

Are traditional medicinal plants and ethnobotany still valuable approaches in pharmaceutical research?

[¿Son las plantas medicinales tradicionales y la etnobotánica aproximaciones valiosas de la investigación farmacéutica?]

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Abstract

Traditional medicinal plants have been the origin and basis of pharmacology and therapeutics. On the other side, over the last decades, natural product and medicinal plant research have been cut down within pharmaceutical companies claiming economic and availability reasons. However, traditional medicinal plants have played an important role in drug discovery. For these reason, ethnobotany and traditional medicine may still be a useful strategy and a valuable tool for future pharmaceutical research.

Keywords: medicinal plants, traditional medicine, ethnobotany, drug discovery, pharmaceutical research

Resumen

Las plantas medicinales tradicionales han constituido el origen y las bases de la farmacología y la terapéutica. Por otro lado, en las últimas décadas, la investigación sobre productos naturales y plantas medicinales se ha reducido considerablemente en las industrias farmacéuticas debido a diversos motivos, entre ellos disponibilidad y coste. Sin embargo, las plantas medicinales con usos tradicionales han jugado un papel fundamental y decisivo en el descubrimiento de nuevos fármacos. Por este motivo, la etnobotánica y la medicina tradicional todavía pueden constituir una estrategia útil y una herramienta valiosa para la investigación farmacéutica del futuro.

Palabras Clave: plantas medicinales, medicina tradicional, etnobotánica, descubrimiento de fármacos, investigación farmacéutica

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INTRODUCTION

Nature is a source of biologically active compounds and natural products have been used as medicines throughout the history of mankind. Although natural products include plant, animal and microbial sources, plants have been the origin and basis of pharmacy and pharmacology, constituting remedies in traditional medical systems and still being used as a source of bioactive compounds. An example of this fact may be morphine from poppy (*Papaver somniferum* L., *Papaveraceae*). Dioscorides (70 AD) described *Papaver somniferum* regarding analgesic effects. Currently, it is cultivated to extract poppy juice from which the opioid analgesic morphine is purified to be part of painkiller formulations in chemotherapeutic patients (Samuelsson, 2004).

Natural products have been the active ingredient of medicines for years but they may still be the leads for new drugs (Newman, 2008). Since the 1980s, the influence of natural products in drug discovery has been significant. Between 1981 and 2006, more than 50 % of approved drugs were based on natural product structures: 5.7 % natural products, 27.6 % derived from a natural product often by semi-synthesis, 17.1 % made by total synthesis but the pharmacophore was from a natural product (Newman & Cragg, 2007). In 2001-2002 approximately 25 % of the best-selling drugs worldwide were natural products or derivatives (Butler, 2004). It is also worth mentioning some new plant-derived drugs introduced in the pharmaceutical market in the last years (fig. 1) (Balunas & Kinghorn, 2005). Arteeter (Artemotil[®]) is an antimalarial drug derived from the natural compound artemisinin; artemisinin is a sesquiterpene lactone isolated from *Artemisia annua* L. (*Asteraceae*), a medicinal plant used in traditional Chinese medicine (TCM) to treat malaria. Galantamine (Reminyl[®]), isolated from different species of *Amaryllidaceae*, is approved for Alzheimer's disease. Nitisinone (Orfadin[®]), based on leptospermone from *Callistemon citrinus* Stapf. (*Myrtaceae*), is an orphan drug for the treatment of tyrosinaemia. Tiotropium (Spiriva[®]), based on atropine from *Atropa belladonna* L. (*Solanaceae*) to treat patients with chronic obstructive pulmonary disease. Nabilone (Cesamet[®]), approved in 2006 for the treatment of nausea and vomiting in chemotherapy, is a synthetic derivative of Δ^9 -tetrahydrocannabinol (THC) from *Cannabis sativa* L. (*Cannabaceae*) (Saklani & Kutty, 2008). However,

natural products obtained from other sources are succeeding; for example, Trabectedin (Yondelis[®]), isolated from the marine tunicate *Ecteinascidia turbinata*, was approved in 2007 by EMEA for the treatment of soft tissue sarcoma after failure to standard chemotherapy (Nobili *et al.*, 2009). Among them, arteeter, galantamine, tiotropium and nabilone may be considered as developed based on previous traditional uses of the plants.

