Similarities between various systems of traditional medicine. Considerations for the future of ethnopharmacology

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(Accepted September 6, 1991)

Traditional medicine using herbal drugs exists in every part of the world. The major areas are Chinese, Indian and European traditions. The philosophies of these traditional medicines have some resemblance to each other but differ widely from modern Western medicine. In view of the progress of Western medicine not only new synthetic drugs but also herbal drugs have to fulfill the international requirements on quality, safety and efficacy. Herbal drugs have the advantage of being available for patients in the geographical area of the special traditional medicine. The development procedure of herbal drugs for worldwide use has to be different from that of synthetic drugs.

Key words: traditional medicine; development procedure; requirements for quality, efficacy and safety

Introduction

In the discussion about natural medicine quite often the questions arise: Why are traditional medicines not accepted worldwide and what are the reasons for the reluctance of many Health Authorities against natural drugs? To answer these questions one has to consider the history of medicine. The necessity of helping sick people goes back to the origin of mankind. In many places of the world special ways of medical treatment were found. The experiences were passed on from generation to generation resulting in a scientific approach to a philosophical system. The terms 'Traditional Medicine' or 'Ethnopharmacology' are our present views on this development. These considerations may contribute to the ongoing discussions between traditional and modern medicine. If we look back into history we find that in all continents and in every country some kind of traditional medicine exists or has existed. Basically, we can distinguish between three major areas of traditional medicine: Chinese, Indian and European.

Chinese medicine

The art of practising Chinese herbal medicine stretches back over more than 5000 years. The legendary culture hero, Shen-nong, is said to have tested many herbs for their medical properties. Pen-tsao, the first compilation of herbal remedies, was connected with his name (Unschuld, 1973, 1986, 1988). About 500 A.D., Tao Hongjing wrote the book Shen-nong bencao jing. Already 500 years B.C., at the time of Confucius, the opposing principles were established into the balance of yin and yang forces which are today familiar even to Western scientists. Yin and yang have their own domain within the human body, although these spheres of influence intersect. Yin controls the in-
ternal, the lower and the front portions of the body, while yang dominates the external, upper and back parts. Half the vital organs belong to yin and half to yang. Yin-yang is the symbolic way designating opposite forces that are at work in everything from the solar system down to the minutest cell of the body (Wong, 1990). Herbal medicines redress yin-yang imbalances by supplementing the deficient element.

Since ancient times, the Chinese have divided the world into five symbolic elements: Wood, Fire, Earth, Metal, and Water (Fig. 1) (Reid, 1987). Everything on earth is dominated by one of these elements, and their constant interplay, combined with those of yin and yang, explain all change and activity in nature. The generative cycle proceeds as follows. Wood burns to generate Fire. Fire produces ashes which generates Earth. Earth creates Destroys

- Liver, Gall bladder
- Heart, Small intestine
- Kidney, Bladder
- Lung, Large intestine
- Spleen, Stomach

Wood generates Fire
Fire generates Earth
Earth generates Metal
Metal generates Water
Water generates Wood

Fire subjugates Earth
Earth subjugates Water
Water subjugates Fire
Metal subjugates Water

Wu-Hsing Theory

<table>
<thead>
<tr>
<th>Elements</th>
<th>Organs</th>
<th>Colours</th>
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<tbody>
<tr>
<td>Wood</td>
<td>Liver</td>
<td>Blue</td>
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<tr>
<td>Fire</td>
<td>Heart</td>
<td>Red</td>
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<td>Earth</td>
<td>Spleen</td>
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<td>Metal</td>
<td>Lung</td>
<td>White</td>
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<tr>
<td>Water</td>
<td>Kidney</td>
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Fig. 1. Interaction of 5 elements in Chinese philosophy (Reid, 1987).

Fig. 2. Relation between elements, organs and colours in Chinese medicine.
population. The word Ayurveda is composed of two parts: Ayu (= life) and Veda (= knowledge). The origins of this science of life have been placed by scholars of Ayurveda at somewhere around 6000 years B.C. It is reported that the principles of Ayurveda were elaborated first by Lord Brahma. They were orally transmitted by successive generations. Dhanvantari and Bharadwaja developed the surgical and medical aspects of Ayurveda around the ninth century B.C. The principles were recorded in great detail in compendia which are called Samhitas written on palm leaves (Mazars, 1990).

