

*MEDICINAL PLANTS AND HEALTH IN HUMAN HISTORY:
FROM EMPIRICAL USE TO MODERN PHYTOTHERAPY*

Elisabetta Miraldi, Giulia Baini

Department of Physical Sciences, Earth and Environment, University of Siena, Italy

Abstract. Phytotherapy is the science that deals with the treatment and prevention of diseases through medicinal plants and herbal products. The use of herbs as medicine is the oldest form of healthcare known to humanity and has been used in all cultures throughout history. It is known that even today over 80% of the world population depends on herbal medicines. The quality of herbal medicines is believed to be directly related to its active principles, but herbal medicines can be variable in their composition. Therefore, it is necessary to use an extract that is well defined in its chemical composition and in the quantity of specific active principles; and actually, to obtain constant efficacy and safety, standardized medicinal plant extracts are being used. Clinically confirmed efficacy and best tolerability and safety of standardized or quantified medicinal plant extracts are the key for a successful phytotherapeutic approach.

Key words: Phytotherapy, Herbal Medicine, Extracts, Standardization.

INTRODUCTION

Phytotherapy is the science that deals with the treatment and prevention of diseases through the use of medicinal plants and herbal products. According to the WHO (World Health Organization) “medicinal plants are those which, in any case, introduced or put in contact with a human or animal organism, produce pharmacological activity”.¹ The meaning of the term “official plant” is wider because it includes plants used both in the pharmaceutical sector and in other industrial sectors, such as liquor, cosmetics, food, etc.

HISTORY OF PHYTOTHERAPY

The term Phytotherapy comes from the Greek *phyton* (= plant) and therapy and means “healing with plants.”

Plants are Man’s first medicines. The number of higher plant species on earth is about 250,000. It is estimated that 35,000 to 70,000 species, at one time or another, have been used in some cultures for medicinal purposes. Throughout history, people all over the world have used herbs to improve health: they have been central to the art of healing. A constant process of searching, testing and verification in all cultures across the globe resulted in the development of an empirical science.²

Many of the plants used in antiquity as medicines still play an important role for health today. Suffice it to make an example for everyone: aloe. The first note of aloe is found on the Sumerian clay tables that date

back to 2100 BC. Tables have been created at the time of the King of Akkad, and talk about the medicinal properties of this plant. The Egyptian papyri that date back to 1500 BC confirm antiquity of this plant; the famous “Egyptian Book of medicines” on Ebers Papyrus reveals how to use aloe for medicinal purposes. The Egyptians called aloe “plant of immortality” and they used it in the treatment of infections, against the parasites and for treating skin diseases. Queens of Egypt considered aloe to be the source of their beauty, and pharaohs took it in their afterlife.³ African hunters have used aloe as a natural deodorant. Filipinos used aloe for treating kidney infection. In India, China, Greece and the Roman Empire aloe has been used as a remedy for injuries, bites, burns, infections, inflammation and swelling.⁴ According to the legend, Aristotle advised his student Alexander the Great to conquer the island of Socotra in the Indian Ocean. Socotra was at that time the center of aloe production. According to legend, aloe has made the army of Alexander indestructible. Dioscoride, Pliny the Elder and many other writers have described the properties of aloe in their books. Later, Cristoforo Colombo had aloe in his Caravels and Ghandi believed it was essential to overcome the long fasts. Aloe has gone through 5000 years of history, preserving its properties and its extensive use by man.⁵

And today? Today aloe is reported in the European Pharmacopoeia 9th Edition,⁶ and Europe imports three hundred million euros into aloe-based products, mainly from China and Mexico.

Correspondence to:

Elisabetta Miraldi

Department of Physical Sciences, Earth and Environment, University of Siena, Italy, Strada Laterina 8, 53100 Siena, Italy.

Tel.: +39.0577.233517.

E-mail: elisabetta.miraldi@unisi.it

Currently, many plants have an established place within scientific medicine and are used for a broad range of health conditions.

