Journal of Ethnopharmacology 147 (2013) 92–107

Contents lists available at SciVerse ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jep

Bioprospecting: Evolutionary implications from a post-olmec pharmacopoeia and the relevance of widespread taxa

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ARTICLE INFO

Article history:
Received 13 November 2012
Received in revised form
3 February 2013
Accepted 4 February 2013
Available online 20 February 2013

Keywords:
Biogeography
Biomics
Cognitive anthropology
Co-evolution
Macro-Maya
Phylogeny

ABSTRACT

Ethnopharmacological relevance: "Nothing in biology makes sense except in the light of evolution" [1] The historical legacy and relevance of ethnopharmacology in drug discovery is undisputed. Here we connect the parameters influencing the selection of plant derived medicines by human culture with the concept of evolution.

Aim of the study: In the present contribution we compare global data with local data and try to answer the questions, to what extent are the taxonomic clades included in indigenous pharmacopoeias associated with certain ailment groups, and to what extent can ecology and phylogeny, which we consider a proxy for chemical relatedness and convergence, account for the observed bias?

Materials and methods: We use an approximated chi-square test (χ^2) to check for associations between 12 ethnomedical use-categories and 15 taxonomical clades. With cluster analyses we test for correlations between phylogeny and use-categories. We compare the 67 drug-productive families identified by Zhu et al.[2] with the medicinal flora of the Popoluca and the APG database and compare our results with the phylogenetic target classes evidenced by Zhu et al. Furthermore, we compare the medicinal flora of the Popoluca with the world's weeds (cf. Holm et al.)[3] and discuss our results in relation to anthropological rationales for plant selection.

Results: The null-hypothesis "species from the 15 taxonomic clades are selected proportionally to their share in the treatment of the twelve organ- and symptom-defined use-categories" is rejected. The cluster dendrogram for the clades shows that the use patterns are to a certain extent associated with Angiosperm phylogeny. With the occurrence of 53 families the 67 drug-productive families are overrepresented in the regional flora of the Popoluca. The importance of these families in terms of their share is even more pronounced with the medicinal flora holding around 70% of all individual Popoluca informant responses.

Conclusions: The overall phylogenetic use pattern is influenced by both the inherent pharmacological properties, which depend on phylogeny, biogeography, ecology and ultimately allelopathy, and on culture-specific perception of organoleptic properties. The comparison of the 67 drug-productive Viridiplantae families with the ethnopharmacopoeia of the Popoluca and the APG database, shows that "traditional" pharmacopoeias and plant-derived drugs are obtained from widespread and species-rich taxa. This is not a function of family size alone. We put forward the theory that as a function of

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[2] Zhu et al., 2011. Clustered patterns of species origins of nature-derived drugs and clues for future bioprospecting. Proceedings of the National Academy of Sciences of the USA. 108, 12943–12948.

[3] Holm et al., 1979. A Geographical Atlas of World Weeds. John Wiley & Sons, New York.

http://dx.doi.org/10.1016/j.jep.2013.02.012

evolution, widespread taxa contain a broader range of accumulated ecological information and response encoded in their genes relative to locally occurring taxa. This information is expressed through the synthesis of allelochemicals with a wide ecological radius, showing broad-spectrum biota-specific interactions, including the targeting of proteins of mammals and primates.

1. Introduction

Biological diversity is evidence for chemical diversity and a reliable and proven source for the discovery of new drugs (McChesney et al., 2007; Li and Vederas, 2009; Newman and Cragg, 2012). Although indigenous pharmacopoeias are cultural constructs and embedded in belief systems, the empirical evaluation of medicinal and poisonous plant use has made a considerable contribution to the progress of pharmacology and drug discovery. Notwithstanding this rich and successful historical legacy, the interdisciplinary endeavour of drug discovery from medicinal plants faces several scientific as well as political challenges (Balunas and Kinghorn, 2005; Gertsch, 2009; Cragg et al., 2012).

Higher plants, the predominant source of indigenous pharmacopoeias, produce a rich diversity of secondary metabolites (cf. Hegnauer, 1962–1996). In ecology such metabolites are conceived of as allelochemicals, while organic chemists more neutrally classify them as "natural products" (Feher and Schmidt, 2003; Wink, 2003). Angiosperms are engaged in inter-specific relationships and have had to adapt to herbivorous and microbial attack throughout their evolution (Frohne and Jensen, 1998, p. 5; Wink, 2003). Driven by genetic recombination and mutation and guided by natural selection, plants have developed allelochemicals able to interfere with molecular targets within the tissues and cells of animals, fungi, bacteria and viruses (Verdine 1996; Wink, 2003). Co-evolution has enabled plants to develop synthesis pathways leading to chemical structures mimicking endogenous substrates produced by herbivores such as hormones, neurotransmitters and ion-channel ligands, as well as structures interfering with functional proteins in general (Wink, 2003; Rollinger et al., 2006; Ramesha et al., 2011). By analogy with the strategy of molecular modelling applied in medicinal chemistry, Wink (2003) proposed referring to the shaping of secondary metabolites in plants during evolution as "evolutionary molecular modelling", while Verdine (1996) pointed out that it was nature which first "invented" combinatorial chemistry.

