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Reverse ethnopharmacology and drug discovery

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A B S T R A C T

Ethnopharmacological relevance: Ethnopharmacological investigations of traditional medicines have made significant contributions to plant-derived drugs, as well as the advancement of pharmacology. Drug discovery from medicinal flora is more complex than generally acknowledged because plants are applied for different therapeutic indications within and across cultures. Therefore we propose the concept of "reverse ethnophar-macology" and compare biomedical uses of plant taxa with their ethnomedicinal and popular uses and test the effect of these on the probability of finding biomedical and specifically anticancer drugs.
Materials and methods: For this analysis we use data on taxonomy and medical indications of plant derived biomedical drugs, clinical trial, and preclinical trial drug candidates published by Zhu et al. (2011) and compare their therapeutic indications with their ethnomedicinal and popular uses as reported in the NAPRALERT® database. Specifically, we test for increase or decrease of the probability of finding anticancer drugs based on ethnomedicinal and popular reports with Bayesian logistic regression analyses.
Results: Anticancer therapy resulted as the most frequent biomedicinal indication of the therapeutics derived from the 225 drug producing higher plant taxa and showed an association with ethnomedicinal and popular uses in women's medicine, which was also the most important popular use-category. Popular remedies for dysmenorrhoea, and uses as emmenagogues, abortifacients and contraceptives showed a positive effect on the probability of finding anticancer drugs. Another positive effect on the probability of discovering anticancer therapeutics was estimated for popular herbal drugs associated with the therapy of viral and bacterial infections, while the highest effect was found for popular remedies used to treat cancer symptoms. However, this latter effect seems to be influenced by the feedback loop and divulgence of biomedical knowledge on the popular level. *Conclusion:* We introduce the concept of reverse ethnopharmacology and show that it is possible to estimate the probability of finding biomedical drugs based on ethnomedicinal uses. The detected associations confirm the classical ethnopharmacological approach where a popular remedy for disease category X results in a biomedical drug for disease category X but does also point out the existence of cross-over relationships where popular remedies for disease category X result in biomedical therapeutics for disease category Y (Zhu et al., 2011).

A R T I C L E I N F O

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1. Introduction

Human exploitation of plant diversity for the provision of medicine follows two main strategies. Herbal medicine depends on synergistic effects of mostly water soluble complex multi-compound mixtures, while biomedicine generally relies on the application of single compound drugs derived from plants, whether medicinally used or not. The discovery of new drugs from biological diversity and plants in particular has been allegorized with the search for the needle in the haystack (Cordell et al., 1991). In contrast follow-up to discoveries from random screening guided by taxonomy, chemotaxonomy draws on phylogenetic relatedness in the search of identical or similar bioactive compounds (e.g. taxol, Denis et al., 1988) while therapeutic indications of indigenous drugs are used as a lead in the ethnopharmacological approach (e.g. Artemisinin: Klayman, 1985 and Tu, 2011; Cyclotides: Koehbach et al., 2013).

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The empirical value and legacy of medicinal plant use is often uncritically seen as proof of effectiveness and safety (c.f. Heinrich et al. 2004). More specifically Fabricant and Farnsworth (2001) claim that from 122 plant-derived clinical drugs 88 have the same or similar indications as the medicinal plants from which they are sourced. This claim is, however, a simplification of a more complex reality and statistically not correct in that it does not consider that medicinal plants often have many different uses within and across cultures, including those listed in Fabricant and Farnsworth (2001). Multipurpose medicinal applications, at times even apparently contra-dictive, complicate the selection of bioassays and the ethnopharmaco-logical search for new drugs. Although ethnopharmacology uses anthropological concepts and tools such as cross-cultural comparisons and consensus analysis in order to assess the culturally most accepted uses of medicinal plant species (Berlin and Berlin, 2005; Leonti and Weckerle, 2015), the question remains as to how far consensus on ethnomedicinal uses and their scientific interpretations correlate with biomedical disease concepts, phytochemical profiles and meaningful screening results (Gyllenhaal et al., 2012; Leonti et al., 2013a). As a practical example, exemplifying the inherent difficulty in using ethnomedicinal information as a guide for drug discovery, the case of *Catharanthus roseus* may serve: Madagascar periwinkle is widely used against diabetes in traditional medicines and consequently initially investigated for its alleged hypoglycaemic activity. Instead of finding effects on the blood glucose level, during the biological validation the cytotoxic properties became apparent, giving way to the development of vincristine and vinblastine into anticancer drugs (van der Heijden et al., 2004; Guéritte and Fahy, 2005).

Natural products, including plant metabolites, are known for their importance in the development of anticancer remedies (Pezzuto, 1997, Butler, 2005; Cragg and Newman, 2005). A query of the NAPRALET® database for species ethnomedicinally used against cancer and cancer related symptoms yielded over 500 distinct records for more than 350 plant species (Graham et al., 2000), which corresponds to a relatively low consensus. Symptoms of oncological diseases are, in fact, multi-faceted, potentially affecting all kinds of body parts and organs, and therefore, "cancer" is generally poorly recognized in ethnomedicinal systems, which complicates the search for anticancer drugs with ethnopharmacological resources (Cragg and Newman, 2005).

Intriguingly, Spjut and Perdue (1976) found during a retrospective study of the NCI vaults that plants with an ethnomedicinal background, particularly those associated with poisonous uses were more likely to show cytotoxic effects than biomedical collections in general. The highest cytotoxic activity was for plants used as anthelmintics (29.3%), fish-(38.6%) and arrow-, ordeal- and homicidal poisons (45.7%; Cordell et al., 1991; Spjut and Perdue, 1976; Spjut, 2005). Spjut (2005) concluded that poisonous plants, including the ones used in local and traditional medicines, have a higher probability of exhibiting significant cytotoxic activity with respect to plants collected at random.

The observations made by Spjut and Perdue (1976) as well as Spjut (2005) and the case of *C. roseus* was our inspiration for testing here, in analogy to "reverse pharmacognosy" (see Do and Bernard, 2004; Vaidya, 2006; Patwardhan et al. 2008) the concept of "reverse ethnopharmacology".

A biomedical perspective during the ethnomedicinal enquiry defines the "reverse" in terms that we look for patterns and associations between therapeutic indications of plant derived biomedical drugs and the ethnomedicinal use of the source plants. We propose "reverse ethnopharmacology" as a drug discovery tool for visualizing hidden associations between ethnomedicinal uses and biomedical indications of plant derived drugs. To this end we compare the therapeutic indications of angiosperm and gymnosperm derived biomedical drugs with the ethnomedicinal uses of the same taxa (mostly species) with a set of statistical tools.

For the biomedical uses of plant derived drugs we rely on the census by Zhu et al. (2011). Inspired by the seminal work of Newman and Cragg (2007), Zhu et al. (2011) compiled taxonomic and therapeutic data on all approved, clinical trial and preclinical natural product drugs. From the 457 existing angiosperm and gymnosperm families (APG IV) 62 families account for all 225 angio- and gymnosperm drugs, clinical trial or preclinical drug producing taxa (see Zhu et al. 2011). These 62 families are largely widespread taxa, embracing, according to the APG system, 152.712 species altogether or more than half of the 286.467 existing angiosperms and gymnosperms. A possible explanation for this over proportional share of species is that plant taxa distributed over wider geographical extensions experience more diverse ecological interactions resulting in the production of secondary metabolites able to interfere with a broad spectrum of biological targets (Leonti et al., 2013a, 2013b). Corresponding ethnomedicinal uses were quantitatively extracted from the NAPRALERT® database and available for 186 of the 225 taxa. Special attention was given to the relation between the largest therapeutic category of use of the popular/ ethnomedicinal domain (pGYN, i.e. women's medicine) and the largest biomedical domain (bCAN, i.e. biomedical cancer therapy).

With a dual statistical approach, one based on citations (i) and a second based on plant taxa (ii) we tested for (i) associations between the biomedical and ethnomedicinal uses by means of usual statistical association tests on joint frequencies of biomedical and ethnomedicinal uses. Moreover, (ii) we estimated the increment/decrement generated by ethnomedicinal categories on the probability of finding biomedical drugs and specifically anticancer drugs and leads (bCAN). Analyses estimating the increment or decrement of probabilities of biomedical use were performed by means of logistic regression. A problem we did not account for in this approach is the chicken and egg situation and the questions, which use established first (the popular or the biome-dical?) and which use influenced which (the popular the biomedical or *vice versa*?).

