plants prepared in the form of extracts (herbs, stating the name of the species), or one or more isolated active substances from the plant/plants (active herbal compound). The effects of various biologically active compounds (saponins, flavones, flavonoids, terpenes, anthraquinones, resins, lactones, etc.) responsible for medicinal activities were studied in 2785 articles, while 5889 articles focused on the effects of the extract of the whole plant or different plant parts (leaf, seed, root, fruit, bark, etc.). In the majority of the analyzed articles (85.43%), only one plant species was studied, while less than ten plant species were studied in 10.46% and more than ten species in 4.11% of the total. Other categories included herbal preparations from ATM, TCM, KM, TTM and AM. Eight categories of herbal medicine type were identified, and their contribution in the total sample is presented in Fig. 7.

PCA for the types of herbal products and organ system disorders was performed on a correlation matrix, 23 organ system disorders (samples) x 9 types of herbal products applied (variables). PCA explained 65.95% of the total variance for the two main axes (axis 1, 51.65% and axis 2, 14.30%) (Fig. 8). The greatest impact on the formation of axis 1 was due to the herbal products HAC, HMP and H (applied to organ system disorders: CD, GD, Cf&a, GP). The greatest impact on the formation of axis 2 was due to the herbal products ATM and TKM (applied to organ system disorders ND, InD, NonD).

Correlations between model systems, pharmacological activities of tested plants and organ system disorders were assessed through principal component analysis. PCA was performed on a correlation matrix 7 model system (samples) x 55 variables comprising pharmacological activities and organ system disorders (variables). PCA explained 76.47% of the total variance for the two main axes (axis 1, 57.60% and axis 2, 18.87%, respectively) (Fig. 9). The following pharmacological activities had the greatest impact on the formation of axis 1: Am, Ad, Cv, Me, Pre, Pro, T, W, Ai, and disorders of organ systems ED, GD, ND and GP (in a balanced ratio). The following pharmacological activities had the greatest impact on the formation of axis 2: Ac, Apy, G, I, Rgl, and organic disorders C&T, CD, Cg&D, Cf&a. Based on the figure, pharmacological effects and the testing of particular disorders were distributed among the model systems: rat (pharmacological activities: Cv, G, Me, Pre, Pro, RS, U; disorders: ED, GD, MetD, SD, UD), *in vitro* studies (pharmacological activities: Ac, I, Rgl, St, Su, T, W; disorders: C&T, Cf&a, Cg&d, GP), human (C, DenD, Wb), mouse (MenD, PD), pathogens (Apa, InD).

In the whole data set, the pharmacological activities of 3941 plant species were studied. They belong to 256 families. Leguminosae was the most represented family in this study, followed by Compositae, Lamiaceae, Araliaceae, Apiaceae, Zingiberaceae and Apocynaceae. The most studied species were *Panax ginseng*, *Salvia miltiorrhiza*, *Curcuma longa*, *Astragalus propinquus* (also referred to *A. membranaceus*), *Scutellaria baicalensis*, *Ginkgo biloba*, *Viscum album*, *Panax notoginseng*, *Camellia sinensis*, *Zingiber officinale*, *Allium sativum* and *Pueraria montana var. lobata* (often referred to as *P. lobata*).

4. Discussion

Based on the review of available scientific literature over 13 years, it is safe to conclude that scientific interest in ethnobotanical research is growing, and herbal medicine is widely recognized as an alternative/complementary therapy of great significance for human health and well-being. It would seem that many highly-ranked journals have opened their pages to printing

