

From Ethnobotany towards Modern Botanicals as Paradigm of the Medicinal Plants Research: The Case of Ayurveda

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Editorial

The research and the ongoing upgrading of the knowledge about medicinal plants compulsorily start from the ethnobotanical uses of plant sources and their cultural meaning in a social context. Ethnobotanical data can drive the research towards health uses, functional and coherent with social and cultural evidence concerning medicinal plants and reflecting phytochemical and biological evidence reported by modern research. Moreover, the crucial role of ethnobotany is enhanced by the fact that it might provide historical evidence about medicinal uses of certain plants suggesting efficacy and safety aspects of their modern usage as botanicals. This latter concept is particularly important because it fills in part the gap given by the absence of clinical evidence to pharmaceutically attest the efficacy and safety of plant preparations giving the opportunity to market crude drugs, extracts and traditional preparations as Generally Recognized As Safe (GRAS) botanicals.

In this context, the knowledge of those cultures and societies strongly and historically characterized by uses of plants as health tool emerges as an essential starting point of the research about medicinal plants. Currently, the European and US herbal markets are characterized by botanicals prepared following prescriptions on the basis of native ethnobotany and modern research evidences, but they are also strongly influenced by those natural medicines commonly known as effective, also against severe diseases, and safe in light of their ancient history. The success of these natural medicines, better known as non-conventional under a normative point of view, is also due to the suggestive history, culture, and way of life and in some cases religion too, which permeate the use of particular plants as medicines (Chinese Traditional Medicine, Ayurveda, etc.). However, the most evident critical points which should be generally ascribed to all these traditional medicines are 1) the lack of knowledge about chemical characterization of the plant sources and of the preparations; 2) about the synergisms responsible of the biological activities reputed to the traditional preparations, i.e. which compounds and their concentrations really determine the functional health properties; 3) clinical evidences next to never emphasized; 4) the presence of plants and their derivatives in herbal market scarcely or next to never investigated for their possible interactions with drugs. Therefore, it emerges the strong need to create science incubators - such as Medicinal and Aromatic Plants journal, or specific databases, for e.g. - aimed to collect the past and present knowledge about medicinal plants and their preparations driving and promoting research profiles focused on finding answers to all these criticisms.

Taking the ayurveda as paradigm of the traditional medicines recognized as non-conventional ones by the European Union and by most Member States, it could be stressed that it uses more than 7000 plants for therapeutic purposes, most of them scarcely known under all or some of the aspects above considered. Moreover, the effects on human health of the often complex ayurvedic formulations are well described in the ethnobotanical literature sources, but the biological basis proving their efficacy is still poorly investigated. Despite this lack of knowledge, often associated with a non-coherent and fragmented research, several plants belonging to the ayurveda are commercially

available in food supplements distributed within the EU, in the absence of a precise legal status. Furthermore, neither plant drugs used by ayurvedic medicine nor formulated products prepared according to the instructions of the Indian ayurvedic pharmacopoeia are mentioned within the reports of committees like EMEA and are absent in the lists of drugs allowed / not allowed by the Ministry of Health of Countries belonging to European Community. This context related to ayurveda as paradigm of traditional medicines supports the general premises related to the lack of knowledge about i) botanical sources of traditional medicines and their preparations, ii) their quality control, iii) the efficacy and safety of these herbal drugs and their derivatives. Thus, very little information are available to the legislator limiting the possibility to validate ethnomedicines and their botanicals as effective health remedies also under a normative point of view, minimizing *de facto* also their market. To fill this gap, the following project profile is purposed as research pattern about studying medicinal plant. The research, still in progress, is funded by MIUR (Research and University Italian Ministry) of Italy with the aim to shed a light on some ayurvedic preparations and the above mentioned related criticisms (project code: 2009LR9YLF; results acquired reported at www.ayurprint.org/).