2. Research question

Our research questions are: (i) Are there associations between therapeutic indications of plant derived biomedical drugs and the ethnomedicinal uses of the source plants? And if so (ii) what kind of associations can be found?In the ethnopharmacological approach for drug discovery or the validation of traditional medicines a drug used against disease category X is tested in a biological model representing characteristics of disease category X. Here we estimate the probability of finding a biomedicine for disease category X based on popular uses against disease category Y. We address the question as to "which popular uses augment or reduce the probability of discovering certain biomedical applications".

3. Methods

3.1. Data sampling

3.1.1. Angiosperms and Gymnosperms used in biomedicine. The Supplementary information (S5–7) provided with the article by Zhu et al. (2011) was used for the extraction of the taxonomic data and the therapeutic indication of biomedical (S5), clinical trial (S6) and preclinical drugs (S7) derived from angiosperm and gymnosperm taxa. The 225 drug or clinical trial drug producing angiosperms and gymnosperms belong to 62 families (58 angiosperm families including 213 species and 4 gymnosperm families including 12 species; see Appendix A or Zhu et al. (2011)). The names of genera and species in Appendix A were updated according to APG IV and theplantlist.org (The Plant List, 2013). In Zhu et al. the drug types are classified according to Newman and Cragg (2007) into "natural products" (N), semisynthetic derivatives of natural products (ND), "natural product mimics" (NM) and compounds, which are synthesized based on a

natural product pharmacophore (S). The vast majority of drugs developed from these 225 taxa are pure natural products or semi-synthetic derivatives.

3.1.2. Sampling of ethnomedicinal data for comparison. In order to avoid sampling biases the NAPRALERT® database containing "ethnomedicinal information on more than 20.000 species of plants" (http://www.napralert.org/), was used for extracting the traditional and popular uses of the 225 taxa (Appendix A). Ingredients of multi-component remedies were not considered. Since no database is complete and as not all taxa are used in popular medicine or ethnomedicine, for 39 of them the NAPRALERT® database returned no ethnomedicinal information and hence, the comparison was performed with 186 taxa (Appendix A).

3.2. Classification of biomedical and ethnomedicinal uses into categories of use

In order to allow for comparison the biomedical and ethnomedicinal uses were consistently classified into the same symptom and organ defined categories according to Staub et al. (2015): ANT: antidote (snake bites and other venomous animals); APH: aphrodisiac (stimulant, anti-stimulant, impotency); CAN: Cancer, malignant ulcers; CAR: cardiovascular (anti-arrhythmic, cardiotonic, dropsy, blood circulation, haemorrhoids and varicose veins [both internal applications], hypertension); DER: dermatologic disorders, incl. infections, tonsillitis, mouth and throat infection, haemorrhoids and varicose veins [external applications]; MET: Metabolic syndromes, diabetes, immunological problems; EAR: Ear ache (otitis); EYE: Ophthalmic problems; FEV: Fever (incl. viral infections); FOO: Food (spice, vegetable, tea); GAS: Gastrointestinal problems (incl. liver); GYN: Gynaecology (women's medicine); INF: Infections (protozoal, bacterial and viral); NER: Nervous system (peripheral and central, incl. headache and insomnia, analgesics and unspecific spasmolytics, stimulants and hallucinogens); PAR: Parasites (helminths, lice, insects); POI: Poisons (arrow poisons, fish poisons); RES: Respiratory complaints (tonsillitis, mouth and throat infection, asthma, pulmonary problems); SKE: Skeleto-muscular system (rheum, muscle relaxant, gout); URO: Urological problems, infections, dropsy, prostate (diuretic action); VAR: Various disorders (e.g. tonic, diaphoretic).

In order to better distinguish the alleged biological properties for the logistic regression the popular and ethnomedicinal uses related to gynaecological disorders (GYN), were split into GYN-1 including uses related to/as: abortifacients, labour stimulants, expulsion of placenta, contraceptives, dysmenorrhoea, menorrhagia, menstruation (emmenagogues), vaginal infections or inflammation (leucorrhoea) and GYN-2 including uses related to/as: galactagogues, mammary gland, hormonal action (climacteric, anti-galactagogue), sustain pregnancy (anti-abortive), fertility enhancer while infections (INF) were split into bacterial and viral (INF-BAC-VIR) as well as protozoal (INF-PRO). See Supplementary excel Table 1 for primary data matrix.

Biomedical use categories are indicated by a "b" in front of the category's abbreviation while popular/ethnomedicinal categories are distinguished by a "p" in front of the abbreviation (e.g. bCAN, pCAN) and hitherto referred to popular uses or use-categories while the terms "popular" and "ethnomedicinal" are used interchangeably.

3.3. Comparison and statistical analyses

We first describe the associations between biomedical (20) and popular use-categories (20) of the same taxa based on the frequency of popular use-citations (Figs. 1 and 2; Appendix B). The analysis is based first on the joint counts of popular use-citations and biomedical uses. We then estimate a general association by means of a Chi-square test and subsequently investigate the relation with binary correspondence

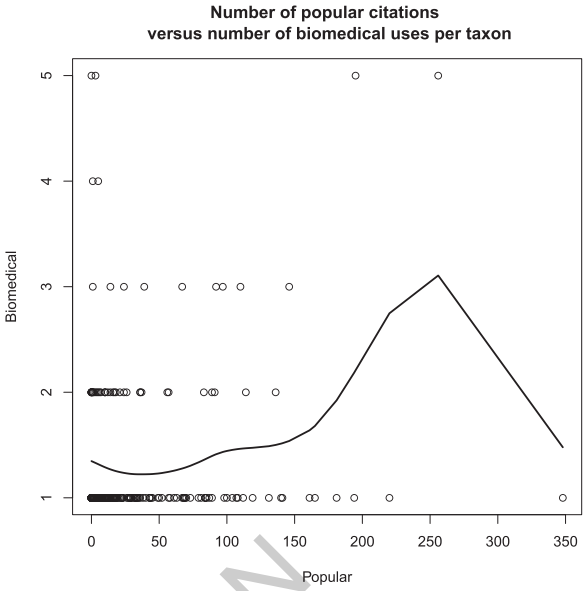

Fig. 1. Number of ethnomedicinal citations in NAPRALERT® in relation to number of biomedical drugs per taxon according to Zhu et al.

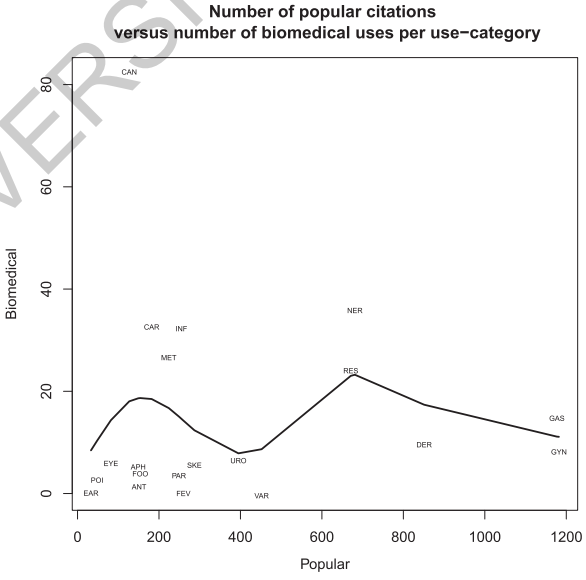

Fig. 2. Number of ethnomedicinal citations in NAPRALERT® in relation to number of biomedical drugs per use-category with the application of a smoothing-spline interpolating the points.

analysis in order to visualize associations (Fig. 3). Second, using the same data but singularly for each taxon (with 22 popular use-categories) we specifically evaluate the significance of every single association between a popular and a biomedical use-category by means of logistic regression.

By focusing on the frequency of citations we get an insight into the relation between biomedical and popular uses, while focusing on the taxa we can estimate the probability of a taxon to be used for the development of biomedical drugs due to its uses in popular or traditional medicine. For the first analysis we use contingency table where the data matrix crosses for each biomedical indication the corresponding number of popular citations (**Supplementary Table 2**) and binary correspondence for the analysis of associations between the popular and the biomedical use-categories (Fig. 3).

