· Review Papers ·

Challenges in Research and Development of Traditional Chinese Medicines

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Abstract: This review is briefly to recall the history of research and development (R&D) of Chinese materia medica (CMM) and to discuss the challenges of Chinese traditional and herbal medicines (CTHM) facing the modern science and technology. The R&D of CTHM is thought to be an important pathway for new drug discovery. Since1949, about 140 approved new drugs have been developed, among which about 80 originated directly or indirectly from medicinal plants. CTHM has gained interest from the international medical, biomedical, and pharmaceutical institutions as a valuable source of potential medicines. For the modernization of CMM and innovative research of CTHM, there are following challenges to be faced: (1) to evaluate the efficacy, pharmacological properties, action mechanism, and active chemical constituents; (2) to develop new methodologies for the quality and safety of CTHM; (3) to apply new "-omics" techniques to accelerate drug discoveries developed from CTHM; and (4) to apply international practices including good agricultural practice, good manufacturing practice, good laboratory practice, and good clinical practice in the R&D of CTHM.

Key words: Chinese traditional and herbal medicines; efficacy; modern research and development; Pharmacopoeia; safety; sustainability of resources; traditional Chinese medicine

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Introduction

Chinese materia medica (CMM) is an important part of Chinese traditional and herbal medicines (CTHM). CMM have been used since the age of mythical medicine. The first book on CMM, *Herbal Classics of the Divine Plowman* (*Shennong Bencao Jing*), known as "the canon of CMM" was written in the second century B.C. under the pseudonym of Shen-nong, the holy Farmer. China is one of the countries to use medicinal plants extensively and it remains so. Discoveries of drugs were closely connected with studies on edible plant material, as evidenced by numerous writings on materia medica at different ages in history (Liu and Xiao, 1992; Liu *et al*, 2000). Continued development has taken place and thus medicinal plants are playing a critical role under the framework of National Health Services in China. The latest edition of the *Pharmacopoeia of the People's Republic of China* (PPRC) (2005) documented more than 1146 Chinese drugs originated from medicinal plants.

The first edition of national pharmacopoeia called PPRC was issued in 1953, but there was no CMM recorded. The second edition was published in 1965 in two volumes, of which volume I includes CMM and their related products. So far the PPRC has being updated and published in 1985 and then every five years as 1990, 1995, 2000, and 2005 (Table 1). Based on the survey from recent six editions of PPRC, at least

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80% of Chinese traditional and herb drugs are derived from plants. In China total 7295 plant species with therapeutic value have been identified (Liu *et al*, 2000a, PPRC, 1953; 1965; 1977; 1985; 1990; 1995; 2000; 2005).

Table 1 Summary of single herb and compound formulas collected in PPRC of 1977–2005 editions

Edition	Single herbs	Compound formulas	Total
1977	744	270	1014
1985	566	207	773
1990	506	275	781
1995	522	398	920
2000	531	461	992
2005	580	566	1146

Commonly used CMM includes about 500 species from plants, which names, origin, and parts used were well documented (Liu and Xiao, 1986; 1992; 2000). The families containing over 100 medicinal plants are listed in Table 2, and the genera containing over 15 medicinal species with higher proportion of therapeutic application are listed in Table 3.

This huge collection of medicinal plants indicated that China has long accumulated rich experience in the use of medicinal plants to treat various diseases and to tackle toxicity and side-effects. Owing to a variety of

Table 2 Families containing over 100 medicinal plant species

Family	Species/genera	Examples of important genera medicinally used
Compositae	778/155	*Artemisia, Senecio, Aster, Saussurea, Atractylodes*
Leguminosae	490/107	*Cassia, Sophora, Crotalaria, Glycyrrhiza, Indigofera, Astragalus*
Ranunculaceae	420/34	*Clematis, Anemone, Coptis, Aconitum, Delphinium, Thalictrum*
Labiatae	436/75	*Salvia, Rabdosia, Nepeta, Clinopodium, Scutellaria, Thymus*
Liliaceae	358/46	*Fritillaria, Polygonatum, Smilax, Ophiopogon, Veratrum, Allium*
Rosaceae	360/39	*Crataegus, Prunus, Rosa, Chaenomeles, Rubus, Potentilla*
Orchidaceae	287/76	*Dendrobium, Gastrodia, Habenaria, Liparis, Bletilla*
Umbelliferae	234/55	*Angelica, Heracleum, Bupleurum, Ferula, Ligusticum, Peucedanum*
Rubiaceae	219/59	*Uncaria, Hedyotis, Morinda, Rubia, Gardenia*
Euphorbiaceae	160/39	*Euphorbia, Glochidion, Croton, Mallotus*
Saxifragaceae	155/24	*Astilbe, Bergenia, Hydrangea, Saxifrage*
Papaveraceae	135/15	*Corydalis, Meconopsis, Papaver*
Polygonaceae	123/8	*Rheum, Polygonum, Fagopyrum*

Table 3 Genera containing over 15 medicinal plant species with higher proportion of therapeutic application

Genera	Species/total species	Main ethnopharmacological data
Aconitum	46/167	Anodyne, antirheumatic
Aralia	19/30	Dispelling, internal cold, arrow poison, asthmolytic, cardiotonic
Aristolochia	31/39	General tonic, antirheumatic, promote circulation for various infections, snakebite, treatment of abdominal,
Berberis	67/200	Antidysentery, various infections, antipyretic, antidote
Codonopsis	26/50	Tonic, invigorate the functions of the digestive system, for weakness
Corydalis	73/150	Anodyne, treatment of coronary heart diseases, febrile, and detoxicant
Delphinium	35/113	Anodyne, antirheumatic
Dendrobium	35/60	Tonic, for febrile diseases with thirst and dry mouth, dry cough, and chronic tidal fever
Hypericum	16/50	Antimicrobial, emenogogue, treatment of hepatitis
Lysimachia	28/50	Invigorating blood circulation and eliminating blood-stasis, asthmolytic, for menstrual disorders
Rabdosia	30/90	Antimircobioal, anticancer, febrifugal, and detoxicant
Salvia	41/78	Antimicrobial, treatment of coronary heart diseases
Swertia	22/70	Treatment of hepatitis, bitter-tonic, febrifugal, and detoxicant
Thalictrum	39/67	Antipyretic, antimicrobial, for various infections, anticancer
Gentiana	53/247	Antipyretic, antidote, stomachic, anti-inflammatory
Scutellaria	33/102	Antipyretic, antidote, promote circulation

geographical and ecological conditions in China, both the flora and medicinal plant resources are abundant. In recent decades, the Chinese government has highly supported the systemization and further development of traditional Chinese medicines (TCM). As a result, the use of TCM is popular in China.

As seen from the above information, CTHM significantly contributes to the health of the Chinese people. Now it also plays an important role in modern drug research and development (R&D), particularly in new drug discoveries from medicinal plants.

This review summarized the major achievements on R&D of CTHM since 1949, analyzed difficult issues in modern research of TCM, and discussed the challenges faced in modern R&D of CTHM, in the hope that the full medical potential of resources of CTHM, especially from medicinal plants, can be unlocked.

Currently, CTHM is facing great and serious challenges in the modern R&D of CTHM. The first challenge is to test the efficacy, pharmacological properties, mechanism of action, and active chemical constituents. The second challenge is to evaluate the drug safety, to improve the research methodologies, to establish the quality and value of research in TCM, and to provide appropriate regulation and registration of CTHM products. The third challenge is to apply high-throughput "-omics" techniques and tools to expedite drug discovery and development for better CTHM products. The fourth is to apply international practices including good agricultural practice (GAP), good manufacturing practice (GMP), good laboratory practice (GLP), and good clinical practice (GCP).

Sustainability for resources of medicinal materials

The development pathways of resources

Medicinal resource is the foundation of development and application of CTHM. The resource development covers the fields related to Chinese crude drugs, geo-authentic (*Didao*) crude drug, conservation and implementation, introduction, acclimatization and cultivation, and GAP for crude drugs. Geo-authentic crude drugs are parts of Chinese crude drugs, but they are different from common Chinese crude drugs. Chinese crude drugs are the raw medicinal materials collected and primarily processed from the medicinal parts of plants or animals. Geo-authentic crude drugs are the traditional Chinese crude drugs with specific germ plasma, produced at specific sites, or prepared by specific productive techniques and processing methods.

Due to forest destruction, meadows overgrazing, industrialization and urbanization, as well as excessive collection in the wild of rare and endangered plants or animals, the natural resources of medicinal plants or animals are being gradually and significantly reduced. We must plan and act on medicinal resource utilization and conservation to meet the urgent need.

Conservation and implementation

Collection of any medicinal plant should be guided by present knowledge of the species, including its locality, time of maturation, the parts to be collected, and its conservation needs. Steps should be taken to avoid over-exploitation and excessive collection. The gathering of rare and endangered species, such as *Panax ginseng* C. A. Mey, *Coptis chinensis* Franch., *Gastrodia elata* Blume, and *Paris polyphylla* Smith should be prohibited.

Genebanks of medicinal plants should be established. Up to now, about 500 kinds of important Chinese medicinal plants have already been preserved in genebank under the auspices of several agricultural institutions.

Introduction and acclimatization

Some plants listed in the ancient CMM were of foreign origin and even today some of them prescribed in China are imported products, e.g. American Ginseng from the United States and Canada, *Amomum kravanh* Pierre ex Gagnep from Thailand. To meet the high demand for local plantation, several botanical gardens in China have started introducing these foreign plants

for acclimatization. The introduction also includes those non-official crude drugs of wild origin and of practical medication use, such as *Pananx quinquefolium* L., *Amomum kravanh* Pierre ex Gagnep, *Strychnos nux-vomica* L., *Rauvolfia vomitoria* Afzuelia, *Syzygium aromaticum* (L.) Merr at Perry, *Cassia acutifolia* Senna, and *Vinca minor* Vines, etc. Indigenous species of wild origin include *Schisandra chinensis* (Turcz.) Baill., *Gentinana scabra* Bunge, *Cistanche desrticola* Y. C. Ma, *Asarum sieboldii* Miq., *Scutellaria baicalensis* Georgi, *Bupleurum chinense* DC., *Atractylodes lancea* (Thunb.) DC., *Anemarrhena asphodeloides* Bunge, *Fritillaria unibracteata* Hsiao et K. C. Hsia, *Alpinia osyphylla* Miq., and so on.

