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RESEARCH AND DISCOVERY TRENDS OF CHINESE MEDICINE IN THE NEW CENTURY

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Chinese medicine and other alternative therapies are widely used throughout the world. Thus, a current research trend is to use Chinese Materia Medica (CMM) for the discovery and development of high quality dietary supplements, as well as effective and safe new drugs in order to improve quality of life, prevent illness, and treat chronic, age-related, as well as recalcitrant diseases, which are hard to treat with Western medicine. The production of high quality dietary supplements requires stringent quality control, and there are three approaches for developing effective safe world-class medicines from CMM. These approaches include the development of pure single active principles, active fractions, and effective, and safe traditional Chinese medicine (TCM) formulations verified by modern scientific technology. This lecture will focus on the discussion and illustration of the trends involved in the research and development methodology as well as new perspectives.

Chinese Materia Medica (CMM, *Chang Yao*) is an important part of the ancient system of Traditional Chinese Medicine (TCM, *Chung Yi Yao*). Its efficacy has been validated by a long history of practical use and documented in classical literature. CMM is prescribed according to TCM theory and is directed at multiple targets to treat a totality of symptoms. The processed crude multicomponent natural products of CMM are used to restore equilibrium in the body, for example, to balance Yin and Yang. Individual herbs/drugs of CMM have different properties and effects, leading to different results on the body. Such properties include the 4 essences (cold, cool drugs for Yang diseases; warm, hot drugs for Yin problems), 5 flavors (pungent, sour, sweet, bitter, salty), 4 directions of action (ascending, floating, descending, sinking), and 7 effects (single, additive, synergic, antagonistic, inhibitive, destructive, opposite). Thus, from 4 to 12 individual herbs with different pharmacological actions are generally contained in CMM herbal formulas. Hundreds to thousands of different combinations of formulas have been documented and prescribed, from 110 in *Chin Kuei Yao Leuh* to 100,000 in *I Fang Chi Chieh*.

Thus, CMM has been used for centuries both as drugs (TCM herbal formulations) and dietary supplements (*Yao Shan*) and, along with other botanicals and herbal medicines, represents an ever-growing international industry.

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Table 1. Challenges to the International Development of CMM

Main Challenge	Specific Issues
The basic theory of TCM cannot be explained well by modern science.	4 essences, 5 flavors, 4 directions of action, 7 effects of drugs, processing methods & others
Source of high quality CMM is difficult to control well	Particularly for the authentic drugs (species, production site, choice of collection time, assurance & production of authentic CMM, storage, processing method, extraction methodology
Preparation of CMM lacks stringent quality control (QC) standards	The quality of CMM is still evaluated based upon experience; physical and chemical methods must be established
Difficult to assue clinical efficacy	Lacks placebo-controlled Western-style clinical trials evidence
Evidence for efficacy is still not well established	Need to establish & develop clinical pharmacology & pharmacodynamics for CMM Need to evaluate potential benefits by combining CMM & Western medicine, as well as the possibility of interactions of these two types of drugs
Dosage forms of CMM still need improvements	CMM mostly available through powder/granules, but controlled-release & target-oriented dosage forms are needed
A suitable screening model for developing new medicines from CMM has not been established	Very difficult to develop a screening method that reflects TCM theory
Intellectual patent system has not been well established	Difficulties in obtaining patents & protection of inventions related to CMM hinders rapid development
A large international market still has not been established	Currently, CMM is used mainly in Asia; the vast European & American markets must be established

Consumers are increasingly interested in alternative treatment modalities for treating chronic and age-related diseases to improve their quality of life, and CMM is especially attractive for disease prevention, health maintenance, and sicknesses that are recalcitrant to current Western medicine. CMM has unique and potential benefits that also attracting worldwide attention from scientists.

Worldwide, CMM now accounts for more than $3 billion annual sales as compared with more than $15 billion (with 20 % annual growth rate) for Western herbal medicine and $300 billion in the mainstream pharmaceutical market. In Taiwan, over NT$10 billion is spent annually on CMM. In China, CMM accounts for 2,500 hospitals, ca. 360,000 medical doctors, ca. 30 advanced schools, and ca. 60 research institutes. Thus, CMM plays both primary and rising roles in the Asian and international nutraceutical and pharmaceutical industries.