The Sushruta Samhita emphasizes surgical aspects of therapy, whereas Charak’s teachings concern drug therapy. These writings were amended to 8 books or tantras which correspond to disciplines of modern medicine (Dahanukar and Thatte, 1989; Dash and Junius, 1987).

Compared with modern anatomy and physiology Ayurveda is based on certain fundamental doctrines, known as the Darshanas, such as the seven dhatus (Fig. 3). They can be described not exactly as organs but as body constituents (Lad, 1984). The three malas are the excretion products. The three doshas — vata, pitta and kapha are regulators of cell function in various ways (Fig. 4).

The Circulation of Nutrients and Transformation of Dhatu

![Diagram of the seven dhatus in Ayurvedic medicine (Lad, 1984).]
A balance of the three *doshas*, good quality of tissues and a certain character of excretory products, is essential for maintaining health. Unbalance of the *doshas* creates disease (Lele, 1986).

Drug therapy is very well developed in Ayurveda. There are up to 8000 recipes for the preparation of different drug combinations. Drugs used in Ayurveda are derived from a wide range of materials such as plants and minerals. Drug therapy in Ayurveda is highly individualized. The choice of drugs as well as their doses are not only influenced by the disease process, but also by the constitution of individuals and environmental conditions which affect the balance of the *doshas* and therefore the response to drugs. Again, the basic philosophy is far away from modern Western medicine.

**Traditional medicine in Europe**

Traditional European medicine goes back to the time of Egyptian and Babylonian-Assyrian culture. The fundamentals of Babylonian-Assyrian medicine were based on the idea that illness was a divine punishment and healing a purification (Mazars, 1990). Illnesses have been caused by demons which had to be expelled by exorcism (Lyons, 1980). Medicine attained a fixed place in the religious ideology. The famous papyrus *Ebers* was written around 1500 B.C., being more than 20 m long, describing more than 700 drugs in more than 800 formulations (Edelstein, 1945). The drugs were drawn from plants, animals and mineral, but botanic drugs predominate for internal use, some of them being still used at our time, such as garlic and poppy seeds.

Egyptian and Assyrian culture was taken over by the Greeks and later on by the Romans (Lyons, 1980; Baisette, 1990). The mythological creator of the Greek materia medica was Apollo. Herbal medicine was identified with Chiron the Centaur. In the legend we find that Chiron taught Asklepios his pharmaceutical knowledge about drug plants. Asklepios became the most famous god for health, aided by his two daughters, Hygeia (Walton, 1894; Catow, 1900; Edelstein, 1945) and Panacea. Later on, in historical times, Greek philosophers such as Empedocles, Aristotle and Pythagoras, all of them around 500 B.C., influenced medicine a great deal. They created the theory of the Four Elements which were proposed to be the components of all matter, including animal and man (Schöner, 1964). These Four Elements were Water, Air, Fire and Earth.

The most famous physician at the time around 400 B.C. was Hippocrates. He is considered to be the author of many books and the originator of the so-called Hippocratic oath (Adams, 1891; Pournaropolou, 1967; Deichgrächer, 1971). Although the regulation of diet occupies the most important place in the Hippocratic corpus, we also find between 200 and 400 drugs, mainly of vegetable origin. In the first century A.D. the physician Dioscorides from Kilikia described approximately 600 herbal drugs in his books *De materia medica* written first in Greek but translated and copied later on in Latin (Gunther, 1968).

The most famous physician in the Greek-
Roman period was Galenus, living in the 2nd century A.D. in Pergamum and Rome (Siegel, 1960). His ideas on physiology are based on three digestion processes from chyle to bile and then to blood which is mixed with pneuma. In spite of his knowledge of anatomy his ideas on physiology were very different from our present knowledge so that also pathology and treatment of diseases were quite different from today's approach. Nevertheless, his name coined the pharmaceutical science. At this time the remedies mainly consisted of herbal drugs.

European medicine has been influenced by Arabian medicine, mainly by the physician Ali ibn Sina, who is known in Europe under the name Avicenna (Gruner, 1939, Sournia, 1990). His books were translated into Latin and his *Canon medicinae* has influenced European medicine for centuries. Moreover, he is considered to be the founder of Unani medicine (Razzack, 1991).