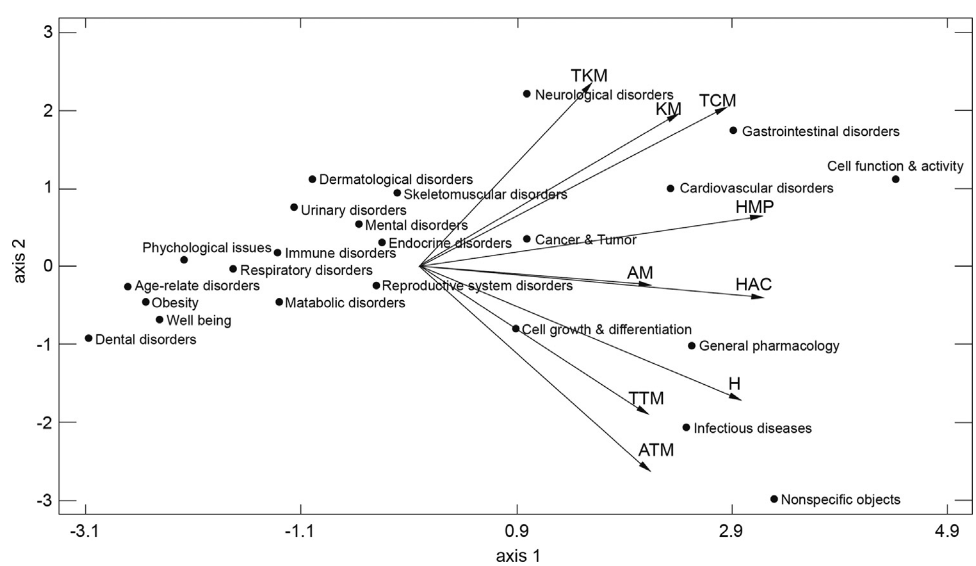

Fig. 8. Graphical visualization of PCA of 23 organ systems disorders and 9 types of herbal product applied on the plane of axes 1–2.

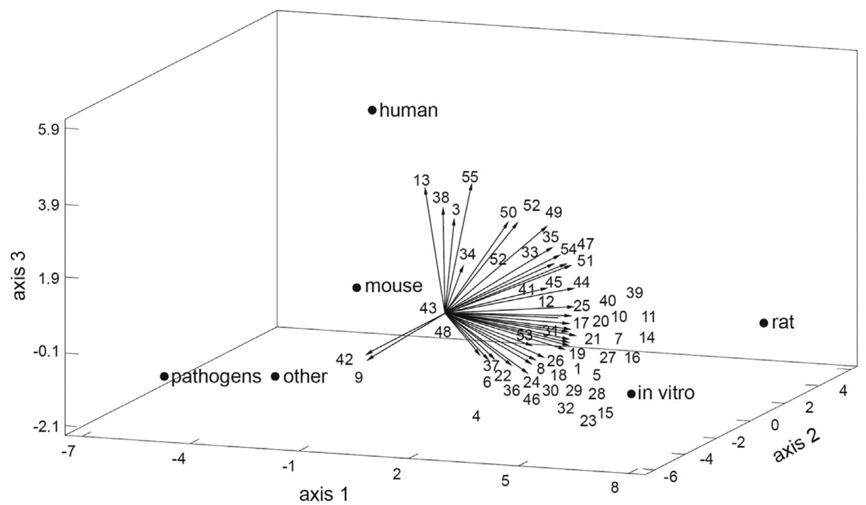

Fig. 9. Graphical visualization of PCA of 7 model system disorders and 55 variants of pharmacological activities and organ system disorders on the plane of axes 1–3. Numbers indicate pharmacological activities studied (–32, listed in the List of Abbreviations) and organ systems disorders treated (33–55, listed in the List of Abbreviations); positions of the numbers are approximate, because of the graph clarity.