For the estimation of the probability of a plant taxon to be used in biomedicine with respect to the citations received in popular medicine we use a classical approach to estimate parameters of logistic regres-

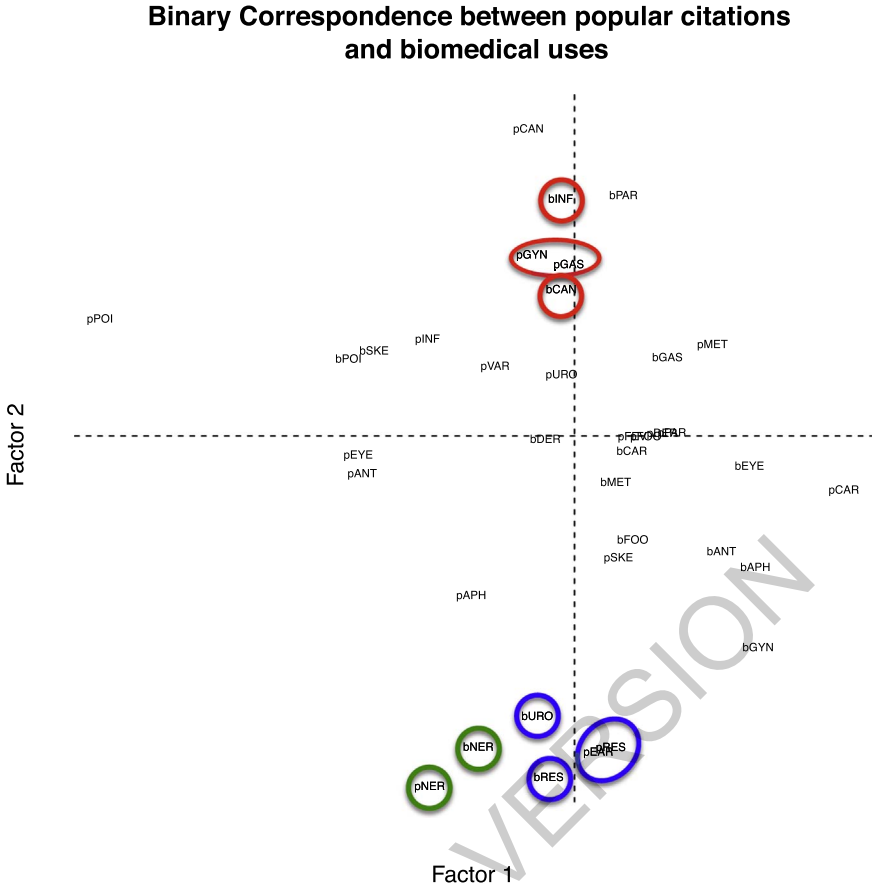

Fig. 3. Binary correspondence showing associations between the biomedical indications and popular citations.

sion. Finally for the specific analysis directed towards bCAN, a Bayesian logistic regression is applied (e.g. Congdom, 2003, Chap. 3) considering also that the plant family of the specific taxon can increase this biomedical use regardless of its popular use. This is to account for confounding factors in the popular/biomedical association.

3.3.1. Comparison between biomedical uses and ethnomedicinal citations. In order to describe, without making any inference, the relation between biomedical uses and popular citations (Appendix B), a smoothing-spline (e.g. Wasserman, 2006) was fitted in order to establish eventual trends between these two quantities (Figs. 1 and 2). The smoothing-spline is a non-parametric regression function that avoids the imposition of explicit forms (linear, quadratic, cubic, etc.) established beforehand. **Supplementary Table 2** shows the marginal counts for biomedical and popular uses and citations.

3.3.2. Contingency table. We analyzed the contingency table containing the citation frequency of popular uses of all taxa for each biomedical use (**Supplementary Table 2**) applying Pearson's Chi-square test with simulated p-values (based on 1000 replicates) of the associations between popular citations and biomedical uses.

3.3.3. Binary correspondence. The analysis of Binary Correspondence (A.Co.Bi; see Greenacre and Blasius (2006)) visually illustrates the relations between rows and columns of the contingency table (**Supplementary Table 2** and Fig. 3). The frequency in a cell, of this contingency table, represents an association when the corresponding uses are in close distance on the graph and far from the origin of the axes.

3.3.4. Multiple testing approach for logistic regression. With the classic logistic model we perform a regression for each possible combination of biomedical and popular use citations where the popular use citations are predictive for the biomedical use. For each regression we test the hypothesis that there exists a true relationship between the specific biomedical use and the specific popular use. However, as this results in a lot of single tests, that is one for each combination of a popular with a biomedical category of use (theoretically 20×22) we might find, just by chance, a relationship at a certain significance level (for example a *p*-value less than 5%). This is, in fact, a kind of artifact present in many statistical tests. In order to comply with this multiple testing problem, we apply the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995), which controls the rate of false discoveries in such a multiplicity of tests. **Supplementary excel Table 1** holds the primary data matrix used for the calculations.

Finally, in order to investigate the specific relation between anticancer drugs (bCAN) and all popular uses we estimate a Bayesian logistic regression model accounting also for the family of each taxon. In this case, due to the large number of parameters the posterior distribution has been approximated using Integrated Nested Laplace Approximation (INLA, see Rue et al. 2009). With this model we estimate the effect of all popular use-categories together on the probability of developing bCAN. In this analysis a general effect common to all popular uses (referred to as intercept) as well as use-specific effects are considered. Moreover, a random effect of plant families has been included. A very vague prior was assumed for these effects in order to let the data speak for themselves so that the analysis

can be considered objective. This analysis can further be regarded as objective because of the number of taxa used (225), which is a sample size considerably larger than the number of parameters in the model (22 coefficients, one for each popular category of use).

4. Results

In the supplementary of Zhu et al. (2011) the 225 taxa were associated with 300 biomedical uses altogether to which we added the cardiovascular use of *Salix* spp. (cardioaspirine®), resulting in 301 biomedical uses. The 186 taxa retrieving ethnomedicinal records through NAPRALERT® (Appendix A), have 252 biomedical uses and 7610 ethnomedicinal use citations in NAPRALERT® (Appendix B).

The relation between the number of biomedical uses and the number of popular citations per taxon is shown in Fig. 1. Except from two outliers (*Allium sativa* and *A. cepa*) more popular or ethnomedicinal use-citations do not correlate with the number of biomedical drugs developed from a taxon.

With 82 taxa being used for the development of oncological therapeutics (bCAN), cancer therapy was by far the most frequent biomedical use of all 225 taxa. While of the 186 taxa for which we found ethnomedicinal uses in the NAPRALERT® database 70 are used for the development of anticancer drugs, 29 for infections (bINF), 27 for cardiovascular diseases (bCAR) and 25 for metabolic disorders (bMET; Appendix B).

The most important popular use-category in terms of number of use-citations was women's medicine (pGYN) with 1182 (15.5%) citations followed by gastrointestinal (pGAS, 1177, 15.5%) and dermatological problems (pDERM, 851, 11.2%; Appendix B**,** Fig. 2).

For the 70 taxa used in the development of anticancer drugs, 3042 ethnomedicinal records were retrieved through NAPRALERT®. The importance of the use-categories changed with respect to the larger initial data set. Gynaecological uses now held a proportion of 18.5% (563) and gastrointestinal disorders 16.1% (489) while dermatological uses dropped slightly to 10.6% (328; Appendix B).

4.1. Contingency table and binary correspondence

We show that the relations between the biomedical and ethnomedicinal uses are not random with a contingency table analysis (**Supplementary Table 2**). The observed χ^2 (around 1869) of the association between the corresponding popular citations and biomedical indications is highly significant ($p < 0.0001$). The analysis of Binary Correspondence (Fig. 3) illustrates associations between the biomedical indications and the ethnomedicinal citations in **Supplementary Table 2**. Points close to each other and far from the origin of the factorial axes indicate associations such as for example pGAS and pGYN with bCAN, pGYN with bINF, pNER with bNER or pRES and pEAR with bRES and bURO. While joint points near to the origin do not necessary indicate strong association. This is just because these points lie in a space of 20×20 dimensions and we projected it into two dimensions (the most relevant ones), hence two points maybe near in the origin because of a defect of projection, essentially by chance and not because they are associated in the original 20×20 dimensions.