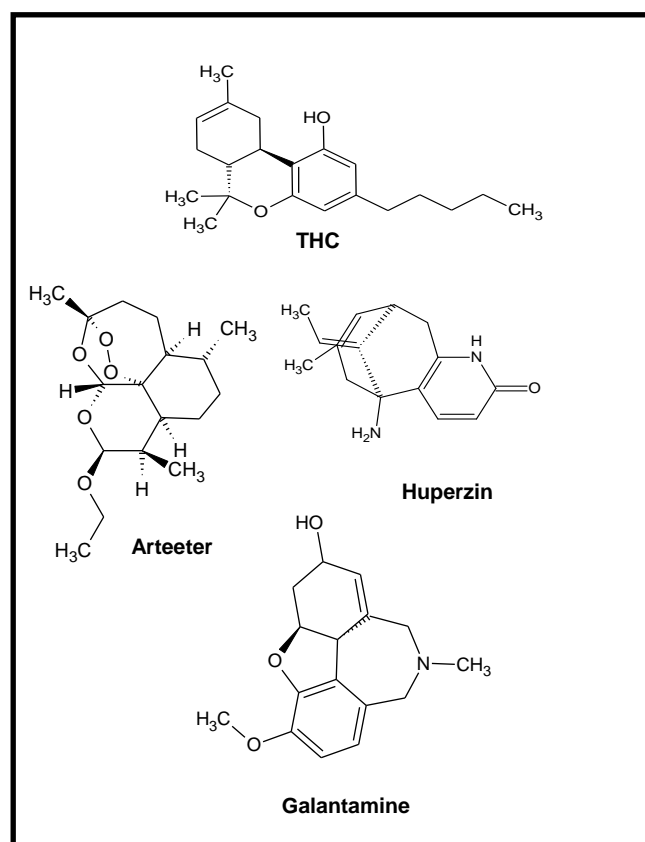


Figure 1. Plant-derived drugs recently developed based on traditional uses of the plant source

In 2008, over 100 natural product-based compounds were under clinical investigations at different stages (Harvey, 2008). Almost the same amount is in preclinical research which means that natural products have been a great source of leads for drug discovery. Most of them are plant-derived drugs, followed by semi-synthetics, microbials and from animal origin, the main therapeutic categories being anticancer, anti-infective and neurological drugs (Harvey, 2008). Calanolide A, a coumarin isolated from *Calophyllum lanigerum* var. *austrocoriaceum*

(Whitmore) P.F. Stevens (*Clusiaceae*) by the National Cancer Institute, is currently in clinical trials for its anti-HIV and anti-tuberculosis activities (Kashman *et al.*, 1992); other calanolides are also under pre-clinical stage. ZT-1 is a pro-drug of huperzine isolated from *Huperzia serrata* (Thunb. ex Murray) Trev. (*Lycopodiaceae*) that is also undergoing trials for the treatment of Alzheimer's disease due to working as N-methyl-aspartate receptor antagonist and acetylcholinesterase inhibitor. Dexabinol is a neuroprotective non-psychotropic cannabinoid undergoing Phase III trials for brain injury. Many plant-based products are in clinical development as anticancer drugs: daidzein, an isoflavone from soybean, protopanaxadiol, a tetracyclic triterpene from ginseng, and kahalalide F, a peptide toxin from the mollusc *Elysia rubefescens* (Saklani & Kutty, 2008).