Modern phytotherapy

The modern phytotherapy started with the rise of organic chemistry. The first active substance isolated from a plant was in 1803, when a German pharmacist Friederich Sertürner isolated morphine from opium. For the first time in history it was possible to isolate an active ingredient. This was followed in quick succession by many other substances, which were referred to as phyto-pharmaceuticals.

More than eighty years ago, Professor Rudolf Fritz Weiss (1895-1991), the founder of scientific herbal medicine, publisher of the renowned phytotherapy journal *Zeitschrift für Phytotherapie* and author of the seminal work *Lehrbuch der Phytotherapie* (Herbal Medicine) also published in English, Danish and Japanese, stated: "We must prove that herbal medicine does not in any way lag behind other areas of medicine in terms of scientific thoroughness and practical usefulness".²

Gradually, numerous other constituents were isolated, their structures explained, and their empirical effects were scientifically proven. Once the chemical structure of the natural substances had been found, this was soon followed by synthetic manufacture within a laboratory.

As a consequence, in many cases, the plant was no longer required. A medicine containing the entire spectrum of active substances found in a plant was replaced by a medicine containing only one molecule or pharmacologically active substance.

With the advent of synthetic drugs, medicinal plants took a back seat. People preferred the precise chemical definition of synthetic medicines and the fact that the effects could be measured immediately and clearly in experiments, and they were excited to be able to reproduce the results at any time.

Although, in many countries, herbal medicinal products (HMPs) play a subordinate role in the medical treatment of patients, a change of thinking has become apparent throughout the world in recent years: since 1980 there has been a gradual increasing appearance of herbal medicines and their galenic preparations from medical practice and pharmacy shelves.

It is in the twenty-first century that "Natural Medicine", provided the basis for the scientific development of modern Phytotherapy.⁷ Recently the WHO has estimated that at least 80% of the world's population find in plants the main, if not exclusive, therapeutic source.⁸ Medicinal plants directly contribute to modern medicine with active substances (use of plants, after pulverization, in sachets for teas, tablets, etc.) or can be used for the preparation of extracts (raw, purified or concentrated) or still can be used indirectly (use of the active principles as such or as molecular models used for the design and production of synthetic drugs).

COMPETENT AUTHORITIES FOR PHYTOTHERAPY

This return to things more "natural" has been recognized by the World Health Organization (WHO) which has campaigned to promote more research on and the better use of medicinal plants.^{9,10}

The Herbal Medicinal Products Committee (HMPC) is a working group of the European Medicines Agency (EMA) which produced numerous "Community plant monographs" in which plants or plant parts, their constituents, their type and method of use, their effect and their safety are described and scientifically evaluated. HMPC plant monographs are fundamental and authoritative documents for the licensing of plant-based drugs in the EU.

The Commission E worked from 1984 to 1994 on behalf of the former Federal Health Office (BGA) in Berlin – today the Federal Institute for Drugs and Medical Devices – BfArM Bonn.¹¹ At that time it was used to accelerate the renewed authorization of herbal medicines. This commission worked on the scientific material of 312 drugs (processing monographs) and respectively made and appraisal of the benefit-risk ratio. Today the Commission E has a consultative role in the BfArM.

Like the Commission E in Germany, a working group is assigned to the European Scientific Cooperative on Phytotherapy (ESCOP) at European level, for the development of harmonized assessment criteria for herbal medicines. Its members come from universities and professional societies of numerous European countries.¹²

The European Pharmacopoeia defines the quality parameters of all drugs independently of whether they are of a chemical-synthetic,⁶ herbal or animal nature. It also states the methods used to check the quality of the drugs. The European Pharmacopoeia, currently the 9th edition with the corresponding addenda is valid and has the force of law in all countries of the European Union and Switzerland.