4.2. Logistic regression

Since popular uses for women's medicine (pGYN) were associated

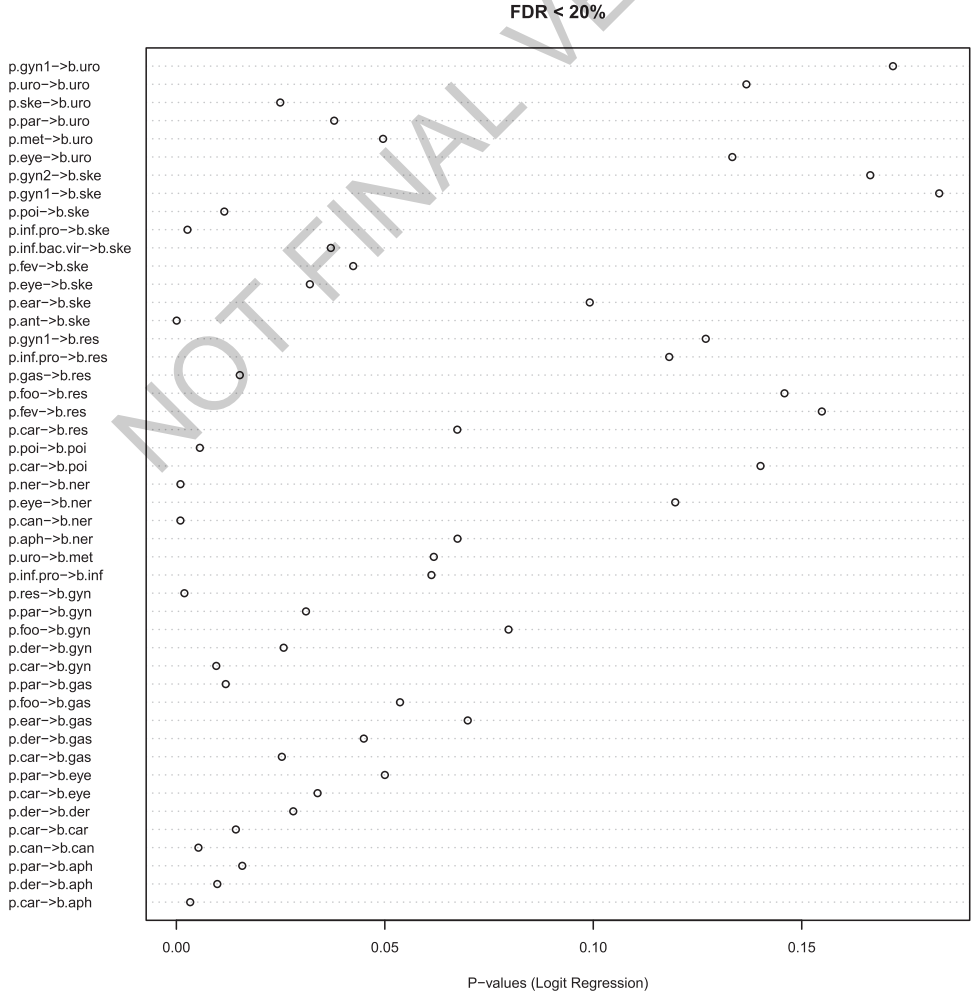

Fig. 4. p-Value of the classic logistic regression based on data of each taxon for a popular use-category on the probability of being used for the development of a certain category of drug.

with biomedical cancer therapy (bCAN; Fig. 3) and since pGYN and bCAN were the largest use-categories of their respective medical domain (p and b) we were particularly interested in the comparison of these two use-categories. Thus, we conducted additional analyses with pGYN split into pGYN1 and pGYN2 and also divided pINF into pINF.BAC.VIR and pINF.PRO.

4.3. Classic logistic regression

Figure 4 reports the p-value of the classic logistic regression based on data of each taxon (225 in total and 2 parameters in each logistic regression) for a popular use-category on the probability of being used for the development of a certain category of drug. **Supplementary Tables 3** and **4** also report the coefficient whose scale represents the log of the relative risk. A positive relative risk of 1 indicates that the probability that drugs produced from that use-category (taxa with that popular/ethnomedicinal indication) increases by a factor of exp(1) =2.7, and vice versa, a risk of −1 means that such probability decreases by a factor 2.7 with respect to a general common level which is the average frequency of a produced drug (or biomedical use) among all taxa. Significant coefficients (i.e. the coefficient significantly differs from zero) are regarded as all relations with a low p-value according to the Benjamini-Hochberg procedure, which guarantees a False Discovery Rate (FDR) less than 20% in the set of all relations declared as significant. The full list is reported in the **Supplementary Table 4** and only coefficients and corresponding p-values reported in Fig. 4 can be interpreted as relations that are statistically significant.

With the classic approach the most significant effect (p=0,0001) was found for traditional remedies used as antidotes (pANT), which showed a positive effect (+1,50) for developing biomedicines for skeletomuscular disorders (bSKE). A significant (p=0,001) and negative effect (−3,48) was found for popular anticancer remedies (pCAN) and the development of neurological disorders and analgesics (bNER). Also highly significant (p=0,001) was the relatively low positive effect (1,09) of pNER on the probability of bNER (**Supplementary Table 3,** Fig. 4).

4.4. Bayesian logistic regression

The increment or decrement in the logit scale of the probability that a certain popular use-category leads to the development of anticancer drugs (bCAN) is represented by Fig. 5. This is estimated based on the ethnomedicinal citations of all 225 taxa with the application of Bayesian logistic regression. The figure shows the general common level and the effects of the ethnomedicinal citations on the probability of producing anticancer drugs. An effect is regarded as significantly positive or negative if its value and its corresponding 95% credible interval are completely above or below zero. The scale represents the log of the relative risk, where a positive relative risk of 1 indicates that the probability that drugs produced from that use-category (taxa with that popular/ethnomedicinal indication) increases by a factor of exp(1) =2.7, and vice versa, a risk of −1 means that such probability decreases by a factor 2.7 with respect to general common level (**Supplementary Table 5**). The bullet point is the mean effect and the bars indicate the 95% posterior probability interval for the effect (i.e. according to the Bayesian point of view the effect is a random variable; Fig. 5). Thus all intervals that do not include zero are regarded as significant effects in the sense that they are with a probability of 95% different from zero given the observed data.

Bayesian logistic regression indicated the highest probability of finding anticancer drugs with popular therapies related to bacterial and viral infections (pINF.BAC.VIR: 1–75%) and for uses related to abortion, contraception, menstruation problems and vaginal infections (GYN1: 1–9%) while anti-cancer ethnomedicines (pCAN) showed an increase in the probability of finding anticancer drugs between 28%and 94%. Intriguingly also the category of use comprising mixed conditions and treatments that were not possible to classify otherwise and termed "various health disorders" (pVAR) showed a positive effect

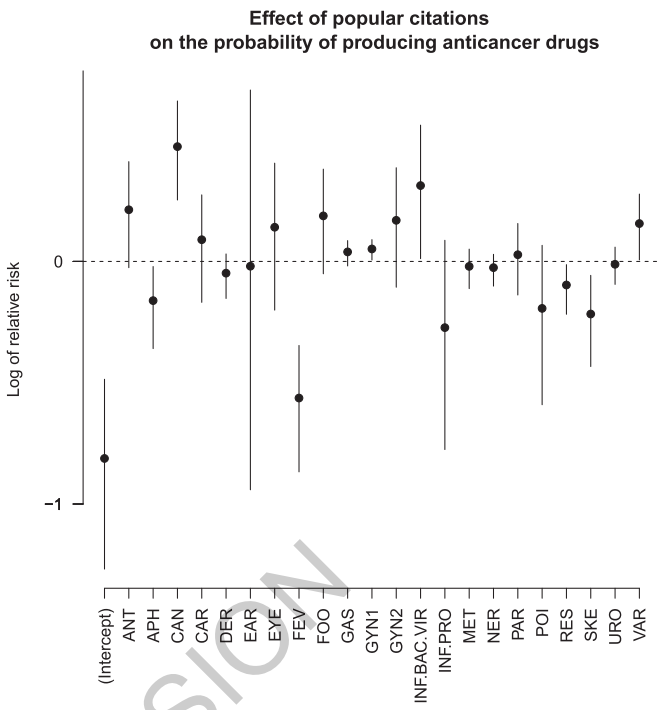

Fig. 5. 95% Probability interval for the effect of the popular uses on the probability of producing anticancer drugs (bCAN).

between 1% and 32% (**Supplementary Table 5**). Random effects of plant families have been found to be not significant.

