Indian Journal of Traditional Knowledge
Vol. 14(4), October 2015, pp. 605-608

Selection of medicinal plants - Evolutionary considerations for Ethnopharmacology and drug discovery

Marco Leonti

Department of Biomedical Sciences, University of Cagliari, Via Ospedale 72, 09124 Cagliari (CA), Italy
E-mails: marcoleonti@netscape.net; mleonti@unica.it

Received 17 April 2015, revised 7 Sepember 2015

Biological diversity is evidence for chemical diversity. Secondary metabolites are adaptive traits, similar within members of a taxon and occasionally also between taxa exposed to similar ecological selection pressures. Chemo diversity is thus not distributed evenly across plant biodiversity. But how are biodiversity, drug discovery, traditional medicines and ethno pharmacology related? Only 62 out of a total of 457 Angiosperm and Gymnosperm plant families are used as a source for biomedical drugs (Zhu *et al*., 2011, PNAS). Plant taxa used in traditional and local medicines belong to an over-proportional extent to the same 62 families. A cross-check with the Angiosperm Phylogeny Website showed that these 62 families are over-proportionally species-rich and widespread. We hypothesized that as a function of evolution, widespread taxa contain a broader range of ecological information encoded in their genes with respect to taxa with a local evolution history (Leonti *et al*., 2013, JEP). We argued that as a consequence widespread taxa synthesize metabolites with a wider ecological than taxa with a geographically limited geographical distribution.

Keywords: Selection of medicinal plants, Medicinal flora, Biomedicine, Herbal medicine, Biogeography, *Popoluca* tribe

IPC Int. Cl.[8]: A61K36/00

The definitions of "bioprospecting" vary with respect to the research focus and the disciplinary backgrounds. While for ethno botanists the term "bioprospecting" includes the "search for value in the biological world"[1], for natural product chemists bioprospecting means "the process if discovery of bioactive principles…from natural sources"[2].

Although I am aware that there is a paradigm shift in drug discovery in that network pharmacology and its associated synergistic and antagonistic multi-mechanistic interactions is gaining therapeutical acceptance, the present retrospective contribution is dedicated to bioprospection for single compound drugs.

The focus of bioprospecting is nature's chemo diversity and since biological diversity is evidence for chemical diversity the biodiversity hotspots have always stood at the center of bioprospecting endeavours[3,4]. The compounds of interest are secondary metabolites referred to by ecologist as "allele chemicals". Allelo-chemicals are adaptive traits similar within members of a phylogenetic lineages and taxonomic groups and occasionally also between unrelated taxonomic groups exposed to similar ecology driven selection pressures[5,6]. Co-evolution and natural selection led to the development of biosynthesis pathways able to synthesize chemical structures mimicking endogenous substrates of herbivores such as hormones, neurotransmitters and compounds able to interact with functional proteins in general[6]. Since, chemo diversity is not distributed evenly across plant biodiversity the question is as to how biodiversity and drug discovery are related.

This question is currently addressed by an EU-funded interdisciplinary research project called "Med Plant" (www.MedPlant.eu) with phylogeny as the overarching theme. The whole project is divided into three work packages:

1 "Evolution of Chemical Diversity", investigating the correlation between phylogenetic and chemical diversity[7-9],

2 "Development of Pharmacopoeias", exploring the interface between human cognition, phylogeny, the selection of medicinal plants and development of pharmacopoeias[10,11],

3 "Sustainability and safety of medicinal plant use" utilizes sequence data to characterize the distribution of medicinal plant diversity[12].

Development of herbal pharmacopoeias and the selection of medicinal floras

In the following I focus on the composition of pharmacopoeias from a taxonomic and phylogenetic point of view. The process of medicinal plant selection, the development and shaping of pharmacopoeias depends on parameters and forces driven by cultural as well as biological factors and can be described by the social as well as the natural sciences[13].

On the flowchart (**Fig. 1**) I tried to pin down some central factors that influence the selection of medicinal plants and herbal pharmacopoeias (medicinal floras). In this trans-disciplinary flow chart the outer, larger ring represents the natural sciences, while the inner circle shows the social sciences. Since, the chart is about evolution and co-evolution, the arrows always point into both directions, because all factors condition each other. Notably, due to our ability of genetic engineering cultural history also influences phylogeny and taxonomy.

Factors influencing the selection of medicinal plants and herbal pharmacopoeias accessible with natural sciences are:

1 Phylogeny - Taxonomy
2 Pharmacology - Epidemiology
3 Secondary metabolites – Allelo-chemicals
4 Chemical Ecology - Allelopathy
5 Biogeography

Factors influencing the selection of medicinal plants and herbal pharmacopoeias accessible with social sciences are:

1 Cultural history - Anthropology of medicine
2 Perception, cognition, meaning response - placebo effect
3 Local and global availability through marketing and cultural exchange
4 Vertical, horizontal and oblique ways of knowledge transmission

The questions deriving from this flowchart and central our project are two:

A) Why and how does a plant become a medicinal plant?