Cultivation

Cultivation of medicinal plants is necessary to guarantee supplies to meet their increasing demands. Currently about 100 species of medicinal plants are being cultivated, covering about 460 000 hectares of land. The most valuable cultivated medicinal plants are *P. ginseng*, *P. notoginseng* (Burt.) F. H. Chen, *Astragalus mongholicus* Bunge, *Angelica sinensis* (Oliv.) Diels, *Coptis chinensis* Franch., *Codonopsis pilosula* (Franch.) Nannf., *Rehmannia glutinosa* (Gaertn.) Libosch., *Paeonia suffruticosa* Andr., *Cinnamomum cassia* (Blume), *Amomum villosum* Lour., and *Atractylodes macrocephala* Koidz. They are all commonly used traditional CMM.

Several wild growing medicinal plants are still in great demand but still being introduced and cultivated, e.g. *Glycyrrhiza uralensis* Fisch., *Rheum palmatum* Linn., *Cistanche deserticola* Ma, *Poria cocos* (Schw.) Wolf., *Dioscorea nipponica* Makino, etc. Modern biological technology, such as tissue culture for propagating, has been used in the production of *Lithospermum erythrorhizon* Sieb. et Zucc., *P. quinquefolium* L., *Corydalis yanhusuo* W. T. Wang, *Scopolia tangutica* Maxim, and some others.

Sustainability for resources

In the nationwide general survey for medicinal plant materials in 1983, there were 12 809 kinds of such resources species found in China counted according to species. But there were only more than 6000 kinds of medicinal plant materials remained based on the similar investigation conducted in 2001. The number decreased sharply to half in less than 20 years. Since medicinal plant materials are basic points for the modernization of TCM, therefore, it is necessary to achieve the continuous use of the resources. Thus in order to ensure the quality and quantity of CTHM, the bases for standardized culturing of medicinal plants were established. In 2002, China State Drug Administration (SDA) initiated a guideline of GAP for Chinese Crude Drugs (SDA, 2002). In 2004 World Health Organization (WHO) published a set of guidelines for good agricultural and collection practices (GACP) for medicinal plants (Anonymous, 2004). These guidelines specifically aimed to protect the resources of medicinal plants and animals, promote the plant cultivation, collection, and use in a sustainable manner. Standardized and large GAP bases for the production of Chinese crude drugs became a necessary condition for industrial development of TCM. Currently there are 448 bases for standardized culturing medicinal plants (Fig. 1 and Fig. 2) distributed in 24 provinces of China, among them the standardized culturing areas in 18 provinces reach about 9 233 000 hectares.

The GAP for Chinese crude drugs was passed by the SDA at the Administration Affairs meeting on March 18, 2002. The GAP for Chinese crude drugs was issued to regulate the production of Chinese crude drugs, ensure their quality, and facilitate the standardization and modernization of TCM. This GAP provides the basic requirement for the production and quality management of Chinese crude drugs and is applicable to the producers who are responsible for the particular production process of Chinese crude drugs, producers should adopt standardized management and quality control to protect resources of natural crude drugs and the ecological environment, and realize sustainable utilization

Fig. 1 GAP cultivation site of *A. annua* in Chongqing, China (http://yyzyc.2008red.com/yyzyc/)

Fig. 2 GAP cultivation site of *A. sinensis* in Minshan, Gansu, China (http://www.mx.gansudaily.com.cn)

based on the principle of "maximum sustainable yield".

The environmental condition of production sites for Chinese crude drugs should meet the national standards such as Grade 2 for air quality in *Atmospheric Conditions Standard*, Grade 2 for soil in *Soil Quality Standard*, and Grade 2 for irrigation in *Farm Irrigation Water Standard*. An appropriate area for cultivation should be determined. Standard operating procedures for cultivation should be formulated and subjected to the growing and developing needs for medicinal plants. Types, period, and amount of fertilization should be determined according to the nutritional requirements of the medicinal plants and soil fertility. Organic manures should be the main fertilizing agent, and fertilizers could be applied sparingly in accordance with the growing and developing needs of plants. Field management should be strengthened in accordance with growing and developing characteristics of medicinal plants and their parts for use, and topping, deflowering, pruning, shading, and other measures should be taken timely to adjust the growth and development of plants so as to increase the yield of the crude drugs and maintain the consistency of quality.

Integrated pest management should be adopted for the control of diseases and pests. If necessary, minimum effective input of pesticides with high-efficacy, hypotoxicity and low-residue could be used according to the *Regulations for Pesticides Management of the P. R. China*, so as to reduce residues of pesticides, avoid heavy metals contamination, and protect the ecological environment.

Collection of wild and semi-wild medicinal plants or animals should match the principle of "maximum sustainable yield". Their fostering, rotation, and conservation should be planned and carried out to benefit their propagation and renewal of resources. Appropriate collection time (seasons and years) and methods should be determined in accordance with the quality and yield of the plants with reference to traditional experience, etc. After collection, the medicinal parts should be selected, washed, cut or trimmed, etc. Those that need drying should be dried timely by using appropriate methods and techniques, with controlled temperature and humidity. The contamination of Chinese crude drugs should be prevented and degradation of their active constituents should be avoided.

The producer should establish a quality management department, which is responsible for supervision

and quality control for the entire production process, and should have adequate staff, premises, instruments and equipment to meet the requirements of the scale of production and species identification. The quality management department has the following main responsibilities: to monitor the environment and hygienic management; to test production materials, packaging materials, and the crude drugs, and to issue testing reports; to develop training plans and supervise their implementation; to formulate and manage quality documents, and to manage the original records of production, packaging, and testing, etc.

Development of Chinese medicinal preparations based on pharmacology and therapeutics

A survey of development history

The history of Chinese medicinal preparations (including patent medicines and prescription preparations) can be traced back to the Dynasty of Warring States (475–221 B.C.). Some years before that there was a Han Tomb dug out at Mawangdui in the Changsha city of Hunan. There 52 recipes were discovered from the antiquities and records of Chinese patent medicines found among other items. According to archaeological studies (Jia, 1979), it was said to be a pharmaceutical works of Warring States.

Huangdi Inner Channels had concocted a recipe composing in principle: monarch, subjects, assistant, and errand. In this book, nine kinds of medical preparations were listed including different doses of pill, powder, and pellet.

At the end of East Han Dynasty ZHANG Zhong-jing (154–219), a noted medical scientist, had edited on *Various Diseases of Typhoid Fever*. This work documented more than 60 kinds of Chinese medicinal recipes. Most of them are still clinically used today. The preparation of patent medicine and the application of assorted dose forms were also documented.

Zhouhou Beiji Recipes, compiled by GE Hong in Jin Dynasty (284–364) had collected dozens of patent medicines and new developments in preparation and manufacturing methods had been achieved, such as a sheep liver pill which used the sheep liver together with *C. chinesis* for curing ocular diseases. Afterwards, *Beiji Qianfang* Recipes and *Qianjin Yifang* Recipes, which were edited by SUN Si-miao (581–682) of Tang Dynasty, had collected more recipes of patent medicines. Among these, well-known recipes such as *Cizhu* Pill, *Zixue* Pill, etc. have been handed down and are even be used present day.

Up to Song Dynasty, by means of the invention of printing, the dissemination of pharmacology had been very much broadened and *Taiping Shenghui* Recipes and *Shengji Zonglu* Recipes were published in 992 and 1117, respectively. Over 20 000 kinds of patent medicinal recipes were collected in these two big volumes of pharmacological book. At that time a well-known doctor, CHEN Shi-wan compiled in 1102–1106 and classified Chinese patent medicine prescriptions and edited and published *Taiping Huimin Hejiju* Recipes. The book was the first pharmacopoeia laid down by royal decree in Chinese history, and it recorded 785 kinds of patent medicines with an appendix of appliance, scope, and manufacturing methods. Some patent medicines, such as *Haixi* Dan, had been the beginning of chemical preparations and these recipes exerted tremendous influence over many centuries. In Song Dynasty, these books had stored up quite a number of patent medicine recipes, such as *Xiaoer Yaozheng Zhijue* writen by Qian Yi, which recorded 114 kinds of recipes.

Toward the Dynasties of Jin (1115–1234) and Yuan (1279–1368), there were four main schools of thought being formed, these were: (1) LIU Hu-jian, who initiated *Fangfeng Tongshen* Pill, *Liuyi* Powder, *Yiyuan* Powder, etc.; (2) LI Dong-yuan, who initiated *Buzhong Yiqi* Decoction for reinforcing vital energy of the body and *Zhusha Anshen* Pill for alleviating heart diseases and relieving uneasiness; (3) ZHANG Zi-hou, who initiated *Muxiang Binglong* Pill using betel nut for reinforcing vital energy; and (4) ZHU Da-xi, who initiated *Dabuyin* Pill for treating "*yin*" deficiency and

reducing internal heart.

During the period of Ming (1368–1644) and Qing (1644–1911) Dynasties, there were a number of medical books written, including the *Orthodox of Surgery* by CHEN Shi-gong which recorded recipes for external use, e.g. *Bingpeng* Powder for treating aphtha, *Ruyi Jinhuang* Powder for dressing, were all having outstanding curative effects.

Since the founding of the P. R. China in 1949, TCM has been significantly developed. Chinese patent medicine has been systematized and scientific research has achieved great result. The theory of Chinese medicine has been elaborated and elevated to a higher level according to new findings.

Traditional processing of Chinese crude drugs and pharmacological effects

Processing of Chinese crude drugs means preparing medical materials with proper methods and techniques according to the theories of TCM to meet clinical requirements of dispensing prescriptions and make ready-made medicines.

Processing of Chinese crude drugs consists of cleansing, cutting into smaller pieces with guillotine, reducing toxicity, changing their properties, enhancing therapeutic action, correcting unpleasant taste or smell, and separating different parts of a drug for different uses.

Cleansing and trimming includes selecting, sieving, winnowing, shaking, brushing, wiping or scraping, digging, squeezing, rubbing, picking, tearing and peeling, striking, embracing, rolling and tying, washing, floating, soaking, rinsing, filtering, moistening, retting, refining, powdering medicine by prescription, burning over flames, drying over small fire, sunning, airing, and staining.

Cooking, includes stir-frying, scalding, simmering or baking in hot ashes, roasting, broiling with fluid substances in a pan, calcimining, quenching, steaming, boiling, reproducing, reducing into powder after removal of oil or preparation of frost-like powder fermentation, germination, efflorescence, squeezing juice, etc.