In medical times the system of pathology and therapy, originating from Galenus, dominated Western medicine at this time (Fig. 5). The fundamental principle in so-called galenism was the transformation of humoral pathology into a rigid dogma. Already the school of Hippocrates had formulated the theory of the Four Humors (paralleling the Four Elements), the correct balance of which meant health, while every disturbance of this balance caused disease (Siegel, 1968). The Four Humors were: Blood (coming from the heart), Phlegm (supposed to come from the brain), Yellow Bile (supposed to be secreted from the liver), and Black Bile (supposed to come from the spleen and the stomach). Each of these humors had definite qualities. Blood was moist and warm; Phlegm moist and cold; Yellow Bile warm and dry; Black Bile cold and dry. Furthermore, there was a definite connection between predominance of one humor in the metabolic system and an individual’s temperament such as sanguine, phlegmatic, choleric, and melancholic. The similarities with the Wu-Hsing theory of Chinese Medicine and the Darshana Doctrine of Ayurvedic Medicine cannot be neglected.

Saint Hildegard of Bingen (Müller, 1982) was one of the most famous physicians and pharmacists in the 12th century, being the abbess of a monastery. She wrote many books on human nature and the use of herbal drugs. The German physician Theophrastus Bombastus von Hohenheim, called Paracelsus, living in the 15th century, was a great reformer of European medicine (Aschner, 1926, Temkin, 1941). He used not only herbal drugs, but also minerals. One of his ideas was that in nature a remedy can always be found against every disease. The Latin sentence *Ubi natum ibi remedium* was the core idea of the signature theory indicating that the shape or the colour of the plant gives hints against which disease the herbal drug can be used.

In all these three major areas of traditional medicine, the European, the Chinese and the Indian, the therapeutic armamentarium consists mainly of herbal drugs, partially also coming from minerals and animals. The underlying philosophical principles of these traditional medicines have some similarities but in any case, they are quite different from modern medicine.

**Development of modern medicine**

Western medicine made its most important achievements in several areas such as diagnosis, infectious diseases, endocrinology and medicinal chemistry.
Diagnosis as the recognition of pathological conditions has been greatly influenced by cellular pathology as founded by Virchow (Pagel, 1906) in the 19th century. The intensive use of the microscope in medicine with histological comparison of diseased and normal organs allowed the change from humoral to cellular pathology. Diseases are described as symptoms, related to morphological changes and histological pictures as found in pathology. Changes in body fluids as found in clinical chemistry are attributed to morphological entities describing the disease. Also, our most recent diagnostic developments like computer-assisted tomography or magnetic resonance tomography try to give pictures of anatomical deviations from normal. Even if we do not see gross anatomical changes, we think about malfunction of organs based on a cellular level. The biggest progress of Western medicine was in infectious diseases. Vaccination procedures were elaborated, for example, by Edward Jenner against smallpox, by Louis Pasteur against rabies and by Jonas Salk against poliomyelitis. Since the pioneering work of Emil von Behring (Bieling, 1954) the therapy with sera against diphtheria and tetanus was established.

The first success in chemotherapy by Paul Ehrlich with Salvarsan was followed by Gerhard Domagk with sulfonamides. Bacteriology as founded by Robert Koch became a well-defined science. The most spectacular success was the introduction of antibiotics beginning with penicillin by the discoveries of Alexander Fleming and Ernst Boris Chain.

Another field where modern Western medicine has achieved great success is endocrinology. The importance of steroid hormones, secreted by the gonads, was found by scientists like Adolf Berthold, C.E. Brown-Sequard, Adolf Butenandt, and Leopold Ruzicka. The effect of steroid hormones from the adrenal gland was elucidated by Thomas Addison, Tadeusz Reichstein, E.C. Kendall, P.S. Hench and A. Wettstein.

The central role of pituitary and hypothalamic hormones was clarified by Harvey Cushing, H.M. Evans, Andrew Schally and Roger Guillemin. Several of these scientists were Nobel Prize winners. Due to this knowledge, hormonal imbalances can be treated efficiently. Due to the work of Oskar Minkowski, Frederic Grant Banting and Charles H. Best (Banting and Best, 1922) diabetic patients can survive.

Medicinal chemistry as an important science started not more than 100 years ago. The active principles of plants were the starting point for syntheses such as morphine from *Papaver somniferum* for analgesics and spasmodylitics; atropine from *Atropa belladonna* for synthetic spasmyotics; cocaine from *Erythroxylon coca* for local anaesthetics; ephedrin from *Ephedra sinica* for cardiovascular drugs; xanthines from *Coffea arabica* and *Theobroma cacao* for vasotherapeutics such as pentoxifyllin. Recently potential antiedentical drugs have been synthesized as derivatives of physostigmin from *Physostigma venenatum*.