ACTIVE INGREDIENTS IN HERBAL MEDICINAL PRODUCTS

The quality of herbal medicines is believed to be directly related to its active principles: these components have been referred to as "secondary metabolites". However herbal medicines contain other substances, often neglected and poorly understood, which are very important for the biological activity. In herbal medicines there is a phytocomplex, that is the complex of active principles drawn from a plant, that has a specific biological activity. The biological activity of the complex of active principles is usually stronger than the sum of activity of the single active molecules and the presence of substances apparently having no specific activity can

have a very important synergistic effect. Unlike a single chemically defined substance, whether of herbal or synthetic-chemical nature, you always have a complex mixture of chemical ingredients in a plant. These target various receptors, enzymes, membranes, DNA of cells or tissues in the body (multi-target theory). The effects that occur increase in strength and thus show a demonstrable efficacy overall.

The advantages of the phytocomplex can be so summarized as: several and various mechanisms of action, synergy, better bioavailability, better tolerance and minor toxicity.¹³

Drug

The term "Drug" describes the dried plant parts that have been used to cure diseases since ancient times. Drying it preserves the plant and thus it can be stored. Depending on the plant part, drugs could contain more or less high moisture (max. 12%). This is sufficient but not enough for the formation and propagation of fungi and other micro organisms, so that drug can be stored in dry, well ventilated areas for several months or even years. The storage time should not exceed two years, because with contact to atmospheric oxygen, changes in the appearance and the ingredients are to be expected. Today, according to the definition of the Pharmacopoeia,⁶ the term "drug" is understood to include both the fresh and the dried plant or plant part.

In English usage, the term drug (in the translation of "drug") has a broader meaning and refers to all drugs and medicines, be they plant or chemical origin. Via this route the German term drug has also changed over time and now refers to the "intoxication drug", regardless of whether it is vegetable or synthetic of origin (hashish, cocaine, heroin, LSD). To clarify the distinction between the herbal products (drug) and the synthetic-chemical drugs, therefore, the term "herbal drug" is now widely used in professional circles.

Basically, these are herbal remedies which are prepared from herbal substances like dried plant parts such as leaves, blossom, herb, bark, or the roots traditionally already known to cure undesired conditions or illnesses.

Extracts

Today, most herbal preparations are "extracts" from herbal substances in optimized form with known extraction solvent, drug-extract ratios and processing steps finalized as pharmacologically active dry extract.

Here the ingredients of the drug are removed from its packaging (plant cell) and turned into a finished drug in a processable form. Extraction gains enrichment in the ingredients achieved and the undesirable impurities such as chlorophyll, fibre and proteins are mostly left behind. To clearly distinguish the quantitative relation between the drug and drug-preparation to make clear, a so-called drug-extract ratio is specified (DER) for each extract.¹²

The drug-extract ratio specifies the initial amount of

drug used for the preparation of a certain amount of extract. DER means the ratio between the quantity of herbal substance used in the manufacture of an herbal preparation and the quantity of the herbal preparation obtained. The number (given as the actual range) written before the colon is the relative quantity of the herbal substance; the number written after the colon is the relative quantity of the herbal preparation obtained.

For a dried extract with a DER of for example 10:1, it means that 1 part of dried extract of 10 parts of drug was collected and then used for the preparation of 10 g of dried extract for 100 g of drug. With the dosage of the herbal medicine, this number can always be calculated on the number of drugs used for this purpose.

This means that various dried extracts of a drug can be compared in their quality and conclusions can be drawn as to the enrichment of the ingredients.

- i. *Dried extracts* have, depending on the used plant part, a DER of 5 to about 50:1
- ii. *Fluid extracts* (liquid extracts) have a DER of 1:1 to 1:2
- iii. *Thick extracts* (viscous extracts) for example 3-6:1
- iv. *Tinctures* and *other alcoholic extracts* usually 1:7 to 1:9 or 1:4 to 1:4.5, depending on the amount of alcohol used for extraction of the drug.