The selection of Chinese medicines for treatment, in accordance with the differentiation of syndromes, is essentially along the latitude of their properties. (1) "*Si-qi-wu-wei*", the four temperaments, cold, hot, warm, and cool, and the five tastes, pungent, sweet, sour, bitter, and salty (2) "*Sheng-jiang-fu-chen*", ascending and descending, floating and subsiding, and (3) "*Gui-jing*" or attribution to meridian channels. However, these properties might be changed by processing, e. g. *Radix* et *Rhizoma Rhei, Rhizoma Coptidis,* and *Radix Scutellariae* which are commonly used. They are all bitter in taste and cold in temperament. Their actions are cooling heat and subsiding fire but their attributions to meridian channels are different. *Radix* et *Rhizoma Rhei* is used for subsiding the fire of the intestine. *Radix Scutellariae* for the same in the lung. When these three drugs are treated with wine, their cold property is reduced and changed their destination actions. *Radix* et *Rhizoma Rhei*, which originally targets at the blood, is now changed to eliminate the fire in the head, and the other two are then able to ascend and subside the fire in "*Shang-jiao*" or the upper portion of the body cavity. Another example is *Amomum xanthioides* Wall. ex Baker, this drug can promote circulation of the vital energy, activate the function of the spleen, and improve appetite. After being broiled in salt, it conducts vital energy to the kidney and then it warms the organ and eliminates dampness. Thus it is clinically indicated for polyuria.

The above-mentioned examples show the changes as the results of different processing methods. Physicians should not neglect the quality of Chinese drugs, as well as their properties in crude form. Otherwise, the treatment will definitively fail.

New achievements in scientific research

Chinese medicinal research was undertaken to show the pharmacological basis of TCM by using modern science and technology, as encouraged by a central notices of China (Liu and Yaniv, 2005).

Much research efforts aim to develop new or improved products of Chinese medicine and patent medicine. For example, the ingredients realgar, bezoar,

and musk of *Lushen* Pill are found working in co-ordination with each other as cardiac stimulant and the coordination of musk, bezoar, and toad venom have multiple effects in controlling granulation swellings. Tests indicate that the best proportion in the coordinated use of bezoar, musk, and toad venom is 2∶3∶2. In addition, the three ingredients angelica, chuanxiong, and safflower together are more effective than short of any one or two in compound recipe *Chinese Angelica* Injection to improve the blood circulation in coronary artery.

On the other hand, evaluation of compound recipes can be simply formulated by discarding some non-essential ingredients. For instance, the recipe of *Suhe* Pill has ingredients from 15 herbs. Now it can be simplified to six herbs to form *Guanxin Suhe* Pill. It can be further condensed to two herbs to form *Subing* Dropping Pill. Even though the ingredients and quantity are much less; they are effective in alleviating angina pectoris.

Chinese medicine products are not limited to pill, powder, plaster, and pellet in dose forms. There are a wide variety of new dose forms, including tablet, injection, syrup, sprayer drop, condensed pill. For example, *Suxiao Jiuxin* Pill based on *Chuanxiong* is fast acting especially in alleviating angina pectoris. It is also long lasting and has few side effects. *Niuhuang Jiangya* Pill is useful in lowering and maintaining the blood pressure. Its characteristic effect is rather mild. *Xiezhining* Pill (or Tablet) is effective in lowering the blood lipids and lipoproteins and useful in treating high blood pressure. *Tianjin Ganmao* Tablet and *Yinqiao Jiedu* Tablet are effective in treating common cold.

Safety matters of indigenous medicine in CTHM

In Chinese history, safety of CMM was ensured by clinical experience. In *Shennong Herbs* (*Shennong Bencao Jing*) written between the first century B.C. and the first century A.D., the drugs were divided into three classes: superior, intermediate, and inferior drugs. The superior drugs are strengthening drugs, they can be administered for a prolonged period without harmful effects. The intermediate drugs are effective against diseases with the species toxicity dependent on dosage. The inferior drugs possess specific therapeutic activity, but can be toxic and should not be taken for any prolonged period of time. In *Huangdi Inter Medicine* (*Huangdi Neijing*, 475–221 B.C.), the toxic drugs can cause sympotomatic reactions and adverse/side effects. No overdose should be given.

Recent trends of pharmacovigilance in CTHM

In September 1997, the Pharmacovigilance Conference on Communicating Drug Safety Information was held in Erice, Italy. The conference announced the *Erice Declaration*, which set forth the principles of good communication practices. The *Declaration* stated that industry, doctors, and patients have different – but not contradictory – points of view when drug safety is of question. Trust and partnerships among different groups were considered important, and a wider public debate was deemed in order to help the public understand the risk. Crisis management is also an important matter where communication plays a major role. Several aspects of the communication of benefit-risk information were outlined in the *Declaration*. Important lessons were learned from experience in the safety issues associated with antiretroviral drugs used to treat HIV since HIV therapies, which authorization is usually expedited. In clinical trials with small numbers of patients relatively little information on safety can be obtained, and that efficacy is measured using surrogate markers rather than clinical parameters.

In large scale use of drugs, adverse events are often obvious. The scenarios are even more complicated when several drugs are given for combination therapy, or for opportunistic infections. The numbers of patients in clinical trials and the duration of treatment should be maximized, and exclusions should be minimized. Safety data should be collected and thoroughly analysed, and relevance of surrogate markers questioned. Post-

authorization safety surveillance is also important and should be planned in advance.

Pharmacovigilance aims at detecting, assessing, understanding, and preventing adverse effects or any other possible drug-related problems to establish a signal suggesting a possible causal relationship between an adverse event and a drug, usually more than a single report is required, depending upon the seriousness of the event and the quality of the information.

Significant enhancement of health systems performance can be achieved by preventing adverse events in particular, and improving patient safety and health care quality in general, so as to develop global norms, standards, and guidelines for the definition, measurement and reporting of adverse events, and to provide support to countries in developing reporting systems, taking preventive action; and to promote framing of evidence-based policies, including global standards that will improve patient care, with particular emphasis on such aspects as product safety, safe clinical practice and safe use of medicinal products and medical devices, and creation of a culture of safety within health care organizations.

Today, less than 1% of the drugs in CTHM are toxic. The long exist "eighteen incompatible medicinal herbs" and "nineteen mutual restraining medicinal herbs" summarize the clinical experience of drug interaction and co-administration of herbs in Jin and Yuan Dynasties (1115–1368). Severe side effects may result when incompatible or mutual restraining drugs are administrated together.

The renal toxicity induced by *Caulis Aristolochiae Manshuriensis* was first reported in 1964 (Wu, 1964). Then it was also reported by Zhou *et al* in 1979 and 1988, respectively. The renal toxicity induced by medicinal plants was also called herb nephropathy (Kukak, 2000). It was concluded that Chinese herb nephropathy was mainly induced by the aristolochic acid contained in *Akebia quinata* (Thunb.) Decne. and *Cocculus laurifolius* DC. Therefore, some researchers suggested that Chinese herbs nephropathy should be renounced as aristolochic acid nephropathy. Recent studies showed that aristolochic acid is the causative agent of renal toxicity of *Aristolochia debilis* Sieb. et Zucc. and *Aristolochia fangchi* Y. C. Wu ex L. D. Chou et S. M. Hwang. Other safety issues of CMM include: (1) overdose administration; (2) administration for long times; (3) unsuitable combination administration of one drug with other drugs; (4) mixed use of different specious drugs, such as *A. fangchi* is used as *Stephania tetrandra* S. Moore; (5) preparation of herbs; and (6) patient's individual differences in drug reactions, pharmacogenes, metabolism, and allergic functions. To tackle these safety issues, Chinese researchers applied modern scientific tests, e.g. fingerprinting to control quality and production practice. In clinical studies, TCM doctors implement GCP. In clinical practice, doctors carry out individual therapeutic principles according to the theory of CTHM. In basic research, toxicology, pharmacokinetics, and metabono- mics were applied to determine the toxicity, effects, action mechanism, and drug-drug interaction. For example, we reviewed by CTHM the induction and inhibition of cytochrome P450 activities. It was suggested that combined use of CTHM and conventional therapeutic products may change the plasma levels of therapeutic agents which would increase the adverse events in patients. Conversely, the interaction between CTHM and conventional therapies may also affect safety profile of the CTHM. Health care professionals must recognize and understand the potential risk of herb-drug interactions (Ge *et al*, 2005; Lu *et al*, 2005; Liu, 2005).

Conventional recognition of the safety of Chinese drugs

Up to the present, among the 534 kinds of Chinese herbal drugs collected in the PPRC, 49 clinical herbal drugs have high toxicity, such as *Semen Strychni*, *Rhizoma Pinelliae*, *Caulis Aristolochiae Manshuriensis*, *Radix Aconiti*, *Radix Sophorae Tonkinensis*, and *Rhizoma Anemones Raddeanae*, etc.; and 22 drugs have low toxicity, such as *Radix Zanthoxyli*, *Rhizoma Dryopteris Crassirhizomae*, and *Cortex Meliae*, etc.,

while the other 463 drugs are in the record non-toxic. The conventional recognition of the toxicity and safety of Chinese drugs is based on traditional experience and can no longer meet the demands of modern society (Xiao and Liu, 2004).

Re-understanding the safety matters of Chinese drugs

The National Program for Modernization of Traditional Chinese Medicine (2002–2010) focused on the quality and standardization of Chinese drugs. Formation of the norms, including GAP, GMP, GCP, and good supply practice (GSP) has established a good basis for safety usage of Chinese herbal medicines. In 2001, China government released re-newly *Drug Administration Act* and *Drug Registration Regulation* to standardize research, development, and marketing of new drugs of chemical products and TCM. When registration of Chinese traditional and herbal products, applicant must provide enough application documents including scientific test data. These data consist of 6 review documents, 12 pharmaceutical documents (including production techniques, quality and standard, and formulation preparation), 10 pharmacology, toxicology, and pharmacokinetics documents and 5 clinical trial documents (SDA, 2002).

According to statistics, 6061 cases involved in intoxication and adverse effects from Chinese drugs have been reported in 110 issues of periodicals published between 1915 and 1994, of whom 2217 cases were reported in the 1980s, and 3 272 in the four years from 1991 to 1994 (Yuan, 2000). As to the injection form of Chinese drugs, it was reported that 72 cases suffered from adverse reaction to 14 prepared Chinese herbal injections, and further more, all of these incidents took place in one hospital from June 2000 to June 2003 (Wu and Wu, 2004). Lots of monographic papers were published to address these issues (Wang and Lu, 1999; Yu *et al*, 2003; Wang and Ren, 2002).

Measures for improving the safety of CTHM

The toxic-side effects and adverse reaction of Chinese herbal medicines should be recognized. One-sided advertisement and propaganda to claim the Chinese herbal preparations are "pure natural drug without any toxic-adverse effect" should be repudiated. The processes for clinical herbs, e.g. purification, combination, turning into injection or in combined use with Western drugs should be actively mentioned.

Empirical evaluation of the safety of Chinese drugs should be launched to classify the commonly used Chinese drugs in terms of their safety. We have put forward a five-grade evaluation system. The evaluation system is listed as follows:

Grade I Herbs that have been used as food for a long time, but have some medical function; or LD_{50} could not be detected in animal experiments, or the maximum tolerant dosage is higher than 10 g/kg; long-term toxicity (30 d feeding) could not be detected, with no evident adverse effect and toxicity when 100 times of human adult dosage was administrated; the three-genesis tests (carcinogenesis, teratogenesis, and mutagenesis) should be negative. Decision of herbs in this grade is based on *Ingredients of Foods in China* (2002) (Yang *et al*, 2002).