5. Discussion

In the following discussion we try to explain some of the associations found with classic logistic and Bayesian logistic regression. We use pharmacological literature in an attempt to track the natural product drugs listed in Zhu et al. (2011) and to link them with the popular uses retrieved from NAPRALERT®.

5.1. Popular and biomedical use-patterns

The reason for the frequent clinical use of drugs developed from angiosperms and gymnosperms in cancer therapy (bCAN) is related to natural products' pharmacology, epidemiology and research emphasis. With respect to the frequency of citations, individual use-reports and number of remedies mentioned, dermatologic illnesses and gastrointestinal disorders are usually the most important use-categories in ethnomedicine and ethnopharmacological field-studies. It is remarkable that uses related to women's medicine (pGYN) were the most frequent in association with the 186 taxa in the NAPRALERT® database while it is intriguing that the 70 taxa used in the development of anticancer drugs showed an even higher proportion of pGYN. Since Binary Correspondence indicated associations for pGYN and bCAN (Fig. 3) and Bayesian logistic regression showed a positive effect of pGYN on bCAN (Fig. 5) in sections 5.3 and 5.4 we focus on this specific association.

5.2. Classic logistic regression

The high significance for the relation pNER/bNER found by the classic logistic regressions seems to confirm the validity of the idea of reverse ethnopharmacology as well as the classical ethnopharmacological approach (**Supplementary Table 3,** Fig. 4**)**. Since the approach to assure oneself of the effects of central nervous system active plant drugs is straightforward, and because the techniques to isolate

alkaloids are relatively simple, many of the first pure compounds isolated from plant drugs pertain to this class. The reason for the positive effect of pANT on bSKE has to do with the ethnomedicinal use of *Strychnos* spp., *Chondrodendron tomentosum*, *Cissampelos pareira* and *Datura metel* as antidotes, and lies probably in the pronounced toxicity of tubocurarine, strychnine, cissampeline and tropane alkaloids, all exerting effects on the skeletomuscular system.

The positive effect of pRES on bGYN is most likely due to *Justicia adhatoda* containing vasicine mediating oxytocic effects but having also bronchodilatory activity explaining the herb's use for respiratory tract ailments (NAPRALERT®, Claeson et al., 2000; Zutshi et al., 1980). Responsible for the same effect are *Allium cepa*, *A. sativum* and *Populus balsamifera*, which are mentioned in Zhu et al. to be used for the development of gemeprost, an analogue of prostaglandin E1 prescribed as an abortifacient and to treat bleeding during pregnancy or postpartum period. Intriguingly, in contrast with Zhu et al. no literature regarding the involvement of *Allium* sp. or *P. balsamifera* in the production of gemeprost could be found.

5.3. Fabaceae in women's medicine and anticancer activity

The Fabaceae are characteristic for the overall result of this analysis with 15 species or genera used for the production of anticancer drugs and 122 reports for gynaecological disorders (**Supplementary excel Table 1)**. However, with the exception of *Crotalaria* spp. and *Indigofera tinctoria* all anticancer related uses of the Fabaceae are due to the occurrence of isoflavones, also referred to as phytoestrogens. The reliance on Fabaceae for women's medicine is likely also condi-tioned by the presence of isoflavones. The NAPRALERT® database reports the roots of *Cicer arietinum,* seeds of *Pisum sativum,* tubers and herb of *Pueraria* spp., seeds of *Vicia faba* and those of *Vigna radiata* as contraceptives, whereas leaves of *Cicer arietinum*, seeds of *Glycine max*, seeds and herb of *Medicago sativa*, root and flowers of kutzu (*Prueraria* spp.), herb of *Trifolium pratense* and seeds of *Vigna radiata* as abortifacients. Genistein, daidzein and to a higher degree its metabolites equol and *O*-desmethylangolensin, bind to the estrogenic receptor of mammals transmitting estrogenic effects (Morito et al., 2001; Atkinson et al., 2005; Crozier et al., 2006). Phytoestrogens can affect the reproductive capacity of grazing mammals by disrupting the female reproductive system (Hearnshaw et al., 1972; Jefferson et al., 2007). Through this mechanism the pulses are thought to influence indirectly the population density of their predators. Probably also humans have experienced this effect through the consumption of Fabaceace products as food or/and human pastoralists have observed the effect leguminous plants can have on farm animals and adopted this knowledge for their own reproduction control. Isoflavones show multiple biological interactions. They are predominantly found in the Fabaceae where their occurrence is conserved across species and genera. Indeed, genistein has not only estrogenic effects but is also a potent DNA topoisomerase poison (Bandele et al., 2008), while daidzein was shown to induce apoptosis through a caspase dependent pathway triggered by the generation of reactive oxygen species (Jin et al., 2010). Also the isoflavone analogue phenoxodiol acts through the inhibition of topoisomerase II (Constantinou and Husband, 2002). Currently genistein and daidzein are under clinical trial with respect to prostate cancer and its prevention (Perabo et al., 2008; http://www. cancer.gov/search/results).

Indigofera tinctoria (only one record for women's disease in NAPRALERT®) contains the bis-indole dye and anticancer drug indirubin, which was found to be a potent inhibitor of cyclin-dependent kinases and glycogen synthase kinase (Hoessel et al., 1999; Cragg et al., 2009). The toxic pyrrolizidine alkaloid monocrotaline from *Crotalaria* spp. reported from around the world as an abortifacient (14 times) and contraceptive (five times) was found to have anticancer activity against hepatocellular carcinoma and was under clinical trial (Kusuma et al., 2014; Zhu et al., 2011).

5.4. Ethnomedicines for dysmenorrhoea as emmenagogues, contraceptives, abortifacients (pGYN) and anticancer therapy (bCAN)

Catharanthus roseus, the source of the potent anticancer drugs vinblastine and vincristine has 10 records against dysmenorrhoea, 8 as an emmenagogue and 5 entries as an abortifacient in the NAPRALERT® database. *Solanum aculeatissimum* was reported four times for the control of dysmenorrhoea in the NAPRALERT® database. Together with other *Solanum* spp., they contain the steroidal alkaloid glycoside solamargin with apoptosis inducing properties (Liu et al., 2004; Ding et al., 2013). A mixture of solamargines is currently used as a topical application against non-melanoma skin cancer (McDaniel and Goldman, 2002; Newman and Cragg, 2012). The NAPRALERT® database reports the use against menstrual complaints for the white birch, *Betula pubescens* (syn.: *Betula alba* L.) and *Corylus avellana*, the hazel tree. White birch contains betulin and the more active betulinic acid, which has a pronounced apoptosis inducing property against a range of cancer cell lines and tumours without affecting normal cells (Pisha et al., 1995; Tan et al., 2003; Alakurtti et al., 2006). *Corylus avellana* is a natural source of taxanes including paclitaxel, 10-deacetylbaccatin III, baccatin III, paclitaxel C and 7-epipaclitaxel (Ottaggio et al., 2008). *Podophyllum peltatum* had only two records for women's medicine, once against dysmenorrhoea and once as an emmenagogue. The major constituent of *P. peltatum*, the lignan podophyllotoxin induces cell cycle arrest during mitosis through the inhibition of tubulin polymerization but its semisynthetic, marketed anticancer drug derivatives etoposide and teniposide have a different mode of action (Lee and Xiao, 2005).

Drimia maritima (syn.: *Urginea*, *Scilla*, *Charybdys*) from which the clinical trial anticancer compound scillaren A is obtained was described in the *Corpus Hippocraticum* for different gynaecological problems such as pain and dislocation of the uterus applied as a plug (Aliotta et al., 2003, p.: 296). Here a link between anti-tumour properties and the ethnomedicinal treatment of secondary dysmenor-rhoea due to endometriosis, ovarian cysts, uterine leiomyomata and adenomyoma could theoretically exist but no records related to women's medicine are contained in the database.

