Committee 2
Holistic Medicine in Modern Health Care

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The Potential of Modern Clinical Phytotherapy as a Whole System Science

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(1) Introduction. Phytotherapy works most reliably for what kinds of patients?

Botanical medicine, or phytotherapy, is the dominant form of medical treatment in the world. The World Health Organization (WHO) estimates that 80% of the world's population relies principally on traditional style medicines, in which phytotherapy almost always plays a central role (1). Traditional Chinese Medicine (TCM) and its numerous variants is the most pervasive form of medical therapy in east Asia. Even in Japan 70% of physicians prescribe botanical formulas from the Chinese medical tradition ("*Kampo*")(2). In the industrialized West the use of herbs and botanical extracts plays an increasing role in health care. Between 3000 and 4000 physicians in France alone use phytotherapy for primary care. Great Britain licenses "Medical Herbalists." German medical schools teach phytotherapy. In the U.S. the sale of herbs is undergoing significant growth. Sales of herbal medicines increased 59% in 1997 and are growing 20% a year, with the largest growth of sales in retail pharmacies (3).

Because of the renaissance of interest in phytotherapy in the industrialized West, there has been an increase in clinical research to determine which herbs "work" for which diseases. The issue of how to evaluate herbal efficacy raises larger issues of how patients are initially evaluated and how herbs are selected for prescription.

In traditional herbal prescription methodologies, herbal prescription is individualized according to a "functional" nosology. A functional nosology organizes symptoms and signs according to terms used to describe physiological activity. For example, in Chinese medicine "Spleen *qi*" would be used to describe physiological activities like peristalsis, digestive absorption and the circulation of lymph. The conventional ontological-localized nosology of disease names is not necessarily relevant to the "functional" diagnosis. In the ontological-localized nosology, a disorder is described as a lesion or anomaly within a given anatomical system. A typical example is a gastric ulcer, a nosological entity consisting of a lesion (ulceration) and a locus (stomach). In the case of a gastric ulcer as a main complaint, there might be an evaluation the Chinese practitioner would not be guided by this diagnosis in the phytotherapy evaluation. The relevant Chinese functional nosological entities might be disorders of Spleen *qi* or Liver *qi*. "Spleen *qi* vacuity," "Spleen dampness" or "Liver *qi* congestion (4)."

But each of these nosological entities, as in all functional nosologies, are disorders of the patient's entire physiology. A "Spleen vacuity" could mean an enzyme deficiency or disorder of immunity. A "Spleen damp" condition might be indicative of a mucous membrane hypersecretion. A "Liver *qi* congestion" might indicate biliary dyskinesia or a psychogenic disorder. Each of these nosological

entities can have a variety of manifestations. Spleen dampness can manifest as gastrointestinal disorders, arthritic disorders, bronchitis, or even epilepsy. Diagnosis of these functional conditions in all cases requires a thorough history and physical examination. New research strategies in Japan and China have endeavored to accommodate for this dissonance between holistic and reductionistic paradigms.

(2) Prospective Research

"Nobody likes to ask if a model is really correct, since if they did, most work would have come to a halt."

Francis Crick, *What Mad Pursuit*, 1988

The double-blind placebo-controlled study is the gold standard for determining efficacy in the evaluation of drugs. Double-blind paradigms are, in fact, fraught with uncertainty (5). There are also questions about the scientific definition of a placebo (6). The frequency at which pharmaceutical drugs, supposedly determined to be safe and effective through this process, have been subjected to review (50%) and even removed from the market also casts doubt on the scientific infallibility of this practice. It is likely, however, that the double-blind placebo-controlled study will maintain its status for the foreseeable future.

Newer methods of evaluation such as outcome studies are acceptable to the academically oriented, but are less acceptable to more conservative and less intellectually advanced government regulating bodies.

Botanical medicines were already on the market and were even included in the National Health Insurance systems in Japan and France. But it has been economically unwise for herbal manufacturers to do controlled clinical trials on their products. Controlled studies which could yield negative results were avoided as unnecessary risks, especially with the game rigged to their disadvantage. The conventional profession complained, "Why don't they want to test their medications? What have they got to hide?" But if you test an herb for gastric ulcer, you have nothing to gain, because no one herb is effective for treating all patients. You also face different genetic types, different etiologies and different balances of physiological parameters. Because of the paucity of clinical trials, coverage by the National Health Insurance was lost, but this has not stopped the Japanese or the French from being among the highest consumers of herbal products in the world.