Grade II Herbs that have been historically served both as food and drugs, LD_{50} more than 10 g/kg or long-term toxicity could not be detected (30 d feeding), with no evident adverse effect and toxicity when 100 times of human adult dosage was administrated; the three-genesis test should be negative. Decision of herbs in this grade is based on Document File No.51 (See Table 4) (Ministry of Health, 2002).

Grade III This grade includes herbs taken as health-keeping food for a long time, such as drug diet and drug tea, which have some therapeutic functions and effects, with no toxic-adverse effect found when more than 2 g/kg of the extract or more than 5 g/kg of crude drug was administered; but long-term toxicity could be detected (30 d feeding): mild nonfatal, reversible adverse effect and toxicity could be detected when 100 times of human adult dosage was administrated. Decision of herbs

Table 4 List of Chinese herbs approved by Ministry of Health, P. R. China to be used both as foods and drugs

Types	Names of Chinese herbs
Bulbus	*Bulbus Allii Macrostemi*
Concha	*Concha Ostreae*
Cortex	*Cortex Cinnamomi*
Endothelium	*Endothelium Corneum Gigeriae Galli*
Flos	*Flos Caryophylli, Flos Chrysanthemi, Flos Lonicerae, Flos Sophorae, Flos*（*Flores*）*Aaurantii Amarae*
Folium	*Folium Nelumbinis, Folium Perillae, Folium Mori*
Fructus	*Fructus Alpiniae Oxyphyllae, Fructus Amomi, Fructus Anisi Stellati, Fructus Cannabis, Fructus Chaenomelis, Fructus Citri, Fructus Citri Sarcodactylis, Fructus Crataegi, Fructus Foeniculi, Fructus Gardeniae, Fructus Hippophae, Fructus Hordei Germinatus, Fructus Jujubae, Fructus Lycii, Fructus Momordicae, Fructus Mori, Fructus Mume, Fructus Rubi, Fructus Phyllanthi, Fructus Piperis, Fructus Canarii*
Herba	*Herba Cichorii, Herba Houttuyniae, Herba Lophatheri, Herba Moslae, Herba Cirsii, Herba Menthae, Herba Pogostemonis, Herba Portulacae, Herba Taraxaci*
Radix	*Radix Angelicae Dahuricae, Radix Glycyrrhizae, Radix Puerariae, Radix Platycodonis*
Rhizoma	*Rhizoma Alpiniae Officinarum, Rhizoma Dioscoreae, Rhizoma Imperatae, Rhizoma Phragmitis, Rhizoma Zingiberis, Rhizoma Polygonati, Rhizoma Polygonati Odorati*
Semen	*Semen Armeniacae Amarum, Semen Brassica Juncea, Semen Canavaliae, Semen Cassiae, Semen Coicis, Semen Euryales, Semen Ginkgo, Semen Lablab Album, Semen Myristicae, Semen Hoveniae, Semen Nelumbinis, Semen Persicae, Semen Phaseoli, Semen Pruni, Semen Raphani, Semen Sesami Nigrum, Semen Sojae Preparatum, Semen Sterculiae Lychnophorae, Semen Torreyae, Semen Ziziphi Spinosae*
Others	*Agkistrodon, Arillus Longan, Exocarpium Citri Rubrum, Pericarpium Citri Reticulatae, Pericarpium Zanthoxyli, Poria, Thallus Laminariae, Zaocys, Colla Corii Asini*

in this grade is based on Document File No.51 (See Table 5) (Ministry of Health, 2002).

Grade IV Herbs that are of evident medical function or effect possess active ingredients of intensive pharmaceutical effect, liable to lead into toxic-adverse effect when improperly used; LD_{50} could be detected, long-term toxicity could be detected (30 d feeding) in its extract when dosage is less than 2–5 g/kg; nonfatal, non-incapacitant adverse reaction could be caused by 50 times of the dosage for human adults, but no evident toxic-adverse effect is found in administration of 30 times of the dosage for human adults; certain individual kinds of them could induce positive reaction of three-genesis test.

Grade V Drugs with evident toxic-adverse effects, with statement of being mildly, moderately or potently toxic having to be given out in the direction, containing ingredients (such as digitoxin) with potent toxicity, easy to induce toxic-adverse effect; LD_{50} of the extract less than 1 g/kg, and that of the crude drug less than 2 g/kg; long-term toxicity (30 d feeding) could be detected; 30 times of the dosage for human adults could induce toxic-adverse, or even fatal, incapacitant, and un reversible reaction; positive reaction to three-genesis test; mother perinatal toxicity test shows mother-child intergenerational toxicity (Ministry of Health, 2002).

According to the principle of evidence-based medicine, we should review the available reports, and characterize the adverse reactions to Chinese herbs through systematic reviews and meta-analysis. The systematic reviews of adverse reactions should include large to ensure objective conclusions through rigorous statistical meta-analysis.

In 2003, a nationwide adverse drug reaction surveillance system was established in China. In 2001, case reports concerning adverse reactions to Chinese drugs accounted for 10%–14% of the total number of adverse drug reaction (ADR) reports, which are significantly lower than those to chemical agents, suggesting that Chinese drugs are still safer than chemical agents.

International cooperation on ADR of Chinese drugs,

Table 5 Chinese herbs approved by Ministry of Health, P. R. China to be used as health-keeping food

Type	Names of Chinese herbs
Bulbus	*Bulbus Fritillariae Cirrhosae, Bulbus Fritillariae Thunbergii, Bulbus Fritillariaae Hupehensis, Bulbus Fritillariae Ussuriensis*
Carapax	*Carapax et Plastrum Testudinis, Carapax Trionycis*
Caulis	*Caulis Bambusae in Taenia, Caulis Polygoni Multiflori*
Cortex	*Cortex Acanthopanacis Giraldii, Cortex Lycii, Cortex Moutan, Cortex Eucommiae, Radix Rubiae, Cortex Magnoliae Officinalis, Cortex Mori*
Fetus, Flos	*Fetus Cervi, Flos Carthami, Flos Chrysanthemi Indici, Flos Rosae Rugosae*
Folium	*Folium Ginseng, Folium Eucommiae, Folium Gingkgo, Folium Illicis Kudingchae, Folium Sennae, Folium Apocyni Veneti*
Fructus	*Fructus Ginseng, Fructus Ligustri Lucidi, Fructus Corni, Fructus Schisandrae, Fructus Arctii, Fructus Amomi Kravanh, Fructus Aurantii, Fructus Aurantii Immaturus, Semen Platycladi, Fructus Piperis Longi, Fructus Vaccinii, Fructus Sophorae, Fructus Tribuli, Fructus Psoraleae, Fructus Chebulae, Fructus Tamarindi, Fructus Rosae Davuricae, Fructus Rosae Laevigatae*
Herba	*Herba Seu, Herba Equiseti Hiemalis, Herba Plantaginis, Herba Dendrobii, Herba Gynostemmae, Herba Eupatorii, Herba Leonuri, Herba Centellae, Herba Epimedii, Herba Ecliptae*
Radix	*Radix Ginseng, Radix Notoginseng, Radix Cirsii Japonici, Radix Cyathulae, Radix Salviae Miltiorrhizae, Radix Aucklandiae, Radix Asparagi, Radix Pseudostellariae, Radix Morindae Officinalis, Radix Glehniae, Radix Arctii, Radix Rehmanniae, Radix Polygoni Multiflori, Radix Paeoniae Alba, Radix Panacis Quinquefolii, Radix Angelicae Sinensis, Radix Paeoniae Rubra, Radix Polygalae, Radix Scrophulariae, Radix et Rhizoma Rhei Preparata, Radix Polygoni Multiflori Preparata, Radix et Caulis Acanthopanacis Senticosi, Radix Ophiopogonis, Radix Codonopsis, Radix Achyranthis Bidentatae, Preparata, Radix Astragali*
Rhizoma	*Rhizoma Smilacis Glabrae, Rhizoma Gastrodiae, Rhizoma Chuanxiong, Rhizoma Cimicifugae, Rhizoma Bletillae, Rhizoma Atractylodis Macrocephalae, Rhizoma Anemarrhenae, Rhizoma Curcumae Longae, Rhizoma Atractylodis, Margarita, Radix Rehmanniae Preparata, Rhizoma Drynariae, Rhizoma Cyperi, Rhizoma Alismatis, Rhizoma Rhodiolae, Rhizoma Fagopyri Dibotrys*
Semen	*Semen Plantaginis, Semen Allii Tuberosi, Semen Astragali Complanati, Semen Trigonellae, Semen Cuscutae*
Others	*Calyx Hibisci Sabdariffae, Concha Haliotidis, Cacumen Platycladi, Cornu Cervi Elaphi Pantotrichum, Pericarpium Citri Reticulatae Viride, Os Cervi Elaphi, Os Magnoliae Officinalis, Gecko, Pollen Typhae, Propolis, Aloe, Ramulus Mori*

includes drafting the WHO guidance for herbal drug supervision, establishing the Forum on Harmonization of Herbal Medicine, and promoting the international supervision and information exchange of adverse reactions to herbal drugs. As a technical cooperation program with WHO, the Institute of Chinese Materia Medica, China Academy of Traditional Chinese Medicines, completed the *Guidance for Safety of Commonly Used Chinese Herbal Medicines* (Chinese Diagram) in 2004.

R&D of new drugs from CTHM

CTHM has gained interest from the international medical, biomedical, and pharmaceutical institutions as a potential source of valuable medicinal agents (Xiao and Fu, 1986; Liu and Xiao, 1988, 1992, 1993, 2000; Xiao, 1980, 1981, 1983, 1986, 1988; Xiao and Liu, 1999; Liu, 1987; Liu *et al*, 2000).

There is a quite surprising amount of information on ethnopharmacological applications throughout China. For instance, over the past 40 years just our two institutes have collected 400 000 items of such information. Since 1949, there have been thousands of scientific reports on studies of Chinese medicinal plants covering botanical, chemical, pharmacological, and clinical studies. Inter-disciplinary systematization aided by computational technique will certainly help identify promising candidates for further investigation.