While western medicine is mainly focused on pathogens and on external tools for diseases control, ayurveda is mainly characterized by therapeutic strategies aimed to the patient and his internal equilibrium for diseases control. With a language proper to hippocratic medical-health tradition, these therapeutic concepts could be tentatively translated in a global approach to control and re-equilibrate organic homeostasis compromised by pathologies, obviously lost in translation with the simple and traditional dualistic model “active compound-disease”. As a consequence, ayurveda gives relevant importance to phytocomplexes, for their complex and synergic chemical and biological interactions aimed to physiological health. The research about these health approaches is further on encouraged by the lower side-effects incidence given by phytocomplexes if compared with synthetic drugs, suggesting a better compliance and acceptance of these natural therapeutic products by consumers [1]. As numerous non conventional medicines, ayurveda has always established its therapeutic approaches on one or more phytocomplexes activities, administered with different

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preparations and dosages driven by an anthroposophical rather than strictly scientific pattern. The new health and pharmaceutical research frontiers consist in translating these anthroposophical concepts in pharmacological and toxicological solutions proper for western medical tradition based on evidences [2], with the aim to give efficacy and safety validations. In the world, many institutions are engaged in studying the ayurvedic preparations under this cultural translation and research point of view: the most important is the Central Council for Research in Ayurveda and Siddha (www.indianmedicine.nic.in) and it has been developing for years clinical investigations about diffused pathologies as malaria, epilepsy, neuromuscular disorders, bronchial asthma, peptic ulcer, hepatic pathologies, anal-rectal pathologies, prostatic hyperplasia, kidney stones, cancers, psoriasis, obesity, ischemic heart diseases and hepatic infections. In particular, during the last decade, pharmacological research has been performed, including plants which are the subject of the present project such as *Azadirachta indica*, *Hemidesmus indicus*, on raw extracts or pure isolated compounds, and phytochemical investigations aimed to new chemicals characterization. From *Azadirachta indica* leaves, for example, plant known since ancient times as Neem tree, about 140 molecules have been isolated such as isoprenoids, polyphenols, flavonoids, tannins, aliphatic compounds and primary metabolites; leaves phytocomplexes and isolated chemicals have been also tested for antifungal, antibacterial, antimalaric, contraceptive, antipyretic, anti-inflammatory, analgesic, antiulcerogenic, anti-hypertensive, antihyperglycemic, neuropharmacological, anti-dermatophytic, hepatic-protective, immune-stimulant, antioxidant, anti-genotoxic, anti-carcinogenic, fibrinolytic, against snakebites (cobras and vipers) activities [3,4]. Notwithstanding many results were collected, many biological and pharmacological aspects need to be clarified yet for giving to researchers and health market appropriate tools to determine ayurvedic crude drugs quality. Although these drugs are commercially purchasable, for many of them adequate pharmacognostic quality control standard methods (identity, sophistication check), phytochemical (quality and quantity of active chemicals) and biological (scientific validation and safety use) protocols are not set up. It is to be stressed that, from bibliographic data, the ayurvedic crude drugs bio-activities are due to active chemicals with different molecular structure and to mixtures chemically very diversified; this means to imply studies which relate the phytochemical complexity of ayurvedic preparations to diversified biological properties [5,6]. In light of these considerations, the metabolomic analyses (NMR) of phytocomplexes, and the authentication of plant matrices by molecular biology strategies, correlating then the functional activities to phytochemical evidences through data multivariate processing represent an innovative research approach. Also in terms of crude drugs safety use, ayurvedic crude drugs represent an important challenge for European health market. The most important safety qualifications for herbal preparations are represented by the absence of sophistication, adulteration or deterioration, negative actions, both intentional and due to inexperience, performed during all the processing chains. Sometimes, sophistication represents not only and simply as an economic detriment but also a potential health risk for consumers; above all, drug vigilance recommendations about poisoning due to scarce authenticity and purity of crude drugs employed for products coming in Europe from eastern markets (India, China) are frequent. On the whole, three kinds of beneficiaries could avail themselves of the availability of ayurvedic crude drugs monitoring tools: consumers, for better safety guarantee; importers, for the possibility to check in advance possible sophistication; researchers, for the possibility to develop research strategies to better relate identity, chemical composition and pharmacological activities. Molecular