China has integrated reductionistic research methodology with holistic prescription systems. Chinese diagnostic criteria are identical to the WHO criteria for hypertension, a Western diagnostic entity. But in Chinese research, patients

fulfilling these criteria are divided into subcategories: "Exuberance of Liver fire," "Vacuity of yin with an exuberance of yang," "Vacuity of yin and yang," and "Accumulation of phlegm-dampness." In Chinese hepatitis studies, all patients are evaluated with standard blood tests for liver enzymes and antibodies. Then clinical evaluation subdivides the population into groups of "Spleen vacuity with invasion of toxicity," "Damp-heat of Liver and Spleen," "Vacuity of yin with heat in the blood," and "Blood stagnation and obstruction in the Liver channel." Cerebral vascular accident is subdivided into no less than nine differential diagnostic categories (7). Each category of diagnosis indicates a different type of herbal prescription. As results are obtained, they are collated and evaluated collectively according to the "Western" diagnoses.

In Japan similar attempts to individualize treatment in research design were met with suspicion. Some of the original research was well-publicized in the media, but disparaged by the medical community as lacking controls and rigorous research design, because it allowed individualized treatment with different herbal formulas according to the patient's symptom-sign complex.

Although criticized, the Japanese results were good enough to get the attention of researchers who did further studies using more reductionistic research designs. Unfortunately there have been some negative effects from using the same

herb formula for *all* patients with hepatitis C or liver cirrhosis. Minor Bupleurum Combination, from laboratory science criteria, seemed a good candidate for a "one-size-fits-all" hepatitis treatment (8). Bupleurum (*Bupleurum falcatum*), which contains saikosaponins *a*, *b*, *c* and *d*. Saikosaponin *b* has been shown to be an active principle especially effective for treating intractable chronic hepatitis (9). Minor Bupleurum Combination also contains licorice (*Glycyrrhiza glabra*) which increases interferon production. Glycyrrhizin, an active compound of licorice, has been used intravenously for chronic hepatitis B and has caused complete recoveries on occasion (10). Minor Bupleurum Combination contains ginseng (*Panax ginseng*), which contains saponins that protect liver cells from carbon tetrachloride-induced hepatotoxicity and accelerate regeneration of liver cells (11). Another ingredient of Minor Bupleurum Combination is Scute, also called Chinese skullcap (*Scutellaria baicalensis*), which has been shown to stimulate the production of interleukins (IL-5, IL-6 and IL-10) in hepatitis C patients (12).

Four patients taking Minor Bupleurum Combination (*Shousaikotou*) for chronic hepatitis C developed interstitial pneumonitis possibly caused by interferon or the combination of interferon with the formula. Interstitial pneumonitis is also induced by granulocyte colony-stimulating factor (G-CSF). It was subsequently found that that G-CSF production was increased in peripheral blood mononuclear

cells in proportion to the increase in Minor Bupleurum Combination levels (13).

The traditional-style herbalist would ask whether these negative results were caused by not individualizing treatment, damaging the yin in susceptible patients, or were an immune system reaction to mobilizing too many necrotic liver cells at once? Numerous variations of bupleurum-based formulas treat a variety of symptom-sign complexes and types of patients. When immune system mechanisms go into action in the presence of hepatitis B virus, some people recover and others die, *not* because of severity of the virus, but because of individual differences in disposing of it. With 10 people there can be 10 different types of hepatitis.

Applying conventional research methodologies to phytotherapy research has created numerous other paradoxes. Combinations display different properties than their component herbs, and single herbs behave differently from "active principles (14)." Formulas' synergies depend not only on their combination of herbs but also on their method of preparation. Formulas are designed to individualize treatment. Standardized research protocols based on treating "diseases" are inappropriate for evaluating their therapeutic potential. Researchers found that saikosaponins *a* & *d* were not available in Minor Bupleurum Combination, but saikosaponin *b* was abundant (15). In other bupleurum combinations used to stabilize psychic and nervous system function saikosaponins *a* & *d* were available, but not *b* (15). The

synergy of components in the formulas causing different chemical reactions was the explanation for the discrepancies. Researchers found that when they decocted licorice root with coptis root (*Coptidis chinensis*), new compounds were formed that were not present in either herb.

Synergies of herbal formulas challenge a paradigm based on active principles. Researchers found that serum levels of the active principle of *ma huang* (*Ephedra sinensis*), ephedrine, were higher in patients that had been given *Ma huang* and Apricot Seed Combination than in patients that were given pure ephedrine (16). Serum ephedrine levels were obtained when *ma huang* was decocted in the traditional formula *Ma Huang* and Gypsum Decoction with no new compounds formed from the decoction process (17). Licorice was found to potentiate the activity of the ephedra even though it decreased the plasma level of ephedrine.