evidence-based, scientifically proven studies on ethnobotany and herbal medicine. Quantitative studies on the growth rate in science indicate that traditional scientific publishing in peer-reviewed journals is increasing, although there are considerable differences among fields (Larsen and Von Ins 2010). In-field studies showed an increased number of published papers in all investigated sub-fields (Pautaso 2012), or increasing and decreasing trends for certain sub-fields, respectively (Bojović et al. 2014). According to our data, Herbal medicine shows the greatest increase in published articles in I&C Medicine (highest number of articles, and an exponential growth pattern). Its relative share in the total scientific output in I&C Medicine is of great importance for the emerging trends of the whole subject area. Moreover, based on the statistical procedures applied, it can be predicted that the increasing trend in publication activity will continue up to 2020. It is well known that the number of citations strongly depends on the age of the paper, and in a short-time period (i.e. 5 years) has no significant predictive power regarding a paper's scientific impact; the same applies for the IF of the journal where paper was published. A decreasing trend in the number of citations of a paper over time is common, and more recent papers have lower averages (Wang et al., 2013). Furthermore, the number of citations differs significantly when comparing data from the Web of Science (database of published peer-reviewed content) and Google Scholar (a diverse and larger set of publications including published articles, preprints, theses, books and court opinions) (http://wokinfo.com/googlescholar/), although both databases provide valuable information on scientific output. The decreasing trend of a paper's citations over time is usual in all scientific fields; the more recent papers have lower average number of citations and the articles published in the last three years are mostly not cited (Wang et al., 2013). Thompson Reuters Essential Science Indicator Database provides average citation rates per field (21 scientific fields) in the past 10-year period; citation rates range from 2.99 (Mathematics) to 24.75 (Molecular biology), with an average rate for all fields of 9.70 (http://wokinfo.com/products_tools/analytical/essentialscienceindicators/). The same criteria were applied to calculate the average citation rate for herbal medicine based on our dataset, giving the value of 12.89. The average citation rate depends rather on the average number of references presented in the paper and optimal time passed from the date of publishing (typical for the research field) than on the scientific influence (Wang et al., 2013). Ethnobotanical studies exhibit a growing trend in the numbers of published and cited papers, and growing numbers of studies are rounding up the microgeographic areas within a region/state. This trend has already been noted by Alexiades (2003), who has pointed out different socio-economic and political factors that work in favor of the rising interest in traditional knowledge and biological resources.

The development of modern pharmacognosy in western countries (Europe, North America) resulted in the assimilation and incorporation of traditional knowledge of ethnobotany and herbal medicine over the centuries. On the European continent, the ancient Greeks, Romans and Arabs significantly contributed to the systematic development of the use of herbal drugs, and consequently to the preservation of traditional ethnobotanical knowledge, which has been continuously expanded by many regional influences coming from local folk practices and traditions. These practices and knowledge are to a great extent incorporated in modern western pharmacognosy, and some regions of great botanical diversity inhabited by more or less isolated local populations continue to be investigated to this day, e.g. in Spain, Italy and Western Balkan countries (Quave et al., 2012). Ethnobotanical knowledge and ethnomedicinal herbal remedies utilized by native practitioners on the North American continent were adopted by the early settlers and incorporated in the Pharmacopoeia of the United States, thereby preserving a large portion of the thousand years of culture and tradition, and today we do not get much ethnobotanical data from that area (Ford, 1981). Much of the complex healing system practiced by the Aborigines in Australia was lost before it could be systematically recorded; however, it still merits the attention of ethnobotanists not only in Australia but around the world (Pearn, 2004). Chinese traditional medicine, dating back 5000 years, well-documented and systematized, has not, according to our investigation, presented ethnobotanical research in recent years, rather concentrating on research on the application of plants and plant remedies in studies on biological activity, and increasingly, clinical studies (Zhou et al., 2005). Akin to this are the healing practices originating from South Asian countries that are being recorded and developed, with scant new data from recent years. Arab herbal medicine is also well preserved and documented, and ethnobotanical surveys to date indicate that the eastern region of the Mediterranean has been scientifically recognized as specific for its rich inventory of medicinal flora (Saad et al., 2013). Based on their concentration on the world map, recent research exhibits hot-spots of current scientific interest in the spheres of ethnobotany and ethnomedicine (Fig. 4). The Indian healing practice Ayurveda is one of the most ancient medicinal traditions, considered to be the origin of systemized medicine and preserved over the centuries through oral and written records (Patwardhan et al. 2004). Even though the ethnobotanical knowledge of the past has been for the greater part documented and incorporated into healing systems, scientific interests in this type of data remains high, resulting in large numbers of studies located in India and the surrounding countries. Since the floristic composition of plant communities and the availability of some plants (especially exploited species) is changing, and there still are spatially isolated ethnic groups that employ completely traditional healing systems, this interest is fully justified scientifically, both from the botanical and anthropological aspects, and is expected to maintain the same high level in years to come. Besides India, Africa and Central and South America are also noticeable hot-spots for ethnobotanical studies. African traditional medicine is among the oldest in the world, resting on a vast biological and cultural diversity, with a developed medical system, and has to this day remained poorly recorded (Gurib-Fakim, 2006). The same can be said for the region of Central and South America, with rich and diverse healing cultures barely studied to date, but assumed to be a source of novel herbal remedies in the coming years (Gurib-Fakim, 2006).