The obvious answer would be: "Because it works!"

B) Why is a medicinal plant indicated for (a) specific health condition(s)?

The obvious answer would be: "Because it works exactly against that or these symptoms and illnesses for which it is used!"

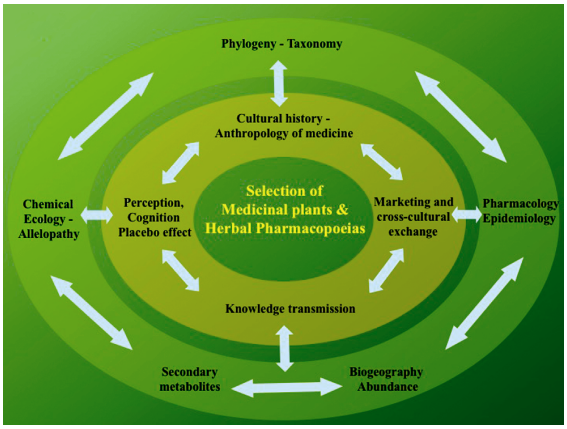

Fig. 1—Social sciences (inner circle) and natural sciences (outer circle) able to describe the selection of medicinal plants and herbal Pharmacopoeias

If these answers were always strictly correct there would be no need for our research project entitled "the development of pharmacopoeias" and ethnopharmacology would be a comparatively easy game.

In their review Fabricant & Farnsworth[14] claim that from 122 plant-derived clinical drugs 88 have the same or similar indications as the source plant in traditional medicine. This claim is, however, statistically not correct because one needs to consider that these species have more than just one indication in traditional medicines.

In fact, what makes it difficult for bioprospecting medicinal floras is that medicinal plants have often many different uses[15]. Rue (*Ruta graveolens* L. and *R. chalepensis* L.) for instance was and is used for and against almost everything since the classic Graeco-Roman period[16]. Although it cannot be excluded that there is a reasonable pharmacologic explanation for several different applications of Rue[17]it makes bioprospecting attempts certainly not easier. Apart from this, plants are ideal media for transmitting a placebo effect or as Moerman & Jonas[18] called it - "meaning response" - in ceremonial and therapeutic practices. Although we generally rely on cultural and cross-cultural consensus analyses when follow ethnomedical cues for bioprospecting we have to be aware that these cues are subjected to changes over time in accordance to the epidemiological situation of populations.

Taxonomic and phylogenetic patterns in biomedicine and ethnomedicine

A census by Zhu *et al.*[19] of all approved and clinical trial natural product drugs has shown that a

significant proportion is obtained from clustered and disjunct taxonomic groups. Currently the Angiosperm Phylogeny Group III distinguishes 457 angiosperm and gymnosperm families with a total of 268.467 species (see also: http://www.mobot.org/MOBOT/research/APweb/). Today only 62 Angiosperm and Gymnosperm plant families are contributing to the development of biomedical drugs including 225 different species or genera[19]. Neither are medicinal floras random selections of the available flora. It has been shown that unrelated people from different holarctic environments chose similar plant families for the selection of their medicines[20,21]. Neither for biomedicine nor in traditional or local medicines are plants, therefore, evenly selected with respect to their taxonomic or phylogenetic share.

According to the Angiosperm Phylogeny Website the 62 drug producing plant families comprise 152.467 plants species altogether and contain thus more than half of all existing angiosperm and gymnosperm species.

These 62 families are also over represented in medicinal floras: While 52 of these 62 families are present among the overall flora in the Sierra Santa Marta in southern Veracruz (Mexico) they just represent 25% of all Angio- and Gymnosperm families occurring in that area but they make up for more than one half of all angiosperms and gymnosperms growing there. Of the 128 Angio- and Gymnosperm families used by the *Popoluca* ethnic group in the Sierra Santa Marta for extracting their medicine 46 are among the biomedical drug producing families but they make up around 66% of the Popoluca medicinal flora[22,23]. Therefore, these 62 drug producing angiosperm and gymnosperm families are not only important at the global level and in biomedicine but also at the local level and in herbal medicine also. Besides being species-rich through a cross-check with the Angiosperm Phylogeny Website we could also confirmed that biomedical and herbal drug producing families are by trend geographically widespread[22,23].

Conclusion

The source of plant derived biomedical drugs as well as local herbal medicines are widespread and species-rich plant taxa. In order to appreciate how skewed the bias in favor of the large families is one needs to consider that the 62 drug producing angio- and gymnosperm families comprise 152.467 species while from the other 395 Angio- and Gymnosperm families comprising 116.000 species no biomedical drugs have yet been produced.

We hypothesized that the broader range of ecological information encoded in the genes of geographically widespread taxa led to the development of biosynthesis pathways able to synthesize allele-chemicals with larger ecological amplitudes, including the targeting of proteins in mammals and primates than taxa with a more local evolutionary history.