Since organisms are adapted to deal with the ecological constraints of the environment where they evolved, secondary metabolites represent adaptive traits that are similar within members of a taxon, and occasionally between taxa exposed to similar, ecologically driven selection pressures. Consequently Hegnauer (1962–1996) and other scholars embarked on chemotaxonomy using the presence or absence of chemical markers as evidence for phylogenetic relatedness (cf. Hegnauers' "Chemotaxonomie der Pflanzen"). This approach allowed for generalizations about the taxonomic distribution pattern of secondary metabolites (Grayer et al., 1999; Wink and Waterman, 1999; Rønsted et al., 2012). However, chemical convergence, or the ability of unrelated taxa to synthesize the same class of metabolites occurs quite frequently. Therefore, chemical markers alone are not sufficient to establish a phylogenetic system reflecting pure genetic relationships (Grayer et al., 1999): Only the comparative analysis of nucleotide sequences from the chloroplast gene *rbc*L, obtained from a total of 974 seed plants by Chase et al. (1993), resulted in a cladogram based on purely genetic cues. Pursuance of the molecular approach by The Angiosperm Phylogeny Group (2009), continuously updated via their Website (Stevens 2001 onwards, http://www.mobot.org/MOBOT/research/APweb/), is approximating taxonomy by reflecting evolutionary relationships across plant biodiversity.

Humans however, do not evenly exploit biological diversity for medicinal purposes. Neither in the compilation of indigenous pharmacopoeias nor in the development of modern biomedicine, is biodiversity represented proportionally with respect to its phylogenetic share. A recent census by Zhu et al. (2011) revealed that an overwhelming part of FDA approved and clinical-trial natural product drugs are obtained from clustered and disjunct taxonomic clades. Moreover, phylogeny was found to be associated with target classes (Zhu et al., 2011). Nor are medicinal plants contained in pharmacopoeias selected proportionately from the available floral clades. Moerman (1979), and subsequently several different authors, have shown that indigenous pharmacopoeias are biased in favour of certain phylogenetic clades and taxa (for an overview see: Weckerle et al., 2011). Different quantitative and systematic approaches to the analysis of ethnopharmacopoeias, integrating phylogeny, phytochemistry and pharmacology in an attempt to develop methods for identifying promising plant taxa for drug discovery, or with the aim of revealing universal concepts of phytotherapy, have been proposed and discussed (e.g., Moerman et al., 1999; Leonti et al., 2003a; Saslis-Lagoudakis et al., 2011; Weckerle et al., 2011; Gyllenhaal et al., 2012; Adams et al., in press). Based on the outcome of a combined analysis of a genus-level molecular phylogenetic tree and data from medical ethnobotany, Saslis-Lagoudakis et al. (2012a) claim that "phylogenies reveal predictive power of traditional medicine in bioprospecting". A systematic approach to the question as to whether samples from traditional medicine, or random sample collections, achieve higher number of hits in biomedical screening systems, resulted in ambivalent results by showing a patterned support for some ethnomedical disease categories, such as tuberculosis and malaria, although intriguingly, plants used against viral and central nervous system diseases showed the highest number of hits in the antiplasmodial screen (Gyllenhaal et al., 2012; Soejarto et al., 2012). An evaluation of archive data from the National Cancer Institute (NCI) showed that plant species used in "traditional" medicine achieved higher number of hits in experimental tumour systems when compared to random collections (Spjut and Perdue, 1976; see also Cordell et al., 1991), while medicinal plants from Peru used to treat ailments caused by bacterial infections were significantly more likely to show activity in an antibacterial *in vitro* screening with respect to medicinal species used for other kind of disorders (Bussmann et al., 2011). However, in contrast to etic and biomedical approaches towards the evaluation of the effectiveness of ethno-medicine, is the emic perspective of its perceived "efficacy". Therefore, "efficacy" depends on the specific socio-cultural context (Etkin, 1988). On the other hand, the persistence of [etically] "ineffective" medical treatments has been explained by Tanaka et al. (2009) through the implementation of mathematical models simulating cultural evolution. They based their model on the plausible assumption that ineffective treatments are practiced and thus demonstrated more persistently than successful treatments and consequently have a more prolonged impact on social learning and copying (Tanaka et al., 2009). Similarly, the repeated unbiased and uncritical copying – and putting into practice – of textual information, assures that ineffective or even harmful medicinal treatments persist (Leonti, 2011).