When analyzing connections between geographic regions/countries and the most frequent type of study, it can be noticed that in addition to listing the total medical flora of a particular area, some studies document medicinal plants with specific pharmacological properties. Based on our dataset, the predominant ethnobotanical interest in several African countries focuses on documenting plants with antimalarial and antidiabetic activity, while the largest number of plants traditionally used against urogenital disorders was documented in Central America and South Asia. Many healthcare systems pay significant attention to local areas in the geographic and socio-economic sense, based on a defined geographic area where the disease predominantly appears, and some diseases are treated ethnobotanically through spatial studies of diseases and their possible etiologies (Bimal, 1985). For some diseases, a drug can be expected to be found within the area where the disease occurs. Ethnomedicinal treatment of diseases can be verified through cross-cultural data on the medicinal uses of the same or related species from geographically diverse areas. Some authors state that ethnobotanical data are useful for diseases that are traditionally easily recognized “for example intestinal worms, dysentery, and skin ulcers”, but not for newly discovered diseases or for those that must be revealed by modern diagnostics “such as HIV/AIDS or Chagas disease” (Willcox et al., 2011). However, non-insulin-dependent diabetes mellitus, frequently thought to be a disease of Western civilization, has been mentioned as a specific condition treated by plant remedies by ancient physicians. Based on ethnobotanical data, many plants are thought to be effective in the treatment of this disease, although only one drug derived from a medicinal plant has been approved (Oubre et al., 1997).

According to the data presented here, it is clear that the number of published papers from the sphere of herbal medicine in I&C Medicine journals has shot up (exhibiting a tendency for exponential growth) during the investigated period, especially in the last 5 years. Since our study was limited to the I&C Medicine subject area, it is safe to assume that the total production of papers on herbal medicine is much higher. For example, bibliometric analysis of publications on herbal medicine in psychiatry included a great many journals from the subject area Medicine and Pharmacology, and the authors restricted their study to 20 journals with the highest impact factors; their data showed an exponential growth of scientific production over 20 years (García-García et al., 2008).

The countries that lead in the publication of articles on herbal medicine are China, India, South Korea, USA, Taiwan and Brazil. According to the authors' affiliations, the same medical centers and research institutes conducting classical biological and medical studies also conduct studies in herbal medicine, and are gradually including it as a complementary treatment (World Health Organization, 2004).

Research in the sphere of herbal medicine to a great degree rests on information gleaned from ethnobotanical and ethnomedicinal research, i.e. the first step in the phytochemical determination and screening of plants' and/or their active compounds' biological activity is the established use of certain species in traditional medicine (Benzie and Wachtel-Galor, 2011; Bone and Mills, 2013).

Many of the papers' titles paraphrase “From Ethnobotany to Phytotherapy”, or their abstract points out that the study of a certain plant is scientifically justified by its use in ethnomedicinal practice (implying the scientific rationale for research).