STANDARDIZATION

Considering all the factors affecting the biosynthesis of the active principles and consequently on the quantitative composition of the plant it is extremely important to adopt a method that defines with accuracy and in a constant manner the composition of the extract one wants to use.

In fact, one of the main problems of the Phytotherapy is the standardization of herbal preparations.¹⁴⁻¹⁶ If a preparation of a given herb is shown to be effective, this does not necessarily mean that another preparation of the same drug is similarly effective: herbal medicines must be of standardized quality in order to have the requested efficacy.

On the other hand, the standardization of herbal drugs is not so simple: the vegetable material has a complex and inconstant chemical composition, depending on a variety of factors: age and origin, harvesting period, specific parts of the plant to be processed, extraction methods employed, drying and storage, etc. Probably a correct drying is the most important phase in the whole process of production, in order to obtain from a standard herb a standardized herbal.¹⁷

Therefore, it is necessary to use an extract that is well defined in its chemical composition and in the quantity of specific active principles.¹⁸ In other words it is necessary to quantify the active principles, the so-called "markers". These compounds are chemically defined constituents or groups of constituents of herbal sub-

stances, herbal preparations or herbal medicinal products which are of interest for control purposes independent of whether they have any therapeutic activity. Markers serve to calculate the quantity of herbal substances or herbal preparations in the herbal medicinal product if the marker has been quantitatively determined in the herbal substance or herbal preparations. There are two categories of markers: active markers, constituents or groups of constituents which are generally accepted to contribute to the therapeutic activity and analytical markers, constituents or groups of constituents that serve only for analytical purposes.

EMA suggests the quantification of the herbal products that is adjusting the herbal preparation to a defined range of constituents exclusively achieved by blending different batches of herbal substances and/or herbal CPMP/QWP/2819/00 Rev 1 EMA 2006 11/11 EMA/CVMP/814/00 Rev 1 preparations (e.g. quantified extracts).

Good extracts always contain defined amounts of these active ingredients; likewise contains undesired substances that can be removed to avoid side-effects. For example, "Ginkgo biloba L. standardized dry extract", means the extract of ginkgo biloba leaves identified with the initials "Egb761", which has the following composition: 24% flavonoid derivatives, 6-7% terpenic compounds. Efficacy and safety of this extract have been sufficiently proved.¹⁹

Standardization means unifying quality

Quality is a basic requirement for the safety and constancy of the therapeutic effect of both synthetic and natural drugs.^{20,21}

The extreme variability of the active principles contained in vegetable drugs makes quality control very important,²² so that the OMS recommendations in this sense have been adopted by the pharmacopoeias of the community countries and at present there is an effort to bring into agreement legislation in all the countries.²³

In addition, to attention to the raw material used, careful control of all steps in the manufacturing process is crucial for the quality of the preparations. As in the manufacture of all other medicines, the production of herbal medicines is also subject to official rules, which are known as "Good Agricultural and Collection Practices (GACP) for Medicinal Plants".²⁴ This term refers to European and global guidelines for quality assurance in the production of medicines (and sometimes of foodstuffs and food supplements). They guarantee the consistent quality of products.

CLINICALLY PROVEN PHYTOTHERAPY

The highest demands are made on clinically proven phyto-pharmaceuticals. Their effect and safety have to be verified in randomized, double-blind, (placebo)-

controlled clinical trials.²⁵ They are developed and scientifically evaluated in the same way as conventional medicinal products.²⁶

This is very different to traditional phyto-pharmaceuticals, where the use is primarily based on experience, for example the administration of tannin-containing black teas for diarrhoea. Traditional herbal medicinal products are Medicinal Products for human use that fulfill the conditions laid down in article 16a (1) of Directive 2001/83/EC, as amended.