The observation that species used to induce abortion are also relied upon as contraceptives and *vice versa*, has become apparent from the study of cuneiform texts from ancient Babylon, which do not distinguish abortifacients from agents that limit fertility (Böck, 2013). Although in classic times the conceptual distinctions between contraceptives and abortifacients were made, the drugs were interchangeably used (Riddle, 1994).

Elliptinium acetate, for instance, is a DNA intercalating agent and topoisomerase II stabilizer derived from ellipticine occurring in Apocynaceae (Rouëssé et al., 1993; http://www.cancer.gov/drugdictionary?cdrid=39231) such as *Aspidosperma* spp., with 7 records as a contraceptive and 6 as an abortifacient or *Tabernaemontana* spp. mentioned twice against dysmenorrhoea and once as a contraceptive in NAPRALERT®. Combretastatins are a group of stilbenoid compounds present in species of *Combretum* (Pettit et al., 1987; Eloff et al., 2005; Schwikkard et al., 2000) with inhibitory properties on tubulin polymerization (Cirla and Mann, 2003). Ethnomedicinal records of *Combretum* spp. related to women's medicine in NAPRALERT® show a consensus for abortifacients (9 times), contraction of the uterus (4 times), and menstrual pains (4 times). Brookes et al. (1999) confirmed the uterotonic activity of a hot water extract obtained from *Combretum kraussii* Hochst. while also a semipolar fraction containing combretastatin B-1, combretastatin B-1 glucoside and combretastatin A-1 glucoside exhibited contraction of isolated uterine tissue.

Maytansin and other maytansinoids are present in small quantities in different species of *Maytenus* and can block the assembly of microtubules by binding to tubulin leading to inhibition of cell division (Yu and Floss, 2005). In the NAPRALERT® database *Maytenus* spp. are mentioned 17 times as a contraceptive, twice as an abortifacient and 8

times for menstruation problems. From the roots of *Rubia cordifolia* a hexacyclodepsipeptide named RA-VII can be obtained able to cause G_2 arrest by changing the conformational structure of actin (Fujiwara et al., 2004). The root of *R. cordifolia* is used above all in India as an emmenagogue and for amenorrhea (21 times) and dysmenorrhoea (4 times).

The seeds of *Daucus carota* are mentioned as an abortifacient and contraceptive (14 times), an emmenagogue (14 times) and as a labour stimulant (4 times), coinciding with the uses of carrot seeds in European antiquity (Jansen and Wohlmuth, 2014). Alitretionin is the 9-cis form of retinoic acid deriving from provitamin A present in carrot roots (Theodosiou et al., 2010) and approved for the treatment of skin lesions in AIDS related Kaposi's sarcoma (Lawrence et al., 2001), but compounds of the provitamin A class such as beta-carotene seem to be absent from carrot seeds (Özcan and Chalchat, 2007).

Twigs of *Taxus baccata*, a source of the potent anticancer compound paclitaxel, are reported six times as an abortifacient and once as a contraceptive. Tubulin depolymerisation agents such as combretastatins, maytansinoids, vincristine and vinblastine, tubulin stabilizers such as paclitaxel, stabilizers of filamentous actin such as RA-VII and topoisomerase poisons such as ellipticine mediate cytotoxic effects in biological systems affecting above all fast growing tissues such as tumours but also embryos.

The popular use of contraceptives, especially abortive medications, often shows high concomitant toxicity at times leading even to the death of the patient herself (Ciganda and Laborde, 2003; Grimes et al., 2006). Linked with uses as herbal abortifacients and emmenagogues (310 GYN1-ABO-MEN reports for species associated with bCAN) as well as contraceptives (71 GYN1-CON reports for species associated with bCAN) are also oxytocic and uterotonic activities (Ciganda and Laborde, 2003) but only 58 reports are associated with bCAN for the induction of labour or the expulsion of the placenta (GYN1-BIR). Although there is an obvious lack of clinical studies with respect to noxious exogenous substances, the first trimester of gestation is regarded as the most delicate for the embryo (Ebert et al., 1997).

5.5. Pharmacological congruence, feedback-loop and limitations

Vincristine and vinblastine, obtained from *Catharanthus roseus*, are prescribed for the treatment of leukaemia and Hodgkin's disease, while the intercultural ethnomedicinal consensus in the NAPRALERT® database of *C. roseus* lies on diabetes and women's disease. However, there are also six entries reporting its anticancer use, from India, Mexico, Peru and the Cook Islands, two specifying the use against Hodgkin's lymphoma. The alkaloid homoharringtonine, occurring in several *Cephalotaxus* species (one ethnomedicinal record in NAPRALERT® against cancer), leads to apoptosis by the inhibition of protein synthesis preventing substrate binding to the 60 s ribosome subunit (Itokawa et al., 2005; Abdelkafi and Nay, 2012) and is currently assessed in different clinical trials for chronic myeloid leukaemia (Pan et al., 2010).

Several ethnomedicinal reports related to anticancer activity are probably conditioned by the feedback loop exerted by globalization and the divulgence of biomedical knowledge (c.f. Leonti, 2011). Whether this knowledge is also translated into medical applications or just stored passively is yet another question. Other uses, however, such as that of *Artemisia annua* as a home-based treatment for malaria are actively promoted (Willcox et al., 2011). The influence of biomedical knowledge on local medicine is, however, not always clearly recogniz-able and often remains ambiguous as well as the apparent similar uses of taxa in biomedicine and ethnomedicine. The ethnomedicinal con-sensus for *Berberis vulgaris* is “gastrointestinal disorders” (34 out of 84 records), which coincides quite well with the biomedical consensus for berberine, which is bacillary dysentery (Fabricant and Farnsworth, 2001) but zooming in on the exact indications the picture gets ambiguous with 18 reports against stomach and liver disorders (incl. jaundice), six citations as a laxative or purgative, two as a blood rectifier and only six reports mentioning the use against diarrhoea and typhus.

The ethnomedicinal records for *Juniperus sabina* in NAPRALERT® mention the induction of abortion (20 times) and its use as a contraceptive (once). The essential oil of *Juniperus sabina* is highly toxic and the twigs of this species are used since antiquity to induce abortions (Matthioli, 1568, Book I, p. 136). The monoterpenoid perillyl alcohol can be obtained from the essential oil of various plant species, including *Juniperus sabina* and is under phase II clinical trial for different oncological diseases (da Fonseca et al., 2008; Zhu et al., 2011). However, perillyl alcohol has a low toxicity towards normal cells and was shown to specifically induce apoptosis in tumour cells *in vitro* (Belanger, 1998) acting via a caspase-3 pathway (Yeruva et al., 2007). The case of *J. sabina* is clearly not an example validating the reverse ethnopharmacology approach since the active principles selected for treatment are different between the biomedical and ethnomedicinal domains. The same accounts for carrot seeds, which do not contain provitamin A derivatives or for *Maytenus serrata* (Hochst. ex A.Rich.) R.Wilczek (unresolved), which afforded scanty 0.2 mg maytansine per kg of dried plant material (Yu and Floss, 2005) and is thus practically not bioavailable in an ethnomedicinal setting. However, the observation made by Spjut (2005), that poisonous species show a higher rate of activity in cytotoxicity screens, is paralleled by our finding that plants used for the development of anticancer drugs are associated with remedies used to control dysmenorrhoea as well as contraceptives and abortifacients.

Reasons why the category pVAR showed a positive effect in Bayesian logistic regression on the probability of finding anticancer leads might be that among the health conditions we were not able to assign into any of the more precisely described categories of use, neoplastic disease related symptoms are included.

We tried to explain the observed associations between popular gynaecological uses and anticancer therapy through published pharmacological and biological data. However, statistics does not provide absolute answers but rather indications with degrees of certainty as to where the truth may lie and therefore the cultural and pharmacological reasons for each association would need to be further assessed.