So there is a need for testing methods appropriate to botanical medications. Most formal attempts to validate herbal medications focus on which chemical components are active for certain symptoms or diseases. Ignoring the details of personal history and physical examination will neither validate the traditional uses of herbs nor develop their therapeutic potential. When traditional formulas were reintegrated into the health care system in Japan in the early 1970's, the Japanese

Medical Association took the position that conventional diagnostic methods were not sensitive enough to make prescriptions of traditional formulas. Prescription of the herbal formulas depended on the subjective criteria of evaluation at the clinical visit of the symptoms and signs traditionally associated with the formulas The use of traditional formulas was adopted without validation studies because it was believed that modern methods of laboratory evaluation could coexist with the traditional clinical observations (18).

The rewards of developmental research in phytotherapy may be rich. Doctors in France using a whole system model are able to individualize diagnosis and use botanical medications to regulate nervous system and endocrine function to a sophisticated degree, treating even disorders like diabetes and hypothyroidism without the use of hormones. They are able to treat even severe infections without antibiotics utilizing the powerful disinfectant properties of essential oils (19).

Several botanical medications show promise in cancer treatment. The Chinese herbal combination known as PC-SPES proved effective in the treatment of prostate cancer (20). An intravenous herb drip and oral preparation of the herb semen coicis has been used to induce remission of different types of cancer, especially digestive tract cancers (21). Previous claims stated that Chinese herbal medicine only prolonged the life of patients, and protected their immune systems.

Clinical trials indicated that their cancers were effectively treated with few side effects. In Europe as well, intravenous *Chelidonium majus* (22), *Helleborus niger* (23), and *Dionaea muscipula* (24) have demonstrated dramatic effects not only in tumor reduction, but also in strengthening the function of the immune system.

Herbal extracts are used in Chinese hospitals for treating cardiovascular disease, autoimmune diseases, bacterial infections, kidney diseases and burns, to name a few of the types of pathology that are successfully treated (25). These breakthroughs in herbal treatment are being made in countries conducting developmental research, as opposed to efficacy research, that only asks "Does it work?" Developmental research asks "What kind of problems can we solve with these materials?"

(3) Standards

In the U.S. today, much of the controversy over herbal products in the marketplace is about standards of quality. The 1994 Dietary Supplement Health and Education Act (DSHEA) classification of herbs, vitamins, minerals, etc. as nutritional or dietary supplements has been criticized for allowing these supplements to be marketed without testing for efficacy, safety or quality. In fact, the safety definition for dietary supplements is actually stricter for supplements

than it is for foods or drugs. Dietary supplements, including herbs, are considered unsafe if they "present a significant or unreasonable risk of illness or injury." Foods are unsafe if "ordinarily (i.e. always) injurious to health." Drugs are permitted to present "significant" risks, as long as risks are outweighed by benefits. By law, statements made about supplements must be supported by scientific evidence (26). The U.S. Food and Drug Administration is required to prove a product unsafe before it can be taken off the market. Regulating agencies in Germany, France, the United Kingdom, Canada and Japan also enforce standards of herb quality, as well as safety assessment of herbal product manufacturers (27) (28).

There remain several uncertainties with regard to the issue of standards. Standards of potency are resolved by standardizing the quantity of an "active principle" of an herbal extract. Critics of standardization also claim that destroying the integrity of an herb's natural chemical balance by adding a substance, sometimes a synthetic one, to standardize the product does not enhance quality (29). Many herbs have numerous substances that could be deemed "active." Another controversy arises over which component of many is *the* active one. Potency of substances is also affected by growing conditions, storage, handling, as well as subsequent methods of preparation. France's solution confers

pharmaceutical grade status on botanical extracts containing minimum levels of all constituents designated pharmacologically active.

Accurate plant identification is another important issue in standards of quality. Bogus echinacea has appeared on the market. There have also been cases of fraudulent ginseng labeling (32). Herbs have also been misidentified with dangerous results, as in the case where belladonna poisoning occurred among consumers of an herbal tea in New York City (30). In another case digitalis poisoning resulted from ingesting a mislabeled extract of plantain (31). Mistakes can also be made when the wrong part of the plant is used, for many plants have parts with various types of activity.

Contamination of herbal raw materials can pose a problem. Crude plant substances in warehouses can be subjected to spraying with pesticides. Different countries have different standards regarding agricultural pest control. Pesticides banned in the U.S. are still widely used in other countries. Heavy metal residues in Chinese herbal patent medicines have been detected in the U.S., perhaps as a result of pesticide contamination (33). But it should be statedthat many Chinese companies conform to international standards of quality and purity in their manufacturing practices.