Being registered drugs, herbal medicinal products were all listed in the official pharmacopoeias of different countries or in reference texts such as World Health Organization Monographs on Medicinal Plants (volume 1 to 4),²⁷⁻³⁰ European Scientific Cooperative on Phytotherapy (ESCP) Monographs¹⁰ or monographs of deutsche Commission E.¹²

GOOD TOLERANCE

In principle, phyto-pharmaceuticals show high tolerability and safety, but can bear the same risks as other medicinal products. They can have contraindications, there is a risk of undesired side-effects and drug interactions are possible. However, in general phyto-pharmaceuticals are well tolerated and often have a lower risk potential than synthetic chemical medications. Phyto-pharmaceuticals have a broad therapeutic margin and thus work well for simple and chronic symptoms. Due to their high tolerability and rather low interaction potential, they are well suited for elder patients with multiple medications.

Finally, the safety of herbal medicines depends on their correct use.³¹ Herbal medicines, like any medicine, are double-edge word, therefore, both patients and doctors must be able to make the risk/benefit assessment, before using any herbal medicine. We must not forget the fundamental principle of toxicology proposed by Paracelsus (1493-1541): *sola dosis facit venenum*.

Phyto-pharmaceuticals are not homeopathic products

Phyto-pharmaceuticals contain pharmacologically active ingredients that interact with protein structures in the human body, the so-called drug targets. They are, therefore, substantially different to homeopathic remedies, which are highly diluted so that little or nothing of the initial active ingredient is actually left.

In fact, good herbal medicines are standardized and their active principles are quantified; on the other hand, standardization is not possible in homeopathic products, because active principles are too diluted. In contrast to Phytotherapy, homeopathy has no solid scientific evidence and is considered an alternative, complementary therapy approach. The concept of homeopathic products is fundamentally contrary to that of modern medicinal products.

Phytotherapy and conventional medicine

Herbal medicine was and is still often associated with the “alternative therapy scene”, and for as long as phytotherapy (*i.e.* the use of medicinal plants on sick people) is not a subject in the training of doctors or pharmacists, it will have to overcome a whole host of obstacles before being completely accepted by the medical profession.

However, many operators in the sector have already recognized that rather than being an alternative to conventional medicine, Phytotherapy is part of modern, scientifically oriented medicine and an important element of therapy.

This is because, with their broad pharmacological and therapeutic effect, herbal medicines fill therapeutic gaps when treating certain conditions, increasing the therapeutic choices for preventing and treating acute and chronic illnesses.

They also offer a good risk-benefit balance, with good efficacy and are generally safe and well-tolerated. The main areas of use are in illnesses with mild to moderate severity. Herbal medicines are also being increasingly used in the care of the elderly.

As a complementary therapy that strengthens the immune defence system and supports a patient’s self-healing powers, herbal medicines can also be useful as a supplementary measure for serious illnesses.

CONCLUSIONS

Consumer surveys repeatedly show an increasing demand for natural medicines, especially herbal medicines. Over the last 30 years, the number of people using natural medicines has risen constantly.

These increases can be found in both men and women, all age groups and all social classes. Although herbal medicines are widely used in self-medication, many people believe it is “important” or “very important” for doctors to understand and be able to prescribe natural remedies. This highlights the fact that, for many people, herbal medicinal products have become almost indispensable.

Modern phytotherapy is today focused on the study and evaluation of herbal medicines that must respect quality, safety and therapeutic efficacy, in the same way as so-called “synthetic” drugs. In fact, it is not true that “all that is natural does not hurt”: even herbalists can, if used incorrectly, have heavy side effects. So, it is good to deepen the knowledge of natural active ingredients, their effectiveness, individually and in phyto-complex; control the quality of plant products through standardization and confirm the effectiveness of the plant drug, its safety and harmlessness.

Vegetable substances used as a mild remedy, in the prevention or treatment of mild pathologies, are today very many and all completely natural. A wider use of

these natural medicines does not constitute a step back in time; around an art as old as man, today an experimental science flourishes giving great and real hopes for the future.

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