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Reflections on Scientific and Normative Bases of Current Phytotherapy (**)

Riassunto — La fitoterapia tradizionale, basata sull'impiego delle piante medicinali in toto o dei loro estratti grezzi, e quella moderna, che usa invece principi attivi purificati, vengono paragonate e discusse nel contesto attuale.

La prima presenta ancora oggi gli stessi limiti che in passato ne hanno ostacolato lo sviluppo: incostanza degli effetti terapeutici, dispersione dei principi attivi, presenza nella stessa droga di più componenti ad azione sinergica o antagonista. La fitoterapia moderna supera i limiti di quella tradizionale ma presenta altri vantaggi quali l'elevato costo di sviluppo ed i rischi rivelati dal loro impiego.

Per un rilancio della fitoterapia tradizionale occorre:

- 1) sottoporre le piante medicinali a studi rigorosi che ne permettano la caratterizzazione farmacotossicologica e la titolazione in principi attivi;
- 2) definire il loro campo d'impiego, delimitandolo alle forme morbose in cui la loro efficacia è comprovata;
- 3) emanare norme precise sulla produzione e sul commercio delle piante medicinali, in modo particolare per quanto riguarda il controllo di qualità.

The advent of synthetic drugs and other factors discussed here, led to a declining interest in medicinal plants. Today, phytotherapy is enjoying rediscovery. One has only to look at the number of products based on medicinal plants that have reappeared on the shelves of pharmacies, or note the ever-growing number of herbalist shops. In economic terms, consumption of medicinal plants, in both industrialized and developing countries, is booming. Recent statistics published by the U.N. Organization for Economic Cooperation and Development (O.E.C.D.), show that imports of medicinal plants in member coun-

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tries have jumped from 52.9 to 71.2 million dollars, an overall increase of about 34 per cent. Interestingly, the biggest increase is that of Japan, a highly industrialised nation.

International organizations such as the E.E.C. and W.H.O. have for some time been looking into the question of medicinal plants. The E.E.C. has issued guidelines for the setting up of university courses in pharmacognosy and allied subjects. The W.H.O. has promoted numerous research projects, including a study of vegetable drugs with anti-cancer or contraceptive activity.

The current reappraisal of phytotherapy is part of the wider back-to-nature movement, advocated by diverse modern schools of thought. We wonder, however, whether this return to nature is rational or is merely a passing, emotional phenomenon due mainly to the growing awareness in the industrialised populations of the dangers of super-advanced technology and the indiscriminate use of chemicals.

To answer this question we need to analyse the various facets of phytotherapy and trace its history from the early origins to the latest developments. In doing so, we shall distinguish *traditional phytotherapy*, meaning the use of whole plants or crude extracts, from *modern phytotherapy*, that is the use of preparations made from medicinal plants, containing their purified active principles.

From time immemorial, the human being's fear of bodily suffering and disease has urged him to seek out and exploit natural resources, helped by instinct, chance and observation. Everything that Nature offers, by way animals, minerals and plants, has been used by trial and error, to treat disease; but the favourite source was always the plant kingdom, which was both rich in active principles and readily accessible. Hence the extraordinary importance of phytotherapy in ancient medicine.

The most important document in the history of *Materia Medica* is the ancient Egyptian papyrus discovered in 1873 by George Ebers, and named after its discoverer. Although dated 1555 B.C., it contains prescriptions that probably date from the earliest dynasties, that is, 3300-2600 B.C. One of the oldest pharmacopoeias, this papyrus lists numerous vegetable drugs; many of these, such as senna, castor seeds, acacia gum, mint, thyme, pomegranate and henbane (*Hyoscyamus niger*), are still used today.

Ancient Egyptian learning spread especially to Mesopotamia, where the most commonly used drugs were opium, cannabis, mandrake, carob, myrrh, alum and sulphur. Belladonna was used in Mesopotamia to relieve bladder cramps, cough and asthma. For this information we are indebted to the cuneiform tablets at Nineveh, dating back to 2000 B.C.

In Egyptian, Assyrian and Babylonian times, remedies were skillfully prepared by the priesthood, who kept the secrets of their preparations closely guarded in the temples.