Research under the guidance of TCM

There are no records of the term “chronic mylocytic leukemia” in the classics of TCM. However, based on the theories and methods of TCM, diagnosis of this condition can be made and treated according to the

symptoms involved. A complex prescription *Danggui Luhui* Pill has been used for this purpose and was confirmed with clinical trial on 22 patients. The prescription consists of the following: *Angelica sinensis* (Oliv.) Diels (root), *Aleo vara* L. (dried juice), *Gentiana acabra* Bunge (fructus), *Gardenia jasminoides* Ellis. (root), *Scutellaria baicalensis* Georgi (root), *Phellodendron amurense* Rupr. (sterm bark), *Coptis chinensis* Franch. (rhizoma), *Rheum palmatum* Linn. (root and rhizoma), *Indigo naturalis*, a product derived from the leaves of *Saphicacanthus cusia* (Nees) Brem, and *Aucklandis lappa* Decne. (root). Subsequent experimentation conducted with the animal model of leukemia 7212 (L7212) in mice revealed that only the *Indigo naturalis* among the ingredients of the prescription was effective, but with some side effects. In an effort to increase the therapeutic effect and reduce the side effects, further study of the *Indigo naturalis* has been made. Indirubin was identified as the active antitumor principle. The compound showed various inhibitory activities against Walker carcinoma in rats and Lewis lung cancer in mice, as well as mammary cancer (Ca 615) and leukemia 7212 in mice. Toxicological studies showed that when indirubin was given daily for a month at an oral dose of 100–500 mg/kg, no toxicological reactions, including the inhibition of bone marrow, were observed. Further clinical trial was carried out 314 cases with chronic mylocytic leukemia. Among these 314 patients, 82 achieved complete remission, partial remission and 87 beneficial effects; the total effective ratio was 87.3%. In the clinical observation, side effects such as abdominal pain and diarrhea sometimes occurred. Indirubin has been shown to have similar therapeutic effect as Myleran in treatment of chronic mylocytic leukemia. It possesses neither serious side effects nor inhibition of bone marrow.

It is well known that α-dichroine isolated from Chinese traditional antimalarial drug *Dichroa febrifuga* Lour. has shown an anti-malarial activity about 98–152 times as strong as quinine hydrochloride. After systematic investigation of another Chinese traditional antimalarial drug, *Artemisia annua* L., it has been found that the neutral fraction of the ether extract showed marked malariacidal effects in *Plasmodium berghei* in mice and *Plasmodium inui* and *Plasmodium cynomolgi* in monkeys. Toxicological studies showed no obvious side effects in animals. A clinical study of 30 cases also showed satisfactory results. Further investigation led to the isolation of an active compound called Qinghaosu. Clinical studies on different Qinghaosu preparations were carried out involving 2099 cases of malaria; among these 1511 were *Plasmodium vivax* and 558 were *Plasmodium falciparum* malaria. All patients were clinically cured.

Study on ancient literatures of TCM

In the ancient classic *Treatise on Febrile Diseases* (*Shanghanlun*, edited by ZHANG Zhong-jing), it is recorded that *Gegen* Decoction, a decoction of the root of *Pueraria lobata* (Willd.) Ohwi as its chief ingredient, in recommended for the treatment of stiffness and soreness in the neck. As a part of the pursuit of this therapeutic lead, a series of clinical trials of preparation of *P. lobata* gave satisfactory results. The active components of this plant were isolated, they are isoflavones daidzein, daidzin, puerarin, and daidzein-4', 7-diglucoside. Pharmacological studies revealed that either the total isoflavones or the single compound puerarin was capable of increasing the cerebral and coronary blood flow, decreasing the oxygen consumption of the myocardium, increasing the blood oxygen supply and depressing the production of lactic acid by the blood oxygen deficient heart muscle. The above mentioned actions could partially explain the mechanism of the *Pueraria* Preparation used for the relief of hypertensive diseases agent pectoris, migraine, and scudded deafness. Daidzein has shown a papaverine-like spasmolytic action, and the clinical trial of this compound has demonstrated that it has an action similar to the total isoflavones preparation (Liu and Yaniv, 2005).

Exploration of the effective and so-called secret

prescriptions

The first example to be offered in this category is the discovery of new antiepileptic agent called "antiepilepsirine" which possesses a wide anti-convulsive spectrum and a low toxicity. Piperine was found to be the active compound of an effective prescription for an anti-epileptic, which consisted of pepper and turnip. Based on this interesting clue, a series of derivatives of piperine were synthesized. One of these derivatives was "antiepilesirine" which was found to possess a strong anticonvulsive action. After clinical trial, it has been established as an antiepileptic agent having minimal side effects. One hundred piperine derivatives were screened in animal models for central nervous system actions. Four of these derivatives, *N*-(*p*-chlorocinnamoyl) piperidine, *N*-(cinnamoyl) piperidine, *N*-cyclo-pentyl-p-chlorocinnamoylamide, and *N*-(iso-propyl-*p*-hlorocinnamoyl) amide were found to be more effective than antiepilesirine against experimental animal epilepsy (Liu and Yaniv, 2005).

In 1970, secret prescription for anti-taenia used by old peasant in northeast China was explored. The method of treatment was to take it orally on an empty stomach, a powdered portion of *Agrimonia pilosa* Ledeb. Five to six hours after administration of the drug not only the segments, but also the scolex of the worm could be eliminated. Sixty-eight patients were then treated in hospital by similar regimen of drug administration with the effectiveness as high as 98.5%. The active principle of *Gemma Agrimoniae* was then isolated by Chinese chemists. Its structure was elucidated and named agrimophol. This compound was submitted to clinical study and its efficacy was fully substantiated. As this drug enjoys the advantaged of only nil side effects and high anthelmintic effect (Liu and Yaniv, 2005).

Study on the treatment principles of TCM

There are TCM treatment principles in common with the Western diagnosis as summarized in Table 6.

Table 6 Treatment principles of CTHM and their possible correlation to the Western diagnosis

Treatment principles	Relation to Western diagnosis	Examples of treat drugs
Mobilization on blood circulation and treatment of stasis	Cardiovascular diseases, thromboangiitis, obliterans, cerebral embolism	*Ligusticus chuanxiong* Hort., *Typha latifolia* L., *Crataegus pinnatifida* Bunge, *Angelica sinensis* (Oliv.) Diels, *Paeonia lactiflora* Pall., *Salvia miltiorrhiza* Bunge
Promotion of vigo and stability of vitality	General tonic for the treatment of weakness, and probably with an immuno-stimulating action	*Astragalus* Bunge var *mongholicus* (Bunge) Hsiao, *Panax ginseng* C. A. Mey., *Codonopsis pilosula* (Franch.) Nannf., *Acanthopanax senticosus* (Ruper. et Maxim.) Seem
Treatment of fever and inflammation along with detoxification	Antibacterial antivirotic, anti-cancer, and possibly with an immuno stimulating action	*Coptis chinensis* Franch., *Indigo naturalis*, *Scutellaria baicalensis* Georgi

For instance, after an investigation of the so-called blood circulation stimulating drug *Ligusticum chuanxiong* Hort., more than ten compounds were isolated from this plant, among which tetramethylpyrazine was found to be the active principle, which was present only in minute amount in the plant. Pharmacological and clinical studies showed that tetramethylpyrazine hydrochloride could improve microcirculation in the mesenteroids of rabbits and could also dilate capillary vessels *in vitro*. Tetramethyl-pyrazine not only inhibited platelet aggregation caused by adenosine diphosphate (ADP), but also disaggregated the aggregated platelets (Sun *et al*, 2008). Clinically, it can be used with satisfactory results for the treatment of occlusive cerebral blood vessel diseases, including cerebral embolism.

It was found that using crude cotton seed oil for salad dressing led to infertility in young men. A series of clinical investigations involved over 8000 healthy men

with gossypol (an ingredient of cotton seed) treatment for more than six months found that gossypol is a reliable antifertility agent for men and is relatively safe to use, at the effective antifertility dosage. When oral administration of gossypol was discontinued, fertility was gradually recovered (Qian and Wang, 1984).

Wuweizi (*Fructus Schizandra Chinensis*), a Chinese traditional drug commonly used as an astringent, had therapeutic effects on hepatitis (Liu, 1988), particularly in lowering the elevated serum glutamate-pyruvate transaminase (SGPT) level. Detailed chemical and pharmacological studies found that the active principles responsible for lowering elevated SGPT levels were a series of derivatives in the dibenzo (a,c)-cyclooctene series. Among the derivatives of schizandren, schizandrol B, and schizandrin C showed the best protection from liver damage induced by chemical substances.

Lingzhicao (*Ganoderma*), fungus, has a broad range of pharmacological actions and has long been widely used for treating neurasthenia, chronic hepatitis, cardiovascular disease, and chronic ulcers of the digestive system. The water-soluble preparation of *Ganoderma capense* (Lloyd) Teng had no effect in treating progressive muscular dystrophy and atrophic myotonia. Hyperaldolasemia as one of the biochemical conditions in muscular dystrophy was induced in mice by the administration of 2, 4-dichlorophenoxy acetic acid. The effect of *Ganoderma* was attributed to uracil and uridine. Clinical trials with uridine injection to patients with progressive muscular dystrophy achieved significant alleviation of symptoms.

Scopolia tangutica Maxim (*Tangchom Nagbo*) is a traditional Tibetan medicine usually used in Qinghai, Western inland province of China. Over dosage of this medicine caused atropine-like toxicity (Xu and Chen, 1994). Phytochemical investigations found not only hyoscymine and scopolamine, but also anisodamine and anisodine. Pharmacological studies indicated that the effect of anisodamine on the central nervous system is 6–20 times weaker than that of atropine, while the effect of anisodine on the peripheral nervous system is weaker than the effect of both atropine and scopolamine. Clinically anisodamine has been used for treating of septic shock in toxic bacillary dysentery, fulminant epidemic meningitis, and hemorrhagic enteritis. Anisodine is now used for treating migraine and diseases of the fungus occuli caused by vascular spasm, organophosphorus poisoning, and acute paralysis caused by cerebral vascular accident. It is also being used as an anesthetic in TCM. The above examples show that CTHM studies did lead to valuable drug discovery.

Active compounds isolated from CTHM

About 600 pharmacologically active compounds have been identified. One hundred or so have been subjected to systematic chemical, pharmacological, and clinical studies. Approximately 60 new drugs have been developed from active compounds in Chinese medicinal plants or their derivatives (Liu *et al*, 2000).

The chemical classification of pharmacological active principles from Chinese medicinal plants is shown in Table 7. Alkaloids (202), phenolic compounds (177), and the terpenes (135) constitute most of identified active compounds.