Generations upon generations of Chinese people have used CMM for thousands of years to treat diseases; a history that clearly demonstrates CMM's potential as a unique, fundamental basis for modern drug discovery and development, particularly when combined with today's advanced scientific technology. However, to increasingly

escalate CMM's role in the mainstream pharmaceutical market, several fundamental issues must be addressed, in particular, Supply, Quality Control, Safety, Proven Efficacy, and Publication in Mainstream Journals and the Media. Table 1 lists many of the current problems facing the international development of CMM.

Accordingly, strategies for dealing with the above problems include the following six steps, which will be discussed in more detail below.

(1) Gain approval from US FDA for development into excellent world-class drugs

(2) Develop high quality material sources & elevate production technology

(3) Establish quality control (QC) & standardization

(4) Evaluate efficacy & safety

(5) Use 3 approaches for developing new medicines from CMM

(6) Establish pertinent screening models

(1) Guarantee US FDA approval for excellent world-class CMM-based new medicines

A world-class research and development (R&D) center should be established that will research CMM using the most modern scientific technology. Toward this aim, beginning in 2002, the Taiwan Ministry of Economic Affairs launched a five-year program to promote CMM industry Technology. Under this program, three centers will develop the platform technology to assist academia and industry with gaining IND (Investigational New Drug) approval from the US FDA & establishing follow-up clinical trials. This center will enable Taiwan to be the leading R&D and production center of CMM in the world.

It is obviously important to know and contrast the US FDA's requirements for approval of both botanical durgs and dietary supplements as shown in Table 2.[1]

(2) Develop high quality CMM resources & production technology:

Good agriculture practice (GAP) guidelines must be established to cultivate & improve wild-type CMM, with a priority to cultivate unique products endemic to Taiwan with high economic value. Extraction and processing technologies should be improved. Authentic CMM should be produced, as well as production of their active principles improved, by using modern biotechnology (bacteria, enzymes, fermentation engineering, tissue culture, tissue unification & gene techniques). Substitutes should be developed for endangered & rare CMM (tiger's bone, rhinoceros horn, bear's gall secretion, cattle gallstone bezoar, deer antler, winter worm/summer plant). Finally, zero-polluted authentic CMM must be developed and produced that is free from insecticide, heavy metal, bacteria contamination.

(3) Establish standardization and quality control of CMM:

Worldwide acceptable QC evaluation standards and guidelines must be established to assure safety, efficacy, stability, and globalization of CMM, good manufacturing practice (GMP) methods must be followed to produce modern dosage forms for convenience of storage, shipping, handling, and administration, and new dosage forms,

Table 2. US FDA Requirements for Botanical Drugs and Dietary Supplements

Botanical Drugs	Dietary Supplements
Regulated by Center for Drugs, FDA	Regulated by the Center for Food Safety and Nutrition, FDA
Manufacturers must demonstrate the product is safe and efficacious	Manufacturers must demonstrate the product is safe (contaminations, dosage) and notify FDA prior to marketing
INDs* (clinical trials in humans)-Guidance document, 8/2000**	
Good Manufacturing Practice (GMP) requirements-Drug GMP, in process control	GMP requirements-New Guidance
Disease treatment/prevention claims are allowed on the label	Only structure/function claims are allowed on the label, e.g., *This claim is allowed*: Cranberry helps to maintain a healthy urinary tract *This claim is not allowed*: Cranberry helps to prevent urinary tract infection

*An application for an IND for FDA's approval must contain two key parts: a clinical protocol, which is similar to that for single chemical drugs, and chemistry and manufacturing control (CMC), which includes product quality control and lot-to-lot consistency of source material, intermediate, and final product. The most importsnt aspect of QC is the source of material. Items to be considered include good agricultural practice (GAP), contaminations, species identification, chemistry (LC, LC-MS, chemical fingerprinting), bioactivities (cytokine production, receptor binding, cell proliferation, cDNA microarray), and acceptable limits. In addition to the items above, the final product must adhere to product specifications and stability concerns.

**URL: www.fda.gov/cder/guidance/122ldft.pdf
Highlights includes the following: Phase I & II combined, can use historical data for safety, no need to identify each component, can use fingerprint to show lot-to-lot consistency, can rely on bioassay and in-process control.

including controlled-release and target-oriented products, must be improved and developed.