The first written record of medical knowledge in India is to be found in the Vedas, books of knowledge, thought to have been written between 1500 and 800 B.C.. The Atharvaveda, especially, gives remedies for rheumatism, bron-

chitis, gout, neuralgia and so on. Myriads of drugs are also described here: opium, rauwolfia, nux vomica (the poison nut), datura leaves (stramonium), mustard, sulphur, gold (thought to be highly potent), woman's milk. However, at that time Indian cures relied mainly on magic, miracles and the supernatural. Though herbs were part of the treatment for disease, they were never considered effective without the help of the gods.

The origins of medical treatment in China are recorded in the *Pen ts'ao* (*Materia Medica*), and particularly in *Chen nong Pen ts'ao King*, attributed to the famous emperor *Chen nong*, who lived in about 2700 B.C. Among the innumerable drugs mentioned in this text some have been surpassed, many others still survive, notably opium, aconite, castor oil, rhubarb, camphor, ginseng root and artemisia. The emperor *Chen nong* described the diaphoretic and stimulant effects of *ma-huang*, the shrub that was used in Chinese medicine for five thousand years, before the isolation of its active principle, ephedrine. The emperor also noted the antipyretic effects of *ch'ang shang* (*Dichroa febrifuga*), which is now known to contain antimalarial alkaloids.

But it was principally the Greeks, and through them the Romans, who inherited the elements of medicine from the Egyptians, and developed them further. The first reliable record of medicinal plants used by the Greeks is found in Herodotus (5th century B.C.). Among other observations, he describes the cultivation of castor seeds and the extraction of castor oil. Early news of Greek medical practices comes too from Hippocrates, born on the island of Kos in 460 B.C., the author of a treatise in 100 volumes that forms the "*Corpus Hippocraticum*". Theophrastus (370-287 B.C.), a contemporary and pupil of Aristotle, in his famous book "*Historia Plantarum*", describes the morphology of plants known at that time and their therapeutic uses, though his work does contain some mistakes and inaccuracies.

Dioscorides, born in Asia Minor in the 1st century A.D., was the author of a treatise "*De Materia Medica*", in which he described more than 500 drugs obtainable from animal, vegetable and mineral sources. This compendium earned Dioscorides recognition as the true founder of medical science and "*De Materia Medica*" was the bible of pharmacology until the early 18th century. Dioscorides appreciated the influence of the ground on medicinal plants; he studied the problems involved in harvesting and storing drugs, their quality and purity, and explained how adulterations and substitutes could be recognized. Even though in the light of present-day knowledge the work has obvious limitations, Dioscorides must be acknowledged as the greatest pharmacognosist of ancient times.

The Greco-Roman period reached its height with Galen (131-c.200 A.D.), who was born in the ancient city of Pergamum in Asia Minor. He went ahead methodically with the work done by Dioscorides and, drawing from all the existing medical and therapeutic methods, developed a system that was for many centuries to be considered the most complete reference. Galen distinguished the use of dried wild herbs from the use of preparations, later described as *Galenicals*. These were extracted using solvents such as alcohol, water or vinegar

and used to prepare ointments, plasters (emplastra) and so on. Dioscorides and Galen are thus thought of as the fathers of modern pharmacy.

In the West, after the fall of the Roman Empire and during the Middle Ages the use of plants for medicinal and other purposes made little progress. Science, magic and witchcraft were often intermingled; the herbs henbane, belladonna and mandrake were considered to originate from the devil.

At this time the Arab world was enjoying a period of great scientific activity. Arab medicine, born from the fusion of the Greco-Roman, Arab and Indian medical systems, soon spread by way of Spain, all over Europe. With the Arab influence came new medicaments such as cinnamon, musk, manna, lemon, nutmeg, senna tamarind, and buckthorn (*Rhamnus frangula*). Among the many famous Arab physicians worthy of mention are Avicenna, Averroës and Ibn Baithar (13th century), who listed more than 1400 medicinal plants with their botanical description, geographical location and biological actions.

During the Middle Ages in Europe, the custodians of past learning were the monks, who were profound scholars of Latin and Greek. Many monasteries proudly tended their "garden of simples", herbs with supposed medicinal properties, needed to treat the sick. A Benedictine sister, St. Hildegard of Bingen from (1089-1179), was the author of a number of treatises, given the name of "Physica"; here we find the first descriptions of plants such as mouse-ear hawkweed (*pilosella*) and arnica.

