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Reverse ethnopharmacology and drug discovery

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ABSTRACT

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 ethnopharmacology" 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).

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 contradictive, complicate the selection of bioassays and the ethnopharmacological 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, multifaceted, 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 biomedical?) 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