The development of CMM as world-class dietary supplements and new medicines suffers greatly from an actual or perceived **lack of standardization**. Unless the efficacy/safety and quality/consistency of herbal products are guaranteed, they cannot be patented or tested in clinical trials. With such assurances, commercialization is stalled and CMM cannot be marketed as high quality dietary supplements or developed as new drugs. Accordingly, the much needed guarantees include high quality (as demonstrated by strict quality control of correct plant species, strain, and part and of growing, production, processing, manufacturing, and storage methods), consistency (from manufacturer-to-manufacturer and from batch-to-batch), and efficacy/safety (as shown by assured lack of contamination and toxicity, in controlled clinical trials, and by identifying the modes of action and the possible interactions of all constituents).

From the very beginning, plant origin must be authenticated and identified. The plants must be grown using standard production and good agricultural practice (GAP) methods with controlled inspections of contaminants, including insecticides, heavy metals, and bacteria. Standards must be established for processing products from raw materials and for extraction and concentration methods, including continuous solvent extraction, supercritical fluid extraction, and membrane as well as other concentration methods. Fingerprinting standards for chemical properties

should be selected, including pertinent chemical markers and appropriate analytical methods (TLC, HPLC, GC, UV, IR, LC-MS-MS, and their related methods) for QC. Bioactivity-directed fractionation and isolation (BDFI) methods can be used to isolate and characterize the chosen bioactive chemical markers. Pharmacological fingerprinting standards should be followed using pertinent in vitro and in vivo bioassay methods. At the manufacturing and formulation stages, GMP-grade factory methods are required to maintain batch-to-batch consistency, an appropriate dosage forms (pill, soft or hard gel, granule, tablet, cream, paste, patch) must be selected, and storage/shipping conditions determined.

(4) Evaluate the efficacy & safety of CMM:

A Western medicine model must be used to carry out preclinical studies and follow-up clinical trials on CMM in order to develop products acceptable worldwide. New pertinent screening models should be established and emphasis placed on researching herbal formulas to elucidate efficacy, safety, active principles, and mechanism of action. Importantly, appropriate preclinical and clinical trials must be established for CMM-derived new drug candidates, including pharmacokinetic and metabolic studies and animal models for efficacy and safety (toxicity, allergic response, mutagenicity, etc.) evaluations, especially for formulas based on TCM theories. Co-administration of Chinese & Western medicines should be evaluated for both beneficial effects and possible drug interactions. Finally, to continually assure the safety of CMM, surveillance & information systems should be set up for reporting adverse effects caused by CMM.

(5) Develop new medicines from CMM through 3 Approaches:

In the past, new medicines have been developed from bioactive natural compounds found in CMM, as will be discussed subsequently; however, in this new century, new CMM-derived medicines should not only be developed from single pure compounds, but also from active herbal fractions and effective and safe herbal prescriptions (formulas). Both single and formulated herbs can be used as dietary supplements or subjected to bioactivity-directed fractionation and isolation to obtain the active single compounds or fractions. The former single compounds can be identified using modern spectroscopic methods and also modified through analog synthesis. Both the derived single compounds and the active herbal fractions must subsequently undergo preclinical and clinical trials evaluation to become marketable as new drugs. Effective and safe prescriptions obtained directly from formulated herbs could also be marketable as new drugs after strict quality control, reevaluation of efficacy and safety. The corresponding levels of standardization of herbal medicine materials from these three approaches are shown in the figure below.

From Effective and Safe Prescriptions

All of the herbal material is used; thus, this approach requires the highest levels of standardization at all stages, beginning from raw material to drug substance to finished product

From Active Fractions

Only active fractions are used; thus, standardization is less strict for this approach

From Active Principles (Single Pure Compounds)

The finished product is derived from only one pure compound; correspondingly, standardization is even less crucial or might not be needed

(6) Establish Pertinent Screening Models for CMM:

Because it is very difficult to develop screening models that reflect diagnosis and treatment as based on TCM theory; consequently, at the present stage, it would be advantageous to use the established Western medicine screening models (enzymes, cell culture, animal, high throughput receptor binding) to establish efficacy of the active principles, fractions, or formulas. Gene or protein chips (which reflect different disease types as well as different constitutions of the body) and microarray technologies could be used to screen CMM in order to elucidate the effects of the active or toxic principles of CMM upon the expression and control mechanisms of significant genes and proteins.