The Middle Ages in Europe also saw the rise of medical schools, in Salerno (c. the 9th century) and in Montpellier; that enjoyed prestige and fame until the 15th century.

The Renaissance, with the arrival of direct experimentation and observation and the coming and going of explorers to the Indies and America, saw the beginning of scientific progress, and the knowledge of plants and their properties advanced. At the beginning of the 16th century the Swiss physician Paracelsus tried to isolate the "soul", the quintessence of plants, in other words the source of their therapeutic properties, today called the active principles. He is thus considered to be the father of pharmacology.

A contemporary of Paracelsus, the Italian Pier Andrea Mattioli, annotated Dioscorides' work, discovered the properties of the horse chestnut, and described 100 new plant species.

The first botanical gardens were created in Pisa (1544) and Padua (1590). In 1653 Louis XIII of France founded the "Jardin du Rè", later to become the National Museum of Natural History.

At this time great botanists such as Mathias de Lobel, Guillaume Rondelet, Jean and Gaspard Bauhin, all taught at Montpellier. They greatly enriched the systematic classification of plants, now ever more essential with the wealth of newly acquired knowledge. Their efforts resulted in the appearance in 1735 of C. Linnaeus' "Sistema Naturae", which gave birth to the modern binomial botanical system, and botany became a science in its own right. Meanwhile at the end of the 15th century, the opening up of sea routes made Europe the

centre of the world, into which products flowed from far off lands, together with numerous foreign plants including curare, china and coca. These new arrivals provided the starting point for fresh investigations.

However, even though millenniums had passed since its birth, phytotherapy had not yet made much progress. The end of the 17th century was a decisive turning point. In the late 18th century Scheele isolated the first oxalic acids. In the early nineteenth century Serturmer extracted morphine from opium. Pellettier and Caventou isolated emetine from ipecacuanha root (1817), strychnine from *nux vomica* (1818) and quinine from cinchona bark (1820).

From then on use was made not only of medicinal herbs as such, but also of their purified active principles. Very soon these constituents were synthesized in great quantities at relatively low costs. This marked the decline of traditional phytotherapy and the arrival of modern phytotherapy. The latter has had a notable impact on medicine, supplying pharmacology with many of its prototypes and making it possible to cure many diseases. The majority of drugs in the therapeutic armamentarium today are of vegetable origin. Too numerous to list, we can but mention cardio-active glycosides, salicylates, atropine and other drugs acting on the autonomic nervous system, reserpine, vincristine and other anti-cancer drugs, the ergot alkaloids, alkaloids from opium, emetine, quinine, theophylline and lastly tubocurarine. Drugs of vegetable origin are used to prevent or treat virtually all types of disease.

The reasons behind the decline of traditional phytotherapy and the obstacles that hinder progress today practically coincide; they can be summarized as follows:

- 1) The variability in therapeutic effects, due to the fact that the amount of active principles contained in a vegetable drug varies considerably according to natural factors (age, climate, latitude, altitude, type of soil) and artificial factors (method of collection, drying and storage).
- 2) The presence in medicinal plants of other components that may act synergistically with, or as antagonists to, the active principles, modifying their effectiveness and thus increasing the variability of the response.
- 3) The dispersion of the active principles throughout the plant, meaning that a larger quantity is required to obtain a therapeutic effect.
- 4) The difficulty in obtaining and storing many vegetable drugs, that hinders widespread use.

Modern phytotherapy has overcome the basic limitations of traditional phytotherapy since pure active principles can now be measured accurately, thus ensuring a constant reproducible pharmacological action. But new problems have arisen. Using a medicinal plant is a very different matter from using its purified active principles. These are artificial man-made products whose properties are not identical to those of the whole plant from which they were obtained. The purified principles are absorbed and metabolized quite differently, thus the degree and type of pharmacological action also differs. One merely has to compare morphine with opium. From this point of view, purified active principles

of vegetable origin have the same drawbacks as new synthetically produced drugs; both involve new experimentation, full of risks and uncertainties.

As we all know, after the thalidomide tragedy, the therapeutic use of artificial drugs was subjected to strict controls based on complex trials in the laboratory and in man. This testing has slowed up development of new drugs, in addition to increasing production costs astronomically.