Apart from being a source of compounds, medicinal plants constitute by themselves herbal remedies used in rational phytotherapy and/or complementary medicine. Concerning traditional herbal remedies, some examples may be remarked due to its high use worldwide. The roots and rhizomes of valerian (*Valeriana officinalis* L., *Valerianaceae*) are worldwide appreciated as a mild sedative (Bent *et al.*, 2006). Other herbal remedies working on CNS are St. John's Wort (*Hypericum perforatum* L., *Clusiaceae*) with antidepressant clinical efficacy (Kasper *et al.*, 2008) and roots of *Panax ginseng* C.A. Meyer (*Araliaceae*) considered as an adaptogenic that increases inespecific resistance of organism (Naval *et al.*, 2007; Wu *et al.*, 2009). Aloe preparations, made with the parenchyma of different species of the genus *Aloe*, are very popular for skin affections (Feily & Namazi, 2009) and herbal teas such as chamomile or pennyroyal as digestives (Kato *et al.*, 2008).

It seems obvious that medicinal plants are a source for pharmacologically active products in developed countries but they have also been the basis of different traditional medical systems in developing areas. According to WHO, most of the world's population still relies on plants for their healthcare. In some Asian and African countries, 80% of the population depends on traditional medicinal plants for primary healthcare, as they are either the most accessible or the only available treatment (Gurib-Fakim, 2006).

It is estimated that the number of higher plant species on the planet may be over 250,000 and only 10% have yet been biologically studied (Harvey, 2000). In this sense, the potential for finding new

medicinal plants and new lead compounds for new generations of drugs is enormous.

Advantages versus disadvantages in medicinal plant research

Exploring natural resources for drug discovery and development may represent advantages compared to some other approaches (Lam, 2007). Natural products offer chemical diversity, structural complexity and a range of biological activities that is not comparable to synthetic approaches. Natural compounds can be used as templates to obtain new chemical entities of pharmaceutical interest. Drugs from natural origin have helped to discover human physiological pathways. For example, cannabinoids from *Cannabis sativa* (the hemp plant) led to the elucidation of the endogen cannabinoid system or salicylic acid from *Salix alba* (white willow bark) led to the discovery of COX enzymes related to inflammation (Bosch & Banos, 1998). Digoxin from foxglove (*Digitalis purpurea* L., *Scrophulariaceae*) led to the discovery of the sodium-potassium ATP-ase pump biochemistry and enabled a better understanding of cardiac pathologies (Rishton, 2008). Muscimol from *Amanita muscaria* (fly agaric mushroom) has been crucial in differentiating the pharmacology of GABA_A and GABA_B receptor subtypes related to a range of central nervous system disorders. Due to the fact that natural products have been produced by a living organism, they frequently exert adequate pharmacokinetic properties in terms of absorption, distribution, and metabolism, as happened with streptomycin, amphotericin B, cyclosporine A or lovastatin, marketed without modifications. Traditional herbal remedies have been selected by mankind through trial-and-error for centuries, which may give clues about interesting biological properties (Gurib-Fakim, 2006). Several plant-derived drugs have been developed on the basis of ethnomedical-ethnobotanical information as for instance galantamine isolated from the genus *Galanthus* and relatives of the Amaryllis family registered for the treatment of Alzheimer's disease under the name Reminyl® (Heinrich & Lee, 2004).

Despite the success of natural products in drug discovery and therapeutics, pharmaceutical companies have decreased their efforts in natural products and medicinal plant research due to some disadvantages and difficulties mentioned below (Fabricant & Farnsworth, 2001; Lam, 2007). Biological systems (plant, animal, microbial) have a potential variability that results in differences in terms of composition and

therefore biological activity. Collection of plants and other samples may be difficult and conditioned by abundance and accessibility; for instance, collection of marine organisms requires qualified people and expensive facilities. The issue of intellectual property rights; the Convention on Biological Diversity (CBD) drew up its objectives in 1992 in Rio de Janeiro (Gurib-Fakim, 2006): “...*the conservation of biological diversity, the sustainable use of its components and the fair and equitable sharing of the benefits arising out of the utilization of genetic resources, including by appropriate access to genetic resources and by appropriate transfer of appropriate technologies, taking into account all rights over those resources and to technologies, and by appropriate funding*”. Natural products are synthesized and presented in small quantities in complex-mixtures involving an intensive purification and isolation process. Natural products are sometimes complex structures, being a challenge for combinatorial chemistry.