6. Conclusions

With the application of Bayesian logistic regression we introduce the concept that it is possible to estimate the probability that a plant taxon produces biomedical drugs based on ethnopharmacological cues. Reverse ethnopharmacology confirmed the validity of the classic ethnopharmacological strategy but also the existence of cross-over relationships focusing on cancer therapy, where ethnomedicinal cues generally have a limited predictive power. Our data suggests that traditional and popular remedies used against viral and bacterial infections, and those used to control dysmenorrhoea and applied as contraceptives and abortifacients have a higher probability of providing anticancer drugs or their leads than average ethnomedicinal collections. These ethnomedicinal uses are conceptually related to fighting off exogenous agents including embryos, ovules, germs and neoplastic tissues with the help of medicinal plants exerting cytotoxic effects through the inhibition of mitosis, DNA and ribosomal protein synthesis. Promiscuous molecular interactions of isoflavones, including the targeting of the estrogenic receptor and proteins crucial in anticancer therapy seem to account for the uses in women's medicine of several Fabaceae herbal drugs.

Ethnobotanical and ethnopharmacological field-studies are accumulating a vast body of knowledge about the use of herbal drugs in local and traditional medicines from around the world. Globalization accelerates the intermingling of biomedical knowledge with popular medicinal uses generating a confounding effect, which should be considered. Finally, a statistical significant result does not definitively prove anything but can elude to patterns and correlations, thus

"reverse ethnopharmacology" needs to be further assessed with experimental data to show that these observations are indeed real (correlation to causation).

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Appendix A. List of all 225 drug or clinical trial drug producing taxa taken from Zhu et al. (2011, S5–7). For 186 taxa popular and ethnomedicinal uses were available through the NAPRALERT® database and used for the comparison. Species were crosschecked with theplantlist.org for accepted Latin binomials before the database search was performed. Species in brackets and with italic numbers (*39*) retrieved no ethnomedicinal records from the NAPRALERT® database

1.	**Acanthaceae**
1	*Justicia adhatoda* L.
2	*Spinacia oleracea* L.
2.	**Amaranthaceae**
3	*Spinacia oleracea* L.
3.	**Amaryllidaceae**
4	*Allium cepa* L.
5	*Allium sativum* L.
6	*Lycoris radiata* (L'Hér.) Herb.
(1)	(*Galanthus elwesii* Hook.f.)
(2)	(*Galanthus nivalis* L.)
(3)	(Galanthus woronowii Losinsk.)
(4)	(*Leucojum aestivum* L.)
(5)	(*Lycoris squamigera* Maxim.)
(6)	(*Narcissus pseudonarcissus* L.)
4.	**Annonaceae**
7	*Artabotrys* spp.
5.	**Apiaceae**
8	*Ammi majus* L.
9	*Ammi visnaga* (L.) Lam
10	*Carum carvi* L.
11	*Daucus carota* L.
12	*Centella asiatica* (L.) Urb.
13	*Apium graveolens* L.
14	*Petroselinum crispum* (Mill.) Fuss
15	*Lomatium* spp.
6.	**Apocynaceae**
16	*Acokanthera oblongifolia* (Hochst.) Benth. & Hook.f. ex B.D.Jacks.
17	*Acokanthera oppositifolia* (Lam.) Codd
18	*Asclepias syriaca* L.
19	*Aspidosperma quebracho-blanco* Schltdl.
20	*Catharanthus roseus* (L.) G.Don
21	*Hoodia gordonii* (Masson) Sweet ex Decne.
22	*Marsdenia* spp.
23	*Rauvolfia serpentina* (L.) Benth. ex Kurz
24	*Rauvolfia vomitoria* Afzel.
25	*Tabernaemontana* spp.
26	*Vinca minor* L.
(7)	(*Ochrosia elliptica* Labill.)
(8)	(*Strophanthus gratus* (Wall. & Hook.) Baill.)
7.	**Araliaceae**
27	*Panax ginseng* C.A.Mey.
8.	**Arecaceae**
28	*Serenoa repens* (W.Bartram) Small
29	*Areca catechu* L.
30	*Cocos nucifera* L.
9.	**Asparagaceae**

31	*Convallaria majalis* L.
32	*Drimia maritima* (L.) Stearn
10.	**Asteraceae**
33	*Artemisia annua* L.
34	*Artemisia argyi* H.Lév. & Vaniot
35	*Artemisia dracunculus* L.
36	*Artemisia maritima* L.
37	*Cynara scolymus* L.
38	*Cynara cardunculus* L.
39	*Dittrichia viscosa* (L.) Greuter
40	*Matricaria chamomilla* L.
41	*Inula britannica* L.
42	*Silybum marianum* (L.) Gaertn.
43	*Stevia rebaudiana* (Bertoni) Bertoni
44	*Xanthium strumarium* L.
45	*Chrysanthemum* spp.
46	*Doellingeria scabra* (Thunb.) Nees
11.	**Berberidaceae**
47	*Berberis vulgaris* L.
48	*Dysosma pleiantha* (Hance) Woodson
49	*Leontice leontopetalum* L.
50	*Podophyllum peltatum* L.
(9)	(*Sinopodophyllum hexandrum* (Royle) T.S.Ying)
12.	**Betulaceae**
51	*Corylus avellana* L.
52	*Betula pubescens* Ehrh.
13.	**Bignoniaceae**
53	*Tabebuia* spp.
14.	**Boraginaceae**
54	*Cordia verbenacea* A.DC.
55	*Symphytum officinale* L.
15.	**Brassicaceae**
56	*Brassica nigra* (L.) K.Koch
57	*Brassica oleracea* L.
58	*Brassica rapa* L.
59	*Sinapis alba* L.
60	*Rorippa indica* (L.) Hiern
61	*Isatis tinctoria* L.
16.	**Burseraceae**
62	*Commiphora wightii* (Arn.) Bhandari
17.	**Calophyllaceae**
63	*Calophyllum* spp.
18.	**Campanulaceae**
64	*Lobelia inflata* L.
19.	**Cannabaceae**
65	*Cannabis sativa* L.
20.	**Celastraceae**
66	*Tripterygium wilfordii* Hook. f.
67	*Maytenus* spp.
21.	**Colchicaceae**
68	*Colchicum autumnale* L.
22.	**Combretaceae**
69	*Combretum* spp.
23.	**Convolvulaceae**
70	*Ipomoea violacea* L.
71	*Turbina corymbosa* (L.) Raf.
72	*Cuscuta australis* R.Br.
73	*Cuscuta chinensis* Lam.
24.	**Cornaceae**
74	*Camptotheca acuminata* Decne.
25.	**Cucurbitaceae**
75	*Hemsleya* spp.
26.	**Cupressaceae**
76	*Juniperus sabina* L.
77	*Thuja occidentalis* L.
27.	**Ephedraceae**

78 *Ephedra* spp.
28. **Ericaceae**
79 *Vaccinium vitis-idaea* L.
29. **Erythroxylaceae**
80 *Erythroxylum coca* Lam.
30. **Euphorbiaceae**
81 *Croton sublyratus* Kurz
82 *Croton lechleri* Müll.Arg.
83 *Euphorbia esula* L.
84 *Euphorbia peplus* L.
85 *Euphorbia serrata* L.
86 *Ricinus communis* L
87 *Homalanthus nutans* (G.Forst.) Guill.
(10) (*Croton stellatopilosus* H.Ohba)
(11) (*Hippomane mancinella* L.)
31. **Fabaceae**
88 *Acacia berlandieri* Benth.
89 *Acacia catechu* (L.f.) Willd.
90 *Acacia farnesiana* (L.) Willd.
91 *Senna alexandrina* Mill.
92 *Castanospermum australe* A.Cunn. & C.Fraser
93 *Ceratonia siliqua* L.
94 *Cicer arietinum* L.
95 *Crotolaria* spp.
96 *Genista tinctoria* L.
97 *Glycine max* (L.) Merr.
98 *Glycyrrhiza glabra* L.
99 *Indigofera tinctoria* L.
100 *Lens culinaris* Medik.
101 *Lonchocarpus* spp.
102 *Medicago sativa* L.
103 *Melilotus officinalis* (L.) Pall.
104 *Mucuna pruriens* (L.) DC.
105 *Phaseolus lunatus* L.
106 *Pisum sativum* L.
107 *Pueraria* spp.
108 *Sophora alopecuroides* L.
109 *Sophora flavescens* Aiton
110 *Trifolium pratense* L.
111 *Vicia faba* L.
112 *Vigna angularis* (Willd.) Ohwi & H.Ohashi
113 *Vigna radiata* (L.) R.Wilczek
114 *Vigna unguiculata* (L.) Walp.
(12) (*Acacia rigidula* Benth.)
(13) (*Cullen corylifolium* (L.) Medik.)
(14) (*Melilotus albus* Medik.)
(15) (*Phaseolus coccineus* L.)
(16) (*Physostigma venenosum* Balf.)
(17) *(Sophora pachycarpa C.A.Mey.)*
(18) (*Sophora prostrata* Buchanan)
32. **Himantandraceae**
115 *Galbulimima belgraveana* (F.Muell.) Sprague
33. **Icacinaceae**
(19) (*Mappia foetida* (= *Nothapodytes nimmoniana* (J.Graham) Mabb.))
34. **Lamiaceae**
116 *Lavandula* spp.
117 *Mentha spicata* L.
118 *Perilla frutescens* (L.) Britton
119 *Salvia officinalis* L.
120 *Thymus vulgaris* L.
(20) (*Monarda didyma* L.)
(21) (*Plectranthus barbatus* Andrews)
35. **Lauraceae**
121 *Cinnamomum camphora* (L.) J.Presl
122 *Laurus nobilis* L.
(22) (*Ocotea glaziovii* Mez)