Thus modern phytotherapy, that is, the use of purified active principles, on the one hand solves many problems inherent in traditional phytotherapy, but on the other has all the disadvantages of synthetic drugs, the risks of iatrogenic disease and high cost of development.

Nevertheless, we still feel that phytotherapy has a great deal to offer today. But if medicinal plants are to take their proper place in the therapeutic armamentarium, beside the so-called artificial drugs, then phytotherapy must be founded again on new lines.

Above all, a clear definition is required as to the possible applications of medicinal plants. At this stage, it would be unrealistic to think of employing vegetable drugs alone, to treat serious diseases; in these cases one would clearly resort to heroic drugs. Nonetheless, medicinal plants could regain a significant role in slight or moderately severe disorders and in functional, non-somatic complaints, for example, where a bland sedative action is necessary or in certain digestive upsets. In these instances, well-tried medicaments that have been known for thousands of years may even be better and safer than artificial man-made products. Besides, comparatively little red-tape is involved in the registration of preparations based on medicinal plants. As these substances have already undergone trials by being used over the years, they require less animal experimentation. They also cost far less to develop than the exorbitant sums spent on synthetic drugs. Even the large pharmaceutical companies would therefore benefit by concentrating research on more serious diseases and exploiting medicinal plants for the treatment of minor complaints.

In the reappraisal of traditional phytotherapy, another matter that cannot be overlooked is legislation. Explicit regulations must be laid down concerning the production, storage, distribution and quality control of medicinal plants. As in other countries, a new pharmacopoeia of vegetable drugs will be necessary, consisting of monographs with biological or chemical essays for each drug.

Lastly, a fundamental requirement in the reevaluation of traditional phytotherapy is scientific research. In comparing experimental findings, one of the frequent obstacles that pharmacologists and pharmacognosists encounter is the variety of solvents used for extracting vegetable drugs (water, methanol, ethanol, chloroform). Whether extracts are purified, chemically fractionated or raw, sooner or later they deteriorate and this is yet another variable that affects the results of research.

To overcome these difficulties, extraction methods for medicinal plants should, first of all, be standardized. Each drug or its extract should have a "fingerprint", in other words a map of its constituents, that allows the drug to be

identified, and indicates the possible quantitative and qualitative differences in its composition. In our view, this would render research more homogeneous; results would be easier to repeat and compare.

Medicinal plants also require improved drug toxicity studies. This problem has been tackled in our department and we have designed a series of laboratory tests to determine scientifically the pharmacology and toxicity of medicinal plants.

In studying vegetable drugs, the commonest approach is to confirm experimentally, by laboratory testing, the pharmacological actions attributed to the drug by popular tradition and then to try to isolate the active principles. In a modern context this method of planning studies of vegetable drugs seems to us somewhat restrictive. We should also establish the specificity of the actions observed. That is, we should see how these fit into the overall pharmacological and toxicological picture. Every plant investigated should be regarded as a completely new, unknown product. As such, it must be thoroughly investigated and its entire therapeutic potential explored.

In our view, the proper way to study medicinal plants is to subject them both to tests specifically designed to demonstrate in the laboratory the properties attributed to the plant by popular tradition and to general pharmacological tests to reveal effects on other apparatus or organs. The special pharmacological tests would be carried out on standardized extracts and also on the various drug preparations used in popular medicine (decoctions, infusions).

At the same time, the drug must undergo acute and chronic toxicity tests. It is essential to analyze all the results, using strict statistical methods specially designed for each type of experiment.

In our experience, these investigations have not always confirmed all the therapeutic properties with which medicinal plants have been credited. Medicinal herbs used to treat epilepsy or ascites, for example, proved not to possess their respective anticonvulsant or diuretic effects. This does not necessarily mean that they are inactive; their therapeutic activity could depend on other as yet unknown mechanisms. In such cases, the study of a medicinal plant may open up new horizons in pharmacological research, as happened years ago with *Rauwolfia serpentina*. Medicinal plants are thus important not only for their practical applications, but also for their value in basic research. We therefore consider that if its dignity as a science is restored, if it is given a firm scientific basis and adequate legislation, then phytotherapy has a great deal to offer today.