All these facts mentioned above are not within the scope of pharmaceutical firms in which time-cost is a limiting factor. The drug discovery process is estimated to take 10 years and cost 800 million dollars (Dickson & Gagnon, 2004). For every 5000 lead compounds only one would reach the approval for marketing. Drug discovery from medicinal plants is generally longer and more expensive than other strategies. Owing to this, the current main strategies for drug discovery are combinatorial chemistry and high-throughput screening (HTS) techniques.

Traditional medicine (TM), ethnobotany and ethnopharmacology

Throughout history, different cultures have developed knowledge about herbal remedies that has been passed from generation to generation constituting what is called traditional medicine (Gurib-Fakim, 2006). But the concept of traditional medicine is wider. According to WHO, TM is defined as diverse health practices, approaches, knowledge and beliefs incorporating plant, animal and/or mineral based medicines, spiritual therapies, manual techniques and exercises applied singularly or in combination to maintain well-being, as well as to treat, diagnose or prevent illness (WHO, 2002).

Taking into account that practically 80% of the world's population lives in developing countries and about 80% of these people use TM systems, it is obvious that most of the world's population still depend on traditional remedies for their primary

healthcare. This wide use in the developing areas such as Africa, Asia and Latin America is due to affordability and accessibility of the natural sources. On the contrary, developed countries are increasing their use of traditional medicinal plants in forms of rational phytotherapy, dietetics and complementary or alternative medicine (WHO, 2002)

The term ethnomedicine or TM is sometimes used as synonym of ethnobotany and ethnopharmacology to express the same idea although there are substantial differences between them. Ethnobotany may be defined as the science of people's interaction with plants (Turner, 1995). The objectives of ethnobotany include contribute to the knowledge of biodiversity (Bonet & Valles, 2002) and to the cultural meaning of plant sources (Bonet *et al.*, 1999) and explore biodiversity for new sources of natural products with pharmaceutical interest (bioprospecting) (McClatchey *et al.*, 2009).

In addition, ethnopharmacology is a multidisciplinary area of research concerned with the observation, description and experimental investigation of indigenous drugs and their biological activities (Rivier & Bruhn, 1979). While ethnopharmacology deals with drugs from animal, microbial or plant sources, ethnobotany is only focused on plants.

These three concepts have a common area, which is the use of herbal remedies by the different cultures. It is difficult to understand them individually as in many cases ethnobotanical/ethnopharmacological/ethnomedicinal studies have common objectives and may be valuable approaches for drug discovery. Farnsworth *et al.* (1985) identified up to 122 compounds used in therapeutics that were from plant origin and nearly 80 % were used for the same or related disorder than in traditional medicine. Some examples of current drugs with an ethnomedicinal origin are described in Table 1.

Traditional medicinal plants of importance in western medicine

African medicine is considered to be the oldest (Gurib-Fakim, 2006) as the ancient African continent is the origin of mankind. It is considered a holistic system as it involves the body and the mind. African traditional medical practice may include medical elements as well as psychological, spiritual and cultural aspects (Stafford *et al.*, 2008). These techniques are usually practiced by a traditional healer that is also a religious leader. Plants are used as a pharmacological tool but it is also a living organism

that generates a “vital force”. Well-known African medicinal plants are *Harpagophytum procumbens* (Burch.) DC. ex Meissner (*Pedaliaceae*) and *Prunus africana* (Hook. f.) Kalkman (*Rosaceae*), that are used in western countries as anti-inflammatory and for the treatment of benign prostatic hyperplasia, respectively. *Aspalanthus linearis* (Burm.f.) R. Dahlgr. (*Fagaceae*), known as rooibos tea, is consumed in developed countries as a relaxing herbal tea. *Aloe ferox* Miller (*Asphodelaceae*) is widely used externally for skin

problems due to its calming and regenerative properties and internally for the treatment of constipation. Studies on *Catharanthus roseus* (L.) G. Don.f. (*Apocynaceae*) from Madagascar led to the isolation of vincristine and vinblastine as anticancer agents. Finally, a steroid glycoside from *Hoodia gordonii* (Masson) Sweet ex Decne (*Apocynaceae*), a traditional plant used by the people of Kalahari desert to avoid hunger, is undergoing Phase II clinical trials for the treatment of obesity (Saklani & Kutty, 2008).