France uses high performance liquid chromatography (HPLC) for analysis

of components as well as in the detection of contaminants in products designated pharmaceutical grade. In Japan, since 1976, the Pharmaceutical Affairs Bureau of the Ministry of Health and Welfare regulates the quality of botanical formulas, monitoring specific plant constituents so that the herbal ingredients of each formula meet precise standards of quality (34).

(4) Medical Education

The greatest concern to physicians in the U.S. today is herb-drug interactions. In comparison to the number of herbal products in the marketplace, limited information is available on this subject, but it is gradually becoming available. In the U.S., physicians are beginning to notice that over 60 million Americans use herbs; the number is even higher if other supplements are included. This number is expected to increase, especially in medical use, as insurance companies begin to cover herbal use. National health care in Germany and Japan already covers herbal products prescribed by physicians. There is a great need for information on these interactions in the U.S. In the U.S. the likelihood of interactions between drugs and herbs is higher because doctors in the U.S. are more likely to prescribe a prescription drug than an herb compared to Germany or Japan where many doctors already use alternatives.

It is desirable that all health care providers have some basic knowledge of herbs, but it is also necessary for training to be available for those practitioners who wish to become specialists or experts in phytotherapy. The potential for development of phytotherapy depends on the commitment of interested professionals to go beyond the "patent medicine" approach heavily promoted by manufacturers. A patent medicine is a medicament for a specific symptom or condition that has alleged benefits for all potential users. This is a symptomatic approach that simplifies the complexity of herbs and herbal extracts into the mold of a drug with a single type of application. This is the one-dimensional approach that advocates St. John's Wort (*Hypericum perforata*) for depression, feverfew (*Tanacetum parthenium*) for migraines, or ginger (*Zingiberis officinalis*) for motion sickness.

The complex properties of herbs are studied and applied within more complex "functional" whole system models of pathophysiology. These systems are widely used even in official medicine in east Asia, and to a lesser extent in the U.S. and Europe. Whole system models of clinical practice individualize treatment of each patient based on patients' personal traits, body type or "terrain," and the "balance" of physiological functions. If an exudative type of patient suffers from bronchitis, then herbs for hypersecretion would be used to dry up the

condition. If a patient also suffers fatigue, is elderly or has low adrenal function, an adrenal cortex stimulant like black currant might be added. If a bronchitis patient has a spasmodic cough with bronchial constriction, a disinfectant substance like essential oil of thyme, considered "vagolytic" by French phytotherapy doctors might be recommended. If a bronchitis patient has a diabetic tendency, oil of eucalyptus, considered to be hypoglycemiant, might be chosen instead (35). As in French phytotherapy of the terrain, Ayurvedic and Chinese medical systems have long traditions of diagnosis that adjust treatment according to a complex of symptoms and signs.

It is important to understand these models of phytotherapy as being problem-solving methodologies, or clinical "software," and not merely cultural artifacts or metaphysical ideologies. Although Ayurveda and some systems of Chinese medicine may appear metaphysical, they also contain the elements of patient-centered practice. These systems are taught in China, Japan, India and in some western European nations. In the U.S., many acupuncture specialists study traditional-style Chinese phytotherapy. When successful, a whole system approach will match the patient's pathophysiology correctly and preclude the possibility of side effects. In reality there are no "*side* effects" for any medication. There are only *effects*. The goal of whole system treatment is to seek the correct

combination of herbs to balance out unwanted effects or one-sided effects from individual herbs.

Teaching whole system models for herbal prescription to practitioners of phytotherapy, will gradually produce a population of clinical experts with capabilities beyond the "patent medicine" approach. Instruction in entry-level patent medicine approach should be made widely available to practitioners who do not intend to become specialists, but wish to offer the benefits of nontoxic treatment to their patients.

(5) Public Awareness

In the U.S. in recent years, articles have appeared in new media about the dangers of herbs. The American public has been told that just because something is natural, it is not necessarily safe. Alleged hazards are largely overstated to the point of even being classified as "fear propaganda." But the alleged dangers do not appear to represent a public health problem. According to the Poison Control Center in Atlanta, 1997, the rate of occurrence of herbal poisonings is one out of every million. The most frequent cause of herbal poisoning is ingestion of house plants, usually by children, and mushroom poisoning. There have been no poisoning fatalities from commercial products and fewer than "a half-dozen cases

in five years (36)."