Table 7 Pharmacological active principles from CTHM

Chemical type		Number of compounds
Alkaloids		**202**
Terpenes		**135**
	Monoterpenes	27
	Sesquiterpenes	32
	Diterpenes	33
	Triterpenes	43
Cardiac glucosides		**23**
Phenolic Compounds		**177**
	Quinones	25
	Chromones	5
	Flavonoids	34
	Coumarins	27
	Lignins	21
	Phenyl propanoids	17
	Others	48
Acids and miscellaneous		**34**
Total		**571**

Classification of pharmacological activities

Since 1949, there have been thousands of pharmacological reports on Chinese medicinal plants. Structure-activating relationship studies found that the alkaloids of bisbenzylisoquinoline type are potential leads for analgesic, sedative, antimicrobial, and cardiovascular drugs (Liu and Yaniv, 2005). The propane-type alkaloid such as anisodamine and anisodine isolated from *Scopolia* L. plants are probably effective on modulating microcirculatory systems. The diterpene-type alkaloids isolated from plants of *Aconitum* L. and *Delphinium* L. provide drug effective against anodyne, arrhythmia, and cardiotonic drugs. The alkaloids related to harringtonine may exert antileukemic actions. Among phenolic compounds, flavonoids (such as scutellaria, icariin, isorhanetin, and puerarin), and the coumarins (such as daphnetin and daphnoretin) can be considered to have cardiovascular activity. As to terpenoids, many monoterpenes are effective against respiratory problems. Several peroxide substances, such as Qinghaosu and Yingzhaosu A, are promising antimalarial agents. Among the 140 new drugs originated directly or indirectly from Chinese medicinal plants, 36 are used for the cardiovascular, 23 for anticancer, 21 for nerve, 15 for respiratory, 18 for antimicrobial, 14 for digestive, 9 for antiparasitic, 5 for family planning, and 1 is for eye medicine. All these drugs can also be divided into four categories according to their characteristics: (A) known compound for new use; (B) new compound for new use; (C) semi-synthesis, chemical modification of the active principles of medicinal plants, and (D) total synthesis based on the active principle isolated from medicinal plants (Liu and Yaniv, 2005).

Ethnopharmacological data are important sources for new drugs. Since medicinal plants have been used for centuries by billions of people, there have been ample trials to find satisfactory medical agents and to solve problems of toxicity and side effects. However, this approval is not efficient enough and now deemed unethical.

Modern approach looks carefully into for medicinal plants and conduct well-designed multidisciplinary research including pharmacognostical, chemical, pharmacological, and clinical studies.

Achievements in new drug discovery and development

Salvicine

Salvicine [4, 5-seco-5, 10-friedo-abieta-3, 4-dihydroxy-5 (10), 6, 8, 13-tetraene-11, 12-dione] (Fig. 3), a diterpenoid quinone compound synthesized by structural modification of a natural product isolated from the traditional Chinese medicinal plant *Salvia prionitis* Hance (Labiatae) is a Topo II inhibitor and induces Topo II-mediated DNA breaks (Meng *et al*, 2001). It is a structurally modified derivative of a natural product from *S. prionitis* (Huang *et al*, 1990). Its pharmacological activity was evaluated against human tumor cells (Meng *et al*, 2001) and xenografts (Qing *et al*, 1999). Salvicine is equipotent to etoposide against three leukemia cell lines (Zhang *et al*, 1999). Additionally, salvicine has a significant cytotoxic effect on multidrug-resistant cell lines. Salvicine, like most chemotherapeutic drugs, exerts its antitumor effect by inducing cancer cell apoptosis, equally effective in K-562 and K-562/A02 cells (Qing *et al*, 2001) and in HL-60 cells (Meng *et al*, 2001; Liu *et al*, 2002). The compound has significant *in vitro* and *in vivo* activity against malignant tumor cells and xenografts, particularly in human solid tumor models, and is now in clinical trial in China. Now this compound was entered into phase II clinical trial with cancer patients (Zhou *et al*, 2008).

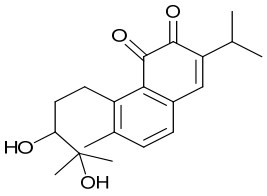


Fig. 3 Chemical structure of salvicine

Schiprzine

Schiprzine (ZT-1), *N*-[2-hydroxy-3-methoxy-5-chlorobenziliidene] and Huperzine A (Hup A) (Fig. 4) is a

novel potent cholinesterase (ChE) inhibitor, which is rapidly transformed into the active metabolite Hup A. (Zhu *et al*, 1999). Originally isolated from Chinese club moss by Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Hup A was demonstrated to have neuro-protective activities. ZT-1 was selected out of over 100 Hup A derivatives identified at the same institute. Fig. 4 shows the chemical structure of ZT-1 and Hup A. *In vitro* pharmacological tests showed a marked concentration dependent inhibition of acetylcholinesterase (AchE). *In vivo* investigations conducted in mice, rats, and monkeys showed that ZT-1 is equipotent to Hup A and more potent than Donepezil and Tacrine (Zhu *et al*, 1999 and 2000; Anonymous, 2004b). Preclinical studies have been finished in China and phase I clinical trial has also been completed in Switzerland and China (Xu *et al*, 2005; Li *et al*, 2005; Wei *et al*, 2005, 2006). A phase II clinical trial for treating of Alzheimer's disease (AD) is being conducted in patients with mild to moderate AD (Anonymous, 2004b).

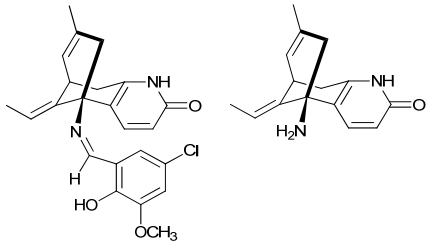
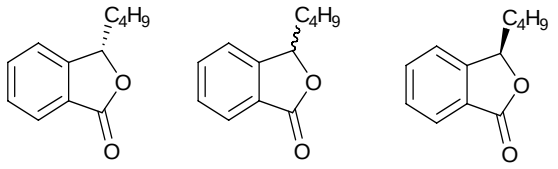


Fig. 4 Chemical structures of ZT-1 and Hup A

Butylphthalide

S-(–)-3-*n*-Butylphthalide [*S*-(–)-NBP] (Fig. 5) was extracted as a pure component from seeds of *Apium graveolens* Linn (Yang and Chen, 1984). Then, (±)-NBP was synthesized and developed as an anti-cerebral ischemic agent, recently, it has finished phase III clinical trial. In 2002, (±)-*n*-Butylphthalide Soft Capsule was approved by SFDA of China to market in China.



S-(–)-NBP (±)-NBP *R*-(+)-NBP

Fig. 5 Chemical structures of *n*-butylphthalide

There is a chiral center in the molecule of NBP and a pair of enantiomers was synthesized. NBP has been reported to have many anti-ischemic effects, including: reducing the area of cerebral infarct in middle cerebral artery occlusion (MCAO) rats (Liu and Feng, 1995), attenuating neuronal damage after delayed cerebral injury (Yao *et al*, 1998), ameliorating mitochondria dysfunction (Xiong and Feng, 1999, 2000), during cerebral ischemia, improving energy metabolism in complete brain ischemic mouse (Feng *et al*, 1995), ameliorating brain edema and blood-brain barrier damage in MCAO rats (Deng and Feng, 1999; Chong and Feng 1999), enhancing regional blood flow in MCAO and subarachnoid hemorrhage model (Yan *et al*, 1998; Chong and Feng, 1998), improving micro-circulation in pial arterioles in MCAO rats (Xu and Feng, 1996), and delaying the life span and improving neurological deficit in stroke prone spontaneously hypertensive rats (Zhang and Feng, 1996). A number of studies have shown that neuronal cell loss after cerebral ischemia involved apoptosis. After focal cerebral ischemia in rats, the predominant localization of apoptotic cells at the inner boundary of the ischemic lesion suggested that the apoptotic process largely contributed to the expansion of the ischemic damage (Li *et al*, 1995). Moreover, several laboratories have demonstrated that antiapoptotic maneuvers could reduce neuronal death and infarct volume (Linnik *et al*, 1995; Du *et al*, 1996). The effects of (±)-NBP on hypoxia/hypoglycemia-induced apoptosis of rat cortical neurons have been previously reported (Dong and Feng, 1999). Based on the fact that the biological activities and toxicities of drugs are closely related to their optical activities, the present study was designed to compare the action potency of *S*-(–)-, *R*-(+)-, and (±)-NBP on cerebral ischemia-induced apoptosis and clarify the enantiomer that played a main role.

The apoptotic pathway involves at least three cells

receive death stimuli; an effecter phase dependent on bcl-2 family members and on apoptogenic proteins released from mitochondria; and a degradation phase, dependent on caspases. The participation of mitochondria in the mechanism of cell death has received much attention in recent years. Mitochondria is assumed to be involved in apoptosis by releasing apoptogenic proteins, such as cytochrome C, to the cytoplasm where it activates caspase-3, a cysteine protease of the IL-1b-converting enzyme family, which has been reported to trigger apoptosis (Liu *et al,* 1996; Green, Reed, 1998). The protective effects of NBP on ischemia-induced mitochondrial injury and mitochondrial morphological changes have been previously reported and it was therefore of interest to investigate the effects of chiral NBP on the release of cytochrome C and on the activation of caspase-3 after transient focal cerebral ischemia (Xiong and Feng, 1999; 2000). Chang and Wang's study indicated that NBP, especially its *S*-(–)-enantiomer, could potently reduce the release of cytochrome C, decrease the activation of caspase-3, and inhibit DNA fragmentation after transient focal cerebral ischemia. The findings on the beneficial effects of NBP on cerebral ischemia-induced apoptosis might have important implications for the study and treatment of ischemic cerebrovascular diseases (Chang and Wang, 2003).

S-(–)-NBP, as an anti-cerebral ischemia agent, has been shown to have therapeutic effects on learning and memory deficits induced by chronic cerebral hypoperfusion and β-amyloid (Aβ) intracerebroventricular infusion in rats. In the present study, we investigated the neuroprotective effects of *S*-(–)-NBP on Aβ (25–35)-induced neuronal death/apoptosis and potential mechanisms in rat hippocampal neurons and human neuroblastoma SH-SY5Y cells. Aβ (25–35) signify-cantly reduced cell viability and increased the number of apoptotic-like cells, indicating that Aβ (25–35)-induced neurotoxicity. In addition, tau protein functional distinct phases: an initiation phase during which hyperphosphorylation was found to increase after Aβ exposure. All of these phenotypes induced by Aβ (25–35) were markedly reversed by *S*-NBP. Pre-treatment with l-NBP prior to Aβ (25–35) exposure significantly elevated cell viability, and reduced Aβ (25 – 35)-induced nuclear fragmentation and early apoptosis. Furthermore, immunoreactivity for hyperphosphorylation tau protein was significantly decreased by *S*-(–)-NBP treatment. The results suggest that *S*-(–)-NBP may protect neurons against Aβ-induced neurotoxicity *via* inhibiting tau protein hyperphosphorylation (Feng *et al*, 2008).