analyses based on DNA have recently allowed recognizing plant chemicals present in herbal remedies [7,8]. The development of these research strategies allow to have better reliability, minor subjectivity, and a rapid processing. The coordination of molecular biology activities with metabolomic techniques, based on chromatography and spectroscopy methods (NMR in particular), is particularly innovative for all those standardization and fingerprinting strategies to validate pharmacological efficacy replicability and to monitor batch-to-batch industrial repeatability. Efficacy evaluation is more frequently focused on the capacity to interact with redox systems and their fall consequences, at the base of numerous and severe disorders and pathologies [9]. To this aim, particularly lacking are studies about interactions between plant derived chemicals and oxido-reduction *in vitro* and *ex vivo* systems with pre-clinical projection and their implications with metabolic and organic disorders. Therefore, the present project is planned to relate evidences from *in vitro* screening assays (TLC-DPPH bioautographic assay, beta carotene bleaching test, photochemiluminescence), with investigation models which reflect more defined disorders. A very interesting scientific problem in relation to pathogenesis is represented by the involvement of the uncontrolled formation of free radicals in tissue damages, inflammation processes, atherosclerosis, ischemia, ageing [10]. However, the anti-proliferative evaluation of plant chemicals from ayurvedic crude drugs against cancer cell lines as effective tumor-inducing and cytotoxicity simulators results important with reference to the genotoxic and anti-genotoxic determination by short-term tests, assays widely employed and developed also in our laboratories, correlated with antioxidant and radical scavenging determinations [11]. K562 cells, for example, represent a good screening model to evaluate both anti-tumor and erythroid differentiation induction for developing new treatments for beta thalassemia and sickle cell anemia. The study in erythroid precursors of mRNA increasing for alpha, beta and gamma globins and fetal hemoglobin level are linked [12]. Potential anti-inflammatory properties of plant source extracts and their derivatives have been also extensively investigated [13], in particular regarding their capacity to inhibit the interaction between transcriptional factors and DNA, for example the interaction NF- κ B/DNA, their effects on inflammatory processes, in important pathologies such as chronic lung inflammation, and related complications such as cystic fibrosis [14]. WHO has certified obesity as one of the most important public health problem in the world. Obesity is mainly linked to lipid metabolism disorder. Enzymes involved in this metabolism, as pancreatic lipase, could be possible targets to research new anti-obesity drugs. Nowadays, the pharmaceutical potential of anti-obesity chemicals derived from plant sources is scarcely investigated, but it is evident that there is a close relation between antioxidant activity and involved enzymes inhibition capacity. The employ of plant derived antioxidant compounds reduces risks of neurovegetative pathologies [15,16], as Alzheimer disease (AD), nowadays mainly are treated with acetylcholinesterase inhibitors. The research about new acetylcholinesterase drugs derived from plants is due to the need of pharmaceuticals with lower toxicity and reduced adverse effects than the drugs usually employed [17,18]. In light of these state of art, some ayurvedic preparations (decoctions) of *Hemidesmus indicus* R. Br. (Ranunculaceae; roots), *Azadirachta indica* A. (Meliaceae; leaves), *Boerhaavia diffusa* L. (Nictaginaceae; roots), *Convolvulus pluricaulis Choisy* (Convolvulaceae; whole plant), *Curculigo orchioides* Gaertn. (Amarillidaceae; tuberous root) were considered together with hydro-alcoholic extract of the same crude drugs, since the latter preparation is one of the most used and marketed in Europe at the expense of ayurveda indications. Phytochemical characterization is performed by chromatographic systems, single and coupled (HPTLC-

MS, HPLC-DAD-ELSD, HPLC-MS, GC-MS) associated with NMR evaluations and it is followed by a bioassay-guided approach performed to identify bioactive compounds really involved in the processes of homeostasis and, more generally, in biological assays correlated to various disorders and illnesses (eg. diabetes, Alzheimer's disease). This bioassay guided strategy is crucial and allow shedding a light on both the really active constituents and synergisms, the latter quantified by multivariate statistical analyses. The biological assay employed need to confirm the ayurveda indications and possibly should be oriented to find new health uses for western herbal markets, both under efficacy and safety point of view. The choice of the assay pattern should be oriented to perform multiple methods for each activity in order to clarify and strengthen the results achieved, and limit the gap given by the possible absence of clinical evidences. All chemical and biological data should be collected in a database shared among the researchers: such tool will serve as a guide towards the implementation of the steps and goals to pursue, through constant comparison of results and establish a correlation on multivariate statistical basis. As future target, the study of medicinal plants, above all about the synergisms among chemicals, could be lead on the use of the single pure natural compounds reputed as most active from different plant source and with concentrations different from those in the extracts, in preparing artificial phytocomplexes, optimizing the efficacy and safety of the natural compounds in modern preparations.

In conclusion, the modern study of medicinal plants needs to have phytochemical and biological research strategies strictly interactive and supported by a multi-disciplinary approach. Only through this perspective, the research on medicinal plants will reach important targets regarding 1) scientific validation of crude drugs and preparations; 2) quality control parameters; 3) safety protocols and drug vigilance parameters definition with marketing importance; 4) new health perspectives for natural lead compounds, phytocomplexes and their fractions.

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