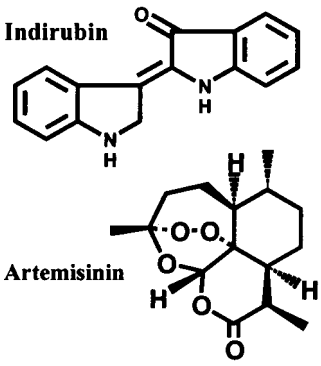
HERBAL MEDICINE FOR MODERN DRUG DISCOVERY & DEVELOPMENT

CMM and other natural products were mankind's first medicine and, accordingly, herbs are selected for scientific investigation based on reported practical medicinal experience. The targeted crude drug or herbal prescription then begins a process of BDFI to discover new lead compounds.[2,3] This lead discovery stage is followed by a lead improvement stage using rational drug design-based chemical modification and structure-activity relationship studies, coupled with mechanism of action, drug metabolism, molecular modeling, and combinatorial chemistry studies. A selected new drug lead then undergoes efficacy and toxicity determination and preclinical/clinical trials. Examples of new drugs or drug candidates are given below.

(1) The folkloric uses of CMM have led to many instances of corresponding successful drug development. For example, *Ephedra sinica* or Ma Huang is frequently used in TCM formulas to treat bronchial asthma, nasal congestion, and head colds is the source of both the bronchodilator(-)-ephedrine and the decongestant pseudoephedrine.

(-)-Ephedrine, R = –OH
Pseudoephedrine, R = ···OH

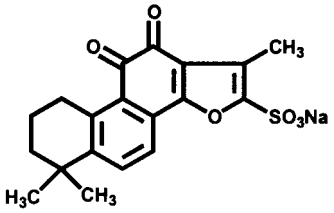
(2) *Indigo naturalis* (also *Baphicacanthus cusia* and *Indigofera tinctoria*) is one of the herbs found in the prescription "Dang Gui Lu Hui Wan". Its leaves contain the alkaloid indirubin, which together with its synthetic analogs are now used to treat chronic myeloctyic leukemia.[4]



Artemisinin

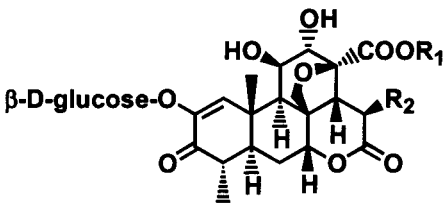
(3) The Chinese medicinal plant Qing Hao (*Artemisia annua*), which was prescribed as a folkloric tea to cure malaria fever, is the source of artemisinin (quinghaosu), which is a safe and effective antimalarial drug.[5,6]

(4) The rhizome and roots of *Salvia miltiorrhiza* (Tan Shen or sage) are used in TCM to treat various cardiovascular diseases. Accordingly, as its water-soluble sodium sulfonate salt, the terpenoid tanshinone II-A is used to treat angina pectoris and myocardial infarction.[7]

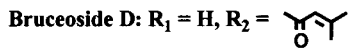


Sodium Tanshinone II-A Sulfonate

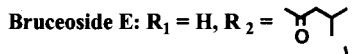
(5) Similarly, the discovery and development of bioactive natural products and their analogs as therapeutic agents are the goals of my Natural Products Laboratory. Numerous examples of the diverse natural products identified from CMM sources and investigated as new drugs leads have been discovered. For example, the herb *Brucea javanica*, Ya Tan Tzu, is commonly used in TCM to treat fevers, dysentery and warts. It contains many natural quassinoids, including the group called bruceosides, which show cytotoxicity in leukemia, melanoma, and non-small cell lung, colon, central nervous system (CNS), and ovarian cancer cell lines. Brusatol demonstrated potent cytotoxic antileukemic activity in mice.[8-10]