In several instances semisynthetic derivatives are used such as ergot derivatives from *Claviceps purpurea* and cardiac glycosides from *Digitalis lanata*. Moreover, medicinal chemistry produced synthetic compounds which have no example in nature such as phenothiazines, benzodiazepines or pyrazolones. Antagonists against physiological messengers were developed such as β-blockers, calcium-antagonists, H₂-antagonists and angiotensin converting enzyme (ACE) inhibitors.

Registration of drugs by health authorities

The general requirement for new drugs worldwide is quality, safety and efficacy. As far as efficacy is concerned, herbal drugs have to be compared with a synthetic drug as standard. However, against many diseases we do not have an efficient therapy with synthetic drugs, but experience during centuries tells us that herbal drugs may be effective. This is especially true for chronic diseases where we do not have appropriate pharmacological models. Unfortunately, a few synthetic drugs caused unexpected side-effects, like fetal malformations by thalidomide. Therefore, the requirements for development of a synthetic drug are rather stringent. Before coming to this point we should look to other differences between traditional herbal remedies and synthetic drugs.

Compared with modern medicine, traditional medicine has specific shortcomings. Usually, we do not have double-blind studies or even well...
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described case records. If the results of treatment with a drug are submitted to Health Authorities anywhere in the world this cannot be done by anecdotical observations in single patients but based on the results of comparative trials in patients suffering from a well-defined disease. The experiences gathered in one cultural area are mostly accepted by the Health Authorities of this individual country but not by another Health Authority elsewhere. Another basic difficulty is the fact that traditional medicine usually consists of many herbal or animal or inorganic ingredients. Herbal drugs per se consist of many components, some of which are active, some not. There is even a wide variation in the quantity of pharmacological active substances in each plant. Differences in methods of extraction and purification influence the results. Quite often sufficient quality control and drug standardization is lacking for traditional recipes. The question arises whether or not the various ingredients of a plant or even the multi-drug formulation can be analyzed by pharmacological means. The difficulties are the same if mixtures of synthetic drugs or mixtures of herbal drugs have to be tested. Simple mathematical calculations show the impossibility to analyze a combination by classical pharmacological models if more than four combination partners are involved. Therefore, at present usually a traditional medicine is only accepted in one country or in one cultural area.

Requirements for registration of a synthetic drug

The development procedures for a synthetic drug as being carried out in a large pharmaceutical company at the present time are rather extensive. A synthetic drug originates from the research work of groups of chemists and pharmacologists mainly at institutes of the pharmaceutical industry. Formerly, new chemical entities were screened randomly in pharmacological tests. During the last years the screening procedures are more target-directed. Based on ideas of mode of action or in analogy to natural drugs many compounds are synthesized and tested for biological activities. Usually groups of chemists and pharmacologists are devoted to one project, e.g. search for a new antihypertensive drug, based on ACE-inhibition. Knowing some structure-activity relationships, effective compounds are found. These compounds are compared with the most active compound being used in therapy or being known from literature. Only if a new compound has advantages in pharmacology over known compounds it can be selected for development. The advantages can be higher potency, different spectrum of activity and/or less side-effects. The development process can then be started. The overall goal in drug development is quality, safety and efficacy. All measures in development are directed to this goal.

The development course of a compound is divided into various steps. In the first step special pharmacology and/or bacteriology is performed in order to demonstrate the superiority of the new drug against reference compounds. Therefore, dose response experiments have to be performed in pharmacology, using various methods.

Furthermore, preformulation work is started, acute toxicity and pilot toxicity in two animal species are performed. In addition, pilot studies on kinetics and metabolism in two animal species and the first mutagenicity test, usually Ames test, are carried out. The most important studies at this step are safety pharmacology. These experiments are performed using doses which are several times higher than the ED₉₀ value of the desired effect. The influence of the new drug on all physiological organ systems is tested, such as the influence on the central nervous system, the influence on intermediary metabolism such as carbohydrate and lipid metabolism, the influence on renal, pulmonary and gastrointestinal function.

Most important is the cardiovascular pharmacology, where not only the influence on the heart but also on the peripheral vascular system is tested.

All further studies have to be performed according to the Good Laboratory Practice (GLP) guidelines. These studies include acute toxicity with other applications and in further species, sub-chronic toxicity in two species with at least three doses including histopathology, eventually with other applications. Kinetics and metabolism in animals are continued in more detail and a method is developed which is suitable for picking up blood levels in the forthcoming human studies. Mutagenicity tests are continued. For CNS-active compounds drug addiction studies are performed.
Only if all these preclinical studies are at hand indicating a sufficient safety margin and after a very careful assessment of the benefit/risk ratio can the first trial in volunteers be started.