Table 1. Examples of plant-derived drugs developed on the basis of ethnobotanical information

Drug	Current use	Lead compound	Botanical source	Ethnomedical information (Origin)
Acetylsalicylic acid	Anti-inflammatory Antiagregant	Salicin	<i>Salix sp</i> (<i>Salicaceae</i>)	Inflammation (Europe, Asia, America)
Arteeter	Antimalarial	Artemisinin	<i>Artemisia annua</i> L. (<i>Asteraceae</i>)	Antimalarial (China)
Atropine	Anticholinergic	(-)Hyosciamine	<i>Atropa belladonna</i> L. (<i>Solanaceae</i>)	Pan relief, asthma, (Europe)
Colchicine	Antigout	Colchicine	<i>Colchicum autumnale</i> L. (<i>Liliaceae</i>)	Poison (Europe)
Chromoglycate	Anti-inflammatory in asthma	Kellin	<i>Ammi visnaga</i> (L). Lam. (<i>Apiaceae</i>)	Inflammatory conditions (North Africa)
Galantamine	Cholinesterase inhibitor (Alzheimer)	Galantamine	<i>Galanthus sp</i> (<i>Amaryllidaceae</i>)	Nerve pain (Eastern Europe)
Digoxin	Cardiotonic	Digoxin	<i>Digitalis sp</i> (<i>Scrophulariaceae</i>)	Dropsy (Europe)
Etoposide	Antitumour	Podophylotoxin	<i>Podophyllum peltatum</i> (<i>Berberidaceae</i>)	Laxative, skin infections (North America)
Morphine	Opioid analgesic	Morphine	<i>Papaver somniferum</i> L. (<i>Papaveraceae</i>)	Pain relief (Western Mediterranean)
Pseudoephedrine	α -adrenergic agonist (nasal decongestant)	Ephedrine	<i>Ephedra sinica</i> Stapf (<i>Ephedraceae</i>)	Cough suppressant (China)
Rivastigmine	Cholinesterase inhibitor	Physostigmine	<i>Physostigma venenosum</i> Balf. (<i>Fabaceae</i>)	Poison (Africa)
Vinblastine, Vincristine, Vinorelbine	Antitumour	Vinblastine, Vincristine	<i>Catharanthus roseus</i> (L.) G. Don. f. (<i>Apocynaceae</i>)	Hypoglucemiant (Madagascar)

Traditional Chinese medicine (TCM) is another holistic medicine where balance and harmony are of great importance. This system is believed to be 5000 years old and still remains as in primary health care (Heinrich *et al.*, 2003). The five-elements theory explain that the earth is divided into wood, fire, earth, metal and water, each of which is associated with a vital organ (liver, heart, spleen, lungs, kidneys, respectively). The disease is understood as a result of external forces (wind, cold, heat...) and emotions (joy, anger, anxiety, fear...). The treatments are focused in restoring the harmony and medicinal plants are usually given in complex mixtures. Examples of Chinese plants that led to important drugs are *Ephedra sinica* Stapf (*Ephedraceae*), *Artemisia annua* L. (*Asteraceae*), and *Ginkgo biloba* L. (*Ginkgoaceae*), sources of ephedrine, artemisinin and ginkgolides, respectively. Other plants widely used in western phytotherapy are ginseng (*Panax ginseng* C.A. Meyer, *Araliaceae*), ginger (*Zingiber officinalis* Rosc., *Zingiberaceae*), salvia (*Salvia miltiorrhiza* Bunge, *Lamiaceae*) and soybean (*Glycine spp.*, *Fabaceae*). Huperzine A isolated from *Huperzia serrata* (Thunb. ex Murray) Trev. (*Lycopodiaceae*) has attracted attention as a novel drug candidate for Alzheimer's disease (Ma *et al.*, 2007).