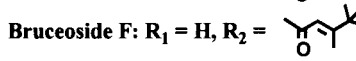
Bruceoside D: R_1 = H, R_2 =



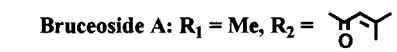
Bruceoside E: R_1 = H, R_2 =

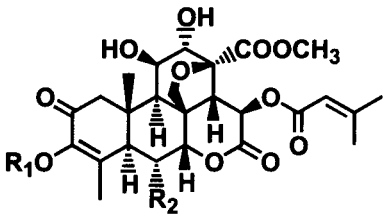


Bruceoside F: R_1 = H, R_2 =



Bruceoside A: R_1 = Me, R_2 =





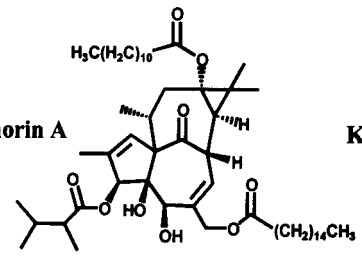
Bruceoside B: R_1 = b-D-glucose, R_2 = H

Bruceoside C: R_1 = b-D-glucose, R_2 =

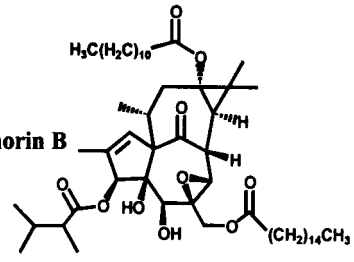
Brusatol: R_1 = R_2 = H

(6) *Euphorbia kansui* was listed in the lower class drug of "Shen Nung Pen Tsao Ching" and currently is used in China as an herbal remedy for ascites and cancer. The NPL isolated several antileukemic diterpenes, including kansuiphorins A and B, which were potent against P-388 leukemia in mice with T/C values of > 176 and 177 % at 0.1 and 0.5 mg/kg, respectively. Subsequently, kansuiphorin A showed significant in vitro cytotoxic activity against various leukemia, melanoma, and non-small cell lung, colon, and renal cancer cell lines.[11]

Kansuiphorin A

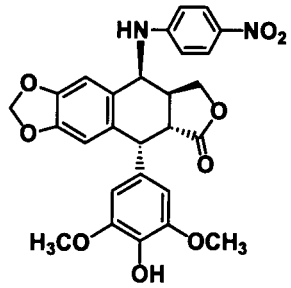


Kansuiphorin B



(7) *Podophyllum pelatum* (Knei Chin), listed in the lower class drugs of "Shen Nung Pen Tsao Ching", is used traditionally as a contact cathartic. Podophyllotoxin was isolated as the cytotoxic principle from his herb. Subsequent modification of podophyllotoxin led to the discovery of GL-331[12] as an analog of etoposide and teniposide, two clinically useful anticancer drugs. GL-331 completed Phase I clinical trials as an anticancer drug.[13] Its Phase II clinical trials are being planned.

GL-331



CONCLUSIONS

CMM holds much promise for the discovery of new drugs by three appreaches 1) bioactive pure single lead compounds, 2) active fractions, and 3) effective and safe prescriptions. Highly efficient BDFI, characterization, analog synthesis, and mechanistic studies are used by my and other research laboratories for the development of new single compounds and active fractions as clinical candidates for world-class new drug development. However, modernization of CMM and CMM-derived products, including genetic approaches, is essential and can only lead to improved products and more worldwide acceptance. Advanced scientific technology provides measures to prove the efficacy and safety of all single herbs and traditional or modern prescriptions using reliable pharmacological and toxicological methods as well as GCP (Good Clinical Practice) standards and principles-based clinical trials, establish both qualitative & quantitative quality controls on single herbs and prescription formulas, and standardize official measures for herbal products by using both biological and chemical markers. Continued scientifics study will certainly develop new, effective, and safe world-class dietary supplements drugs from CMM that will be accepted and used worldwide by physicians and consumers.[14]

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新世紀中藥研發之新趨勢

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中藥及其替代療法現已風行全球。利用中藥以研發高品質之健康食品與有效、安全之新藥，藉以改善生活品質，預防疾病，治療慢性病與老年病，以及西醫束手無策的疑難雜症，已成爲一種新趨勢。高品質健康食品之生產端賴乎嚴謹之品質管制。由中藥開發出有效安全之世界級新藥可通過三個途徑：有如西藥之純化合物療效成分，活性部位，及經過現代科技確認有效且安全之中藥方劑。本演講將針對上述之研發趨勢、方法與展望，舉例說明。

聯絡人：李國雄，美國北卡大學，藥學院，天然產物實驗室。