Bromotetrandrine

Stephania tetrandra S. Moore, containing bisbennzylisoquinoline alkaloids is commonly used as anti-inflammatory and analgesic medicine in China. Recent studies show that the alkaloids enhanced the cytotoxicity of anticancer drugs in P-gp-dependent tumor cells. Synthesized derivatives of tetradrine reversed some multidrug resistance (MDR) *in vitro* and *in vivo*. (Wang *et al*, 2005). Bromotetrandrine (BrTet, Fig. 6) showed significant MDR reversal activity *in vitro* and *in vivo*. Its activity may be related to the inhibition of P-gp overexpression and the increase in intracellular accu- mulation of anticancer drugs. BrTet may be a promising MDR modulator for eventual assessment in the clinic (Jin *et al*, 2005). Now the preclinical studies of BrTet, including pharmaco-dynamics, pharmacokinetics, pharmacology and toxicology, quality control tests, and phase I clinical trials have been completed in China (Xiao *et al*, 2004, 2005), suggesting that BrTet may be good modifiers of MDR in cancer chemotherapy.

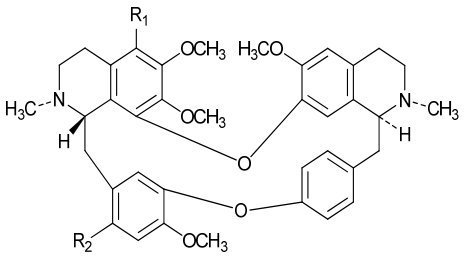


Fig. 6 Chemical stucture of bromotetrandrine (R_1 = Br, R_2 = H)

Kanglaite Injection prepared form *Semen Coicis*

Semen Coicis is the seed of *Coix laryma-jobi* L. (family Gramineae). In TCM, *Semen Coicis* serves several functions. They stimulate the function of spleen and lung, remove heat (which helps in the drainage of pus) and induce diuresis. *Semen Coicis* is also used to treat the symptoms of diarrhea and arthritis. The action mechanism of the Kanglaite (KLT) Injection, which is an extract including active ingredients (Fig. 7) from *Semen Coicis*, is known as follows: (1) inhibits the mitosis of tumor cells during G2/M phases, (2) induces apoptosis of tumor cells, (3) affects the genetic expression of tumor cells by up-regulating FAS/Apo-1 gene expression and down-regulating Bc1-2 gene expression, (4) inhibits the tumor angiogenesis, (5) counteracts the cachexia of cancers, and (6) reverses the multi-resistance of tumor cells to anticancer drugs and the resistance modification in some of chemotherapeutics (Li, 2006).

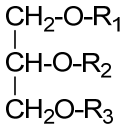


Fig. 7 Chemical structures of the main active ingredients in seeds of *C. lacryma-jobi*

Hexadecanoic acid (C16) R1, R2, R3 = - CO $(CH_2)_{14}CH_3$

Octadecoic acid (C18) - CO $(CH_2)_{16}CH_3$

Octacenic acid (C18-1) - CO-$(CH_2)_7CH$=CH $(CH_2)_7 CH_3$

Octadedienoic acid (C18-2) - CO-$(CH_2)_7$-CH=CH-CH_2CH=CH $(CH_2)_4CH_3$

KLT Injection effectively treated a variety of malignant tumor, such as carcinomas of lung, liver, stomach, esophagus, colon, pancrease, kidney, ovaries, malignant lymphoma, and leukemias for more than 200 000 cases. Prospective, randomized and large-scale 1 408 cases clinical studies showed that KLT could not only inhibit cancer cells, but also enhance immunity. Moreover, KLT has synergistic and toxicity-reducing effects when combined with chemo- or radio-therapy. It could also relieve pains, improve patient life-quality, and prolong survival (Qian, 1998; Shen, 1998; Li, 1998; Jin, 1999; Li, 2006). *Semen Coicis* extract is formulated into an emulsion for injection, which has been proved to be an effective and safe CMM preparation by preclinical antitumor studies, and pharmacokinetics and safety studies. Liu *et al* study supports the notion that fatty acid synthetase is a novel target for anticancer activity and provides a theoretical foundation for the wide application of *Semen Coicis* extract in traditional medicine (Yu *et al*, 2008). Phases I, II, and III clinical trials and tens of thousands of clinical applications proved that the preparation has adjunctive therapy effects to cancer patients. When combined with chemo-therapy, radiotherapy, and surgery, it could improve the response rate, regulate the energy of advanced patients, and improve life quality so as to prolong the survival time. In 2001 and 2002, clinical trial of KLT Injection has been started in USA and Russia, respectively. The USA Food and Drug Administration (FDA) approved a phase II clinical trial to test its efficacy in treating non-small-cell lung cancer in 2003. It is the first drug derived from traditional Chinese herbal remedy to go into clinical in the United States (Li, 2004).

Berbamine

Berberis L. plants have a long history in TCM and are used as raw materials. The medicinal resource of *Berberis* L. is widely distributed in China. About 200 species of *Berberis* L. plants were found in China (Liu *et al*, 1983). The main alkaloid ingretients are berberine, palmatine, jatrohizine, columbamine, berbamine, oxyacanthine, and isoterandrine. Berbamine is a bisbennzyl-isoquinoline alkaloid (Fig. 8). It was found in 32 species of *Berberis* L. plants (Fig. 9).

The berbamine contents in different species varied from 0.68% to 3.84% (Liu *et al*, 1991). It is economically valuable that *Berberis* L. resource can

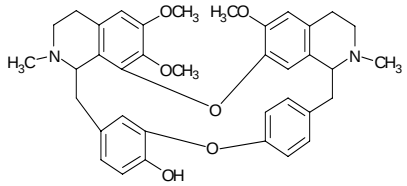


Fig. 8 Chemical structure of berbamine

be comprehend sively used to develop new drugs and discover new pharmacological activities (Liu, 2000b). Pharmacological studies showed that berbemine possesses significant leukogenic effect in rats and dogs injured by anticancer agents and radiation. The leukogenic effect was demonstrated in a clinical trial with 405 patients suffering from leukopenia. Now the alkaloid is used as a leukogenic drug in the treatment of leukopenia induced by toxic substances, anticancer, and radiotherapy. It is also used as an adjuvant cancer chemotherapy or radiotherapy to protect the haematogenic function of bone marrow.

The challenges in modern R&D

According to the WHO report, about three-quarters of the world population currently rely upon traditional and herbal medicines for health care (Gilani and Rahman, 2005). CTHM plays an important role in the health care needs of Chinese and other oriental countries. As mentioned above, CTHM is a potential source for new and improved medicinal agents. Recent research and development have been trying to unlock the full medical potential of resources of CTHM, particularly medicinal plants.

Fig. 9 Plant resource of *Berberis* spp. in China

Northeast China: Two species *Berberis poiretii, B. amurensis* **North China**: Two species *B. poiretii, B. amurensis*
East China: Two species *B. virgetorum, B. kawakami* **South China**: Two species *B. virgetorum, B. kawakami*
Northwest China: Eleven species: *B. johannis, B. hemsleyana, B. vernae, B. heteropods, B. ibensis, B. diaphana, B. kansuensis, B. dubia, B. circumserrata, B. dasystachya, B. soulieana*
Southwest China: Fifteen species: B. wilsonie, B. polyantha, B. sargentiana, B. jamesian, B. pruunoca, B. macrocarpa, *B. silvatraroucana, B. dictyphylia, B. criacanthophora, B. gyalaica, B. gagnepainii* var. *lanceifolia, B. ferdinandi-coburgii, B. virescen*

The first challenge: Discovery and development of new drug from CTHM

We are facing many challenges in scientific and technological development for CTHM, particularly in: (1) establishing standards for characterization of medicinal plants and products; (2) application of analytical methods to standardize methods; (3) analytical assays for safety

evaluation; (4) scientific verification of efficacy; (5) isolation of desired active fractions or compounds for discovery of leads in new drug development; and (6) compliance with international practice guidelines for R&D of new drugs, as well as production of pharmaceuticals (Liu and Xiao, 2002). These international practice guidelines include GLP, GCP, GAP, and GMP, etc.

Novel standardization methods significantly raise the medical potential and quality of CTHM. DNA finger-printing techniques and cutting-edge genechip-based methods were used to control the quality of botanicals and products of CTHM. Different genera, different families, and even different species can be distinguished. By using distinct cDNA sequences derived from *Fritillaria cirrhosa* D. Don and *Fritillaria thunbergii* Miq. and a genechip contained different oligonucleotide probes corresponding to the different species of *Fritillaria* L. plants.

New drug discovery and development processes in CTHM have been implemented in many institutions in China. Fig. 10 presents a basic process. *In vitro* or *in vivo* bioassay methods are used to guide the isolation of active compounds form extracts of medicinal plants. Then pharmacology, toxicity and safety, as well as clinical trials of the selected active compounds are carried out.

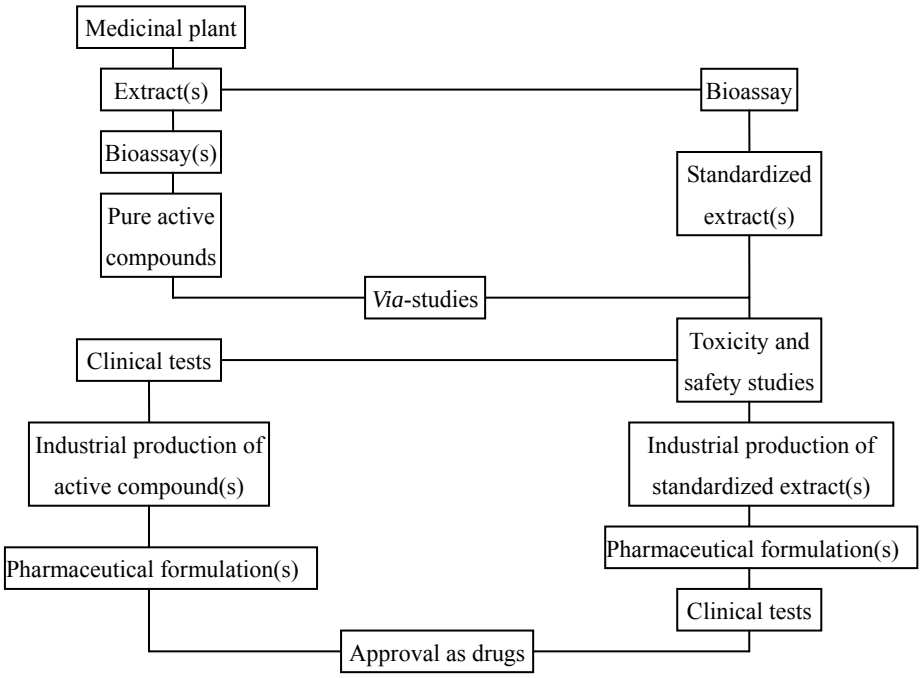


Fig. 10 A basic process for study of plants used in traditional medicines

Using the above methods in combination with clinical trials and *in vitro* and *in vivo* pharmacological studies, information about the activity of medicinal plants and their extracts can be obtained. Moreover, systems biology approach integrates "-omics" data for different extracts of the medicinal plant or fractions. The "-omics" of medicinal plants are in rapid development to enable studies of activity, action mechanism, drug interaction, drug safety, and relation of medicinal plants with environment.