Ayurveda (Indian traditional medicine) is another holistic system that means knowledge of life and is considered to be the oldest systematized traditional medicine (Gurib-Fakim, 2006). It has similarities with Chinese traditional medicine. For example, the five elements (space, air, fire, water and earth) that are manifested in the body as three humors. Illness is believed as an imbalance of the elements and treatments include herbal remedies, yogic breathing and other techniques. Research in ayurvedic plants led to interesting compounds such as alkaloids for hypertension from *Rauwolfia serpentine* Benth. ex Kurz (*Apocynaceae*), anti-inflammatory curcumin from *Curcuma longa* L. (*Zingiberaceae*) or guggulsterons from *Commiphora mukul* Engl. (*Burseraceae*) as hypolipidemic agents. Black pepper (*Piper nigrum* L., *Piperaceae*) is used in Ayurveda as a digestive remedy. In recent years, many studies have been carried out in *Withania somnifera* Dunal (*Solanaceae*), considered an Indian ginseng due to adaptogenic properties (Kulkarni & Dhir, 2008). This plant contains steroidal alkaloids and lactones that may be useful in neurodegenerative and neuropsychiatric disorders.

Latin American traditional medicine is still practised, especially in rural areas of Central and

South America, by a traditional healer or shaman that combines medical knowledge with cultural and religious beliefs. The remedies are often kept secret by the healer and have not been properly recorded as in TCM or Ayurveda. Some important medicinal plants originating from Latin America are mentioned below: *Myroxylon balsamum* (L.) Harms (*Fabaceae*) used as antiseptic and expectorant, *Peumus boldus* M. (*Monimiaceae*) for gastrointestinal disorders, *Pilocarpus jaborandi* Holmes (*Rutaceae*) for the extraction of pilocarpine used in glaucoma patients, *Passiflora incarnata* L. (*Passifloraceae*) for sleep disorders, *Cinchona pubescens* Vahl (*Rubiaceae*) as an antimalarial drug, *Uncaria tomentosa* (Willd.) DC (*Rubiaceae*) as an anti-inflammatory remedy and *Lepidium peruvianum* Chacón (*Brassicaceae*) as an adaptogenic plant food. Other plants of cultural importance are *Theobroma cacao* L. (*Sterculiaceae*), *Erythroxylum coca* Lam. (*Erythroxylaceae*), *Paullinia cupana* H.B.K. (*Sapindaceae*) known as "guaraná" and *Ilex paraguariensis* St. Hil. (*Aquifoliaceae*) as "mate".

CONCLUSION

Medicinal plant research has been cut down in many companies as it involves some disadvantages such as chemical complexity and/or availability but the main being that is very cost intensive. Because of these arguments, the current trends for drug discovery in the biomedical industry are combinatorial chemistry and high throughput screening techniques (Samuelsson, 2004; Harvey, 2008).

However, it is a fact that purified plant-derived compounds play a special role in human health care and botanicals are also part of pharmaceutical formulations such as nutraceuticals, dietary supplements and herbal medicinal products. In this sense, we believe that plants are still a useful source of bioactive constituents with medicinal properties (Newman *et al.*, 2003; Tulp *et al.*, 2006; Newman & Cragg, 2007; Newman, 2008).

Furthermore, it has been estimated that almost 50% of drugs in western-developed countries are based on natural products (most of them coming from plants of cultural importance) and most of the population in developing countries still use plants as primary remedies. Taking these facts into consideration, we are called to increase our research interests in traditional plants.

Combining high throughput technology with selection of plants based on ethnobotanical information is likely to succeed in finding new

biological activities and compounds. We should consider ethnobotany a pharmaceutical research tool for present and future with important perspectives in drug discovery.

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