In contrast, the fourth leading cause of death in the U.S. is fatalities from prescribed drugs. The number of deaths exceeds 100,000 a year. Every year prescription drugs cause 1 million injuries so severe they require hospitalization, and another 2 million drug-related injuries occur *during* hospital care (37). In a review of one ten year period by the Government Accounting Office, more than half of newly-approved drugs were recalled due to unexpected side effects, problems that had not yet surfaced duringthe long and expensive research conducted for the FDA approval process (38). These numbers, while horrifying, do not negate the importance of physicians' concerns over herbal safety. The chief danger of herb use is in potential herb-drug additive interactive effects with prescription drugs the patient already is using.

Many patients in the U.S. and Europe seek nontoxic "soft" therapy first and use dangerous substances as a backup or last resort. In France, Germany, Japan, and China, physicians have adapted to this strategy. In Japan in the 1960's there was a public uprising, now referred to as the "*Kampo* Boom," against the excessive use of pharmaceuticals, when public demand rehabilitated the traditional herbal medicine. Even though this has not solved the problem with the overuse of drugs, it now offers an alternative within the mainstream (39).

Estimated sales of herbal medicine in the U.S. reached $1.2 billion in 1996 (40). According to a survey by Applied Biometrics of North Palm Beach, Florida, 62% of American consumers take herbs for disease prevention, 54% to increase energy, 40% to improve fitness, 31% to increase alertness and 27% to reduce stress (41). Consumers would be well advised to consult with experienced practitioners in Asian or Western phytotherapy regarding the long term use of any botanical substance or combination. Consumers using prescription drugs should consider obtaining medical advice regarding potential problems resulting from herb-drug interactions. Women should exercise special caution if pregnant or lactating. Consumers who are self-medicating using packaged products should shop for those that label the expiration date, lot number, botanical name of the herb, strength of the recommended dose and the name and address of the manufacturer. No reasonable person would oppose efforts to develop standards, or a grading system for botanical products with respect to their proper identification, safe handling, proper storage, potency and their influences on pathophysiology. All efforts to do so are salutory, beneficial for the public and for the health care professions.

(6) Cost-Effectiveness

Formal cost-effectiveness studies are rare even in east Asia where the economic impact of herbs in the medical marketplace has the greatest longevity. One reason Americans self-medicate is that they cannot afford prescription drugs (10% of Americans) (42). In Third World nations, drugs become a prohibitive expense for an even larger portion of the population.

There are other ways to measure cost-effectiveness. As a rule, herbal medications as a rule are less expensive than prescription pharmaceutical drugs. When an herb can be shown to be as effective as a pharmaceutical drug for a medical disorder, it can be a significant cost reduction factor. In Germany, Bayer Corporation markets St. John's Wort as an antidepressant. In Canada Nytol maker Block Drug Company, sells valerian as a sleep aid, and Johnson & Johnson sells feverfew for migraine treatment. Studies have shown saw palmetto (*Serenoa repens*) berry extract as effective as finisteride for benign prostatic hyperplasia (43). Herbal medications are potentially effective for withdrawing patients from benzodiazepine drugs (44), at a significant savings in cost as well as in quality of life. Herbs have also been tested for a variety of other complaints including nausea (45), hyperglycemia (47), circulation problems (48), hypercholesterolemia (49), and hormone regulation for disorders of climacteric (46). The potential to reduce health care costs with herbs and herbal extracts is a rich field to be

harvested.

The use of nontoxic therapies can also be contrasted with the cost-effectiveness of a system based primarily on pharmaceutical drugs. As one counts the miracle drugs that have appeared and disappeared over the history of pharmaceutical companies producing dangerous products that are later quietly removed from the market, one gets the impression of a general failure to provide safe, inexpensive care. In 1994, Dr. Brian Strom, Associate Director of Medicine and Pharmacology at the University of Pennsylvania School of Medicine estimated that drug side effects result in the hospitalization of 1.6 million people at a cost of more than US$20 billion each year (50). If we include quality of life issues, the problem is less quantifiable, but no less significant. Side effects such as loss of sexual potency, loss of equilibrium, depression, or shortened life span underscore the need to develop an accounting of risks versus benefits that is not just quantitative. These dangers are a significant reason that $11 billion was spent by 1/3 of Americans on alternative health care (51).

The future development of phytotherapy in world medicine will require a new level of research promising discoveries for treatment of cancer, AIDS, cardiovascular disease, chronic pain and other health care problems that burden public health provider systems. There is a need for comparison of how

phytotherapy is integrated into national health care delivery systems, and of how the problems of quality standards, efficacy and third party payment can be approached.

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