Acknowledgement

Author would like to thank the local organizing team of the 2nd SFEC Nagpur, India February 20th-22nd for the invitation, good food and the perfect organization. The research leading to these results has received funding from the People Programme (Marie Curie Actions) of the European Union's 7th Framework Programme FP7/2007/2013 under REA grant agreement no. 606895.

References

1 Mc Clatchey W, Medicinal Bioprospecting and Ethnobotany Research, *Ethnobot Res Appl*, 3 (2005) 189-190.

2 Gertsch J, Cross-cultural comparisons of medicinal floras-What are the implications for bioprospecting? *J Ethnopharmacol*, 139 (3) (2012) 685-687.

3 Mc Chesney JD, Venkataraman SK & Henri JT, Plant natural products: back to the future or into extinction? *Phytochemistry*, 68 (14) (2007) 2015-2022.

4 Li JW & Vederas JC, Drug discovery and natural products: end of an era or an endless frontier?, *Science*, 325 (5937) (2009) 161-165.

5 Grayer JR, Chase MW & Simmonds MSJ, A comparison between chemical and molecular characters for the determination of phylogenetic relationships among plant families: an appreciation of Hegnauer's ''Chemotaxonomie der Pflanzen'', *Biochem Syst Ecol*, 27 (4) (1999) 369-393.

6 Wink M, Evolution of secondary metabolites from an ecological and molecular phylogenetic perspective, *Phytochemistry*, 64 (1) (2003) 3-19.

7 Larsson S, The "new" chemosystematics: phylogeny and phytochemistry, *Phytochemistry*, 68 (22-24) (2007) 2904-2908.

8 Rosén J, Gottfries J, Muresan S, Backlund A & Oprea TI, Novel chemical space exploration via natural products, *J Med Chem*, 52 (7) (2009) 1953-1962.

9 Rønsted N, Symonds MR, Birkholm T, *et al.*, Can phylogeny predict chemical diversity and potential medicinal activity of plants? A case study of amaryllidaceae, *BMC Evol Biol*, 12 (2012) 182.

10 Ramesha BT, Gertsch J, Ravikanth G, *et al.*, Biodiversity and chemodiversity: future perspectives in bioprospecting, *Curr Drug Targets,* 12 (11) (2011) 1515-1530.

11 Leonti M & Casu L, Traditional medicines and globalization: current and future perspectives in ethnopharmacology, *Front Pharmacol*, 4 (2013)92.
12 Kool A, de Boer HJ, *et al.*, Molecular identification of commercialized medicinal plants in southern Morocco, *PLos One*, 7 (6) (2012) e39459.
13 Leonti M, The future is written: impact of scripts on the cognition, selection, knowledge and transmission of medicinal plant use and its implications for ethnobotany and ethnopharmacology, *J Ethnopharmacol*, 134 (3) (2011) 542-555.
14 Fabricant DS & Farnsworth NR, The value of plants used in traditional medicine for drug discovery, *Environ Health Persp*, 109 (Suppl. 1) (2001) 69-75.
15 Spjut RW, Relationships between Plant Folklore and Antitumor Activity: An Historical Review, *SIDA*, 21 (4) (2005) 2205-2241.
16 Pollio A, De Natale A, Appetiti E, Aliotta G & Touwaide A, Continuity and change in the Mediterranean medical tradition: *Ruta* spp. (rutaceae) in Hippocratic medicine and present practices, *J Ethnopharmacol*, 116 (3) (2008) 469-482.
17 Rollinger JM, Schuster D, *et al.*, In silico Target Fishing for Rationalized Ligand Discovery Exemplified on Constituents of *Ruta graveolens, Planta Med*, 75 (3) (2009) 195-204.
18 Moerman DE & Jonas WB, Deconstructing the placebo effect and finding the meaning response, *Ann Int Med*, 136 (6) (2002) 471-476.
19 Zhu F, Qin C, Tao L, Liu X, *et al.*, Clustered patterns of species origins of nature-derived drugs and clues for future bioprospecting, *Proc Nat Acad Sci USA*, 108 (31) (2011) 12943-12948.
20 Moerman DE, Pemberton RW, Kiefer D & Berlin B, A comparative analysis of five medicinal floras, *J Ethnobiol*, 19 (1) (1999) 49-67.
21 Leonti M, Ramirez-R F, Sticher O & Heinrich M, Medicinal flora of the Popoluca, México: a botanico-systematical perspective, *Econ Bot*, 57 (2) (2003) 218-230.
22 Leonti M, Cabras S, Castellanos ME, Challenger A, Gertsch J, *et al.*, Bioprospecting: evolutionary implications from a post-olmec pharmacopoeia and the relevance of widespread taxa, *J Ethnopharmacol*, 147 (1) (2013) 92-107.
23 Leonti M, Cabras S, Castellanos ME, Challenger A, Gertsch J, *et al.*, Erratum: Bioprospecting: Evolutionary implications from a post-Olmec pharmacopoeia and the relevance of widespread taxa, *J Ethnopharmacol*, 148 (1) (2013) 346-347.