The second challenge: Safety of CTHM products

In many parts of the world, phyto-therapeutic products are only OTC products. The clinical safety and interactions of these products have become an issue, often requiring careful monitoring and reporting, followed by substantial scientific study and communication to affect public awareness and enhance safety. In some developing countries, traditional medicine products are easily marketed as therapeutic products although their quality control is poor or missing.

Because of the absence of definitive and harmonized regulations regarding quality control and marketing, the issues of safety and efficacy are often understated and neglected. An over program for safety evaluation of products based on traditional medicines is needed for consumers in China and in the world. But the first key factor is to obtain standardized and controlled products or preparations in quality for safety evaluation studies (Cordell and Colvard, 2005).

The WHO has issued a set of general guidelines for the study of traditional medicines (Anonymous, 2000). China government has also issued a set of guidelines for safety and efficacy studies of CTHM products (SFDA, 2005). The aims of these guidelines are to harmonize the terms being used, summarize the issues for developing research methodologies, improve the quality and value of research in CTHM, and provide appropriate evaluation methods to facilitate the regulation and registration of CTHM products (Liu *et al*, 2007). While these guidelines are crucial, we found them not adequate for continuous improvement of CTHM products in health care.

Safety evaluation of products of traditional medicines will protect consumers in China and in the world. Fig. 11 gives an outline of safety evaluation (Cordell and Colvard, 2005; Liu *et al*, 2007). As the first key factor, standardized and controlled products or preparations of CTHM must be free of contaminants such as insects, herbicides, pesticides, solvent residues, heavy metals, aflatoxins and other toxic microbial metabolites, and radioactivity.

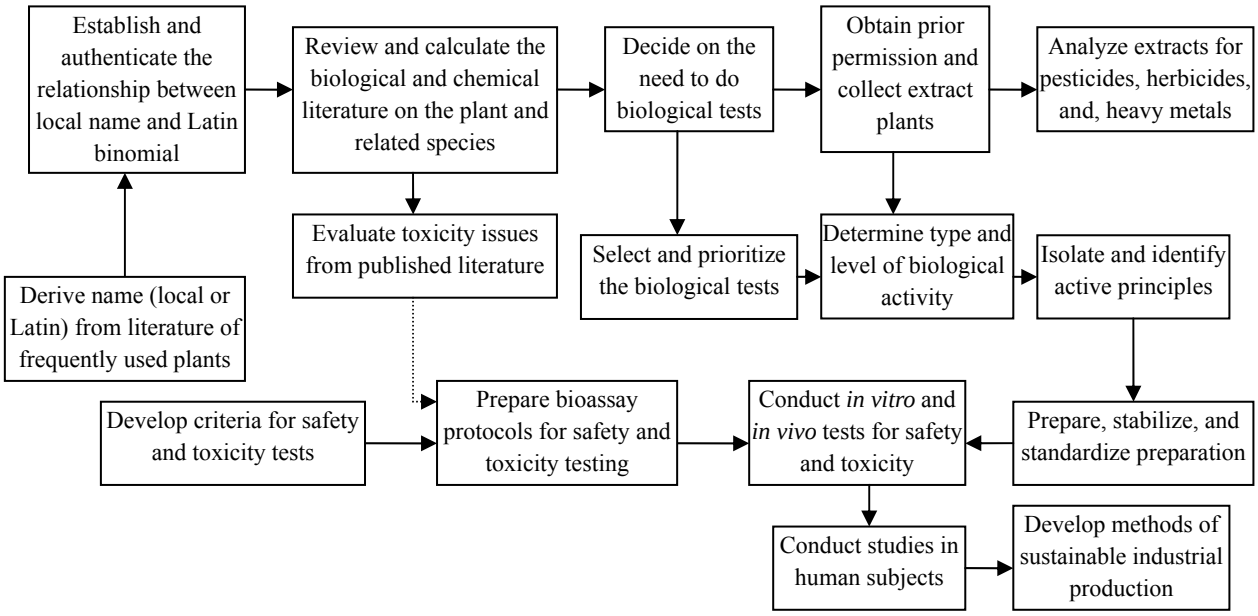


Fig. 11 An over program for safety evaluation of products based on traditional medicines

The third challenge: Application of modern techniques and methods

Modern techniques and methods are readily available and being further developed. Now we can measure gene expression, and conduct "-omics" experiments to study the activity, action mechanism, and efficacy of CTHM. We will understand better the drug actions in terms of the changes in transcriptome, proteome, metabolome/metabonome. Biomarkers as identifiable by NMR or LC-MS/MS analyses enable diagnosis of a variety of diseases, measurement of liver or kidney toxicity, and monitoring the drug action. A selected group of metabolites in an organism can be monitored qualitatively and quantitatively, and thus a fingerprint of metabolites can be obtained. Omics approach can be applied at any stage in drug discovery and development processes, when used in one or more of the following settings: (1) predictive biomarkers for

drug-related effects in animal models; (2) understanding of the biochemical mechanisms of action to target-organ or to target-organ pathologies in animal to man; (3) developing biomarkers for toxicities in non-clinical development; and (4) predictive biomarkers for drug-related effects in man during phase II and phase III clinical trails (Liu, 2004a, 2004b, 2005; Liu *et al*, 2004). We have applied metabonomics technology in studies of action mechanism of complex *Gensing* Injection (*ShenMai* Injection) for the treatment of cardial disease and complex Ucncaria-stem mixture for the treatment of hypokinetic syndrome in children (Liu, 2004a; Huang *et al*, 2005; Wu, 2005).

The fourth challenge: Application of international practices

The fourth is to apply international practices including GAP, GMP, GLP, and GCP in the R&D of CTHM products. We recognize the importance of quality, efficacy, and safety of products of CTHM. However, the scientific data of quality, efficacy, and safety are originated from scientific R&D procedures with international practices and standards.

In the Chinese medicinal plants (raw medicinal materials) market, the quality of the supply is hinged closely on the origin of the herbs. Practitioners who prescribe the herbs also specify the origin that is firmly believed to be crucial for the quality. With full recognition of the modern interpretation of the supply of herbs, GAP is aimed at the production of herbs that are not only of identical morphological characteristics, but also of ideal chemical and biological profiles (Leung, 2005). The establishment of GAP recommendations is world trend basing on practical needs. China had a quick response to the need in 2002. However, GAP in China is particularly difficult, not only because the current practice of growing herbs, their marketing and distribution have been counter productive to the introduction of the new system of GAP. The problems are now the GAP initiative will not be able to elevate the quality of herbs, because the coverage is too limited; And GAP evaluated herbs might enjoy unqualified benefits, and the monopoly of GAP evaluated herbs might lead to new problems.

The efficacy and safety of CTHM products encounter challenges or problems during the course of pre-clinical and clinical research. The key problems are (1) the quality of raw materials, (2) appropriateness of pharmacological activity assessment methodology and data interpretation, (3) pharmacokinetics, metabolism, and bioavailability of active constituents, (4) clinical dosage formulation, and (5) clinical study designs and outcome measures (Fong *et al*, 2005). For standardization procedures of pre-clinical studies, quality control analysis of active marker chemical compounds can be accomplished by colourimetric, spectroscopic, and chromatographic methods. More modern methods for the chemical analysis of secondary chemical constituent in CTHM products involve some form of chromatography. Thin layer chromatographic (TLC) procedures have the advantage of being simple, rapid, and can provide useful characteristic profile patterns. However, their resolving power is limited and quantitative data for minor constituents are difficult to obtain. Gas chromatography (GC) can provide high resolution of the more volatile complex mixtures, but is of limited value in the case of more volatile polar compounds. High performance liquid chromatography (HPLC) is capable of resolving complex mixtures of polar and non-polar compounds. HPLC can be coupled with a wide range of analytical detection techniques including UV, ELSD, and MS to produce a fingerprint of the CTHM products, and to quantify the concentration of one or more active marker compounds. In the safety and efficacy evaluation of CTHM products, an important consideration is the dosage formulation, which can affect the bioavailability of the active markers present in the standardized formulation.

Evidence of efficacy and safety of CTHM products can be generated by clinical studies under GCP. As with many clinical studies conducted under GCP, the major

challenge that we encountered is due to experimental in the inability to enroll and randomize the desired number of subjects into the study within the prescribed period. However, it should be noted that even when studies are designed to incorporate GCP employing well characterized and standardized CTHM preparations, other obvious, but nevertheless, important problems, or challenges abound that require attention.

Conclusion

This article provides an overview of the past and current R&D of CTHM, and identifies the challenges faced in future R&D of CTHM. As Chinese medicine is a great treasure not fully exploited, efforts must be made to explore and refine them. We showed an important pathway for new drug research into and out of CTHM. International collaboration of research into CTHM led to further discovery of a number of valuable medicinal agents. All these interests and efforts are crucial to unlock the full medical potential of TCM, particularly medicinal plants.

CTHM plays an important role in the health care needs of Chinese and other countries in the world. As mentioned above, CTHM is a potential resource for new and improved medicinal agents. Recent R&D have been trying to unlock the full medical potential of resources of CTHM, particularly medicinal plants. We recognize the importance of quality, efficacy, and safety of products of CTHM. The scientific data on quality, efficacy, and safety are key problems for inter-nationalization and modernization of CTHM. As medicinal products for the treatment and prevention of diseases, Chinese medicine products must establish an acceptable level on quality, efficacy, and safety characteristics to the world modern medicine. CTHM products have to face the presented challenges.

There are challenges to CTHM innovations. The first challenge is to evaluate the efficacy, pharma-cological properties, action mechanism, and active chemical constituents; The second is to develop safety design, nor the lack of study volunteers. The problem lies research methodologies for quality of CTHM products; the third is to apply new "-omics" techniques to innovate drug discovery-development from CTHM products; The fourth is to apply international practices including GAP, GMP, GLP, and GCP in the R&D of CTHM products.

We are facing many challenges in scientific and technological development for TCHM, particularly, in establishing standards for characterization of TCHM products, application of analytical methods to standardize methods, analytical assays for safety evaluation, scientific verification of efficacy, use of novel bio-sensors for studying macromolecular interactions and for high throughput screening, discovery and development of new drug, and compliance with international practice guidelines for R&D of new drugs, as well as production of pharmaceuticals.

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