Most of the studies were oriented toward the biological activity of a plant, i.e. the extract obtained from the whole plant or one of its parts. A great many species have been studied, most of which were merely screened for a couple of pharmacological activities (antioxidative, anti-inflammatory), most often *in vitro* and on induced oxidative stress or inflammation. Apparently, many of the studied species supported the pharmacological activity implied by traditional therapeutic postulation, and are candidates for further testing from the biological to the pharmacological and clinical level. Still, a number of studies lacked relevant botanical data, i.e. the scientific name was not properly written, and for example *Stryphnodendron barbatimao* sensu Brenan is a misapplied name; in the past this name was erroneously used to refer to *Stryphnodendron obovatum* Benth. Other examples are: *Zolernia ilicifolia* instead of *Zollernia ilicifolia*; *Broussnetia papyrifera* instead of *Broussonetia papyrifera*; *Patrinia scabiosifolia* instead of *Patrinia scabiosaefolia*; *Phyllanthus rheedii* instead of *Phyllanthus rheedei*; *Myrtus nivellei* instead of *Myrtus nivelii*; *Orostachys japonicus* instead of *Orostachys japonica*; *Picrasma quassiodes* instead of *Picrasma quassioides*, and others. It became obvious that these are not misprints, the erroneous name appearing in the title and throughout the text. Extracts from studied plants are prepared using different extraction methods; sometimes extraction is conducted for the purpose of measuring and extracting specific compounds believed to be responsible for a plant's biological activity, while sometimes the purpose is to identify all the plant compounds according to the concept of their synergistic activity. All of these differences in botanical and chemical details demand a serious approach to the interpretation of the results and comparison of the data (Brinker, 2009). Very few plants were studied for several pharmacological activities, *in vitro* and *in vivo*, some of them even in clinical practice. Besides the constantly re-confirmed medical function (i.e. *Panax ginseng, Gingko biloba*, *Hypericum perforatum*, and others), the studies of these plants also merit the interest of scientists engaged in fundamental research for the purpose of their physiological characterization, the pathways in the biosynthesis of active compounds, and the genetic/environmental factors modulating their biosynthesis (Briskin, 2000). This confirms the fact that scientific interest in species with an already proven biological activity does not cease, and that they continue to be studied from the aspect of multiple pharmacological effects, bioavailability, safety, interactions with other herbs and drugs (Halberstein, 2005; Bone and Mills, 2013). Finally, the growing amount of data on the overall biological activity of plants is in accordance with the request for the standardization of herbal products, which is a fundamental step toward their pre-clinical and clinical trials (Leonti and Casu, 2013).

Active herbal compounds were either isolated from plants or synthetically engineered. There is an abundance of standardized synthetic compounds on the market and their availability facilitates experimental design and makes results comparable. Of the herbal preparations based on traditional recipes, TCM herbal formulations have been the most frequently studied and tested. TCM has a long and rich tradition, and in China, herbal medicines are accepted and valued as well as conventional medicine. Herb manufacturers comply with required standards (quality control and good manufacturing practice (GMP) standards), and some of these products have already been subjected to randomized controlled trials with humans (Zhou et al., 2005). Traditional herbal recipes from other countries were studied in fewer articles, even though these countries have long traditions of herbal use. However, the implementation of GMP standards is an ongoing process in a number of countries, and an increase in the number of standardized herbal products can be expected in the years to come (Rivera et al., 2013).

A great many clinical trials concerning diseases that affect the organ system, and even conditions such as obesity or the overall quality of life (well-being) of healthy or reconvalescent people, support the fact that herbal medicine, according to traditional knowledge, can provide solutions/recipes for the treatment of many health disorders and conditions. The generally accepted need to integrate herbal medicine into modern clinical practice comes with a few requirements: quality assurance/quality control of the source material and GMP, along with the monitoring and reporting of adverse events, including potential drug–herb interactions (Zhang et al., 2011).

5. Conclusions

Ethnobotany and herbal medicine occupy a significant portion of scientific interest in I&C Medicine. Over 50% of the articles published in this subject area between 2001 and 2013 belong to these fields, with a constant growth trend over the studied time period. Ethnobotanical research covers a wide spectrum of geographic areas, and many traditional medical practices have still not been documented. Hot-spots for the documentation of medical flora and indigenous healing practices are India and neighboring countries, Africa, southeast Europe, Central and South America. The research in the sphere of herbal medicine follows several trends: (1) many new plant species originating from traditional medicine are studied through screening for basic biological activities under *in vitro* conditions; (2) a number of species with proven medical activities are studied in detail, especially as regards general pharmacological effects in biological systems, (3) some plants and plant preparations have already entered clinical trials and become complementary medical treatments. This study revealed the most studied geographic regions for new records of floristic and ethnomedicinal diversity, the biogeographic areas with medicinal flora used for specific medical conditions, and the most promising therapeutic indications for the integration of herbal remedies in curative processes. Among the many investigated pharmacological activities, quantitatively the studies are dominated by curative, i.e. clinical trials conducted to cure or restore health in patients with different medical conditions. Consequently, we are acquiring increasing volumes of data for different evidence-based and rational therapies, which in turn increases the need to develop suitable standardization methods for herbal remedies. All of these processes require the introduction of the most up-to-date molecular biology techniques to these studies, and contribute to the speedy development and modernization of herbal medicine. In addition, the increased number of properly conducted clinical trials is expected to provide verification of its clinical, pharmacological and other pharmacodynamic effects.

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