36. **Loganiaceae**
123 *Strychnos* spp.
37. **Malvaceae**
124 *Theobroma cacao* L.
(23) (*Theobroma angustifolium* Sessé & Moc. ex DC.)
(24) (*Theobroma bicolor* Humb. & Bonpl.)
38. **Melanthiaceae**
125 *Veratrum album* L.
39. **Meliaceae**
126 *Dysoxylum* spp.
127 *Aglaia* spp.
40. **Menispermaceae**
128 *Anamirta cocculus* (L.) Wight & Arn.
129 *Chondrodendron tomentosum* Ruiz & Pav.
130 *Cissampelos pareira* L.
131 *Curarea* spp.
(25) (*Anomospermum grandifolium* Eichler)
(26) (*Stephania rotonda* Lour.)
41. **Moraceae**
132 *Morus alba* L.
42. **Myrtaceae**
133 *Leptospermum* spp.
134 *Syzygium cumini* (L.) Skeels
(27) (*Callistemon citrinus* (Curtis) Skeels)
(28) (*Syzygium claviflorum* (Roxb.) Wall. ex A.M.Cowan & Cowan)
43. **Oleaceae**
135 *Fraxinus ornus* L.
44. **Papaveraceae**
136 *Corydalis ambigua* Cham. & Schltdl.
137 *Glaucium flavum* Crantz
138 *Papaver somniferum* L.
139 *Sanguinaria canadensis* L.
(29) (*Papaver bracteatum* Lindl.)
45. **Pinaceae**
140 *Cedrus deodara* (Roxb. ex D.Don) G.Don
141 *Pinus sylvestris* L.
142 *Tsuga canadensis* (L.) Carrière
(30) (*Larix sibirica* Ledeb.)
46. **Piperaceae**
143 *Piper methysticum* G.Forst.
47. **Plantaginaceae**
144 *Digitalis purpurea* L.
(31) (*Digitalis lanata* Ehrh.)
48. **Poaceae**
145 *Oryza sativa* L.
146 *Triticum* spp.
147 *Zea mays* L.
(32) (*Cymbopogon martini* (Roxb.) W.Watson)
49. **Quillajaceae**
148 *Quillaja saponaria* Molina
50. **Ranunculaceae**
149 *Adonis vernalis* L.
150 *Thalictrum* spp.
(33) (*Hydrastis canadensis* L.)
51. **Rosaceae**
151 *Agrimonia eupatoria* L.
152 *Malus domestica* Borkh.
153 *Prunus tomentosa* Thunb.
154 *Pyrus* spp.
(34) (*Potentilla fragarioides* L.)
52. **Rubiaceae**
155 *Cinchona* spp.
156 *Coffea arabica* L.
157 *Galium odoratum* (L.) Scop.
158 *Pausinystalia* spp.
159 *Rubia cordifolia* L.

(35)	(*Ophiorrhiza pumila* Champ. ex Benth.)
53.	**Rutaceae**
160	*Citrus limon* (L.) Osbeck
161	*Pilocarpus* spp.
(36)	(*Sarcomelicope* spp.)
54.	**Salicaceae**
162	*Populus balsamifera* L.
163	*Salix* spp.
55.	**Sapindaceae**
164	*Aesculus hippocastanum* L.
165	*Paullinia cupana* Kunth
56.	**Simaroubaceae**
166	*Brucea antidysenterica* J.F.Mill.
57.	**Solanaceae**
167	*Atropa belladonna* L.
168	*Hyoscyamus niger* L.
169	*Mandragora officinarum* L.
170	*Capsicum annuum* L.
171	*Capsicum frutescens* L.
172	*Datura metel* L.
173	*Datura stramonium* L.
174	*Nicotiana tabacum* L.
175	*Solanum aculeatissimum* Jacq.
176	*Solanum americanum* Mill.
177	*Solanum incanum* L.
(37)	(*Anisodus tanguticus* (Maxim.) Pascher)
58.	**Taxaceae**
178	*Taxus baccata* L.
179	*Taxus brevifolia* Nutt.
180	*Taxus wallichiana* Zucc.
181	*Cephalotaxus fortunei* Hook
(38)	(*Cephalotaxus harringtonii* (Knight ex J.Forbes) K.Koch)
59.	**Theaceae**
182	*Camellia sinensis* (L.) Kuntze
60.	**Thymelaeaceae**
(39)	(*Pimelea* spp.)
61.	**Zingiberaceae**
183	*Zingiber officinale* Roscoe
184	*Curcuma longa* L.
62.	**Zygophyllaceae**
185	*Larrea tridentata* (Sessé & Moc. ex DC.) Coville *Larrea*
186	*divaricata* Cav.

Appendix B. Number of biomedical drugs (according to Zhu et al., 2011) and popular use-citations (according to NAPRALERT®) associated with the disease categories.

	ANT	APH	CAN	CAR	DER	EAR	EYE	FEV	FOO	GAS
Biomed Total	1	5	82	33	10	0	6	0	4	15
Biomed/Nap.	1	4	70	27	9	0	5	0	4	12
Popular	151	149	127	182	851	33	82	260	154	1177
Popular %	1.98	1.95	1.67	2.39	11.18	0.43	1.08	3.42	2.02	15.47
Pop./bCAN	65	60	78	73	323	13	36	74	70	489
Pop./bCAN %	2.14	1.97	2.56	2.40	10.62	0.43	1.18	2.43	2.30	16.07

	GYN	INF	MET	NER	PAR	POI	RES	SKE	URO	VAR
Biomed Total	8	32	27	36	3	3	24	6	6	0
Biomed/Nap.	5	29	25	23	3	3	22	6	4	0
Popular	1182	255	224	681	249	48	671	287	395	452
Popular %	15.53	3.35	2.94	8.95	3.27	0.63	8.82	3.77	5.19	5.94
Pop./bCAN	563	104	87	232	93	14	211	91	170	196
Pop./bCAN %	18.51	3.42	2.86	7.63	3.06	0.46	6.94	2.99	5.59	6.44

	TOTAL
Biomed Tot.	**301**
Biomed/Nap.	**252**
Popular	**7610**
Popular %	**100%**
Pop./bCAN	**3042**
Pop./bCAN %	**100%**

Biomed/Tot. = Total number of drugs and clinical trial drugs deriving from the 225 taxa; Biomed/Nap. = Number of drugs and clinical trial drugs deriving from the 186 taxa retrieving popular results with NAPRALERT®; Popular = Number of popular use-citations associated with the 186 taxa in NAPRALERT®; Pop. % = Percentage of popular use-citations; Pop./bCAN = Number of popular use-citations associated with the 70 taxa used for the development of anticancer drugs; Pop./bCAN % = Percentage of popular use-citations associated with the 70 taxa used for the development of anticancer drugs.

Appendix C. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jep.xxxx.xx.xxx.

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