The first Phase I is performed on human volunteers. Starting with low doses tolerability is tested. As soon as we come up to the range of the anticipated therapeutic dose, blood is withdrawn to study the blood level of the original compound. With these data the half-life of the compound can be calculated. In order to get more insight into kinetics and metabolism in human beings radioactive studies have to be performed. For these studies safety experiments in animals, such as organ distribution of radioactive material, are done in order to get a so-called ARSAC application. Side-effects during these Phase I studies are carefully monitored. If possible, dynamic studies are performed, for example influence on blood pressure in healthy volunteers after application of an antihypertensive drug. In several cases the therapeutic effect cannot be measured in healthy persons. One has to study the therapeutic effects in carefully monitored Phase IIa studies in patients. Usually the toxicological data available at this time, include 1- or 3-month toxicity in two species. In order to extend the studies in patients beyond 4 weeks, we have to perform long-term toxicity studies in two animal species including histopathology. Additional toxicity studies are done during this period such as nephrotoxicity, teratology, antigenicity and further mutagenicity tests. At the same time kinetic and metabolism studies in animals are continued in order to identify the metabolism both qualitatively and quantitatively.

Only if definite prerequisites are met such as tolerability in human volunteers, sufficient human data on kinetics and metabolism and hints for therapeutic efficacy can Phase IIb be started.

In Phase IIb the most important pivotal clinical studies are performed. These include dose-finding studies in order to achieve dose-response curves and very carefully planned double-blind studies against placebo or a standard drug. Furthermore, the dosage regimen is established including food interaction studies. During this time additional paraclinical studies such as chronic toxicity in two, eventually three species, carcinogenicity in two species and further studies on teratology and fertility have to be performed.

If the pivotal clinical studies are positive, the clinical trials can be expanded into Phase III. During this time data on several thousands of patients in various well-defined indications are collected. Studies in patients with impaired renal and hepatic function are performed as well as interaction studies with other drugs. At all time the side-effects are carefully monitored. During this time preclinical work, such as long-term toxicity and carcinogenicity including histopathology is continued.

Only after very careful evaluation of the analytical expert report indicating the quality requirements of the new drug, the pharmacological-toxicological expert report indicating the benefit/risk ratio from the experimental point of view and the clinical expert report indicating the benefit/risk ratio from the clinical point of view, are the data are submitted to the health authorities, e.g. a submission of a New Drug Application (NDA) to the FDA.

Figure 6 gives an overview on the development system for synthetic drugs. Three clinical phases and many preclinical studies have to be performed until a NDA can be filed. The approval of NDA usually takes years before the new compound comes on the market and is available for patients. Even then it is carefully monitored in drug surveillance studies in Phase IV.

The development course for a synthetic drug is straightforward from the beginning to the market. It needs approximately 10 years and costs more than 200 million dollars. During this time the drug is available only for those patients who are included into the controlled studies. From those compounds which are taken into development only a few reach the market. Recent calculations showed that out of hundreds of new compounds entering development only approximately 7% could be brought on the market. All others were dropped due to several reasons, mostly because of the results of animal toxicity studies.

Development and registration of herbal drugs

The development system for herbal drugs is much less established. We have to acknowledge that the herbal drug is being used in one geographical area
Synthesis of many (thousands) of new chemical entities

Random or target directed pharmacological screening

Selection of one compound

Safety pharmacology

Subchronic toxicity

Chronic toxicity

Teratology

Mutagenicity

Cancerogenicity

Fig. 6. Development system for synthetic drugs.

Fig. 7. Proposed development system for herbal drugs.

as a traditional recipe and is therefore available for the patient. The situation is the same for traditional medicine in Europe and in Asia. In each case the drug has been available to the public for many years, in some cases for centuries. Since the herbal drug has been used for a long time in patients a good proof for safety is available and less safety studies in animals are necessary. In this way the herbal drug is not really a new one but only an improvement of the older medicine. The development of a herbal drug is therefore more like a circle or a spiral rather than a straight line as for synthetic drugs (Fig. 7).

Therefore, one may propose a development procedure tailor-made for herbal drugs. Traditional medicine usually consists of a mixture of herbal drugs. In the first step the therapeutic efficacy of the traditional medicine has to be confirmed. Of